Ninth Edition

API Textbook of MEDICINE

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Textbook of Medicine



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9th
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The Association of Physicians of India

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Ninth Edition

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9th Edition

PREFACE

Over four decades ago, a new compendium of medicine was published under the aegis of Association of Physicians of India. This was due to the vision and hard work of the stalwarts at that time. The first edition of the book was edited by an internationally famed physician Dr Rustam Jal Vakil. The book was well accepted all over the country. Enthused by the response of Indian physicians, eight more editions of the book have been published. Each new edition was an attempt to improve and incorporate the changing profile of medicine.

In the last decade, the progress has far outstripped the progress made in the previous decades. It is in this milieu of continuous change that I have the pleasure of presenting to you the 9th edition of the popular, API Textbook of Medicine. The book is completely revised, updated and better illustrated. There are around 2200 pages with nearly 1588 figures and 1384 tables. There has been a marked 20% increase in the number of figures and nearly 100 new tables have been added than the last edition. This has been done so that the information is easily understood and the reading is not a strain. The book has been divided into 28 sections and each section deals with a special set of medical disorders.

An entirely new section has been added, 'Clinical Approach to Key Manifestations'. This section deals with the common symptoms and signs with regard to how to scientifically and systematically analyse the problem to arrive at a definitive diagnosis in a timely and cost-effective manner. New authors have been requested to contribute new chapters so that the book is entirely re-written in most of the parts and some of the chapters have been exhaustively revised by the previous authors. A few chapters and figures have been reproduced from the 8th edition. I, on my own behalf and on behalf of the Editorial Board of the 9th edition, express our thanks to the erstwhile Editor-in-Chief, Dr Siddharth N Shah of the 8th Edition for having given us this permission.

The explosion of knowledge in medicine is phenomenal and fast so it outpaces the printed textbook of medicine. Therefore the 9th edition endeavours to reflect on some of these changes occurring in medicine during the preceding few years. A number of new chapters have been added like Non Invasive Ventilation under Critical Care. Pharmacotherapy of Cardiovascular Diseases has been added in the section of Cardiology. In the Section of Gastrointestinal Disorders, a new chapter on the Gastrointestinal Symptoms due to Systemic Diseases has been added. The Neurology section has been enriched by adding a chapter on Neuroimaging and separate chapters have been written covering Amyotrophic Lateral Sclerosis and Hyperkinetic Movement Disorders. In the field of Rheumatology, Emergencies have been discussed as a separate chapter altogether which reflects the new way of thinking of treatment and diagnosis of various rheumatic emergencies. The section of Medical Genetics has been thoroughly revised and updated. Genetics is better understood and human genome has been completely delineated. This has tremendous potential for change in the way we practice medicine. Vascular Injury to Kidney and Chronic Dialysis under the section of Nephrology have been discussed in separate chapters because of the better understanding and growing importance of various facets of kidney disorders and diagnosis. An entirely new chapter on Nano Technology and Nano Medicine has been added which is going to be a new paradigm in the field of Clinical Pharmacology. The other sections have been duly revised and updated so that they provide contemporary information and clinical thinking.

The expanse of medicine is vast and varied. The presentation of all disorders in a concise and systematic manner in a book of this size has to be a joint collaborative effort. This has been possible due to the support, constructive criticism and useful editorial guidance from all the members of my editorial team for which I am grateful to them. I am especially indebted to Prof. SK Sharma who has been instrumental in guiding and planning this assignment at the cost of his precious time despite his multifarious academic activities. Dr AK Agarwal and Dr RK Singal have been closely associated and have provided useful inputs and suggestions in preparation of this book for which I am grateful to them. Dr Milind Y Nadkar and Dr Sandhya A Kamath provided useful inputs as to how to circumvent some of the key issues while editing a book of this nature because of their past experience of the 8th Edition of the Textbook. Dr Shyam Sundar, Dr Subhash Varma and Dr Pritam Gupta were forthcoming in their help and suggestions for which I owe my thanks to them. Dr Siddharth N Shah, the Emeritus Editor has guided and supported whenever his help was sought for in the production of this book. I am obliged to him for all his help. The Sectional Editors were generous with their time and suggestions while the authors of chapters contributed their chapters in time and as per the common format which was agreed upon. For all this, I convey my sincere thanks to them.

In the era, of information technology, in consonance with the international practice, a new website for the book, 'API Textbook of Medicine', has been created (www.apitextbook.com). It is a novel feature starting from this edition with online access which will be easily available to all those people who purchase the book. Periodically, the website will be upgraded and new information will be added.

During the entire course of past three years of compiling of this book, my wife Dr Rama Munjal, son Dr Akshay Munjal and daughter Er. Jaya Munjal were a source of great strength and motivation. They showed tolerance and forbearance at all times during the preparation of this book. For all their support I wish to place on record my heartfelt thanks. On the completion of this major task, I feel more humble and ever so grateful to the Governing Body of API for having given me this opportunity to carry out this job for and on behalf of our organisation.



Dr Yash Pal Munjal
Editor-in-Chief
API Textbook of Medicine
9th Edition

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The 9th Edition of the API Textbook of Medicine is now available to you. This has been possible due to the collaborative, co-operative and untiring efforts of the Editorial team and many others. On the occasion of the successful completion of this marathon job, it would be appropriate to acknowledge and express my gratitude to all those who have helped in getting this job well done. I am especially grateful to Dr Anupam Prakash and Dr Ghan Shyam Pangtey. They have been associated from the stage of conceptualisation and planning to the final production of this manuscript and have provided unstinted help all through this exercise with dedication and commitment. Dr AP Misra, Dr Anurag Saxena, Dr DG Jain and Dr Sumit Singla have provided useful help at various stages which is duly acknowledged. The task of proof reading and organising the manuscripts was painstakingly and continuously carried out by Mr RK Gupta, Mr DK Sahu, Mr MS Muddur and other members of their team. The efforts of Mr RK Gupta especially stand out and I would like to express my thanks to all of them. I would like to express my thanks to Mr Sanjeev Chaudhry of 'Initials' for having done the initial type setting of the book.

The final production of the book has been possible due to the hard work put in by the staff of Jaypee Brothers Medical Publishers. The good work done deserves our appreciation and gratitude to Shri Jitendar P Vij, Chairman and Managing Director of Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, which is now the second largest Medical Publishers in the world.

Mr Tarun Duneja (Director Publishing) has been instrumental in getting the final shape of the book. The other members of Jaypee Brothers, Ms Shikha Gupta (Editor), Mr Manoj Pahuja and Mr Ankit Kumar (Graphic Designers), Mr Pramod Kumar Rout and Mr Kapil Dev Sharma (DTP Operators), and Mr KK Raman (Production Manager) have done a marvellous job and put in hard work in the production of this book. They were receptive and wore the brunt of this task willingly. They coordinated with the office of editorial board as a team and carried out the instructions diligently. They deserve our appreciation and thanks.

I would like to express my sincere thanks to my Secretary, Ms Pushap Lata, for having taken up the additional responsibility with a smile on her face at all times. Ms Neha Garg, who joined at a later stage in the book production, was enthusiastic and co-ordinated the work very effectively and efficiently both in compiling as well as proof reading in the final stages of the book.

I would be failing in my duty if I do not express my sincere thanks to Shri Autar Krishna, Chairman and Shri Bhuwan Mohan, Secretary of Shri Banarsidas Chandiwala Sewa Smarak Trust Society for providing the office space and allowing the use of infrastructure during the entire course of the publication of this assignment. Not only they provided the infrastructural support but they also encouraged me in my task as the 'Editor-in-Chief' of this book.

The help of Sectional Editors for editing the section diligently and providing editorial inputs which were very useful and timely is highly appreciated. I would like to extend our thanks on behalf of the Editorial Board and the authors who have been provided useful assistance by their colleagues in preparation of their respective manuscripts.

Dr YP Munjal
and the Editorial Board

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Section 1

Introduction

The Practice of Medicine

Yash Pal Munjal

1.1 The Practice of Medicine

Yash Pal Munjal

INTRODUCTION

The history of practice of medicine is as old as the history of mankind. Over the years, medicine has gradually evolved and the modern medicine in its present form came into existence about 400 years ago. The last century has seen tremendous progress which is phenomenal and a lot more than in the preceding three centuries. Despite this explosion of knowledge, medicine still remains 'an art and science' to be practiced with compassion, empathy, and effective communication with the patient. *In today's practice, the patient is an informed partner in the plan of his management.*

This sea change in the medical practice is due to the emergence of new technologies which facilitate a physician to delve into the disease at its molecular level with the help of various biochemical, immunological, and genetic tests. There has been a marked improvement in the imaging technology. We have travelled a long distance from the time of conventional radiology to an era of PET and SPECT scanning. These have improved our capabilities to look into every nook and corner of the body and its organs. This has helped in arriving at a correct diagnosis and also to evaluate the functional status of the organ system. All these investigations with their sensitivity and specificity have armed the clinician to arrive at a diagnosis, plan effective treatment and prevent disease, if possible. Not only science has made rapid strides in diagnosis but also there has been a very significant improvement in the therapeutic modalities. The growing knowledge of genetics and immunology has enabled the clinician to provide treatment based on the molecular defect and individualising therapy accordingly.

The advent of information technology and internet has changed the way we learn medicine and keep our knowledge up-to-date about the latest innovations in medicine. It has given us the capability of maintaining medical records in a comprehensive manner so that they are more useful to the patient as well as help the doctor to follow the patients very effectively. Difficult clinical problems can be solved easily. Patient's records can be transmitted to other institutions and doctors for information. Telemedicine as a discipline has a great relevance, particularly in the context of developing countries, especially India, where there is a shortage of trained and expert medical manpower. This helps to provide medicare to patients in remote places where trained personnel are not available. Even sitting at one place, a senior surgeon can guide surgical procedures at more than one centre.

In this phenomenal progress of scientific knowledge, the basic goal remains to diagnose and treat the patient effectively and as early as possible. In this exercise, due consideration has to be given to the quality of life achieved and cost benefit ratio. It is the latter part which is the practice of the 'art' of medicine. This is learnt and mastered by practice, experience, and gradual understanding of the diverse human nature over the years.

AMALGAMATING THE ART AND SCIENCE OF MEDICINE

The scientific technology has enabled the physician to arrive at a diagnosis at the molecular level. It is now possible to understand the cause and complex mechanisms involved in the pathogenesis of disease. This constitutes the science of medicine. Once the diagnosis is established, the doctor has to inform the patient about the diagnosis, plan of management, and prognosis. He has to get the concurrence from the patient for the line of management to be followed. It is this communication skill of the clinician which wins confidence, faith and builds a healthy relationship between the doctor and the patient. This is an 'art' to be nurtured.

The task of a physician becomes rather delicate especially in situations which involve management of incurable and terminal stages of diseases. In a situation like this, the scientific knowledge at the command of a doctor is to provide adequate and effective relief from symptoms. The doctor and his team should not be carried away by the life-saving procedures used in the hospitals. In such situations, the doctor has to inform the relatives and the patient about the gravity and prognosis of the terminal diseases in a manner that the patient can understand and discuss with his doctor properly. It is an exercise to prepare the relatives and the patient to face the grave situation with forbearance and equanimity. This exercise has to be carried out by the doctor with all the compassion and empathy at his command so that he is able to communicate to the patient effectively and subtly. The doctor who can handle such delicate situations effectively earns the respect of the patient and the family. This is in true sense of the word an 'art' which a doctor has to imbibe and master over the years.

PRINCIPLES OF MEDICAL PRACTICE

Clinical Evaluation

The art of clinical evaluation has to be learnt and mastered by everyone studying medicine. *This forms the basic foundation on which the future course and technological advancement can be used effectively and rationally in a cost effective manner.* Therefore, it is absolutely essential for every practising doctor not to lose sight of this part of clinical medicine thinking that technological advances can take away the importance of clinical examination. The clinical evaluation of a patient comprises of two major aspects:

1. History of sickness of the patient
2. Comprehensive physical examination

History

The history of illness should include all the facts of medical significance in a chronological order and in a comprehensive way. Eliciting the history of the patient is an art which a doctor develops over a period of time. He should be able to guide the patient and to encourage him to narrate the history of his

illness with all its details in a manner which is useful and easily comprehensible. He guides the patient to give the details rather than getting into trivia which may be irrelevant to the medical problem. He may pose questions which guide the patient to narrate the relevant details. To complete the history, personal, past, and family history have to be recorded. The family history is important as it can provide useful clues to certain genetic disorders as well as certain communicable diseases which may be transmitted from one member of the family to the other. Similarly, the details of history provided by the family members may be helpful especially in dealing with psychological disorders.

The history taking and talking to the patient is the first step towards developing an effective and unique doctor-patient relationship. The patient is encouraged at all times to narrate his condition in detail. This will give him the satisfaction of having communicated to the doctor all about his sickness. The feeling that the doctor was receptive to his condition and sickness helps in building a rapport between the patient and the doctor.

Physical examination

The physical examination should be carried out at a place which is comfortable, ensures privacy and maintains dignity of the patient. It has to be comprehensive and complete from head to toe. The physical examination has to identify the clinical signs of disease and confirm the structural and functional changes. The clues may have been provided by the patient in his history. There are no shortcuts in physical examination as they may lead to major errors in diagnosis. Competence in physical examination comes by knowledge, experience, and following the methods of clinical examination in all its detail. Progress of clinical disease alters the physical signs from time to time and therefore a good clinician must carry out the physical examination repeatedly and periodically. Not only the ethical attributes of the clinician but also an alert mind is absolutely mandatory for getting the best information from the physical examination. The success of a good history and physical examination yields information which prepares the clinician to prescribe diagnostic tests which will clinch his diagnosis rather than unnecessary and multitude of tests which cause unnecessary escalation of cost and add to confusion (**Figure 1**). The clinical examination provides useful input to the clinician about the line of investigation and whether to give credence to some symptom and physical sign or not depends not only on his knowledge but also is an art of medical practice.



Figure 1: Hippocrates (460–380 BC).

Investigations

The investigations have significantly improved in their sensitivity and specificity so as to provide accurate diagnosis. The diagnostic tests help clinicians to:

- Establish the diagnosis
- Assess the degree of malfunction and extent of disease
- Make a rational plan for management which may be medical, surgical, or palliative
- Assess the benefit of therapeutics and interventions.

A good clinician is able to plan the investigations which are essential and appropriate in a given clinical situation. After the results of constellation of tests are available he should be able to interpret them in the clinical context. The judicious use of investigations limits the cost and helps to arrive at a diagnosis in an effective and useful manner.

Decision-Making in Clinical Practice

A physician has to take decisions at various stages during the clinical course of sickness. These have to be in consonance with the informed consent of the patient. The first level of decision-making is to arrive at a provisional diagnosis based on the history and physical examination. At this level, he has to plan the investigations as well as start provisional treatment so that there is no further deterioration in the condition of the patient. As soon as the results of investigative procedures are available, his clinical skill is once again called into play to arrive at a definitive diagnosis by following the principle of deductive science and plan a definitive course of treatment. This is the second level of decision-making. After the treatment has been initiated and continued, the response can be an improvement in the condition of the patient or there may be no change in the condition of the patient or it may get worse. This is the next level of decision-making where the doctor has to review his previous diagnosis, order fresh investigations so that missing link is detected. In case the patient shows benefit of treatment then he has to decide how long to continue the treatment so that the patient is restored to his health. Not only the subjective improvement but also an objective assessment has to be made based on the clinical and laboratory parameters which have to be decided by him.

Evidence Based Medicine

This concept means that the clinical decisions to be taken are fully supported by data that is derived from prospectively designed randomised controlled clinical trials over a fairly long period of time. This is in marked distinction to the previous concept of following the treatment based on one's experience and bias towards one form of treatment than the other. It is imperative for today's doctor to take decisions based on hard outcome data from large clinical trials. To get this implemented many National and International Organisations have formulated Practice Guidelines which help the physician and other members of his team in making a diagnosis and taking appropriate therapeutic decisions. These guidelines provide the framework for managing patients with a diagnosis or clinical symptoms and also help to create a standard of medical care so that all patients get the benefit of cost effective and proven therapies. They help to protect the doctors from frivolous charges of medical malpractice and cost overruns due to

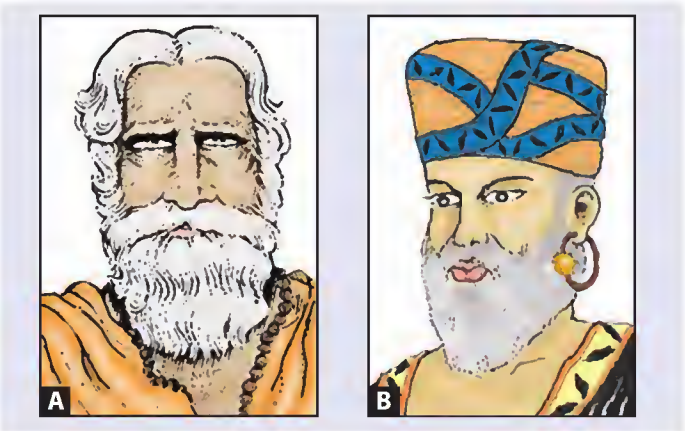
unplanned treatment. However, these guidelines have to be used with caution and must be based on the clinical constellation of a particular clinical condition. In case more than one options are available for treatment which is scientifically proven, the physician cannot be faulted for choosing one option for the other option. In planning a treatment, the other factors which have to be taken into consideration are the age and sex of the patient and associated medical conditions, and drug-drug interaction.

Assessment of the Success of Treatment

Previously the assessment of result was based on clinical examination and subjective feelings. Nowadays the evaluation is based on hard outcomes data to judge the success of treatment. This is in the form of prevention of morbidity and mortality. In case of chronic illnesses where cure is not possible, assessment of treatment is based on not only the symptomatic relief but also by finding out that if the progress of the disease has been stalled and complications have been prevented. Another parameter which helps in assessing the benefit of treatment is the quality of life which the patient enjoys after the treatment. Therefore, summing up in today's context, it is predominantly an objective outcome assessment as compared to the olden times. There are certain modifying situations which can change the parameters of assessment like the age and sex of the individual. The delivery of medical care has to be assessed in the context of available resources and infrastructure. It is essential and obligatory for the doctor to provide compassionate care with empathy, understanding and constant dialogue with the patient (this is always possible) even with limited resources and infrastructure.

MEDICAL ETHICS

As soon as the foundation of the modern system of medicine was laid the practice of medicine was 'put into guiding principles' by the famous Hippocratic Oath. If we delve into the ancient Indian literature, similar guidelines were propounded much earlier by Sushruta/Charak Samhita, Aryabhatta Smriti, etc. (**Figures 2A and B**). They have elaborated on various aspects of code of conduct, qualities of physician as well as human aspects of relationship. Among the qualities and characteristics of physician, special emphasis was laid on character (purity, honesty, and integrity), qualification (knowledge, skill, and experience), professional attitude (alert, responsive, communicative, and responsible), and behaviour (friendly, respectful, and compassionate). The basic tenets of these guidelines were to 'provide patients good doctors'. The good doctors are supposed to make patient care their first concern and, therefore, they need to be competent (good medical education). They should keep their knowledge and skills up-to-date (continuing medical education). They should maintain good relationship with the patients and professional colleagues, be honest particularly to themselves and act with integrity (Ethics of Medicine). The various national and international agencies have provided guidelines for the practice of doctors in their respective countries. In India, the Code of Conduct has been framed by the Medical Council of India. This is modified from time to time based on the socio-cultural needs and advancement of medical knowledge. The responsibilities and duties of a doctor formulated by various organisations are based on the following principles enumerated in **Table 1**.



Figures 2A and B: (A) Sushruta (800 BC); (B) Charak (300 BC).

Table 1: Responsibilities and Duties of a Doctor

Patient care should be your first priority
Keep the dignity and privacy of every patient and he should be dealt with politeness and consideration
Do not be judgmental. Listen to the patients and respect their information
Communicate in a manner the patients understand and make patients equal partners in decision-making
Keep your professional knowledge and skills up-to-date
You must practise and manage patients to the level of competence and knowledge acquired by you
Refer patients at appropriate time to a higher centre or a super specialist at the earliest possible occasion, if required
Keep the information given to you confidential and to be divulged only under extremes of circumstances
Do not abuse your position as a doctor
Your dealings with the colleagues and pharmaceutical industry should not raise conflict of interest and your conduct should be in the best interest of the patient
Provide adequate information and take 'informed consent' before any drug trial or 'off label use' of any drug

Implementing Medical Ethics

Medical ethics are also concerned with the standards of care and the ethical issues raised by the practice of medicine. Recent scientific knowledge and their usage have thrown many difficult ethical problems which are still in the process of debate. In these situations the doctor has to decide based on his belief and the sociocultural milieu. Some of the issues under debate are cloning, genetic medicine, abortion, care of the brain dead for organ transplant, and need of live tissues. Another issue which is a matter of concern and debate is the issue of assisted suicide or euthanasia. In clinical practice the ethics come into play in three vital areas. The clinical ethics are concerned with the relationship between the doctor and the patient. Another area is the conduct of research on patients which is guided by the research ethics while public health ethics deal with the health of the community, state, or country as a whole.

CLINICAL ETHICS

In clinical ethics, four principles are important and they can be abbreviated to autonomy, beneficence, non-maleficence, and justice.

Autonomy

The respect and dignity of the patient has to be maintained at all times. Truthful communication with the patient is always a must though it is not essential to inform him of the facts in the first instance especially in critical illnesses or certain disorders (HIV) which have a lot of social stigma attached.

Informed consent

It is the fundamental right of an individual that his body is inviolable. Therefore, a doctor needs to have permission from the individual for his examination, investigations and therapeutic procedures including interventions and surgeries. The patient has to be informed about the method adopted for diagnosis and the line of his management. In case, there are more than one options for treatment then the details of all the options with their pros and cons have to be explained. This communication must be done in a manner that the patient understands and in his language. After this, he should give his consent in writing to carry out that treatment or procedure. Legally and morally, the patient has the absolute right to take a decision about what is right or wrong for him. Sometimes, the choice of the patient may seem irrational and not in accordance with the professional advice. But it should not be construed that he lacks the capacity and mind to take appropriate decision for himself. In situations where he is incapacitated to take a decision on his own, e.g. in children, unconscious patients or insane individuals, the treatment may be planned in consultation with the explicit permission of the relatives. In case the relatives are not available then a group of physicians may take a decision on behalf of the patient depending on the local laws and culture.

Confidentiality

The details of the history, treatment, and prognosis have to be kept confidential. All communications and other records relating to the patient's care are to be treated as confidential documents. This information can be shared between health care professionals if the patient is referred to another institution or a consultant. In other situations, the authorisation in writing by the patient is a must. The confidentiality clause can be rescinded for due process of law and in cases of insurance or a medical claim. This right of confidentiality has been over-ruled in cases where the condition is infectious (e.g. HIV or AIDS) by right to healthy life of the other person who is likely to be in his contact or where the community interest suffers.

Beneficence

This means acting in the best interest of the other person. In clinical ethics, it means the benefit of individual patient based on the patients' point of view as well. In situations where there is a conflict of interest between the benefit of the individual patient over that of the community, the declaration of Geneva by World Medical Association entitles a doctor to follow the dictum "Health of my patient will be my first consideration".

Non-Maleficence

This means do no harm. In traditional medicine, the concept followed is 'primum non nocere'. In the practice of medicine beneficence and non-maleficence have to be balanced (benefit versus risk). Relevant information on the above two grounds must be shared with the patient so that he is able to make an informed decision.

Justice

This means availability and access to the health care by every individual irrespective of caste, creed, social and economic status. It mandates an equitable distribution of health care resources. One associated concept is that of utility, i.e. greatest good for the greatest number must be evaluated for an individual patient. Justice means being fair to him and it involves evaluation of the needs of the patient, respecting his rights as well as the merit.

PUBLIC HEALTH ETHICS

Public health involves the health of the community, state or country as a whole; no direct doctor patient relationship exists. This involves preventive measures like education, mass vaccination, mass screening for diseases and precautions to be taken at the community level. In prevention of certain lifestyle diseases like diabetes, coronary artery disease and obesity, there may be a conflict of interest with the corporates who are dealing with the marketing and advertisement of such substances like alcohol, tobacco, junk food, etc. To resolve these situations of conflict of interest social organisations and medical professionals may have to lobby with the politicians to educate the society to demand action against the sale, marketing and use of these substances if necessary, by laws. In India, a major step has been implemented that all advertisements pertaining to tobacco and its derivatives (e.g. cigarettes, bidis, hookah and chewing tobacco) have been banned and even at the individual level their use at public places is prohibited (by law).

Restrictive measures may at times become a necessity. In an explosion of epidemic to prevent its further spread certain legislations may have to be passed. This was recently amplified and implemented in cases of severe acute respiratory syndrome (SARS) and avian flu. Such interventions are for the good of the general community at large. Another important aspect of public health ethics is the uniform and equitable distribution of funds for various disorders with a view that maximum people may draw benefit.

RESEARCH ETHICS

The conduction of research is a vital component of medical practice. It may provide a sound basis of care for a better and more effective treatment for subsequent patients. The principles of information, beneficence, non-maleficence and justice should be strictly adhered to in all research protocols. The guidelines for conduct of good research have been formulated and must be strictly followed. The patients consenting for trial should be offered due care and they must be compensated both for their time, travel and reimbursement of the other expenditure incurred by them. Such reimbursement should not appear to be an inducement to the patient, health care institutions and the doctors.

END OF LIFE SITUATIONS

A doctor is faced with the dilemma of communicating the diagnosis of certain incurable diseases or a disease in its terminal stage to the patient and/or his relatives. In such situations, the

doctor must be sure about the diagnosis that the disease is incurable, or it has advanced to such an extent that it is in its terminal stage. The doctor is not necessarily bound to divulge the complete information at the time of first contact with the patient, but it is imperative for him that he must confide, educate the patient and the relatives about the gravity of situation and its consequences. This can be done slowly and progressively. The physician should provide this information in a manner that it is easily understood by the patient and other persons attending him so that they can appreciate the gravity of the situation. The doctor should be willing to discuss the details and answer necessary questions of the patient or his family members. This exercise has to be done with compassion, empathy, and it is an art which a physician has to master and practice by knowledge and understanding. The doctor sometimes gets overwhelmed with the prospect and availability of advanced life saving methods (e.g. ventilators, pacemakers, etc.) in an aggressive manner. But it is always important for him to remember the basic fact about the gravity of the sickness and its consequences. Symptomatic and pain relief have to be addressed aggressively to provide comfort to the patient round the clock. During the terminal stages of any disease it is not only the medical treatment which has to be provided but religious, cultural and other supportive measures also have to be used judiciously, and they should be facilitated so that the patient and his relatives are at peace and comfort.

ENVIRONMENTAL MEDICINE

A number of chronic and infectious diseases are emerging and posing a threat to the health of countries. It is believed that due to rapid industrialisation and urbanisation which has led to the degradation of the environment polluting the air, water, and significant lowering of the hygiene. According to WHO estimates, nearly one-fourth (24%) of the global disease burden and 23% of all deaths can be ascribed to environmental factors. This deterioration in the environment can lead to a spurt in the infectious diseases, chronic non-communicable diseases, and trigger certain genetic disorders due to mutation of genes. Due to global warming and increasing carbon dioxide in the atmosphere, it is estimated that the prevalence of vector borne diseases, like malaria and some of the infectious diseases, are likely to increase manifold. The environmental factors that lead to genetic variation concerning the cholesterol synthesis may precipitate increase of coronary artery disease significantly. A physician has to be well-versed with the various environmental pollutants, environment at work place, and have a working knowledge of some of the environmental and occupational diseases.

DISASTER MANAGEMENT

The environment and nature are friendly to the human beings most of the times but at times the ravages of nature can bring death, destruction and disease in a sudden and unexpected manner. Some natural disasters that have struck in the recent times where thousands of lives were lost—Tsunami in South India and Sri Lanka and a few years later we had a very severe Tsunami and earthquake in Japan. These natural disasters led to the outbreak of many infectious diseases and there was an associated increase in vector borne illnesses. The marvel of technological advancement by science is useful to the mankind most of the time but due to an accident it may lead to a disaster. To mention a few examples of technology related disasters are—the Gas leak in Bhopal (MP) in 1984 the so called Union Carbide Gas Leak, the Chernobyl Russian Nuclear Power Plant Explosion in 1986, and the radiation spread by the damage of the Nuclear reactors in the area of Tsunami in Japan in 2011 have led to disastrous consequences. Man himself can unleash disasters like the bombing of Hiroshima and Nagasaki in Japan, chemical and biological warfare. It is the management of such emergencies in which there are mass casualties that it needs courage, presence of mind and a well-planned action so that misery can be minimised. In this situation, the health care professionals have to work in close collaboration with the society. The various phases in which the emergency management has to be carried out are described below.

Mitigation

Mitigations are concerted efforts to prevent hazards from developing into disasters altogether or to reduce the effects of disasters when they occur. The mitigation phase differs from the other phases because it focuses on long-term measures for reducing or eliminating risk. Mitigation is the most cost efficient method for reducing the impact of hazards while it may not always be feasible.

Preparedness

It is to train people to fight the disease and, therefore, it involves planning, organising, training, equipping, exercising, evaluation and improvement over a period of time. It helps to ensure co-ordination and increased capability to deal with disasters, terrorist attacks and man induced disasters.

Response

This phase includes the mobilisation of the necessary emergency services and first responders in the disaster area.

Recovery

The recovery phase aims at restoring the affected area and population to its normal state. The focus of this phase is different from response phase, recovery efforts are started after immediate needs are addressed. In recent years there has been a shift in emphasis from response and recovery to strategic risk management and reduction. There is more emphasis on community participation rather than a Government centred approach. Efforts involve the provision of emergency management training for first responders, the creation of a single emergency telephone number and the establishment of standards for emergency medical staff, equipment and training. The physician therefore has to learn how to handle acute emergencies especially in situations where there are mass casualties.

In India, the Disaster Management Authority of India has been set up by the Government of India to deal with such situations and prepare the infrastructure in the country.

MEDICAL GENETICS

The study of genes and their function in health is called Genetics in Medicine while the understanding of the aberrations in the function and structure of genes is Medical Genetics. The advent of medical genetics has profound

influence on our understanding of the pathophysiology of disease and has opened new vistas of therapy especially the concept of planning and executing individual requirement based therapy. The greatest breakthrough was achieved in the spring of 2003 when complete sequencing of human genome was officially announced and released. This has ushered in an era of immense possibilities of not only cloning of species but repairing of many organ systems. The science of genetics has provided us the speed to understand the pathogenesis of disease epidemics. The discovery of new variant of coronavirus as a causative agent for SARS and the virus of avian flu; this has helped to quickly plan the management of these conditions.

The understanding of genetic disorders and how we can manipulate them has provided a new dimension to the art of genetic counselling in which the patient can be briefed about the likelihood of the genetic disorders which the offspring is likely to suffer. In case it is possible to correct the genetic defect the same may be done by genetic engineering. If it is as yet not correctible then counselling can be done about the consequences of the genetic disorder and its prognosis so that the parents can take appropriate decision at the beginning of the conception.

Another important area of genetics is pharmacogenomics. It deals with pharmacological manipulation of the genes for correction of

(a) Genetic defects or management of certain disease states especially cancer

(b) Choosing the appropriate medicine for a particular disease based on the genetic profile of the individual

(c) Another aspect of this is the use of stem cells. Stem cells are totipotent cells which can grow up into various tissues. These are now being used in many areas of clinical medicine like coronary artery disease, diabetes mellitus, healing of the wounds and rejuvenating organs.

Stem cells are being extracted from the cord blood on the birth of the child. These can be preserved for a number of years and are capable of providing treatment or repair of certain damaged organs at a later stage in life. These stem cells provide the individual with homologous graft.

The interaction between the genes and environmental factors i.e. phenotype can predispose to the common chronic diseases of the 21st century like obesity, diabetes, hypertension, and coronary artery disease which can be partially prevented or ameliorated by modifying the lifestyle factors.

CONTINUING MEDICAL EDUCATION

The science of medicine is galloping at a fast pace and, therefore, it is essential for the practising physician to learn new skills and knowledge so that he can serve the best interest of his patients. A doctor has to keep learning all through the time he is practising. The avenues available for medical education these days consist of learning from the peers in the field, the books and journals which are being brought at a fast pace.

The technological advancement has significantly improved the way one can learn medicine. The availability of internet and video conferencing has added new tools with great potential of learning skills for a clinician who can take the benefit of the same at a place and time of his convenience. Video conferencing provides useful tool for interactive learning and teaching a large number of students at different locations by an expert in the field from a common site. Live case demonstrations and procedures can be learnt by direct telecast. The other advantage is that one can assess his grasp of the subject by taking web based examinations in the privacy of his chamber. The internet has also served the purpose of educating the patients about their sickness and disease.

COMPLEMENTARY AND ALTERNATIVE SYSTEMS OF MEDICINE

Complementary and alternative medicine (CAM) is a diverse group of health care medical systems which does not conform to the commonly practised modern system of medicine. CAM is used and practised globally and in one survey it was found that 36% of people opted for CAM in the year 2002 in USA, while in a recent survey in UK, homoeopathy was used as a method of treatment in approximately 48% of patients. If we include faith, spiritual healing and prayers, then the number goes to approximately 62%. In India, this percentage is much higher and the various commonly used alternative systems of medicine are Ayurveda, Unani, Siddha, Homoeopathy (**Figure 3**), religious, yogic practices, and household remedies. Systems from other countries, such as accupuncture, reflexology, and osteopathy, have also been used quite frequently in recent times.



Figure 3: Christian Friedrich Samuel Hahnemann, Founder of Homoeopathy (1755-1843).

The large acceptance of CAM therapy is due to the perception that it does not have side effects (which may not always be true); it is easily accessible and comparatively cheaper form of therapy. All these therapies are based on perception and individual beliefs. The other major disadvantage and shortcoming of this therapy is that it is not backed by clinical evidence and poor or no standardisation of the medicines is done.

Since this form of therapy is used very widely and frequently, therefore gradually and universally people and politicians are taking it up and certain regulatory bodies are established. In India, also there is a registering body which registers the doctors

who are trained in Homoeopathy, Ayurvedic, or Unani systems of medicine.

The government is making efforts to put these forms of medical management on scientific basis and trying to amalgamate it with the modern system of medicine. This concept of integrated health care is being developed. Therefore, today's physician has to know the good and bad of CAM so that he can keep abreast with the changing times and practice of medicine.

Integrated Health Care

This concept of amalgamated complementary and alternative medicine with modern system of medicine in a manner that it is useful to the patient is gradually evolving itself. How effective and useful will it be to medical profession and patients? The coming few years may answer this question a little more definitively.

The 21st Century Physician

The science based technology has expanded at a very fast pace in the later part of 20th century. The cytomolecular basis of disease is better understood. The progress in imaging modalities has improved the sensitivity and specificity of tests. The complete sequencing of genes, the ease and the cost with which it can be mapped and modified have raised immense possibilities of even managing certain incurable and difficult clinical conditions. It has opened vistas of individualised and highly specific treatment. The use of stem cell therapy has enabled to cure and repair organs. This relentless progress is likely to continue during this century. Therefore a physician has to be well informed and trained in these advances and their rationale use. In this backdrop, the importance of clinical skills to provide a good humane treatment with kindness, justice, and autonomy, to the patient will remain of prime importance for centuries to follow.

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Section 2

Clinical Approach to Key Manifestations

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2.1 Pain—Mechanisms and Management

D Rama Rao, Niranjan P Moulik

Pain serves to protect the body from harm and promotes healing of damaged tissues. The International Association for the Study of Pain defines pain as 'an unpleasant sensory and emotional experience associated with tissue damage and/or described in terms of such damage'. It is important to recognise that pain is a perception and not a sensation. The perception of pain is believed to be the summation of sensory-discriminative component (e.g. location, intensity, quality), a motivational-affective component (e.g. depression, anxiety), and a cognitive-evaluative component (e.g. thoughts concerning the cause and significance of pain). The patient's account of pain should be evaluated and treated as per the patient's perception of pain. This can be irrespective of the existence and severity of tissue damage. A noxious stimuli is sensed by the body's 'nociceptive' system and generates a physiological and behavioural response. This stimulus can be generated by traumatic, inflammatory, neoplastic or other mechanisms, and sustained by neuroplastic changes even after healing. It is believed that it is this neuroplasticity which maintains chronic pain, although the exact pathophysiology of chronic pain is yet to be elucidated.

Nociceptive stimuli are carried by primary afferent neurons the cell body of which lie in the dorsal root ganglia (**Figure 1**). These are small diameter nerve fibres, type A delta and C fibres and are usually free nerve endings found in the skin, muscle, joints and some visceral tissues/organs. The processes of transduction, transmission, modulation and perception are all involved in the activation of the sensory system. The first order neurons relay to the axons of second order neurons, the cell bodies of which lie in the thalamus and they in turn transmit the sensations to the somatosensory cortex in the post-central gyrus of the cerebrum. However, there are considerable areas of modulation in the central as well as the peripheral components of the pain pathways; and these form the basis for differing action of various pain-alleviating therapies.

Nociceptive pain primarily involves injury to somatic or visceral tissues. However, neuropathic pain results from direct injury or dysfunction of the nervous system (central or peripheral). Pain is classified usually as acute (short-duration and usually remittent) or chronic (longer duration and persistent).

ASSESSMENT OF PAIN

A comprehensive assessment is required for optimal pain management. The aim is to have a clear understanding of the patient's pain problem, in terms of its aetiology, pathophysiology and syndrome. This requires a detailed history, and systemic examination is carried out to unravel the pain characteristics, impact of pain on multiple domains, relevant pre-morbid conditions, existing co-morbidities, history of substance use, previous investigations carried out and treatment taken.

Although, pain being a subjective phenomenon, is not easy to assess, a variety of validated pain scales are available to assist in the measurement of pain. Pain assessment tools include simple unidimensional scales or multidimensional questionnaires.

Unidimensional scales include the numeric rating scale, the visual analogue scale and the faces pain scale. The former two include pictorial line scales which the patient uses and marks the intensity on a scale of 1 to 10 or no pain at all to worst possible pain. The faces scale has pictures of 6 to 8 different facial expressions depicting a range of emotions again along a 0 to 10 linear scale. It is particularly useful for use in young children, patients with language barriers, or having mild-to-moderate cognitive impairment.

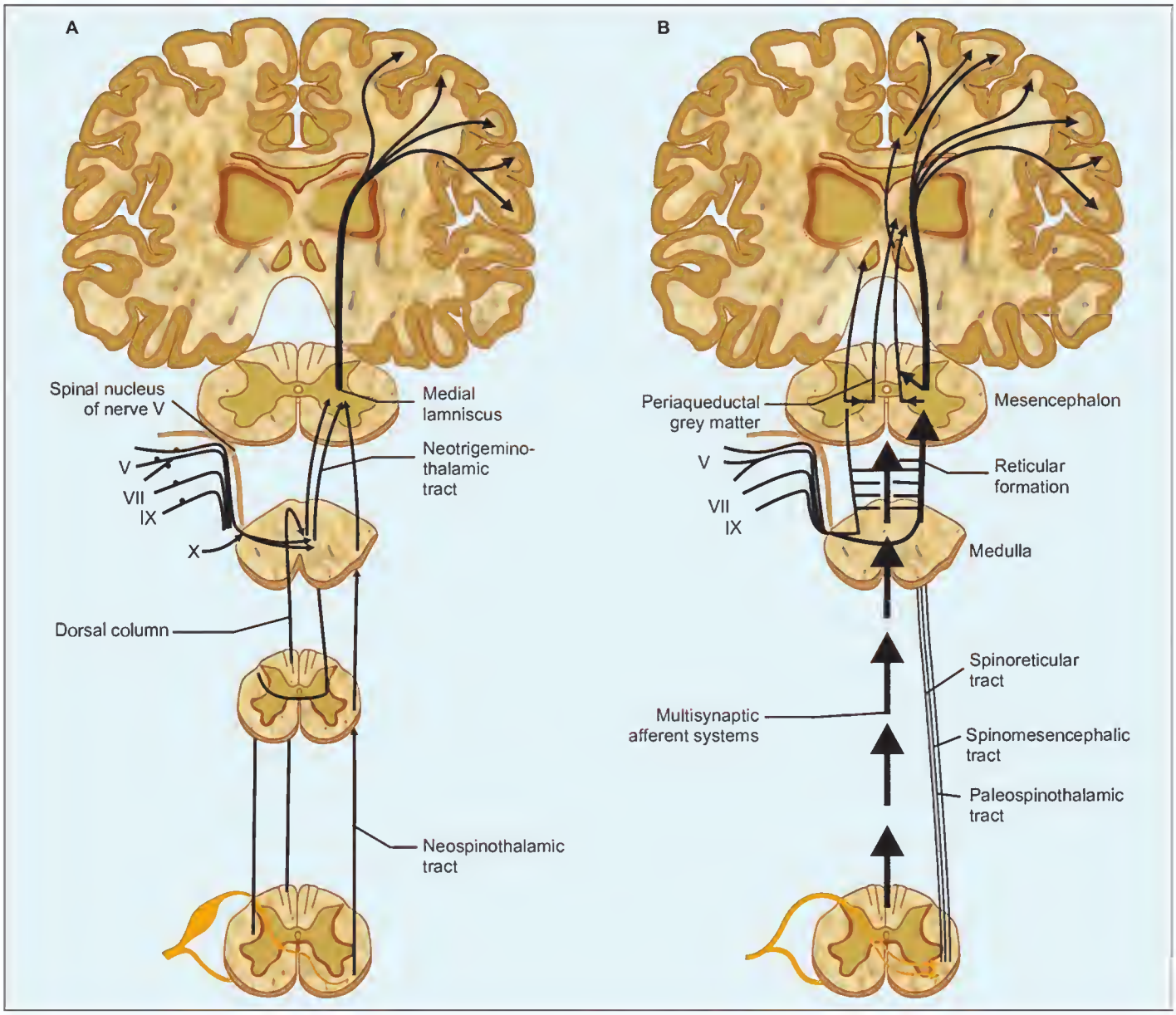
The multidimensional pain scales/questionnaires detail a more comprehensive pain assessment and apart from the intensity of pain also focus on the location and quality and effect of pain on mood and function. They are a bit time-consuming and cognitively-impaired and uneducated may find them difficult. The McGill Pain questionnaire and the Brief Pain Inventory are two such well-validated multidimensional pain measurement tools.

TREATMENT

Pain treatment can be divided into pharmacological, non-pharmacological and alternative medicine approaches. Acute pain effectively responds to nonsteroidal anti-inflammatory drugs (NSAIDs) or to mild-to-moderate efficacy opioids. Acetaminophen and NSAIDs are effective in mild-to-moderate intensity pain while opioids can be used for moderate-to-high intensity pain. A combination of NSAID and opioid can be used for severe intensity pain and has been found to be beneficial in achieving adequate pain relief. Common NSAIDs usually block both cyclooxygenase-1 and -2 enzymes and hence, COX-2 inhibitors were developed. However, use of COX-2 inhibitors has fallen into disrepute and the traditional NSAID like ibuprofen, diclofenac, nimesulide, naproxen, ketorolac, indomethacin continues to be used.

Chronic or persistent pain benefits transiently with these agents. Physiotherapy measures and physical treatments can be offered for chronic pain, while behavioural and psychological therapies do play a significant role as adjuncts in chronically depressed patients. Stimulation therapies like acupuncture and transcutaneous electrical nerve stimulation (TENS) have also been found to be beneficial. Apart from the NSAID and opioids which are also used for chronic pain, other pharmacological agents used include antidepressants (tricyclics, serotonergic uptake inhibitors and selective norepinephrine reuptake inhibitors), membrane stabilising agents like carbamazepine, gabapentin and pregabalin, local lidocaine plasters/patches. The commonly used drugs along with their dosages are listed in **Table 1**.

Despite the availability of numerous analgesic drugs, the clinical relief to patients for chronic pain has remained far from



Figures 1A and B: Pain signals are transmitted to the brain by two main pathways. The lateral system (A) is made up of long thick fibres that transmit information about the onset of injury and its precise location and intensity. They are designed to carry a rapid flow of pain signals to the thalamus to stimulate an immediate anti-nociceptive response. The medial system (B) is composed of phylogenetically older fibres that carry slower signals and probably transmit information related to the persistence of injury and level of response induced.

Table 1: Commonly Used Drug Dosages for Pain

Anti-depressants
- Tricyclic anti-depressants—amitriptyline 10 to 25 mg bedtime, increase step-wise to 150 mg twice/day
- Duloxetine 30 mg twice/day, increase to 120 mg/day.
- Venlafaxine: 25 mg tid

Anti-convulsants
- Carbamazepine 200 mg tid;
- Clonazepam 0.5 mg tid;
- Gabapentin 100 to 300 mg at bedtime to 3,600 mg/day in 3 divided doses;
- Pregabalin: 75 mg twice daily to 600 mg/day

Opioid agonist

Tramadol 50 mg once or twice to maximum of 400 mg/day

Morphine Analogues:
- Morphine 30 mg every 4 hours or as needed;
- Codeine 200 mg every 3 to 4 hourly.

Nonsteroidal anti-inflammatory drugs:
- Aspirin 650 mg 4 to 8 hourly

Contd...

Contd...

- Indomethacin 50 mg 8 hourly
- Piroxicam 20 mg 24 hourly
- Ketoprofen 50 mg 8 hourly
- Ibuprofen 400 mg 6 hourly
- Diclofenac 50 mg 8 hourly

satisfactory. Researchers are presently investigating role of nerve growth factor monoclonal antibodies, targeting sodium and calcium membrane ion channels and mechanisms based on activated microglia (non-neuronal cells implicated in the pathophysiology of chronic pain) to achieve breakthrough in alleviating chronic pain.

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2.2 Headache

K Ravishankar

INTRODUCTION

Headache is one of the most common of human complaints. It could be due to a number of causes ranging from a mild head injury to a serious brain tumour or more often it could be a disorder unto itself such as migraine.

Headaches can be primary or secondary. Primary headaches are benign headaches where clinical examination and investigation including imaging are normal, e.g. migraine, tension-type headache and cluster headache. Secondary headaches have an underlying structural, vascular, metabolic or infective cause, e.g. headaches due to brain tumours, meningitis or subarachnoid haemorrhage. Approximately 90% of headaches seen in practise are primary headaches.

The skull, much of the pia-arachnoid, the dura over the convexity of the brain, and the parenchyma of the brain are insensitive to pain. The pain-sensitive structures in the head are given below:

1. The skin, subcutaneous tissue, muscles, extracranial arteries, and the periosteum of the skull.
2. The intracranial venous sinuses, especially in the pericavernous region.
3. Parts of the dura at the base of the brain and the arteries within the dura and pia-arachnoid.
4. The middle meningeal and superficial temporal arteries.
5. The structures of the eye, the ear, the nasal cavities, and the sinuses.
6. Optic, oculomotor, trigeminal, glossopharyngeal, vagus and the first three cervical nerves.

Sensory stimuli are conveyed to the central nervous system through the trigeminal nerve, particularly the first and to some extent the second division; they carry impulses from the forehead, orbit, anterior and middle cranial fossa. A specific classification system — 'the classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain' was proposed by the International Headache Society in 1988 and the same was revised in the year 2004. All headache disorders have been organised into 14 major groups and divided into 257 different subtypes. Groups 1 to 4 cover primary headaches and groups 5 to 14 cover secondary headaches.

APPROACH TO THE PATIENT WITH HEADACHE

History

Pattern recognition is most important for headache diagnosis. The same patient can have more than one type of headache. It is better to generate a routine set of questions under pre-set headings. The following aspects of the history are important in arriving at a diagnosis.

Temporal Profile

The mode of onset and progression are critical in deciding whether one is dealing with a benign or a serious headache. A chronic recurrent headache or a chronic non-progressive daily headache represents a primary headache, such as migraine, cluster headache or tension-type headache. Sudden onset of a severe headache suggests possible vascular involvement such as a subarachnoid bleed or an acute infective cause like meningitis. There are some forms of primary headaches which may have a sudden onset such as coital headache or crash migraine and although the suddenness and severity may suggest an organic illness, it may be possible to diagnose them in retrospect only after their recurrent nature manifests. Progressively worsening headache suggests increasing intracranial pressure or uncontrolled systemic disease. Although presence of focal or lateralising features makes the diagnosis easier, it is the subacute headache which is more difficult to interpret. These headaches develop over weeks or months and the aetiology could be benign or serious. Therefore, specific information regarding progressive worsening needs to be sought.

Some headaches like cluster headache may occur at the same time everyday. In some the headaches may increase towards the evening as with tension-type headache, and in some like migraine, the headaches may occur first thing in the morning and awaken the patient from sleep. Rare primary headaches like cluster headaches and their variants are grouped together as trigemino-autonomic cephalgias (TACs). These are short-lasting and occur several times in a day and are diagnosed by their characteristic pattern and associated autonomic features like conjunctival injection, lacrimation or rhinorrhoea.

The age of onset is also important. Migraine begins at a younger age and is more common in females aged 25 to 40 years whereas tension-type headache is common in middle age. Headaches beginning after 50 years of age should be investigated for potential secondary causes. Any change in headache pattern should always raise suspicion of an organic pathology. The longer the history the more the likelihood of a benign underlying cause.

When the head pain is chronic and occurs on a daily or near daily basis for more than 15 days per month, one uses the label of chronic daily headache (CDH). It is essential to establish if we are dealing with primary CDH or secondary CDH. The following entities are included under the heading of long-lasting primary CDH:

1. Chronic migraine
2. Chronic tension-type headache
3. Hemicrania continua
4. New daily persistent headache

All these conditions may present with or without medication overuse. When faced with a patient who has CDH, it is essential

to determine the duration of the headache. With an arbitrary time limit of 4 hours, daily headaches can be grouped as short-lasting (< 4 hours) or long-lasting (> 4 hours). Examples of short-lasting CDH are cluster headache and other TACs. Recurrent attacks of short duration head pain would favour the diagnosis of cluster headache or one of its variants like chronic paroxysmal hemicrania.

Location and Type of Headache

The type of pain, its location and severity are important for diagnosis. Unilateral pulsating or throbbing headaches indicate an underlying vascular involvement as in migraine but migraine headaches are also known to be bilateral. Other vascular headaches can also be throbbing in nature. Cluster headaches are almost always unilateral in the same location during a cluster period, and rarely shifts sides. Tension-type headaches are diffuse, dull and generally bilateral. With secondary headaches, the location of the headache, the nature and severity would vary depending on the anatomical location of the lesion and the mechanism involved in pain production. In addition to getting the patient to describe the site and quality of the pain, rating the severity on a 10-point scale is useful in assessing progress of the headache and in gauging the response to treatment.

The Accompaniments

In all patients with headache, one must establish the presence or absence of nausea, vomiting, hypersensitivity to light and noise and associated neurological involvement. Absence of an established history of recurrent headaches or precipitation by triggers should prompt consideration of an underlying organic cause. Associated features like fever, arthralgias and malaise suggest systemic disease. Associated neurological deficits or auras, such as transient visual symptoms or hemisensory deficits, support a diagnosis of migraine with aura. Other neurologic accompaniments need appropriate investigations to differentiate between complicated migraine and transient ischaemic attacks (TIAs), vascular anomalies or a seizure disorder.

The typical behaviour of a migraine patient who tries to sleep undisturbed in a dark room is in contrast to that of the patient with a cluster headache who cannot stay still and keeps pacing around. A positive family history can provide a clue to the diagnosis of migraine.

Headache that occurs regularly just before or during the menstrual periods is likely to be menstrual migraine. Hypertensive headache is more common in the morning, sinusitis headache is worse on bending, eyestrain headache occurs more towards the evening and the headache of cervical arthritis is more intense after a period of inactivity.

Provoking and Relieving Factors

Primary headaches such as migraine can frequently be provoked by missing meals or going out in the hot sun. Trigger factors in the Indian setting are listed in **Table 1**.

Medical History

Careful questioning for systemic illnesses is essential, e.g. malignancy anywhere in the body should raise the possibility of cerebral metastases. Likewise vascular headaches in a patient with a history of spontaneous abortions or thromboembolic events should raise the possibility of antiphospholipid antibody syndrome. Systemic diseases can be a contraindication to the use of certain drugs, e.g. beta blockers would be contraindicated in a diabetic or an asthmatic.

Table 1: Migraine Triggers

Food items	Cheese, dairy products, paneer (cottage cheese), citrus fruits, chocolates, onions, sea food
Food additives	Monosodium glutamate (MSG), aspartame, nitrates, caffeine
Alcohol	Red wine, beer
Hormonal changes	Menstruation, ovulation
Physical exertion	Excessive exercise, fatigue
Visual stimuli	Bright lights, glare
Auditory stimuli	Loud noise or music
Olfactory stimuli	Perfumes and certain odours
Sleep	Too much or too little
Weather changes	
Head or neck trauma	
Hunger	
Stress and anxiety	

EXAMINATION OF THE PATIENT WITH HEADACHE

Routine examination helps exclude hypertension, meningitis, or systemic febrile illnesses. Additional examination may be necessary in order to increase the yield in headache patients. Palpation over the head and neck is necessary to detect tender trigger-points; auscultation over the skull, the carotid and vertebral vessels can identify bruits; temporomandibular joint and cervical spine palpation for tenderness and movement limitations; look for temporal artery tenderness; check the mental status, the cranial nerves and look for asymmetry in power and look for reflexes.

INVESTIGATION OF THE PATIENT WITH HEADACHE

Certain features in the history or examination (**Table 2**) should raise the suspicion of ominous disease and warrant further work-up. These are termed as danger signals' or 'red flags'.

Table 2: Headache Danger Signals

Sudden onset of a new severe headache
Progressively worsening headache or change in the pattern of the headache
Headache that is unresponsive to treatment
Onset of headache with exertion, such as sexual activity, coughing or sneezing
Onset of headache after 50 years of age
Headache associated with change in neurological status
Headache with abnormal examination findings

Laboratory Testing

The CBC, erythrocyte sedimentation rate (ESR) and relevant blood chemistry should be obtained in all patients. It helps to rule-out unsuspected systemic diseases. In an elderly patient suspected with giant cell arteritis, ESR and C-reactive protein are helpful.

Cerebrospinal Fluid Examination

Cerebrospinal fluid (CSF) examination must be considered in patients when there is fever or associated cranial nerve deficit. Opening and closing pressures must be documented, particularly in cases of pseudotumour cerebri or idiopathic intracranial hypertension which can sometimes present with

intractable migraine-like headache and may not always be associated with papilloedema.

Neuroimaging

Imaging must be done whenever there are danger signals. Avoid imaging scans if there is a history of similar headaches in the past or if examination is normal, or if the headache improves with treatment.

Magnetic resonance imaging (MRI) is now rapidly becoming the standard diagnostic test for head and face pain, particularly with the advantage of non-invasive evaluation of the vasculature by MR angiography and MR venography. An MRI has many advantages over a CT in a headache patient. In the appropriate setting one must investigate further with digital subtraction angiography (DSA).

PRINICIPAL HEADACHE VARIETIES

Primary Headaches

Migraine

Migraine manifests with recurrent headaches associated with nausea, vomiting, photophobia or phonophobia with or without an aura. It is more common in women (2 to 3:1) and a family history is often present (60% of cases). Attacks begin in late childhood, adolescence and early twenties. Majority of the patients with migraine, 80% have migraine without aura.

Clinical features

Migraine should always be thought of as a complex neurological disorder with headache being one of the common presenting features. There may be other accompanying neurological, gastrointestinal or autonomic features as shown in **Table 3**.

Table 3: Accompaniments of Migraine

Gastrointestinal: Anorexia, nausea, vomiting, diarrhoea
Visual disturbances: Blurring, photophobia
Motor abnormalities
Brainstem features: Vertigo, ataxia, diplopia, dysarthria
Autonomic disturbances: Hypertension, hypotension, tachycardia, bradycardia, nasal congestion, and peripheral vasoconstriction
Fluid retention
Psychological upsets, confusional states

The typical attack of migraine consists of a sequence of events divided into four different phases, that blend imperceptibly with each another: the prodrome, the aura, the headache and the postdrome.

Pathophysiology

The possibility that a migraine attack may be initiated by cortical spreading depression is the most favoured hypothesis. This condition is a transient disruption of neuronal activity in the brain accompanied by a flux of sodium, calcium ions into the cells. This results in a brief burst of electrical activity followed by electrical silence, which progresses as an expanding concentric wave through the brain at the same rate as a developing migraine aura.

Migraine variants

Depending on the accompanying neurologic deficit, there are different variants of migraine, such as hemiplegic migraine and basilar migraine. Status migrainosus is the term applied to severe unrelenting migraine attacks that last more than 72 hours.

Management

Once trigger factors are identified, preferably with the help of a 'headache diary or headache calendar', drug treatment needs to be selected depending on the severity and the level of disability. Ideal management of migraine should concentrate on three major areas:

1. Control of trigger factors
2. Treatment of the acute attack
3. Long-term prophylactic medication

Pharmacotherapy

For mild-to-moderate attacks, simple analgesics like aspirin or acetaminophen suffice. Combining with an anti-emetic like metoclopramide or domperidone, which increases gastric motility and enhances the absorption of other drugs, is more beneficial. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also effective in mild to moderate cases.

For moderate-to-severe attacks, triptans and ergotamine are useful as abortive drugs. When the patient is vomiting, injectable diclofenac or ketorolac is recommended. Narcotic injections should not be used in migraine. Sumatriptan is a 5-HT_{1D} agonist that blocks neurogenic inflammation in the trigemino-vascular system. It is available as 25 mg, 50 mg, and 100 mg tablets and as a nasal spray. Unlike ergotamine, it is effective when given at any time during the attack and has a better safety profile; it works rapidly and also relieves nausea, vomiting, photophobia and phonophobia. Recurrence of headache because of the short half-life is a major disadvantage with sumatriptan, but is less with the newer second generation triptans, like rizatriptan, eletriptan, zolmitriptan and naratriptan. Chest symptoms including tightness and pressure in the throat, neck and chest are more common with sumatriptan than with other triptans. Contraindications to triptans include ischaemic heart disease, uncontrolled hypertension or concomitant use of ergotamine derivatives or other 5-HT_1 agonists. Rizatriptan is available as 5 mg and 10 mg tablets. Steroids may occasionally be used as alternatives when all other drugs fail.

Recurrent episodes of migraine need simultaneous prophylactic treatment. Beta-blockers, calcium-channel blockers, methysergide, cyproheptadine, tricyclic antidepressants and anticonvulsants like divalproex and topiramate are used prophylactically. In most instances, prophylaxis need not be continuous, but is used for specific trial periods with drug-free intervals until the frequency is controlled.

Tension-Type Headache

Tension-type headache occurs more commonly in patients subjected to stress, anxiety and depression. It begins as episodes and progresses to a chronic form where headaches occur almost daily and do not appear to be associated with any overt psychological factors.

Clinical features

The headache is usually generalised and of long duration. The patient experiences a constant pain and obtain temporary relief with analgesics and sleep. There are no associated symptoms,

like vomiting, photophobia or phonophobia. The diagnosis can be established by a good history.

Treatment

The physician should attempt to identify the stress or emotional problem underlying the headache. Anxiety may be controlled by use of a mild antidepressant. Depressed patients may benefit from a tricyclic antidepressant such as imipramine or amitriptyline. When sleep is disturbed, it is important to establish a normal sleep pattern using short-acting hypnotic agents. When tension-type headache is associated with an emotional problem, the patient should be referred for psychiatric evaluation and treatment.

Cluster Headache

Cluster headache is a devastating painful headache, mostly affecting men. The term 'cluster headache' reflects the clustering of headache attacks in time. It is considerably less common than migraine and begins in the second or third decade of life. There is a periodicity to the attacks with seasonal clustering. Typically pain peaks lasts from 30 to 180 minutes and may occur 1 to 3 times per day. The pain is usually spontaneous, but can be provoked by alcohol. Patients describe the pain as excruciating or penetrating and on the same side during each cluster. The pain is accompanied by lacrimation, rhinorrhoea or ptosis. Differential diagnoses include diseases of the orbit, tumours of the brainstem or occipitocervical junction, infiltration/infection of the brainstem and cavernous sinus disorders. MRI should be done in all patients with cluster headache.

Treatment

Symptomatic treatment includes oxygen inhalation at about 7 litres per minute, parenteral dihydroergotamine (DHE), or parenteral sumatriptan 6 mg. Zolmitriptan nasal spray has been found to be useful for the acute treatment of cluster headache. Drugs for the prophylactic therapy of cluster headache include:

1. *Verapamil* given in doses as required, starting with 120 to 240 mg daily.
2. *Lithium carbonate* in a dose of 150 mg twice daily with periodic check-up of drug levels and watch for side-effects.
3. *Steroids* are very effective in preventing attacks, but are not indicated for long-term use.
4. *Methysergide* is an effective medication in treating chronic cluster headaches; 2 mg is the starting dose and the dosage is gradually increased, but retroperitoneal fibrosis is a side-effect.
5. *Divalproex and other anticonvulsants* like topiramate have also been found to be useful in prevention of cluster attacks.

Other Trigemino-Autonomic Cephalgias (TACs) and Short-Lasting Headaches

There are some head pains which are considered variants of cluster headache, but they differ in being very responsive to indomethacin and in their short duration and high frequency of attacks. The best example of this is chronic paroxysmal hemicrania which is characterised by frequent daily attacks of severe, short-lasting, unilateral, orbital, or temporal pain of 20 to 45 minutes duration with associated autonomic features. It is seen mostly in females and is usually responsive to indomethacin.

Secondary Headaches

Raised intracranial pressure

Any lesion that increases intracranial pressure is likely to cause a progressively increasing headache. Headache as a presenting feature will depend on the nature and location of the mass. Posterior fossa lesions raise intracranial pressure rapidly. The headache is usually generalised, may not fit into any particular pattern, slowly increases in intensity and leads to drowsiness and confusion following which focal neurological signs develop. Neuroimaging helps in the early detection of some of these lesions.

Intracranial haemorrhage

Head trauma can lead to epidural or subdural haematomas. Intracerebral haemorrhage is usually sudden in onset and can produce incapacitating headache with focal neurological symptoms and depressed consciousness. A subarachnoid haemorrhage due to rupture of an aneurysm or arteriovenous malformation produces an explosive incapacitating headache with vomiting, decreased level of consciousness and signs of meningeal irritation. This possibility should be kept in mind in every patient who presents with sudden onset headache and the diagnosis must be confirmed by doing a CT or lumbar puncture.

Meningitis

The headache is usually accompanied by fever, stiff neck, vomiting, and the diagnosis is confirmed by CSF examination.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension or pseudotumour cerebri presents with headache and visual obscurations along with other signs of increased intracranial pressure. It usually occurs in young, obese women; CT/MRI reveals small ventricles and on examination the patient may have decreased vision and usually but not necessarily there is papilloedema. Lumbar puncture shows evidence of increased opening pressure. MR Venography is a must in these patients.

Medication overuse headache

Medication overuse headache has been variously referred to as analgesic/ergotamine/drug-rebound headache. The headache sufferer who consumes medications for acute attacks on a regular, repeated and predictable basis is at risk of developing chronic daily headaches that are caused by overuse of medication. The most significant feature is that the headache typically persists throughout the whole day, is present on waking and is described as a dull, diffuse headache. Complete withdrawal of the analgesic is the only effective treatment. Withdrawal headaches can be treated with NSAIDs and, if detoxification fails, in-patient treatment with chlorpromazine or intravenous dihydroergotamine or subcutaneous sumatriptan can be tried.

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2.3 Chest Pain

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INTRODUCTION

Chest pain is a very common complaint most often caused by benign conditions, but occasionally it may be due to life-threatening medical emergencies. Chest pain may be caused by almost any condition affecting the thorax, abdomen or internal organs. The approach to chest pain, therefore, is to exclude benign conditions and to rapidly identify and treat potentially fatal and serious conditions. So, it is critically important to distinguish the two major presentations of chest pain: emergent and nonemergent. Many patients are aware that it is a warning of potentially life-threatening disorders and seek evaluation for minimal symptoms. Other patients, including many with serious disease, minimise or ignore its warnings. Pain perception (both character and severity) varies greatly between individuals as well as between men and women. So chest pain as a symptom should never be dismissed without an explanation for its cause.

CAUSES

Chest pain may originate from the cardiovascular, pulmonary, gastrointestinal, neurologic, or musculoskeletal systems (**Table 1**).

Table 1: Common Causes of Chest Pain

Cardiovascular	**Pulmonary**
Acute coronary syndrome	Pulmonary embolism
Aortic dissection	Pneumothorax
Pericarditis and cardiac tamponade	Pneumonia
Stable angina pectoris	Pleurisy
Chest wall	**Gastrointestinal**
Costochondritis or Tietze's syndrome	Oesophageal reflux disease
Fibromyalgia	Hiatus hernia
Radiculopathy	Cholecystitis
Herpes zoster	Gastritis
Psychological	Pancreatitis
Somatisation disorder	**Others**
Anxiety and panic disorders	Da Costa's syndrome
Hypochondriasis	Bornholm disease

Overall, the most common causes are:

- Chest wall disorders (i.e. those involving muscle, rib, or cartilage)
- Pleural disorders
- GI disorders (e.g. oesophageal reflux or spasm, ulcer disease, cholelithiasis)
- Idiopathic
- Acute coronary syndromes

PATHOPHYSIOLOGY

The thoracic viscera provide afferent visceral input through the same thoracic autonomic ganglia as the chest wall. A painful stimulus in these organs is typically perceived as originating in the chest but because afferent nerve fibers overlap in the dorsal ganglia, thoracic pain may be felt (as referred pain) anywhere between the umbilicus and the ear, including the upper extremities. When the sensation is visceral in origin, many patients deny having pain and insist that it is merely 'discomfort'.

APPROACH TO THE PATIENT

While the priority in any patient who presents with chest pain is to exclude catastrophic or life-threatening (cardiac) causes, non-life-threatening aetiologies, which may be functionally disabling, are much more common. The diagnosis of chest pain is difficult but the history often gives an indication of the underlying cause. If there is any suspicion of an acute coronary syndrome (ACS) or other serious cause or any concern regarding the patient's general well being, then urgent hospital admission should be arranged.

The history and physical examination, complemented by selected tests such as an electrocardiogram or chest radiograph help to reach an accurate diagnosis for most causes of chest pain, especially CAD, and to judge which patients are likely to have a benign aetiology (**Tables 2 and 3**).

DESCRIPTION OF THE CHEST PAIN

A thorough description of the pain is an essential first step in the diagnosis of chest pain.

Quality of the Pain

The patient with myocardial ischaemia often vigorously denies feeling chest 'pain'. More typical descriptions include squeezing, tightness, pressure, constriction, strangling, burning, heartburn, fullness in the chest, a band-like sensation, knot in the centre of the chest, lump in the throat, ache, a heavy weight on the chest and toothache (when there is radiation to the lower jaw). In some cases, the patient cannot qualify the nature of the discomfort, but places his or her fist on the centre of the chest (the Levine sign).

A 'sharp' or 'stabbing' pain with a pleuritic or positional component that is fully reproducible by palpation, in patients who have no history of angina or myocardial infarction, probably indicates a low-risk for the episode being ischaemic.

Region or Location of the Pain

Ischaemic pain is a diffuse discomfort that may be difficult to localise. Pain that localises to a small area on the chest is more likely of chest wall or pleural origin rather than visceral. Referred pain is an exception.

Table 2: Causes of Chest Pain

Cause	Suggestive findings	Diagnostic approach
Cardiovascular		
Myocardial ischaemia (acute MI/unstable angina/angina)	Acute, crushing pain radiating to the jaw or arm Exertional pain relieved by rest (angina pectoris) S_4 gallop Sometimes a systolic murmur	Serial ECGs and cardiac markers Stress imaging test considered in patients with negative ECG findings and no elevation of cardiac marker
Thoracic aortic dissection	Sudden, tearing pain radiating to the back Some patients have syncope, stroke, or leg ischaemia Pulse or BP may be unequal in the extremities	Chest X-ray, transthoracic or transoesophageal echocardiography CT scan of aorta for confirmation
Pericarditis	Constant or intermittent sharp pain often aggravated by breathing, swallowing food, or supine position and relieved by sitting leaning forward Pericardial friction rub	ECG and echocardiography usually diagnostic
Myocarditis	Fever, dyspnoea, fatigue, chest pain, recent viral or other infection Sometimes findings of heart failure, pericarditis, or both	ECG, serum cardiac markers ESR, C-reactive protein Usually echocardiography
Gastrointestinal		
Oesophageal reflux (GERD)	Recurrent burning pain radiating from epigastrium to throat that is exacerbated by bending down or lying down and relieved by antacids	Clinical evaluation, endoscopy Sometimes motility studies
Peptic ulcer	Recurrent, vague epigastric or right upper quadrant discomfort in a patient who smokes or uses alcohol excessively that relieved by food, antacids, or both	Clinical evaluation, endoscopy Sometimes testing for *H. pylori*
Pancreatitis	Pain in the epigastrium or lower chest that is often worse when lying flat and is relieved by leaning forward Vomiting, upper abdominal tenderness Often history of alcohol abuse or biliary tract disease	Serum amylase and lipase Sometimes abdominal CT
Pulmonary		
Pulmonary embolism	Often pleuritic pain, dyspnoea, tachycardia Sometimes, mild fever, haemoptysis, shock	D-dimer, echocardiography, CT scan of chest, chest X-ray, lower limb Doppler study
Pneumonia	Fever, chills, cough, and purulent sputum Often dyspnoea, tachycardia, signs of consolidation on examination	Chest X-ray
Pneumothorax	Sometimes, unilateral diminished breath sounds, subcutaneous air	Chest X-ray
Pleuritis	May have preceding pneumonia, pulmonary embolism, or viral respiratory infection Pain with breathing, cough, pleural rub	Usually clinical evaluation
Other		
Musculoskeletal chest wall pain (including trauma, overuse, costochondritis)	Often suggested by history Pain typically persistent (typically days or longer), worsened with passive and active movement Diffuse or focal tenderness	Clinical evaluation
Herpes zoster infection	Sharp, band-like pain mid-thorax unilaterally Classic linear, vesicular rash Pain may precede rash by several days	Clinical evaluation

Table 3: Clinical Features Associated with Specific Diagnostic Categories of Chest Pain

Clinical Features	Cardiac	Diagnostic Category Gastrointestinal	Musculoskeletal
Predisposing factors	Male sex Smoking Hypertension Hyperlipidaemia Family history	Smoking Alcohol use	Physically active New activity Overuse Repeated activity
Onset	At consistent level of exertion	After meals or on an empty stomach	With or after activity
Duration	Minutes	Minutes to hours	Hours to days
Character	Pressure or tightness	Pressure or gnawing pain	Sharp, localised and movement related
Relieved by	Rest, sublingual nitrate	Food, antacids	Rest, analgesics, NSAID

The pain of myocardial ischaemia may radiate to the neck, throat, lower jaw, teeth, upper extremity, or shoulder. A wide extension of chest pain radiation increases the probability that it is due to myocardial infarction. Radiation to both arms is an even stronger predictor of acute myocardial infarction. Acute cholecystitis can present with right shoulder pain, although concomitant right upper quadrant or epigastric pain is more typical than chest discomfort. Chest pain that radiates between the scapulae may be due to aortic dissection.

Temporal Elements

The time course of the onset of chest pain may be a very useful distinguishing feature:

- The pain associated with a pneumothorax or a vascular event such as aortic dissection or acute pulmonary embolism typically has an abrupt onset with the greatest intensity of pain at the beginning.
- The onset of ischaemic pain is most often gradual with an increasing intensity over time. A crescendo pattern of pain can also be caused by oesophageal disease.
- 'Functional' or nontraumatic musculoskeletal chest pain might have a much more vague onset.
- The duration of pain is also helpful. Chest discomfort that lasts only for seconds or pain that is constant over weeks is not due to ischaemia. A span of years without progression makes it more likely that the origin of pain is functional.
- The pain from myocardial ischaemia generally lasts for a few minutes; it may be more prolonged in the setting of a myocardial infarction.
- Myocardial ischaemia may demonstrate a circadian pattern. It is more likely to occur in the morning than in the afternoon, correlating with an increase in sympathetic tone.

Provoking Factors

The patient should be asked about factors that provoke or make the pain worse:

- Discomfort that reliably occurs with eating is suggestive of upper gastrointestinal disease.
- Post-prandial chest pain may be due to gastrointestinal or cardiac disease; in the latter case it can be a marker of severe myocardial ischaemia (e.g. left main or three-vessel CAD).
- Chest discomfort provoked by exertion is a classic symptom of angina, although oesophageal pain can present similarly.
- Other factors that may provoke ischaemic pain include cold, emotional stress, meals, or sexual intercourse.
- Truly pleuritic chest pain is worsened by inspiration and may be exacerbated when lying down.
- Causes of pleuritic chest pain include pulmonary embolism, pneumothorax, viral or idiopathic pleurisy, pneumonia, and a pleuropericarditis.

Relieving Factors

Factors that make the pain better should be established:

- Pain that is reliably and repeatedly palliated by antacids or food is likely to be of gastro-oesophageal origin.
- Pain that responds to sublingual nitroglycerin may be of either oesophageal or cardiac aetiology.
- Relief of pain following the administration of a 'GI cocktail' (e.g. viscous lidocaine and antacid) does not reliably distinguish gastrointestinal from ischaemic chest pain. On the other hand, pain that abates with cessation of activity strongly suggests an ischaemic origin.
- The pain of pericarditis typically improves with sitting up and leaning forward.

Severity

The severity of pain is not a useful predictor of CAD. As many as one-third of myocardial infarctions may go unnoticed by the patient.

ASSOCIATED SYMPTOMS

Associated symptoms may not reliably distinguish between a cardiac and gastrointestinal origin of chest pain.

- Belching, a bad taste in the mouth, and difficult or painful swallowing are suggestive of oesophageal disease, although belching and indigestion also may be seen with myocardial ischaemia.
- Vomiting may occur in the setting of myocardial ischaemia (particularly transmural myocardial infarction), in addition to gastrointestinal problems such as peptic ulcer disease, cholecystitis, and pancreatitis.
- Diabetic ketoacidosis, which can be precipitated by acute myocardial infarction, is another cause of vomiting.
- Diaphoresis is more frequently associated with myocardial infarction than with oesophageal disease.
- *Dyspnoea:* Exertional dyspnoea is common when chest pain is due to myocardial ischaemia and may precede the sensation of angina. Dyspnoea that occurs concurrently with chest pain may be due to myocardial ischaemia or a number of pulmonary disorders including diseases of the airways, lung parenchyma, or pulmonary vasculature.
- *Cough:* The differential diagnosis of chest pain and cough includes infection, as well as congestive heart failure, pulmonary embolus, and neoplasm. Cough, hoarseness, or wheezing may also be the result of gastro-oesophageal reflux disease.
- *Syncope:* The patient with myocardial ischaemia may present with presyncope. However, syncope associated with chest pain should raise a concern for aortic dissection, a haemodynamically significant pulmonary embolus, a ruptured abdominal aortic aneurysm, or critical aortic stenosis (particularly if the patient has a history of exertional dyspnoea).
- *Palpitations:* Patients with ischaemia can feel palpitations resulting from ventricular ectopy, or may have an abnormal awareness of their sinus rhythm. While atrial fibrillation is associated with chronic CAD, new onset, isolated atrial fibrillation is uncommon in patients with acute myocardial infarction.
- *Psychiatric symptoms:* Symptoms of panic disorder, generalised anxiety, depression, or somatisation may occur in patients with chest pain. Panic disorder is present in 30% or more of patients with chest pain who have no or minimal CAD; it may also coexist with CAD.

RISK FACTORS

The clinical impression raised by the patient's description of pain must be interpreted together with other aspects of the history, including risk factors for various aetiologies of chest pain.

Knowledge about such risk factors provides important information regarding disease likelihood, which may ultimately guide the type and extent of evaluation performed. The presence of hyperlipidemia, smoking, cocaine use, or a family history of premature CAD increases the risk for myocardial ischaemia. Hypertension is a risk factor for both CAD and aortic dissection. Cigarette smoking is a nonspecific risk factor for serious diseases; it is associated with CAD, thromboembolism, aortic dissection, pneumothorax, and pneumonia. A recent infection, especially viral or tuberculosis may precede an episode of pericarditis. Other risk factors for pericarditis include a history of chest trauma, autoimmune disease, recent myocardial infarction or cardiac surgery, and the use of certain drugs such as procainamide, hydralazine, or isoniazid. Age is an important risk factor for CAD; among patients older than 40 years, chest pain resulting from stable CAD or an acute coronary syndrome (unstable angina or myocardial infarction) becomes increasingly common. Men older than 60 years are most likely to suffer aortic dissection, while young men are at the highest risk for primary spontaneous pneumothorax.

PAST HISTORY

A past history of CAD, symptomatic gastro-oesophageal reflux, peptic ulcer disease, gallstones, panic disorder, bronchospasm, or cancer is very helpful in making a diagnosis. It is important to establish if the present symptoms are similar to those which occurred when the diagnosis was previously established. A history of diabetes mellitus should heighten the concern for a nonclassic presentation of CAD. It is important to exclude recent blunt trauma to the chest that can result in pneumothorax, disruption of the aorta, tracheobronchial tree, and oesophagus, myocardial or pulmonary contusion, or chest wall injury with associated musculoskeletal discomfort.

PHYSICAL EXAMINATION

The focused physical examination is used to support or disprove hypotheses generated by the history. Thus, the extent of the examination is primarily determined by the diagnoses that are being considered.

General Physical Examination

- The general appearance of the patient suggests the severity and possibly the seriousness of the symptoms (e.g. pallor, diaphoresis, cyanosis, anxiety).
- A full set of vital signs can provide valuable clues to the clinical significance of the pain, and may in some cases aid in establishing its origin.
- A marked difference in blood pressure between the two arms suggests the presence of aortic dissection. So pulses are palpated in both arms and both legs, BP is measured in both arms. Carotid artery is auscultated for a bruit.
- The neck is inspected for venous distension and venous wave forms are noted.

Chest Wall Examination

Palpation of the chest wall may evoke pain; if so the patient should be asked if this sensation is identical to the chief complaint. Chest wall tenderness may be present concomitantly with myocardial ischaemia. Hyperesthesia, particularly when associated with a rash, is often due to herpes zoster.

CVS Examination

A complete cardiac examination including auscultation and palpation should be performed in a sitting and supine position to establish the presence of a pericardial rub or signs of acute aortic insufficiency or aortic stenosis. Ischaemia may result in a mitral insufficiency murmur or an S4 or S3 gallop.

Respiratory System Examination

Determine if the breath sounds are symmetric and if wheezes, crackles or evidence of consolidation is present.

Abdominal Examination

A careful examination of the abdomen is important, with attention to the right upper quadrant, epigastrium and the abdominal aorta.

Findings which Raise Suspicion of a Serious Aetiology of Chest Pain

- Abnormal vital signs (tachycardia, bradycardia, tachypnoea, hypotension) and pulsus paradoxus > 10 mmHg
- Signs of hypoperfusion (confusion, ashen colour, diaphoresis).
- Shortness of breath.
- Asymmetric breath sounds and pulses.
- New heart murmur.

DIAGNOSTIC TESTING

ECG is important in critical evaluation of chest pain particularly when a cardiac aetiology is a possibility. Presence of ECG changes of ischaemia or infarction warrants admission to a CCU. Chest radiography (when cardiac or pulmonary disease is a consideration) may support the initial diagnosis and help avoid missing serious aetiologies of chest pain such as aortic dissection, pneumonia, pulmonary embolism or pneumothorax. Serial measurement of cardiac biomarkers, i.e. creatine kinase (CK), CK-MB and cardiac troponins (I and T) are useful in the emergency department for evaluation of acute chest pain. However, markers may take several hours after the onset of infarction to rise, hence treatment should not be delayed awaiting the results of enzyme levels.

Other Useful Investigations

Other useful investigations are:

- Complete blood counts (to exclude anaemia)
- Renal function tests blood sugar
- Liver function test (Cholecystitis) and amylase (pancreatitis)
- Exercise electrocardiography and stress echocardiography for evaluation of coronary artery disease in non-acute chest discomfort
- Endoscopy for gastrointestinal causes of chest pain.

KEY POINTS/CONCLUSION

- With careful history taking and physical examination, supplemented by targeted diagnostic tests, chest pain caused by serious conditions can often be quickly identified for early and immediate treatment.
- Immediate life threats must be ruled out first. Quick review of ECG is useful.
- Some serious disorders, particularly coronary artery disease and pulmonary embolism, may not have a classical presentation.

2.4 Acute Abdomen—Non-Surgical Causes

Sumeet Singla, AK Agarwal

Acute abdomen is defined as a recent or sudden onset abdominal pain (usually within 24 to 72 hours) with frequently associated gastrointestinal symptoms and signs. Acute abdomen is taught classically as a 'surgical' topic. A significant number of patients presenting with acute abdominal pain suffer from non-surgical conditions. Hence, an effective approach to the patient with acute abdomen must take into account the realisation that 3 out of every 4 such patients will be suffering from disorders requiring non-surgical intervention. This chapter is focussed on the approach to non-surgical causes of acute abdominal pain.

APPROACH TO DIAGNOSIS

The most important attribute of the physician evaluating a patient with acute abdominal pain is the ability to think 'out of the (abdomen) box'. One must be familiar with the various causes of this presentation and then proceed to refute or confirm the individual entities. A structured approach (**Figures 1A to C**) is easy to remember, fast, useful in resource-poor settings and minimises errors. Once a surgical cause has been excluded (no signs of peritonitis, perforation or obstruction), one can search for medical causes (**Table 1**). A non-rigid abdomen suggests a medical cause. However, certain surgical processes, initially confined to the visceral peritoneum, manifest as a non-rigid abdomen and only later progress to frank peritonitis when the parietal peritoneum is involved. Such a progression invariably portends the need for surgery.

CLINICAL CLUES TO MEDICAL AETIOLOGIES

History

- ***Age >65 years*** consider coronary artery disease, abdominal atheroemboli causing mesenteric ischaemia/infarction.
- ***Sex*** in females specific causes like ectopic pregnancy, threatened abortion, endometriosis, ovarian cyst and pelvic inflammatory disease (PID) must be looked for; in males epididymo-orchitis, prostatitis, and varicocoele are common causes of lower abdominal pain.
- ***Nature of the abdominal pain***
  - Insidious onset, diffuse or midline pain—visceral pain
  - Colicky pain—acute enteritis
  - Dysaesthetic type of pain—radiculopathy, neuropathy
- ***Radiation of the pain***
  - To the back—pancreatitis, pericarditis
  - To the right shoulder—Budd-Chiari syndrome, congestive hepatomegaly
  - To the left shoulder—splenic infarct, massive splenomegaly
  - Testicular/penile radiation—epididymo-orchitis
  - Lateralised and radiating from back to front of abdomen—spinal pain associated with radiculopathy
- ***Aggravating factors***
  - Increased on deep inspiration/coughing—pleurisy, pleural effusion, pneumonia, spinal pain
  - Increased during menstruation—endometriosis
  - Increased in supine position—pancreatitis
- ***Associated features***
  - Vomiting—if vomiting precedes pain, a medical cause is more likely
  - Appetite—retention of appetite is more likely in a medical cause
  - Diarrhoea, dysentery—indicates infection or inflammation of the bowel
  - Rectal bleeding—seen in bowel ischaemia/infarction, inflammatory bowel disease

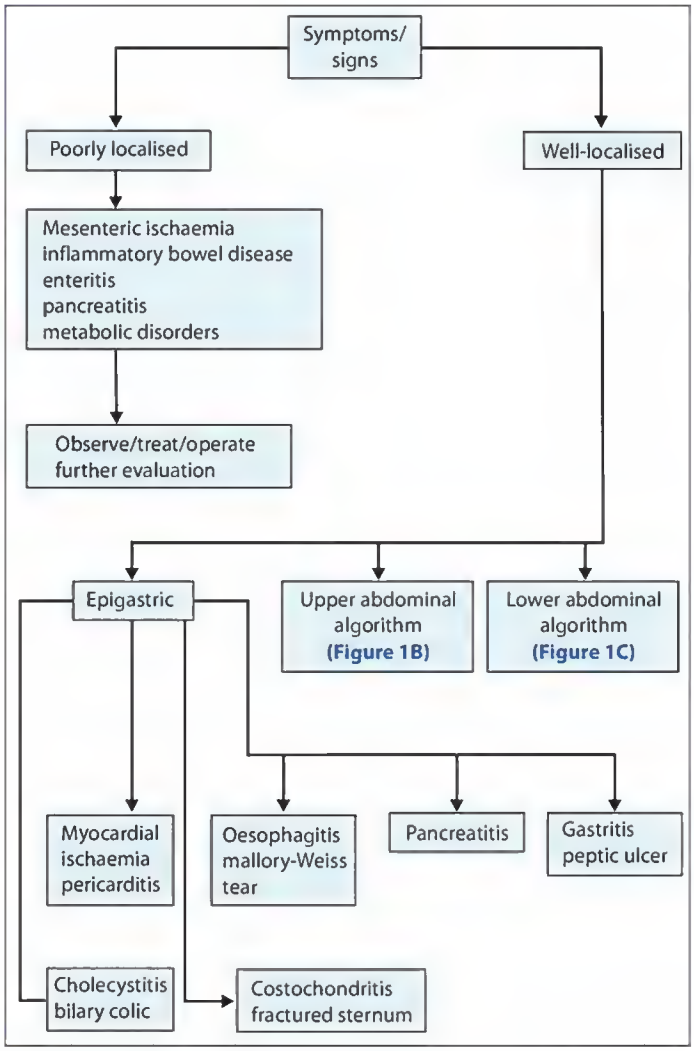


Figure 1A: Approach to the diagnosis of a non-rigid acute abdomen.

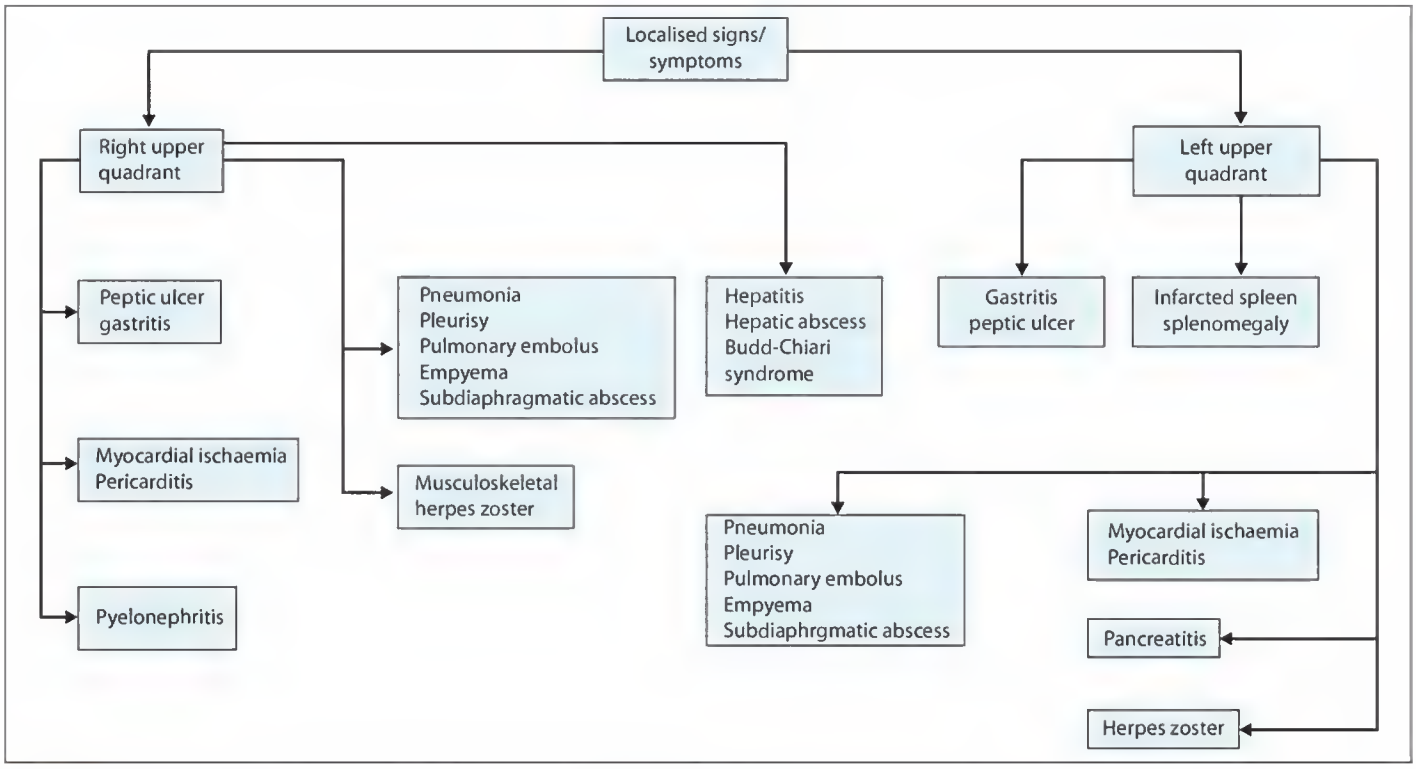


Figure 1B: Algorithm for diagnosing medical causes of upper abdominal pain.

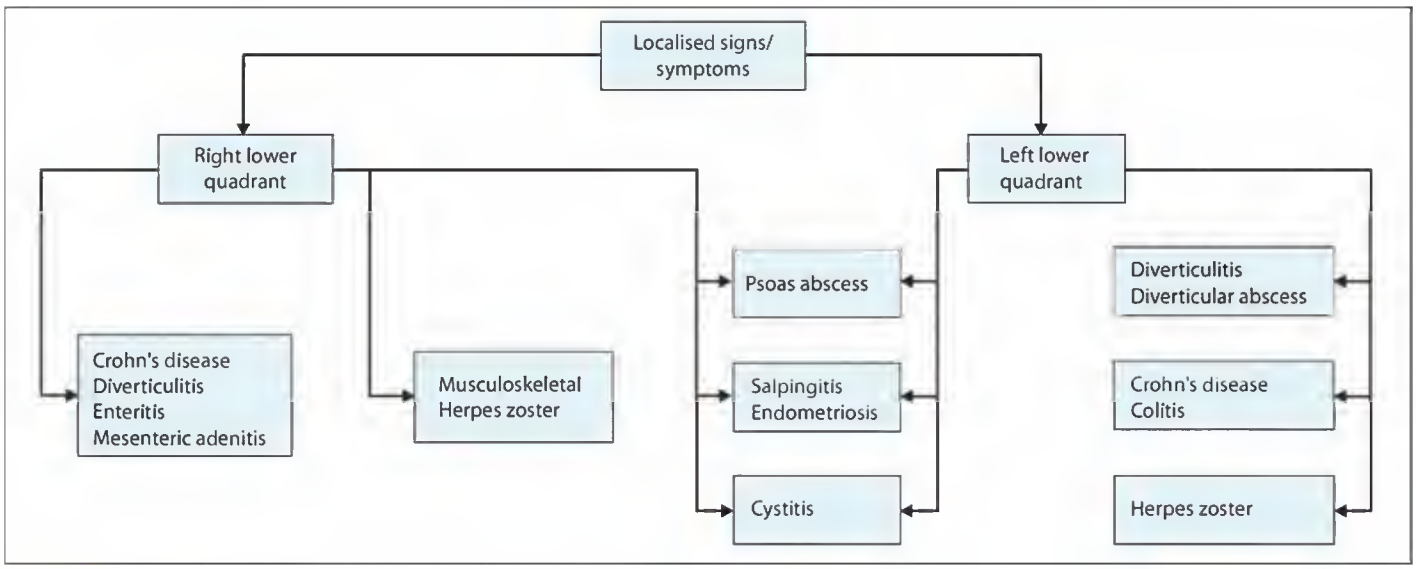


Figure 1C: Algorithm for diagnosing medical causes of lower abdominal pain.

(Figure 1A, 1B, 1C based on Martin RF, Rossi RL. The acute abdomen. An overview and algorithm. Surg Clin North Am 1997; 77: 1227-43).

  - High grade fever with/without chills—suggests pyelonephritis, enteritis, pneumonia
- Urethral/vaginal discharge—suggestive of pelvic inflammatory disease, STD.
- Frequency and urgency of urine associated with dysuria/haematuria/graveluria/lithuria—urinary tract infection.
- Bloody/unusually dark urine—haematuria, haemoglobinuria due to intravascular haemolysis, acute intermittent porphyria.
- Drug history—nonsteroidal anti-inflammatory drugs (NSAIDs) (acute erosive gastritis), vincristine (recent chemotherapy), anti-coagulants (intra-abdominal or abdominal wall haematoma), neuroleptics (neuroleptic malignant syndrome), drugs which can precipitate acute intermittent porphyria (barbiturates, phenytoin, rifampicin, oral contraceptives, etc).
- Drug withdrawal—steroids (withdrawal may precipitate acute Addisonian crisis), narcotics, alcohol, and nicotine.
- Occupational exposure to heavy metals like lead (battery makers, brass makers, cable makers, foundry workers, paint factory workers and painters), mercury (tube light, CFL and mercury vapour lamp industry), arsenic (production of glass or wood preservation), copper (mining, electrical wires, electroplating industry), asbestos (miners, stone crushers,

insulations, asbestos sheet industry); risk of scorpion (black widow spider) or snake bites (common krait or Bungarus caeruleus)—farmers, rural areas, sleeping on the floor, living in mud huts.

- Recent travel to areas endemic for malaria, typhoid, enteric infections.
- Menstrual history—relation of pain with menses; amenorrhoea.
- Psycho-social history—unemployed, living alone, divorced, diminutive personality, treated for anxio-depressive disorders, underlying psychoses. In these groups, a higher possibility of psychosomatic causes exists.

Physical Examination

The overall appearance of the patient can be very helpful. Patients whose pain is relieved by leaning forward may have pancreatitis. Most patients would be having tachycardia; unusual bradycardia should suggest typhoid, inferior wall myocardial infarction, drugs/toxins, and hyperkalaemia. Marked hypertension could signify porphyria, connective tissue disorders, uraemia, and hyperthyroidism. A patient may be dyspnoeic because of underlying pneumonia, pulmonary embolism, massive pleural or pericardial effusion, myocarditis, myocardial infarction, or metabolic acidosis (Kussmaul breathing). Tachycardia, mildly raised blood pressure and

Table 1: Differential Diagnosis of Medical Causes of Abdominal Pain

Metabolic/Haematologic

A. *Familial metabolic*
- Acute intermittent porphyria
- Haemochromatosis
- Hereditary angioneurotic oedema

B. *Endocrine*
- Diabetic ketoacidosis
- Addisonian crisis
- Hyperthyroidism/hypothyroidism
- Hypercalcaemia (hyperparathyroidism)

C. *Haematologic*
- Sickle cell crisis
- Acute haemolytic states
- Leukaemia
- Coagulopathies

Inflammatory Conditions

A. *Infections*
- Enteric infections
  - *Salmonella*, typhoid fever
  - *Shigella*
  - Staphylococcal
  - *Yersinia*
  - *Campylobacter*
  - Tuberculosis
  - Viral enterocolitis
  - Parasitic
- Spontaneous bacterial peritonitis
- Hepatitis (viral, Q fever, malarial)
- Mesenteric lymphadenitis
- Infectious mononucleosis
- Mumps
- AIDS-related disorders

B. Non-infectious
- Acute rheumatic fever
- Systemic lupus erythematous
- Polyarteritis nodosa
- Henöch-Schoenlein purpura
- Inflammatory bowel disease
  - Crohn's disease
  - Ulcerative colitis
- Pancreatitis

Drug-and toxin-related Conditions
- Heavy metal poisoning—Pb, Hg, As, Cu
- NSAIDs
- Mushroom ingestion
- *Staphylococcus* toxin
- Black widow spider bite
- Anti-coagulants
- Narcotic, steroid withdrawal
- Neuroleptic malignant syndrome
- Krait envenomation

Referred: Extraperitoneal Causes

A. *Pulmonary*
- Pneumonia
- Pulmonary embolism
- Pleurisy
- Spontaneous pneumothorax

B. *Cardiac*
- Angina: acute myocardial infarction
- Pericarditis
- Myocarditis
- Congestive hepatomegaly

C. *Urologic*
- Pyelonephritis
- Renal infarct
- Cystitis
- Prostatitis

D. *Obstetric, gynaecologic*
- Non-pregnant
  - Ovarian cyst
  - Salpingitis
  - Dysmenorrhoea
  - Endometriosis
- First-trimester pregnancy
  - Ectopic pregnancy
  - Normal pregnancy
  - Threatened/incomplete abortion

E. *Neurologic; spinal*
- Multiple sclerosis
- Tabes dorsalis; gastric crisis
- Diabetic thoracic radiculopathy
- Herpes zoster
- Abdominal migraine
- Abdominal epilepsy

F. *Abdominal wall—rectus sheath haematoma, myositis*

G. *Skeletal*
- Thoracolumbar spine
  - Osteomyelitis
- Hip—arthritis

H. *Adynamic ileus and pseudo-obstruction*
- Uraemia
- Hypokalaemia
- Constipation

I. *Splenic infarct*

Functional
- Somatisation disorders
- Hypochondriasis
- Malingering

tachypnoea may be seen in an apprehensive patient. The elderly, diabetic, uraemic, and immunosuppressed may be normothermic despite being seriously ill. Next, the head and neck should be examined for intraoral lesions, icterus, cyanosis, lymphadenopathy, jugular venous pressure, smell of ketones in the breath, carotid bruits, and lead line on gums. Fundus should be examined for emboli and lipaemia retinalis. Nailbeds should be inspected for infarcts or splinter haemorrhages. Pallor may signify external or internal blood loss, plumbism, addisonian crisis, and haematologic causes such as sickle cell disease, leukaemia or acute haemolysis; patients suffering form chronic diseases such as cirrhosis, uraemia, AIDS and connective tissue disorders, who have become acutely ill, may also be anaemic. Pedal oedema signifies congestive cardiac failure or chronic liver disease. A general visual survey may help characterise the nature of rashes; photosensitive rash of acute intermittent porphyria; purpuric rash of Henöch-Schoenlein purpura or leukaemia; vasculitic rash of systemic lupus erythematosus, polyarterits nodosa or scleroderma; nodular painful rash of fat necrosis in acute pancreatitis; ulcers in sickle cell disease; vesicular rash of herpes zoster and eruptive xanthomas in hyperlipidemia. Examination of joints for active arthritis and of the spine for local tenderness, deformity and paraspinal muscle spasm (suggestive of spinal disease) is not to be missed.

The examination of the cardiovascular and respiratory systems may provide very important information *viz.* rubs, rhonchi, crackles, and murmurs. Examination of the abdomen starts with a careful visual inspection of the skin looking for rashes, discolouration (Grey-Turner's sign, Cullen's sign), distension (ascites). Palpate the abdomen for assessing the site of maximal tenderness, presence or absence of rigidity, any intramural swelling/tenderness (haematoma of the rectus sheath), hepatosplenomegaly (leukaemia, malaria, or tuberculosis), shifting dullness (ascites), and costovertebral angle tenderness (pyelonephritis, pyonephrosis, or perinephric abscess). While a diffusely rigid abdomen strongly points to an underlying surgical cause, a soft, non-rigid abdomen increases the likelihood of a medical cause. As a corollary, when abdominal signs are minimal, but the patient's distress is severe, the physician should consider a medical condition as the cause of pain. Abdominal bruits signify that vascular occlusion may be the cause of pain, as do splenic rubs. A digital rectal examination is not to be omitted. It provides an opportunity to look for perianal skin tags, fistulae and sinuses (Crohn's disease), to detect blood in the anal canal [inflammatory bowel disease (IBD), colonic infarction], to examine the male external genitalia (epididymo-orchitis, varicocoele) and is especially useful in patients with lower abdominal pain (pelvic abscess, mass, prostatitis) and when a rigid abdomen prevents adequate examination. Likewise, *per vaginum* examination by a gynaecologist may provide valuable information. It is a good practice to involve a gynaecologist in the evaluation and management of young female patients with acute lower abdominal pain due to the far higher frequency of gynaecological (and hence, surgical) causes in this group. Finally, a neurological examination should be done in patients with gross neurological deficits (weakness of limbs or cranial muscles, sensory deficits, paraesthesiae, seizures and altered sensorium). Lack of objective clinical findings is most often due to observer error; but, if repeated examinations (and laboratory investigations) do not yield anything, a non-organic cause must be considered.

Table 2: Imaging Studies in Acute Abdominal Pain

Retroperitoneal disease—CT scan
Right upper quadrant and epigastric symptoms—Ultrasound
Left upper quadrant symptoms—CT scan with IV contrast
Left lower quadrant symptoms—CT scan with IV and oral contrast
Right lower quadrant symptoms—Ultrasound

Table 3: Clues to the Diagnosis of Medical Causes of Abdominal Pain

Abdominal pain associated with:
Neurological symptoms and signs—porphyria, snake (krait bite), plumbism, barium carbonate poisoning, collagen vascular disorders, illicit drug use
Dark/cola coloured urine—porphyria, acute haemolysis, renal infarction
Jaundice—cirrhosis with spontaneous bacterial peritonitis, congestive hepatomegaly, acute Budd-Chiari syndrome, acute hepatitis
High fever with/without chills—acute pyelonephritis, atypical pneumonia, basal pneumonia, bacterial enterocolitis, malaria, typhoid fever
Multisystem involvement—SLE, PAN
Anaemia—sickle cell disease, leukaemia, haemolysis, plumbism, coeliac disease, inflammatory bowel disease
Alcoholism—hepatitis, pancreatitis, abdominal tuberculosis, spontaneous bacterial peritonitis
Dyspnoea—metabolic acidosis (DKA, sepsis, mesenteric ischaemia, poisonings), pneumonia, myocardial infarction
Rectal bleeding—inflammatory bowel disease, enterocolitis, bowel infarction
Diabetes—diabetic ketoacidosis, thoracic truncal radiculopathy, acute pancreatitis, acute inferior wall myocardial infarction, mesenteric ischaemia
Arthritis—Henöch-Schoenlein purpura, connective tissue disorders, inflammatory bowel disease, reactive arthritis associated with enteric infections
Pleural effusion—acute pancreatitis, congestive cardiac failure, disseminated tuberculosis, pulmonary embolism, pneumonia, empyema, SLE
Ascites—acute pancreatitis, congestive cardiac failure, spontaneous bacterial peritonitis
Skin rash—herpes zoster, Henöch-Schoenlein purpura, vasculitides
Azotaemia or uraemia—prerenal causes (diarrhoea, dehydration, acute blood loss), acute glomerulonephritis, collagen vascular disorders
Weight loss—tuberculosis, diabetes mellitus, AIDS, chronic liver disease, inflammatory bowel disease
Recurrent episodes of acute abdominal pain—acute pancreatitis, porphyria, vaso-occlusive crisis of sickle cell disease, chronic lead poisoning, peptic ulcer, inflammatory bowel disease, mesenteric ischaemia

DIAGNOSIS

Laboratory/radiologic investigations must be viewed as confirmatory rather than screening tools. Other than a haemogram and a routine urine examination, all other investigations need to be justified keeping in mind the diagnoses being sought. A low haemoglobin suggests blood

loss or haemolysis. Leucocytosis is rather non-specific; however, a neutrophilic leucocytosis suggests an infectious pathology. A lymphocytic or monocytic leucocytosis would be more in line with a viral aetiology, such as infectious mononucleosis. Leucopenia portends a grave prognosis and may be due to severe sepsis, leukaemia, SLE or typhoid. Surgical illness is rare when both TLC and DLC are normal. A routine urine examination is useful in diagnosing urinary tract infections, urolithiasis, glomerulonephritis and diabetic ketoacidosis. An electrocardiogram should be obtained when evaluating a patient with risk factors/past history of atherosclerotic disease and may reveal inferior wall myocardial infarction, myocarditis or pericarditis. A radiograph of the chest is required if physical findings are suggestive of pneumonia, effusion, embolism or congestive cardiac failure. Serum amylase and lipase are required when acute pancreatitis is a strong possibility; beware of false positives due to non-pancreatic hyperamylasemia. Imaging helps to differentiate the two. In a patient with right hypochondrial pain with/without jaundice and hepatomegaly, it is prudent to order serum bilirubin, AST, ALT, and ALP levels. Serum sodium and potassium estimation may help in diagnosing certain conditions. Hyponatremia may be seen in porphyria, acute Addisonian crisis, and diabetic ketoacidosis. Only 45% of patients in Addisonian crisis will have hyponatremia and potassium levels will be typically normal (as opposed to 65% who have hyponatremia and 95% who have hyperkalemia in chronic Addison's insufficiency). Microscopic examination of the stool is useful in patients with fever and diarrhoea/dysentery. Arterial blood gas estimation is useful for patients in cardio-respiratory distress, suspected illicit drug use, poisonings, and unexplained causes (unexplained metabolic acidosis is the hallmark of mesenteric ischaemia). In young female patients with lower abdominal pain with/without amenorrhoea, it is mandatory to obtain a urine β-hCG test to rule-out pregnancy. Free fluid in the peritoneal cavity/pleural cavity should be tapped if the situation demands or if the diagnosis is unclear. In critically ill patients, peritoneal lavage is a good bedside test to detect peritoneal inflammation. A red cell count of ≥100,000/mm^3 and/or a white cell count of ≥500 /mm^3 in the lavage fluid represent a positive finding, as does the return of grossly purulent material, enteric contents, or other fluids that should not be present in the peritoneal cavity. A surgical cause, and the need for surgery, is then much more likely. Imaging of the abdomen should be a planned activity and not ordered blindly. When considering the use of imaging, the presence of localised symptoms can be useful in directing the choice of study as shown in **Table 2**.

A simplified, syndromic approach for the diagnosis of medical causes of acute abdomen is shown in **Table 3**.

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2.5 Cough

Suman Kirti

Cough is a sudden, explosive, often-repetitive expiration, which helps to clear the tracheobronchial tree of secretions, irritants, foreign particles and microbes. Often called the watchdog of the respiratory tract, it is the commonest and most important respiratory symptom.

MECHANISM

Cough can be initiated voluntarily or reflexively. The cough reflex has an afferent limb with receptors in the sensory distribution of trigeminal, glossopharyngeal, superior laryngeal, and vagus nerves, that carries impulses to the cough centre located in the tractus solitarius in the medulla of the brainstem, which is connected to the central respiratory generator. The efferent limb consists of the recurrent laryngeal nerve and the spinal nerves. Cough starts with a deep inspiration followed by glottic closure, relaxation of the diaphragm and muscle contraction against a closed glottis causing airway pressure to rise (50 to 300 mmHg). This causes marked rise in positive intrathoracic pressure that results in tracheal narrowing. As the glottis opens the large pressure differential between airways and the atmosphere coupled with tracheal narrowing produces rapid flow rates (600 to 800 km/hr) through the trachea. These shearing forces aid in the elimination of mucus and foreign materials.

AETIOLOGY

Exogenous irritants like smoke, fumes, dust, foreign bodies or endogenous irritants like upper airway secretions or gastric contents may trigger cough, by stimulating the receptors in the upper airway (pharynx or larynx) or inhalation or aspiration in the lower airways (tracheobronchial tree). Endogenous irritants from postnasal drip or gastric contents may go unrecognised and cough may continue. Prolonged exposure to irritants initiates airway inflammation, which sensitises the airway to other irritants, and both cause persistent cough. Gastro-oesophageal reflux disease (GERD) causes cough by aspiration of gastric contents into the upper airways as well as vagal reflex secondary to acid in the distal oesophagus.

Cough occurs whenever there is inflammation, constriction, infiltration or compression of the airways. Inflammation occurs due to infections like viral or bacterial bronchitis or bronchiectasis. Viral bronchitis is usually acute, but persistent inflammation can cause a prolonged cough. Pertussis can also cause prolonged cough in adults. Constriction and inflammation occur in asthma and the diagnosis is made clinically. Rarely, there is a cough-variant asthma where there is cough without wheezing or dyspnoea. Tropical pulmonary eosinophilia (TPE) also causes cough. Infiltration of airways with granulomas as in tuberculosis (TB), which is common in India or endobronchial sarcoidosis, or by neoplasms like bronchogenic carcinoma and carcinoid, also triggers cough. Extrinsic compression of airways from lymph node masses, mediastinal tumours or rarely aortic aneurysm also causes cough.

Parenchymal lung diseases causing cough are pneumonia, interstitial lung disease and lung abscess. Congestive heart failure (CHF) can cause cough by interstitial as well as peribronchial oedema.

A dry cough may occur with angiotensin-converting enzyme (ACE) inhibitors in 5% to 20% of users usually within a week or up to 6 months of starting the drug, possibly due to accumulation of bradykinin or substance P which are degraded by ACE. The angiotensin II receptor antagonists do not increase bradykinin levels and do not cause cough.

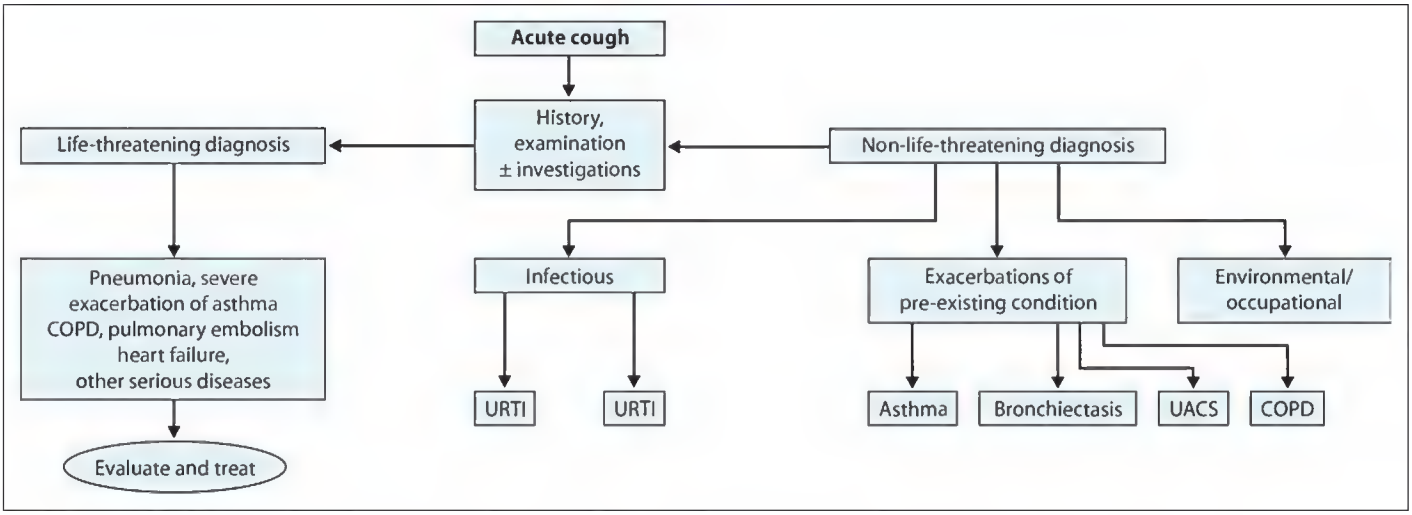


Figure 1: Acute cough algorithm for the management of patients ≥15 years of age with cough lasting <3 weeks.
Based on: Irwin RS et al. Chest 2006; 129: 1S-23S. (With permission).

Beta-blockers can cause increased airway resistance due to unopposed para-sympathetic activity especially in patients who already have obstructive airway disease.

CLASSIFICATION

Cough can be classified by its onset and duration, character, quality, and timing. The onset may be acute (<3 weeks) which is most often due to upper respiratory infections like common cold, bacterial sinusitis and pertussis; or lower respiratory tract infections like pneumonia, acute exacerbation of chronic obstructive pulmonary disease (COPD); acute episodes of asthma. CHF and pulmonary embolism can also present with acute cough. Inhalation of a foreign body is another cause. An algorithm for evaluating acute cough is shown in **Figure 1**.

Sub-acute cough (3 to 8 weeks) is commonly post-infectious due to persistent airway inflammation and/or postnasal drip following viral infection, pertussis or *Mycoplasma* or *Chlamydia* infection. In India, TB and TPE are important causes. An algorithm for the approach to a case of sub-acute cough is shown in **Figure 2**.

Causes of chronic cough (> 8 weeks) include TB, TPE, sarcoidosis, cystic fibrosis, COPD and bronchogenic carcinoma. In non-smokers with a normal chest radiograph, the common causes are postnasal drip [PNDs now called upper airway cough syndrome (UACS)], asthma, GERD, non-asthmatic eosinophilic bronchitis (NAEB) and ACE inhibitors. Left ventricular failure can cause sub-acute or chronic cough. Evaluation of chronic cough can be done using the algorithm shown in **Figure 3**. The differential diagnosis of sub-acute and chronic cough is shown in **Table 1**.

Cough can be dry or productive of sputum, the product of mucus glands and goblet cells of the bronchial walls. In a normal individual, 100 mL of secretions are produced daily. In respiratory disease, secretions may be mucoid, mucopurulent or purulent. Mucoid sputum is white or colourless, and gelatinous [as in chronic bronchitis (CB)]. Purulent sputum is yellow or green due to pus from infection. Large number of eosinophils can give a yellow colour. Foul smelling sputum can occur in bronchiectasis and lung abscess.

Cough may occur more at night (asthma, left heart failure, pulmonary eosinophilia) or early morning (CB). It may be seasonal as in asthma.

Cough may be aggravated by or related to occupational irritant exposure (e.g. byssinosis). It may increase after eating as in GERD or in tracheo-oesophageal fistulas and swallowing disorders. Sometimes GERD may complicate asthma or COPD.

Cough may be postural as in patients with bronchiectasis, lung abscess or bronchopleural fistula. These patients have large amounts of sputum. Sputum increases on waking in the morning in CB. Worsening of cough in CB may herald a bronchial carcinoma.

The character of cough may be like barking in children with croup. Staccato cough is seen in *Chlamydia pneumoniae*. Patients with chronic postnasal drip try to clear the throat and cough. Patients with bronchial and lung parenchymal diseases have a deep, 'loose' cough; those with tracheal compression have a brassy cough and those with laryngeal paralysis have a 'bovine' sounding cough.

DIAGNOSTIC APPROACH

History

Is it acute, sub-acute or chronic? Are there any symptoms of infection? Is it seasonal? Aggravating factors? Nasal discharge, frequent throat clearing, tickle in the throat (postnasal drip)? Is there heartburn or a sensation of regurgitation (GERD)? Postural? Description of sputum produced. ACE-inhibitor or beta-blocker use? Risk factors like smoking, environmental exposures, HIV risk factors, immunosuppressive agents, chronic renal disease (opportunistic infections).

Examination

General physical

Signs of heart failure, primary non-pulmonary neoplasm, cervical lymph nodes suggestive of tuberculous infection,

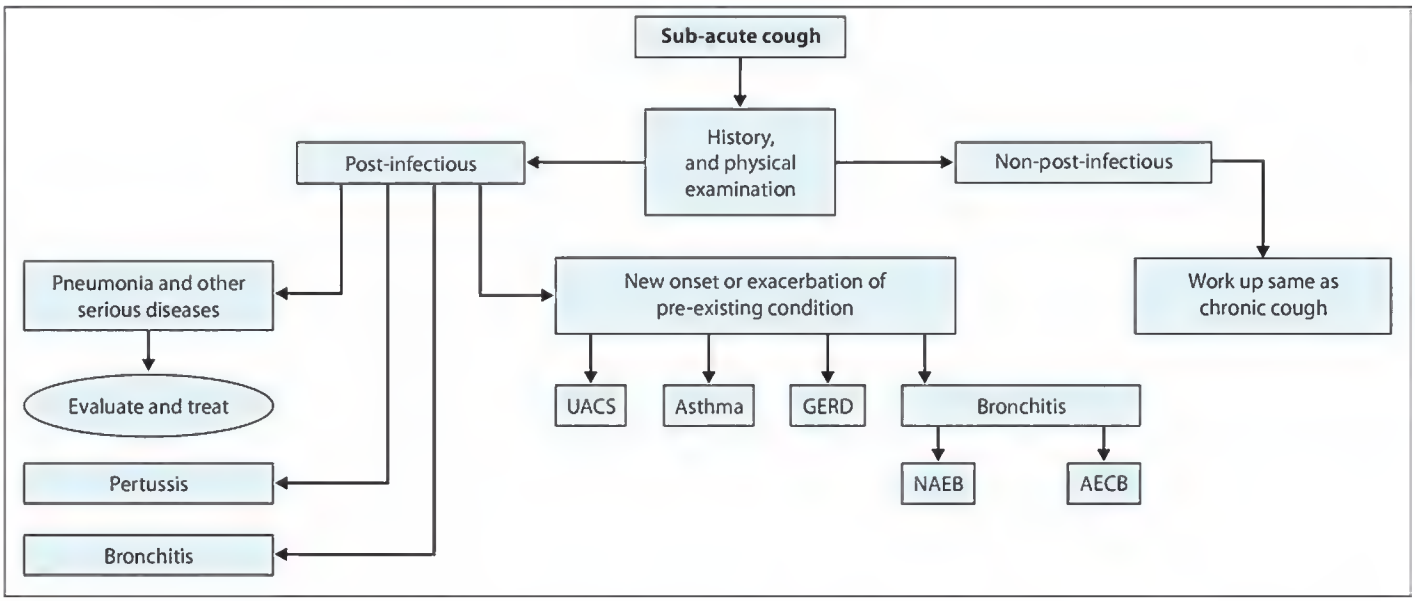


Figure 2: Sub-acute cough algorithm for the management of patients ≥15 years of age with cough lasting 3 to 8 weeks.
Based on: Irwin RS et al. Chest 2006;129: 1S-23S. (With permission).

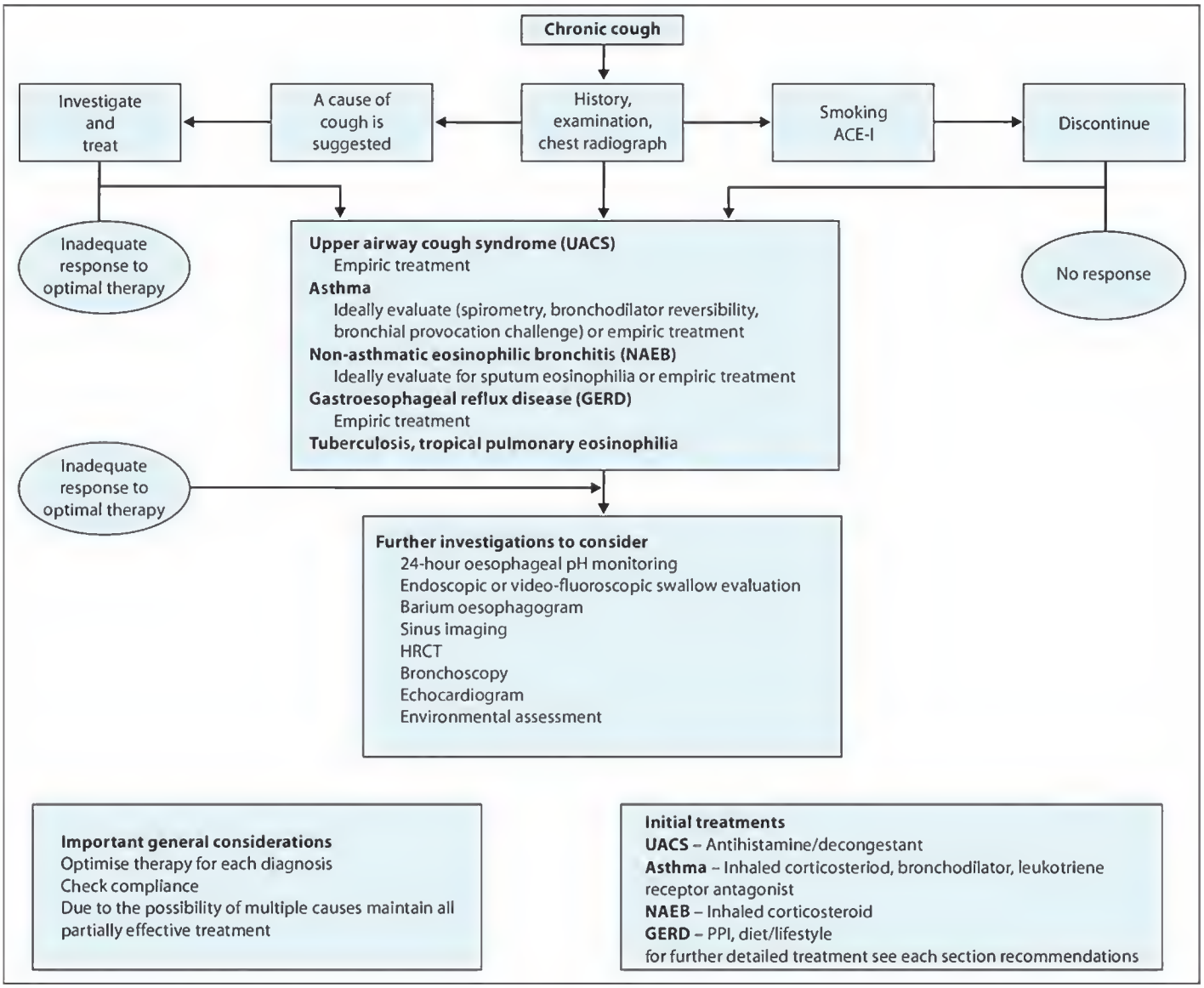


Figure 3: Chronic cough algorithm for the management of patients ≥15 years of age with cough lasting >8 weeks.
Modified from: Irwin RS et al. Chest 2006; 129: 1S-23S. (With permission).

fever, rash, cyanosis, clubbing. Oro-pharynx may show oro-pharyngeal mucus or erythema, 'cobblestone' mucosa (postnasal drip).

Examination of the Chest

Inspiratory stridor in upper airway disease, rhonchi or expiratory wheezing in lower respiratory disease, inspiratory crackles in lung parenchymal disease like pneumonia, interstitial lung disease (ILD) or pulmonary oedema.

Examination of Blood and Stool

Complete blood counts may reveal leucocytosis, high erythrocyte sedimentation rate, and marked eosinophilia in TPE and hemoparasites on peripheral smear. Stool examination may reveal helminths that cause TPE.

Chest Radiography

May reveal fibro-infiltrative or cavitatory lesions suggestive of TB, reticulo-nodular shadows with prominent hila suggestive of TPE, diffuse interstitial or alveolar disease, honey-combing or cysts as in bronchiectasis, or bilateral hilar adenopathy as in sarcoidosis, or a mass lesion.

Sputum Examination

Purulent sputum is seen in CB, bronchiectasis, pneumonia and lung abscess. Haemoptysis occurs in the same conditions as well as in TB and tumours. Sputum eosinophils >3% in patients without asthma suggests NAEB. Gram-stain, acid-fast bacilli stain and sputum culture will identify bacteria, TB and fungal infections. Cytology will help in identifying malignancy.

Pulmonary Function Tests

Assess functional abnormalities of the lung. Reversible airflow obstruction is seen in asthma. If airflow rates are normal but there is strong suspicion of asthma broncho-provocation tests may be done with methacholine or cold-air inhalation or capsaicin to show bronchial hyper-reactivity. Restrictive pattern and abnormality in diffusion studies are seen in diffuse ILD. Oxygen saturation and arterial blood gas analysis are also useful in assessing lung function.

Fibreoptic Bronchoscopy

Helps diagnose endobronchial granulomas (TB, sarcoidosis, fungi), tumours, foreign bodies, and collection of secretions

Table 1: Differential Diagnosis of Sub-acute and Chronic Cough

Common Causes	Clinical Features
Transient airway hyper-responsiveness	Cough persistent for many weeks, resolves (e.g. post-viral upper-respiratory infection)
Rhinosinus infection/inflammation	Cough follows infection or exposure to allergen; post-nasal drip is common
Asthma	Worse at night, on exercise, or following exposure to allergen, cold air or dust
Cough-variant asthma	Absence of wheezing or dyspnoea, dry nocturnal cough, bronchial hyper-responsiveness
Non-asthmatic eosinophilic bronchitis	No variable airflow obstruction; no hyper-responsiveness; sputum eosinophils >3%; Increased CO_2 in exhaled air
Chronic obstructive pulmonary disease	Usually seen in smokers. When smoking, and environmental irritants stop, cough eventually ceases
Gastro-oesophageal reflux	Heartburn, acid reflux, throat clearing, hoarseness or asymptomatic reflux
Pulmonary tuberculosis	Constitutional symptoms (fever, night sweats, weight loss, haemoptysis)
Bronchiectasis	Productive sputum, often purulent; cough (and sputum production) often positional
Tropical pulmonary eosinophilia	Cough, dyspnoea, wheeze, scanty sputum, blood and sputum eosinophilia, helminthic infestation
Bronchial carcinoma	Cough worse than usual in a smoker; sometimes, new persistent cough
Less Common Causes	
Repeated bronchial aspiration	Oesophageal disorders, neurological swallowing disorders
Pulmonary fibrosis	Patient is breathless; cough 'dry'
Aspirated foreign body	May have no history of aspiration
Lung compression (e.g. pleural effusion, mass)	Sometimes positional
Drug-induced cough	ACE-inhibitors: dry cough; beta-blockers: cough and usually wheezing
Pneumocystis jiroveci	Immune deficient patients with persistent cough
Psychogenic	Patient otherwise well; no cough at night or when distracted; no response to cough suppressants

Based on: Symptoms and Signs. Medicine International (Indian Ed) 1995; 9: 222; Philp EB. Chronic cough. Am Fam Physician 1997; 56: 1395-1408.

and endobronchial biopsies and transbronchial lung biopsies helps in further diagnosis.

High Resolution Computed Tomography (HRCT)

Helps in diagnosing ILD and can confirm the presence of bronchiectasis. CT of para-nasal sinuses can help in diagnosing UACS.

COMPLICATIONS

The complications of coughing can be classified as either acute or chronic. Acute complications include cough syncope due to markedly positive intrathoracic and alveolar pressures, decreased venous return, and decreased cardiac output when cough is prolonged and forceful, insomnia, cough-induced vomiting, sweating, rupture of bullae causing pneumothorax, sub-conjunctival haemorrhage, cardiac arrhythmias, seizures, splenic and venous ruptures, disruption of surgical wounds, coughing defaecation, cough syncope and in women with a prolapsed uterus, urinary incontinence. Chronic complications are common and include abdominal or pelvic hernias, fatigue, fractures of lower ribs and costochondritis.

TREATMENT

Specific treatment can be given once the cause is evident such as stopping smoking or an ACE-I, or beta-blocker, treating post-nasal drip or GERD, infections, bronchodilators for airway obstruction, inhaled glucocorticoids for NAEB, treating TB, TPE, sarcoidosis and ILD, tumours, bronchiectasis. In patients with chronic unexplained cough empirical therapy with antihistamines, decongestants, nasal glucocorticoids, nasal ipratropium may help improve UACS. In the absence of an appropriate response, empirical treatment for asthma, NAEB and GERD can be tried. Symptomatic therapy for cough is given when the cause is unidentified or no specific treatment is available or there is sleep disturbance and distressing cough. Dextromethorphan or codeine are cough suppressants and provide relief in dry irritating cough. Productive cough should not be suppressed, as the sputum will be retained in the respiratory tract and result in reduced ventilation. Cough suppressants should be strictly avoided in obstructive airway disease.

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2.6 Haemoptysis

Randeep Guleria, Jaya Kumar

INTRODUCTION

Haemoptysis is defined as coughing up of blood from the respiratory tract. It can range from streaks of blood in the expectoration to coughing up of large quantities of blood. Haemoptysis is alarming for the patient and can be caused by a spectrum of disorders ranging from a respiratory tract infection, bronchogenic carcinoma and rarely with systemic diseases which causes alveolar haemorrhage. Sometime, a minimal haemoptysis initially may be followed by a bout of massive haemoptysis which can be life-threatening. Massive haemoptysis is a medical emergency, most often due to asphyxiation which occurs due to flooding of the airways and alveoli with blood and also due to significant haemodynamic compromise. Despite a lot of focus on the management of massive haemoptysis the definition is highly variable. It is most commonly defined as expectoration of 100 to 600 mL of blood in 24 hours. The problem with this definition is that it is very difficult for a patient to quantify haemoptysis. Also the morbidity and mortality depends on the rate of bleeding, the condition of the underlying lungs and the ability of the patient to clear the airways of the blood rather than on the absolute quantity of blood loss. Any amount of haemoptysis which causes haemodynamic instability or respiratory embarrassment should be considered massive. Life-threatening haemoptysis is recommended as a better term which encompasses the quantity of haemoptysis, haemodynamic instability and impairment of gas exchange. The unpredictable course of haemoptysis with a possibility of potentially life-threatening massive haemoptysis and the various serious aetiologies mandates a prompt and focused assessment and management.

AETIOPATHOGENESIS

Vascular Anatomy

It is important to understand the blood supply of the lung to get an idea of the mechanism of significant haemoptysis. The lungs have a dual blood supply from the pulmonary and bronchial circulation. The pulmonary circulation is a low pressure system which is responsible for gas exchange. The pulmonary arteries run along the bronchial tree and carry the entire cardiac output for oxygenation in the pulmonary capillaries, but the only interaction with the airways is at the level of the terminal bronchioles where the pulmonary capillary bed arises around the alveoli for gas exchange. The bronchial tree on the other hand carries a small portion of the cardiac output but has a pressure at par with the systemic pressure. The bronchial arteries arise from the aorta or the intercostals arteries and supplies blood to the airways, hilar lymph nodes visceral pleura and parts of the mediastinum. They branch along the bronchial tree and form an extensive plexiform network in the peri-bronchial space and in the submucosa of the bronchial wall. Bleeding from the pulmonary vasculature is less common and minimal as it is a low pressure system. Also hypoxic pulmonary vasoconstriction diverts blood away from the diseased portion of the lung. Massive haemoptysis originating from the pulmonary circulation is therefore uncommon. The bronchial circulation is a more important cause of significant haemoptysis as it runs along the bronchial tree and supplies blood to the airways. Inflammation in the airways leads to hypertrophy of the bronchial vessels and an increased propensity to bleed. Also being a high pressure system it leads to more profuse bleeding and accounts for most cases of massive haemoptysis.

Causes

Haemoptysis has a varied aetiology with the common causes being tuberculosis (TB), bronchiectasis, bronchitis, bronchogenic carcinoma and pneumonia in different proportions depending on the population studied. The causes can be categorised according to the site of origin within the lung and the underlying disorder (**Table 1**).

The frequency of the different causes of haemoptysis varies in the developed and developing world. Recent literature from the developed world shows TB to be an infrequent cause of haemoptysis. The leading causes of haemoptysis in these countries are bronchitis, pneumonia, bronchiectasis and bronchogenic carcinoma with TB accounting for only 1.4% to 8% in different studies. In our country and most of the developing world TB still remains the most common cause for haemoptysis. In a study from Lucknow, India, the TB accounted for 79.2% cases of haemoptysis followed by bronchogenic carcinoma.

Various mechanisms are responsible for haemoptysis in active TB and post-tubercular sequelae:

A. Active tuberculosis

1. Bronchiolar ulceration and necrosis of adjacent vessels and alveoli.
2. Erosion of a vessel wall of a cavity.
3. Tubercular involvement of the vessel wall causes formation of aneurysms called Rasmussen's aneurysm. Rupture of these aneurysms can cause massive haemoptysis.

B. Sequelae of tuberculosis

1. Bronchiectasis due to destruction of the normal lung architecture by TB.
2. Aspergilloma formation in an old tubercular cavity.
3. Erosion of bronchial arteries due to healed, calcified nodes rupturing through the bronchial tree.
4. Scar carcinoma.

Table 1: Causes of Haemoptysis

- **A. Pulmonary**
  - *1. Airway disease*
    - Bronchiectasis
    - Bronchitis (acute and chronic)
    - Neoplasms
      - Bronchogenic carcinoma
      - Endobronchial metastatic carcinoma
      - Bronchial carcinoid
      - Kaposi's sarcoma
    - Foreign body
    - Airway trauma
  - *2. Parenchymal disease*
    - Infectious
      - Tuberculosis
      - Pneumonia/lung abscess
      - Aspergilloma
      - Lung parasite (ascariasis, schistosomiasis)
    - Inflammatory or immune disorders
      - Wegener's granulomatosis, SLE
      - Good pasture's syndrome
      - Idiopathic pulmonary haemosiderosis
      - Other pulmonary vasculitis
  - *3. Vascular causes*
    - Pulmonary embolism
    - Pulmonary arteriovenous malformation
- **B. Cardiovascular**
  - Pulmonary hypertension per se, Mitral stenosis
  - Tricuspid endocarditis
  - Aortic aneurysm
- **C. Trauma**
  - Chest injury
  - Iatrogenic
    - Percutaneous lung biopsy
    - Bronchoscopy with bronchial biopsy or transbronchial lung biopsy
    - Swan ganz catheterisation causing pulmonary artery perforation
- **D. Miscellaneous**
  - Drug induced (anti-coagulants, penicillamine, bevacizumab, cocaine)
  - Pulmonary endometriosis
  - Cryptogenic

Table 2: Differences Between Haemoptysis and Haematemesis

Haemoptysis	Haematemesis
Clinical evidence of lung disease	Clinical evidence of gastric or hepatic disease
Bright red or pink blood Liquid clotted appearance	Brown to black, coffee ground appearance
Cough, breathlessness chest pain present	Nausea vomiting, abdominal pain
Malaena rare	Malaena may be present
Examination shows macrophages or neutrophils	Mixed with ingested food particles
Alkaline pH	Acidic pH

DIAGNOSTIC APPROACH

A good history is very essential as it guides towards a likely aetiology. The first step is to distinguish haemoptysis (bleeding from the upper respiratory tract) from haematemesis (bleeding from upper G.I. tract) (**Table 2**). Once haemoptysis is confirmed the history should include assessment of the quantity of haemoptysis as an aggressive approach is required for massive haemoptysis. Also history of associated symptoms, including fever, cough, expectoration, dyspnoea, constitutional symptoms related to the underlying aetiologies helps the physician to narrow the differential diagnosis and develop a focused approach. History related to any suspected, underlying systemic illness, smoking, use of any drug, past illnesses like TB, severe or recurrent pneumonia should also be included. A complete physical examination including the vitals, general physical examination, respiratory and cardiovascular system is essential.

The priority in massive haemoptysis is to protect the airway, maintain ventilation and circulation and avoid the other lung from flooding. An evaluation for cause would follow once the patient is stabilised. Non-massive haemoptysis entails an evaluation for the cause of haemoptysis so as to start treatment for the same. Initial evaluation, depending on the presentation, should include—haemogram with haematocrit , white blood cell count and platelet count, erythrocyte sedimentation rate (ESR), arterial blood gas analysis, sputum for acid fast bacilli (AFB), Gram-stain, culture, and cytology, blood urea and serum creatinine, serum chemistry, HIV serology, autoimmune work-up and urine analysis if systemic vasculitis is suspected; prothrombin time, partial thromboplastin for coagulation disorders; D-dimer for suspected pulmonary embolism.

The evaluation for the aetiology begins with a chest radiograph and has changed drastically with the advent of computed tomography (CT) scans and bronchoscopy. When the chest radiograph is normal with a history suggestive of airway disease and there is no apparent risk factors for carcinoma lung the patient can be observed. No further evaluation is necessary if bleeding does not recur. Further evaluation with a contrast enhanced and high resolution computed tomography (HRCT) is indicated even if the chest radiograph is normal if bleeding recurs or if risk factors for carcinoma lung are present or the history is not compatible with bronchitis. When the chest radiograph shows parenchymal involvement sputum for AFB must be done. If the sputum is negative for AFB, the CT of the chest is required followed by treatment of the underlying disease, if a specific diagnosis is established. Further evaluation with bronchoscopy is advised when the CT chest does not suggest a specific diagnosis. When a chest radiograph reveals a mass, further evaluation with CT chest, bronchoscopy and a biopsy from the mass is indicated.

CT scan of the chest specially contrast enhanced HRCT has changed the diagnostic algorithm for haemoptysis. CT scan can help diagnose several conditions where the chest radiograph is normal or help in further characterising lesions seen on the radiograph. These include bronchiectasis, lung carcinoma, sequelae of TB, aspergilloma, pulmonary aneurysm and lung nodule. In addition it may also help to direct fine needle aspiration cytology (FNAC) and biopsy. Also it may help in deciding the better mode of tissue sampling in a particular case, bronchoscopic biopsy or CT guided per-cutaneous biopsy.

Flexible fiberoptic bronchoscopy (FOB) along with HRCT chest is the mainstay of diagnosis in patients with haemoptysis.

Bronchoscopy helps in the diagnosis when the radiology is normal or non-localising and if done acutely may help identify the source of bleeding. It is specifically useful in diagnosing endobronchial lesions, bronchitis and subtle mucosal abnormalities. A bronchoscopy should always be done in a patient with haemoptysis if there are risk factors for lung carcinoma even if the CT scan is normal.

The rigid bronchoscopy is being more and more infrequently used as the flexible scope gives greater access to the distal airways, but it has the advantage of providing better airway control and suctioning and can be used to remove large clots or foreign bodies. Bronchial and pulmonary angiography is rarely done as a diagnostic test with the advent of CT and bronchoscopy. It is done when bronchial artery embolisation is planned to stop bleeding. Specific tests like CT pulmonary angiography, ventilation perfusion scan and echocardiography may be required depending on the underlying aetiology.

MANAGEMENT

The goal of the management is to stop the bleeding, prevent asphyxiation and to treat the underlying disorder. The most important step is to quantify the haemoptysis and ensure that airway, breathing and circulation are maintained. It is important to remember that a minor bleed may herald a massive, life-threatening haemoptysis.

Management of Non-Massive Haemoptysis

Non-massive haemoptysis can be managed on an out-patients basis. However, the patient should be advised to report immediately to the emergency, if the haemoptysis increases or does not settle. The management is based on preventing further bleed from occurring and to find and treat the underlying cause. Basic investigations including a chest radiograph, haemogram and sputum for AFB must be done. Once the cause of haemoptysis is found appropriate treatment should be initiated. To prevent further bleeding cough suppressants, haemostatic agents and anxiolytic should be used. A broad spectrum antibiotic is given at times to prevent secondary bacterial infection in the lung.

Management of Massive Haemoptysis

It is a medical emergency, as it can cause sudden death by asphyxiation. The first step is to protect ABC—airway, breathing and circulation. Protection of the airway is of utmost importance, as asphyxiation is the most common cause of death in these patients.

The steps in management include:

1. Airway protection and haemodynamic stability: The patient should be admitted in the intensive care unit. If the site of bleeding is known the patient should be placed in a lateral position with the bleeding lung in the dependent position. This helps to protect the non-bleeding lung from spillage. Endotracheal intubation with a wide bore tube is indicated in patients with massive ongoing haemoptysis, haemodynamic instability and inadequate gas exchange. This also helps in better airway protection, suction and resuscitation in case of cardio-respiratory arrest.
2. Localisation of the bleed and protection of the non-bleeding lung: Bronchoscopy is the procedure of choice to identify the side and specific site of bleeding. If the side is identified but the specific site cannot be seen selective single intubation of the lung can be done to prevent flooding of the other lung. Double lumen endotracheal tube can be used in experienced centres when the side cannot be localised and bleeding persists. Rigid bronchoscopy may be required when there is massive bleeding because it is difficult to visualise the airway with an FOB in such a situation.
3. Bronchoscopic measures to stop bleeding: Once the specific site of bleeding is located, specific measures can be used to control the bleeding.
   - Bronchial lavage with iced saline has been successfully used in several studies.
   - Vasoconstrictive agents like epinephrine can be used to control bleeding.
   - Bronchoscopic balloon tamponade: A 4 French, 100 cm fogarty catheter is inflated in the segmental/sub segmental bronchus leading to the bleeding site for 24 to 48 hours. It is deflated for several hours after 1 to 2 days and removed if bleeding does not recur.
   - Laser photocoagulation and electrocautery have been tried in endobronchial tumours to control bleeding.
4. Angiography and embolisation: Patients who continue to bleed despite above measures can be taken up for angiography to localise the bleed and the bleeder can then be embolised. This procedure is used as a bridge to surgery or in patients who are not candidates for surgery. It is considered to be semi-definitive as rebleeding can occur in 10% to 20% patients in the next one year. Currently bronchial artery embolisation is a commonly used method to stop massive haemoptysis in most centres. It is also used in patients who have recurrent moderate to massive haemoptysis and are not candidates for definitive surgery.
5. Surgery: It is the only definitive option in massive haemoptysis not responding to above mentioned measures. Unfortunately most patients are not fit for surgery which is contraindicated in patients with diffuse/bilateral disease, active TB and in patients with poor respiratory reserve. Also the mortality and morbidity is much higher in emergent surgery in comparison to elective surgery in the non-bleeding patient.

PROGNOSIS

The outcome of haemoptysis varies in various series depending on the underlying aetiology, the number of patients with massive haemoptysis and the expertise of the treating centre. The mortality is 8% to 10% in various studies. The prognosis is improving with the newer modalities of treatment. All patients with haemoptysis, minimal or massive should be aggressively managed at well equipped centres to further improve the outcome.

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2.7 Jaundice

Aparna Agrawal

Jaundice is a common presentation of liver and biliary tract disease, characterised by yellowish discoloration of skin, sclerae and mucous membranes. It is clinically detectable when serum bilirubin is >3.0 mg/dL. It manifests more in tissues with – high elastic content (skin, sclera, blood vessels), high blood flow, low interstitial fluid and in fluids with high protein content (urine, sweat, semen, milk, exudates, etc.).

It manifests less in paralysed parts and oedematous areas.

Yellowing of the skin can also occur in carotenoderma (spares the sclera), with use of quinacrine and with excessive exposure to phenols.

CLINICAL EVALUATION

- Inspection should be done in bright day light to detect jaundice.
- Inspect the sclera, tongue, hard palate, skin and fingers.
- Ask the patient to look down and inspect the unexposed portion of the sclera because bulbar conjunctiva can be discoloured due to dust.
- Note whether the hue is lemon yellow (unconjugated hyperbilirubinaemia stains the tissues lightly because of its water insolubility); orange yellow (in patients with hepatocellular and cholestatic jaundice there is increase in conjugated bilirubin which penetrates body fluids more because of its water solubility), or greenish yellow (in prolonged cholestasis because of formation of biliverdin).
- Staining of clothes by secretions is a good clue (specially urine, sweat, milk and semen).
- Look for high coloured urine and pale coloured stools (avoid early morning specimen).

AETIOPATHOGENESIS

Jaundice results from a disorder of bilirubin metabolism in the form of increased formation or a decrease in hepatic clearance of bilirubin. Unconjugated bilirubin is lipid soluble and it is converted to water soluble bilirubin mono-and-diglucuronide by conjugation, which allows its excretion into the bile.

Some Practice Points

- In late stages of cholestatic or hepatocellular jaundice, despite high serum bilirubin levels, none can be detected in the urine. This is due to a third type of bilirubin—a bilirubin mono conjugate (not mono-and-diglucuronide), covalently bound to albumin, which is not filtered by the glomerulus, hence absent in the urine.
- The high elastic content of tissues is responsible for the disparity between the depth of jaundice in the skin and sclera and serum bilirubin levels during recovery from hepatitis or cholestasis.
- In unconjugated hyperbilirubinaemia due to haemolysis, usually serum bilirubin is < 5 mg/dL. If it is more than this, check for combination of haemolytic anaemia with an inherited disorder of bilirubin metabolism—Gilbert's syndrome or Crigler Najjar syndrome, coexistent renal and hepatocellular dysfunction or acute haemolytic crisis.

CLASSIFICATION AND CAUSES OF JAUNDICE

These are given in **Table 1.**

APPROACH TO JAUNDICE

A careful history, physical examination and standard laboratory tests help us in arriving at an accurate diagnosis in >80% of patients. In adult patients with a new-onset jaundice, the following disorders account for >95% of the diagnosis:

- Viral hepatitis.
- Alcohol-induced liver disease.
- Drug induced liver disease.
- Infections involving the liver including liver abscess and sepsis.
- Chronic hepatitis (all causes).
- Gall stones and their complications.
- Pancreatitis.
- Carcinoma of the pancreas.
- Haemolytic anaemia.

I. History

The onset, evolution and duration of jaundice should be noted. The associated features should also be enquired into.

History suggestive of acute viral hepatitis

- Low grade fever for 1 to 2 days, usually associated with headache, myalgias, anorexia, nausea and vomiting followed by jaundice.
- Change in taste and smell of food.
- Contact with individuals with jaundice.
- Needle stick exposure or any injection, body piercing, tattoos, shared razors or tooth brushes.
- Blood or blood product transfusions.
- Intravenous drug abuse.
- Health care professionals.
- Sex with commercial sex workers, multiple partners or with individuals with hepatitis B or C.
- History of sexually transmitted disease.
- Travel to endemic areas or eating raw shell fish (especially for hepatitis A).
- Occasionally, pain with or without swelling of joints and transient skin rash may indicate hepatitis B or C.

Table 1: Classification and Causes of Jaundice

Type	Cause	Basic Laboratory Abnormalities
Pre-hepatic	**↑ Bilirubin production** Haemolysis (a) Intravascular haemolysis – G6PD deficiency, PNH, malaria – Blood transfusion – Ineffective erythropoiesis	Unconjugated ↑ SBR Normal STA + ALP
	(b) Extravascular haemolysis – Pneumonia, PTE, resorption of haematomas, haemoglobinopathies	
Hepatic	(a) **↓ Hepatocellular uptake** – Drugs (Rifampicin, probenecid, ribavirin) – Gilbert's syndrome	
	(b) **↓ Conjugation** – Gilbert's syndrome, Crigler-Najjar Syndrome I and II – Physiologic jaundice of newborn – Drugs (e.g. Indinavir)	
	(c) **↓ Transport** i. Congenital hyperbilirubinaemia – Dubin-Johnson syndrome – Rotor's syndrome	Conjugated ↑ SBR Normal STA+ALP
	ii. Acute/ subacute hepatocellular disease – Viral hepatitis A-E, EBV, CMV, HSV – Hepatotoxins (ethanol, Amanita Phalloides) – Drugs – Dose dependent (Acetaminophen) Idiosyncratic (INH, phenytoin, etc.) – Ischaemia (hypotension, Budd-Chiari syndrome, hepatic veno-occlusive disease) – Metabolic disorders (Wilson's disease, Reye's syndrome) – Pregnancy related (AFLP, pre-eclampsia)	Mixed ↑ SBR (↑ SBR + ↑ STA ± ↑ ALP)
	iii. Chronic hepatocellular disease – Viral hepatitis (B, C, D) – Alcohol – Hepatotoxins (Vinyl chloride, Vit. A. hypervitaminosis) – Autoimmune hepatitis – Metabolic (haemochromatosis, Wilson's disease, NASH, α_1-antitrypsin deficiency) – Coeliac sprue	
Cholestatic	(a) Hepatic disorders with prominent cholestasis i. Diffuse infiltrative disease of liver – Granulomatous disease (Mycobacterial infection, Brucella, fungal disease, sarcoidosis, lymphoma, drugs, Wegener's granulomatosis) – Amyloidosis – Malignancy	↑ SBR + ↑ STA + ↑ ALP
	ii. Inflammation of intrahepatic bile ductules and/or portal tracts – Primary biliary cirrhosis – Drugs (erythromycin, trimethoprim-sulphamethoxazole) – Graft versus host disease	
	iii. Miscellaneous – Benign recurrent intrahepatic cholestasis – Intrahepatic cholestasis of pregnancy – Drugs (estrogen, anabolic steroids) – Total parenteral nutrition – Infections – Post-operative cholestasis – Vanishing bile duct syndrome	
	(b) Obstruction of bile ducts i. Choledocholithiasis – Cholesterol gall stones – Pigment gall stones	
	ii. Diseases of the bile ducts – Cholangiocarcinoma – Inflammation/Infection – Primary sclerosing cholangitis – AIDS cholangiopathy – Post surgical strictures	Conjugated ↑ SBR + Normal STA + ↑↑ ALP
	iii. Extrinsic compression of the biliary tree – Neoplasms (pancreatic carcinoma, hepatocellular carcinoma, nodes at porta hepatis) – Pancreatitis – Vascular enlargement (e.g., aneurysm, cavernous transformation of portal vein)	

SBR = Serum bilirubin, STA = Serum transaminases, ALP = Alkaline phosphatase, AFLP = Acute fatty liver of pregnancy.

History suggestive of chronic hepatitis/cirrhosis with portal hypertension

- Recurrent jaundice.
- Swelling of feet.
- Distension of abdomen.
- Massive haematemesis or melena may indicate portal hypertension and variceal bleed.
- Amenorrhoea.

History suggestive of alcohol-induced liver disease

- Details of quantity and type of alcohol being consumed now or in the past should be obtained from the patient, friends and family members. (The threshold for alcohol-induced hepatic injury appears to be 30 gms/day for women and 60 gms/day for men if ingested over 5 to 10 years. Less, if additional factors for liver disease are present).
- History of binge drinking and day time drinking should be noted.
- History of withdrawal symptoms or seizures should be taken. CAGE criteria (cut down, annoyed, guilty, eye opener) should be looked for as indicators of excessive alcohol usage.
- History suggestive of other alcohol related illness, e.g. pancreatitis, gastritis, peripheral neuropathy should be taken.

History suggestive of drug induced liver disease

- Review all prescription medications.
- Enquire specifically about alternative forms of medicine being taken.
- History of pruritic rash, joint pain or swelling related to some drug intake.

History suggestive of infections/liver abscess

- Fever moderate to high grade with chills/rigors, with dull aching pain right upper abdomen especially when associated with dysfunction of other organs.
- Rule-out leptospirosis in patients with combined renal and hepatic dysfunction.

History suggestive of cholestatic jaundice

- High coloured urine with pale coloured stools.
- Pruritus.
- Colicky pain right upper abdomen associated with fever, rigors/chills (suggestive of choledocholithiaisis with ascending cholangitis).

History suggestive of pancreatitis

- Recurrent upper abdominal pain with radiation to the back.
- History suggestive of steatorrhoea.
- Fever with severe pain and distension of the abdomen may be suggestive of acute pancreatitis.

History suggestive of haemolytic anaemia

- History of pale coloured urine with mild yellow discolouration of eyes.
- History of anaemia not responding to haematinics and requiring regular blood transfusions.
- History of recurrent jaundice or non-healing ulcer.
- Family history of anaemia.
- Known haemoglobinopathy or having artificial heart valves.

Miscellaneous

- Age and sex: Type A hepatitis decreases as age advances but no age is exempt from hepatitis B and C.
  - A multiparous, middle-aged, obese female with dyspepsia may have gall stones.
  - Chances of malignancy increase with increasing age.
- Occupation should be noted (particularly involving alcohol, other hepato-toxic industrial chemicals or contact with rats for Weil's disease).
- Painless jaundice—check for malignancy.
- Significant weight loss—check for malignancy.
- History of joint pain or swelling (check for hepatitis B or C, autoimmune hepatitis, drug induced hepatitis, inflammatory bowel disease with primary sclerosing cholangitis or granulomatous disorders such as sarcoidosis).
- Diabetes, arthritis and pigmentation—check for haemochromatosis.
- Chronic obstructive pulmonary disease with jaundice—suspect α_1 antitrypsin deficiency.
- Chronic diarrhoea with blood and mucous—rule-out primary sclerosing cholangitis.
- Family history of liver disease (check for Wilson's disease, haemochromatosis, α_1 antitrypsin deficiency).
- Family history of biliary disease.

Jaundice after biliary tract surgery

Check for:

- Residual calculus
- Traumatic stricture of bile duct
- Sepsis
- Drug induced hepatitis
- Hepatic metastasis in case of malignancy

Jaundice in a liver transplant recipient

Causes:

- Hepatocellular injury resulting from impaired organ preservation
- Vascular occlusion in immediate postoperative period
- Graft rejection
- Obstruction of the bile ducts
- Acute viral hepatitis especially cytomegalovirus infection
- Immunosuppressive drug toxicity
- Recurrent disease (e.g. Hepatitis B or C, primary sclerosing cholangitis)

Jaundice in pregnancy

The following causes are specific to pregnancy:

- Hyperemesis gravidarum (first trimester; self limiting)
- Intrahepatic cholestasis of pregnancy (third trimester; pruritus; resolves within 2 weeks of delivery; tends to recur with subsequent pregnancies)

- Acute fatty liver of pregnancy (third trimester; may be fatal unless delivery is performed promptly)
- Pre-eclampsia (third trimester; associated with hypertension and proteinuria)
- HELLP syndrome (severe form of pre-eclampsia; urgent delivery is indicated)
- Hepatitis E induced fulminant hepatic failure is more common in pregnancy.

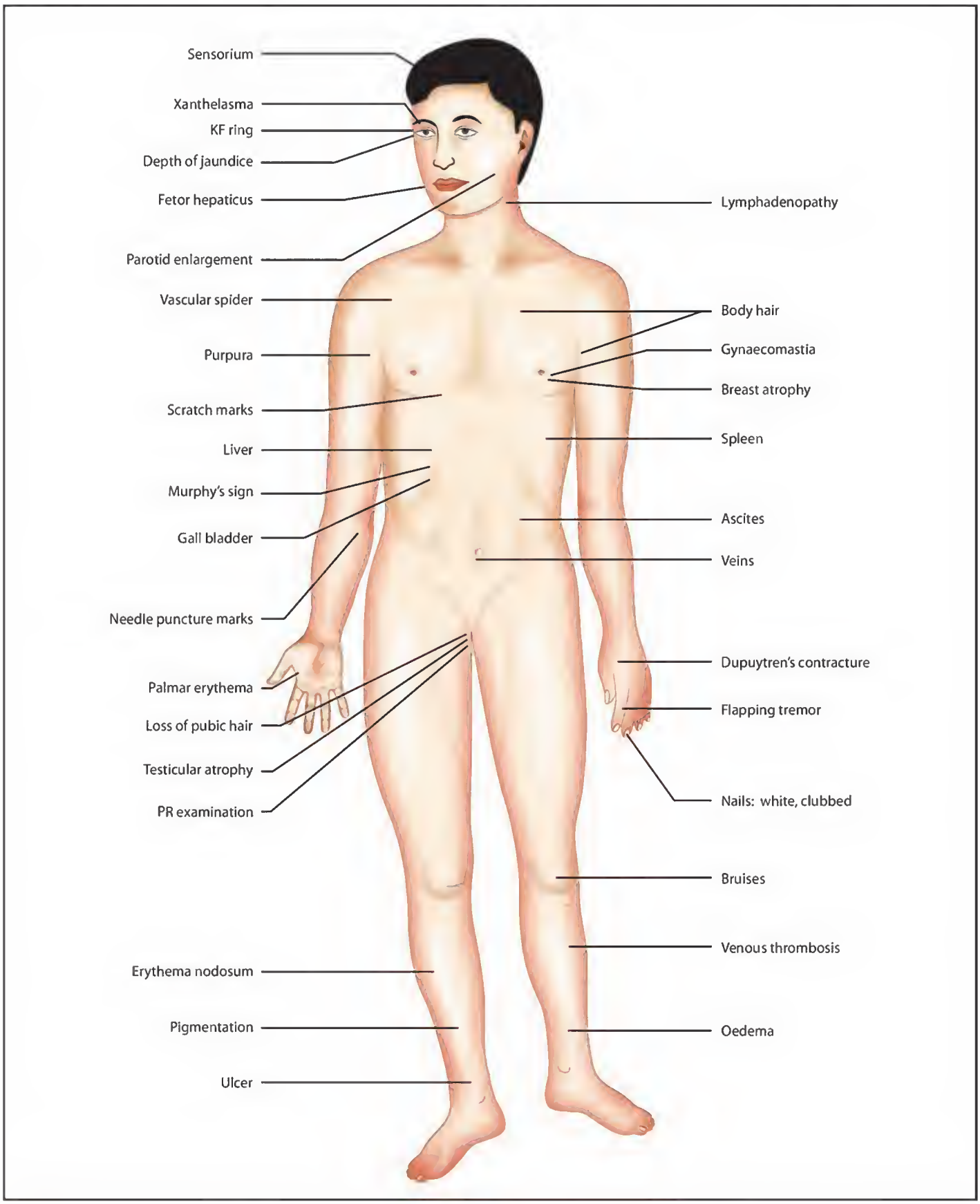


Figure 1: Clinical signs in jaundice.

II. Examination

There are many signs that we need to check in a patient present with jaundice (**Figure 1**).

General examination

- Anaemia may indicate haemolysis, chronic liver disease or malignancy.
- Pedal oedema may indicate chronic liver disease, inferior vena cava obstruction due to malignancy or procoagulant state; severe anaemia with volume overload or hypoproteinaemia due to nutritional deficiency or malabsorption.
- Lymphadenopathy may indicate an infectious aetiology, lymphoma, tuberculosis or sarcoidosis. An enlarged left-supraclavicular node (Virchow's node) or periumbilical nodule (Sister Mary Joseph's nodule) suggests an abdominal malignancy.
- Altered mental state may indicate hepatic encephalopathy, sepsis or brain metastasis in patients with late stages of malignancy.
- Kayser-Fleischer (KF) ring is usually seen in Wilson's disease.
- Xanthomas in primary biliary cirrhosis.
- Pigmentation of the shins and non-healing ulcer may indicate haemoglobinopathy. Hyperpigmentation may also be present in haemochromatosis or in primary biliary cirrhosis.
- Erythema nodosum may be seen in tuberculosis, sarcoidosis or syphilis.
- Migratory thrombophlebitis is suggestive of carcinoma of the body of pancreas.

Abdominal examination

- Dilated abdominal veins can be seen in:
  - Portal hypertension
  - Inferior *vena cava* obstruction (functional or organic—dilated and tortuous veins indicate organic obstruction).

  The direction of flow in the infraumbilical veins helps in distinguishing between portal hypertension (from above-below) and IVC obstruction (from below-up).
- Severe right upper quadrant tenderness with respiratory catch on inspiration (Murphy's sign) suggests cholecystitis or occasionally, ascending cholangitis.
- Ascites may be due to:
  - Cirrhosis
  - Malignancy
  - Infections, e.g. tuberculosis, spontaneous bacterial peritonitis
  - Acute pancreatitis (Grey Turner's sign, i.e. discolouration of the abdomen is highly suggestive).
- Liver: In liver examination the following should be noted:
  (i) The size and consistency of the liver
    - hard liver indicates malignancy.
    - Shrunken liver indicates:
      (a) Cirrhosis
      (b) Fulminant hepatic failure

      [Localised dilatation of the transverse colon (toxic megacolon), fulminant colitis and ileus associated with peritonitis or a perforated viscus may decrease the liver dullness without a decrease in liver size].

  (ii) Massive hepatomegaly (>10 cm below the costal margin) may indicate:
    (a) Malignancy (primary/secondary)
    (b) Congestive liver (chronic congestive cardiac failure (CCF)/Budd-Chiari syndrome)
    (c) Alcoholic liver disease
    (d) Primary biliary cirrhosis
    (e) Prolonged extrahepatic cholestasis
    (f) Infiltrative disease of the liver
      - Myelofibrosis
      - Amyloidosis (especially when associated with macroglossia, peripheral neuropathy, malabsorption, CCF or proteinuria)

    (g) Chronic myeloid leukaemia
- Whether it is tender (infections, congestion, bile stasis) or not.
- Whether the surface is nodular (malignancy, cirrhosis) or smooth.
- Whether the edge is rounded or sharp.
- Whether the left lobe is palpable. A palpable left lobe suggests:
  - Chronic liver disease
  - Malignancy
  - Abscess/cyst
  - Obstruction of left hepatic vein
- Bruit over the liver indicates increased vascularity:
  - Acute alcoholic hepatitis
  - Hepatocellular cancer
  - Hepatic artery aneurysm
  - Hepatic arterio-venous fistula
- Friction rub over the liver suggests
  - Liver metastasis
  - Primary hepatocellular carcinoma
  - Infarction of the liver (as in sickle cell anaemia and polyarteritis nodosa)
  - Liver abscess
  - Haematoma around the puncture site.
- Check for pulsatile liver (indicative of significant tricuspid regurgitation)

Peripheral stigmata of chronic liver disease

- Parotid enlargement
- Gynaecomastia
- Spider angioma (usually found in the distribution of superior *vena cava*; >12 in number indicate portal hypertension)
- Paucity of axillary and pubic hair
- Testicular atrophy
- Palmar erythema
- Dupuytren's contracture

Signs suggestive of decompensated liver disease

Jaundice

Ascites

Hepatic encephalopathy
Oliguria, hepatic failure
Altered behaviour
Fetor hepaticus
Asterixis

- Check for any masses in the abdomen.
- Genitalia must be examined and per rectal examination is a must for piles, growth or nodules in the pouch of Douglas.
- Jaundice with extrapyramidal neurological features suggests Wilson's disease especially in patients born of consanguinous marriage and having KF ring.

III. Laboratory Diagnosis

Integration of the patient's history, clinical examination findings and laboratory results is essential for accurate interpretation because non-specific aberrations in these tests may occur. We can divide all jaundiced patients into three broad categories of patients (**Table 1**).

A. Isolated elevation of serum bilirubin (SBR) with normal serum transaminases (STA) and alkaline phosphatase (ALP)

Hepatocellular disease or biliary obstruction is unlikely in these patients. If SBR is predominantly unconjugated (>80%) we need to check for haemolysis (Hb, peripheral smear, reticulocyte count, Coomb's test, plasma and urine haemoglobin and other special tests for diagnosing the type of haemolytic anaemia). A detailed description is beyond the purview of this chapter.

If there is no evidence of haemolysis on the peripheral smear, the diagnosis is congenital hyperbilirubinaemia in the absence of history of drug intake. These can be definitely diagnosed with the help of special enzyme assays, genetic studies and liver biopsy (black pigmentation on liver biopsy in Dubin-Johnson Syndrome).

B. Increased serum bilirubin with increased serum transaminases and normal to mildly increased alkaline phosphatase

The most likely cause is hepatocellular jaundice (**Table 1**). The patient needs to be evaluated for acute versus chronic liver disease and for aetiology.

Two biochemical tests that suggest chronic liver disease are a low serum albumin (<2.8 gm/dL) and a prolonged prothrombin time (>16 sec. prolonged). A bedside diagnosis of cirrhosis can be made when it is associated with two physical findings of ascites and asterixis. Serum globulin levels are elevated in cirrhosis, resulting in reversal of A:G ratio. Electrophoretic analysis shows increased γ-globulin fraction in hepatocellular jaundice (versus raised α_2- and β-globulins in cholestatic jaundice). The other tests that need to be done in suspected hepatocellular jaundice are:

- Viral markers (serological tests for hepatitis A-E viruses, viral load for hepatitis B and C especially, serological tests for cytomegalovirus and Epstein-Barr virus infection) should be done for suspected acute or chronic viral hepatitis.
- If serum AST:ALT is > 2 : 1, suspect alcoholic hepatitis in the setting of alcoholism.
- Anti-mitochondrial antibody positivity indicates primary biliary cirrhosis.
- ANA, anti-SMA (smooth muscle antibodies) and anti-LKM Ab positivity suggests autoimmune hepatitis.
- Serum Fe, transferrin and ferritin are elevated in haemochromatosis.
- Serum ceruloplasmin is reduced in Wilson's disease.
- Serum ALP: SBR of <2 or AST: ALT of >4, in a young patient with Coomb's –ve haemolytic anaemia and KF ring on slit lamp examination is suggestive of Wilson's disease.
- α_1-antitrypsin phenotype for α_1-antitrypsin deficiency.
- Transglutaminase Abs for coeliac sprue.
- Serum α-fetoproteins for hepatocellular carcinoma.
- UGI endoscopy for any malignancy, evidence of portal hypertension (esophageal or gastric varices and portal gastropathy features).
- Doppler ultrasonogram to detect patency of hepatic veins, portal vein and inferior *vena cava*.
- Liver biopsy is especially indicated in patients with undiagnosed persistent jaundice. It permits diagnosis of viral hepatitis, alcoholic and non-alcoholic steatohepatitis, haemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, fatty liver of pregnancy, primary biliary cirrhosis, granulomatous hepatitis and neoplasms with the use of special stains. Though liver histology may be entirely normal in acute biliary obstruction, it may occasionally provide a clue to unsuspected biliary tract obstruction. Iron and copper content of the liver can also be measured. In patients with prolonged prothrombin time (PT)—a transjugular biopsy is advisable.

C. Increased serum bilirubin with markedly elevated alkaline phosphatase with normal to mildly elevated serum transaminases

It is suggestive of cholestatic jaundice. Prolonged prothrombin time which normalises on Vitamin K administration is suggestive of extra-hepatic biliary obstruction.

Imaging studies are very important in this group of patients with ultrasonogram (USG) of the abdomen being the basic investigation. Dilated ducts on imaging confirm the diagnosis of biliary obstruction (i.e. distinguishes between intra-hepatic and extrahepatic biliary obstruction) and further imaging tests can be planned based on the availability of the procedure, presence or absence of dilated bile ducts on initial imaging, technical expertise, cost of the procedure and risk versus benefit of the procedure.

The various imaging techniques available are:

- Contrast enhanced computed tomography (CECT)
- Magnetic resonance cholangiopancreatography (MRCP)
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Percutaneous transhepatic cholangiography (PTC)
- Endoscopic ultrasound (EUS)
- Nuclear imaging studies

Both ERCP and PTC permit direct visualisation of the biliary tree as well as the pancreatic ducts. Biopsy can be done from any suspicious lesion and therapeutic intervention can be done in the same sitting. ERCP is used for lesions distal to the bifurcation of the right and left hepatic bile ducts whereas PTC is preferable when the level of biliary obstruction is proximal to the common hepatic duct or altered anatomy precludes ERCP. The sensitivity and specificity of MRCP, ERCP and PTC are comparable.

Table 2: Differences between the Three Basic Types of Jaundice

Features	Haemolytic Jaundice	Hepatocellular Jaundice	Extrahepatic Cholestatic Jaundice
Colour of urine	Pale	High coloured	High coloured
Colour of stools	Normal	Normal to dark	Pale coloured
Pruritus	–	–/+	++
Jaundice	Lemon yellow	Deep yellow	Orange yellow/greenish yellow
Antecedent history	H/o anaemia requiring blood transfusions (BT)	Injection/BT/tattoos contact with a jaundiced patient	Biliary surgery or gall stones
Family history	Anaemia	Jaundice	Gall stones
Urine urobilinogen	++	+	–
Haemogram	Evidence of haemolysis	Normal	Normal
Serum bilirubin	↑ <5 mg/dL (usually) (unconjugated)	↑ – ↑↑↑ (mixed)	↑ – ↑↑↑ (predominantly conjugated)
Serum transaminases	Normal	↑ – ↑↑↑	Normal/↑
Alkaline phosphatase	Normal	Normal/↑	↑↑
Ultrasonogram/CT	Hepatosplenomegaly liver ↑/normal spleen ↑ – ↑↑↑	Liver ↑/N spleen N/↑	Liver ↑↑ with dilated ducts

These tests help in delineating the exact site of obstruction, the cause of obstruction (by direct visualisation and biopsy) and the back pressure changes.

Intrahepatic biliary duct may not be dilated in some conditions with extrahepatic biliary obstruction—early or partial biliary obstruction,

- Primary sclerosing cholangitis
- Co-existent cirrhosis (fibrosis prevents dilatation of biliary ducts)

- In patients with suspected cholelithiasis, USG is the primary diagnostic imaging procedure but in patients with suspected choledocholithiasis, ERCP is the preferred diagnostic procedure. Papillotomy may be indicated.
- In patients with obstructive jaundice due to suspected pancreatic carcinoma, EUS is superior to CT scanning with regard of detecting a pancreatic mass but comparable with regard to tumour staging and predicting resectability or nonresectability.
- In patients with unexplained hepatomegaly, either USG or CT scanning are appropriate initial imaging procedures.
- Liver imaging procedures are usually not necessary in patients with a diagnosis of acute viral hepatitis or non-alcoholic steatohepatitis (NASH).
- Increased serum amylase is suggestive of acute pancreatitis.

IV. Therapeutic Options

- Haemolytic anaemia has to be treated with repeated blood transfusions as and when required to maintain adequate haemoglobin level and some patients may require iron chelation if blood transfusion requirement is high. Bone marrow transplantation is an option for thalassaemia , being done in a few centres.
- Hepatocellular jaundice has to be treated as per the cause. Drug induced hepatitis has to be recognised and the offending drug needs to be stopped. Cessation of alcohol, administration of antiviral agents, phlebotomy for haemochromatosis, copper chelation for Wilson's disease and steroids for autoimmune hepatitis are a few of them.
- Supplementation of fat soluble vitamins may be required in some patients with cholestatic liver disease.
- In patients with obstruction of the bile ducts, the obstruction has to be relieved by interventional endoscopic or radiologic approach (sphincterotomy, balloon dilatation and placement of drains or stents) or surgery depending on the location and the likely aetiology of the obstructing lesion.
- The various drugs that can be used for treatment of pruritus are cholestyramine, rifampin, ursodeoxycholic acid and naltrexone.

With the approach outlined above we are able to arrive at an accurate diagnosis in most patients with jaundice. The differences between the three types of jaundice are summarised in **Table 2**.

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2.8 Upper Gastrointestinal Bleeding

JC Vij

Gastrointestinal bleeding is a challenging emergency which is associated with a high mortality. The clinical presentation of GI bleeding depends on the location, rate of bleeding and aetiology of the disease. Haematemesis defined as vomiting of blood indicates upper gastrointestinal (UGI) bleeding and the site of bleeding is above the ligament of Treitz. The blood may be fresh and red coloured or may be old having the appearance of coffee grounds. Malaena is defined as passage of black tarry stools which are often foul smelling. This results from degradation of blood to haematin and other haemochromes. Melena is usually the result of UGI bleeding, but slow bleeding from distal small bowel, caecum and ascending colon can also lead to melena; about 50 to 100 ml of bleeding in the GI tract is required to cause melena. Haematochezia refers to the passage of fresh red blood from the rectum, which suggests a lower GI source of bleeding but can also occur with massive bleeding from the UGI tract (usually more than 1000 mL). About 30% of patients with UGI bleeding present with haemetemesis, 30% with melena and 50% with both.

AETIOLOGY

The common causes of UGI bleeding include peptic ulcer disease, oesophageal/gastric varices, Mallory-Weiss tear, erosive gastritis/duodenitis, malignancy, angiodysplasia and Dieulafoy's lesions. Peptic ulcer disease is the most common cause, accounting for 50%. Bleeding from varices—oesophageal or gastric—accounts for 10% to 30%. Studies from central and north India have described variceal haemorrhage to be more common (45% to 50%). About 10% of patients with portal hypertension may have a non variceal source of bleeding such as peptic ulcer or Mallory-Weiss tear. Mallory-Weiss tear usually occurs in the gastric mucosa at the gastro-oesophageal junction and is considered to be caused by forceful retching. Dieulafoy's lesion denotes erosion of mucosa by an underlying large sized arteriole. Though Dieulafoy's lesions can be located anywhere in the GI tract, they are typically found in the upper part of the stomach.

MECHANISM

Bleeding from an ulcer occurs when it erodes into the wall of a blood vessel. Though the exact cause of haemorrhage from a pre existing ulcer is not clear, a number of factors can predispose an ulcer to bleed. Use of aspirin and other non-steroidal anti inflammatory drugs (NSAIDs) are perhaps the most important factors. The mechanism of action is complex and involves reduced production of prostaglandins, (a cytoprotective agent) and platelet dysfunction. Though controversial, ethanol, *H.pylori* infection and glucocorticoids may potentiate the deleterious effect of NSAIDs and increase the risk of bleeding. Cyclo oxygenase-2 (Cox-2) inhibitors also increase the risk of ulcer bleeding, though the risk is less than with NSAID use. Antiplatelet agents such as clopidogrel, though less injurious to gastric mucosa, increase the risk of bleeding from ulcers as do anticoagulants. The role of intragastric acid in causing peptic ulcer is well established, but its role in causing haemorrhage is not well understood. Several studies have shown the beneficial effects of acid-reducing agents like proton pump inhibitors in controlling bleeding from ulcers, emphasising the important role of acid. Portal hypertension, a serious complication of cirrhosis, is associated with bleeding. The most common cause of portal hypertension is cirrhosis followed by portal vein thrombosis, splenic vein thrombosis, non-cirrhotic portal fibrosis (NCPF), schistosomiasis. Bleeding may occur from various lesions associated with portal hypertension including oesophageal varices, gastric varices, portal hypertensive gastropathy and rarely ectopic varices. In patients with cirrhosis, bleeding from varices carries a high mortality and also a high morbidity. Varices form at the rate of 5% to 15% per year and only 1/3rd of them bleed. The risk of haemorrhage from varices is related to their size and location. Endoscopic appearance, portal pressure and the severity of the underlying liver disease. Large sized varices and those having red wheal sign (a manifestation of thinning of overlying mucosa) carry a high-risk of haemorrhage. Bleeding usually occurs from varices present near the gastro-oesophageal junction. Haemorrhage from varices stops spontaneously in about 50% of cases and the risk of rebleeding is high within six months. Interestingly 50% of re-bleeding episodes occur within 3 to 4 days of the first bleed. Bleeding from gastric varices is usually associated with a very high mortality rate.

DIAGNOSIS

Endoscopy is the best method of diagnosing the cause of UGI bleeding. Barium radiography although can diagnose some of the lesions in the oesophagus, stomach and duodenum, it has no value in patients who are bleeding actively. Besides, endoscopy has tremendous therapeutic value.

MANAGEMENT

Basic management of all patients with GI bleeding whether variceal or non-variceal remains almost the same and includes: monitoring of vital signs particularly hypotension, tachycardia and anoxia and clearing of the airways. Two large bore peripheral intravenous catheters should be placed for aggressive volume replacement in a haemodynamically unstable patient and such patients should be managed in a medical ICU. It is preferable to replace blood loss by packed red cells which may take some time to arrange. In the meantime crystalloids and saline infusion should be started. The hematocrit should be maintained around 30% and haemoglobin level kept approximately at 9 to 10 g/dL. Over infusion of blood or fluids should be avoided in patients with variceal bleed to avoid increase in portal pressure which may precipitate early rebleeding. Coagulopathy and

thrombocytopaenia should be adequately corrected. Patients with aggressive bleeding and/or altered mental status should be intubated. Other supportive measures include administration of prophylactic antibiotics, preferably third generation cephalosporines in patient with cirrhosis and maintenance of urine output above 50 mL/hour. Acid base and electrolyte disturbances should be monitored and treated. The blood glucose level should also be maintained.

Placement of a nasogastric tube, though controversial, is helpful in clearing the gastric contents. Gastric lavage along with intravenous administration of metoclopramide or erythromycin (not available in India) is helpful in improving the examination of the gastric mucosa on endoscopy and decreases the need for repeat endoscopy. Besides, it provides information about the type of blood present in the stomach, which may be helpful in planning the time of endoscopy. Fresh red blood indicates active bleeding and the patient will need early endoscopic evaluation. However, an aspirate negative for blood does not rule-out upper GI bleeding. Use of nasogastric aspiration as a primary tool for assessing GI bleed should not be relied upon. Assessment of vital signs is the most effective means of determining bleeding activity. The use of a nasogastric tube has not been shown to influence the outcome in patients with GI bleeding.

MANAGEMENT OF PEPTIC ULCER BLEEDING

Peptic ulcers are the most common and important cause of upper GI bleeding. Management aims to: (a) stop active bleeding, (b) prevent rebleeding, and (c) treat the peptic ulcer. Endoscopic examination is useful in identifying lesions which have a high-risk of re-bleeding. Ulcers with a clean base, flat pigmented spot are at a low risk of re-bleeding (5%), while those with active bleeding or with non-bleeding visible vessel and adherent blood clot (Forrest classification) are at a high-risk of rebleeding (40% to 55%). The presence of co-morbidities, old age (>60 years), clinical evidence of severe bleeding and ulcers greater than 2 cm in size are associated with a poor outcome. Bleeding stops spontaneously in 70% to 80% of patients with peptic ulcers. In the remaining patients endoscopic therapy controls bleeding in 80% to 90%. Surgery is needed in about 5% to 10% of patients.

Endoscopic therapy is the most effective method of controlling bleeding and to some extent preventing re-bleeding thereby reducing mortality. Endoscopic methods of controlling ulcer bleeding fall into three broad categories: (a) injection therapy, (b) thermal methods, and (c) mechanical devices.

Injection Therapy

Submucosal injection of diluted epinephrine (1:10,000) is a simple, effective and widely practiced method of controlling bleeding. Local injection acts by a tamponade effect on nearby vessels thus causing haemostasis. Besides it causes vasoconstriction and platelet aggregation. It is recommended that a large volume (30 to 45 mL) of epinephrine solution be injected in the four quadrants near an actively bleeding or visible vessel.

Endoscopic Thermal Therapy

This can be divided into two categories: (i) contact thermal; and (ii) noncontact thermal modalities.

Contact thermal modalities include heater probe coagulation and bipolar/multipolar electrocoagulation. Noncontact thermal modalities consist of organ plasma coagulation (OPC) and laser therapy. Contact thermal methods are preferred as besides causing coagulation of tissue due to thermal heat, they also cause tamponade of vessels by direct probe pressure. Noncontact thermal methods are cumbersome and expensive and are not shown to be more efficacious.

Mechanical Devices

These include metal haemoclips, rubber band ligation, endoloops and sewing devices. Haemoclips have been widely used to treat active bleeding ulcers or visible vessels. They act by direct compression of opposing tissues or vessels causing thrombosis and haemostasis.

Several studies have shown that a combination of endoscopic therapy such as injection plus thermal therapy or injection plus haemoclips application are superior to monotherapy alone.

Pharmacological Therapy

Proton pump inhibitors (PPI) due to their inhibitory action on hydrogen potassium adenosine triphophatase raise intragastric pH. They have been found effective when given in high doses intravenously for 72 hours after successful endoscopic treatment of an ulcer with high-risk bleeding signs. They reduce the recurrence of bleeding and need for blood transfusion but not the mortality rate. The recommended dose is 80 mg omeprazole given as an intravenous bolus followed by 8 mg per hour intravenous infusion. In patients with low-risk ulcer bleeding oral proton pump inhibitors in high doses are recommended. In one study it was shown that PPI if administered for 24 to 48 hours before endoscopy significantly lowered the prevalence of high-risk stigmata and decreased the need for endoscopic therapy but did not decrease the incidence of recurrent bleeding, surgery or mortality.

HEALING OF PEPTIC ULCER

Proton pump inhibitor therapy has similar healing rates for bleeding and non-bleeding ulcers. The long-term treatment of ulcers depends on their aetiology. Patients with bleeding ulcers who have been taking NSAIDs should discontinue them. Patients with *H. pylori* infection should receive therapy for *H. pylori* eradication.

MANAGEMENT OF BLEEDING VARICES

Oesophageal variceal bleeding should be controlled swiftly and promptly as continued bleeding is associated with high mortality. The first episode of variceal bleeding is associated with about 30% mortality. Haemostasis can be achieved by pharmacological treatment and endoscopic therapy.

Pharmacological Treatment

In the past, vasopressin, a powerful vasoconstrictor, was widely used to control bleeding from varices. The drug causes splanchnic arteriolar vasoconstriction leading to decrease in portal inflow and thus portal pressure. However, this drug is associated with myocardial ischaemia, mesenteric ischaemia and cerebrovascular accidents. Some of adverse effects of vasopressin can be reduced by concomitant use of nitrates, used as intravenous infusions, sublingual or transdermal route. It is rarely used now because of its adverse effect profile. This led to the development of a safer synthetic analogue—terlipressin

which has a longer biological half life and is administered in a dose of 1 to 2 mg every four hours. Terlipressin is as effective as other vasoactive drugs as well as endoscopic treatment. This drug has been found to be associated with improved survival in several randomised trials.

Somatostatin and its analogues

Somatastatin is a naturally occurring peptide. Its exact mechanism of action is not clear. It causes an increase in splanchnic vascular resistance by causing vasoconstriction and decrease in portal blood flow. Somatostatin is given as an intravenous bolus of 250 ug followed by continuous infusion of 250 ug per hour and therapy is continued for two to five days. Boluses of 500 ug can be administered intermittently if fresh episodes of bleeding occur during the course of treatment. Octreotide, a synthetic analogue of somatostatin, has a longer duration of action, and has been found to be effective in controlling variceal haemorrhage. Octreotide is given in the doses of 25 to 50 ug/hour by a continuous intravenous infusion. Somatostain and octreotide should be started immediately while waiting for more definitive endoscopic therapies to be employed or when endoscopy is not possible due to non-availability of trained personnel or contraindicated because of haemodynamic instability. They can also be used as an adjunct to endoscopic therapies. Both somatostatin and octreotide have an excellent safety profile, with low complication rates. Their use may cause hyperglycaemia and abdominal cramping.

Endoscopic Therapy

Endoscopic therapy is the cornerstone of controlling haemorrhage from varices. These are two principal forms of endoscopic treatment:

(a) Endoscopic sclerotherapy (EST)

(b) Endoscopic variceal band ligation (EVL)

Endoscopic sclerotherapy (EST)

It involves injection of sclerosing agents into the veins causing thrombosis and scarring. Various sclerosing agents used are ethanolamine oleate, aethoxyskerol, sodium tetradecyl sulphate, sodium morrhuate and absolute alcohol. Tissue adhesive such as N-butyl-cyanoacrylate have been used for sclerosing of gastric varices. Variceal injections are started at gastro-oesophageal junction and are restricted to distal 5 cm of oesophagus. Usually 1 to 2 ml of sclerosing agent is injected into each varix and a total of 10 to 15 mL is effective in controlling bleeding. Sclerotherapy is repeated usually at intervals of 2 to 3 weeks. Endoscopic sclerotherapy is associated with some local and systemic complications, which include retrosternal pain, transient dysphagia, fever and mild pleural effusions. Oesophageal stricture leading to dysphagia is seen in approximately 15% of patients. Bleeding from post-EST ulcers and oesophageal perforation are potentially life-threatening complications of endoscopic sclerotherapy.

Endoscopic variceal band ligation (EVL)

It involves applying rubber bands around varices which lead to occluding the veins mechanically. The elastic rubber band strangulates the varix producing thrombosis, inflammation, necrosis and finally sloughing of mucosa that heals by scar formation. EVL is performed by using multiband ligating system. The banding device consists of a cylinder preloaded with 6 to 8 elastic bands. The cylinder is attached to the tip of the endoscope and bands are released by pulling a trigger wire of a device placed over the biopsy channel after the varix is sucked into the cylinder. EVL is associated with fewer complications than EST. The procedure is effective in controlling bleeding in 75% to 85% of patients.

With the available pharmacological and endoscopic treatments, the rate of failure to control acute bleeding is approximately 10% to 20%. Balloon tamponade using Sangstaken-Blakemore balloon, though associated with complications, can accomplish haemostasis in a difficult situation, such as massive variceal bleeding. Transjugular intrahepatic shunt (TIPS) represents an artificial communication by placing a metallic stent between the hepatic and the portal vein. It is an effective method of controlling active bleeding from oesophageal and gastric varices. It also prevents recurrent variceal bleeding. Although the TIPS procedure needs expertise (not available at many centres in India), when placed successfully it can achieve haemostasis in 90% to 100% cases. TIPS is associated with long-term complications of thrombosis and occlusion of stent and hepatic encephalopathy. It is contraindicated in patient with poor cardiac function, pulmonary hypertension and polycystic liver disease.

Prevention of Variceal Bleeding

Non-selective beta-blockers such as propranolol and nadolol in doses that decrease the heart rate by 25% have been shown to be effective in preventing primary and secondary variceal haemorrhage.

The majority of episodes of upper GI bleeding can be controlled with endoscopic and pharmacological therapy. Angiographic therapy or surgery may be needed in those patients where bleeding cannot be controlled or localised or in those with recurrent bleeding.

Upper GI bleeding is a serious emergency which carries a high mortality. Overall survival is improving due to the availability of new therapeutic methods and improved medical care.

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2.9 Fever of Unknown Origin

Priscilla Rupali

Pyrexia or fever of unknown origin (FUO) remains an intellectual and diagnostic challenge. A developing country like India, with its burden of endemic diseases like tuberculosis, fungal infections and limited access to diagnostic facilities, requires a radically different approach from that of the developed countries for arriving at a diagnosis in a patient of FUO.

DEFINITION

In 1961, FUO was defined by Petersdorf and Beeson as fever greater than 38.3°C (101°F) documented on several occasions, for more than 3 weeks with no diagnosis despite 1 week of inpatient investigation. With the advent of acquired immunodeficiency syndrome (AIDS), complex surgical and ICU protocols and increased diagnostic investigations, Durack and Street proposed classifying FUO into four different categories: (1) classic FUO, (2) nosocomial FUO, (3) neutropaenic FUO and (4) human immunodeficiency virus (HIV) associated FUO.

TYPES OF FUO

Classic FUO: The newer definition is similar to the one proposed in 1961. Keeping in mind increasing diagnostic capabilities, this has been modified to fever greater than 38.3°C (101°F) for more than 3 weeks with no diagnosis after 3 outpatient visits or 3 days as inpatient in the hospital or 1 week of 'intelligent and invasive' ambulatory investigations.

Nosocomial FUO: Fever greater than 38.3°C (101°F) on several occasions in a hospitalised patient receiving acute care, not manifesting or incubating an infection on admission with no diagnosis after 3 days of investigations, including 2 days' incubation of cultures.

Neutropaenic FUO: Fever greater than 38.3°C (101°F) on several occasions in a neutropenic (absolute neutrophil count <500 cells/mm^3 or expected to fall to this level in 1 to 2 days) patient with no diagnosis after 3 days of investigations, including 2 days' incubation of cultures.

HIV-associated FUO: Fever greater than 38.3°C (101°F) on several occasions in a HIV-infected patient, with no diagnosis after investigations for more than 4 weeks as an outpatient, or 3 days as an inpatient.

AETIOLOGY

Classic FUO

The major causes of a classic FUO have remained the same over the last 10 decades. The three major categories include infections, neoplasms and non-infectious inflammatory diseases (collagen vascular diseases and sarcoidosis). Other minor categories include drug fever, factitious fever and habitual hyperthermia. In a large series of classic FUO from Eastern India, infections were the most dominant cause seen in 53% (half of these were tuberculosis), neoplasms in 17% and collagen vascular diseases in 11%. Among the infections tuberculosis, abscesses and bacterial endocarditis predominated; neoplasms were mostly non-Hodgkins' lymphoma, Hodgkins' lymphoma and leukaemia and collagen vascular diseases causing fever were systemic lupus erythematosus (SLE), Takayasu's arteritis and mixed connective tissue disease (MCTD). About 14% remained undiagnosed in this series. This is in contrast to that seen in the Western world where infections contribute to less than a third of cases and about 30% to 50% remain undiagnosed.

Nosocomial FUO

There is no systematic series of nosocomial FUO in literature. However, when evaluating a hospitalised patient with fever, the underlying susceptibility of the patient, surgical or investigative procedures done, invasive devices *in situ*, and the patient's own flora need to be taken into consideration. About 50% of nosocomial fever is due to infections. Non-infectious causes include drug fever, deep venous thrombosis, acalculous cholecystitis, pancreatitis and pulmonary embolism. Repeated physical examinations with multiple blood and fluid cultures often yield a clue towards diagnosis. For critically ill patients, intravenous (IV) lines/invasive catheters must be changed swiftly. Empirical therapy with antibiotics after taking at least three blood cultures must be started only if there is evidence of hypotension, acute respiratory distress syndrome (ARDS) or multiple organ damage.

Neutropaenic FUO

Data from Western literature documents that at least 50% of neutropaenic patients who become febrile have an established or occult infection and 20% of febrile patients with absolute neutrophil count (ANC) less than 100 cells/mm^3 are bacteraemic. True neutropaenic FUO with no diagnosis at 96 hours varies in each series from 25% to 40%. Most often these are fungal (*Candida, Aspergillus*) and viral infections [cytomegalovirus (CMV) and herpes simplex virus (HSV)]. A detailed physical examination including the fundus, skin, peri-rectal area and paranasal sinuses is mandatory to localise a possible source of infection. Risk factors for occult infection include the degree of neutropenia, disruption of skin and mucosal barriers, a rapid decline in ANC, prolonged duration of neutropaenia, cancer not in remission, co-morbid illnesses, venous catheters and use of monoclonal antibodies against cellular receptors. Empiric antibiotic regimens recommended for use in India, after at least 3 blood cultures, based on the studies available should include coverage against extended spectrum β lactamase (ESBL) producing Gram-negative organisms like *E.coli, K.pneumoniae,* and *P.aeruginosa* and Gram-positive organisms like *S.aureus*, coagulase negative *Staphylococcus spp.*

HIV-Associated FUO

Prolonged fever in HIV-infected persons is due to an infection in 90% of cases. Risk of an opportunistic infection (OI) depends on the degree of immunosuppression and the burden of

endemic pathogens in the environment. In India, tuberculosis accounts for about 70% of cases of prolonged fever, followed by disseminated cryptococcosis (10%), *Pneumocystis jiroveci* pneumonia (7%), community acquired pneumonia (2%) and liver abscess (2%). A CD4 count, if available, can help and predict which disease could be contributing to the cause of prolonged fever. The spectrum of HIV associated FUO in India is slightly different from that reported in Western literature. *Mycobacterium avium intracellulare* complex (MAIC) is not a common cause of FUO in India. One theory proposed to explain this is that we have so much endemic burden with *Mycobacterium tuberculosis* that it confers some sort of immunity against atypical mycobacteria. With the advent of highly active antiretroviral therapy (HAART) it also becomes imperative for us to consider possible causes for fever after start of HAART. In the initial 6 months after the start of HAART, immune reconstitution inflammatory syndrome (IRIS), drug fever, and antiretroviral therapy associated OIs (when the baseline CD4 counts are really low and the person is still susceptible to OIs) are common whereas after 6 months, causes of prolonged fever include various forms of tuberculosis, neoplasms and non-infectious inflammatory diseases similar to a classic FUO. The common causes in each of these categories are shown in **Table 1**.

- Bites (arthropod or others)
- Pre-existing cardiac abnormalities
- Prostheses *in situ*
- Exposure to other ill people
- High risk behaviour and exposure to sexually transmitted infections
- Co-morbid conditions like alcoholism, IV drug use, HIV and malignancies
- Previous visit to hospital for trauma, burns or laceration
- Foreign bodies like tampons, nasal packs and barrier contraceptives
- Involvement or exposure to any domestic or international bioterrorist activity

On examination, if a person appears ill, investigations should be expedited. A detailed skin and soft tissue examination to look for rashes, eschar, petechiae, dusky skin and discoid lesions should be performed inclusive of the hidden areas like axillae, groin, inframammary folds and behind the ear. Palpation of muscles or spine often reveals myositis and inter/intramuscular abscesses or spinal tenderness. The importance of looking for nuchal rigidity, per-rectal exam to look for prostatic abscess and inspection of the genitalia and oral cavity cannot be over emphasised.

Table 1: Causes of FUO

Classic FUO	Nosocomial FUO	Neutropaenic FUO	HIV-associated FUO
Tuberculosis	Post-operative	Bacterial infections – *E. coli*	Tuberculosis
Abscesses	– abscesses – haematomas	– *Klebsiella spp.* – *Pseudomonas spp.*	Cryptococcosis
Bacterial endocarditis	– foreign bodies Infected prostheses	– *S. aureus* – Coag neg staph	*Pneumocystis jiroveci* pneumonia
Visceral leishmaniasis	Infected catheters	Central venous catheter (CVC) infections	Bacterial pneumonia
Non-Hodgkins lymphoma	*Clostridium difficile* colitis	Invasive fungal infections:	Amoebic liver abscess
Hodgkins lymphoma	Acalculous cholecystitis	Pneumonia and sinusitis	Disseminated histoplasmosis
Acute leukaemia	Deep venous thrombosis	Dental abscesses	Non-Hodgkins lymphoma
Systemic lupus erythematosus	Pulmonary embolism	Perianal infections, cytomegalovirus,	Immune reconstitution
Takayasu's arteritis	Drug fever	Herpes simplex virus infections	inflammatory syndrome

DIAGNOSTIC APPROACH

It is often said that a good clinician is the one who makes least mistakes in diagnosis of common conditions, not the one who makes occasional brilliant guesses. A detailed history and physical examination often reveals potential diagnostic 'clues' which could be critical towards making a diagnosis. The first step would be a consistent documentation of fever (38.3°C or 101°F) on several occasions by a health care professional. Significant weight loss, night sweats and anaemia usually also confirm an organic pathology. A detailed history should include the following:

- Immune status-immunocompromised state (HIV infection, immunosuppressive drugs, neutropenia, lymphopenia, malignancies like lymphomas and congenital immune deficiencies)
- Occupation
- Medications
- Travel
- Immunisations
- Exposure to pets

An initial laboratory evaluation inclusive of a total and differential count, three blood smears for malarial parasites, urine microscopy, chest radiograph, typhidot and blood cultures could rule out a possible cause of an acute undifferentiated febrile illness. If the patient is not in multi-organ system failure, previous antibiotics/drugs should be stopped, the patient observed for at least 72 hours, at which point multiple blood (and fluid, if indicated) cultures should be taken. Increased number of blood cultures and a large volume in each culture bottle increases the yield significantly. A second tier of investigations, depending on the constellation of symptoms and signs, could include liver function test (LFT), cerebrospinal fluid (CSF) analysis, an ultrasound of the abdomen and bone marrow aspiration with a biopsy and routine, mycobacterial and fungal cultures. Rarely, an inappropriately treated enteric fever may be picked-up on a bone marrow culture even when the blood cultures are negative, however, it is extremely rare for typhoid fever to present after 3 weeks as it is most often an acute febrile illness and should not usually present as a FUO. Endemic diseases peculiar to specific geographic locations in

India also need to be kept in mind while evaluating FUO (**Figure 1**). The diagnostic algorithms to evaluate prolonged fever in India also depend on cost-effectiveness and not just diagnostic yield and hence invasive tests like bone marrow aspiration and biopsy with suitable cultures or even liver biopsy may often be done before expensive tests like computerised tomography (CT) scan of the abdomen and thorax or positron emission tomography (PET) scans. It would be difficult to encompass all the FUO causing conditions into one single algorithm, especially as most patients would have clues on history and physical examination. However, there could be certain pointers in a person with prolonged fever and weight loss towards a diagnosis and these are as follows:

- Resident of North-East India with oral ulcers, skin lesions and adrenal enlargement on imaging suggests disseminated histoplasmosis.
- Diabetic or immunosuppressed individual with non-resolving pneumonia with cutaneous, visceral or pleural abscesses suggests melioidosis.
- Resident of Bihar or Jharkhand with pancytopaenia and large spleen suggests visceral leishmaniasis.
- Resident of Karnataka, North India or Kashmir with history of some exposure to animals, either by occupation or consumption of unpasteurised dairy products with skeletal or joint involvement and hepatosplenomegaly suggests brucellosis.
- Resident of Nagaland or Manipur, possibly HIV-infected with anaemia and umbilicated skin papules with evidence of systemic involvement suggests 'disseminated penicilliosis'.
- Oral ulcers, arthralgia and discoid lesions with frothy urine in a young person suggests SLE.
- Young individual with arthragia, maculopapular rash, leucocytosis, lymphadenopathy and hepato or splenomegaly suggests adult onset still's disease.

Despite the fact that there are numerous algorithms available in different textbooks, it would be important to follow 'Sutton's law' or 'look where the money is'. Do not carry out a battery of 'routine' tests in a conventional sequence. Suggested algorithms, with the disclaimer that not all diseases would fit into these, are shown in **Figures 2 to 4**.

ADDITIONAL LABORATORY TESTS USEFUL IN THE DIAGNOSIS OF FUO

Additional tests that may provide clues include thick and thin blood smears to rule out malaria, babesia and trypanosomes if relevant travel history is present. Febrile serology for rickettsial

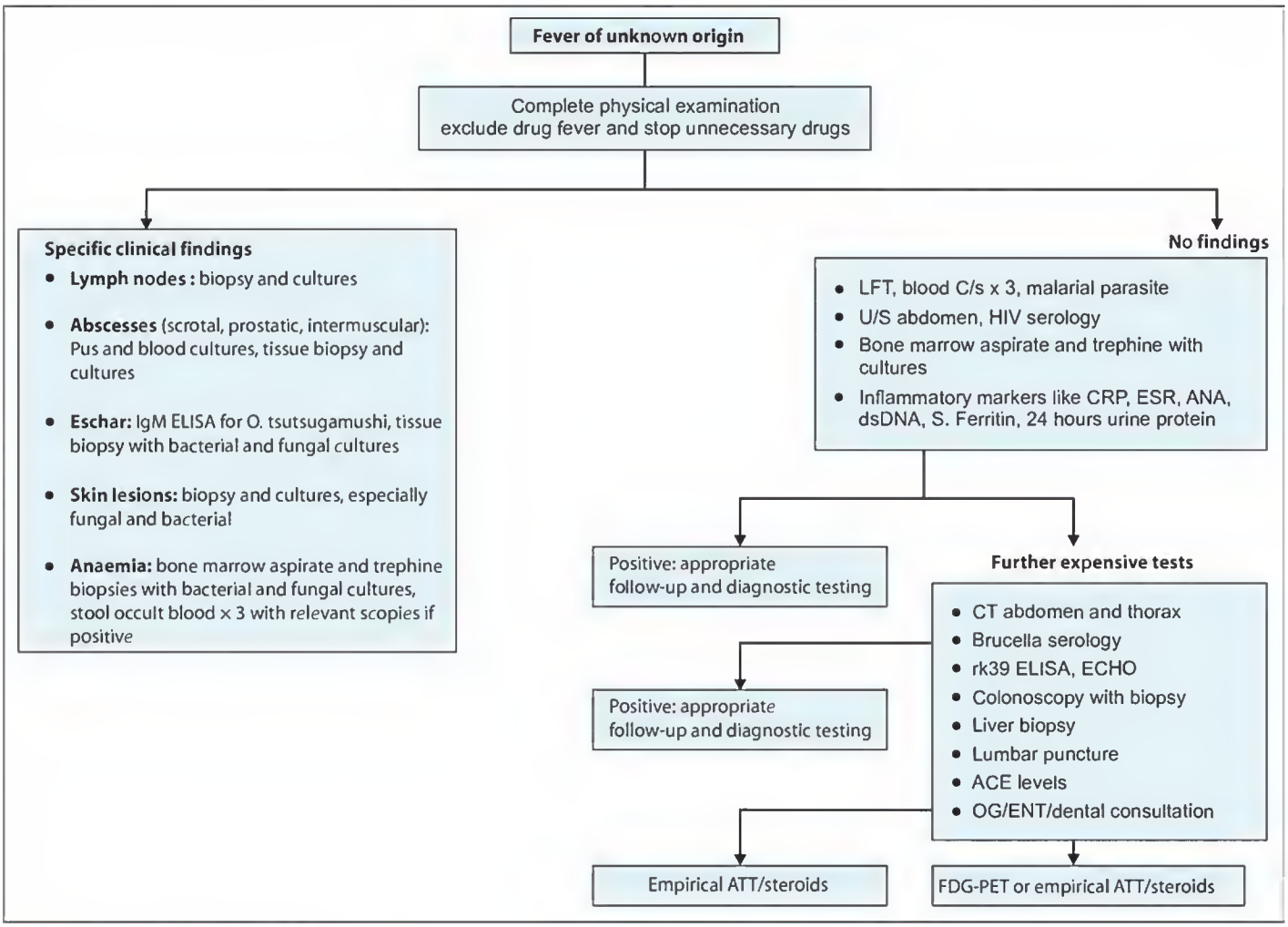


Figure 1: Evaluation of classic FUO in India.

Echo = Echocardiogram; FDG-PET = Fluorodeoxy glucose positron emission tomography; CRP = C-reative protein; ESR = Erythrocyte sedimentation rate; LFT = Liver function test; U/S = Ultrasound; ANA = Antinuclear antibody; ACE = Angiotensin converting enzyme; OG = Obstetrics and gynaecology; ENT = Ear, nose, throat; ELISA = Enzyme linked immunosorbent assay; dsDNA = Double stranded DNA, HIV = Human immunodeficiency virus.

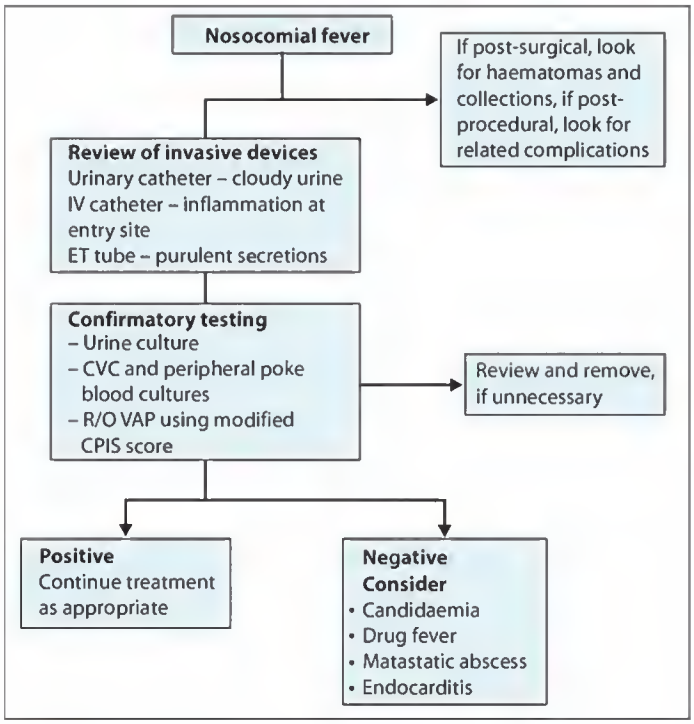


Figure 2: Evaluation of nosocomial fever.

CVC = Central venous catheter; VAP = Ventilator associated pneumonia; CPIS = Clinical pulmonary infection score; IV = Intravenous catheter; ET = Endotracheal tube. Am J (Respir Crit Care Med 1995;152:1982-91).

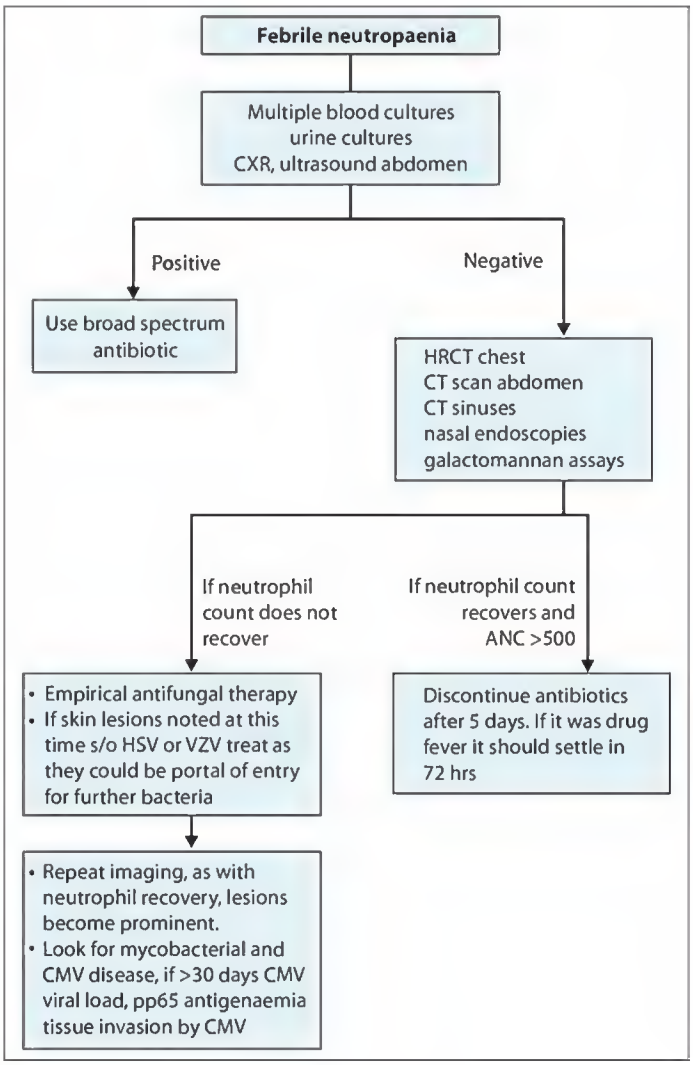


Figure 3: Evaluation of fever in neutropaenic patients.

HRCT = High resolution computerised tomography; CT = Computerised tomography; HSV = Herpes simplex virus, VZV = Varicella zoster virus; CMV = Cytomegalovirus; ANC = Absolute neutrophil count.

infections, salmonella and dengue may not be useful if history of fever is around 3 weeks as most of these diseases would have run through their natural course by this time. However, febrile serology may be useful for brucellosis, visceral leishmaniasis and prolonged mononucleosis syndromes. If bacteremia or endocarditis is suspected, it may be prudent to maintain blood cultures for 2 weeks to rule out HACEK organisms or use alternative blood culture techniques like 'lysis centrifugation' if bacterial load is suspected to be low. Autoimmune work-up should be considered early along with a check-list of signs and symptoms of an autoimmune disorder to allow early categorisation to a specific collagen vascular disease. In an elderly individual with symptoms of anorexia and anaemia, examination for occult blood in stools should be considered with early gastroscopy or colonoscopy as indicated. Diagnostic clues like pancytopaenia may prompt an early bone marrow evaluation. Similarly, an elevated alkaline phosphatase (ALP) concurrent with an elevated gamma glutamyl transferase (GGT) indicative of an infiltrative liver disease or elevated enzymes indicative of a granulomatous hepatitis may prompt a blind or ultrasound guided liver biopsy for histopathology and relevant cultures. Exploratory laparotomy would be advocated only if there is moderate splenomegaly with all other investigations being non-contributory and a high chance of a malignancy localised to the spleen, e.g. splenic lymphoma or T-cell lymphoma.

Non-invasive whole body radionuclide scans like ^{111}Indium-labelled leucocytes, ^{67}Ga-citrate scan and Technetium Tc 99m delineate and localise inflammatory foci. Recently, 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) has replaced other radionuclide techniques as it accumulates in pyogenic infectious foci, malignancies, granulomatous and non-infectious inflammatory diseases. FDG-PET, as a second line or third line procedure in FUO, has a sensitivity of 81% and specificity of 86% in detecting the cause of fever. In most diagnostic protocols of FUO in Western literature, FDG-PET is a second line procedure. This is unrealistic in India due to the enormous cost-constraints and hence we would need to develop our own protocols which would be cost-effective and generalisable in a resource-limited setting.

TREATMENT

In a classic FUO, the emphasis should be on obtaining a diagnosis and empirical antibiotics, anti-tuberculous therapy (ATT), nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids may mask fever while permitting the spread of infection. Hence, these are to be avoided while attempting to make a diagnosis. However, if the patient has deranged vital signs, is asplenic or neutropenic, after taking suitable cultures cautious use of antibiotics appropriate to the local flora or clinical picture may be advised. 'Shotgun therapy' with antibiotics, ATT, NSAIDs and steroids is to be assiduously avoided as it minimises the chance of a future diagnosis. Repeated physical examinations often reveal localising clues as the disease evolves. In the case of non-

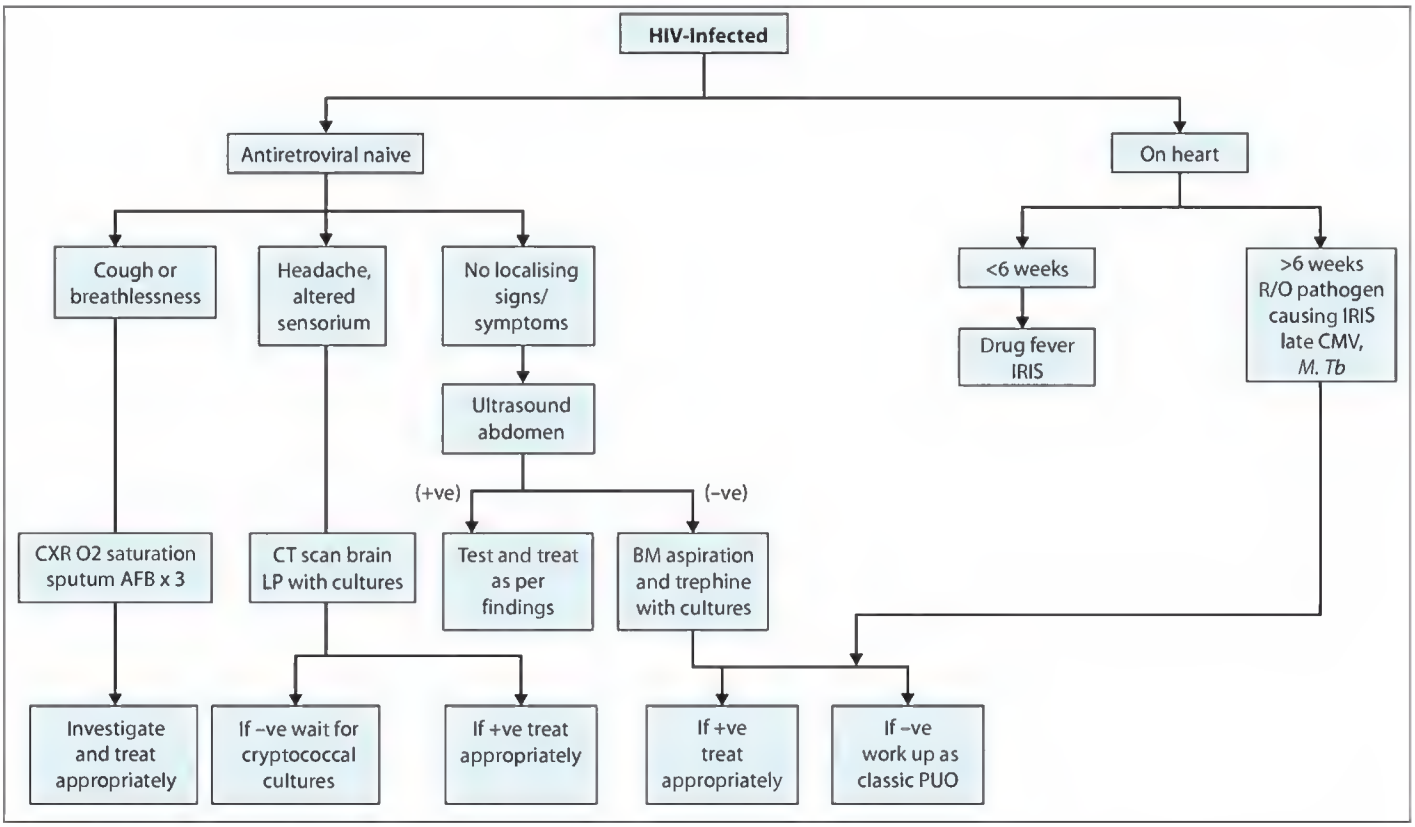


Figure 4: Evaluation of fever in PLWHA (people living with HIV/AIDS).

IRIS = Immune reconstitution inflammatory syndrome; CXR = Chest X-ray; CT scan = Computerised tomography scan; AFB = Acid fast bacilli; M. Tb = Mycobacterium tuberculosis; CMV = Cytomegalovirus; LP = Lumbar puncture; HAART = Highly active antiretroviral therapy; BM = bone marrow.

infectious inflammatory diseases, a repeated evaluation after a follow-up of 2 to 3 months often helps characterisation into a particular autoimmune or granulomatous disease. Over the years, in the many series of classic FUO, the number of patients with no diagnosis ranges from 30% to 50%. However, even if no diagnosis is obtained, the prognosis has usually been good in these patients.

CONCLUSION

- The four types of FUO include classic, nosocomial, neutropenic and HIV related.
- The important causes of classic FUO include the big three, i.e. Infections, neoplasms and connective tissue diseases.
- Nosocomial FUO is most often due to an infection, however non-infectious causes need to be kept in mind.
- Neutropaenic FUO most commonly is due to fungal infections like candidiasis and aspergillosis and viral infections like CMV and HSV.
- Tuberculosis contributes to 70% of the cases of HIV-associated FUO.
- Emphasis in any FUO should be on obtaining a diagnosis. Steroids, antibiotics or empirical ATT often mask the diagnosis and should be avoided unless there is evidence of serious organ dysfunction.

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2.10 Generalised Lymphadenopathy

SK Verma

DEFINITION

Lymphadenopathy is an increase in the size of lymph nodes. Enlargement of lymph nodes in three or more non-contiguous areas is considered as generalised lymphadenopathy.

BACKGROUND

Generalised lymphadenopathy (GL) is a common clinical problem faced by primary care physicians. The majority of cases have infective and non-specific aetiology or a reactive lymphadenopathy whereas less than 1% have malignancy as the aetiology. GL usually occurs in response to systemic causes such as infections, autoimmune diseases, drug reaction but less commonly due to malignant disorders, histiocytoses and storage disorders. As age advances, the incidence of serious illnesses causing GL increases. Hence, it is important to have a systematic approach to GL so as to avoid unnecessary investigations while at the same time not missing a serious disorder.

PATHOPHYSIOLOGY

Lymphadenopathy may be caused by the following:

1. Multiplication of cells within the node, e.g. lymphocytes, monocytes, plasma cells, or histiocytes.
2. Infiltration by cells from outside, such as malignant cells or neutrophils.
3. Lymph nodes draining a source of infection.
4. Depositions or storage disorders.
5. Benign hyperplasia.

CAUSES

Causes of GL include infections, autoimmune diseases, malignancies, histiocytoses, storage diseases, benign hyperplasia, and drug reactions.

Infections

1. *Viral infections:* Human immunodeficiency virus (HIV), infectious mononucleosis, cytomegalovirus, varicella, and adenovirus.
2. *Bacterial infections:* Tuberculosis, brucellosis, plague, *Streptococci, Staphylococci,* cat-scratch disease, chancroid, melioidosis, atypical mycobacterial infection, primary and secondary syphilis, leprosy.
3. *Fungal infections:* Histoplasmosis, coccidioidomycosis, paracoccidioidomycosis.
4. *Chlamydial infections:* Lymphogranuloma venereum.
5. *Parasitic infections:* Toxoplasmosis, filariasis, leishmaniasis, trypanosomiasis.
6. *Rickettsial infections:* Scrub typhus, Q fever, rickettsial pox.

Malignancy: Acute leukaemias, lymphomas, chronic lymphocytic leukaemia.

Autoimmune disorders: Juvenile rheumatoid arthritis, serum sickness, rheumatoid arthritis, systemic lupus erythymatosis (SLE), mixed connective tissue disorder, sarcoidosis and graft versus host disease.

Metabolic and storage disease: Gaucher disease, Niemenn-Pick disease, cystinosis.

Drug hypersensitivity: Phenytoin, mephenytoin, carba-mezapine, pyrimethamine, phenylbutazone, allopurinol, and isoniazid.

Other non-neoplasic aetiologies: Langerhans cell histiocytosis, Epstein-Barr virus (EBV)-associated lympho-proliferative disease, Castleman disease and Kawasaki disease.

APPROACH

Approach to a case of GL requires detailed history, physical examination and appropriate lab testing to find out a possible aetiology before attempting advanced testing and biopsy.

History

Age and duration

Most cases of GL in younger patients are due to infectious or benign aetiology whereas in older adults autoimmune or malignant causes are more commonly seen. GL in younger patients usually resolves within 2 to 3 weeks. Non-resolving GL and progressive increase in size should raise a suspicion and requires further work-up. In adults and in the elderly, GL should be taken seriously at the onset without any delay in work-up.

Exposures

A history of chronic use of drugs, such as anti-epileptic drugs, exposure to pets, animals and insect bites is important and a history of travel to endemic areas must be noted. Occupational and environmental exposures such as smoke, fumes, pesticides, tobacco and radiations must be evaluated.

Personal and family history

Sexual history is important and HIV positivity is associated with increased chances of rare and opportunistic infections and malignancies as a cause of GL. Family history of certain cancers raises suspicion of cancer as a cause of GL.

Specific symptoms

GL associated with fever, upper respiratory symptoms, irritability and anorexia points towards infective aetiology whereas weight loss and cachexia suggest malignancy. The presence of joint pain, mild fever, morning stiffness, skin and constitutional symptoms suggests autoimmune disorder as the cause of GL. Although fever is a very important feature of infection, it may be absent in patients who are diabetic, immunocompromised or those on steroids or immunosuppressive drugs.

Physical Examination

Physical examination includes examination of lymph nodes and their characteristics, presence of splenomegaly, bone tenderness, purpura, skin and complete systemic examination for clues to the underlying cause for GL.

Lymph node examination

Size: Lymph nodes measuring (<1 cm) are often palpable in normal adults and inguinal nodes up to 2 cm in size may be considered normal. Lymph nodes measuring <1.0 cm^2 in area (1.0 cm × 1.0 cm or less) are usually benign or reactive where as lymph node size of 2.25 cm^2 (1.5 cm × 1.5 cm) should be investigated further for the underlying cause. Lymph nodes measuring 1 cm to 2.25 cm^2 in size may be kept under close observation or investigated depending upon other features. However, the presence of even shotty (< 0.5 cm) supraclavicular, scalene, iliac, popliteal or epitrochlear nodes is considered significant. Persistence and increasing size of a lymph node are definite indications for further evaluation.

Texture: A lymph node may be soft, rubbery, firm or hard in consistency, discrete or matted, movable or fixed and may be tender or non-tender with or without features of inflammation. Small, soft, discrete, non-tender nodes are seen mostly with benign conditions. Pain and tenderness is mostly a feature of inflammatory aetiology and rarely due to rapid enlargement of nodes due to acute leukaemia. Large, symmetrical, discrete, rubbery to firm, mobile and non-tender nodes are seen in lymphoma. Hard, non-tender and fixed nodes are highly suggestive of malignant deposits. Matted, firm and non-tender nodes are mostly due to tuberculous lymphadenitis or a malignancy. Development of draining sinuses is characteristic of tuberculous lymphadenitis.

Location: Certain locations may provide a clue to the possible aetiology of GL. Supraclavicular, scalene, iliac, popliteal and epitrochlear nodes are to be investigated to rule out malignancy. Presence of mediastinal nodes with GL points towards lymphoblastic leukaemia, lymphoma, sarcoidosis, tuberculosis, histoplasmosis and coccidioidomycosis. Presence of supra-clavicular nodes suggests lymphoma, tuberculosis, toxoplasmosis, histoplasmosis, and coccidioidomycosis. Abdominal and mesenteric nodes with GL may suggest lymphoma, tuberculosis, ulcerative colitis, brucellosis and salmonellosis.

Systemic Examination

GL is commonly caused by systemic disorders and systemic infections, so detailed systemic examination may provide a clue to its aetiology. Autoimmune disorders and HIV infection may have numerous clues in the history and physical examination. Splenomegaly with GL is seen in lymphoproliferative disorders like lymphoma, acute and chronic lymphatic leukaemia or systemic illnesses like infectious mononucleosis, tuberculosis, brucellosis, salmonellosis, toxoplasmosis, leishmaniasis, filariasis, cat-scratch disease, SLE, rheumatoid arthritis and sarcoidosis. Hepatomegaly and splenomegaly with GL is a common presentation of rare infiltrative, metabolic and storage disorders.

INVESTIGATIONS

Since most patients with GL have benign or reactive lymph-adenopathy, extensive work-up is to be done only in cases suspected to have significant lymphadenopathy on physical examination. Supraclavicular, scalene, iliac, popliteal and epitrochlear nodes should be investigated to rule-out a malignancy. Complete blood counts with blood picture may rule-out leukaemias and immune cytopaenias. Viral serological testing including HIV and immunological markers like anti-nuclear antibody (ANA) should be done when suspected on history and physical examination. Chest radiographs and abdominal ultrasonography may show nodes and provide clues to the aetiology. A computed tomography or magnetic resonance imaging may be used to visualise deep seated nodes like mediastinal and retroperitoneal nodes, when appropriate. Biochemical testing adds little to aetiological diagnosis although lactate dehydrogenase (LDH) is frequently raised in cases of lymphoma.

LYMPH NODE BIOPSY

The decision to obtain a biopsy should be based on lymph node characteristics, systemic examination and laboratory testing. Excision biopsy should be taken from the most representative node. Inguinal nodes are best avoided. Fine needle aspiration cytology is not a good method for initial diagnostic work-up. Indications for biopsy include lymph node area of >2.25 cm^2 (1.5 cm × 1.5 cm), hard, fixed, supra-clavicular, scalene, iliac, popliteal and epitrochlear nodes of any size or increasing size of nodes.

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2.11 Dizziness and Vertigo

M Maiya

'Dizziness' is a common symptom. It refers to various types of abnormal sensations relating to perception of the body's relationship to space. These sensations may be a feeling of rotation or spinning—known as vertigo; or others like non-rotatory swaying, light-headedness, faintness and unsteadiness. This 'Dizziness syndrome' is mostly benign but it may be a manifestation of serious underlying cardiac or neurological disease. Hence, it is essential to analyse the complaint of 'Dizziness'.

The first step in the analysis of dizziness is to differentiate vertigo from other abnormal sensations of imbalance. If the patient complains of a sensation of spinning or motion sickness, one should suspect vertigo. It indicates a vestibular system disorder involving the inner ear or its connection to the brain; whereas the other sensations of imbalance suggest a non-vestibular disorder. The clinical approach to a patient with dizziness is shown in **Figure 1**.

NON-VESTIBULAR DISORDERS

1. *Syncope or pre-syncope:* Pre-syncope is a feeling of light headedness and a sensation of an impending faint (syncope). It is episodic, lasting for a few seconds to minutes. Pathophysiologically, it is due to decrease in cerebral blood flow, due to an underlying cardiovascular disorder.
2. *Disequilibrium:* It refers to a sense of imbalance involving the legs and the trunk, without a sensation in the head. It is seen in cerebellar ataxia and multiple sensory deficit syndromes. The cerebellar diseases are cerebellar degeneration or a tumour in or near the cerebellum. The multiple sensory deficit syndromes involve abnormalities in various proprioceptive systems like visual, auditory disorders and peripheral neuropathy. The patient may complain of dizziness at night.
3. There may be a group of patients who complain of ill-defined light-headedness which the patient finds difficult to define. Such patients usually suffer from anxiety or depression.

VESTIBULAR DISORDER: VERTIGO

Vertigo is a cardinal symptom of vestibular disease. Hence, it is essential to understand the neuro-anatomy and physiology of the vestibular system before analysing the symptoms of vertigo.

Anatomy and Physiology of the Vestibular System

The end organ of the vestibular system consists of 3 semi-circular canals and otolith apparatus (utricle and saccule) on either side, situated in the bony labyrinth of the inner ear. It is concerned with the detection of head position, head movement and control of the vestibulo-ocular reflex (VOR). This reflex automatically compensates for any movement of the head with an equal and opposite movement of the eyes.

The paired vestibular nuclei, situated in the medulla and lower pons receive neural input from three sensory systems—vestibular, visual (retina to occipital cortex) and the somato-sensory system (information from the skin, joints, and muscle receptors). The vestibular nuclei transmit the information to the

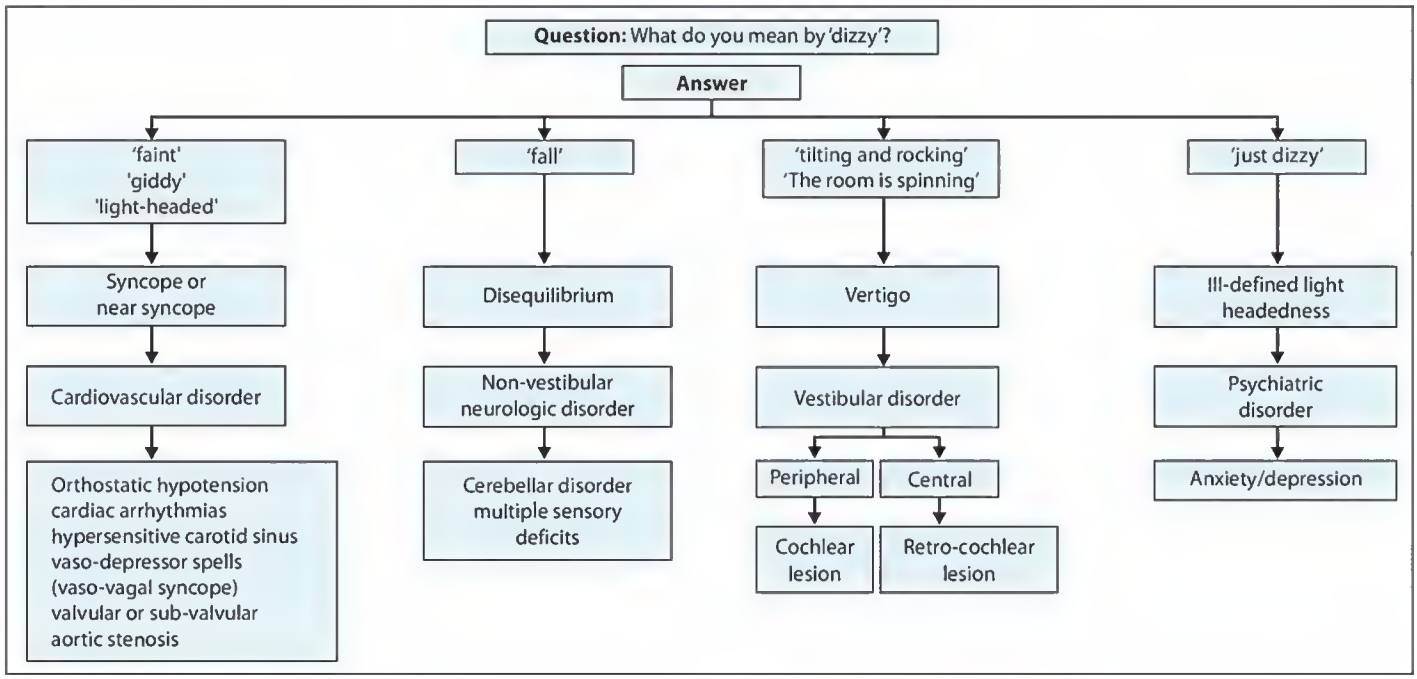


Figure 1: Approach to patient with 'dizziness'.

upper brainstem (nuclei of III, IV and VI cranial nerves), cerebellum, cerebral cortex and spinal cord through neural projections (**Figure 2**).

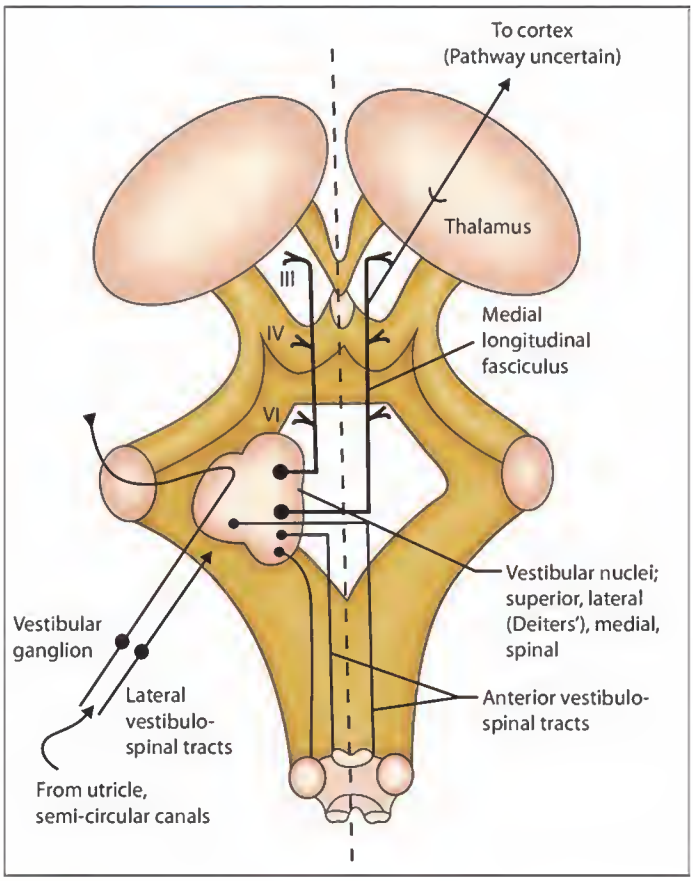


Figure 2: Connections of the vestibular system.

The projection of the vestibular nuclei to the nuclei of the III, IV and VI cranial nerves is essential for VOR. This reflex maintains visual stability during head movement. Lesions of these pathways result in nystagmus. The vestibulo-cerebellar connection helps in modulation of VOR. The abnormal activation and dysfunction of vestibulo-spinal pathway results in postural imbalance and vestibular ataxia. Vertigo itself is due to disturbance of cortical projections. The associated nausea and vomiting are due to activation of the reticular formation and the vomiting centre in the medulla.

Vertigo may be due to physiological or pathological causes. Physiological vertigo is seen in normal individuals with unfamiliar head movements, unusual head and neck position or following spinning.

Pathological vertigo results from lesions of the visual, somatosensory or vestibular system. Visual vertigo is caused by incorrect eye-glasses, and extra-ocular muscle paresis. Somatosensory vertigo is due to myelopathy or peripheral neuropathy and is rarely seen in isolation.

The most common cause of pathological vertigo is vestibular dysfunction. If may involve the end organ (labyrinth), the nerve or central connections. Vertigo is associated with jerk nystagmus frequently accompanied by nausea, postural unsteadiness and gait ataxia.

Clinical Manifestations

Depending on the frequency and duration of attacks, vertigo can be classified into 3 clinical types: prolonged spontaneous attacks, recurrent spontaneous attacks and recurrent positional vertigo. The lesion may be central or peripheral and can be differentiated as shown in **Table 1**.

Prolonged Spontaneous Attacks of Vertigo

This occurs when due to unilateral loss of vestibular function. The vertigo is acute in onset, may last for days and is aggravated by head movement. The patient prefers to sit upright with the head still or to lie with the intact side down. On movement the patient may fall towards the affected side. The vertigo is associated with nausea, vomiting and malaise. This type of vertigo may be peripheral or central. Common causes of this type of vertigo include acute labyrinthine/vestibular dysfunction due to infection, trauma or ischaemia, brainstem or cerebellar infarction/haemorrhage, multiple sclerosis and brainstem tumours/vascular malformations.

Table 1: Features of Peripheral vs Central Vertigo

Sign/Symptoms	Peripheral	Central
Direction of associated nystagmus	Unidirectional; fast phase opposite lesion	Bidirectional or unidirectional
Purely horizontal nystagmus without torsional component	Uncommon	Common
Vertical or purely torsional nystagmus	Never present	May be present
Visual fixation	Inhibits nystagmus and vertigo	No inhibition
Severity of vertigo	Marked	Often mild
Direction of spin	Towards fast phase (away from lesion)	Variable
Direction of fall	Towards slow phase	Variable
Duration of symptoms	Finite (minutes, days, weeks) but recurrent	May be chronic
Tinnitus and/or deafness	Often present	Usually absent
Associated CNS abnormalities	None	Extremely common (e.g., diplopia, dysarthria, hiccups, cranial neuropathies, ataxia, hemi-sensory loss or even paralysis)
Common causes	None, BPPV, infection (labyrinthitis), Meniere's disease, neuronitis, ischaemia, trauma, toxins	Vascular, demyelinating disease, neoplasm

CNS = Central nervous system, BPPV: Benign paroxysmal positional vertigo.

The vestibulopathy can be identified by the head thrust test. Head thrust test is a bed-side test of horizontal VOR. With the patient's head held by the examiner's hand he/she is asked to focus on the examiner's nose. The head is then quickly moved about 10° to one-side. In patients with normal vestibular function the VOR results in the movement of the eye in the direction opposite the head movement, so that the patient's eye remain fixed on the examiner's nose after the sudden movement. The test is repeated in the opposite direction. Loss of VOR will prevent eye movement opposite to the direction of head movements on the affected side.

Recurrent Spontaneous Attacks of Vertigo

The vertigo is sudden, temporary and reversible due to impairment of labyrinthine function. The vertigo of vascular origin like transient ischaemic attacks (TIA) lasts for minutes, whereas, that due to disease of the inner ear may last for hours. The common causes of recurrent spontaneous vertigo include Meniere's disease, autoimmune inner ear disease, syphilitic labyrinthitis, migraine equivalent and vertebro-basilar TIA.

Meniere's Syndrome

This disease is due to recurrent unilateral labyrinthine dysfunction associated with signs and symptoms of cochlear disease. It is characterised by severe vertigo, vomiting, tinnitus, fluctuating and progressive hearing loss with spontaneous recovery over hours to days. The age of onset is 40 to 60 years and the underlying pathology is endolymphatic hydrops due to inflammatory, autoimmune, traumatic or idiopathic aetiology.

Positional Vertigo

Positional vertigo is precipitated by the movement of the head either to the right or to the left from the recumbent position, triggering the vestibular pathway. The peripheral type of positional vertigo is more common than that of central origin and the differentiating features are shown in **Table 2**.

Table 2: Peripheral vs Central Positional Vertigo

	Peripheral	Central
Latency[a]	3-40 seconds	Immediate vertigo and nystagmus
Duration	< 1 min	May persist longer
Fatiguability[b]	Yes	No
Habituation[c]	Yes	No
Intensity	Severe vertigo, marked nystagmus	Mild vertigo, less intense nystagmus
Reproducibility[d]	Variable	Good
Mechanism	Debris moving in semi-circular canal	Damage to central VOP

a = Time between attaining head position and onset of symptoms
b = Disappearance of symptoms with maintenance of offending position
c = Lessening of symptoms with repeated trials
d = Livelihood of symptom production during any examination session

Benign Paroxysmal Positional Vertigo (BPPV)

BPPV is characterised by sudden onset of a peripheral vestibular syndrome with no auditory component. The vertigo occurs when the patient rolls to the side on lying down, or while gazing upwards, or bending forwards. The episode lasts for 10 to 20 seconds. BPPV occurs in bouts lasting for a few days or weeks and may recur after several weeks or months.

BPPV can be caused by head injury, stapes surgery, otitis media, labyrinthine ischaemia and viral infection of the ear. Occasionally, the cause is not obvious. The diagnosis is confirmed by standard positional testing test (Dix-Hallpike test).

Dix-Hallpike Test

With the patient seated, the examiner turns the head of the patient 45° to one-side. Next, the examiner moves the patient to the supine position with tilted head and open eyes. He slightly extends the neck so that the chin moves upwards. The latency, duration and direction of nystagmus is noted along with that of vertigo.

Central Positional Vertigo

Rarely, positional vertigo may be due to lesions near the fourth ventricle affecting the vestibular nuclei or the cerebellar vermis. The common causative lesions are multiple sclerosis, cerebellar tumours and atrophy.

Psychogenic Vertigo

The vertigo develops gradually, increasing with associated anxiety and terminates abruptly. Organic vertigo occurs abruptly and disappears gradually. Psychogenic vertigo is sometimes called phobic postural vertigo, associated with panic attacks or agoraphobia (fear of large open spaces or crowds). The vertigo is not associated with nystagmus or vomiting. Most patients adapt to being 'house-bound', whereas in organic vertigo patients attempt to function in spite of the incapacity.

APPROACH TO THE PATIENT

The first step in the diagnosis of dizziness and vertigo is to take a detailed history focussing on the meaning of 'dizziness'. Does it suggest 'faintness', sense of imbalance, light headedness or a sensation of spinning? This is followed by general medical examination, which should focus on the presence of orthostatic hypotension, cardiac arrhythmias, visual acuity and examination of the musculo-skeletal system for evidence of arthritis and impairment of gait. The neurological examination is done with particular reference to the VIII nerve (vestibular and cochlear component).

Provocative tests to induce cerebral ischaemia or vestibular dysfunction may be necessary where the patient is vague in the description of 'dizziness'. These tests include the Valsalva manoeuvre inducing orthostatic hypotension, and forced hyperventilation which decreases cerebral blood flow.

Vestibular dysfunction is demonstrated by a simple 'head shaking nystagmus test'. The patient is asked to close his eyes and bend his head down 30°. The head is oscillated horizontally 20 times. Elicitation of nystagmus after the manoeuvre suggests vestibular imbalance. Further evaluation of vestibular dysfunction is essential to determine the side of the lesion, the type of lesion and to distinguish central from peripheral lesions. The standard tests include head thrust test, Dix-Hallpike test and electro-nystamography. If a central aetiology is suspected, MRT is mandatory.

MANAGEMENT OF VERTIGO

Treatment of acute vertigo consists of bed rest for 1 to 2 days and use of anti-vertiginous drugs. These drugs give

symptomatic relief in acute vestibulopathy (Meniere's syndrome, vestibular neuritis), acute brain-stem lesions near the vestibular nuclei and prevent motion sickness. These are also used in frequent attacks of vertigo, vomiting and severex BPPV. The drugs used with their recommended dosages are mentioned in **Table 3**. Surgical procedures like labyrinthectomy, and section of 8th nerve are used in selected patients.

Table 3: Drugs Used in the Treatment of Vertigo

Drug Category	Drugs and Dosage
Anti-histamine	Dimenhydrinate 25 to 50 mg 1 to 2 times per day Meclizine 25 mg three times per day Cyclizine 50 mg daily
Anti-cholinergics	Scopolamine – patch 0.5 mg per day
Phenothiazine	Promethazine 50 mg per day Prochlorperazine 10 mg IM or 25 mg rectally Cinnarizine 25 mg per day
Benzodiazepines	Diazepam 2.5 to 5 mg oral or IV Clonazepam 0.25 mg 1 to 3 times per day
Histamine analogue	Betahistine 16 mg three time a day

IM = Intramuscular; IV = Intravenous.

In chronic and recurrent vertigo, exercises which provoke vertigo may be tried in order to habituate the patient. Patients who are refractory to conventional therapy may benefit from a formal rehabilitation programme, habituation customised programme and use of instruments, like tilt tables.

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2.12 Syncope

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Syncope is a clinical syndrome characterised by sudden, transient loss of consciousness and postural tone followed by spontaneous and prompt complete recovery. It is most often due to transient, self-terminating global cerebral hypoperfusion. Syncope accounts for 1% to 3% of emergency department visits and 1% to 6% of all hospital admissions in the USA . The lifetime risk of a syncopal episode is 50%. Advancing age is an independent risk factor for syncope.

PATHOPHYSIOLOGY

Reduction of blood flow to both cerebral hemispheres or to the brainstem reticular activating system leads to loss of consciousness and postural tone. A positional change from supine to erect causes a shift of 300 to 800 mL of blood from the thoracic cavity to the lower extremities. This is well tolerated in normal individuals without any compromise in cerebral blood flow which is maintained within a narrow range due to cerebrovascular autoregulation. Loss of autoregulatory mechanisms or depletion of blood volume will cause a fall in cerebral blood flow. Older patients and patients with hypertension or aortic valve disease tend to have syncope with a relatively small decrease in systemic blood pressure.

DIFFERENTIAL DIAGNOSIS

The first step in the assessment of syncope is to make a correct diagnosis, ruling out other disorders with a similar presentation, especially transient loss of consciousness.

A seizure is a common differential diagnosis. The presence of an aura, cry and tonic-clonic movements are suggestive of a seizure. Unconsciousness lasting more than 5 minutes, disorientation after the event and slowness in returning to consciousness are characteristic of seizures. Clenching of teeth, frothing from the mouth and sphincter incontinence are more commonly seen with seizures. In dizziness, pre-syncope, and vertigo there is no loss of consciousness. Drop attacks present as a sudden fall without loss of consciousness or warning and with immediate recovery. Concussions, metabolic disturbances, intoxications and psychogenic pseudoepilepsy and cataplexy also have to be excluded.

Syncope is often precipitated by exercise, pain, cough, micturition, defaecation or a stressful event. A pre-syncopal prodrome consisting of weakness, light-headedness, sweating and palpitations may precede the loss of consciousness. Episodes rarely occur in the supine position and are often brought on by sitting or standing. Some limb jerking may be seen in 15% of patients during a syncopal event.

CAUSES OF SYNCOPE

Common causes of syncope are listed in **Table 1**. Based on the underlying mechanism, syncope can be divided into different categories. Neurally mediated syncopes are the commonest cause of syncope. This type of syncopal event usually occurs in the standing position and is mediated by reflex mechanisms causing changes in vascular tone, heart rate or both. It is frequently recurrent and commonly precipitated by a hot or crowded environment. Episodes are often preceded by pre-syncopal prodrome lasting seconds to minutes, and rarely occur in the supine position. The two common variants include: vasovagal (e.g. in response to micturition, cough or defaecation) and carotid sinus syncope. Syncope associated with pain, neuralgia, or panic and episodes associated with exercise (without heart disease) are also included in this category. Reflex-mediated syncope does not carry an increased risk of cardiovascular morbidity or mortality.

Table 1: Causes of Syncope

Neurally-Mediated Syncope
Vasovagal (common faint)
Situational: cough, sneeze, laughter, micturition, defaecation, excessive heat, venipuncture (needle or blood phobia), post-parandial
Valsalva induced (weight lifting, brass instrument playing)
Carotid sinus syncope
Glossopharyngeal neuralgia
Post-exercise
Orthostatic Hypotension
Autonomic failure
Primary autonomic failure syndromes (e.g. pure failure, multiple system atrophy, Parkinson's disease with autonomic failure) and Shy-Drager syndrome
Secondary autonomic failure syndromes (e.g. diabetic neuropathy, amyloid neuropathy)
Use of medications (anti-hypertensives, vasodilators, negative chronotropes).
Volume depletion (e.g. haemorrhage, diarrhoea, Addisonism, diuretics)
Alcohol abuse
Postural intolerance syndromes
Neurologic
Migraine
Vascular steal syndromes
Transient ischaemic attacks
Arrhythmias
Sinus node dysfunction (including bradycardia/tachycardia syndrome)
Atrioventricular conduction system disease
Paroxysmal supraventricular and ventricular tachycardias
Inherited syndromes (e.g. long QT syndrome, Brugada syndrome, short QT syndrome, arrhythmogenic right ventricular dysplasia)
Implanted device (pacemakers, defibrillator) malfunction
Structural Cardiac or Cardiopulmonary Disease
Acute myocardial infarction/ischaemia
Obstructive valvular disease
Obstructive cardiomyopathy
Acute aortic dissection
Pericardial disease/tamponade
Pulmonary embolus/pulmonary hypertension
Psychiatric Disorders

Orthostatic hypotension is a drop in systolic blood pressure of 20 mmHg or in diastolic pressure of 10 mmHg within 3 minutes of standing. It is considered clinically important if the reduction in blood pressure is sustained at or beyond 3 minutes and the original symptoms are reproduced during active or passive standing. This occurs when the autonomic nervous system is incapacitated either as a result of age-related physiologic changes, use of certain medications (anti-hypertensives, vasodilators and negative chronotropes), volume depletion, primary autonomic failure or secondary autonomic failure due to diabetes mellitus, amyloidosis or alcohol abuse. Orthostatic hypotension is more common in the elderly because of blunted barorecepter responses resulting in the failure of compensatory cardio-acceleration.

APPROACH TO SYNCOPE

An algorithm for the evaluation of a patient with syncope is shown in **Figure 1.** In the absence of a diagnostic gold standard, history, physical examination and electrocardiography (ECG) are the cornerstones for the assessment of syncope and their combined diagnostic yield is about 80%.

The first step is to differentiate syncope from the other causes of transient loss of consciousness, and the next step is to separate benign causes of syncope from potentially sinister ones. The clinical features suggestive of specific causes of syncope are shown in **Table 2.** Serious causes of syncope, such as critical aortic stenosis, aortic dissection, pulmonary embolism, visceral bleeding, dysrrhythmias, myocardial ischaemia and subarachnoid haemorrhage should first be ruled out. In elderly persons a sudden faint without an obvious cause should arouse the suspicion of a complete heart block or tachyarrhythmia.

Table 2: Clinical Features Suggestive of Specific Causes of Syncope

Type of Syncope	Clinical Features/Precipitants
Neurally mediated syncope	Posture change, coughing, defaecation, micturition, strong emotions, fear, prolonged standing, crowded hot places
Carotid sinus syncope	With head rotation, pressure on carotid sinus (as in shaving, tight collars, tumours)
Syncope caused by orthostatic hypotension	After standing up, autonomic neuropathy
Cardiac syncope	Structural heart disease, during exertion or while in supine position, palpitations, acute or old myocardial infarction, family history of sudden death
Cerebrovasular syncope	
Subclavian steal syndromes	Arm exercise
Aortic dissection	Differences in blood pressure or pulse in both arms
Psychiatric illness	Frequent syncope with somatic symptoms but no heart disease

A complete physical examination should be performed in all patients. Special attention should be paid to the following aspects (**Table 3**):

1. Vital signs: Fever may point to an infection. Blood pressure must be measured in both arms and in supine and standing positions. Tachycardia may be due to pulmonary embolism, hypovolaemia, tachyarrhythmia, or an acute coronary syndrome. Bradycardia may point towards a cardiac conduction defect, an acute coronary syndrome or a vasodepressor cause of syncope.
2. Cardiac rhythm and auscultatory signs of aortic stenosis, pulmonary hypertension, idiopathic hypertrophic subaortic

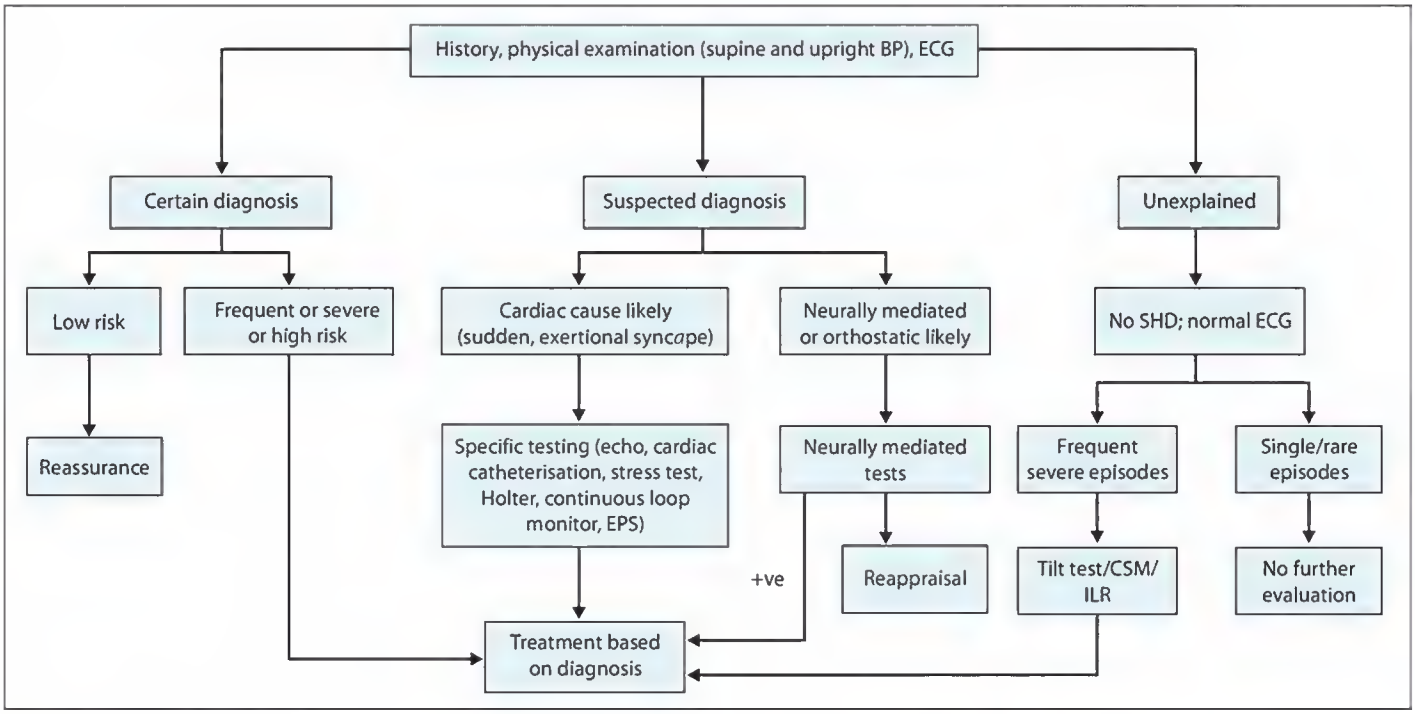


Figure 1: Appraach ta syncape.

BP = Blaad pressure; ECG = Echacardiagraphy; SHD = Structural heart disease; ILR = Insertable loap recarder; EPS = Electraphysialagical studies; CSM = Caratid sinus massage

stenosis, myxomas, congestive heart failure (CHF) or aortic dissection.

3. Carotid bruits, cranial nerve deficits, motor and sensory deficits.
4. Signs of trauma which may be secondary to syncope or may have caused syncope.

Table 3: Clinical Features Suggestive of the Cause of Syncope

Clinical Feature	Likely Cause of Syncope
Orthostatic hypotension	Drugs like beta blockers and clonidine, diabetes mellitus
Murmur changes with position	Atrial myxoma or thrombus
Headache, diplopia, dysarthria, pain in occipital region	Subarachnoid haemorrhage, transient ischaemic attack, subclavian steal, basilar migraine
Tachypnoea, syncope in a bedridden patient or in the post-operative period	Pulmonary embolism
Asymmetric pulses, back pain	Dissecting aneurysm of aorta, subclavian steal
Elevated jugular venous pressure	Right heart failure, myocardial ischaemia, tamponade or pulmonary embolus
Abdominal tenderness or mass in an elderly patient	Visceral bleed (abdominal aortic aneurysm)
Amenorrhoea in young women, uterine spotting, adnexal tenderness	Ruptured ectopic pregnancy

INVESTIGATIONS

Cardiac Evaluation

Electrocardiography

ECG should be performed in all patients. Abnormal ECG findings occur in about 90% of patients with cardiac-induced syncope, but in only 6% of patients with neurally mediated syncope.

Exercise testing

Indicated if clinical evaluation suggests ischaemic heart disease or exercise-induced tachyarrhythmia. In patients with exertional syncope, echocardiography should be done first to exclude hypertrophic cardiomyopathy.

24-hour Holter monitoring

Indicated when symptoms suggest arrhythmic syncope (palpitations with syncope, episodic unconciousness with no prodrome) or in those with an abnormal ECG, heart disease or unexplained syncope.

Continuous-loop event monitoring

Recommended if no arrhythmias are found and no syncope occurs during 24-hour Holter monitoring; in patients with recurrent syncope and a normal heart; syncope of unexplained cause; heart disease and abnormal ECG.

Electrophysiologic studies (EPS)

Patients with underlying organic heart disease and non-diagnostic prolonged ECG monitoring, and those whose hearts are normal, but ECG show conduction disturbances should undergo electrophysiologic studies.

Signal-averaged electrocardiography

The signal-averaged ECG filters multiple QRS complexes to uncover late potentials arising from abnormal myocardium, where re-entry and ventricular tachycardia may arise. It is useful for selecting patients for electrophysiologic studies when ventricular tachycardia is suspected in the presence of ischaemic heart disease.

Head-up tilt table (HUTT) testing

It is recommended in patients with recurrent syncope in whom a cardiac cause of syncope, including arrhythmias has been excluded and in patients with unexplained recurrent syncope. It may also be indicated for differentiation of convulsive syncope from epilepsy and for assessment of recurrent and unexplained falls.

HUTT testing uses changes in position to reproduce the symptoms of the syncopal event by inducing bradycardia or hypotension suggestive of reflex mediated syncope. Pharmacologic augmentation with isoproterenol intravenously or low dose nitroglycerine is required in patients who have a high pre-test probability of neurally mediated syncope but a negative result on a passive tilt table test.

The test should not be performed in pregnant patients. In men older than 45 years of age and women older than 55 years of age should have stress testing before HUTT. A positive HUTT can be used to reassure the patients about the usually benign nature of the diagnosis. It can also be used to minimise, if not eliminate, the unnecessary use of anti-epileptic drugs.

Carotid sinus massage

Carotid sinus massage should be carried out when carotid sinus syncope is suspected (**Table 2**). The contraindications for carotid sinus massage are recent myocardial infarction, transient ischaemic attacks, or stroke, ventricular fibrillation, ventricular tachycardia or a carotid bruit.

Psychiatric Evaluation

Syncope due to psychiatric disorders is usually seen in younger patients with no heart disease and does not cause injury. Such events may be precipitated by anxiety, panic, or major depression as a neurally-mediated response.

Laboratory Studies

The yield of most routine laboratory studies is low. A haemogram, blood glucose levels, serum electrolytes, renal function tests, cardiac enzymes, brain natriuretic peptide (BNP) levels and urinalysis may provide diagnostic clues in selected patients.

Imaging Studies

Computed tomography (CT) and magnetic resonance imaging (MRI) of the head may be useful in the presence of head trauma or neurological deficits.

SYNCOPE IN SPECIFIC SITUATIONS

Exercise-Related Syncope in Young Athletes

Exercise-related syncope, while generally a benign event, can signal sudden death in young adults. It occurs either during or immediately after a period of exercise. Causes of exercise-related syncope include hypertrophic cardiomyopathy , aortic stenosis, critical coronary artery disease, right ventricular dysplasia,

congenital coronary artery anomaly, prolonged QT syndrome, high grade atrioventricular block, idiopathic ventricular tachycardia, hyponatraemia, hypoglycaemia and hyperthermia (heat stroke).

The commonest cause is neuro-cardiogenic syncope. In all cases of unexplained exertional and pre-exertional syncope, an echocardiogram followed by a stress test should be done. In such individuals, temporary restriction from vigorous activity should be considered. Reassuring clinical features are non-recurrent syncope, occurring after exercise, no family history and a normal cardiac examination with ECG, echocardiogram, and stress test being normal. Such athletes may return to vigorous activity with an appropriate follow-up plan.

Syncope in Elderly Patients

Syncope in elderly patients portends a poor prognosis. The high mortality rate is due to co-morbidites. Common risk factors for syncope in the elderly are susceptibility to situational syncope, polypharmacy and adverse drug effects on heart rate, intravascular volume and vascular tone (with use of beta-blockers, calcium-channel blockers anti-arrhythmics, diuretics and anti-depressants) resulting in orthostatic hypotension. Several entities including carotid sinus hypersensitivity, aortic stenosis, myocardial infarction, arrhythmias and transient ischaemic attacks are more common in the elderly.

HOSPITALISATION AND PROGNOSIS

Indications and risk factors for hospital admission in patients with syncope are listed in **Table 4**.

Table 4: Indications for Hospital Admission in Patients with Syncope

Definitely hospitalise patients with 'high risk' who meet any of the following criteria:
History of coronary artery disease, congestive heart failure or ventricular arrhythmia
History of chest pain
Physical signs of congestive heart failure, valvular disease or focal neurological deficit or new stroke, acute pulmonary embolism, aortic dissection
Electrocardiographic findings showing ischaemia, arrhythmia, increased QT interval or bundle-branch block
Cardiac devices (pacemaker or defibrillator) with dysfunction

Strongly consider hospitalising patients with 'intermediate risk' who meet any of the following criteria:
A history of exertional syncope even in the absence of any evidence suggestive of aortic stenosis or left ventricular outflow obstruction
Sudden recurrent loss of consciousness with injury
Age >70 years
Haematocrit <30 mL/dL
Frequent syncope, suspected cardiac disease or arrhythmia (e.g. use of medications associated with torsades de pointes)
Moderate-to-severe orthostatic hypotension
Congenital heart disease
Family history of sudden death

Patients with 'low risk' may be evaluated as outpatients
No structural heart disease and a normal ECG
Suspicion of psychogenic pseudosyncope
Neurally mediated syncope

TREATMENT

The treatment of a patient with syncope depends on the underlying mechanism and identification of precipitants and contributory factors.

1. For neurally mediated syncope, orthostatic hypotension and carotid sinus syncope, patient education is the foundation of treatment. Patients must be reassured about the benign nature of the problem. Measures that help abort an incipient attack include sitting with the knees drawn, squatting, lying with raised legs and performing physical counter-pressure manoeuvres, sustained hand grip and isometric exercises to raise blood pressure. The importance of assuming an upright posture slowly should be emphasised in patients with orthostatic hypotension.

   For long-term prevention of attacks, adequate fluid and salt intake should be advised. In some cases, fludrocortisone for volume expansion and other drugs such as midodrine (an alpha-1 agonist with vasopressor activity) may be needed. Compression stockings may also be beneficial. Medications must be reviewed carefully to eliminate drug associated with hypotension. Beta-blockers are no longer recommended for vasovagal syncope. For situational syncope, it might be possible to ameliorate or avoid triggers. Avoidance of tight collars, neck ties, and abrupt neck movements is prudent advice for carotid sinus syncope, but cardiac pacing may be recommended in some.

2. Syncope related to arrhythmias requires specific therapy. Supraventricular tachycardia may respond to drugs or radiofrequency ablation. Bradyarrhythmias require pacing. Implantable defibrillators are helpful in the treatment of both ventricular tachyarrhythmias and bradyarrhythmias.

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2.13 Coma

B Vengamma

INTRODUCTION

The prompt diagnosis and effective management of a patient with altered consciousness, especially coma, is one of the difficult tasks faced by a physician. The physiologic components that govern conscious behaviour include *content* (sum of cognitive and affective mental function) and *arousal* (appearance of wakefulness). The physiology of arousal emerges from the action of the reticular activating system (RAS), a poorly localised network of cells in the rostral brainstem and the diencephalon. The RAS receives stimuli from the environment via the somatosensory pathways, the autonomic pathways and limbic system inputs. In turn, the RAS stimulates the brain, activating the cortex. Because it is a diffuse network of cells, there is no single transmitter system involved with the RAS. Physicians try to induce arousal in comatose patients by stimulating the RAS. Although the term 'coma' is derived from the Greek word *koma*, meaning a deep (presumably unarousable) sleep, a range of anatomical sites, causes, and mechanisms may be involved in producing coma.

While consciousness is the state of awareness of the self and the environment, coma is its exact opposite. Between the extreme states of consciousness and coma stand a variety of altered states of consciousness (**Table 1, Figures 1 and 2**).

DIAGNOSTIC APPROACH

Early, appropriate diagnosis of the cause of unconsciousness is important because, several causes of coma (e.g. subdural, epidural haematomas, hypoglycaemia) can be fatal if not recognised early and treated. The approach to a comatose patient begins with a good, detailed history and clinical examination.

Functional abnormality of the brain causes unconsciousness, either due to bilateral dysfunction of the cerebral hemispheres or damage or depression of the RAS or due to metabolic damage.

The key to making a correct diagnosis in coma consists of accurate interpretation of a limited number of physical signs that reflect the integrity or impairment of various levels of the brain. The abnormal findings of the examination indicate whether the cause of altered consciousness is supratentorial (starts rostrally and evolves caudally), subtentorial (starts focally in the brainstem), metabolic (produces from the onset signs of diffuse or multifocal dysfunction), or psychiatric (lacks signs of physiologic brain dysfunction (**Table 2**).

Table 1: Various States of Consciousness

Alert
A state where the patient is fully responsive and able to interact with the physician

Confusion
A state of disorientation in time, place and person or situation resulting in bewilderment, perplexity and lack of orderly thought

Delirium
An acute confusional state that may sometimes be marked by periods of irritability and hallucinations

Obtundation
A lesser state of decreased arousal with some responsiveness to touch or voice

Lethargy (somnolence)
Arousal, though diminished, is maintained spontaneously or with repeated light stimulation

Stupor
A state of severely impaired arousal with some responsiveness to vigorous stimuli

Coma
Total or near total unresponsiveness, i.e., the total absence of awareness of self and environment even when the subject is externally stimulated

Vegetative state
Wakefulness accompanied by lack of cognitive function. The patient opens eyes spontaneously in response to verbal stimuli

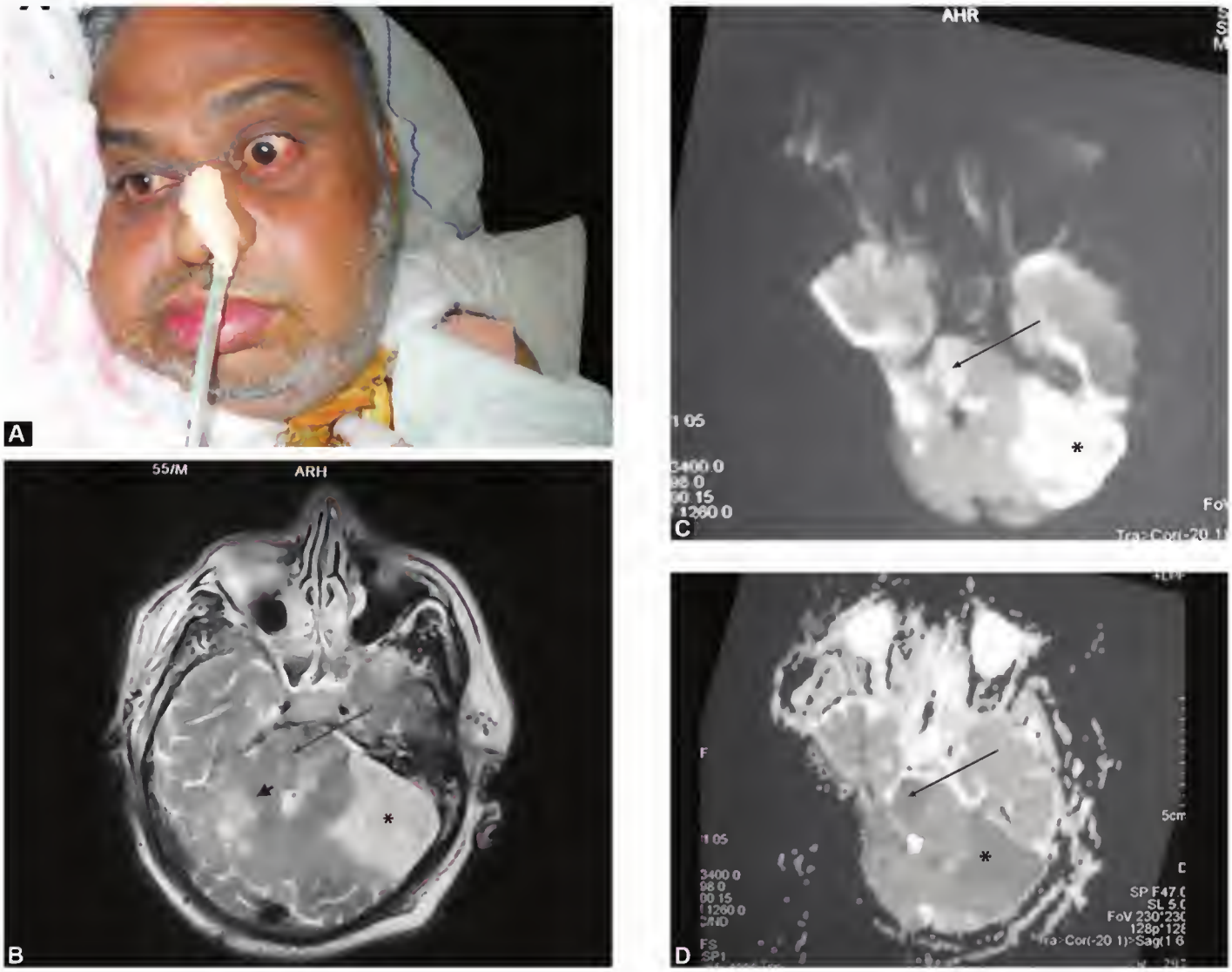
Akinetic mutism
Silent, alert appearing immobility with retainment of sleep wake cycles and absent mental and spontaneous motor activity

Apallic syndrome
Absent neocortical function with relatively intact brainstem function

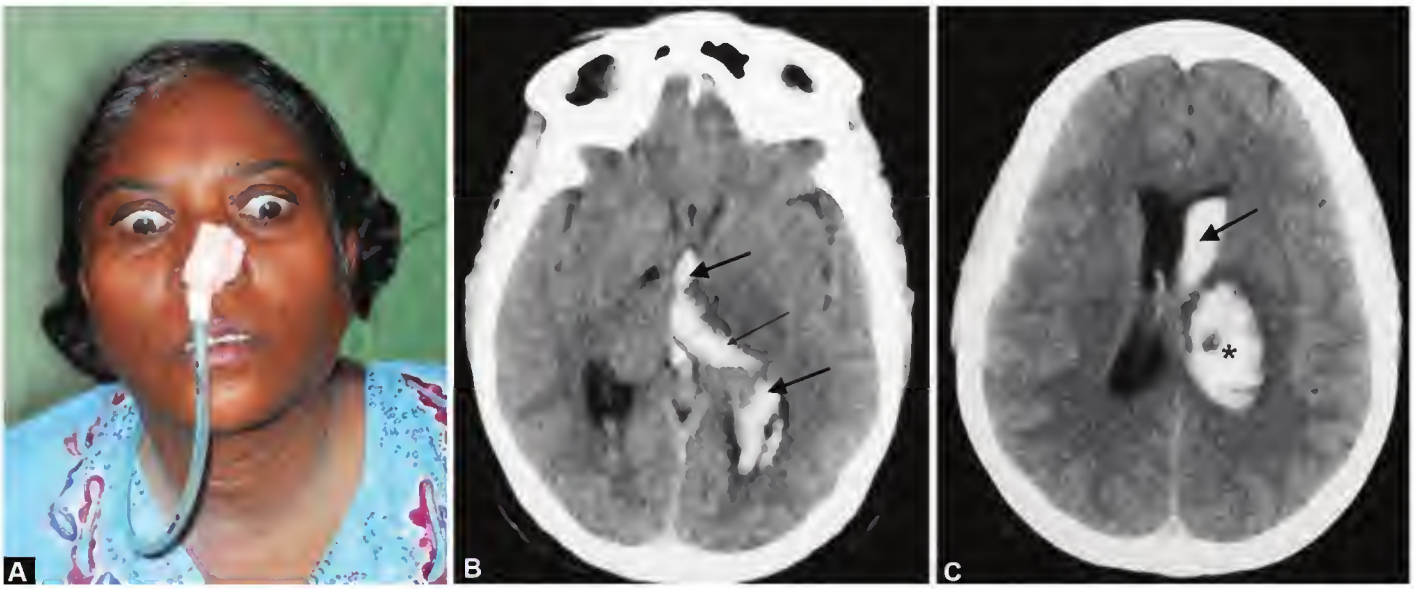
Locked-in syndrome
A state in which weakness of all four limbs is associated with lower cranial nerve paralysis; but, the patient manifests signs of being appropriately aware of himself and his environment and communicates with vertical eye movements

Inattention
A state where a person looks alert or even hyperalert. The eyes are open and the person is looking around, but cannot complete a simple task.

Abulia
A state where the patient is essentially quiet and has complete lack of spontaneity. It is usually associated with bilateral frontal lesions. There is perseveration or repetitive movement



Figures 1A to D: Locked-in state. (A) A patient with weakness all four limbs with lower cranial nerve paralysis. The patient manifests signs of being appropriately aware of himself and his environment and communicates with vertical eye movements. (B) MRI brain (T2 weighted axial image) showing hyperintensity in the pons (arrow). (C) Hyperintensity in right middle cerebellar peduncle (arrow head) and in left cerebellar hemisphere (asterisk). (D) Diffusion weighted images (upper panel right) apparent diffusion coefficient map (lower panel, right) showing acute infarction in pons (arrow) and cerebellum (asterisk).



Figures 2A to C: Clinical photograph showing a delirious patient (A) NCCT head of the same patient showing acute haematoma in the left thalamus (thin arrow) and corona radiate (asterisk) extending into lateral and third ventricles (thick arrow) (B and C).

HISTORY AND GENERAL EXAMINATION

The history has to be obtained from an eyewitness account or from a paramedic who had resuscitated the patient. Recent events or preceding illnesses that lead to the comatose state should be enquired into. A history of trauma, drug or alcohol use is important. Possible ingestion of medications should be evaluated. History regarding any psychiatric illness which might be responsible for coma should also be elicited.

Bedside clinical evaluation should begin with measurement of blood pressure. If blood pressure is elevated, careful evaluation for signs of an acute ischaemic or haemorrhagic stroke, or increased intracranial pressure is indicated. Certain breathing patterns are very classical and facilitate anatomical localisation in a comatose patient (**Figure 3**). Patients with *Cheyne-Stokes breathing* manifest rapid shallow breathing to the point where there is a cessation of breathing and apnoea. Thereafter, there is an abrupt spontaneous return of respirations with deep sighs, and the cycle repeats. This type of pattern is seen in head injury and metabolic conditions. *Biot's breathing*, seen in lesions of medulla oblongata (e.g. head trauma, stroke) refers to an abnormal breathing pattern consisting of rapid, shallow breaths followed by periods of apnoea. This pattern is often confused with *ataxic breathing*. While in Biot's breathing clusters of similar sized breaths occur, in ataxic breathing pattern, the respirations are completely irregular in both rate and rhythm mimicking dysmetria of the extremities. *Kussmaul breathing* is characterised by a deep, rapid breathing rate and is seen in metabolic acidosis. *Apneustic breathing* usually seen in trauma or stroke involving the medulla oblongata is an irregular breathing pattern which is intermixed with irregular periods of apnoea (**Figure 3**). It is important to look for other tell-tale signs of a traumatic injury, an infectious disease process, or an ingestion of drugs leading to the comatose state. Signs of liver cell failure should also be looked for. Odour of the breath (e.g. alcohol ingestion; acetone like in diabetic ketoacidosis DKA, hepatic encephalopathy) can sometimes be helpful.

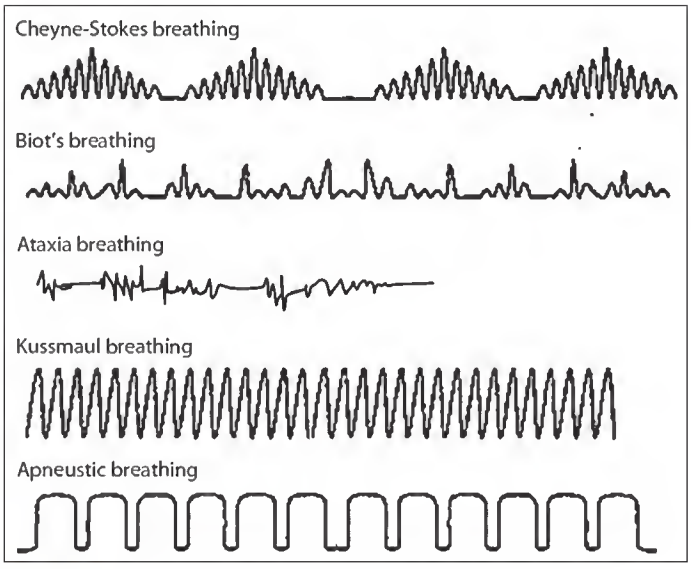


Figure 3: Various breathing patterns and their graphical depiction.

Table 2: Differential Characteristics of State and Causing Sustained Unresponsiveness

Supratentorial mass lesions compressing or displacing the diencephalon or brainstem initiating signs usually of focal cerebral dysfunction
Signs of dysfunction progress rostral to caudal
Neurologic signs at any given time point to one anatomic area (e.g. diencephalon, midbrain-pons, medulla)
Motor signs often asymmetrical
Subtentorial masses
History of preceding brainstem dysfunction
Localising brainstem signs precede or accompany onset of coma and always include oculovestibular abnormality
Cranial nerve palsies usually present
'Bizarre' respiratory patterns common and usually appear at onset
Metabolic Causes
Confusion and stupor commonly precede motor signs
Motor signs are usually symmetrical
Pupillary reactions are usually preserved
Asterixis, myoclonus, tremor, and seizures are common
Acid-base imbalance with hyper- or hypo-ventilation is frequent
Psychiatric Unresponsiveness
Lids close actively
Pupils reactive of dilated (cycloplegics)
Oculocephalics are unpredictable: oculovestibulars physiologic (nystagmus is present)
Motor tone is inconsistent or normal
Eupnoea or hyperventilation is usual
No pathologic reflexes are present
EEG is normal

EEG = electroencephalogram.

NEUROLOGIC EXAMINATION IN COMATOSE PATIENTS

The neurologic examination in comatose patients, should include all parts of the traditional neurologic examination except, perhaps, the gait. But there is an emphasis on the level of arousal, the cranial nerve examination, and the motor movements. Examination of the pattern of reflexes is also important. Most importantly, the general principle underlying the neurological examination in a comatose patient is pattern recognition. The first step involves assessing the level of consciousness (**Table 1**), traditionally using the Glasgow coma scale (GCS), which is composed of eye movements, motor movements, and spontaneous language.

The fundoscopic examination gives information about raised intracranial pressure and pathology. Blink test or menace reflex should be done which gives an idea about visual fields. Other aspects of cranial nerve examination include pupils, eye movements, sensory component of Vth cranial nerves and motor component of VIIth cranial nerves and the gag response as part of cranial nerves IXth and Xth.

The pupils tend to be small and reactive and absent corneal oxycephalic reflex indicates metabolic injury. Symmetry of the pupils is very important in differentiating nonstructural versus structural injuries. Midbrain pupils, reflective of midbrain injury, tend to be midposition, fixed, slightly irregular with intact reaction to light. In contrast, small, thin, pin-point pupils that do not react to light are suggestive of pontine injury and can also be seen in opiate intoxication. Asymmetry in the form of unilateral dilatation of the pupil in a comatose patient suggests unilateral third nerve palsy which could be an indication of an uncal herniation, which is essentially a sign that the brain is swelling to the point where the cortex is impinging on the

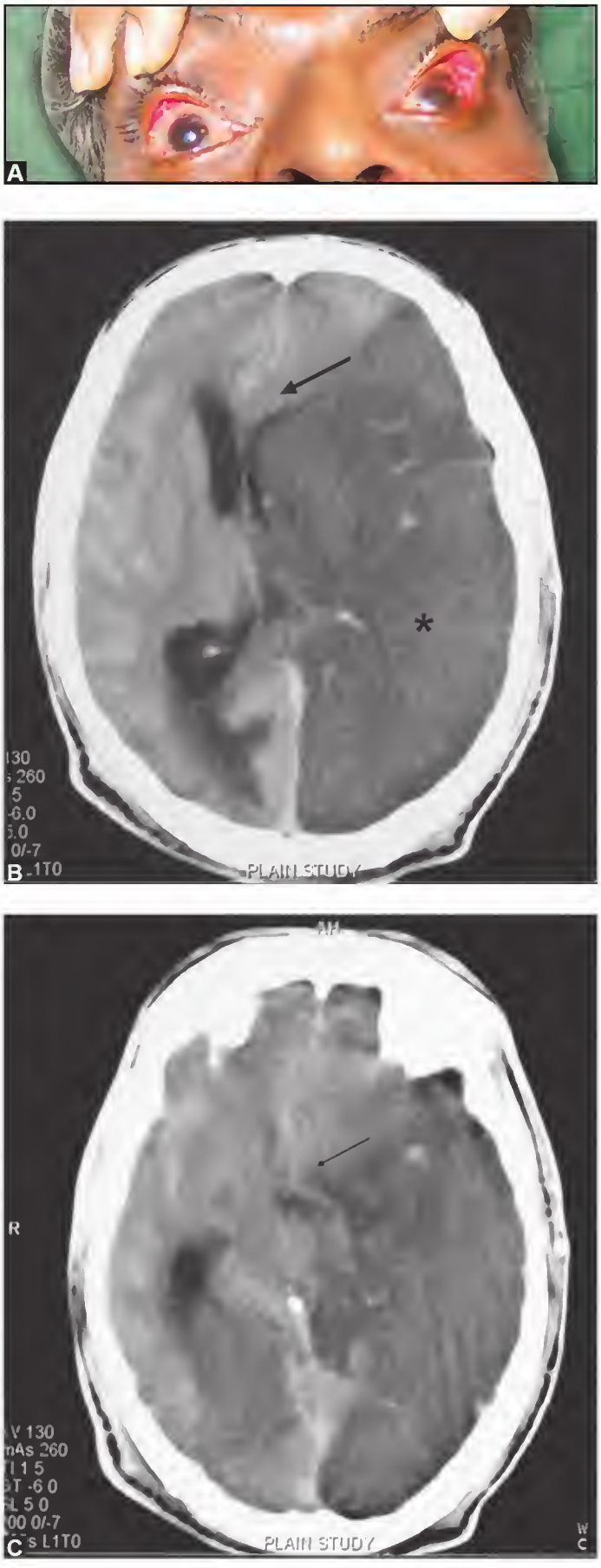
brainstem and the third cranial nerve as it exits from the brainstem itself; such patients may need urgent neurosurgical intervention (**Figures 4A to C**).

In the examination of eye movements, it is most important to open the eyelids and to see where the eyes are at rest. Any gaze deviation away from the side that is weak is essentially a sign of a hemispheric lesion. If it is towards the side of the hemiparesis, it suggests that the lesion is at the brainstem, specifically in the pons or the cerebellum. If the primary gaze is downwards it suggests that the lesion might be within the midbrain, or perhaps even something pushing down onto the midbrain that is causing the eyes to stay down. Spontaneous eye rolling movements suggest bilateral hemispheric dysfunction as seen in metabolic encephalopathies. *Ocular bobbing* (the eyes, when at rest, dip down and come back to the resting position) and *ocular dipping* (the eyes bounce up and have a slow downward phase) are pathognomonic of pontine injury.

The occurrence of eye movements that are spontaneous and saccadic in motion, and rolling eye movements on opening the eyelids excludes the possibility of the patient being in true coma because saccadic movements involve a level of awareness beyond just a level of arousal.

Due to the oculocephalic reflex, normally the eyes move contralateral to the side of head movement. Absent oculocephalic reflex is an indication of bilateral hemispheric injury. This test should be avoided in patients with suspected neck injury. Oculovestibular reflex, also known as a cold caloric test, is another way to gauge brainstem integrity specifically for pontine and cerebellar function. The test is done by keeping the patient's head end of the bed elevated at 30°, instilling about 60 cc of ice water in each ear with a butterfly catheter and a syringe. The normal response involves a tonic movement of the eyes towards and fast saccades away from the side of stimulation. Bilateral absent fast movements are a sign of bihemispheric injury. An asymmetrical response suggests brainstem dysfunction. A negative response to the caloric test (no eye movements) indicates loss of brainstem integrity. In an awake person or a person who is not comatose, this test induces saccadic movements, nausea, and probably also vomiting.

In the motor examination, asymmetry of the response and assessment of tone helps in localisation. The best way to look for this is to look for spontaneous movements, i.e. sit at the bedside and just watch the patient for some time to see whether or not there is any movement whatsoever. If there are no spontaneous motor movements, the patient may be asked to move a limb on verbal commands, Still, if there is no perceptible movement, then sequentially more noxious stimuli are applied to try and induce a response. If the response elicited is a classical decorticate or decerebrate posturing, it has prognostic significance. Decorticate posturing, indicative of a hemispheric injury and damage to corticospinal tracts, is characterised by adduction and flexion of the arms with wrists and fingers flexed on the chest. The legs are extended and internally rotated with plantar flexion of the feet. Lesions located around the red nucleus cause decerebrate rigidity which is characterised by internal rotation (adduction) and extension of arms, pronation of the wrists and finger flexion. The legs are extended with forced plantar flexion of feet. In severe cases, ophisthotonus may be present.



Figures 4A to C: Clinical photograph showing asymmetry of pupils. (A) NCCT head (axial images) of the same patient showing sub-acute infarct in the left cerebral hemisphere (asterisk) with relative sparing of frontal lobe causing subfalcine herniation arrows (B and C).

DIFFERENTIAL DIAGNOSIS

Causes of coma can be classified as structural, non-structural, toxic or metabolic (**Tables 3 and 4**). Among all patients in coma, one-third have an evident structural lesion. The differential diagnosis tends to be trauma or vascular in origin; meningitis, encephalitis, tumours, or hydrocephalus. Toxic or metabolic injuries include post-cardiac arrest with global hypoxic ischaemic injury exposure to a toxin such as carbon monoxide, drugs and electrolyte disorders. Psychiatric disorders, can present as coma. They can be difficult to differentiate from metabolic causes.

Table 3: Some Causes of Coma

Focal disease
- Trauma (contusion, ICH)
- Non-traumatic ICH
- Ischaemic stroke
- Infection (abscess, subdural empyema, focal encephalitis)
- Tumour
- Demyelination (multiple sclerosis, acute demyelinating encephalomyelitis)

Non-focal disease
- *Trauma (elevated ICP, diffuse axonal injury)*
- *Vascular syndrome*
  - Subarachnoid haemorrhage
  - Aneurysm in posterior fossa with mass effect
  - Hypoxic-ischaemic encephalopathy
  - Stroke (focal strokes with non-focal presentations, posterior fossa infarct with mass effect, hydrocephalus)
  - Hypertensive encephalopathy (including ecclampsia)
- *Infection (meningitis, diffuse encephalitis)*
- *Tumour-related*
  - Tumour (brainstem invasion, posterior fossa mass effect, elevated ICP, hydrocephalus)
  - Paraneoplastic syndromes (brainstem and limbic encephalitis, vasulitis)
  - Toxic and metabolic (**Table 4**)
  - Withdrawal syndromes
  - Nutritional deficiencies (Wernicke's encephalopathy, pellagra)
  - Disordered temperature regulation
- *Seizure (postictal state, non-convulsive status epilepticus)*
- *Others*
  - Basilar migraine
  - TGA
  - TTP
  - Sleep deprivation
  - Situational (i.e. ICU psychosis)
  - Psychiatric (conversion, depression, mania, catatonia)

ICH = Intracranial haemorrhage; ICP = Intracranial pressure; ICU = Intensive care unit; TGA = Transient global amnesia; TTP = Thrombotic thrombocytopaenic purpura.

Table 4: Toxic and Metabolic Causes of Coma and Confusion

Sedatives, hypnotics
- Opiates
- Benzodiazepines, barbiturates, and other sedatives
- Tricyclic anti-depressant agents
- Phenothiazines, butyrophenones

Stimulating exogenous toxins
- Amphetamines, cocaine
- Phencyclidine
- Methylphenidate

Agents causing metabolic acidosis
- Aspirin
- Ethyl alcohol, methanol, ethylene glycol, and other hydrocarbons

Metabolic disorders
- Diabetes mellitus: Hyperglycaemia (diabetic ketoacidosis, hyperosmolar coma), hypoglycaemia
- Thyroid disease (myxoedema, thyroid storm)
- Renal failure (uraemia, dysequilibrium syndrome)
- Electrolyte abnormalities (dehydration and volume contraction, hyponatraemia, hypercalcaemia
- Acid-base disorders
- Hepatic failure: Hyperammonaemia
- Hypoadrenalism
- Hypoxia, hypercarbia
- Hereditary metabolic disorders (i.e. porphyria, carbamoyl-transferase deficiency carrier state)

Withdrawal syndromes
- Alcohol withdrawal
- Benzodiazepine and other sedative withdrawal

Table 5: Approach to the Initial Assessment and Management of Coma

Stabilisation
- Airway control
- Oxygenation and ventilation
- Adequate circulation (includes avoidance of hypotension in stroke)
- Cervical stabilisation

Immediate therapies given to all patients
- Thiamine 100 mg IV
- Dextrose 50%, 50 cc IV (may be held if immediate finger-stick glucose check establishes adequate serum glucose)
- Naloxone 0.4 to 2.0 mg IV (may be repeated)
- Life-threatening conditions to be considered early
- Elevated intracranial pressure: Head CT
- Meningitis, encephalitis, or both: Consider LP, blood cultures
- Myocardial infarction: ECG
- Hypertensive encephalopathy: Early therapy
- Status epilepticus: EEG
- Acute stroke: Consider thrombolytic therapy

IV = Intravenous; CT = Computed tomography; EEG = Electroencephalogram

MANAGEMENT

The approach to the initial assessment and management of patients in coma is depicted in **Table 5**. The specific management depends on the underlying cause. At the time of initial evaluation, it is necessary to assess the ABCs namely, assessing the adequacy of airway; ensuring that the patient's breathing is spontaneous and adequate; and that the circulation to the brain and other organs is adequate.

While carrying out the initial stabilisation and laboratory testing, it is important to treat treatable conditions immediately. Correction of hypoglycaemia and the administration of thiamine can be life saving. Hypoglycaemia suppresses the RAS and leads to a metabolic coma. But this is quickly reversed once the glycaemic levels are restored to normal. It is also important to administer intravenous thiamine to prevent Wernicke's encephalopathy. In the appropriate situation, naloxone for

opiate overdosage or flumazenil for benzodiazepine poisoning, should also be considered.

PROGNOSIS

Coma due to toxic or metabolic causes has a better prognosis than that due to a structural lesion, with the exception that traumatic injury fares better than anoxic injury. In other words, patients who have had cardiac arrest tend to have poorer outcome than patients who had a structural injury secondary to trauma. Clinical signs that are important for prognosis include the motor component of the GCS, the duration of coma (which is really a duration of lack of eye-opening) and other signs of brainstem damage.

Certain electroencephalogram (EEG) patterns are helpful in assessing prognosis in patients with coma. Alpha coma, which looks like a normal alpha rhythm but in an unarousable patient carries a higher mortality rate especially with hypoxic injury or traumatic brain injury. The EEG may be sensitive to external stimuli and may not reflect brainstem function and is influenced by sedative drugs that are routinely used in such patients. Somatosensory evoked potentials can be used for testing the brainstem and are helpful in patients with a traumatic injury or anoxic injury. When measured within 5 to 7 days, bilaterally absent cortical somatosensory evoked potentials are strongly associated with the instance of vegetative state or death. Neuroimaging, especially computed tomography (CT), is useful in differentiating structural lesions but, its overall predictive value is less when compared to electrophysiologic tests or even the clinical examination itself.

In coma due to hypoxic ischaemic injury, patients who have a preserved light reflex, motor response is either flexor or extensor and have spontaneous eye movements have better survival. In head injuries, patients with concussion (defined as a loss of consciousness for less than six hours) and those with a normal CT tend to have a good outcome. When a patient has a loss of consciousness for greater than six hours, axonal shearing or diffuse external injury is likely. Magnetic resonance imaging (MRI) shows changes axonal retraction balls and micro-haemorrhages. Long-term recovery for these patients is very variable. Cognitive deficits, motor and behavioural dysfunction persist, and these patients tend to do poorly as far as functional recovery goes.

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Section 3

Diagnostic Imaging

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3.1 Conventional Radiology

Ashu Seith Bhalla, Ankur Gadodia

INTRODUCTION

Since the discovery of X-rays by Roentgen in 1895, conventional radiology has played a vital role in the diagnosis and management of patients affected by various diseases. Newer imaging techniques, such as ultrasound, computed tomography and magnetic resonance imaging, have reduced the role of conventional radiographs in several clinical scenarios. However, conventional radiology still remains of great value, particularly in diseases of chest, musculoskeletal system, contrast studies of gastrointestinal tract and fistulograms. This is owing to simplicity of the procedure, low cost, easy reproducibility and low radiation dose. Advent of digital radiography has further enhanced the quality and reproducibility of the conventional radiographs. The spectrum of the imaging findings of various pathologies is vast and a full discussion of the same is beyond the scope of this chapter. Hence, a brief summary of the present role of conventional radiology and approach to common diseases classified on an organ system basis is discussed below.

CHEST RADIOLOGY

Chest radiograph is one of the most frequently performed radiological examination constituting about 50% to 60% of the workload of any hospital or imaging centre. The standard chest radiograph is an erect posteroanterior (PA) projection (**Figure 1**). Additional radiographic views and their role is summarised in **Table 1**. Normally there are five different densities, in any radiograph lungs, bones, soft-tissues like heart and diaphragm, fat and muscles. Because of the difference in the coefficient of absorption of the X-rays which depends on the atomic number of the elements and density of the tissues, lungs appear black, bones appear white and soft-tissues have an intermediate density. A schematic approach to analysis of the chest radiograph is given in **Table 2**.



Figure 1: Normal chest radiograph (posteroanterior PA view).

Table 1: Additional Chest Radiographic Views and Their Role

Projection	Role
Lordotic projection	Middle lobe collapse/consolidation, apical opacity obscured by clavicle
Lateral decubitus	Small pleural effusion
Lateral	Localise mediastinal masses, posterior basal consolidation
Expiratory films	Air trapping, small pneumothorax
Anteroposterior	Sick recumbent patient intensive care unit (ICU patients)

Table 2: Suggested Scheme for Viewing the PA Radiograph

Patient information sheet
Technical assessment: Centring, inspiration, exposure
Mediastinum: Trachea, aorta, pulmonary arteries, superior vena cava
Lungs: Lucency, localised/generalised abnormalities, hidden areas
Heart: Position, size, configuration
Hila: Density, shape, position
Bones and soft tissues
Diaphragm: Position, outline
Pleural space

Important Signs in Chest Radiology

1. Silhouette sign

Described by Felson and states that "An intra-thoracic radio-opacity, if in anatomic contact with a border of heart or aorta, will obscure that border. An intra-thoracic lesion not anatomically contiguous with a border or a normal structure will not obliterate that border". This sign is useful in detection and localisation of mediastinal and pulmonary diseases. For example, right middle lobe pathology will obliterate the right heart border (**Figure 2**).

2. Hilum overlay sign

Described by Felson and helps in distinguishing enlarged heart from anterior mediastinal mass. Hilum is seen through the mediastinal mass, whereas with enlarged heart, the hilum is displaced laterally. If the bifurcation of the main pulmonary artery is >1.25 cm medial to the lateral border of the cardiac Silhouette, it is suggestive of a mediastinal mass. If the pulmonary artery arises from the lateral heart border, this favours an enlarged heart.

3. *Air-bronchogram*

Branching, tubular air lucency representing a bronchus or bronchiole passing through airless lung parenchyma produces air bronchogram and is seen in lung disease unlike pleural/mediastinal disease (**Figure 3**).



Figure 2: Silhouette sign. Chest radiograph (PA view) showing lingular lobe consolidation silhouetting the left cardiac border. Diaphragm is not silhouetted by the consolidation.



Figure 3: Air-bronchogram in a patient with pulmonary oedema. Chest radiograph (PA view) demonstrates air within the bronchial tree visible due to surrounding airless lung parenchyma.

Pattern Recognition in Chest Radiology

Felson popularised a pattern recognition approach to lung lesions on the basis of classifying them as either alveolar or interstitial. Important features and causes of the alveolar or interstitial lesions are described in **Table 3**.

Atelectasis/Lung Collapse

Collapse is defined as partial or complete loss of the lung volume. Radiographic appearance depends on degree and mechanism of collapse. Signs of collapse may be considered as direct or indirect (**Table 4**).

Table 3: Features and Aetiology of Basic Lung Patterns as Seen on Chest Radiograph

Patterns	Features	Causes
Airspace/ Alveolar pattern (**Figure 4A**)	Poorly defined nodular lesions (4-10 mm) Coalescence Air-bronchogram	Pulmonary oedema Exudate (pneumonia) Pulmonary haemorrhage Malignancy (bronchioalveolar carcinoma, lymphoma) Aspiration
Interstitial (**Figure 4B**)	Reticular Nodular (well-defined, homogeneous and variable sized) Reticulo-nodular	Interstitial lung disease, e.g. Sarcoidosis Miliary tuberculosis Pneumoconiosis



Figure 4A: Air space (alveolar) pattern. Chest radiograph (PA view) shows homogeneous opacity in left lower zone with ill-defined margins of diaphragm see 4B.

Pulmonary Disease

Infections

Pneumonia: Pneumonia is one of the most frequent causes of morbidity and mortality, and chest radiograph plays an important role in the detection and management of patients with pneumonia. The term lobar pneumonia refers to infection that predominantly involves the alveolar space and thus, produces uniform homogeneous opacification of partial or complete segments of lung and occasionally an entire lobe.

Bronchopneumonia is usually multifocal and infection is centered in distal bronchioles. Radiologically, broncho-pneumonia is characterised by bilateral heterogeneous, scattered alveolar opacities. An air bronchogram is usually absent. *Streptococcus pneumoniae* (common cause of community-acquired pneumonia) causes lobar pneumonia whereas *Staphylococcus aureus* and Gram-negative organisms (causes nosocomial infection) produce bronchopneumonic pattern. *Klebsiella pneumoniae* and *Streptococcus pneumoniae* cause lobar pneumonia with bulging fissures. Round pneumonia is cause by *S. pneumoniae* and *S. aureus*. Viral pneumonia is common in infants and children but unusual in adults and produces interstitial pattern on chest radiographs.

Table 4: Signs of Lung Collapse (Figure 5)

Direct Signs	Indirect Signs
Displacement of interlobar fissure	Elevation of hemidiaphragm
Loss of aeration	Mediastinal displacement
Crowding of vessels and bronchi	Hilar displacement
	Compensatory overinflation



Figure 4B: Interstitial pattern. Chest radiograph (PA view) demonstrates coarse reticulonodular opacities in bilateral lung fields.

Pulmonary tuberculosis: The radiological features in pulmonary tuberculosis have been divided into primary and post-primary or reactivation TB.

Primary tuberculosis: Primary TB has two components: parenchymal lesion and extension of the lesion to the lymph nodes. Enlarged hilar or mediastinal nodes (right paratracheal, subcarinal and aorto-pulmonary window) are the radiological hallmark of this form. It may heal completely or leave a calcified focus. Atelectasis of a lobe or a segment is a frequent finding.

Post-primary tuberculosis: Most common sites are apical and posterior segments of the upper lobes and superior segments of lower lobe. Parenchymal lesions are the hallmark of this form



Figure 5: Left lower lobe collapse in a 20-year-old male. Chest radiograph (PA view) demonstrates wedge-shaped left retrocardiac opacity (arrow) with hyperinflation of the left lung.

of TB (ill-defined patchy opacities, linear striations, subsequently nodular and reticular appearance due to fibrosis). Single or multiple thick-walled cavities are the hallmark of active TB. Bronchiectasis and bronchostenosis are commonly seen in post-primary tuberculosis occur due to cicatrisation and fibrosis. Broncho-stenosis can produce persistent lobar or segmental collapse or obstructive emphysema or consolidation. Pleural effusion is usually small and loculated. Radiological findings in primary TB are detailed in **Table 5**.

Table 5: Radiological Features of Primary and Post-primary Tuberculosis

Primary Tuberculosis	Post-primary Tuberculosis
Parenchymal consolidation	Local exudative lesion
Lymphadenopathy (**Figure 6A**)	Local fibroproductive lesion
Miliary tuberculosis (**Figure 6B**)	Tuberculoma
Tuberculoma	Cavitation
Airway involvement	Bronchogenic spread
Pleural effusion	Miliary tuberculosis (**Figure 6B**)
	Bronchostenosis
	Pleural disease

Bronchogenic carcinoma

Bronchogenic carcinoma produces a wide range of radiological appearances depending on histology (small cell vs non-small cell), location (central vs peripheral) and stage of the disease (**Figures 7A and B**). Usually peripheral bronchogenic carcinoma is seen as an intrapulmonary mass. This may be quite small, an incidental finding on chest radiograph (solitary pulmonary nodule) and poses a diagnostic challenge to the clinician and radiologist. Features that indicate malignancy include: size more than 4 cm; thick-walled (≥16 mm) cavity; associated hilar mass and lobulated, umblicated or shaggy outline (sunburst appearance). Plain radiographs have tremendous limitation in



Figure 6A: Primary tuberculosis in a 12-year-old female. Chest radiograph (PA view) demonstrates right hilar and paratracheal adenopathy.



Figure 6B: Miliary tuberculosis in a 24-year-old male. Chest radiograph (PA view) shows miliary nodules (1-3 mm) involving bilateral lung fields.

detecting early manifestations of malignancy and lesions less than 5 mm are not visualised on conventional radiographs. Massive hilar or mediastinal adenopathy without lung lesion is seen in small cell carcinoma whereas bronchioloalveolar carcinoma presents as solitary spiculated mass or as bilateral, multiple ill-defined opacities resembling pneumonia.

Hilar Diseases

Hilum as seen on chest radiograph comprises of proximal pulmonary artery, major bronchi, pulmonary veins and lymph nodes (**Figure 1**). Lymph nodes are not visualised unless



Figure 7A: Peripheral bronchogenic carcinoma in a 72-year-old male smoker. Chest radiograph (PA view) shows ill-defined spiculated mass in the right upper zone with destruction of anterior end of right 2nd and 3rd ribs.



Figure 7B: Central bronchogenic carcinoma with lung collapse in a 60-year-old male. Chest radiograph (PA view) shows ill-defined spiculated left hilar mass with collapse of the left upper lobe.

enlarged. Hilar enlargement can be due to lymphadenopathy (**Figure 8**) or dilated pulmonary artery. Differential diagnosis of unilateral and bilateral hilar enlargement is mentioned in **Table 6**.

Table 6: Differential Diagnosis of Hilar Enlargement

Unilateral Hilar Enlargement	Bilateral Hilar Enlargement
Lymphadenopathy	Sarcoidosis (**Figure 8**)
Infective (TB, Histoplasma, Mycoplasma)	Lymphoma
Carcinoma lung	Lymphangitis carcinomatosis
Lymphoma	Infective (TB, Histoplasma)
Pulmonary artery	Pulmonary artery dilatation
Pulmonary embolus	Pneumoconiosis (Silicosis)
Aneurysm	
Post-stenotic dilatation	



Figure 8: Sarcoidosis in a 30-year-old female. Chest radiograph (PA view) demonstrates bilateral hilar and right paratracheal adenopathy. Lung fields are normal.

Pleural Diseases

Pleural effusion

Pleural effusion is one of the most common abnormalities of the pleura. The radiographic appearances depend on the quantity of the fluid and posture of the patient. A minimum 75 mL of fluid is required to see the fluid above the dome of diaphragm on the lateral view; and a minimum of 175 mL is needed to obliterate costophrenic angle in upright erect film. Lateral decubitus radiograph can detect 10 to 20 mL of fluid.

Pleural effusion produces a homogeneous opacity with concave border facing the hilum producing characteristic meniscus sign. The upper margin of the opacity extends higher laterally than medially (**Figure 9**). Massive fluid obliterates the hemidiaphragm and cardiac border. Further increase in fluid produces shift of the heart and mediastinum, and even inversion of the hemidiaphragm. Supine radiographs are less sensitive in demonstrating pleural effusion and the signs on a supine radiograph are a veil-like opacity over the lung with well preserved vascular shadows; loss of outline of the ipsilateral hemidiaphragm; blunting of the costophrenic angle; clear demarcation of the lateral lung margin from the chest wall; widening of the paraspinal soft tissues; apparent elevation of the hemidiaphragm and poor visibility of the vessels behind the diaphragm. Absence of air-bronchogram and visualisation of the vessels differentiates pleural effusion from pulmonary oedema and massive pneumonia.



Figure 9: Pleural effusion in a 16-year-old male. Chest radiograph (PA view) demonstrates right pleural effusion. Note the upper margin of the opacity is concave and extends higher laterally than medially.

Pneumothorax

Pneumothorax is defined as the presence of air between parietal and visceral pleura. Radiological features include increased translucency with no intervening vessels, and underlying lung margin demarcated by visceral pleura (**Figure 10**). A small pneumothorax is best seen on expiratory film. Inner margin is usually convex as compared to cysts, bulla or cavities which have concave margin towards the chest wall. Pneumothorax in supine film may show any of these signs; relative translucency, increased sharpness of the adjacent diaphragm or mediastinum, deep and tongue-like costophrenic sulci, depression of the ipsilateral diaphragm and simultaneous visualisation of anterior sulcus and dome of diaphragm.

Mediastinal Diseases

A mediastinal mass has its base towards mediastinum, well-defined margins and produces an obtuse angle with the mediastinum. Air-bronchogram is absent. Boundaries of the mediastinum are shown in **Figure 11** and common differential diagnosis in **Table 7**.

Table 7: Differential Diagnosis of Mediastinal Masses

Anterior	Middle	Posterior
Lymphadenopathy (Lymphoma, TB)	Lymphadenopathy	Neurogenic tumour
	Carcinoma bronchus	Paravertebral abscess
Germ cell tumours	Aortic aneurysm	Dilated oesophagus (Achalasia)
Thymoma	Bronchogenic cyst	



Figure 10: Pneumothorax in a 40-year-old male. Chest radiograph (PA view) shows increased right lung translucency with underlying lung margin demarcated by visceral pleura (arrow).

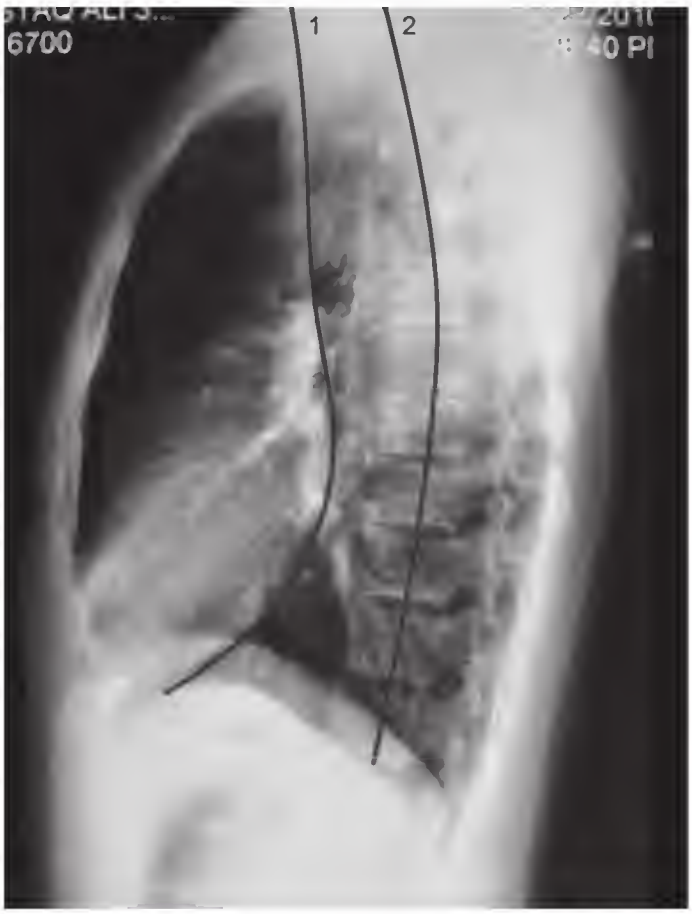


Figure 11: Demarcation of the mediastinum. Line 1 extends along the back of the heart and along anterior margin of the trachea. Line 2 connects a point 1 cm behind the anterior margin of the body of the dorsal vertebrae. Mediastinum anterior to line 1 is anterior mediastinum, between lines 1 and 2 is middle and posterior to line 2 is posterior mediastinum.

CARDIOVASCULAR SYSTEM

Conventional cardiac radiology is supplemented by 2D echo, cardiac CT, catheter angiography or MRI. However, chest radiographs are extremely valuable in demonstration of the cardiac size, contour (individual chambers) and pulmonary vascularity. Chest radiographs are also commonly used to follow the progress of a disease and its treatment. The following five points help in the diagnosis of the acquired or congenital cardiac conditions. These are cardiac size, pulmonary conus, left atrium, aortic knuckle and pulmonary vasculature. Meticulous analysis of the above points gives some indication of the cardiac abnormality in 60% to 65% cases.

The demonstration of the abdominal aorta and its branches was usually done by digital subtraction angiography done through transfemoral route. However now-a-days vascular tree, either arterial or venous is well demonstrated either by CT angiography or MR angiography.

GASTROINTESTINAL SYSTEM

Plain Radiograph

Plain abdominal radiographs are still commonly performed in the clinical setting of acute abdomen or renal colic. A supine abdomen and an erect chest can be regarded as the basic standard radiographs in the work-up of acute abdomen. The erect chest radiograph is superior to the erect abdominal view for the demonstration of pneumoperitoneum (**Figure 12**).

Three to five fluid levels less than 2.5 cm in length may be normally seen in an erect abdominal radiograph, particularly in the right lower quadrant. However, more than two fluid levels in a dilated small bowel (calibre greater than 2.5 cm) are said to be abnormal, and usually indicate paralytic ileus or intestinal

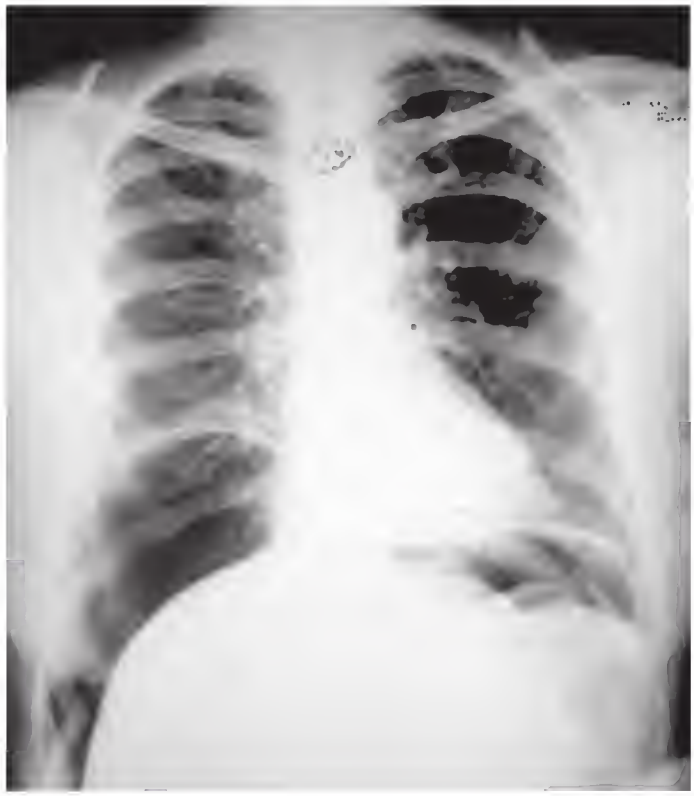


Figure 12: Pneumoperitoneum in a 40-year-old male resulting from perforation of a duodenal ulcer. Chest radiograph (PA view) demonstrates gas under both domes of diaphragm.

obstruction. Demonstration of a zone of transition between dilated and normal/collapsed small bowel is an indicator of mechanical obstruction. Occasionally, plain radiographs can also diagnose the cause of bowel obstruction, like obstructed inguinal hernia, sigmoid volvulus, etc.

Contrast Studies of the Gastrointestinal Tract

The emergence of cross-sectional imaging techniques had a dramatic impact on the imaging of gastrointestinal tract. However, a contrast examination still remains a valuable diagnostic test for evaluating the luminal and subtle mucosal pathologies of the intestinal tract. Barium sulphate, an inert contrast agent comes in a variety of suspensions designed for specific examinations depending on their density and viscosity.

Barium Examinations (Table 8)

1. *Barium swallow:* Barium swallow is the technique of choice for symptoms of the dysphagia, odynophagia, atypical chest pain and gastro-oesophageal reflux. Barium swallow is complementary to endoscopy for oesophagitis and tumours.
2. *Barium meal:* Barium meal is rarely performed with the advent of endoscopy. Barium studies are complementary to endoscopy for most cases of dyspepsia and abdominal pain (peptic ulcer and malignancy). However, they are superior to endoscopy for evaluation of the functional anomalies and submucosal lesions.
3. *Small bowel follow-through:* Indicated in subacute intestinal obstruction, chronic obstruction and inflammatory bowel disease.
4. *Barium enema:* It is used for evaluation of the colonic pathologies. Double contrast study is superior to single contrast for detection of small polypoidal lesions and small ulcerations.
5. *Enteroclysis:* It equires initial placement of a tube in the proximal jejunum prior to barium infusion (**Figure 13**). Enteroclysis is preferred for evaluating subtle mucosal abnormalities, focal small-bowel lesions or to determine the cause of small-bowel obstruction.

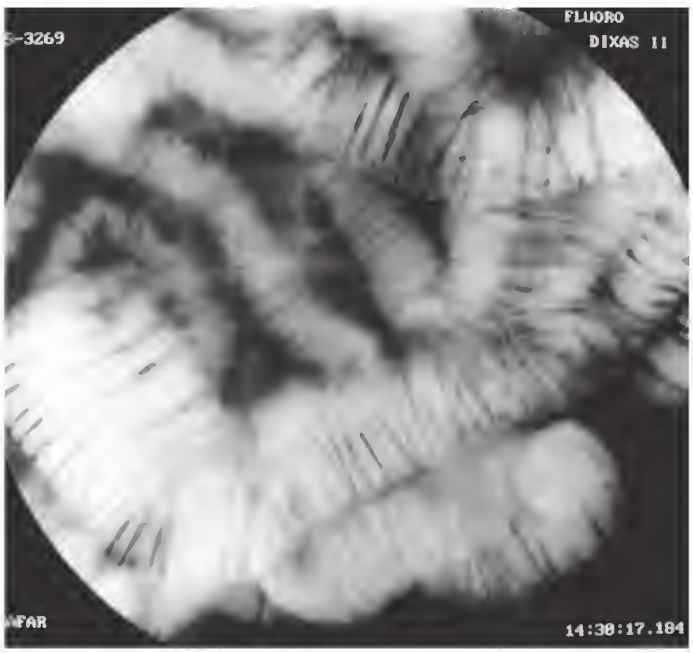


Figure 13: Normal enteroclysis.

Table 8: Contrast Studies of Gastrointestinal Tract: Organs Evaluated and Common Clinical Indications

Contrast Study	Organs Evaluated	Common Clinical Indications
Barium swallow	Oral cavity up to fundus of stomach	Dysphagia, motility disorder (achalasia), carcinoma oesophagus, hiatus hernia, extrinsic compression/ displacement
Barium UGI study	Oesophagus, stomach and duodenum, (single or double contrast techniques)	Epigastric pain, dyspepsia, heart burn, unexplained weight loss, anaemia
Barium meal follow through	Stomach to ileocaecal junction	Tuberculosis, Crohn's disease (**Figure 14**), neoplasm, radiation enteritis, diarrhoea, anaemia/gastrointestinal bleed, partial obstruction
Enteroclysis	Duodenojejunal flexure to ileocaecal junction	Partial small bowel obstruction Crohn's disease-extent, Meckel's diverticulum, malabsorption, tumours of small intestine, occult gastrointestinal bleed
Single contrast barium enema	Colon	Colon obstruction, intussusceptions, fistula, uncooperative/ debilitated patients
Double contrast barium enema	Permits visualisation of mucosal detail	Inflammatory bowel disease (**Figure 15**), polyp

Barium is contraindicated in suspected perforation (causes peritonitis or mediastinitis). Suspected perforation is an indication for use of a water-soluble agent. Post-operative oral

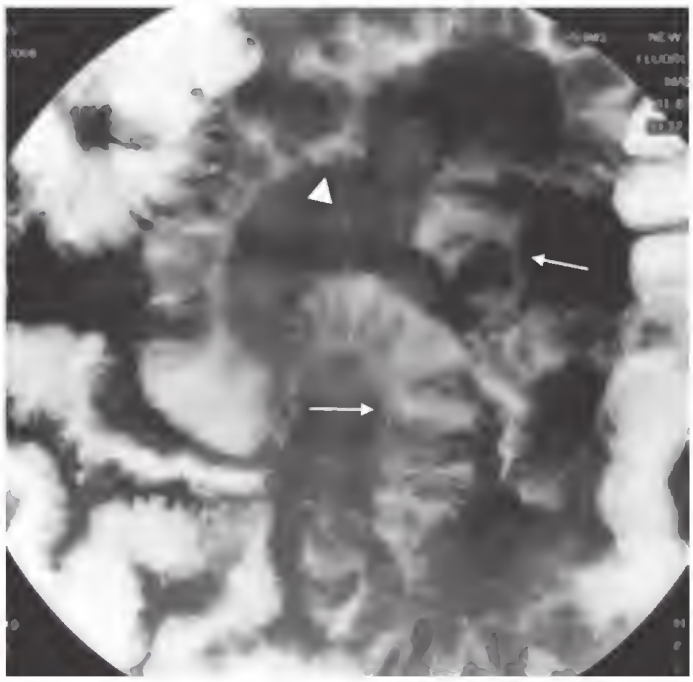


Figure 14: Crohn's disease in a 36-year-old male. Barium meal follow-through shows pseudosacculation involving the jejunum (arrow), longitudinal ulceration involving the mesenteric border (arrowhead).



Figure 15: Ulcerative colitis in a 30-year-old female. Barium enema shows granular mucosal pattern and loss of haustration involving the entire colon.

contrast studies are also done with water soluble agents to look for suspected leaks and patency of anastomosis.

Pattern Recognition in Gastrointestinal Radiology

Following a pattern approach on barium studies facilitates diagnosis of wide spectrum of diseases affecting the alimentary canal (**Table 9**).

Table 9: Features of Basic Patterns as Seen on Contrast Studies of Gastrointestinal Tract

Patterns	Features
Benign stricture	Smooth tapering margin at both ends
Malignant stricture	Irregular, abrupt narrowing, apple core appearance, shouldering at one/ both ends
Extrinsic mass	Intact mucosa, displaced lumen, obtuse angle with luminal surface
Intramural (Submucosal) mass	Intact mucosa, right angle with luminal surface
Mucosal mass	Irregular mucosa with ulcerations, acute angle with luminal surface

Distinction between Small- and Large-bowel Dilatation (Figures 16 and 17)

When a radiograph shows dilated bowel, it is important to determine whether it is small- or large-bowel, or both (**Table 10**).

Table 10: Distinguishing Features between Small- and Large-bowel Obstruction

	Small-bowel Obstruction	Large-bowel Obstruction
Number of loops	More	Less
Distribution of dilated loops	Central	Peripheral
Haustra	Absent	Present
Valvulae conniventes	Seen in jejunum	Absent
Diameter	3-5 cm	≥ 5 cm

Ileocaecal (IC) Tuberculosis

IC TB is the most common form of alimentary tract TB (**Figure 18**). Imaging features of ileocaecal TB are tabulated in **Table 11.**



Figures 16A and B: Small bowel obstruction: Supine (A) and erect (B) radiographs show dilated multiple bowel loops having central position and valvulae conniventes suggestive of small-bowel obstruction. Erect radiograph demonstrates multiple air-fluid levels.



Figure 17: Large-bowel obstruction in a 70-year-old male. Supine radiograph demonstrates gas filled distended large-bowel and caecum. Small-bowel is not dilated due to competent IC valve.

Table 11: Findings of Ileocaecal (IC) Tuberculosis on Barium Examination

Spasm and hypermobility with oedema of the ileocaecal valve
Thickening of an incompetent IC valve with narrowing of terminal ileum (Fleischner sign)
Shallow ulceration
Napkin ring stenoses with a conical, shrunken caecum
Widely open IC valve with fixed and narrowed terminal ileum (Stierlin's sign)
Altered angle of entry of IC junction
Contracted, pulled-up caecum
Skip areas of concentric mural thickening with luminal narrowing in rest of bowel

HEPATOBILIARY SYSTEM

Conventional radiology has no role in the diagnosis of gall-bladder disease. Oral cholecystography has been replaced by ultrasonography, CT and MRI. In liver diseases, ultrasonography, CT, MRI are used to detect focal and diffuse liver diseases. In pancreatic diseases, plain radiograph of abdomen is useful only to demonstrate pancreatic calcification in chronic pancreatitis, but this is also better done using CT. CT, transabdominal and endoluminal ultrasound are most useful in imaging pancreatic pathology and have virtually replaced conventional radiological techniques. Magnetic resonance cholangiopancreaticography shows intra- and extra-hepatic biliary radicals and pancreatic duct and produces images analogous to Endoscopic retrograde cholangiopancreatography ERCP. In majority of cases, ERCP is done for therapeutic purposes only. Similarly percutaneous trans-hepatic cholangiography is no longer used in the diagnosis of biliary obstruction and is used only as a prelude to percutaneous transhepatic biliary drainage.



Figure 18: IC tuberculosis in a 22-year-old male. Barium meal follow-through shows narrowing involving the terminal ileum and IC junction, obtuse angle of entry, contracted caecum and dilatation of terminal ileum.

MUSCULOSKELETAL SYSTEM

Bone and joint radiographs require systematic analysis of bone density, alignment, cortex, medulla, joint space, soft tissue and calcification, and periosteal reaction. The skeletal system may be involved in local (infection, primary tumours) and systemic diseases (endocrine, metabolic marrow pathology, metastatic disease).

Metabolic/Endocrine Disease

Endocrine disorders, such as osteoporosis, osteomalacia, hyperparathyroidism, acromegaly, hyper- or hypo-thyroidism, Cushing's syndrome, pseudohypoparathyroidism, and haemoglobinopathies require skeletal survey. Diseases like hyperparathyroidism and congenital hypothyroidism produce classical radiological changes depending upon the severity. For detection of osteoporosis, bone mineral density by DEXA is the 'gold standard'. Osteomalacia is distinguished from osteoporosis by the presence of looser's zones or insufficiency fractures. Radiological features of common endocrine and metabolic diseases are mentioned in **Table 12**.

Avascular necrosis of the head of femur and other sites is known to occur in steroid therapy, Cushing's syndrome, atherosclerosis, pancreatitis, fat embolism, alcoholism, collagen vascular disease, Caisson's disease, Gaucher's disease and radiation therapy. Radiographs can detect avascular necrosis only late in the course of disease and MRI is the modality of choice for early diagnosis.

Primary Bone Tumours

Broadly bone tumours can be divided into two groups: benign and malignant. Malignant tumours can be primary or secondary (metastatic). Radiographs are the primary imaging modality in diagnosis and characterisation of bone tumours. The

radiographic features that help in characterisation of bone tumours are: site of the lesion (location in the skeleton and in the individual bone); borders (also known as zone of transition); matrix mineralisation (composition of the tumour tissue); pattern of bone destruction (geographic, moth-eaten or permeative); periosteal reaction; adjacent soft tissue, cortical integrity; and multiplicity of the lesions. Benign tumours usually produce well-defined, geographic lytic lesion with sclerotic borders, narrow zone of transition, uninterrupted/solid periosteal reaction, and no soft-tissue mass, whereas malignant lesions demonstrate ill-defined, permeative lytic lesion with wide zone of transition, interrupted periosteal reaction (sunburst/onion skin/Codman triangle) and large soft tissue component.

Table 12: Radiological Features of Common Endocrine and Metabolic Diseases

Osteoporosis	Osteopaenia (prominent in areas of the skeleton rich in trabecular bone, especially in the axial skeleton (vertebrae, pelvis, ribs and sternum) Low-trauma fractures (vertebrae, the distal forearm and the proximal femur)
Hyperparathyroidism (**Figures 19A to C**)	Subperiosteal erosions (radial aspects of the middle phalanges of the index and middle fingers, outer ends of clavicle, symphysis pubis, sacroiliac joints) Intracortical bone resorption Chondrocalcinosis Brown tumours Osteosclerosis (seen in HPT secondary to chronic renal impairment) Metastatic calcification
Rickets (**Figures 20A and B**)	Widening of the growth plate Cupping of the metaphysis Rachitic rosary (expansion of the anterior ends of the ribs) Deformities (genu valgum/varum, coxa vara, Harrison's sulcus, protrusio acetabuli and tri-radiate deformity of the pelvis)
Osteomalacia (**Figure 21**)	Osteopaenia Looser's zones or pseudo-fractures (medial aspect of femoral neck, pubic rami, lateral border of scapula and ribs)
Cushing's disease	Osteoporosis Low-trauma fractures Exuberant callus formation Avascular necrosis of hip

Skeletal Metastasis/Myeloma

Skeletal metastases can be detected by skeletal survey and sensitivity of conventional radiographs in the detection of secondaries in skeletal system is about 60% to 70%. Isotope scanning (99mTc-methyl diphosphonate) is more sensitive but not specific. Osseous secondaries can be osteolytic or osteoblastic. Majority of these are osteolytic; osteoblastic lesions (**Figures 22A and B**) are mainly seen in the carcinoma of the prostate in male and breast malignancy in female. Multiple myeloma produces widespread involvement of the bones having osteopaenia, punched out osteolytic lesions, endosteal scalloping with sparing of the posterior elements and pedicles (Differential diagnosis secondary deposits). The usual sites are spine, skull, ribs, pelvis, long tubular bones and distal ends of the clavicles.



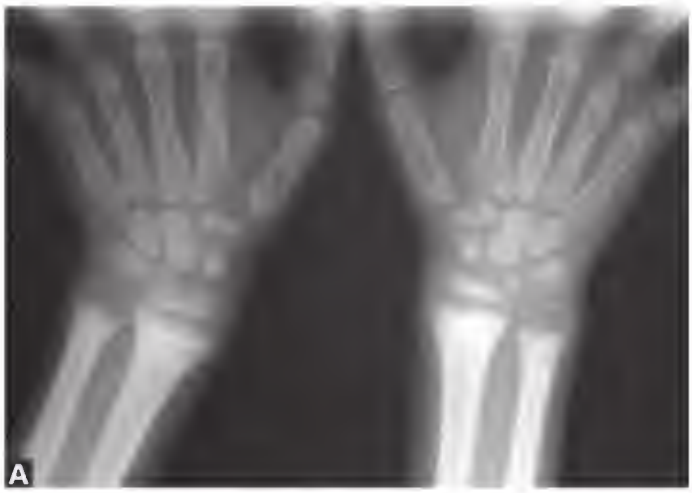
Figure 19A: Primary hyperparathyroidism in a 34-year-old male. Radiograph of hand shows subperiosteal resorption involving the radial margins of the proximal and middle phalanges.



Figure 19B: Radiograph of left hand demonstrates subperiosteal resorption of the proximal and middle phalanx and expansile lytic lesion (brown tumour) involving the middle phalanx of the 4th digit.



Figure 19C: Lateral skull radiograph demonstrates granular texture of the bone (salt and pepper pot appearance) with loss of definition of the both inner and outer table.





Figures 20A and B: Rickets in a 4-year-old male child. (A) Radiograph of bilateral wrist demonstrates diffuse osteopaenia. Growth plate of bilateral radius is widened with metaphyseal cupping, fraying and splaying. (B) Chest radiograph shows widening of the costochondral junction of the ribs suggestive of rachitic rosary.



Figure 21: Osteomalacia in a 48-year-old female. Radiograph of pelvis shows reduced bone density and fuzzy trabecular pattern. Note the presence of Looser's zone (pseudo fracture) involving bilateral pubic rami (arrows).

Arthritis

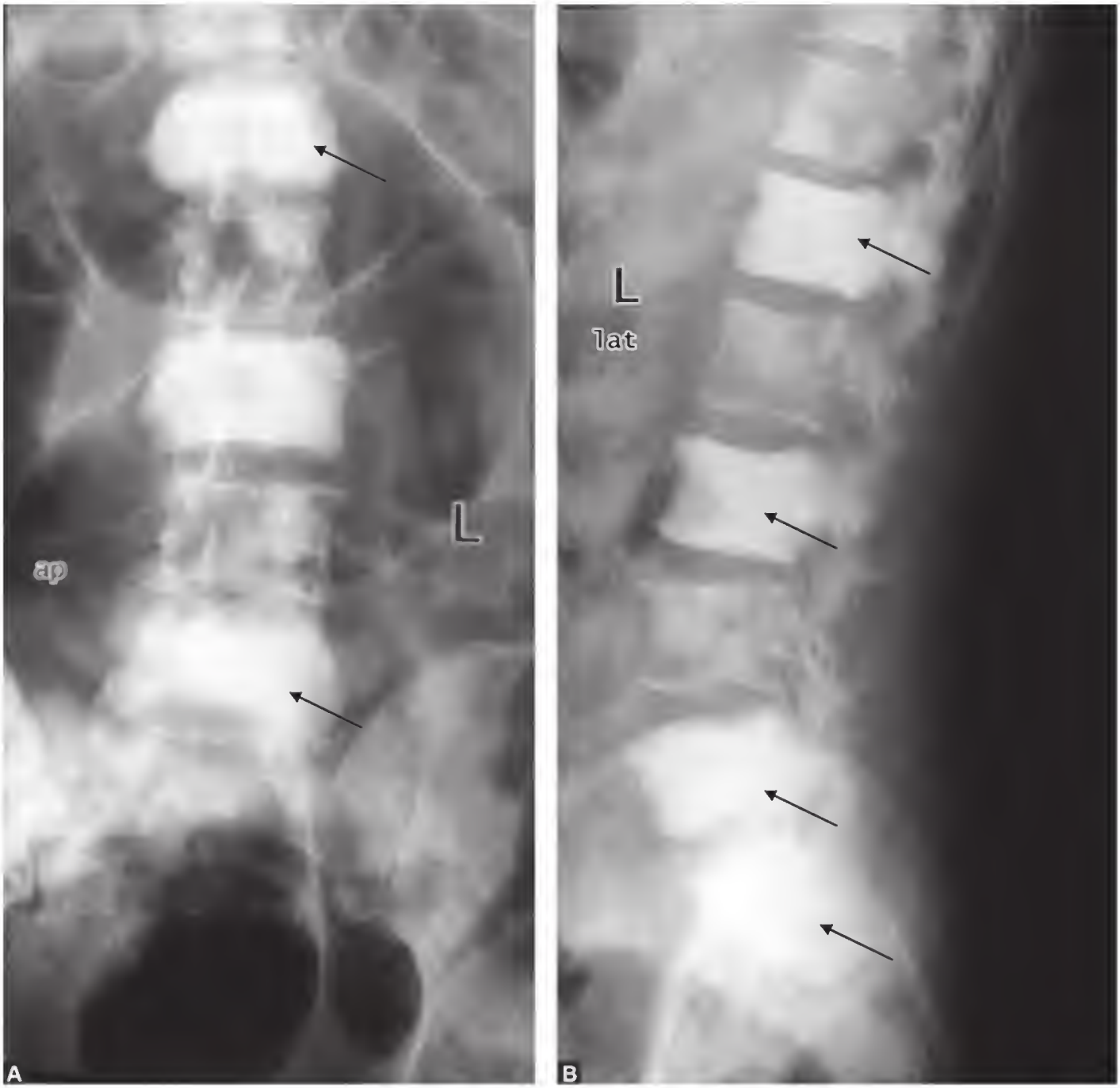
In rheumatoid arthritis small joints (metacarpophalangeal, metatarsophalangeal and interphalangeal joints) are involved. Imaging features include soft tissue swelling, regional/diffuse osteopaenia, joint space narrowing, central or marginal erosions, subluxation and deformities. In osteoarthritis, predominant features are asymmetrical joint space narrowing, osteophytes, subarticular sclerosis with cystic areas. In ankylosing spondylitis, involvement of the bilateral sacroiliac joint is paramount with ligamentous calcification (paraspinal as well as interspinous ligaments). Disorganised joints, marked sclerosis, subluxation and new bone formation are the classical features of neuropathic joints which occur in syringomyelia, spinal dysraphism, diabetes, leprosy and syphilis.

Osteomyelitis

Osteomyelitis can generally be divided into pyogenic and non-pyogenic types. Radiographs are normal during the initial stage of osteomyelitis and contrast enhanced MRI is the investigation of choice. Later, radiograph demonstrates soft-tissue oedema, loss of fascial planes, osteopaenia, metaphyseal lytic lesion and fluffy periosteal reaction. In infants and adults metaphyseal involvement with epiphyseal extension occurs, whereas in children older than 18 months, metaphyseal involvement predominates. Chronic osteomyelitis on radiograph demonstrates dense involucrum (sheath of periosteal new bone), sequestrum (dead bone), and cloaca (sinus tract). Brodie's abscess caused by *Staphylococcus aureus* is a well-demarcated metaphyseal elongated lytic lesion surrounded by reactive sclerosis.

Musculoskeletal Tuberculosis

Musculoskeletal TB accounts for about 1% to 3% of cases of TB (**Table 13**). TB of the spine is the most common form and accounts for approximately 50% of cases. Extra-spinal manifestations are less common. Tuberculous spondylodiscitis has classical appearance of narrowing of the disc with irregularities of the opposing vertebral endplates and paravertebral abscesses (**Figures 23A and B**).



Figures 22A and B: Sclerotic skeletal metastasis in a 72-year-old male with carcinoma prostate. Radiographs of anteroposterior view (A) and lateral view (B) demonstrate sclerosis seen involving the L1, L3, L5 vertebrae and iliac bone.

Table 13: Imaging Features of Musculoskeletal Tuberculosis

Patterns of Involvement	Common Bones/ Joints Involved	Imaging Features
Tuberculous arthritis	Mono-articular involvement (hip and knee–most common)	Narrowing of joint space Peripherally located erosions Juxta-articular osteopaenia
Tuberculous osteomyelitis	Small bones of hand and feet–most common	Poorly defined lytic lesion Periostitis
Tuberculous spondylitis	Upper lumbar/lower thoracic vertebra with involvement of two contiguous vertebrae	Reduction of intervertebral disc spaces End plate irregularities Collapse of vertebrae Paraspinal abscess

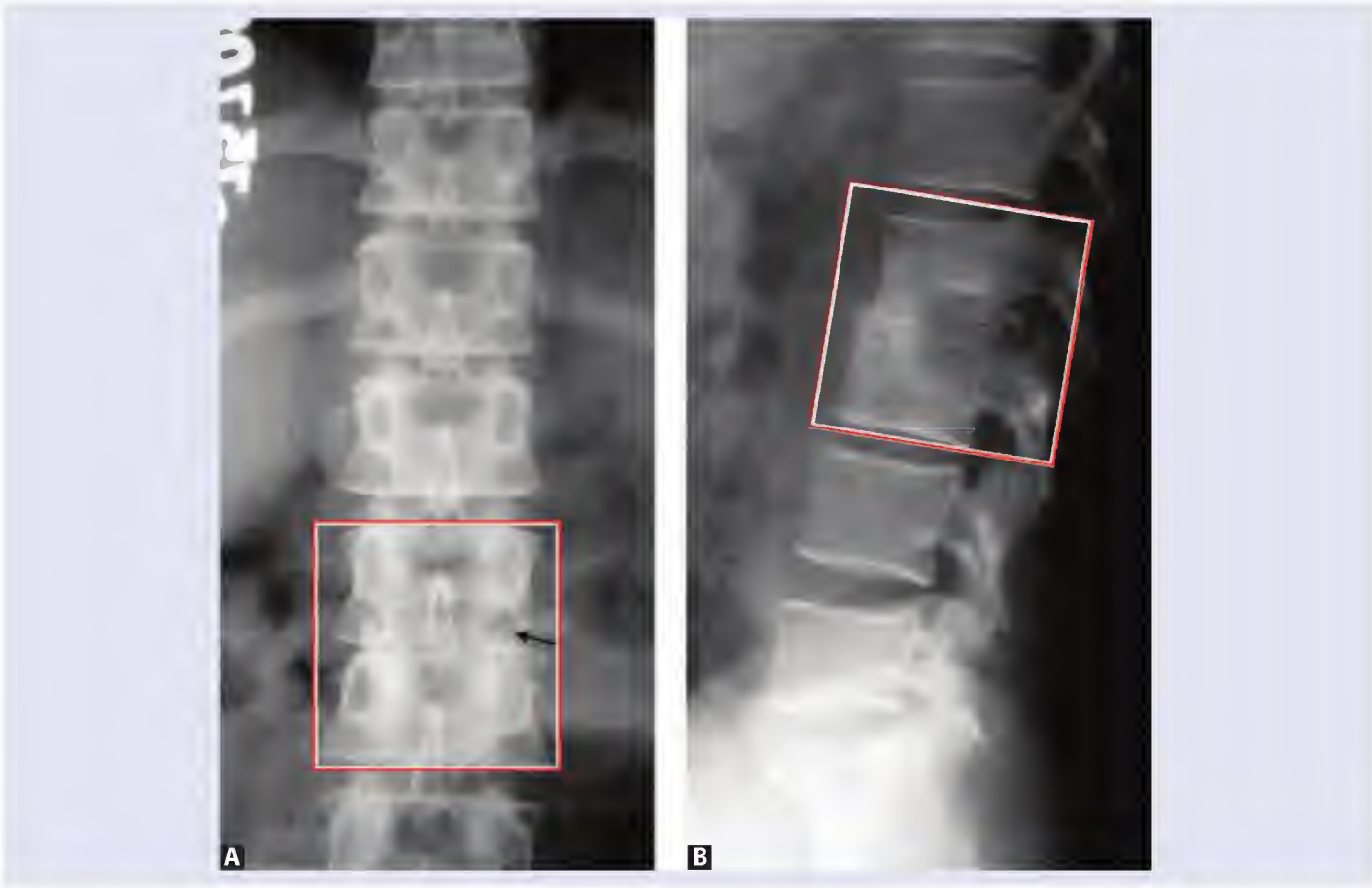
GENITOURINARY SYSTEM

Plain Radiography

Plain abdominal radiography is routinely employed in the evaluation of renal calculi and prior to intravenous urography (IVU) to look for stones in the urinary tract.

Intravenous Urography (IVU)

Current role of IVU (**Figure 24**) is in detection of the congenital ureteric and renal anomalies, early changes of renal TB (**Figure 25**) and papillary necrosis (**Figure 26**). It is complementary to retrograde pyelography and CT in detection of the transitional cell carcinoma. IVP is alternative (suboptimal) to CT for evaluation of nearly all aetiologies of haematuria and flank pain (calculi, tumour, infection and trauma).



Figures 23A and B: Pott's Spine in a 22-year-old male patient. Radiographs of spine anteroposterior view (A) and lateral view (B) demonstrate reduction in the disc space of L2-3 vertebrae, end-plate irregularity with lytic lesion involving body of L2-3 vertebra. Findings are suggestive of spondylodisitis.



Figure 24: Normal IVU. Fifteen minutes IVU demonstrates normal contrast excretion. Bilateral kidneys and ureters are normal.



Figure 25: Genito-urinary TB in a 40-year-old male. IVU shows fuzzy papilla involving the left kidney with delayed contrast excretion and contracted bladder (thimble bladder).



Figure 26: Papillary necrosis due to analgesic nephropathy. IVU demonstrates characteristic egg-in-cup cavities. No focal cortical loss is seen.

Micturating Cystourethrogram (MCU)

MCU is very useful in demonstrating vesicoureteric reflux, bladder abnormalities like diverticulum and filling defects. Obstructive lesions in the urethra, like strictures, valves, diverticuli are readily demonstrated.

Retrograde Urethrogram (RGU)

RGU gives excellent anatomical information concerning the distal urethra as far as the distal sphincteric mechanism.

Hysterosalpingography (HSG)

HSG is a radiographic method for evaluation of the endometrial cavity and the fallopian tubes following direct instillation of contrast media. Current indications of the HSG include infertility, recurrent abortions, detection of suspected uterine anomalies and assessment of tubal patency and morphology.

RECOMMENDED READINGS

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3.2 Ultrasound in Medicine

BS Rama Murthy

Ultrasound (US) has evolved into a first line imaging modality in the investigation of problems encountered in medical practice. Non-invasive cost-effective visualisation of the internal organs without the use of radiation or contrast agents have made US imaging readily accessible even in the remotest regions of our country. The following paragraphs are an attempt to present a few situations in clinical medical practice and the possible US findings which aid in clinching the diagnosis or narrowing the differential diagnosis. US may give vital clues which can help make decisions for further imaging/laboratory investigations.

Apart from grey scale imaging which forms the bulk of basic US usage, one can use Doppler US to assess the vascular status of the organs or regions of pathology. Three-dimensional US gives the ability to view the region of pathology in multiple planes simultaneously.

Special high frequency transducer (the hand-held probe which emits US energy and receives the echoes) design enables the study of superficial structures, such as the thyroid, testes etc. in great detail.

Special transducer design enables intracavitary usage, such as the vaginal, oesophageal, gastroduodenal or rectal routes.

US imaging employs sound waves that are beyond the range of human hearing. Typically 3.0 to 5.0 Megahertz (MHz) is the frequency used for abdominal imaging. Superficial part imaging transducers are capable of producing US of upto 15 MHz. The US energy propogates through the tissues underlying the transducer. The tissue field produces reflections (echoes) which reach the same transducer. These echoes are converted to electrical impulses which after processing produce the image on the monitor. The transducer has an array of piezoelectric crystals which produce US on being deformed by an electric impulse. The reverse process occurs when the echoes reach the transducer.

A region which returns no echoes is termed anechoic. Clear fluid containing structures as urinary bladder, gall bladder and cystic lesions are anechoic. A region which returns echoes similar to the liver is termed isoechoic. We also have the terms hypo- and hyper-echoic signifying solid regions returning lighter or darker echoes relative to the liver respectively.

Like all imaging modalities US interpretations have to be done based on the clinical background.

For the purpose of discussion, the following clinical situations, are discussed:

1. Fever of unknown origin (FUO)
2. Jaundice
3. Hypertension
4. Portal hypertension
5. Stroke/Transient ischaemic attacks
6. Diabetes mellitus.

FEVER OF UNKNOWN ORIGIN (FUO)

Fever under investigation may be due to infection, neoplasia or collagen vascular disease. The US imaging can demonstrate the focus of localised infection as a small liver/kidney abscess or a sub-diaphragmatic abscess (**Figure 1**). It should be emphasised that US is an excellent modality, in demonstrating fluid containing space occupying lesions in solid organs. Extensive tuberculous infection of the peritoneum in its ascitic or plastic forms can be well recognised by US (**Figure 2**). Loculated peritoneal fluid collections traversed by flimsy fibrinous bands are pathognomonic of ascitic form of peritoneal tuberculosis (TB). Omental and mesenteric thickening with adherence seen as 'sandwich sign' is suggestive of plastic form of TB.

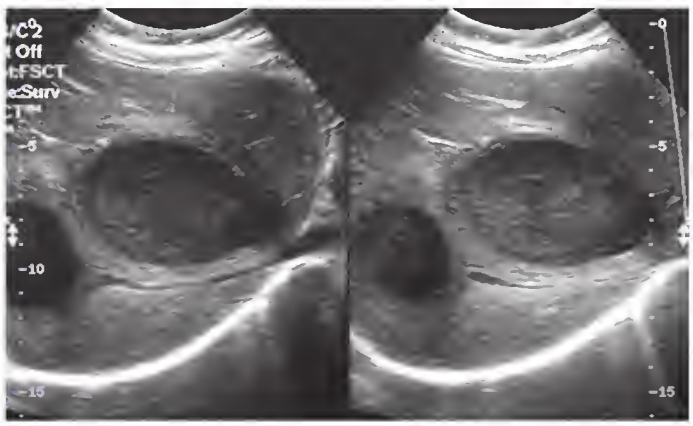


Figure 1: Liver abscesses in case of fever of unknown origin (FUO).

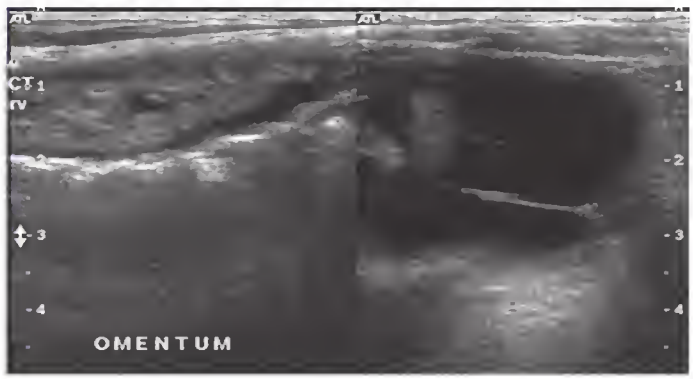


Figure 2: Thickened omentum and loculated fibrinous ascites in peritoneal tuberculosis.

Among neoplasia renal cell carcinoma and lymphoma can present with fever. Abdominal or cervical lymph nodal enlargement can be demonstrated with US (**Figure 3**). Gut wall thickening especially in the ileocaecal region could be due to TB or lymphoma.

Lymphoma is classically hypoechoic with increased vascularity on Doppler examination.

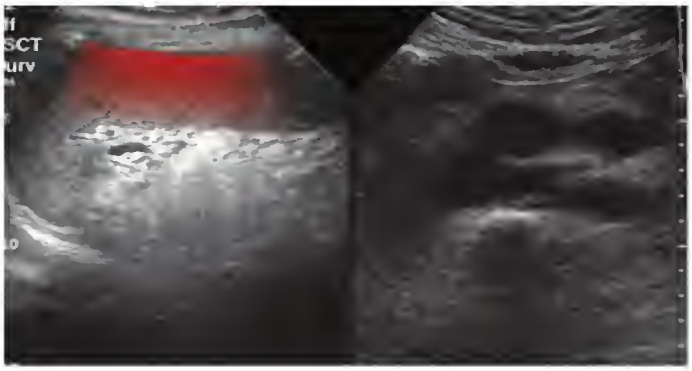


Figure 3: Splenic lesions and juxta-aortic lymph node enlargement in NHL.

JAUNDICE

Jaundice could be due to haemolytic, hepatocellular, cholestatic or obstructive causes. Biliary ductal obstruction at any level results in upstream dilatation. US imaging has a high sensitivity for biliary ductal dilatation and can indeed stratify patients of jaundice into obstructive versus non-obstructive groups. In addition to recognising the presence of obstruction, US also gives information about the level of obstruction and cause of obstruction (**Figures 4A and B**).

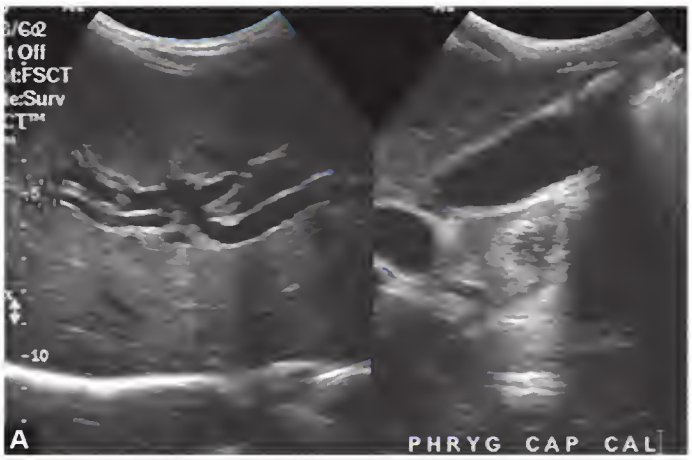


Figure 4A: Intra-hepatic biliary dilatation in a case of common bile duct calculus (**Figure 4B**) also note presence of gall bladder stone in the fundic region.

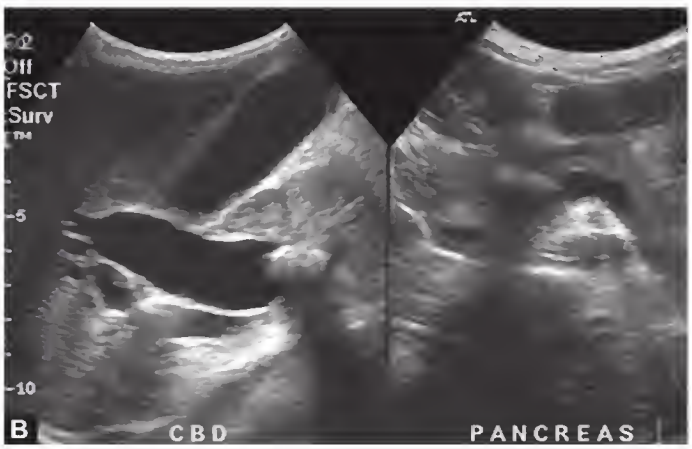


Figure 4B: Calculus in the intra-pancreatic segment of common bile duct. Calculi are typically bright (hyperechoic) with an acoustic shadow.

Normal intra-hepatic biliary ducts beyond the right and left main hepatic ducts are not visualised by US. Dilated intra-hepatic ducts are seen as tubular cystic structures running parallel to the portal radicles and produce the typical 'double barrel' or 'shot gun' appearance.

The normal main bile duct (common hepatic and common bile duct) can be consistently demonstrated by US and is less than 6 mm in caliber. Any diameter above 6 mm in a case with no history of biliary surgery is indicative of dilatation. It must be noted that there could be non-obstructive ectasia as in a choledochal cyst or as in ectasia associated with advancing age. The level of obstruction can be gauged by noting the presence of gallbladder and/or pancreatic duct dilatation. The cause of obstruction may often be demonstrated in the form of a ductal calculus, cholangiocarcinoma, pancreatic mass or a periampullary carcinoma (**Figures 5A and B**). In sclerosing cholangitis and human immunodeficiency virus (HIV) cholangiopathy the main bile duct shows wall thickening.

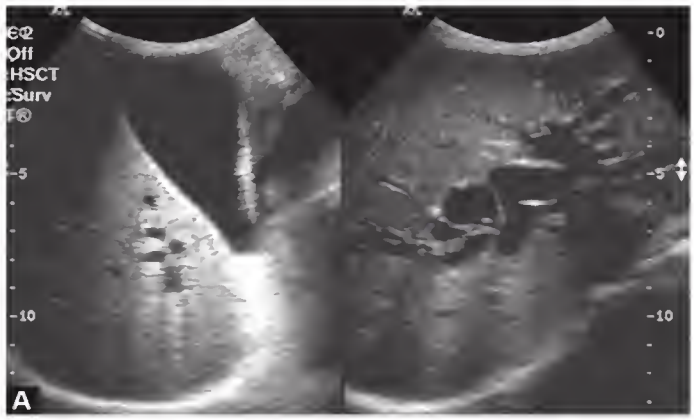


Figure 5A: Intra-hepatic biliary ductal dilatation with gallbladder dilatation in periampullary carcinoma (**Figure 6**).

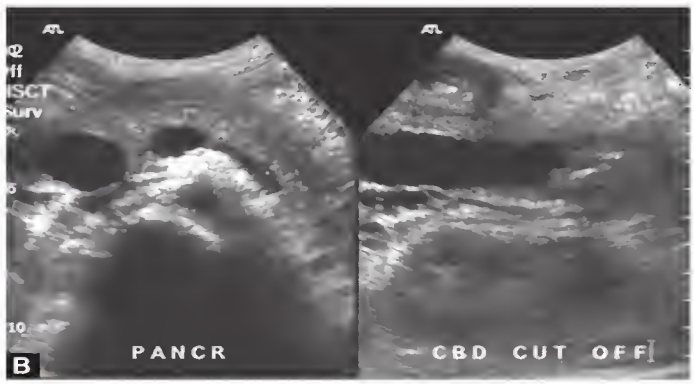


Figure 5B: Terminal CBD cut-off in periampullary carcinoma.

HYPERTENSION

In the setting of hypertension US plays two distinct roles.

1. To look for potential renal or adrenal causes in secondary hypertension.
2. To assess renal status in chronic hypertension.

The renal conditions that can be identified as a possible cause of hypertension include autosomal dominant polycystic renal disease, post-inflammatory renal scarring (focal or global), diabetic nephropathy, acute glomerulonephritis and other parenchymal diseases (**Figures 6 and 7**). These are traditionally

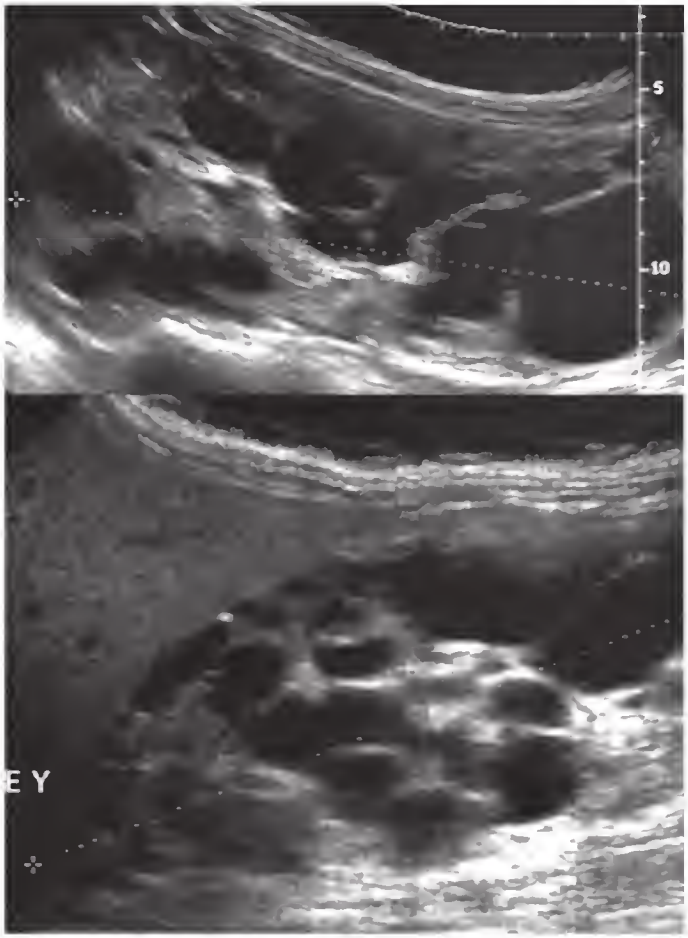


Figure 6: Right and left kidneys replaced by multiple cysts. Note the symmetrical enlargement, in a case of autosomal dominant polycystic kidney disease.

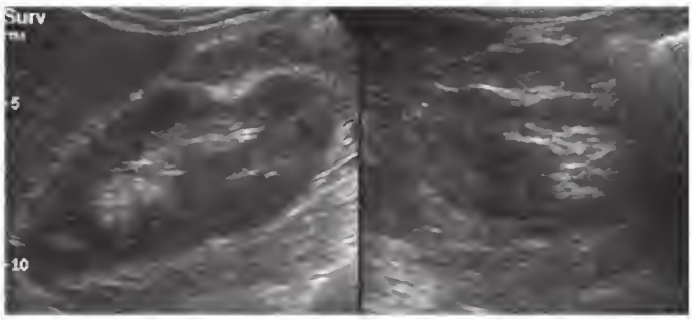


Figure 7: Focal lower pole chronic pyelonephritic scar of the right kidney. Note the presence of focal parenchymal thinning as well as the contour alteration.

classified as renal parenchymal causes and are diagnosed on the basis of B mode imaging.

On the other hand, we have renal vascular cause as in renal artery stenosis (atheromatous plaques or fibromuscular dysplasia).

Duplex Doppler US provides a non-invasive screening technique. The B mode and Doppler findings include:

1. High peak systolic velocity in the stenotic segment (greater than 180 to 200 cm/sec) and an renal artery/aortic ratio (RAR) of 3.5 or more are considered as markers of a haemodynamically significant (greater than 50% diameter reduction) main or accessory renal artery stenosis (**Figure 8A**). The visualisation of the main renal artery is rather dependent on the body habitus, and the operator expertise. Hence, it may not serve its 'screening' role to the expected level.
2. The segmental arteries are consistently seen by colour Doppler and sampling of at least three of them serves as a screening test. In the presence of main renal artery stenosis the intra-renal Doppler spectral waveforms show 'tardus parvus' nature (**Figure 8B**). This means that the systolic velocities are attenuated with a slower acceleration of the slope of the systolic upstroke. Acceleration time greater than 70 milliseconds are indicative of main renal artery haemodynamically significant stenosis.

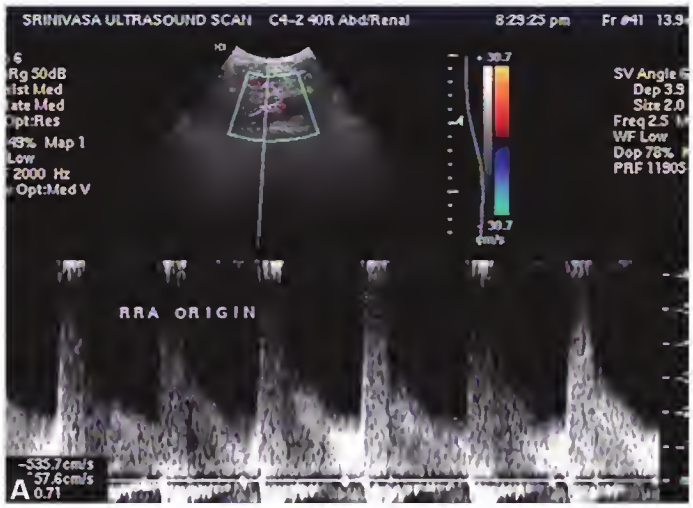


Figure 8A: High systolic velocity in the origin of the right renal artery.

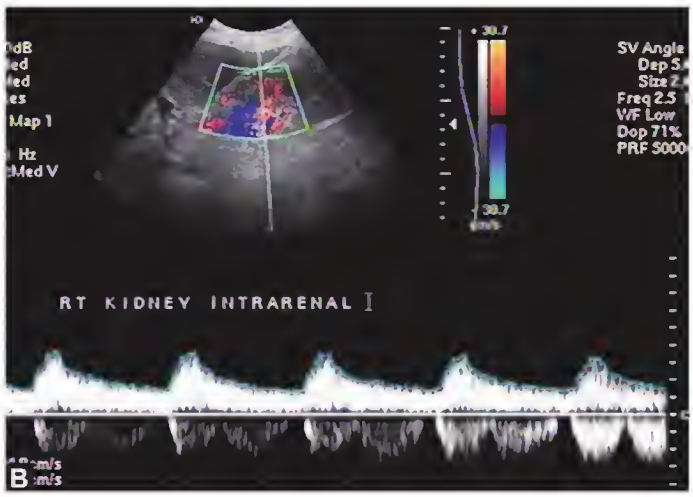


Figure 8B: Tardus parvus intrarenal waveform (segmental artery) in the right kidney of the subject in **Figure 10**.

In addition, the presence of low pulsatility in the intra-renal arteries is indicative of better chance of reversal to normotensive state after stent placement or balloon angioplasty.

Adrenal cause which can be detected by US is a pheochromocytoma or adrenal carcinoma (**Figure 9**).

PORTAL HYPERTENSION

In the clinical setting where portal hypertension is a potential possibility (ascites, splenomegaly, haematemesis, dilated abdominal wall veins), US may help in answering the following questions:

Is Portal Hypertension Present? What Is the Cause?

The splenomesentericoportal venous axis normally shows an inspiratory increase and expiratory decrease in caliber. Decrease or absent respiratory caliber change is a very

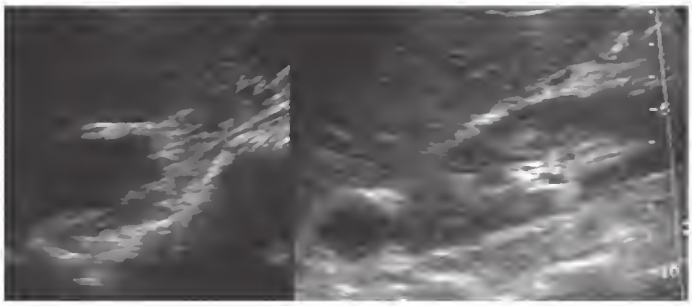


Figure 9: Right adrenal solid mass.

sensitive marker of portal hypertension (**Figure 10**). Upstream dilatation of the splenomesentericoportal venous axis occurs proximal to the site of pathology. For instance, in portal cirrhosis (hepatic cause of portal hypertension) upstream dilatation occurs in the splenic, superior mesenteric and portal veins.

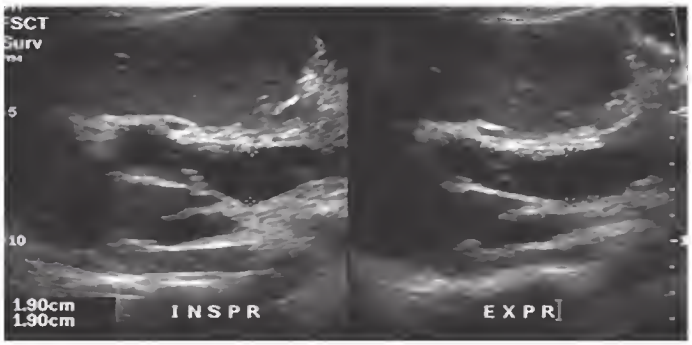


Figure 10: Absent respiratory portal venous caliber change in portal hypertension. Also note portal venous dilatation.

Portal vein is considered dilated when its caliber is more than 1.3 cm. Dilatation of the portal or splenic veins is not as sensitive or specific compared to respiratory caliber change in the diagnosis of portal hypertension. Identification of venous collaterals is a strong confirmatory sign of portal hypertension. Collaterals may be porto-hepatic as in periportal (portal cavernoma) or peri-pancreatic collaterals (**Figure 11**). These collaterals bypass the region of cause of portal hypertension and drain into the portal venous radicals in the liver. In contrast porto-systemic collaterals drain either into the superior vena cava or inferior vena cava territories. Examples of the former include the dilated coronary vein and short gastric collaterals. Examples of the latter include splenorenal or splenoretroperitoneal collaterals and the recanalised umbilical vein.

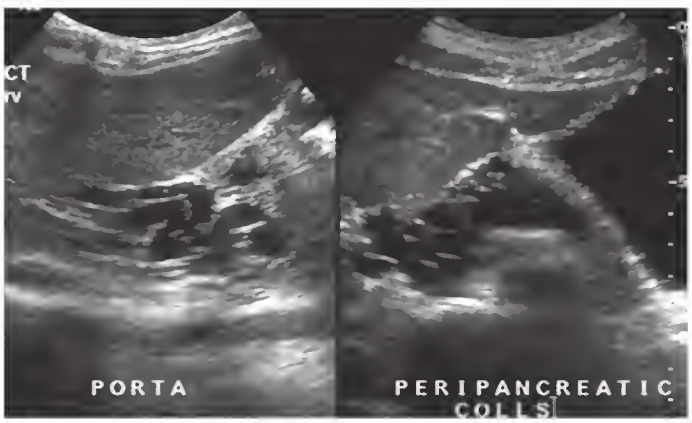


Figure 11: Portal cavernoma and periportal collaterals.

Having obtained as much B mode findings as possible Doppler is used to map the presence and direction of flow in the splenomesentericoportal venous axis and the collaterals. Hepatofugal flow in the portal vein has important clinical implications. This is associated with decreased incidence of variceal bleed but increased incidence of hepatic encephalopathy. Porto-hepatic and porto-systemic collaterals show hepatopetal and hepatofugal flow, respectively.

The cause of portal hypertension in terms of portal venous thrombosis (a portal cavernoma implies portal venous thrombosis in the past), cirrhotic hepatic echopattern or IVC or hepatic vein pathology may be identified.

STROKE/TRANSIENT ISCHAEMIC ATTACKS

Stroke due to atherosclerotic disease is a leading cause of mortality and morbidity. Transient ischaemic attacks are harbingers of stroke. Vast majority of ischaemic strokes are due to emboli. The source of emboli could be from the carotid system or the cardia. It is well documented that the embologenicity in the carotid system increases with the degree of stenosis due to atheromatous plaques. The North American Symptomatic Cartoid Endarterectomy Trial (NASCET) trial has convincingly proved that carotid endarterectomy is more beneficial than medical therapy in symptomatic patients with 70% to 99% internal carotid stenosis. This study has ensured the future of carotid Doppler ultrasound as a screening tool. The indications for carotid Doppler include TIA, stroke, carotid bruit, amaurosis fugax and post-carotid endarterectomy/stenting. The intima medial thickness is being used as a predictor of the possibility of future cerebrovascular or cardiovascular accident.

Carotid Duplex Doppler

Carotid duplex Doppler US enables us to assess the following:

1. *The wall (atheromatous plaque) morphology:* Plaque length, thickness, extent, echogenicity and surface characteristics (**Figures 12 and 13**).
2. *The patent luminal status* is assessed in terms of percentage diameter or area narrowing. This can be done by direct visualisation or by velocity criteria. Velocity criteria include peak systolic ratio, end diastolic velocity and the velocity ratios (ICA/CCA systolic or diastolic ratios). The velocity assessment of stenosis is based on the principle of incremental acceleration of blood flow in the region of stenosis with increasing degree of stenosis.

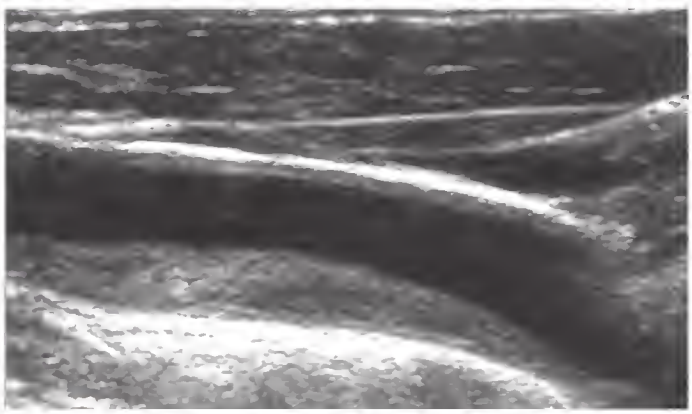


Figure 12: Carotid homogeneous, echogenic, smooth surfaced plaque.

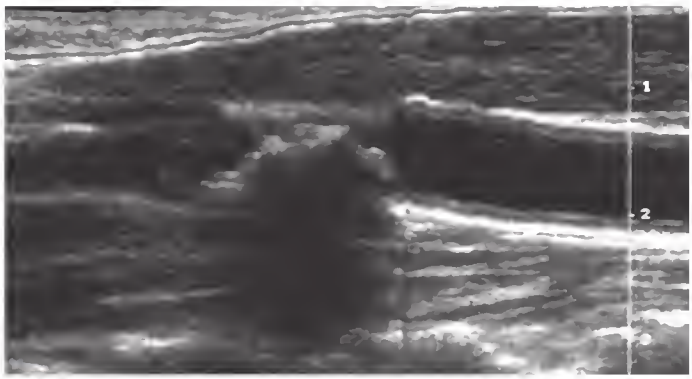


Figure 13: Internal carotid calcific plaque.

Haemodynamically significant stenosis implies more than 50% diameter reduction. Doppler assessment can recognise only haemodynamically significant stenoses.

Carotid duplex Doppler US screening is an excellent non-invasive means of assessing stenosis. Useful information regarding the plaque morphology may be obtained.

DIABETES MELLITUS

US has many roles to play in the context of diabetes mellitus. A few of them may be enumerated below:

1. In terms of aetiology, chronic calcific pancreatitis may be demonstrated. Thinning of pancreatic parenchyma, irregular ductal dilatation and ductular calculi are the defining features (**Figure 14**).
2. In terms of chronic sequelae, we could identify steatotic infiltration of the liver (**Figure 15**), diabetic nephropathy, and steno-occlusive atheromatous disease in the lower limb arterial axis.

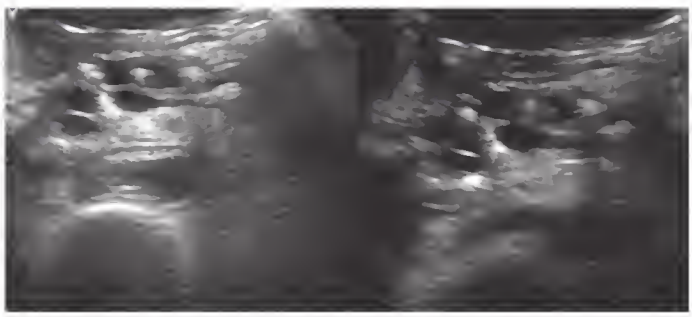


Figure 14: Chronic calcific pancreatitis. Echogenic calculi are seen in the diluted pancreatic duct.

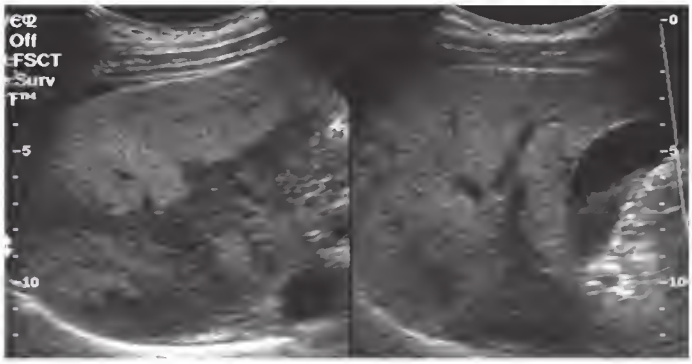


Figure 15: Patchy hepatic steatosis.

3. In terms of infective sequelae, we can identify emphysematous cholecystitis/pyelonephritis.

We will now explore the role of US in the evaluation of various organ systems.

i. *Neonatal brain:* Transfontanellar approach yields coronal and sagittal images of the brain. Hypoxic ischaemic sequelae, intracranial haemorrhage and congenital malformations are assessed and followed-up.

ii. *Neck:* Thyroid, parathyroid, and cervical nodes may be evaluated for enlargement, echopattern and nodules.

iii. *Chest:* US is sensitive for detecting fluid in the pleural cavity. Presence of loculation or fibrinous content may be assessed. Large lung/mediastinal lesions may be characterised as being solid or cystic.

4. *Abdomen*
   (a) Liver: Size may be assessed. The normal liver echopattern is homogeneous. In diffuse liver disorders, the echopattern is altered as happens in cirrhosis. Presence of portal hypertension may be assessed. The strength of US, however; is in its ability to demonstrate space occupying lesions of the liver and characterise them as solid or cystic.

   (b) Biliary system: US can demonstrate the biliary ductal dilatation in obstructive jaundice. The level and cause of obstruction can be determined. Gall bladder disease in terms of calculi, cholecystitis, cholesterolosis and malignancies may be demonstrated.

   (c) Pancreas: Pancreatic swelling and intra- or peri-pancreatic fluid collections in acute pancreatitis and its sequelae may be demonstrated. Ductal dilatation and calculi may be seen in chronic pancreatitis. Pancreatic solid masses may be demonstrated.

   (d) Kidneys: Abnormal location and/or absence of kidneys may be assessed. Obstructive uropathy may be demonstrated. The level of obstruction (pelviureteric or ureterovesical or bladder outflow) may be ascertained. Renal size and the parenchymal echopattern may be evaluated in medical renal disease. Renal artery Doppler may be used to evaluate potential stenosis.

   (e) Adrenals: Adrenal mass lesions may be recognised and described. Adrenal hyperplasia cannot be demonstrated by US.

   (f) Bladder and prostate: Bladder volume, wall thickness and presence of mural polypoid lesions can be assessed. Post-void residue can also be estimated. Prostatic weight and echopattern can be assessed by transrectal ultrasonography.

   (g) Female internal genitalia: Uterine size and presence of fibroids or adenomyosis may be assessed. Ovarian masses can be characterised. Ultrasound has an indispensable role in infertility management. Transvaginal ultrasonography has revolutionised the pelvic imaging.

   (h) Peritoneum: US is very sensitive for fluid in the peritoneal cavity. Further, it can help in characterising

whether the fluid is transudate or exudate. Thickened peritoneum/omentum may be demonstrated as in peritoneal TB or metastasis.

(i) Retroperitoneum: Retroperitoneal lymph node enlargement and their distribution may be evaluated. Retroperitoneal mass lesions may be described.

(j) Abdominal wall: Hernial defects and wall masses can be delineated.

5. *Perineal applications*

Perianal sinuses and fistula can be delineated in terms of extent and length.

6. *Scrotal applications*

Epididymorchitis, torsion, testicular tumours may be recognised.

7. *Musculoskeletal*

Shoulder, wrist, knee, ankle applications.

8. *Orbital and ocular*

Anterior and posterior chamber applications.

DOPPLER ULTRASOUND

1. Carotid and Vertebral

Atheromatous plaque morphology, luminal narrowing and/or occlusion can be demonstrated in cases of transient ischaemic attack or establisted stroke.

2. Transcranial Doppler

It is used to evaluate the Willisian circulation in cases of carotid occlusion. It is also used to evaluate the presence of spasm in subarachnoid haemorrhage.

3. Lower Limb Arterial

Stenosis and/or occlusion can be demonstrated in cases of intermittent claudication, rest pain or gangrene.

4. Upper Limb Arterial

Evaluation of thoracic outlet syndrome and haemodialysis access fistula.

5. Lower Limb Venous

Deep venous thrombosis may be mapped. Incompetency of the valves of the deep veins or communicating veins may be evaluated.

6. Abdominal

Doppler ultrasound contributes to the diagnosis of portal hypertension, renal artery stenosis, renal allograft vascularity, abdominal aortic aneurysm, and mesenteric arterial insufficiency. Evaluation of an abdominal masses for the type of vascularity and main feeder and draining vessels.

INVASIVE APPLICATIONS

US-guided needle placements are now common place procedures. Pleural taps, abscess drainages, renal and other organ biopsies are all done successfully and non-safely under US guidance.

CONTRAST ENHANCED ULTRASONOGRAPHY

Ultrasonography contrast media are microbubbles which when injected enhance the reflectivity of lesions. They have been particularly applied in liver space occupying lesions. Hepatic haemangioma, primary tumour and metastatic lesions have their typical enhancement patterns.

ELASTOGRAPHY/FIBROSCAN

Using US energy, the elastic properties of a tissue (e.g. liver) or a lesion (e.g. breast carcinoma) can be qualitatively or quantitatively assessed. This technique holds promise to distinguish between benign and malignant lesions of the breast. Assessment of the liver for diffuse parechymal diseases (Fibroscan) is another area of promise.

Thus, we have seen a few situations in medical practice where US plays an important role in investigation. However, there are many other situations where US is indicated and where the results have a bearing on the management of the individual case.

3.3 Computed Tomography

Bhavin Jankharia, Nishigandha Burute

INTRODUCTION

The discovery of computed tomography (CT) by Sir Godfrey Hounsfield, Senior Research Scientist in Middlesex, England and South African born Dr Alan Cormack in the 1970s has been a milestone in the history of medical sciences and in the field of radiology. CT literally means writing (graphien) slices (tomos) of the human body with the help of a computation process. CT has not only changed the understanding of many diseases but also impacted the management of various disease processes. Initially, it was called computerised axial tomography (CAT) or computerised tomography, but computed tomography (CT) is currently the preferred name worldwide.

BASIC PRINCIPLES OF COMPUTED TOMOGRAPHY

Working of the CT Scanner

The rays used in a CT scanner are X-rays. The basic principle behind CT is that the internal structure of an object can be reconstructed from multiple projections of the object. The ray projections are formed by scanning a thin cross-section of the body with a narrow X-ray beam and measuring the transmitted radiation with a sensitive radiation detector. The detector adds up the energy of all the transmitted photons. The image is formed by processing of the numerical data from the multiple ray sums by a computer (**Figure 1**).

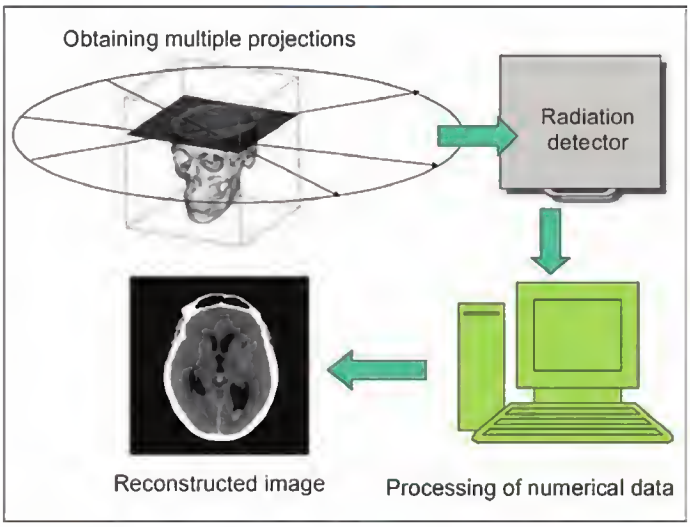


Figure 1: Working of a CT scanner.

CT Image

The CT image is made up of a number of shades of grey. The grey-scale of a tissue depends upon how much the tissue can attenuate the X-ray beam. The unit of attenuation is called Hounsfield unit (HU) (**Figure 2**). The degree of attenuation of an X-ray beam by a particular tissue depends on its density. Air being the least dense (HU: 1000), it attenuates the beam the least and appears black in colour; water being of medium density (HU: 0), it appears grey; dense cranial bone (upto 2000 HU) appears white on the CT image. The differentiation between normal tissue and pathologies can, thus, be made by observing the difference in their shades of grey.

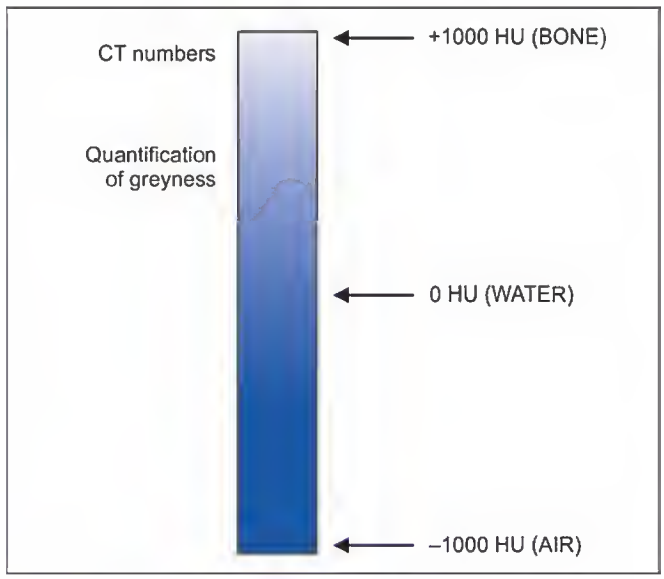
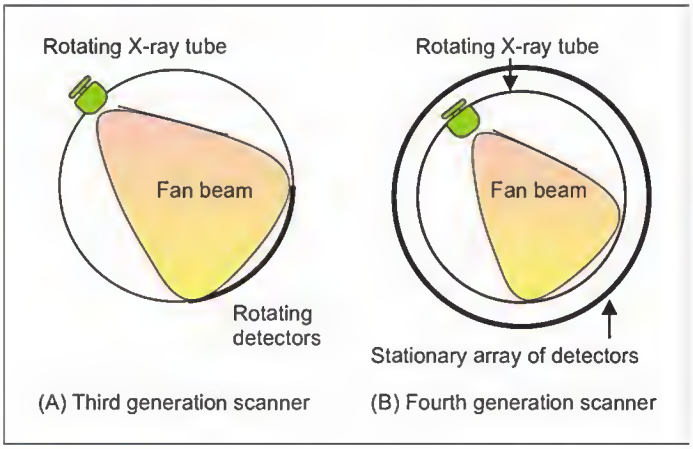


Figure 2: Differentiating tissues with the help of Hounsfield units.

EVOLUTION OF CT SCANNERS

CT scanners have gone through a number of design changes since the technology was first introduced in 1971. The first generation CT scanner used a single pencil beam of X-rays and a single detector and used to take 25 to 30 minutes for a 5-view study of the head. The second generation CT scanner used a fan beam instead of a pencil beam with multiple detectors, with a reduction in the scan time of a head CT to 1 to 2 minutes. The X-ray tube and detector movements were both linear and rotatory (translate-rotate) in the first and second-generation CT scanners. In 1975, third generation CT scanners were introduced in which the translation movement was completely eliminated and only rotation was required with both the X-ray tube and detectors rotating around the patient. A fan beam was used and the unit could produce a head scan in a few seconds (**Figure 3A**). The fourth generation CT scanner used a rotate-fixed configuration of the X-ray tube and detector system, where the detectors formed a ring that completely surrounded the patient. The detectors did not move. The X-ray tube rotated in a circle inside the detector ring (**Figure 3B**). The time required for a CT head, thus, became 1 second.

The advent of spiral/helical CT scanners in 1989 has been considered a major technical advancement in body imaging. It combines continuous gantry rotation with continuous table feed, thus eliminating interscan delay (**Figure 4**). This enables spiral CT acquisition to be much faster than conventional CT. The spiral CT scanner has also matured from a single slice to a 64-slice spiral CT scanner. The development of a dual source multi-slice CT scanner is a recent development, in which two



Figures 3A and B: (A) In a third generation scanner, both the X-ray tube and detectors rotate around the patient. A fan beam is used. (B) A fourth generation scanner has a rotating X-ray tube and a stationary array of detectors. A fan beam is used.

tubes produce 64-slices together. A 256-slice spiral CT scanner is now commercially available.

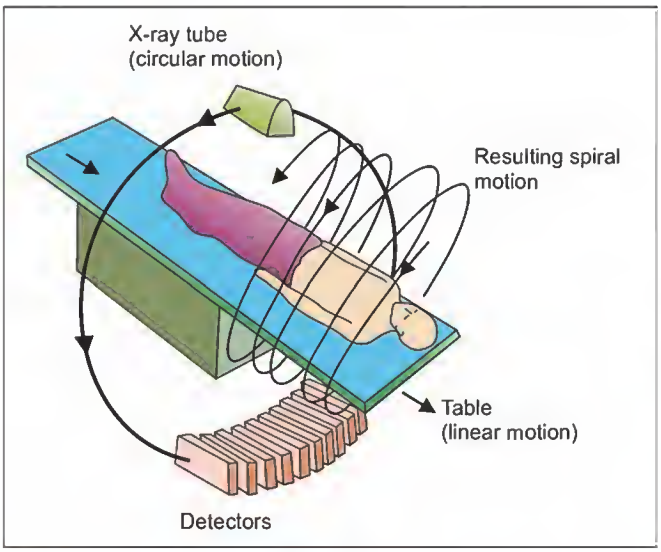


Figure 4: A spiral CT scanner has continuous gantry rotation with continuous table feed resulting in faster image acquisition.

CT CONTRAST MEDIA

Ionic/non-ionic contrast media are used intravenously in appropriate doses for a contrast enhanced CT scan. These opacify blood vessels and in turn the tissues that are supplied by them. The degree of enhancement of a tissue depends on its vascularity and capillary permeability. Thus, contrast media allow better depiction of normal anatomy and help in differentiating normal tissues from disease processes. Contrast media can cause allergic reactions in some individuals. These may range from a simple rash to the rare but fatal anaphylactic reaction.

Contrast media are also used to opacify the bowel loops during abdominal imaging, as they enhance the contrast between bowel loops and the surrounding viscera.

CONTRAINDICATIONS OF CT

X-ray Related

CT utilises X-rays for image production, hence, a CT is contraindicated in the first trimester of pregnancy, which is the period of organogenesis.

Contrast Related

The CT contrast medium is excreted by kidneys; hence, deranged renal function is an absolute contraindication for contrast-enhanced CT. Prior history of a serious reaction to CT contrast agents is also a contraindication.

APPLICATIONS

Due to several recent technical innovations and improvements, new CT applications continue to be added to an already long list of indications. Both positive and negative results of a CT improve the clinician's understanding of the disease and assist him in management decisions.

Head

CT is the modality of choice in head injury patients to look for intracranial bleed, brain contusions and skull fractures (**Figure 5**). It is also useful in acute cerebrovascular stroke to differentiate haemorrhagic from non-haemorrhagic stroke and to detect hypertensive bleeds. It is also helpful in detecting various other intracranial processes, such as granulomas (tuberculomas, neurocysticercosis, etc), hydrocephalous and tumours. CT is the modality of choice for evaluating the bony anatomy of the skull base, temporal bone, cranio-vertebral junction and paranasal sinuses (**Figure 6**). High resolution CT (HRCT) of the temporal bone provides exquisite details of the ear ossicles, middle ear cavity, mastoids and bony labyrinth.

Neck

CT of the neck is used to detect the exact location and spread of various disease processes involving the neck structures, such as the nasopharynx, oropharynx, larynx, cricopharynx, salivary

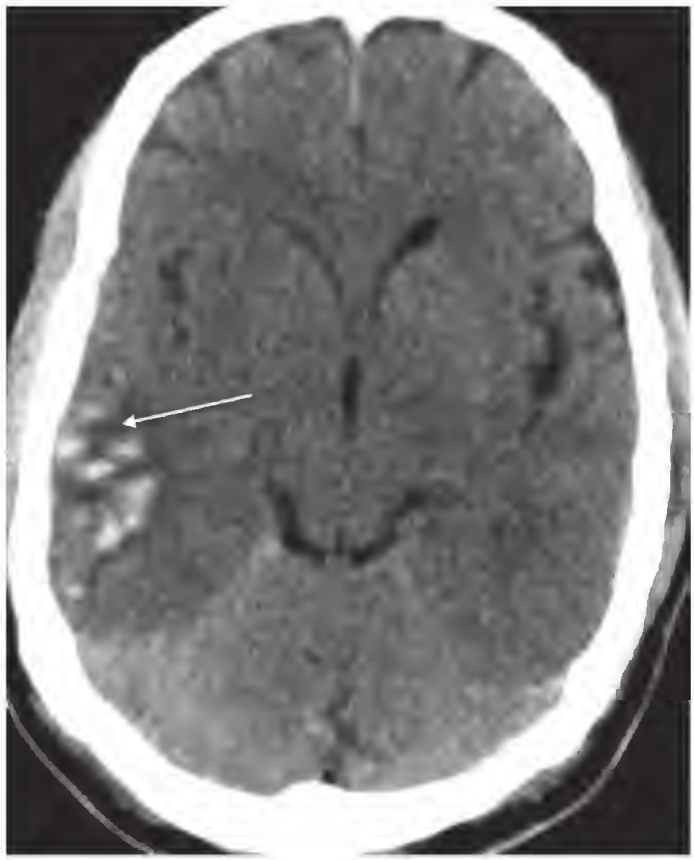


Figure 5: An axial CT of the brain shows haemorrhagic contusion in the right temporal lobe (arrow).

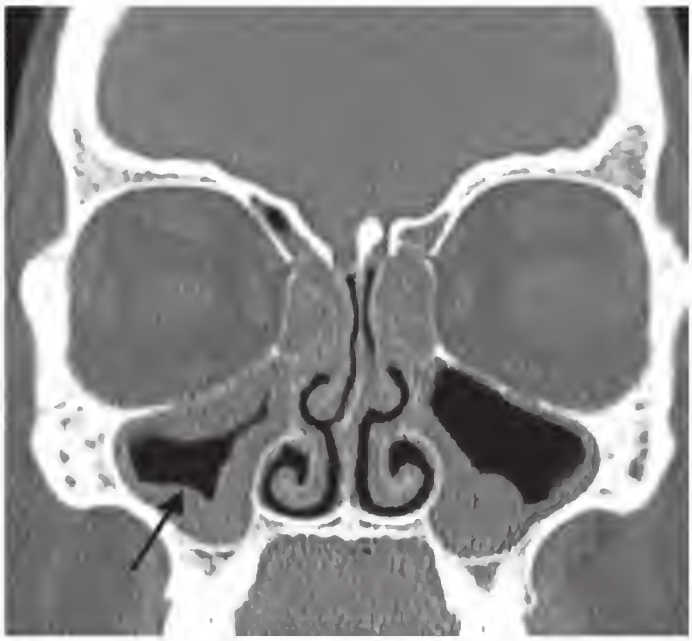


Figure 6: Coronal high resolution CT of the paranasal sinuses shows mucosal thickening (arrow) in the maxillary and ethmoid sinuses.

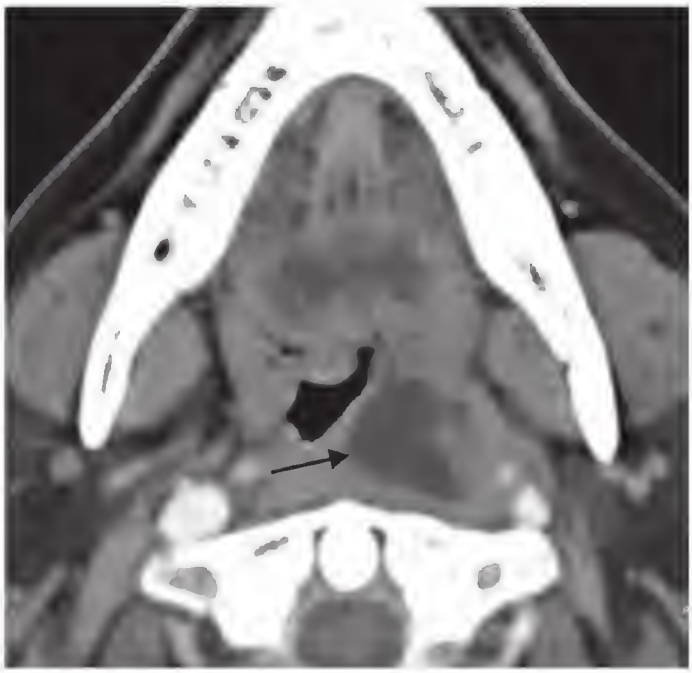


Figure 7: Axial contrast-enhanced CT of the neck shows a retropharyngeal abscess (arrow).

glands, thyroid gland and parapharyngeal space lesions as well as to detect cervical lymphadenopathy (**Figure 7**).

Thorax

CT is the modality of choice for evaluating lung pathologies, such as benign and malignant neoplasms, infections, various interstitial lung diseases (ILDs) and pneumoconiosis. In the pleura, effusions, empyema, pneumothorax and tumours and in the mediastinum, lymphadenopathy and neoplasm are well assessed. HRCT is a technique used for evaluating exquisite details of the lung parenchyma (**Figure 8**). HRCT can detect pathologies, which are not apparent on plain chest radiographs and has changed the management of patient with ILDs and airway pathologies.



Figure 8: HRCT of the lung shows extensive cystic bronchiectasis.

Abdomen

CT is the modality of choice for detecting acute appendicitis, cholecystitis, pancreatitis, acute ureteric colic, and intestinal obstruction with or without perforation (**Figures 9 and 10**). It is also used for the diagnosis, staging and pre-operative planning of various gastro-intestinal and visceral malignancies and benign neoplasms. It is also used for post-operative and post-treatment follow-up of these malignancies.

Vessels

CT angiography, a logical application of spiral technology, is a technique used to produce excellent images of the targetted

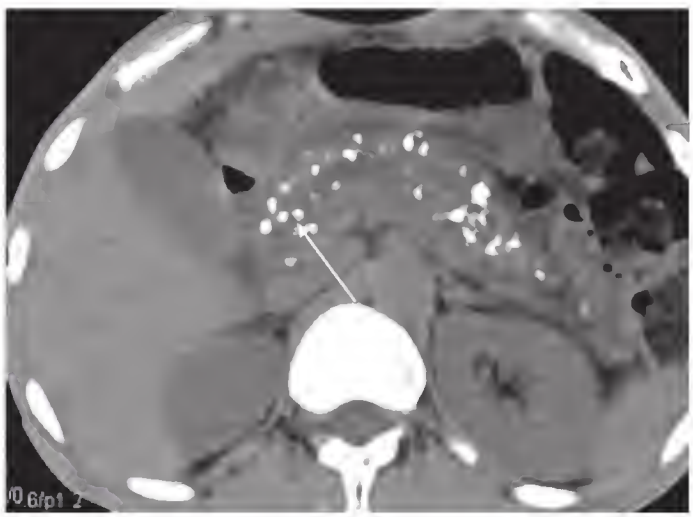


Figure 9: Axial CT of the abdomen shows a bulky pancreas with extensive calcification (arrow), suggesting acute on chronic pancreatitis.

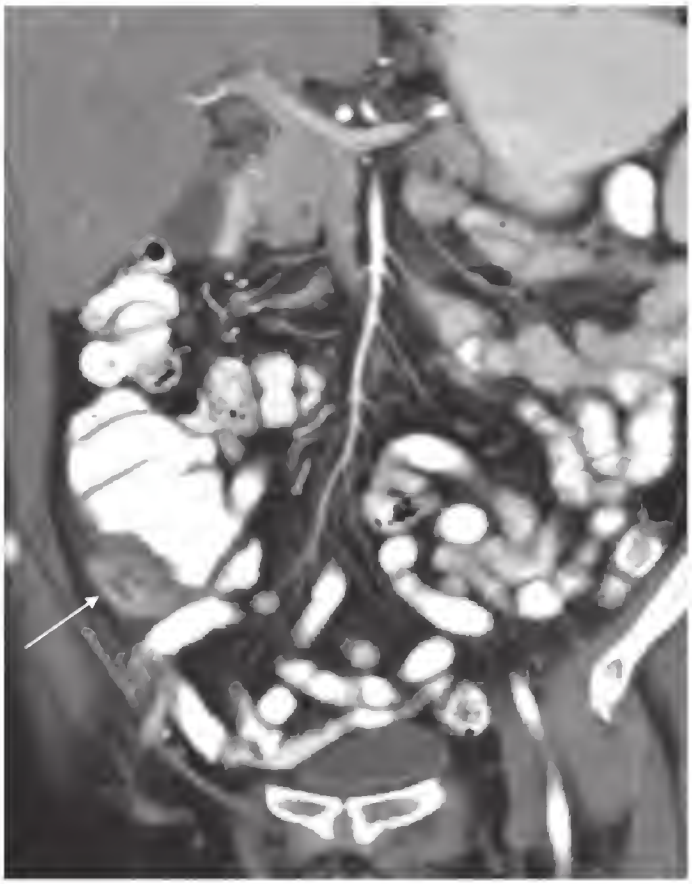


Figure 10: Coronal CT shows acute appendicitis (arrow).

arterial system.The images are displayed as thin collimation axial images or 3D renderings using sophisticated reconstruction techniques, like shaded surface display, maximum intensity projection and multiplanar formats, or can be colour coded using volumetric reconstruction images. Various applications of CT angiography are given in **Table 1**.

Table 1: Applications of CT Angiography

1. Cerebral angiography for detecting lesions of the carotid, vertebral and intracranial vessels, which include stenoses as well as aneurysms and arteriovenous malformation (**Figure 11**).
2. Pulmonary angiography, which is now the 'gold standard' in the evaluation of pulmonary thromboembolism.
3. Aortic angiography for aortic aneurysm, dissections and stenosis (**Figures 12A and B**).
4. Renal angiography for detecting renal artery stenosis.
5. Mesenteric angiography for mesenteric ischaemia.
6. Peripheral angiography for assessing the peripheral circulation of the upper and lower limbs.
7. Portal venography.

Musculoskeletal System

CT is the modality of choice for evaluation of the anatomy and pathology of the skeletal system. It has applications in various congenital anomalies as well as infective, neoplastic and traumatic conditions. The facility of retrospective reconstruction of thin sections and sophisticated 3D evaluation techniques resulting in remarkably high quality multi-planar reformats and shaded rendering is of immense help (**Figure 13**).



Figure 11: Axial cerebral angiography shows the arteries of the circle of Willis.



Figures 12A and B: Aneurysm. Maximum intensity projection (MIP) (A) and volume rendered (VRT) (B) images show a stented descending thoracic aneurysm with another aneurysm in the lower abdominal aorta.

Cardiac CT

Multi-detector CT coronary angiography is emerging as the most reliable non-invasive method for coronary artery disease (CAD) assessment. The newer ultra-fast cardiac CT holds the promise of replacing the standard invasive procedure of conventional coronary angiography as well as nuclear stress thallium, especially in the setting of 'to rule-out'. The standard multi-slice CT that exquisitely produces coronary artery images



Figure 13: Sagittal CT of the spine shows gross osteopaenia and destruction of the L2 vertebral body (arrow).

is a 64-slice CT scanner, but 320-slice and dual-source scanners are now available as well. All scans are gated to the electrocardiogram (ECG) trace, which allows positioning the data acquisition accurately in specific phases (**Figure 14**). Using such modality, one can perform calcium scoring, coronary artery imaging and assess function by reconstructing cine images.

Paediatrics

CT in children is often difficult due to motion artifacts and high respiratory rates. There is often a need to sedate or anaesthetise babies. Multi-slice CT has overcome these problems with sub-second scans and improved image resolution.



Figure 14: Normal cardiac CT angiogram shows the left main (LM), left anterior descending (LAD) and circumflex (CX) arteries.

Trauma

CT provides the high speed of data acquisition needed in trauma patients and to plan triage. CT is the modality of choice in an acute trauma setting for detecting internal bleeding, bone fractures, vascular injuries affecting different systems of the body, and for locating foreign bodies. Vertebral column injuries are well depicted but for spinal cord injures, MRI is the modality of choice. CT is also the modality of choice in patients with metallic implants inside the body, such as metallic rods, plates, fixation screws, etc (**Figure 15**).

Virtual Bronchoscopy and Colonoscopy

Using sophisticated software, it is now possible to get bronchoscopic and colonoscopic views non-invasively. These coloured pictures give better appreciation of the pathology. Virtual bronchoscopy has a role in locating foreign bodies, polyps, tumours, and strictures in the tracheobronchial tree. Virtual colonoscopy is used mainly in screening for polyps, some of which may be pre-malignant lesions.

3D Reconstruction

With the advent of faster scanners, it is possible to achieve 3D images with enhanced spatial and temporal resolution. Multi-planar reconstruction comprises reformatting of a CT image in the axial, coronal and sagittal planes. Multi-planar reconstruction allows better localisation and delineation of structures. Curved planar reconstruction and maximum intensity projection help better visualisation of tubular structures, such as blood vessels and ducts.



Figure 15: Coronal CT of the hip with orthopaedic hardware *in situ*, shows a non-united fracture.

Shaded surface display is useful in the setting of fractures, dislocations and vascular trauma. Volume rendering offers excellent anatomical details, and thus, enhances the visualisation of vessels and is also useful in cardiac imaging.

CT-GUIDED PROCEDURES

Diagnostic Procedures

CT provides an accurate skin entry point and guidance for drainage of intra-abdominal and intra-thoracic collections and abscesses. Under CT guidance, biopsies of mediastinal, pulmonary and intra-abdominal lesions are possible (**Figure 16**).



Figure 16: CT-guided biopsy of an enlarged subcarinal node (black arrow), using an extra-pleural approach (red arrow).

Therapeutic Procedures

Pain management

CT-guided nerve blocks (lumbar sympathectomy, supra-clavicular nerve block) are used for alleviation of pain (**Figure 17**).

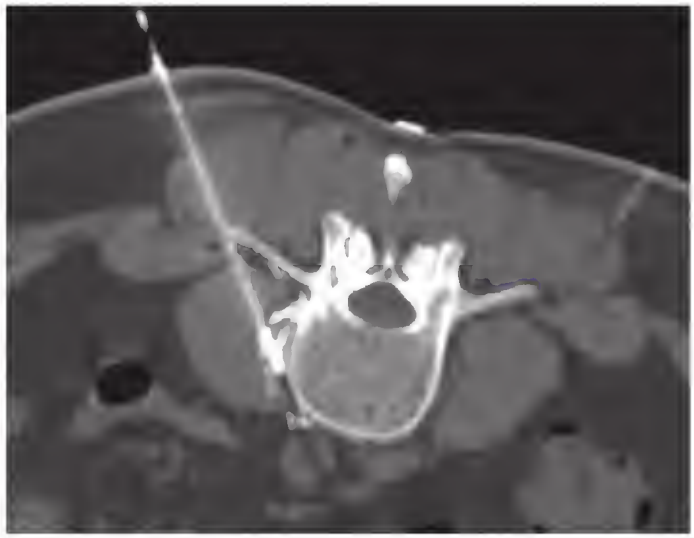


Figure 17: CT-guided lumbar sympathectomy for pain management.

Radiofrequency ablation (RFA)

Radiofrequency ablation of osteoid osteoma and liver and lung malignancies is one of the newer applications of CT.

Vertebroplasty

Transpedicular insertion of a bone biopsy needle in the diseased vertebra under CT guidance, followed by delivery of bone cement into the body of the diseased vertebra is used for management of painful vertebral pathologies.

CT-Guided Radiotherapy Planning

Radiotherapy treatment is usually planned in the axial planes. CT has been extensively investigated as a method of providing pre-treatment data for radiotherapy planning. CT not only provides accurate location and staging of the tumour but also calculates the volume of the tumour to be irradiated using sophisticated software. It is also useful in successive follow-ups.

Liver Volume Estimation in Transplant Patients

CT enables accurate volumetric measurement of a donor liver prior to transplant. This is essential in order to avoid small for size grafts from living donors, which would compromise the outcome of the liver transplant.

POSITRON EMISSION TOMOGRAPHY (PET)/COMPUTED TOMOGRAPHY

The combination PET/CT scanner is a major advancement in imaging technology and patient care. As the name implies, it combines two scanners, the PET scanner, which shows metabolism and the function of cells, and the CT which shows detailed anatomy. The result is that doctors are now able to get highly defined, 3D images inside the human body along with functional information of the same (**Figure 18**).

SAFETY CONCERNS AND RADIATION ISSUES

With the tremendous increase in the use of CT in the past decade, radiation exposure from CT have become a worrisome

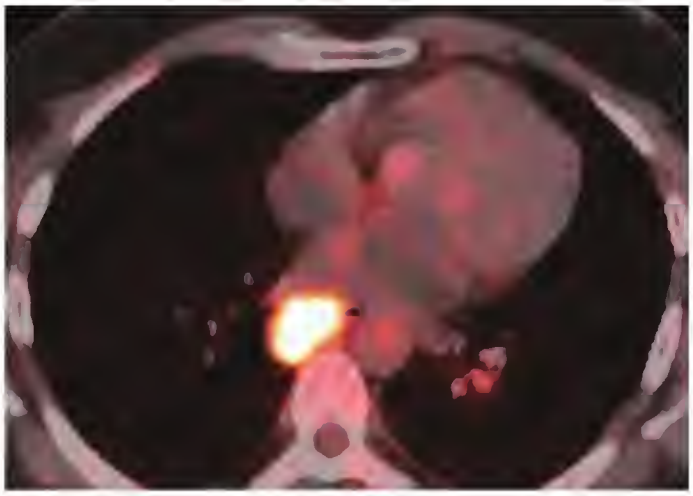


Figure 18: Axial PET/CT shows increased FDG uptake in a subcarinal lymph node.

issue. Recent studies have expressed concern over X-ray-induced cancer risk, especially in children. Proper adjustment of scan parameters, using radiation doses as low as reasonably achievable and avoiding indiscriminate use of this modality are some of the ways suggested for lowering this radiation risk.

CT VERSUS MRI

The soft tissue resolution of CT is not at par with that of MRI, especially in imaging of the brain and spine. However, CT scores in imaging of the lung, bowel and skeletal structures. CT is the modality of choice in acute and trauma settings due to shorter scan times.

CONCLUSION

Although the discovery of CT was a major break-through in the field of diagnostic radiology, the original model has undergone many changes and developments. The list of applications possible on a CT scanner is getting bigger and bigger as newer applications get added. The currently used multi-detector, multi-slice scanners offer sub-second scan times and provide true volumetric data with exquisite 3D renderings. With a large increase in the use of CT, radiation issues are emerging as a matter of concern, and need to appropriately be taken care of.

RECOMMENDED READINGS

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2. *Grainger and Allison's Diagnostic Radilogy;* 4th Ed. Churchill Livingstone, pp 81-99.
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3.4 MRI in Medicine

Raju Sharma, Ankur Gadodia

INTRODUCTION

Over more than two decades since its clinical inception, magnetic resonance imaging (MRI) has found widespread application in nearly every area of medical practise. MR has had major impact on medical diagnosis and has replaced, many previous 'gold standard' invasive diagnostic procedures with safer and accurate alternative non-invasive imaging.

HISTORY

The phenomenon of nuclear magnetic resonance was discovered by physicists in the 1940s and was first utilised for imaging the human body in the late 1970s. The process of acquiring MR images was first illustrated by Lauterbur in 1973.

BASIC PHYSICS

MRI is based on excitation and detection of electromagnetic energy emitted by protons (H^+). Hydrogen nuclei (1H), possess the strongest magnetic moment and are in high abundance in the human body. Consequently, hydrogen is the most widely used element for MR imaging. On application of electromagnetic radiofrequency pulses, these protons emit signal which is received and converted into an image. The greatest advantage is excellent soft tissue contrast resolution. The physics of MRI is extremely complex and a full discussion of the same is beyond the scope of this chapter and a brief summary of the MR principles are discussed below.

The first step in MRI is application of a strong magnetic field. For this the patient is placed within a large magnet, either permanent or superconductive. The nuclei adopt one of two possible orientations: parallel or antiparallel to the external field. A greater proportion of nuclei align in the parallel direction, so that the net vector of their alignment, and hence net magnetic vector will be in the direction of the external field. Each nucleus spins around the line of the field in a motion known as precession. The frequency of this precession is given by the Larmor equation: $F = \gamma B_0/2\pi$ where F is the precessional frequency, B_0 is the strength of magnetic field, and γ is the gyromagnetic ratio of the nucleus.

The net magnetisation vector from the nuclei inside the magnet in its equilibrium state is static and does not produce a measurable signal. To obtain information from the spins, the direction of the net magnetisation vector has to be altered. This is done by applying a radiofrequency (RF) pulse at the same frequency as the Larmor frequency. The RF pulse causes the net magnetisation vector of the hydrogen atom to turn or flip towards the transverse plane, i.e. a plane at right angles to the direction of the external magnetic field. Following the cessation of the RF pulse, the extra energy is dissipated to the surrounding chemical lattice in a process known as T1 relaxation. In addition, the RF pulse brings the precessing protons in phase, i.e. their spins are now in synchrony. The process of the dephasing which occurs due to inhomogeneities in the nuclear magnetic environment is known as T2 relaxation. The component of the net magnetisation vector in the transverse plane induces a current in the magnetic coils (radiofrequency receiver coils). This current is known as the MR signal and is the basis for formation of an image. By varying the time of application of the signal (time to repetition or TR) or the time to acquiring the RF pulse (time to echo or TE) various image contrasts may be obtained.

Advantages of MRI include lack of ionising radiation, true multiplanar imaging, high soft tissue contrast and spatial resolution.

BASIC MR SEQUENCES

There are two basic MR sequences that are frequently used for MR imaging: spin-echo or gradient-echo techniques. Other sequences are modification of these basic sequences.

Spin Echo (SE) Sequences

Conventional spin echo pulse sequences are used to produce T1, T2 or proton density weighted images and are one of the most basic pulse sequences used in MRI. Spin echo sequences are still considered the gold standard in that the contrast they produce is easily understood and is predictable. Spin echo sequences are versatile, available on all scanners, produce true T2 weighting and are gold standard for image contrast and weighting. Disadvantage includes long scan times.

Fast Spin Echo (FSE) Sequences

Fast spin echo (FSE) is a much faster version of conventional spin echo, but may show different contrast and demonstrate decreased magnetic susceptibility effects. Fat appears bright on both T1W and T2W images, muscles appear darker on T2 weighted images and haemorrhage may be missed on FSE sequences. However, ferromagnetic implants do not show as much artefacts as other sequences. FSE sequences are usually used for brain, spine, joints, extremities and the pelvis. Advantages include short scan times, high resolution imaging and decreased magnetic susceptibility.

Gradient Recalled (GRE) Sequences

GRE images should be called T2* weighted not T2 weighted because of the effects of an imperfect magnetic field. Air pockets (sinuses or intestines), dense bone (skull base), and iron-rich blood breakdown products (methaemoglobin or haemosiderin) all change the main magnetic field in their immediate vicinity, so tissues around such inhomogeneities will experience different magnetic fields. One area where the prominent magnetic susceptibility artefacts on gradient recalled images can be used is in detection of haemorrhage. These sequences are typically shorter than routine sequences, and may yield significant image contrast.

Inversion Recovery (IR) Sequences

Short inversion time

Short tau inversion recovery (STIR) sequence has very low signal from fat but still has high signal from fluids. It is used in the spine and musculoskeletal system to visualise marrow oedema, fractures, avascular necrosis, metastases, etc.

Intermediate inversion time

These are used in paediatric neurology to better visualise gray white matter interface, to look for focal cortical dysplasia, heterotopias, etc.

Long inversion time

Fluid attenuation inversion recovery (FLAIR) sequence uses long inversion times (1,800-2,500 ms), depending on field strength, to null the signal from cerebrospinal fluid (CSF). FLAIR is commonly used for neurological imaging to visualise periventricular lesions, white matter lesions. In addition, cortical changes which can also be hard to visualise with T2W sequences are made more prominent (**Figures 1A to C**).

Diffusion Weighted Imaging (DWI)

Diffusion is a term used to describe moving molecules due to random thermal motion. In normal tissues extracellular water diffuses randomly whereas in ischaemic tissue, cells swell and absorb water thereby restricting diffusion. DWI should be interpreted in conjunction with apparent diffusion co-efficient (ADC) maps. Bright area on DWI should also be viewed on ADC maps. If the lesions appear bright on ADC, the bright appearance on diffusion can be due to T2 shine through effect rather than true restricted diffusion, whereas lesions which are dark on ADC map represent restricted diffusion. One of the major uses for diffusion-weighted imaging sequence is in the diagnosis of recent stroke where areas of decreased diffusion represent infarction. DWI has also been used in the evaluation of other organs of the body such as liver, breast, kidneys and prostate. Whole body diffusion imaging is used in oncology for delineation of metastatic disease and response to treatment. Infarcts, encephalitis, abscesses, tightly packed tumours, metastases, epidermoid cysts, etc. also show restricted diffusion.

Perfusion Weighted Imaging (PWI)

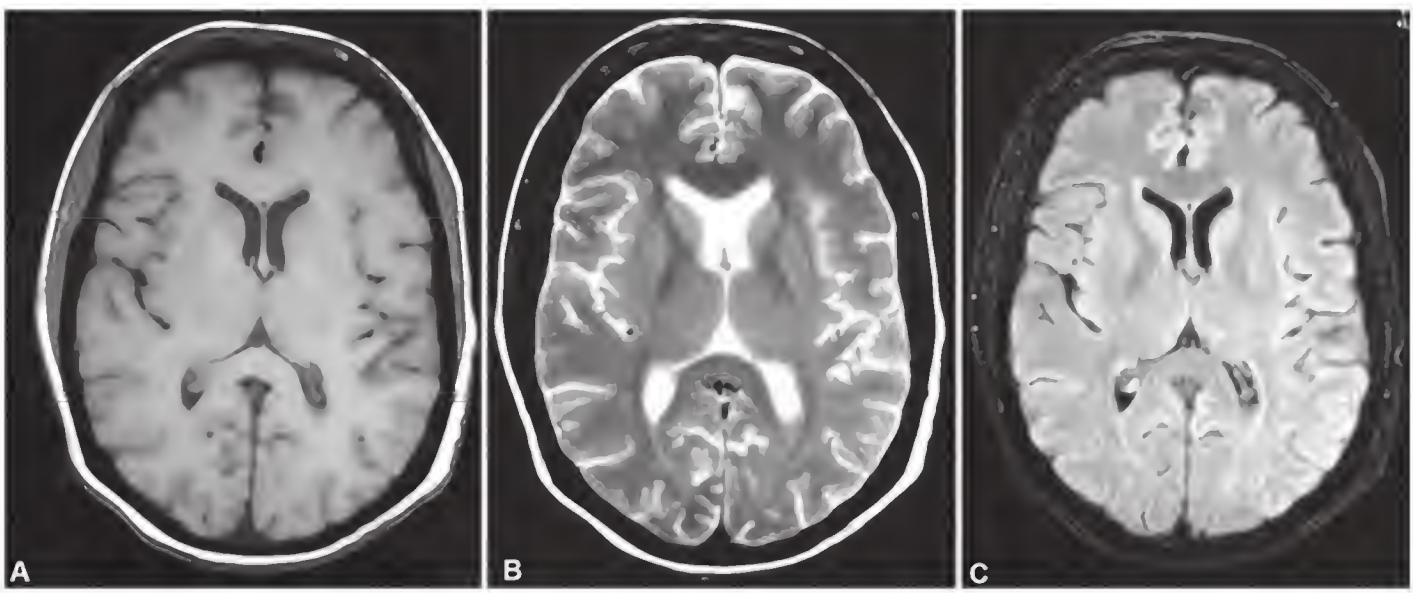
Perfusion is a measure of the vascular supply to a tissue. Since vascular supply and metabolism are usually related, perfusion can also be used to measure tissue activity. Perfusion imaging utilises a bolus injection of gadolinium administered intravenously during ultrafast T2 or T2* acquisitions. This is used for evaluation of ischaemic disease or metabolic activity of tissues. On the cerebral blood volume (CBV) map, areas of low perfusion appear dark (stroke) whereas areas of higher perfusion appear bright (malignancies). Perfusion-weighted MR imaging has applications in the evaluation of a number of disease states, including cerebral ischaemia and reperfusion, brain tumours, epilepsy, differentiation between radiation necrosis and tumour recurrence and blood flow deficits in Alzheimer's disease.

MR Spectroscopy (MRS)

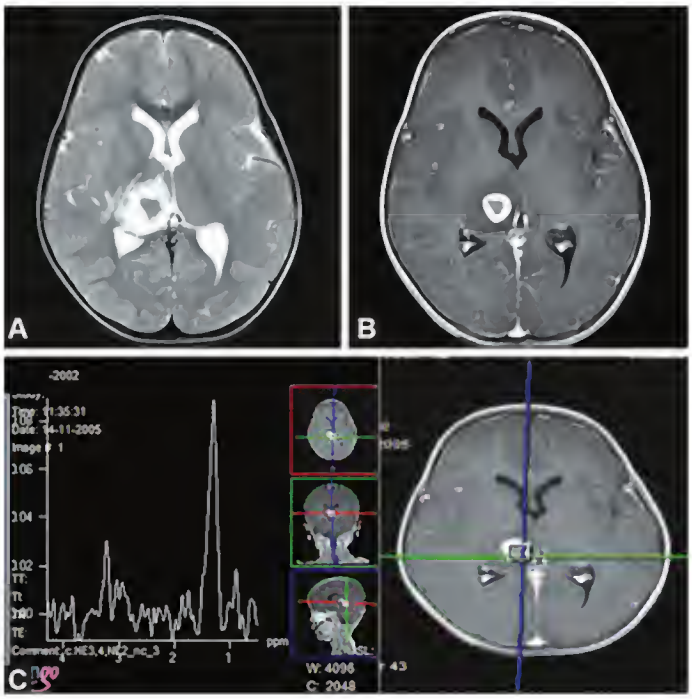
Spectroscopy provides a frequency spectrum of a given tissue based on the molecular and chemical constituents of that tissue. Spectroscopy has now become routine part of MR imaging to evaluate tissue metabolism. Proton spectroscopy has been used primarily for brain applications (**Figures 2A to C**) and recently for other organs, such as the liver, breast, prostate, and soft tissue. The use of spectroscopy expands the repertoire of anatomical information by providing information on intracellular metabolites. The major metabolites detected in the CNS are N-acetyl aspartate (NAA), a neuronal marker; choline, a marker for cellularity and cell membrane turnover; creatine, a marker for energy metabolism; and lactate, a marker for anaerobic metabolism. In addition to these metabolites, other metabolites that can be assessed include alanine, glutamine, myoinositol, and succinate.

Functional Imaging

Functional MR imaging (FMRI) is a rapid MR imaging technique that acquires images of the brain during activity or stimulus and at rest. The two sets of images are then subtracted to depict regional cortical blood flow changes in space and time



Figures 1A to C: Axial T1W (A), T2W (B) and FLAIR (C) images of the cerebrum, mid ventricular level. CSF is hypointense on T1W and hyperintense on T2W images. In FLAIR sequence image, static fluid signal is selectively suppressed.



Figures 2A to C: Tuberculoma in a 23-year-old male. Axial T2W image (A) shows hyperintense lesion with central hypointensity seen involving the right thalamus. On post-contrast image (B) thick nodular rim enhancement is seen. Single voxel MR spectroscopy image (C) shows prominent lipid peak. These findings are suggestive of tuberculosis.

during performance of a particular task. An important clinical application of FMRI is presurgical mapping where relation of the functional areas can be defined in relation to mass lesions, thus selecting the appropriate management strategy (surgical versus non-surgical) and avoid damage to vital neural tissues. Other applications involve the understanding of brain functions, evaluation of stroke, epilepsy, pain and cognitive problems.

MR Angiography (MRA)

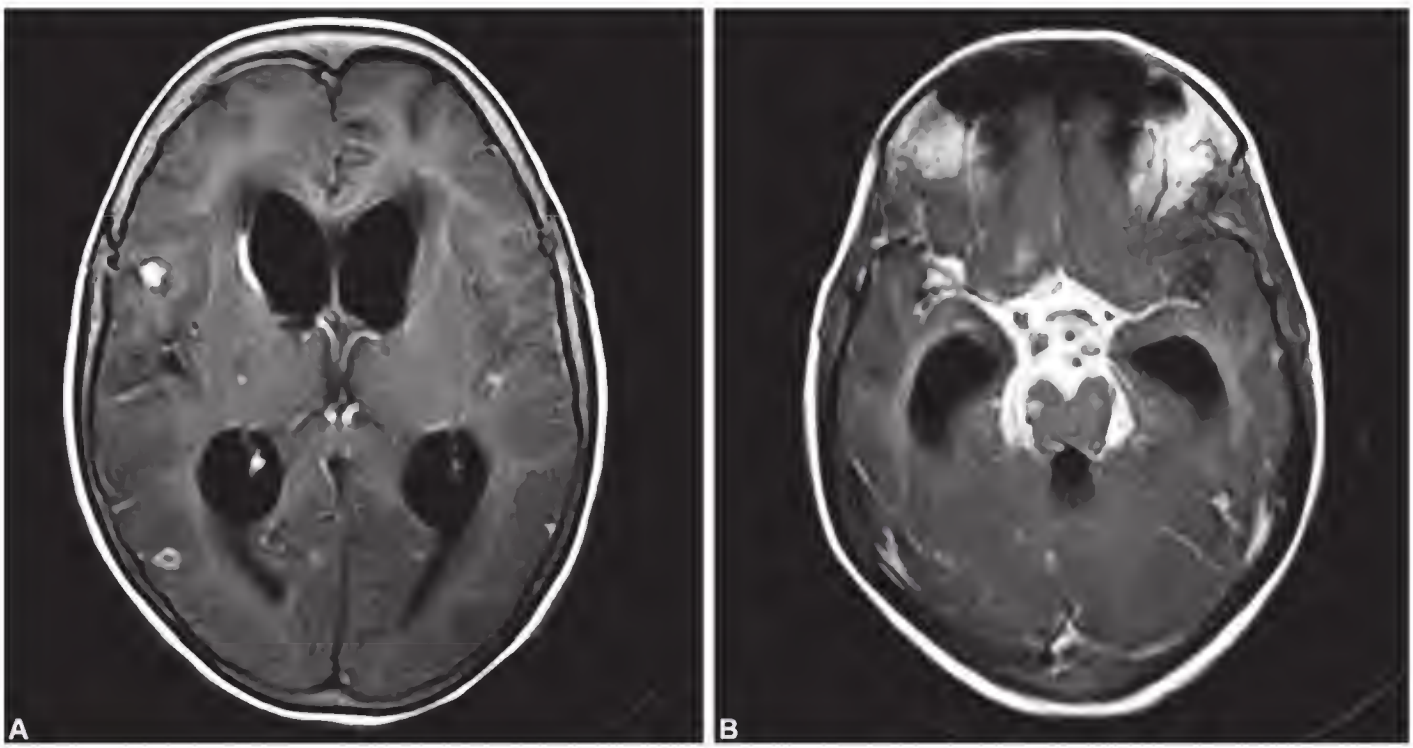
The principle of MRA is to acquire images where the signal returned from the flowing nuclei is high and the stationary nuclei is low. Thus, contrast between vessel and background tissue is achieved. MRA is used for non-invasive assessment of many vascular abnormalities, including aneurysms, dissection, stenosis, vessel anomalies, and coarctation. In many centers, MRA has emerged as the imaging modality of choice in the evaluation of the thoracic and abdominal aorta, and their major branch vessels, including the carotid, renal, and mesenteric arteries. It is also the modality of choice for getting an overview of all major arteries in diseases like aortoarteritis.

MR Contrast Agents

The most commonly used, clinically approved contrast for MR imaging, is a paramagnetic agent (atoms with unpaired electrons in their outer shells) containing gadolinium, a T_1-shortening agent. Contrast enhancement is extremely useful in evaluation of pathology like neoplasm, infection and inflammation. Gadolinium has the ability to pass through the breaks in the blood-brain barrier and thus is invaluable in imaging the nervous system pathologies (**Figures 3A and B**). In body imaging organs like liver, spleen, pancreas and kidneys enhance immediately after contrast injection and thus, rapid dynamic imaging is recommended for their evaluation.

MR HARDWARE

The hardware of a MRI machine consists typically of a cylindrical superconducting magnet surrounding the patient to generate a large, static magnetic field; gradient coils through which flowing current generates small changes in the magnetic field; radiotransmitter/receiver coils; electronics for radiofrequency transmitting and receiving; and a computer to reconstruct the spatial image from the frequency spectra.



Figures 3A and B: Tuberculoma with meningitis in an 18-year-old male. Axial post-contrast images (A and B) show thick enhancing exudates involving the basal cisterns with mild hydrocephalus. Also, note presence of homogenously ring enhancing lesions involving the right frontal and parietal lobes. These findings are suggestive of tuberculosis.

MR SAFETY AND CONTRAINDICATIONS

Any ferrous containing object is potentially dangerous within the MRI scanning room and patients are always advised to remove all ferromagnetic substances. Hearing aids, jewellery, watches, glasses, prostheses, credit cards and any type of implant should be removed before entering the scanner as they can potentially become a dangerous projectile. Current generation of orthopaedic implants including prosthetic joints, rods, screws, nails, clips, etc. are MR compatible and are not contraindications for MRI although they may significantly degrade image quality.

MR imaging is contraindicated for patients with metal implants or foreign bodies, such as intracranial aneurysm clips, intraorbital metallic foci, cardiac pacemakers, or specific types of cardiac valves. In these instances, these objects may be dislodged or damaged by the magnetic field. MR imaging may also be contraindicated for claustrophobic or uncooperative patients who may not respond to conscious sedation protocols. MRI examination poses almost no risk to the average patient when appropriate safety guidelines are followed.

BASIC CONCEPTS IN MR INTERPRETATION

As mentioned previously, various sequences are used to obtain image contrast. Most pathologies appear dark on T1 and bright on T2 and FLAIR (or STIR) images.

T1- and T2-Weighted Imaging

The selection of TE and TR determines the resulting image contrast. T1- and T2-weighted imaging are the most widely used sequences for soft-tissue delineation of anatomic structures and related pathologic conditions. On T1W images, tissues that have short T1 relaxation times (such as fat) appear as bright signal (**Table 1**). Tissues with long T1 relaxation times (such as cysts, cerebrospinal fluid and oedema) show as dark signal. On T2W images, tissues that have long T2 relaxation times (such as fluids) appear bright.

Table 1: Signal Intensities Seen on T1- and T2-W Images

	T1W	T2W
High signal	Fat Fatty marrow Methaemoglobin Slow flowing blood Radiation change Paramagnetic contrast agents Proteinaceous fluid Melanin	High free water (oedema, fluid, bile) Proteinaceous tissue Blood products (oxyhaemoglobin and extracellular methaemoglobin)
Low signal	Collagenous tissue (ligament, tendons) High free water (oedema, fluid, bile) cortical bone, Infection Tumours	Collagenous tissue (ligament, tendons) Cortical bone Bone islands De-oxyhaemoglobin Haemosiderin Calcification
No signal	Air Fast flowing blood Tendons Cortical bone Scar tissue Calcification	Air Fast flowing blood Tendons Cortical bone Scar tissue Calcification

HOW DO YOU DETERMINE THE SEQUENCE FROM THE FILM?

When confronted with a series of MRI images, the first thing to do is identify known areas of fluid, for example, CSF, vitreous chamber, the urinary bladder and renal pelvis. If these areas return a high signal, then the image is T2W. If the fluid is bright and the fat is dark then it is likely to be a fat suppressed T2 image/STIR image. If fat is bright and the fluid is dark then it is likely to be a T1W image. Contrast enhanced scans are usually labelled and are usually T1W sequences with or without fat suppression. Fat in these cases will then be dark and the images are usually compared with the pre-contrast T1W images to ascertain the degree, if any, of enhancement. The way to differentiate a plain scan from a post-contrast study of the brain would be to look at the nasal turbinates on T1W images. Post-contrast studies invariably show enhancement of the turbinates and bright signal.

Second option is to look for the printed TR and TE on the film. T1W images have short TR and TE (TR of the order of under 500-600 ms, while the TE is around 15-20 ms) whereas T2W sequences have longer TR and TE (TR of the order of more than 1,000 ms, TE over 80-100 ms). Inversion time (TI) is in the range of 100-180 ms in STIR and 1,800-2,500 ms in FLAIR images.

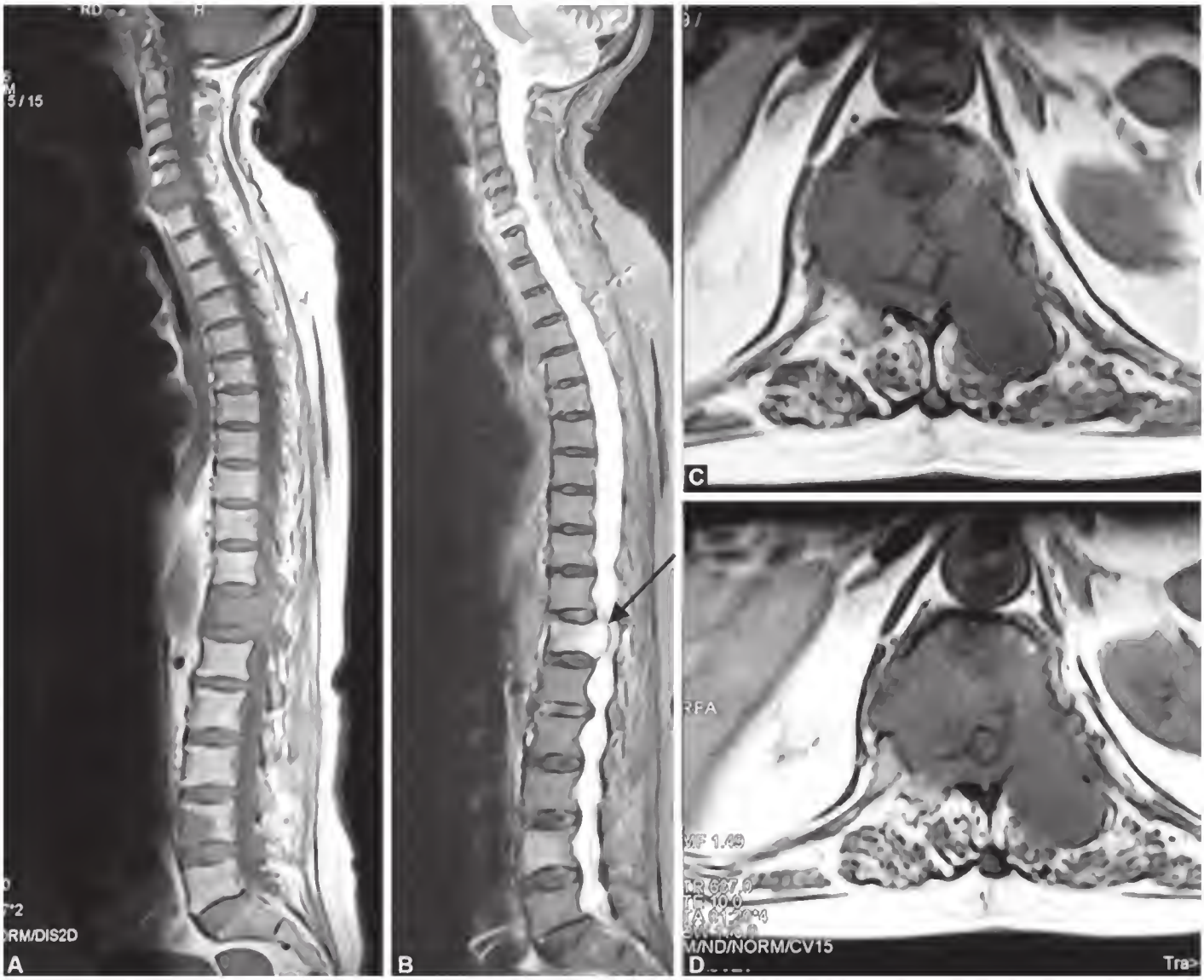
CLINICAL APPLICATIONS

Neurological Disease

Brain MR is the most commonly performed MR examination in most institutions. Common indications include – multiple sclerosis, primary tumour assessment and/or metastasis (**Figures 4A to D**), infections tuberculosis, toxoplasmosis, HIV)(**Figures 5A to D**), infarction (cerebral vascular accident vs. transient ischemic attack), haemorrhage, visual disturbances, epilepsy, trauma and unexplained neurological symptoms or deficit. Typically, most pathology appear hyperintense on T2W and hypointense on T1W images, but depending on the lesion morphology, area of involvement (grey matter vs. white matter), associated features (presence/absence of calcification, haemorrhage) and enhancement patterns one can come to a diagnosis. MR contrast agent (gadolinium) is required for assessment of tumours, infection and inflammation. Infectious process such as abscess shows intense thick nodular rim enhancement. Meninges enhance in infections (tuberculosis, pyogenic or viral meningitis) and leptomeningeal tumour spread. Contrast enhanced MR can also ascertain the age of the infarct.

MRI with diffusion (DWI) and perfusion imaging (PWI) has an important established role in identification of hyperacute infarct and ischaemia. An acute infarct shows on DWI as an area of relatively high signal (**Figures 6A to C**). DWI is the most sensitive imaging test available for the diagnosis of hyperacute infarction. Perfusion weighted imaging can also be used to calculate the relative blood supply of the particular volume of the brain. By combining PWI and DWI methods, if PWI is larger than DWI, then the area depicted may represent 'at risk' or penumbral tissue. Evaluation of these tissue characteristics is important for the targeting of therapeutic measures to optimise clinical outcomes. Thus, MR can accurately diagnose hyperacute infarct and identify ischaemic penumbra.

Owing to the relatively poor visualisation of acute haemorrhage, time taken for the performance of examination and logistic problem with monitoring equipment, MR has not been recommended for the initial screening of acute head trauma. It



Figures 4A to D: Vertebral metastasis in a 68-year-old female. Sagittal T1W (A), T2W (B) MR images showing altered spinal signal intensity (hyperintense on T2W and hypointense on T1W) involving the bodies of multiple vertebrae. Axial T1W (C and D) MR images showing involvement of the both anterior and posterior elements of the vertebrae associated with soft tissue component extending into the spinal canal causing cord compression. Posterior vertebral margins of the involved vertebrae are showing convex borders (arrow).

is most useful in non-acute situation of otherwise stable patient with an ongoing neurological/ cognitive deficit. In particular, MRI is highly sensitive for detection of diffuse axonal injury.

MRA may be used to image cerebral vessels (vascular stenosis, aneurysms and vascular malformations). Sensitivity is similar to catheter angiography for detection of aneurysm of 3 mm or greater. MRA produces three dimensional images that can be rotated, manipulated on a working station, allowing a highly dedicated examination. MRA may also be useful in certain clinical presentation with a high probability of cerebral aneurysm. A common example is isolated third nerve palsy caused by aneurysm of posterior cerebral artery. MRA has largely replaced conventional arteriographic studies for evaluation of atherosclerotic disease, except in cases of critical stenosis (>70%).

Musculoskeletal Applications

Applications in the musculoskeletal system include evaluation of internal derangement of joints (knee/hip/shoulder), soft tissue injury/inflammation, ligaments and tendons, bone marrow for marrow infiltration, bone infarcts or contusions. In musculoskeletal neoplasms, the role of MR is to demonstrate the extent of the lesion prior to surgery rather than primary characterisation for which plain radiographs are the investigation of choice. MR evaluates compartmental involvement (e.g. extension of bone tumours into soft tissues and joints), skip lesions within the bone marrow and status of neurovascular bundle. Role of intravenous contrast in musculoskeletal system is in evaluation of infection (bone, joint or soft tissues) (**Figures 7A and B**) and evaluation of post-operative spine to differentiate between scar tissue from non-enhancing residual disc.

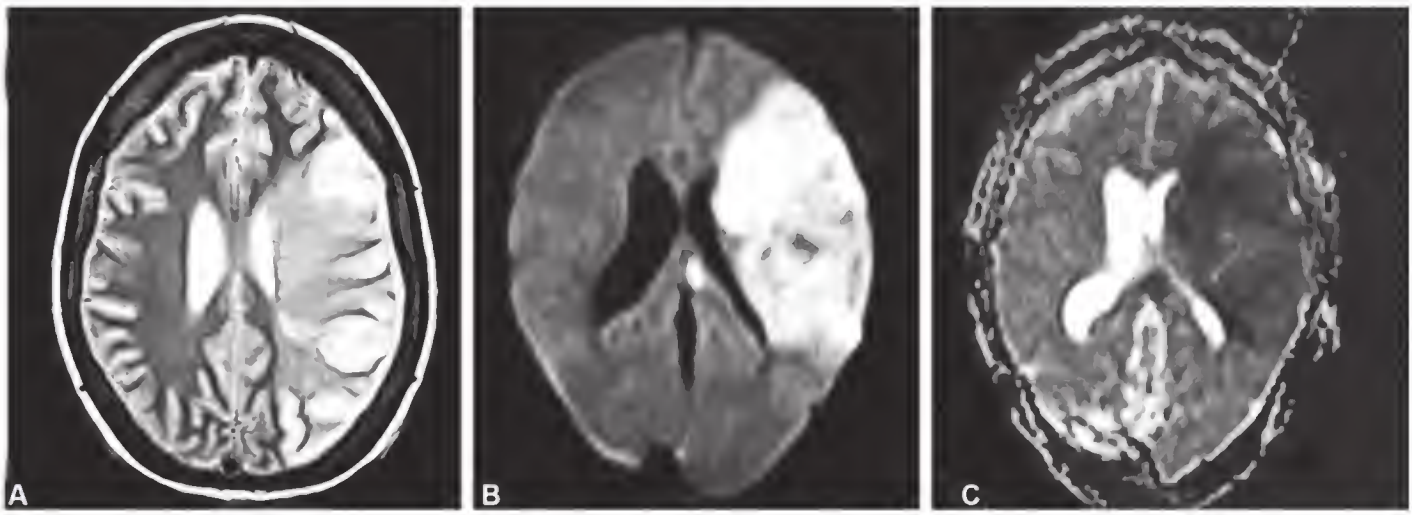
Advanced musculoskeletal MR applications include MR arthrography. In MR arthrography joint cavity is distended by intra-articular injection of dilute gadolinium. It is extremely useful in demonstrating the glenoid and labral tears (shoulder and hip) and in evaluation of the post-operative meniscus.

Hepatobiliary Applications

MRCP uses heavily T2 weighted sequences such as HASTE (half Fourier acquisition with single shot turbo spin echo) or RARE (rapid acquisition with relaxation enhancement) to visualise



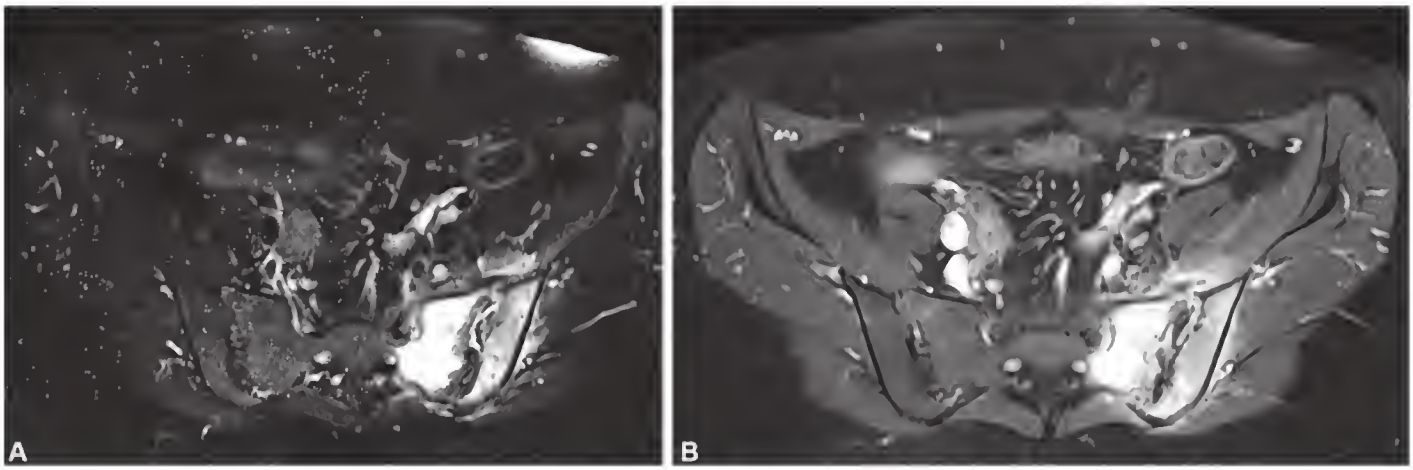
Figures 5A to D: Tubercular spondylodiskitis lumbar spine in a 44-year-old male. Sagittal (A) and Axial T2W (B) image shows hyperintensity and irregularity involving the end plate of two contiguous vertebras, intervening disc with small epidural component. Axial (C) and sagittal (D) post-contrast images demonstrates intense enhancement of two contiguous vertebrae, intervening disc and extradural soft tissue. Also note presence of prevertebral abscess.



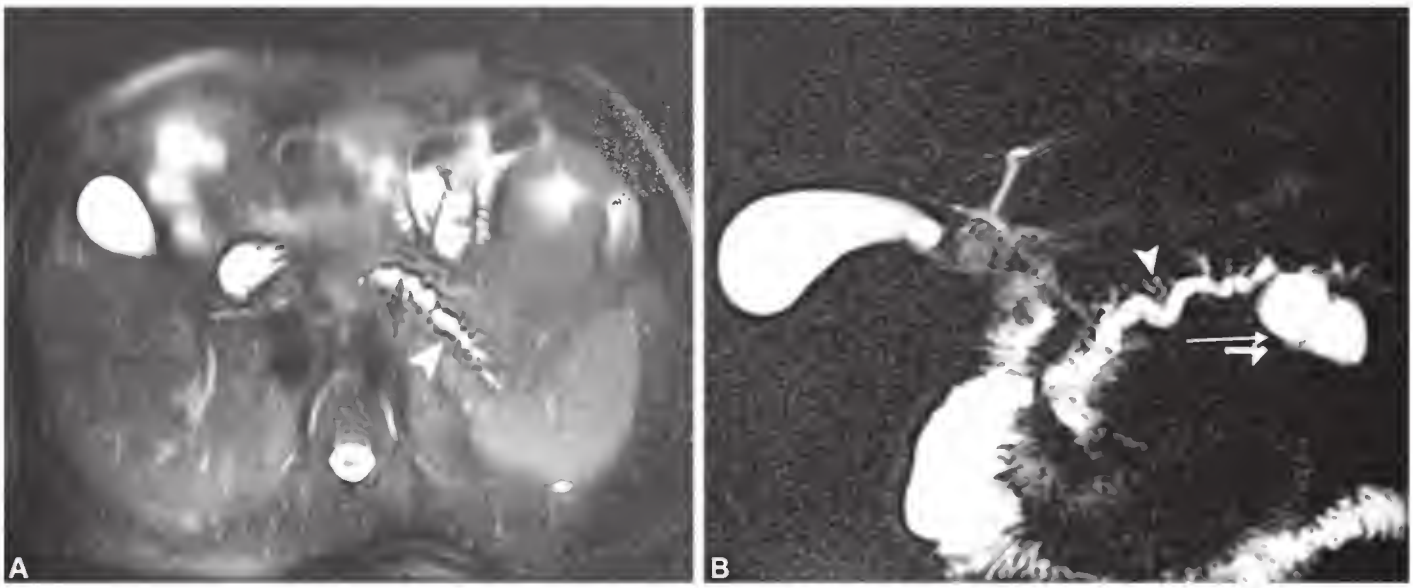
Figures 6A to C: Acute infarct in a 60-year-old male. Axial T2W (A) image shows hyperintensity seen involving the left parietotemporal lobes (MCA territory), with mild mass effect. Diffusion weighted (B) image shows hyperintensity and ADC maps (C) show hypointensity in the corresponding area suggestive of restricted diffusion (cytotoxic oedema).

static fluid in the biliary and pancreatic ducts as high signal intensity. The heavy T2 weighting provides very high (bright) signal of static fluid within the biliary and pancreatic ductal systems, while the background tissues have very low (dark) signal (**Figures 8A and B**). These images look analogous to endoscopic retrograde cholangiopancreatography (ERCP) images.

MRCP is now the primary tool in the evaluation of biliary obstruction (calculi, intrinsic and extrinsic masses), intrahepatic bile duct diseases, post-surgical anatomic alterations, and congenital anomalies of the biliary and pancreatic tract. A potential use of MRCP is the demonstration of aberrant bile duct anatomy before cholecystectomy. MRCP is increasingly becoming the initial imaging modality for the biliary system, with ERCP reserved for only therapeutic indications. MRCP can be combined with other sequences for the comprehensive evaluation of the liver, biliary tree and pancreas. In



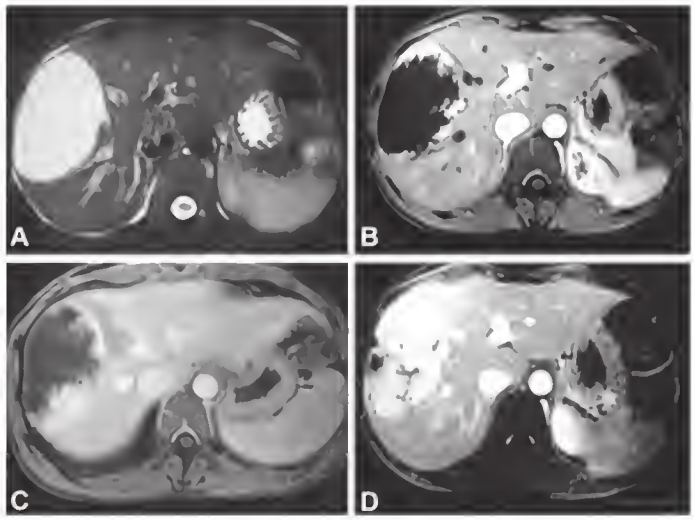
Figures 7A and B: Tubercular arthritis left sacroiliac joint in a 26-year-old female. Axial T2W (A) image shows hyperintensity involving the left sacral ala and the iliac bone, with joint widening and irregularities. Post-contrast (B) T1W image shows intense homogenous enhancement. Findings suggestive of infective sacroillitis.



Figures 8A and B: Chronic pancreatitis in a 37-year-old female. Axial T2W (A) and MRCP projectional (B) images show dilation of the main pancreatic duct (arrowhead) and side branches with a pseudocyst (arrow in B) involving the tail of the pancreas. These findings are suggestive of chronic pancreatitis.

choledocholithiasis/cholelithiasis, calculi appear as dark filling defects within the high-signal-intensity fluid. Benign strictures due to sclerosing cholangitis are multifocal and alternate with slight dilatation or normal-calibre bile ducts, producing a beaded appearance, whereas in malignant obstruction there is abrupt cut-off and eccentric wall thickening. The current limitation of MRCP is its relatively low spatial resolution.

Multiphasic contrast enhanced MR is the investigation of choice for characterisation of focal liver lesions and to look for presence of focal lesion in cirrhotic liver. In cirrhotic livers, MR can be helpful in differentiating between regenerative, dysplastic nodules and hepatocellular carcinoma. Hepatocellular carcinoma enhances in the arterial phase, washes out in the portal venous phase and shows capsular enhancement in delayed phase. On the other hand peripheral nodular discontinuous enhancement of a lesion with delayed fill in is typical of haemangiomas (**Figures 9A to D**). Peripheral arterial phase enhancement and portal venous phase wash out is typical of metastases. MRI is considered a non-invasive diagnostic tool for quantification of iron concentration in haemochromatosis. Liver specific contrast agents (contrast

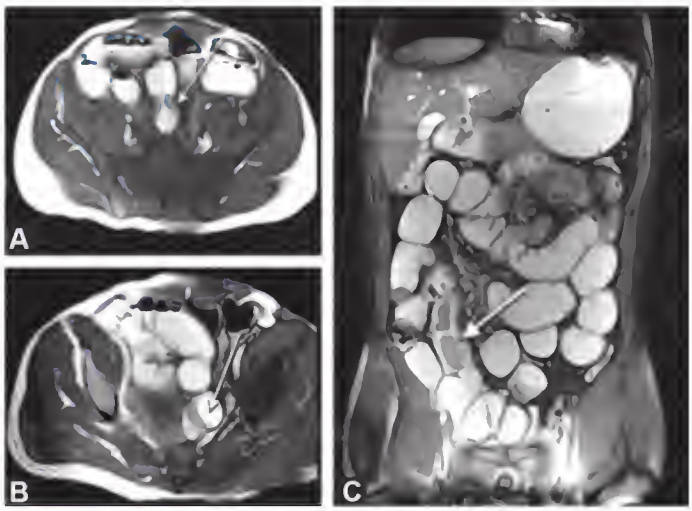


Figures 9A to D: Liver haemangioma in a 43-year-old female. Axial T2W (A), post-contrast arterial phase (B), venous phase (C) and delayed phase (D) images show a well-defined mass lesion involving the right lobe of the liver. Mass is hyperintense on T2W images. Arterial phase image shows nodular discontinuous peripheral enhancement similar to signal intensity of the aorta. Venous and delayed phases show progressive fill on the contrast in the lesion. Findings are suggestive of liver haemangioma.

agents specific to the hepatobiliary or the reticuloendothelial system) add to the diagnostic capabilities of MR in problem cases.

Gastrointestinal Applications

MRI of the bowel has been an under explored field of application for years. High soft tissue contrast resolution, acquisition of multiplanar images and the possibility to obtain functional information make MR a useful imaging technique to evaluate small bowel pathology. Applications include MR enteroclysis, MR colonography and MR virtual colonoscopy. The absence of ionising radiation is an important advantage of MRI examinations because inflammatory diseases such as Crohn's disease (CD) need to be followed up frequently, and are prevalent among young adults. MR enteroclysis (MRE) and MR colonography are emerging techniques for the evaluation (**Figures 10A to C**) of small and large intestinal diseases.



Figures 10A to C: MR Enteroclysis demonstrating tubercular small bowel stricture in a 20-year-old male. Tru-FISP (true fast imaging with steady-state precession) axial (A and B) and coronal (C) images show circumferential short segment wall thickening involving distal illeal loops.

Chest Applications

MRI does not substitute CT in the investigation of most thoracic conditions requiring cross-sectional imaging. MRI in chest has poor spatial resolution due to extremely low proton density of normal lung and strong susceptibility artefacts induced by the multiple air—soft tissue interfaces within the lung, and the consequences of cardiac and respiratory movement. The main indications for chest MRI include characterisation of mediastinal lesions that are equivocal on CT, evaluation of superior sulcus tumours, particularly if brachial plexus involvement is suspected and posterior mediastinal masses.

Cardiovascular Applications

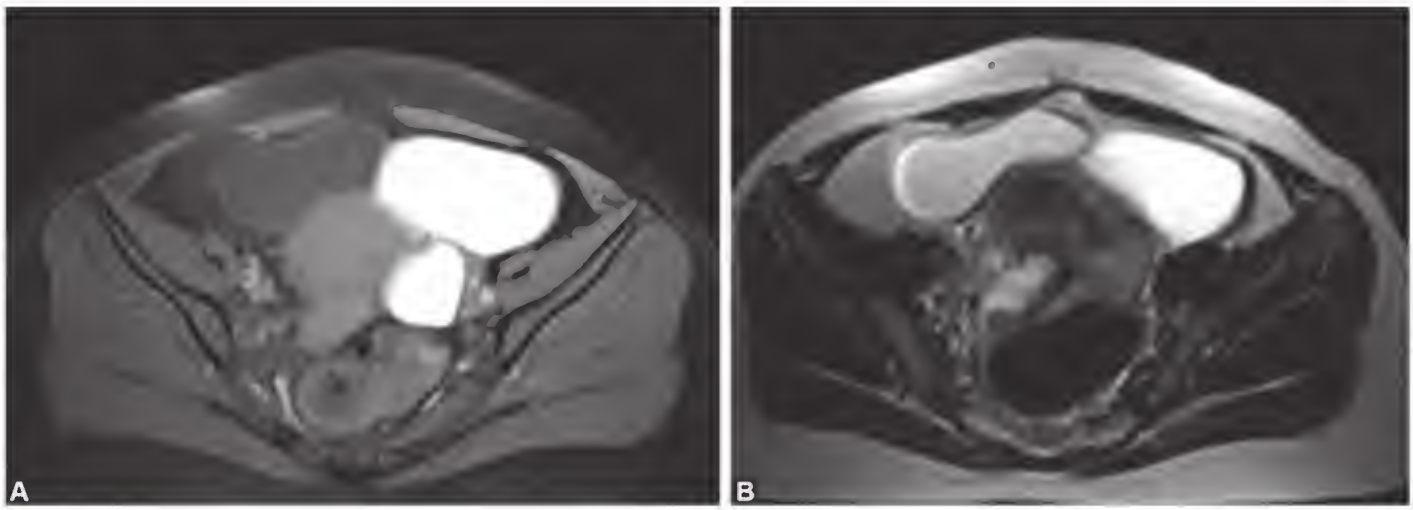
Technical advances in MRI have led to increased application of this modality for comprehensive evaluation of cardiovascular diseases. Gradually, MRI has become the 'gold standard' for the assessment of numerous cardiovascular conditions. Important clinical indications of cardiac MRI include heart failure, ischaemic heart disease, myocardial viability, cardiac masses, congenital heart disease, and diseases of the myocardium, pericardium, valves and the entire vascular tree. Cardiac MR for ischaemic heart disease shows higher spatial resolution and sensitivity compared to stress thallium, particularly for subendocardial infarcts. Disadvantages include: longer scanning time, need for general anaesthesia, various contraindications including pacemaker.

Urological Applications

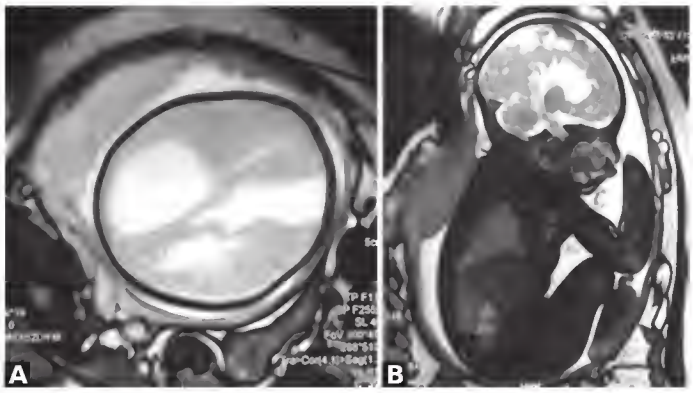
MRI is used as a problem-solving tool in renal imaging, to characterise indeterminate masses on ultrasound and computed tomography. MRI is an alternative to CT and is particularly useful in paediatric or pregnant patients, and in patients with renal insufficiency and when ionising radiation/iodinated contrast is to be avoided. MR urography (MRU) is clinically useful in the evaluation of suspected urinary tract obstruction, haematuria, and congenital anomalies.

Pelvic Applications

These include gynaecological conditions like pelvic pain or pelvic mass, especially to differentiate between uterine and adnexal masses, indeterminate adnexal masses on ultrasound, detection of adenomyosis (blurring and thickening of the junctional zone of uterus on T2 weighted images), differentiation between uterine fibroids and focal adenomyosis (fibroids appear well defined and hypointense on T2 weighted images while focal adenomyosis/adenomyomas appear poorly



Figures 11A and B: Endometriosis in a 24-year-old female. Axial T1W (A) and T2W (B) images show left adenaxal mass lesion. Mass is hyperintense on T1W images and shows mixed intensity (hyperintense upper part and hypointense lower part). These findings are suggestive of endometriosis.



Figures 12A and B: Foetal MR showing corpus callosal agenesis with dorsal interhemispheric cyst at 30 weeks gestation. T2W MR axial (A) and sagittal (B) images show dorsal interhemispheric cyst with absence of corpus callosum and dilatation of occipital horn (colpocephaly).

defined and may show intermediate to hyperintense speckling on T2 weighted images). While both endometriosis and dermoids might appear hyperintense (bright) on T1 and T2 weighted images, endometriosis is identified on T1 fat-saturated images as hyperintense due to haemorrhagic contents (**Figures 11A and B**), while fat in dermoids is suppressed. Another important application is the staging of carcinoma cervix and endometrium.

An important application of MR in the male pelvis includes the early detection of prostatic carcinoma using endorectal coils. Unlike other malignancies, prostatic carcinoma appears hypointense (dark) on T2 weighted images amidst the hyperintense peripheral zone. Early peri-prostatic spread, neurovascular invasion or seminal vesicle invasion is well detected on MR.

Obstetric applications of MR include early detection of foetal anomalies, especially when there is difficulty in sonographic visualisation due to unusual lie of the foetus, complex congenital malformation or insufficient amniotic fluid. Foetal MR is especially beneficial in evaluation of the sonographically occult or indeterminate and complex congenital malformations (**Figures 12A and B**). Foetal MR has an established role in the evaluation of neurological and chest anomalies.

RECENT ADVANCES

MR at 3 Tesla

Imaging at higher field strength (3.0-T MR) provides higher resolution and has already proved superior to 1.5-T systems in neuroradiologic and musculoskeletal applications. In the abdomen, 3.0-T MR imaging is beneficial for hepatic imaging, MRCP, angiography, diffusion-weighted imaging, and colonography.



Figures 13A and B: Takayasu's arteritis in a 16-year-old female. Maximum intensity projections of post-contrast MR angiogram (A) and invert image of A (B) demonstrates the narrowing of the proximal left subclavian artery, infrarenal aorta, bilateral common iliac arteries and left renal artery.

WB-MRI (Whole-Body MRI)

Technical improvements in the MR sequences, the remote movement of the imaging table, and the use of specialised surface coils have rendered whole-body screening with MRI a feasible method. Whole-body magnetic resonance imaging is an accurate, safe and fast technique for the demonstration of disease throughout the entire body. Whole-body MRI is used to depict metastases in disseminated metastasis and lymphoma. Whole-body MR angiography can be very helpful for detecting vascular diseases (atherosclerosis, vasculitis) in different anatomic regions of the body (**Figures 13A and B**).

RECOMMENDED READINGS

1. Adam A, Allison D. *Grainger and Allison's diagnostic radiology*. 5th Ed. Churchill Livingstone, 2007.
2. Sutton D. *Textbook of Radiology and Imaging*. 7th Ed. Churchill Livingstone, 2008.

3.5 Nuclear Imaging

BR Mittal

Nuclear Medicine is a field of medical practice where minute quantities of unsealed radioactive substances, which rely on the process of radioactive decay, are used for diagnosis, therapy and clinical research. These procedures provide supportive service to almost all branches of medicine. This unique ability of imaging and therapy is based on the cellular function and physiology rather than relying on the anatomy. Most diagnostic radionuclides emit gamma rays while radionuclides emitting beta particles are used in therapeutic applications. Radionuclides for use in nuclear medicine are produced either in nuclear reactors or in cyclotrons. The reactor produced radionuclides usually have longer half-lives, whereas those produced in cyclotrons have shorter half-lives. Radioisotopes are also generated by natural decay processes in dedicated generators, e.g. molybdenum/technetium or strontium/rubidium. Radionuclides when combined with other chemical compounds form radiopharmaceuticals which on being administered to the patient, localise to specific organs or cellular receptors. These radiopharmaceuticals emit gamma rays that are detected externally by sophisticated instruments such as gamma camera or PET scanners. This process is unlike diagnostic radiographs where external radiation is passed through the body to form an image.

Gamma camera is the basic equipment in nuclear medicine imaging. The uses of computers in conjunction with cameras provide data and information about the area of body being imaged. Planar studies provide a two-dimensional image whereas tomography provides three dimensional view of physiological and biochemical processes. Tomography is the process of producing a picture of a section through an object. It is performed either by transmitting X-rays through an object (transmission computed tomography, as in CT scanning), by measuring proton density (magnetic resonance imaging) or by tomographically detecting the distribution of radioactivity in a patient (emission computed tomography). The two most widely used emission tomographic studies are Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). The three major categories of emission imaging are projection, longitudinal and transverse section imaging. Longitudinal tomography involves sampling over a limited range of angles and usually involves motion of a detector system parallel to long axis of the body. Transverse section tomography involves rotation of the detector system around the body with slices oriented perpendicular to the patient's long axis. The transaxial data is then rearranged to get coronal, sagittal (slice parallel to the patient's long axis) or oblique algorithms.

SPECT refers to tomography with standard nuclear medicine radiopharmaceuticals that emit single photons upon decay. Though emission tomography was reported by Kuhl and Edwards in 1963, but it was X-ray tomography introduced in 1973 by Hounsfield that had a tremendous impact in diagnostic imaging. Practical application of SPECT came into existence only after the advent of the modern computers and availability of rotating gamma camera system. The most apparent advantage of SPECT is its ability to remove the superimposition encountered in two-dimensional (planar) imaging leading to increased detection of lesions. The end result of the nuclear medicine imaging process is a "dataset" comprising one or more images. Multi-image datasets may be dynamic, representing a time sequence (cine or movie), a cardiac gated time sequence, or a spatial sequence where the gamma camera is moved relative to the patient. The computer provides quantitative information for each of the specific imaging techniques.

Nuclear medicine images can be superimposed, using software or hybrid cameras, on images from other modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) to highlight the part of the body in which the radiopharmaceutical is concentrated. This is called image fusion or co-registration. Presently single photon emission computed tomography/computed tomography (SPECT/CT) and positron emission tomography/computed tomography (PET/CT) equipments are available as single units that are able to perform both imaging studies simultaneously. The fusion imaging technique allows information from two different studies to be correlated and interpreted on one image, leading to more precise information and accurate diagnosis. Nuclear medicine imaging procedures often identify abnormalities very early in the course of a disease, long before some medical problems are apparent with other diagnostic tests. This early detection allows a disease to be treated early in its course when there may be a more successful outcome.

Non-imaging procedures such as thyroid uptake tests, Glomerular filtration rate (GFR) estimations and haematological tests also form part of nuclear medicine. Some of the non-imaging functional studies like clearance studies, dilution techniques are other forms of in vivo diagnostic methods.

Radioimmunoassay constitutes its in vitro application. Radioimmunoassay and radioimmunometric assay were the first methods based on saturation analysis/competitive limited reagent/radiolabelled analyte to measure picomolar concentrations of biomolecules which otherwise is beyond the reach of conventional chemistry. This laid the foundation of modern endocrinology. These assays are also used to measure levels of hormones, vitamins and drugs in a patient's blood.

Beyond diagnosis, nuclear medicine also offers therapeutic applications. However, such applications are limited to a few

diseases like thyrotoxicosis, thyroid cancer, metastatic bone pain, neuroendocrine tumours, rheumatoid arthritis and radio-immunotherapy for some cancers, etc.

HISTORY

The origin of nuclear medicine stems from many scientific discoveries, most notably the discovery of "X-rays" in 1895 and the discovery of radioactivity in 1896 and "artificial radioactivity" in 1934. The first clinical use of artificial radioactivity was carried out in 1937 for the treatment of a patient with leukaemia at the University of California at Berkeley. The most fundamental principle of Nuclear Medicine is the tracer principle, invented by George Hevesy for which he received the Nobel Prize in 1944. Nuclear medicine gained recognition as a medical specialty in 1946 when a thyroid cancer patient's treatment with radioactive iodine caused complete disappearance of the spread of the patient's cancer. Although, the earliest use of Iodine-131 was devoted to therapy of thyroid cancer, its use was later expanded to include imaging of the thyroid gland, quantification of the thyroid function, and therapy for hyperthyroidism. Development of rectilinear scanner by Benedict Cassen and scintillation camera (Anger camera) by Hal O. Anger broadened the discipline of nuclear medicine into a full-fledged medical imaging specialty.

Among many radionuclides that were discovered for medical use, none were as important as the discovery and development of technetium-99m. The development of generator system to produce Technetium-99m in the 1960s became a practical method for medical use. Today, Technetium-99m is the most utilised element in nuclear medicine and is employed in a wide variety of nuclear medicine imaging studies. By the 1970s most organs of the body could be visualised using nuclear medicine procedures. The concept of emission and transmission tomography, later developed into single photon emission computed tomography (SPECT), was introduced by David E. Kuhl and Roy Edwards in the late 1950s. More recent developments in nuclear nedicine include the invention of the PET scanner. Fusion imaging with SPECT and CT was developed by Bruce Hasegawa from University of California San Francisco (UCSF), and the first PET/CT prototype by D.W. Townsend from University of Pittsburg in 1998.

DIAGNOSTIC NUCLEAR MEDICINE IMAGING

A nuclear medicine study involves administration of a radionuclide into the body by intravenous injection, ingestion while combined with food, inhalation as a gas or aerosol (**Tables 1 and 2**). In some studies patient's own blood cells are labelled with a radionuclide (leucocyte and red blood cell scintigraphy). Following administration, the radiotracer is distributed around the body and/or processed differently where disease or pathology is present. Focal increase in radiotracer accumulation results in a 'hot-spot' which represents increased physiological function. In some disease processes a 'cold-spot' may be visualised which represents non-concentration of radiotracer.

Table 1: The Commonly Used Intravenous Radionuclides in Nuclear Medicine

Radionuclide	Symbol	Half-life (T½)	Type of Emission	Energy (Kev) (Photon)
Technetium-99m	Tc99m	6.01 hours	IT	140
Iodine-123	^{123}I	13.2 hours	EC	159
Chromium-51	^{51}Cr	27.7 days	γ	320
Indium-111	^{111}In	2.8 days	EC, γ	171 245
Thallium-201	^{201}Tl	73 hours	EC	69-83* 135 167
Gallium-67	^{67}Ga	3.26 days	EC, γ	93 185 300
Fluorine-18	^{18}F	110 min	β^+	511
Rubidium-82	^{82}Rb	75 sec	β^+	511

*IT = Isomeric transition; EC = Electron capture; γ = Gamma; β^+ = Positron decay; *Mercury X-rays.*

Table 2: The Commonly Used Gaseous/Aerosol Radionuclides in Nuclear Medicine

Radionuclide	Symbol	Half-life (T½)	Type of Emission	Energy (Kev) (Photon)
Xenon-133	^{133}Xe	5.24 days	γ and β^-	81 346 β^-
Krypton-81m	^{81m}Kr	13 sec	IT	190
Technetium-99m DTPA aerosols	Tc99m	6.01 hours	IT	140
Technetium 99m Technegas	Tc99m	6.01 hours	IT	140

γ = Gamma; β^- = Negative decay; IT = Isomeric transition.

CLINICAL APPLICATIONS OF DIAGNOSTIC NUCLEAR MEDICINE

Nuclear Medicine scans may be used to diagnose a number of medical problems. Some of the more frequently performed tests are highlighted below. This is not meant to be exhaustive, and for a more detailed account the reader may refer to the standard nuclear medicine text books, journals and periodicals. Positron Emission Tomography is discussed in a separate chapter of this section.

Endocrine Applications

Thyroid

Thyroid scintigraphy generates one or more images of the thyroid obtained after injection/ingestion of the tracer. Common indications are:

(a) Localisation of ectopic thyroid tissue (i.e. lingual) or to determine whether a suspected thyroglossal duct cyst is the only functioning thyroid tissue present.

(b) To evaluate a neck or substernal mass. Radionuclide scintigraphy may be helpful to confirm if the mass is functioning thyroid tissue.

(c) To assist in evaluation of congenital hypothyroidism.

(d) Differentiation of thyroiditis (i.e. subacute or silent) and factitious hyperthyroidism from Graves' disease and other forms of hyperthyroidism.

(e) Functional evaluation of thyroid nodules and masses (**Figure 1** shows a case of cold nodule of right lobe of thyroid gland).

(f) Distinguishing Graves' disease from toxic nodular goiter, a distinction of significance in determining the amount of Iodine-131 to be given as therapy for hyperthyroidism. (**Figures 2 and 3**).

(g) Post-operative assessment of differentiated thyroid cancer.

(h) Radioactive iodine uptake (RAIU) for calculating Iodine-131 therapy dose for treating hyperthyroidism.

(i) Perchlorate discharge test for identification of organification defects.

(j) Radioimmunoassay/radioimmunometric assay for measurement of free and total T3, T4 and TSH.

Commonly used radiotracers for thyroid imaging are Tc99m (pertechnetate), Iodine-123 and Iodine-131.

Thyroid evaluation is one of the most frequently performed nuclear medicine procedure. Thyroid scintigraphy plays an extremely important role in the classification of thyroid pathology. The radiation dose to the thyroid is meagre with Technetium-99m, but may be significant with Iodine-131. Hence, lower doses of Iodine-131 are utilised and imaging is not ideal when this radioisotope is used.

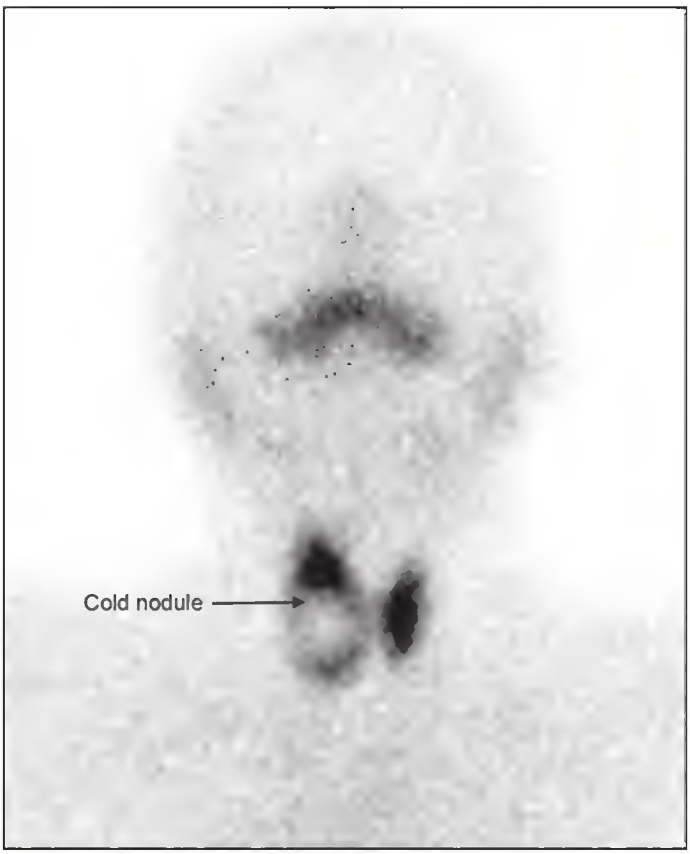
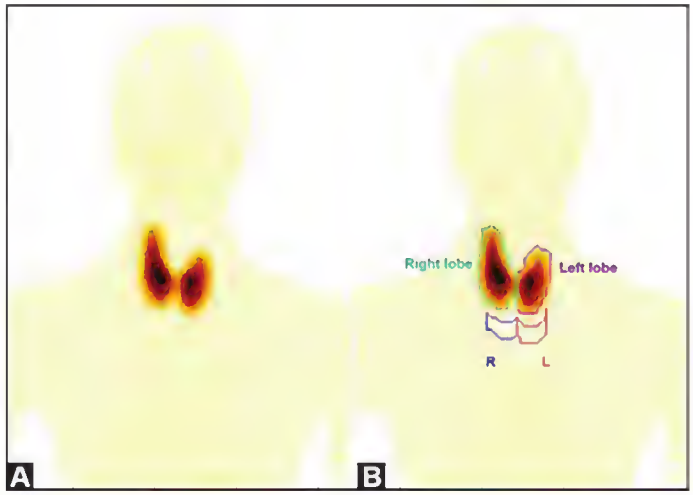


Figure 1: ^{99m}Technetium thyroid scintigraphy showing a non-functional (Cold) nodule in the right lobe of thyroid gland. Rest of the thyroid gland shows homogenous tracer uptake.



Figures 2A and B: ^{99m}Technetium thyroid scintigraphy showing (A) enlarged thyroid gland with increased tracer uptake (B) technetium uptake calculated by drawing ROIs showed 10% uptake (Increased) suggesting hyperthyroidism.

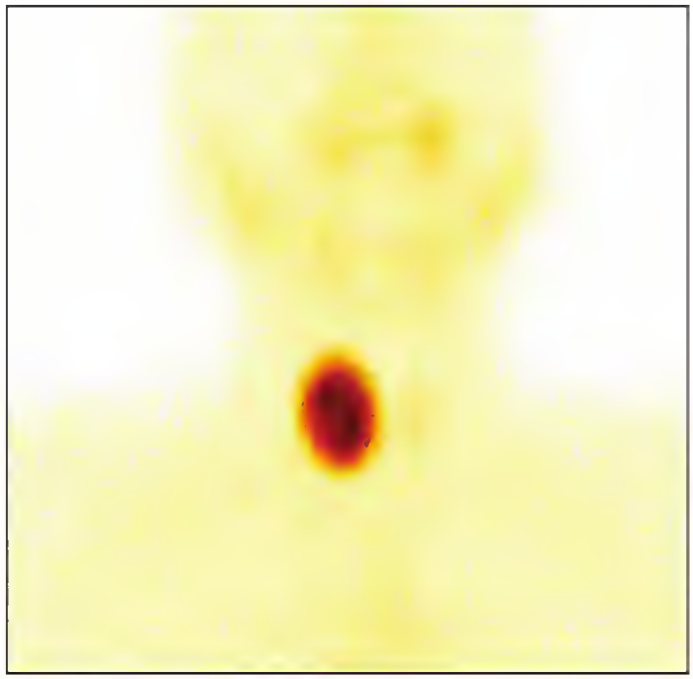


Figure 3: ^{99m}Technetium thyroid scintigraphy showing tracer uptake in a nodule in the right lobe of thyroid gland. Rest of the thyroid gland doesn't show tracer uptake. Findings are consistent with autonomously functioning toxic adenoma.

Parathyroid scintigraphy

(a) Localisation of hyperfunctioning parathyroid tissue (adenomas) in primary hyperparathyroidism and in patients with persistent or recurrent disease.

(b) Gamma probe guided surgery.

Thallium-201 or Tc99m-sestamibi are the tracers employed for parathyroid imaging.

Over 90% of the primary hyperparathyroidism is caused by a single parathyroid adenoma. Most of the parathyroid adenomas are identified by scintigraphy (**Figure 4**) and hence allows limited surgical approach rather than bilateral neck exploration, reducing the morbidity and hospital stay of these patients. Gamma probe guided surgery combined with intra-operative PTH assay has the potential for reduced hospital stay and patient morbidity. Parathyroid scintigraphy has lower specificity in the

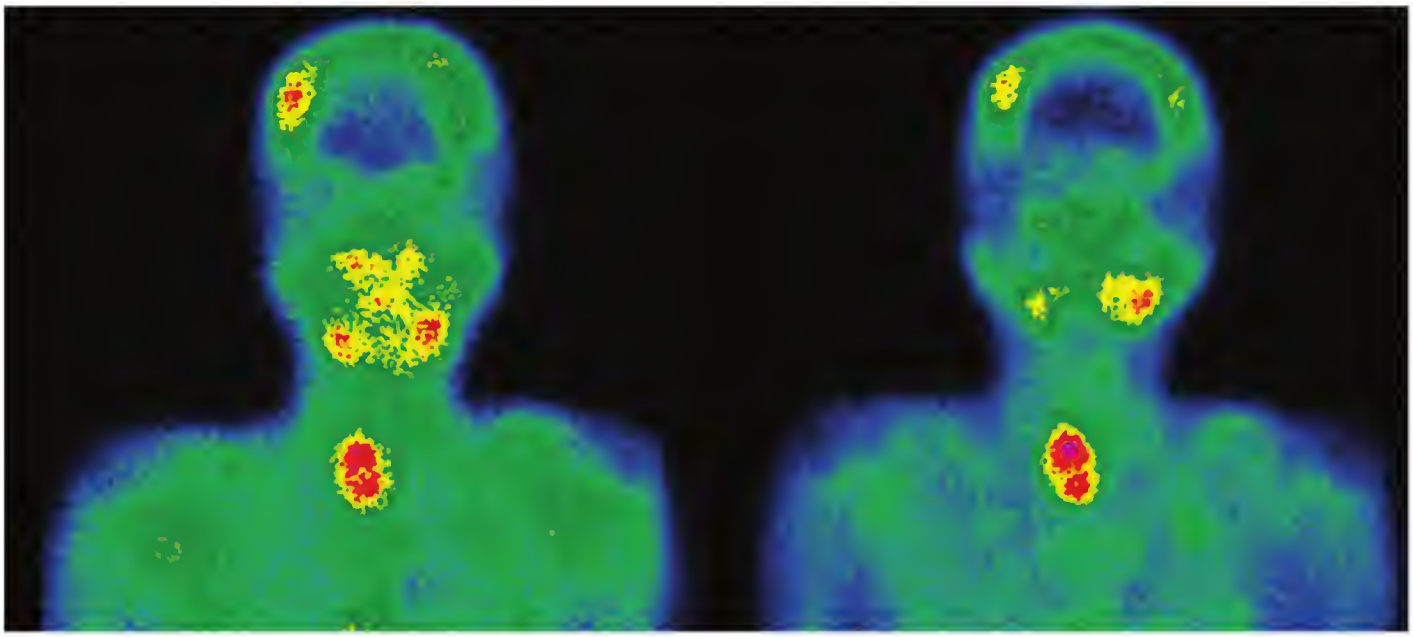


Figure 4: Dual phase Tc99m sestamibi parathyroid scintigraphy shows focal tracer uptake in the region of the right lobe of thyroid. Tracer retention is noted in the lesion at 1 hour. The findings are consistent with large right inferior parathyroid adenoma.

presence of thyroid adenomas. However, the use of subtraction scintigraphy allows reasonable differentiation of thyroid from parathyroid adenomas.

Ultrasonography has high specificity in the diagnosis of parathyroid adenomas but has insufficient sensitivity and inter-observer variability. CT and MRI are also used in the evaluation of parathyroid disorders.

Adrenal medulla

The important tumours of the adrenal medulla are Pheochromocytoma and Neuroblastoma.

The nuclear scan is usually performed with Iodine-123/Iodine-131 labelled Metaiodobenzylguanidine (MIBG). Tc99m HYNICTOC is also used for this.

Iodine-131 MIBG has a specificity of >95% in detection of functioning neuro-endocrine tissue (**Figure 5**) and is mandatory before considering radionuclide therapy with high dose Iodine-131 MIBG. However, sensitivity is lower because of the limited spatial resolution and poor imaging characteristics of Iodine-131. MRI is an excellent modality for the evaluation of adrenal medullary disorders but is incapable of providing the functional status of the lesion. Further, whole body evaluation is possible with scintigraphy.

Adrenal cortex

Scintigraphy is useful in the evaluation of Cushing's syndrome and Conn's syndrome.

Commonly used radiotracer for this is iodine-131 iodocho lestrol/NP-59. With the advent of high resolution cross-sectional imaging like CT and MRI, the role of nuclear medicine in the evaluation of adrenal cortical pathologies has diminished. PET has an extremely important role in the evaluation of adrenal masses and has been shown to exceed CT/MRI in both sensitivity and specificity in evaluation of adrenal masses in known/suspected malignancies.

Genitourinary Applications

Dynamic renal scintigraphy provides information about the blood flow to the kidneys, parenchymal function and drainage from the collecting system. Static cortical scintigraphy is useful in evaluation of relative kidney function and morphological abnormalities. Common indications of renal scintigraphy are:

(a) Diuretic renography for detecting urinary tract obstruction (ureteropelvic or vesicourethral).

(b) Captopril renography to diagnose and prognosticate renovascular hypertension.

(c) Evaluation of kidneys in prenatal Ultrasonography (USG) diagnosis of hydronephrosis.

(d) Renal transplant evaluation.

(e) Measure differential renal function in renal insufficiency.

(f) Renal cortical scintigraphy for detecting pyelonephritis and cortical scars (**Figure 6** shows cortical scars).

(g) Localisation of ectopic kidney and evaluation of anatomical abnomalities.

(h) Radionuclide cystourethrography for vesico-ureteric reflux, (**Figure 7** shows a case of right VUR).

(i) Measurement of GFR/effective renal plasma flow (ERPF).

(j) Detect testicular torsion vs. epididymo-orchitis.

For most purposes the radiotracer used is Tc99m-DTPA or Tc99m-MAG_3 or Tc99m- EC. For anatomical visualisation, the preferred radiotracer is Tc99m-DMSA though sometimes Tc99m-GHA may also be used if DMSA is not available.

Renal scintigraphy has the advantages of providing functional parameters like cortical function and GFR. It plays an extremely important role in the follow-up of patients. The radiation dose delivered by renal scintigraphy is often lower than radiographic procedure like micturating cysto-urethrogram (MCUG) and intravenous pyelograms (IVP). Renal scintigraphy is also less traumatic to the patients.

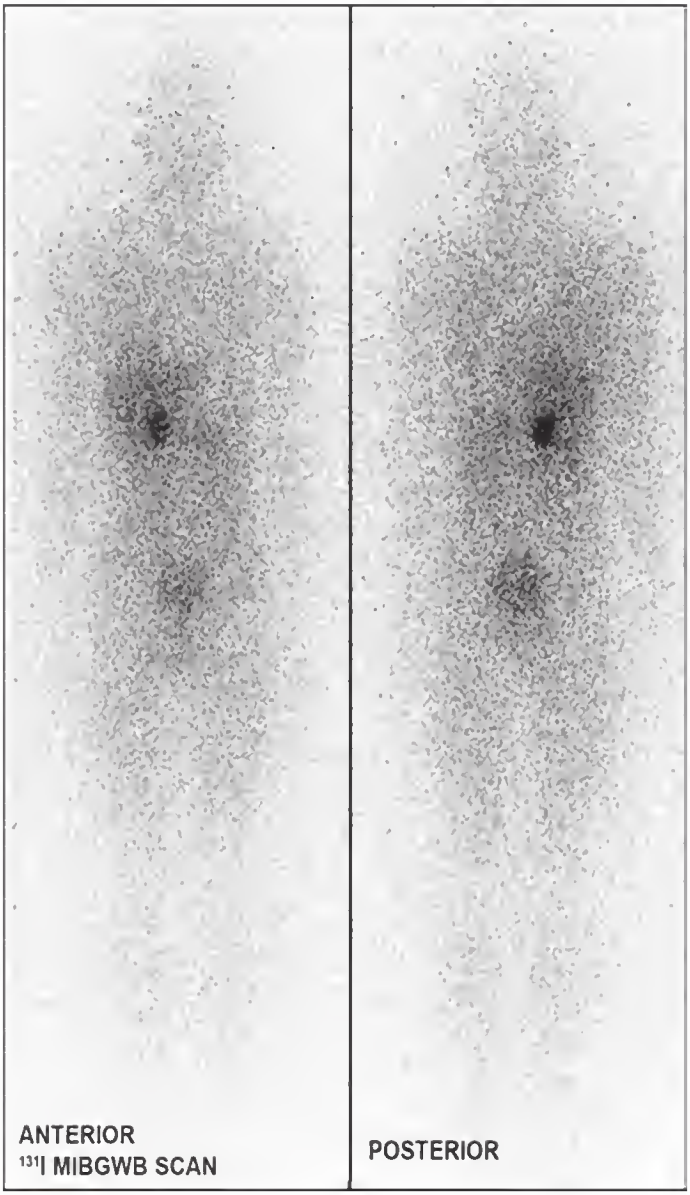


Figure 5: Whole-body ^{131}I MIBG scintigraphy obtained 48 hours after administration of MIBG showing a focus of tracer uptake in the right hypochondrium suggesting a functional neuro-endocrine tumour. The patient had right adrenal pheochromocytoma.

Ultrasonography is an inexpensive initial modality for evaluation of the genito-urinary system. However, operator dependence and inability to differentiate dilated unobstructed systems from obstructed systems mandate further evaluation with scintigraphy. IVP requires bowel preparation and contrast administration and doesn't provide quantitative functional parameters as scintigraphy.

Skeletal System Applications

Bone scintigraphy evaluates the distribution of active bone formation in the body. Whole-body bone scintigraphy produces anterior and posterior planar images of the skeleton, both axial and appendicular. Multiphase bone scintigraphy usually includes blood flow images of the area of region of interest, immediate blood pool static planar images, and delayed images at 3-4 hours. Delayed images may be limited to the areas of interest or may include the whole body (planar or tomographic). Common indications are:

(a) Neoplastic disease: demonstration of skeletal metastasis from various solid malignancies like breast, prostate (**Figure 8** shows a typical case of widespread skeletal metastases).

(b) Early diagnosis of osteomyelitis (**Figure 9**).

(c) Evaluation of diabetic foot for osteomyelitis vs. Charcot's joint.

(d) Evaluation of prosthetic implant for infection or sterile inflammation.

(e) Detection of bone graft viability.

(f) Evaluation of metabolic bone diseases.

(g) Identify occult bone trauma (sports injuries like stress fractures, occult fracture, shin splint).

(h) Diagnosing avascular necrosis of the femoral head.

(i) Evaluate arthritic changes and extent.

(j) Evaluation of chronic regional pain syndrome (CRPS) (Reflex sympathetic dystrophy).

(k) Measure extent of certain tumours and localise sites for biopsy in tumour patients.

(l) Evaluation of otherwise unexplained bone pain, especially low backache.

(m) Identify bone infarcts such as in sickle cell disease.

(n) Distribution of osteoblastic activity before radionuclide therapy for bone pain.

The commonly used radiotracer for bone scan is Tc99m-MDP. Skeletal scintigraphy is extremely sensitive but lacks specificity. With the advent of hybrid scanners, the information obtained from CT is used to increase the specificity of bone scintigraphy. To increase the specificity of bone scintigraphy, a second imaging agent may be used e.g.; positive bone scan patient, in a case of suspected prosthetic infection, may be subjected to labelled WBC scan.

Cardiac Applications

Myocardial perfusion imaging (MPI), multigated radionuclide ventriculography (MUGA), first pass study are the common procedures.

Myocardial perfusion imaging: MPI identifies areas of reduced myocardial blood flow associated with ischaemia or scar. The relative regional distribution of perfusion can be assessed at cardiac stress, rest or both. Imaging can also be performed during acute events such as in the coronary care unit or emergency department. Common indications include:

(a) Diagnosis of physiologically significant coronary artery disease (presence and severity). (**Figure 10** shows a case of ischaemia in the inferolateral wall).

(b) Determine prognosis (risk stratification based on extent and severity of myocardial perfusion abnormalities and left ventricular function.

(c) Differentiate between coronary and non-coronary causes in patients with acute chest pain syndromes seen in the emergency room.

(d) Cardiac risk assessment for patients undergoing major non cardiac surgery.

(e) Differentiate ischaemic from idiopathic cardiomyopathy.

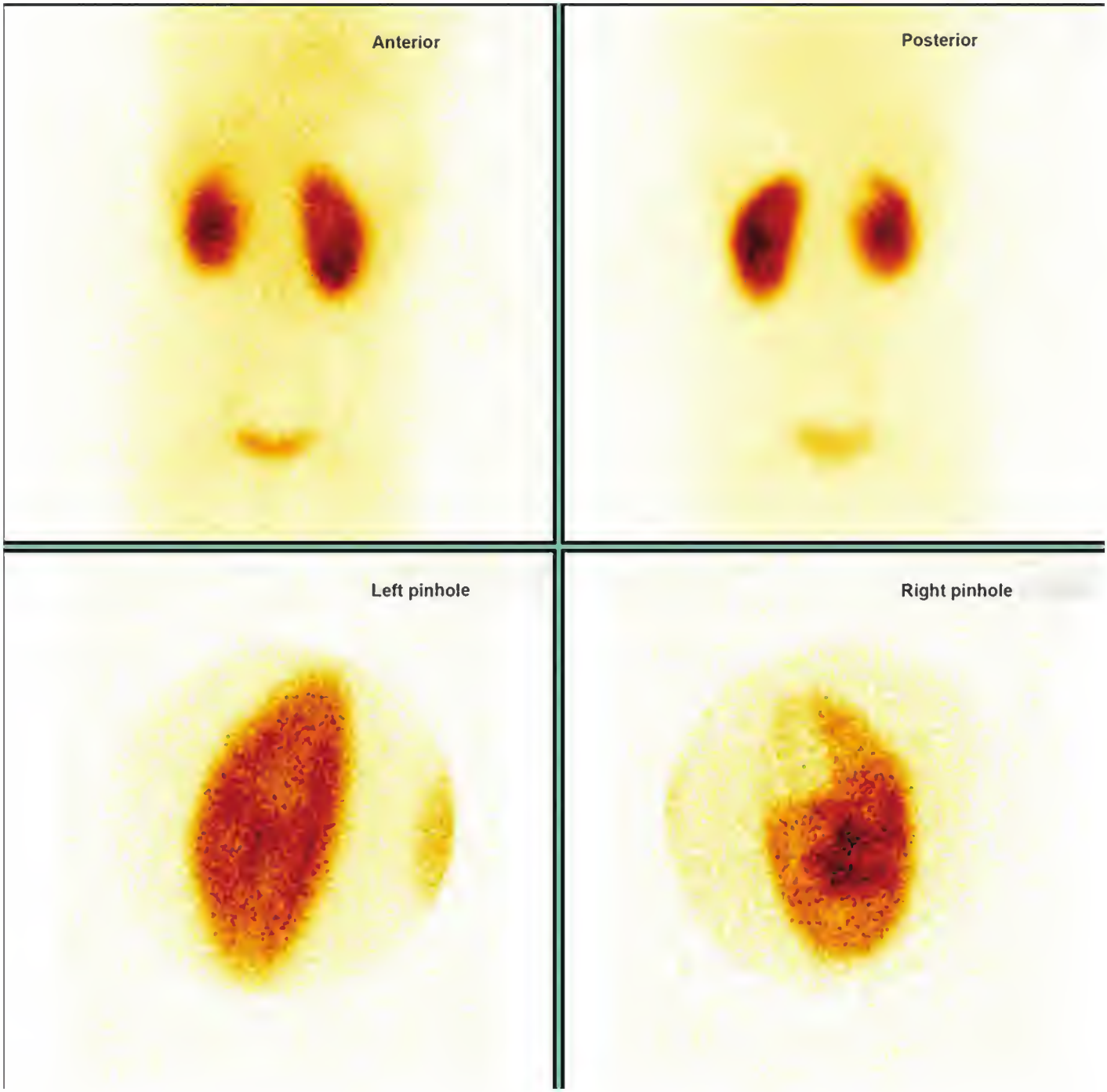


Figure 6: Tc99m DMSA static planar (arterior and posterior) and pinhole images of the kidneys showing smaller right kidney with break in cortical outline in the upper pole of right kidney suggestive of presence of a cortical scar.

(f) Assessment of viable myocardium overlying the infarction to consider revascularisation.

(g) Evaluate the immediate and long-term effects of revascularisation procedures and medical or drug therapy.

Myocardial perfusion imaging is a gate-keeper to invasive coronary angiography. With the advent of CT coronary angiography, there is an increase in the number of equivocal coronary lesion whose physiological significance needs to be evaluated with MPI. MPI, apart from providing information about the perfusion status, also provide various functional parameters like ventricular ejection fraction, systolic and diastolic volumes, myocardial mass and prognostic information. A normal stress MPI has less than 1% risk of contracting any major cardiac event.

Multigated equilibrium radionuclide ventriculography: MUGA is a procedure where patient's red blood cells (RBCs) are radiolabelled and ECG gated cardiac scintigraphy is obtained. Parameters obtained from MUGA include (i) global ventricular ejection fraction, (ii) systolic and diastolic function indices, (iii) regional wall motion, (iv) ventricular volumes, (v) stroke volume ratios. Common indications are:

(a) Evaluation of known or suspected coronary artery disease.

(b) Distinguishing systolic from diastolic causes of congestive heart failure (CHF) in patients with known or suspected CHF.

(c) Measure cardiac toxicity in patients undergoing chemotherapy.

(d) Assessment of ventricular function in patients with valvular heart disease.

(e) Monitoring response to surgery or other therapeutic interventions.

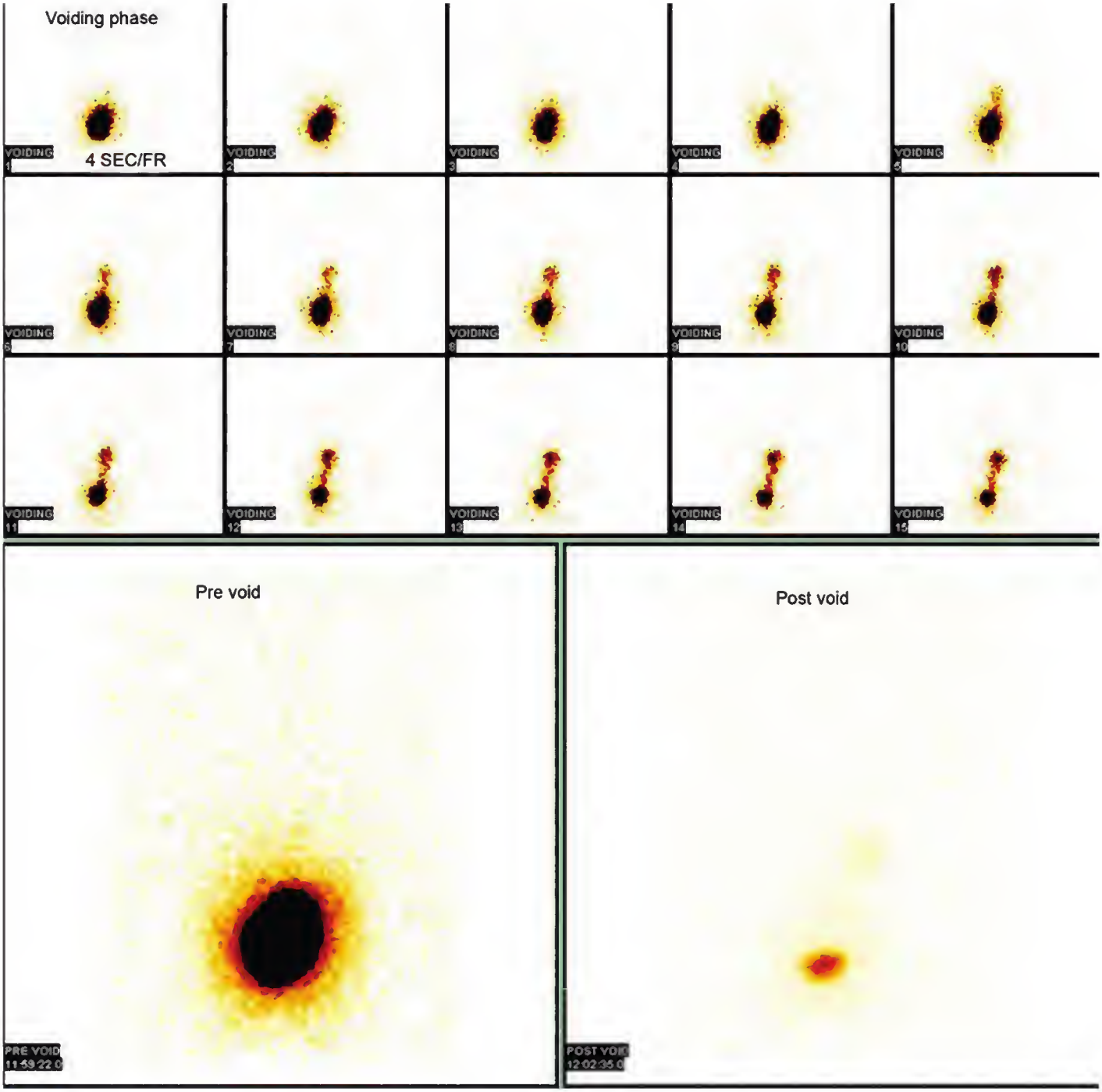


Figure 7: Direct radionuclide cystography (DRCG) study showing left vesico-ureteric reflux. Tracer activity in the urinary bladder is noted refluxing into the left ureter and renal pelvis during the voiding phase of the study.

First pass studies help to identify and quantify shunts and evaluation of right heart failure.

Thallium-201, Tc99m-sestamibi, Tc99m tetrofosmin are the radiotracers for myocardial perfusion imaging. MUGA study is performed with labelled erythrocytes. First pass study to evaluate right heart function or shunts can be performed with any Tc99m labelled tracer.

MUGA study is the current gold standard for the evaluation of LV ejection fraction and is proving indispensable in the evaluation of patients undergoing cardio-toxic chemotherapy.

Pulmonary Applications

Perfusion scintigraphy measures the distribution of pulmonary arterial blood flow. Ventilation scintigraphy records the bronchopulmonary distribution of an inhaled radioactive aerosol within the lungs. Pulmonary lung scintigraphy for pulmonary embolism assesses pulmonary perfusion and often includes ventilation scintigraphy. The most common indications are:

(a) Determination of the likelihood of pulmonary embolism.
(b) Quantify lung ventilation and perfusion as preoperative evaluation.
(c) Evaluation of lung transplantation.
(d) Right-to-left shunt evaluation.
(e) Detect pulmonary complications of AIDS.
(f) Detect inhalation injury in burn patients.

Lung perfusion scan is performed with Tc99m-microspheres of albumin while ventilation scan is performed either with Xenon 133 or with Tc99m-DTPA aerosols/technegas.

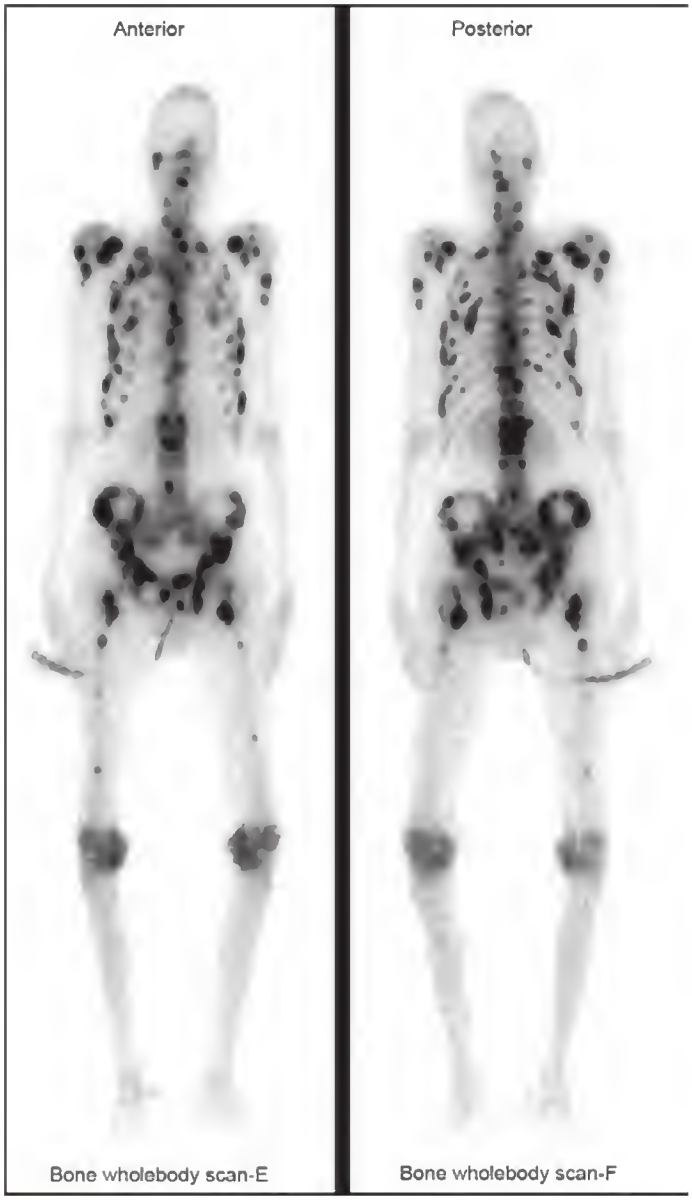


Figure 8: Tc99m-Methylene diphosphonate (MDP) bone scintigraphy showing multiple foci of increased tracer uptake involving several bones. The findings are consistent with widespread skeletal metastasis.

Inspite of the introduction of CT pulmonary angiography, ventilation-perfusion (V/Q) scintigraphy has continued to have important role. V/Q scan delivers far less radiation to the female breast than CT angiography. V/Q scan also serves as a baseline for the evaluation of response to anti-coagulants (**Figure 11**). Of late, the utility of V/Q scintigraphy has also been studied in parenchymal lung disease and asthma. One of the drawbacks of V/Q scan is the large number of indeterminate scans but with the advent of V/Q SPECT, the indeterminate scans have been reduced to <1%. In summary, V/Q SPECT performs equal to CT pulmonary angiography with far less radiation exposure.

Gastrointestinal Applications

Hepatobiliary scintigraphy

Hepatobiliary scintigraphy evaluates hepatocellular function and patency of the biliary system by tracing the production and flow of bile from the liver through the biliary system into the small intestine. Sequential images of the liver, biliary tree and gut are obtained. The common indications are:

(a) Evaluation of suspected acute cholecystitis.
(b) Evaluation of suspected chronic biliary tract disorders.
(c) Determine causes of jaundice and identify obstruction in the biliary passage.
(d) Detection of bile extravasation.
(e) Evaluation of congenital abnormalities of the biliary tree.
(f) Liver and gallbladder scans to evaluate liver and gallbladder function.
(g) Liver (reticulo endothelial cells) scans for cirrhosis, non-cirrhotic portal fibrosis (NCPF), tumours, space occupying lesions, etc.

Scintigraphy suffers from limited anatomical resolution which precludes detection of small lesion and to localise the exact sites of biliary leaks. Some of the studies require many hours to complete.

Gastrointestinal tract motility studies

Gastrointestinal tract motility studies include oesophageal transit, gastro-oesophageal reflux studies, gastric emptying studies, intestinal and colonic transit studies. Gastrointestinal bleeding scans are used to identify bleeding into the bowel.

Gastric emptying and motility: Radionuclide studies of gastric emptying and motility are the most physiologic studies available for studying gastric motor function. The study is noninvasive, uses a physiologic meal (solids with/without liquids), and is quantitative. Serial testing can determine the effectiveness of therapy. Indications for gastric emptying include:

(a) Suspected gastroparesis
(b) Poor diabetic control
(c) Gastro-oesophageal reflux
(d) Following response to therapy for previously documented motility disturbances

Gastric emptying time is the most physiological and the current gold standard for the evaluation of gastric emptying. However, various parameters like the content of the food, acceptability of food to local population, etc. create variations and each centre needs to standardise the procedure.

Meckel's diverticulum scintigraphy and gastrointestinal bleeding: The indication for a Meckel's scan is to localise ectopic gastric mucosa in a Meckel's diverticulum as the source of unexplained gastrointestinal bleeding (**Figure 12**). Scintigraphy may be false negative in active bleeding and in those without adequate gastric mucosa in the diverticulum.

Gastrointestinal bleeding scintigraphy is performed in patients suspected of active gastrointestinal bleeding using Tc99m labelled red blood cells (RBCs). Sites of active bleeding are identified by the accumulation and movement of labelled red blood cells within the bowel lumen (**Figure 13**). Tc99m labelled red blood cells scintigraphy is the most sensitive of all the available investigations in the evaluation of gastrointestinal bleeding. Unlike invasive angiography, scintigraphy is non-invasive, allows follow-up of patients for 24 hours, provides prognostic information and is not associated with risks of contrast administration and renal injury.

Neurologic Applications

Brain perfusion scintigraphy reflects regional cerebral perfusion. Useful in:

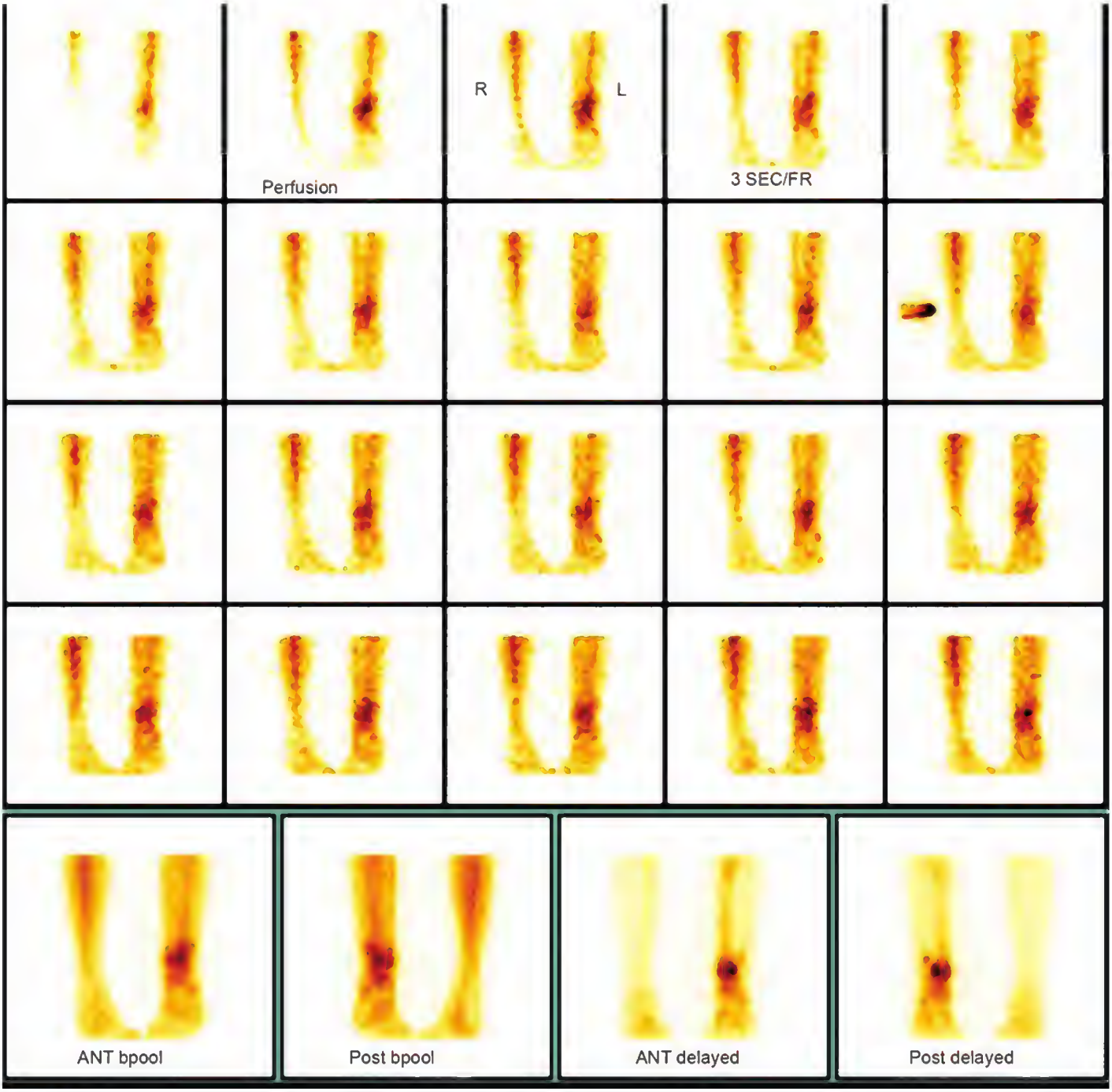


Figure 9: Three-phase MDP bone scintigraphy images of the legs showing increased blood flow and soft tissue pooling of tracer around the lower part of left tibia. Bone phase image acquired at 3 hours shows increased tracer uptake in the same region. The findings are suggestive of active bony infection and inflammation.

(a) Detection and evaluation of cerebrovascular disease.
(b) Evaluating post concussion syndrome.
(c) Evaluation of patients with suspected dementia (Alzheimer's disease, multi-infarct dementia, AIDS dementia).
(d) Presurgical localisation of epileptic foci (ictal and inter-ictal scan).
(e) Evaluation of suspected brain trauma.
(f) Assess brain blood flow in patients suspected of brain death.
(g) Evaluation of patients for carotid surgery.
(h) Evaluation of brain tumours (**Figure 14**) especially follow-up after surgery/radiotherapy.
(i) Cerebrospinal fluid studies for CSF leaks, hydrocephalous, shunt patency, etc.

The commonly used radiotracer for brain perfusion imaging is Tc99m-HMPAO, Tc99m-ECD. Brain tumour imaging may be performed with Tc99m-sestamibi/GHA or Thallium-201. CSF studies are performed with Tc99m-DTPA. The utility of scintigraphy has diminished with the advent of conventional high resolution imaging modalities. Functional disorders like seizures, psychiatric illness are identified with SPECT even when morphological imaging modalities are normal.

Oncologic Applications

(a) Bone scan to evaluate primary bone tumours and to detect skeletal metastases from other malignancies.
(b) Scintimammography (breast scan) to accurately detect and locate cancerous tissue in the breasts.

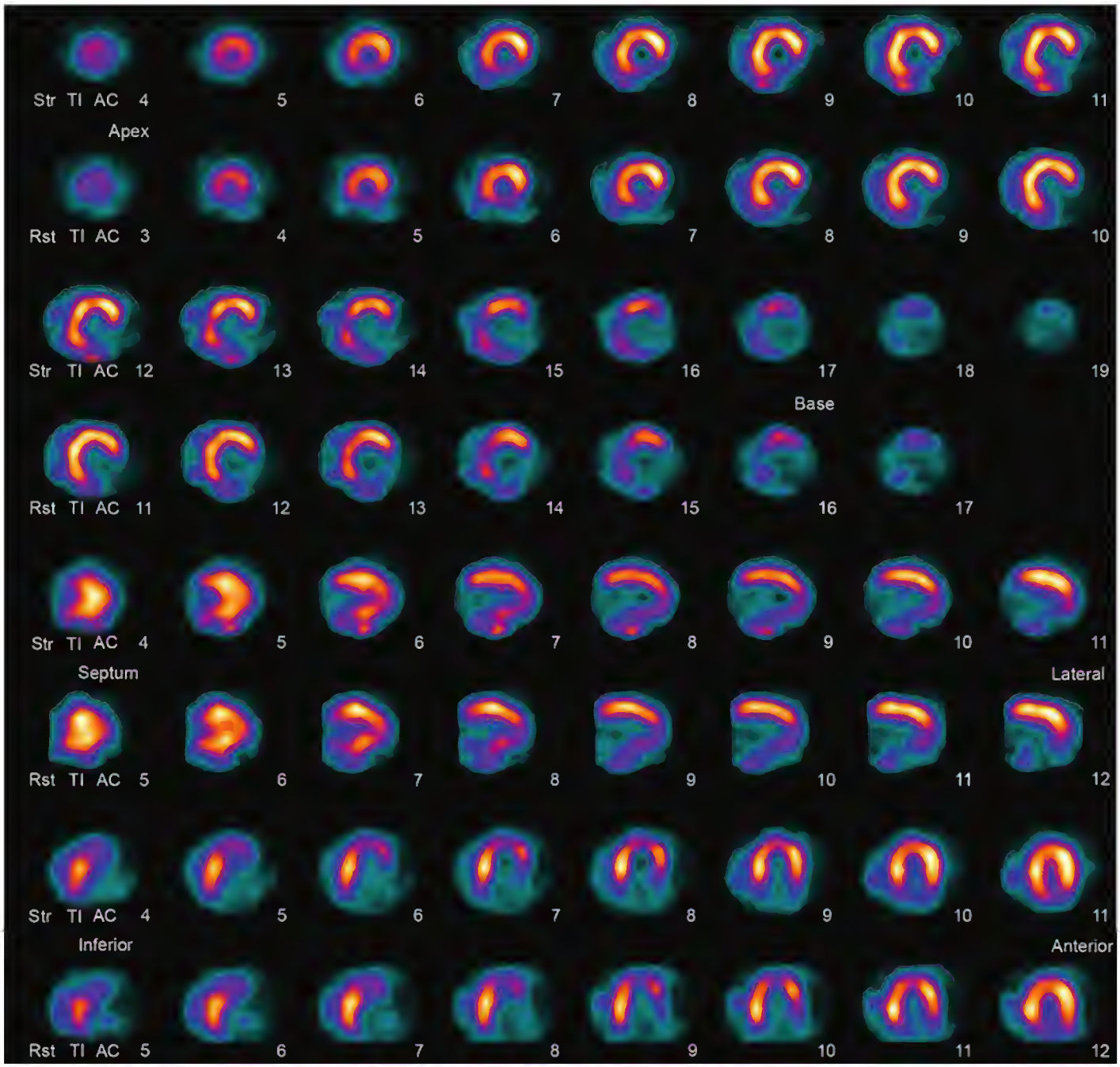


Figure 10: Myocardial perfusion scintigraphy (MPS) performed at stress and rest with Tc99m-Tetrofosmin. Matched stress and rest images [short axis (SA)], vertical long axis (VLA), horizontal long axis (HLA) show impaired tracer uptake in anterior septum and infero-lateral wall of the left ventricular myocardium indicative of stress induced ischaemia.

(c) Sentinel lymph node mapping to localise the lymph nodes before surgery in patients with breast cancer or melanoma.

(d) MIBG and Octreotide scans for neuroendocrine tumours, based on cellular receptors or functions.

(e) Radio-immunoscintigraphy: These imaging tests use monoclonal antibodies. When combined with a radioactive tracer, they are quite useful for detecting various tumours, especially those in the ovaries, colon or prostate.

(f) Gallium scans to evaluate certain types of tumours. Determines the presence or spread of cancer in various parts of the body.

(g) PET/CT scans for initial staging, therapy monitoring and follow-up.

PET/CT has overcome many limitations of routine nuclear medicine procedures like the limited spatial resolution, sensitivity and quantification.

Other Applications

(a) Infection/inflammation detection using gallium-67/labelled leucocytes/ labelled ciprofloxacin.

(b) Venography for deep venous thrombosis (DVT).

(c) Lymphoscintigraphy.

(d) Salivary scintigraphy.

(e) Dacryo-scintigraphy.

(f) Spleen scan.

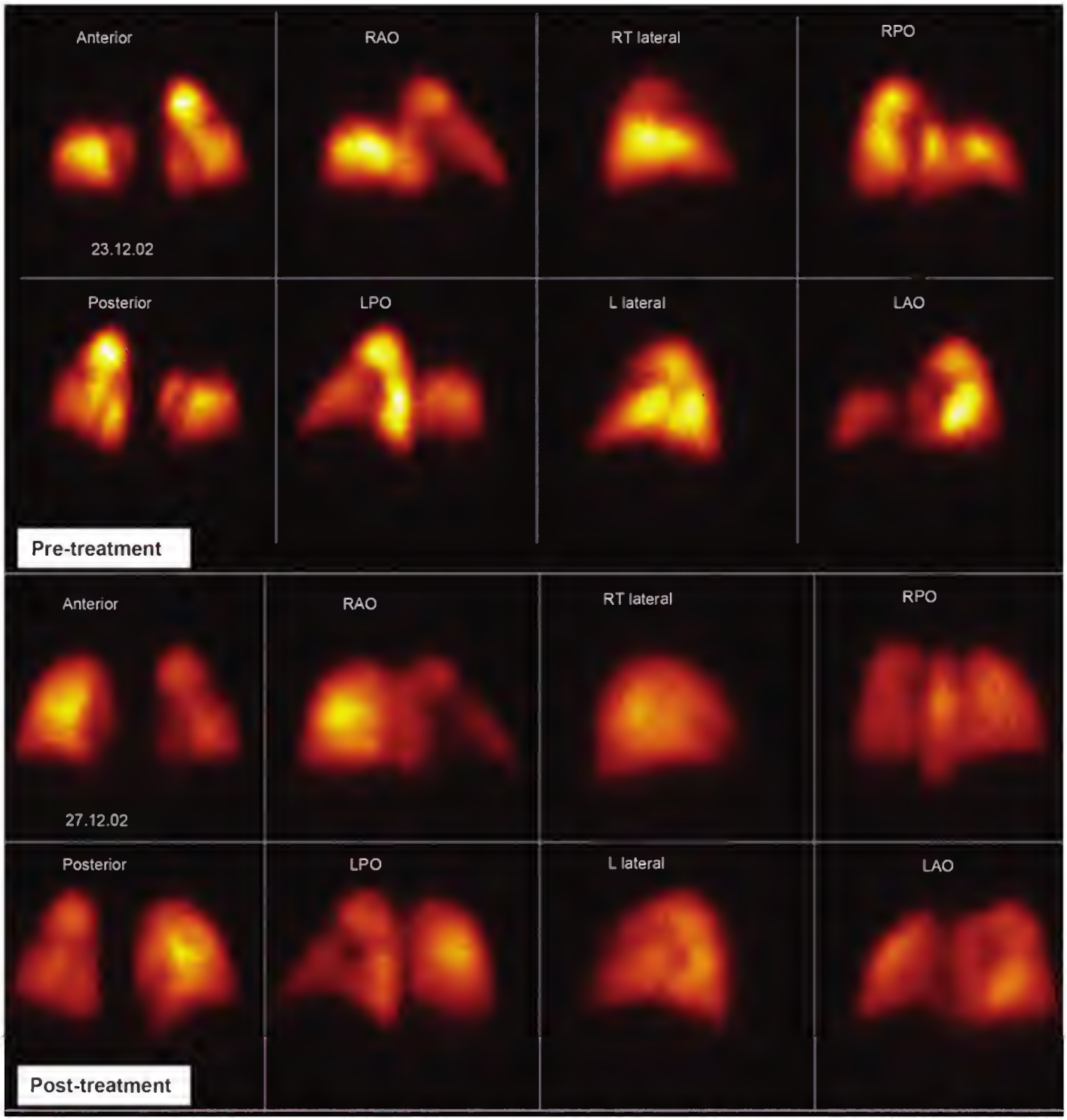


Figure 11: Lung perfusion scintigraphy performed with Tc99m-MAA (macro-aggregated albumin) showing improvement in the follow-up study. Initial perfusion study shows large perfusion defect in the right lung. Follow-up study after treatment with heparin shows restoration of perfusion to the right lung. A small wedge shaped defect in the left lung also improved.

THERAPEUTIC NUCLEAR MEDICINE

Radionuclides are also used for therapy of malignant and non-malignant conditions (**Table 3**). With the use of suitable radio-pharmaceuticals targeted therapy is also possible. In nuclear medicine therapy, the radiation treatment dose is also administered internally (e.g. intravenous or oral routes) rather from an external radiation source as in radiotherapy. The ionising radiation emitted by therapeutic radionuclides travels only a short distance, thereby minimising unwanted side-effects and damage to non-involved organs or nearby structures. Most nuclear medicine therapies can be performed as outpatient procedures since there are few side-effects from the treatment and the radiation exposure to the general public can be kept within a safe limit. Nuclear medicine therapies include:

(a) Radioactive Iodine (I-131) for hyperthyroidism and thyroid cancer.

(b) Iodine-131 MIBG (metaiodobenzylguanidine) for neuro-endocrine tumours.

(c) Palliative therapy for metastatic bone pain using Phosphorus-32 or Samarium-153 or Strontium-89.

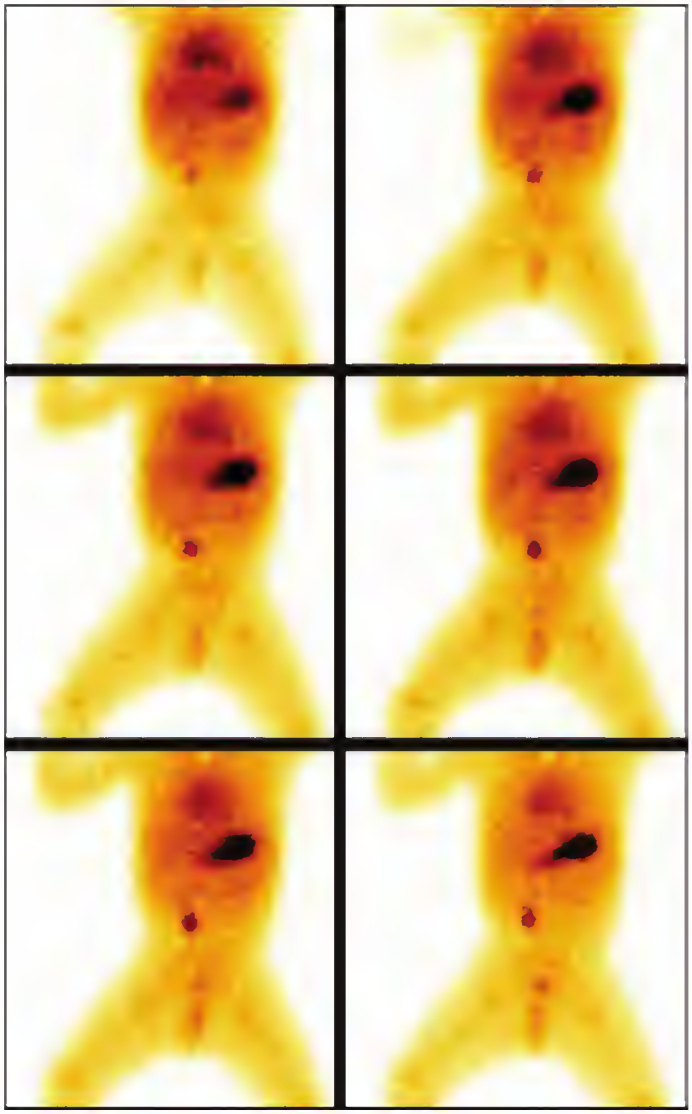


Figure 12: ^{99m}Technetium Meckel's scintigraphy. Multiple static images after intravenous tracer injection shows a focus of tracer uptake in the right iliac fossa. The focus appears alongwith the stomach and shows increasing activity as the study progresses. The findings suggest presence of heterotopic gastric mucosa (Meckel's diverticulum).

(d) Phosphorus -32 for polycythemia rubera vera.

(e) Radionuclides (Yttrium-90, Erbium-169, Rhenium-186) for various arthritis like rheumatoid, psoriatic, haemophilic, etc. (Radiosynoviorthesis).

(f) Iodine-131/Rhenium-186 lipoidal or yttrium-90 theraspheres intra-arterial therapy for hepatocellular carcinoma.

(g) Lutetium-177 peptide therapy for various neuroendocrine tumours.

(h) Radioimmunotherapy - Yttrium-90 Ibritumomab Tiuxetan (Zevalin) and Iodine-131 Tositumomab (Bexxar) for low grade refractory lymphomas.

Nuclear medicine can also guide the choice and extent of surgery not only by demonstrating metastases to the liver, lungs and bones but also by demonstrating tumour limits and involvement of sentinel nodes by probe guided surgery. Nuclear techniques also portray biodistribution and pharmacodynamics/pharmacokinetics of conventional drugs; predict therapeutic abilities of non-radioactive biomolecules and the therapy effects of gene therapy using reporter probes. They also give early indications about the efficacy and or toxic effects of a treatment plan, e.g. PET that provides information about tumour response to a particular chemotherapy schedule; drug resistance in a tumour and cardiotoxicity during adriamycin therapy.

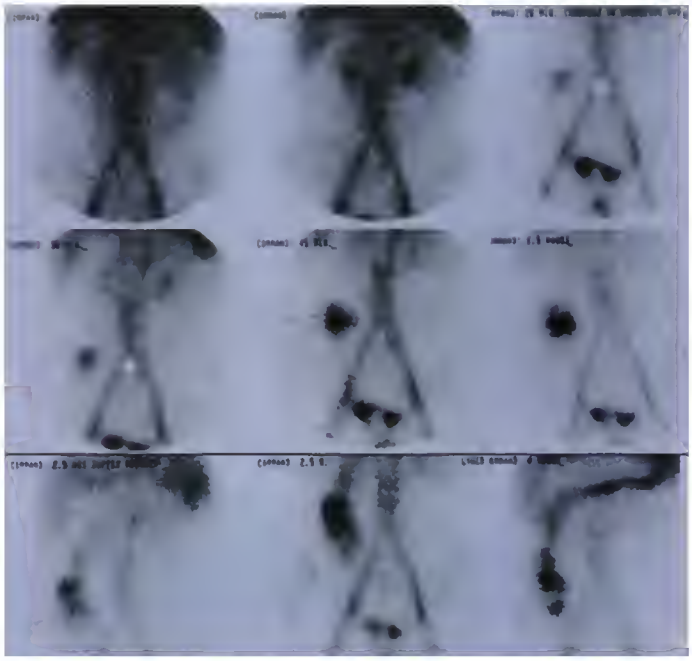


Figure 13: Tc99m labelled RBC gastrointestinal bleed scintigraphy. Multiple static images acquired shows abnormal tracer extravasation in the right iliac fossa. Further imaging reveals further bleeding and antegrade peristalsis into the transverse colon and splenic flexure.

Table 3: The Most Commonly Used Radionuclides for Therapy in Nuclear Medicine

Radionuclide	Symbol	Half-life (T½)	Type of Emission	Beta Energy (Max) (Mev)
Phosphorus-32	^{32}P	14.26 days	β^-	1.71
Strontium-89	^{89}Sr	50.5 days	β^-	1.492
Iodine-131	^{131}I	8.02 days	β^-	0.606
Yttrium-90	^{90}Y	2.67 days	β^-	2.3
Erbium-169	^{169}Er	9.5 days	β^-	0.34
Rhenium-186	^{186}Re	3.72 days	β^- and γ	1.071 0.93
Samarium-153	^{153}Sm	46.7 hours	β^- and γ	0.809 0.707 0.637
Lutetium-177	^{177}Lu	6.65 days	β^- and γ	0.176 0.384 0.497

γ= Gamma; β^-= Negative decay

SAFETY OF NUCLEAR MEDICINE

Nuclear medicine procedures are one of the safest diagnostic imaging examinations available. A patient only receives an extremely small amount of a radiopharmaceutical, just enough to provide sufficient diagnostic information. It results in low radiation exposure, acceptable for diagnostic examinations. Thus, the radiation risk is very low compared with the potential benefits. There are no known long-term adverse effects from such low-dose exposure. Allergic reactions to radiopharmaceuticals are extremely rare and are usually mild.

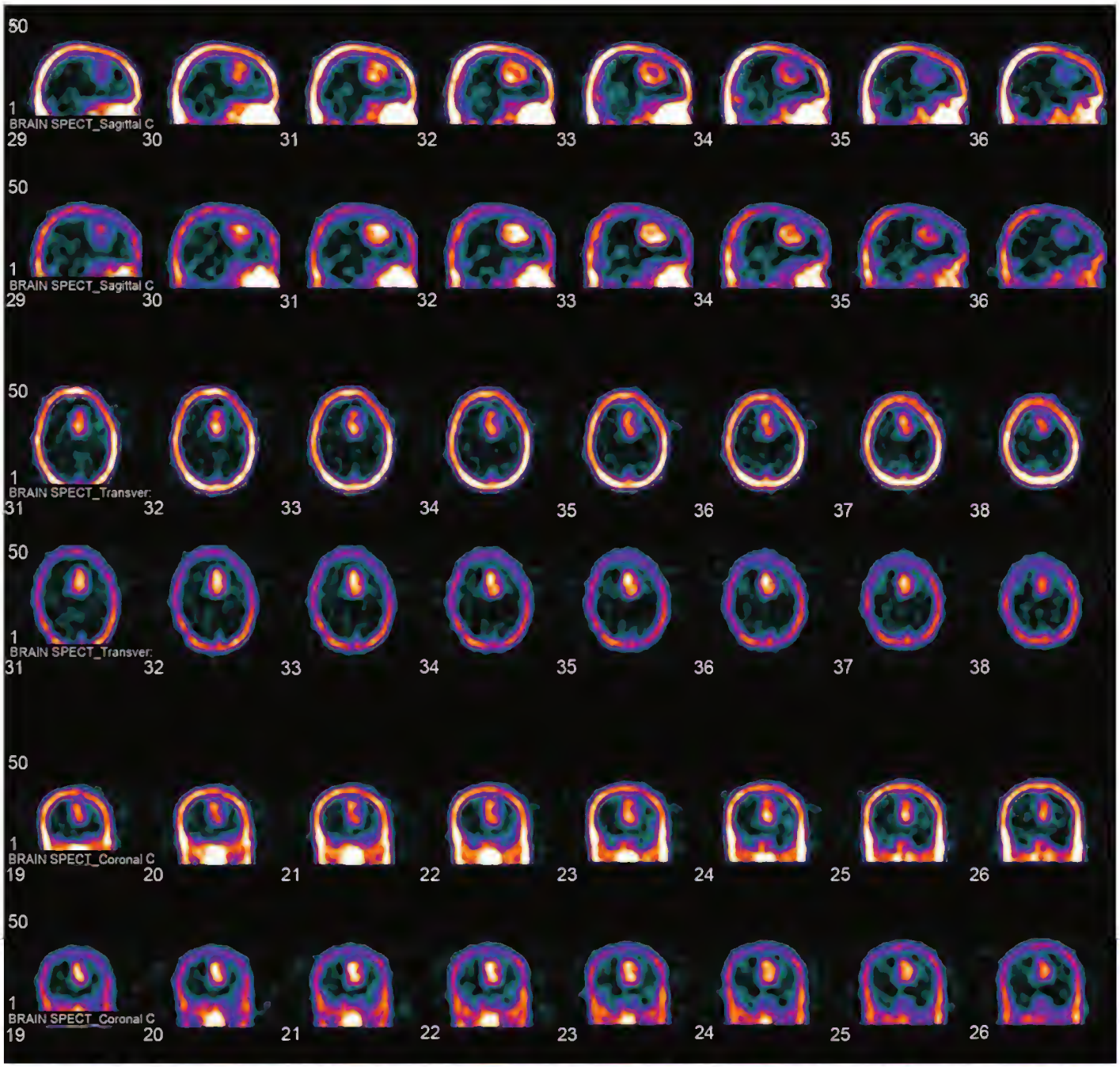


Figure 14: Tc99m-GHA brain tumour imaging focal tracer uptake is noted in the right frontal region. The patient has high grade glioma. The uptake in the scalp is physiological.

Women should always inform, if there is any possibility that they are pregnant or if they are breastfeeding their baby.

Radiation Dose

The amount of radiation from diagnostic nuclear medicine procedures is kept within a safe limit and follows the ALARA (As Low As Reasonably Achievable) principle. The radiation dose from nuclear medicine imaging varies greatly depending on the type of study. The effective radiation dose can be lower than or compatible to the annual background radiation dose. The amount of radiation from a nuclear medicine procedure is comparable to, or often times less than, that of a diagnostic X-ray except that the dose is delivered internally rather than from an external source such as an X-ray machine. The radiation dose from a nuclear medicine investigation is expressed as an effective dose with units of sievert (usually given in milli sieverts, mSv). The effective dose resulting from an investigation is influenced by the amount of radioactivity administered in megabecquerel (MBq), the physical properties of the radiopharmaceutical used, its distribution in the body and its rate of clearance from the body.

RECOMMENDED READINGS

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3.6 Positron Emission Tomography

Rakesh Kumar, Varun Shandal

INTRODUCTION

Positron emission tomography (PET) is a functional diagnostic imaging technique which can study metabolism of various biological processes like glucose, amino acid, phospholipids, receptors, etc. James Robertson and his associates in 1961 built the first single-plane PET.

Combined PET and computed tomography (CT) has better specificity and sensitivity than either PET or CT alone, as it can provide the functional and morphological details of the tissue to be studied with better localisation, all-in-one procedure. Although many radiotracers are used for PET and PET-CT but the most widely used radiotracer is Fluorine18-fluorodeoxyglucose (^{18}F-FDG) which is an analogue of glucose. Since the neoplastic processes, infection foci, etc. have increased metabolism of glucose, resulting in higher FDG accumulation which makes their visualisation better with PET-CT. For interpreting the images accurately, the knowledge of normal physiological distribution of FDG is must. Tissues with higher metabolic rate such as skeletal muscles, gut, brown fat, glandular breast, bone marrow, spleen, lymphoid tissues and urinary tract (normal excretion) accumulate more FDG which may sometimes interfere with image interpretation. There is a better quantitative way for evaluating the images by measuring standardised uptake value (SUV) which directly correlates with FDG metabolism in the tissue. PET-CT is the one of the latest functional imaging modality with wide clinical applications in the fields of oncology, infectious diseases, cardiology and neurology. As it is still in the early stages of development, its applicability in other disease conditions are still being explored. The major drawbacks of the PET-CT are the limited availability, its high cost and sometime difficult differentiation between infection and malignancy. In the following section major approved uses of the PET scan are discussed in brief.

PET-CT IN ONCOLOGY

The PET-CT imaging has revolutionised the approach and management of cancer patients. It has proven benefit in all stages of cancer, starting from detection of the lesion, its characterisation, determining the extent of the tumour, initial staging, evaluating the therapy response and detecting the recurrence of the disease. It has been also found useful for monitoring the treatment response, re-staging of disease as well as prognostication of various cancers.

Diagnosis

Solitary pulmonary nodule (SPN) and bronchogenic carcinoma

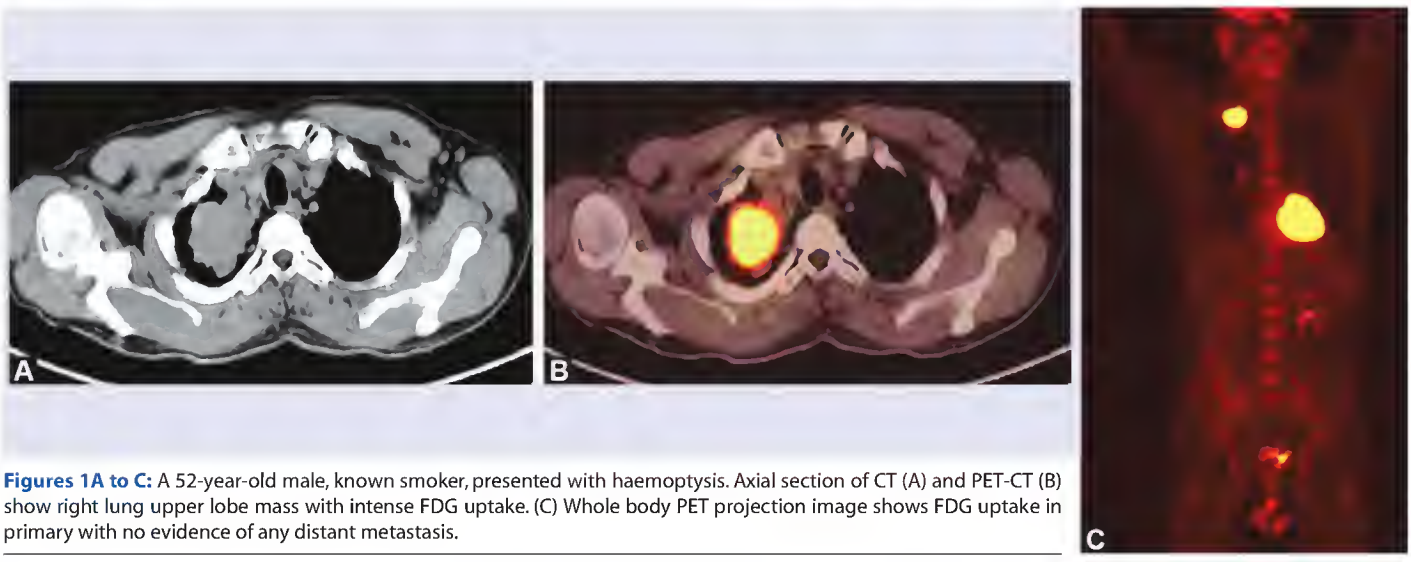
PET-CT provides additional functional information and is useful as a non-invasive diagnostic test for SPN that differentiates benign lesions from the malignant ones (**Figures 1A to C**). PET-CT has low sensitivity in detecting low-grade tumours, like bronchoalveolar carcinoma and bronchial carcinoid.

Breast carcinoma

In breast cancer patients, mammography is the most readily used imaging technique for the diagnosis of primary tumour but it has lower sensitivity in women with radiographically dense breasts and patients with breast implants. PET-CT is found to be useful in patients with dense breasts and patients with breast implants (**Figures 2A to C**). PET has also been found to be useful in detecting additional primary in contralateral breast in known breast cancer patients. However, magnetic resonance imaging (MRI) remains the gold standard for this purpose.

Other malignancies

PET-CT has the ability to differentiate pancreatic cancer from benign lesions like cystic lesions, especially in patients with chronic pancreatitis. It has a higher accuracy of 94% in detecting



Figures 1A to C: A 52-year-old male, known smoker, presented with haemoptysis. Axial section of CT (A) and PET-CT (B) show right lung upper lobe mass with intense FDG uptake. (C) Whole body PET projection image shows FDG uptake in primary with no evidence of any distant metastasis.

malignancy in cystic lesions than conventional CT (accuracy 80%). The ^{18}F-DOPA whole-body PET-CT is highly sensitive and specific for the detection of pheochromocytomas and paragangliomas and helps in detecting metastasis from malignant pheochromocytomas, especially when used after negative metaiodo-benzyl guanidine (MIBG) study. The FDG-PET has excellent diagnostic performance in differentiating adrenal lesions detected on CT or MRI in patients with known malignancies. PET-CT also has high diagnostic value in endometrial carcinoma and gall bladder mass, but in rest of the cancers it has less or no value for the purpose of diagnosis.

Initial Staging

Initial staging refers to assessing the extent of malignant neoplasms and in differentiating localised from disseminated disease.

Bronchogenic carcinoma

Non small cell lung cancer (NSCLC), which is the most frequent type of lung cancer, needs invasive procedures such as thoracotomy, mediastinoscopy for nodal staging. Also, CT and MRI are not useful in this condition if the tumour has involved less than 1 cm of area. PET-CT has overcome all these limitations by being a non-invasive investigation, giving the metabolic picture of all sites involved in one setting. It is important for the management aspect of NSCLC as the therapy to be used depends entirely on the extent of the disease.

Colorectal cancer

In colorectal cancer (CRC) patients, metastasis is usually present in majority of them at initial presentation. CT is used as initial investigation for staging but PET-CT is superior in detecting unexpected liver metastases and extra-hepatic lesions. Mucinous adenocarcinoma is one type in CRC which is less FDG avid giving false negative results most of the time.

Lymphoma

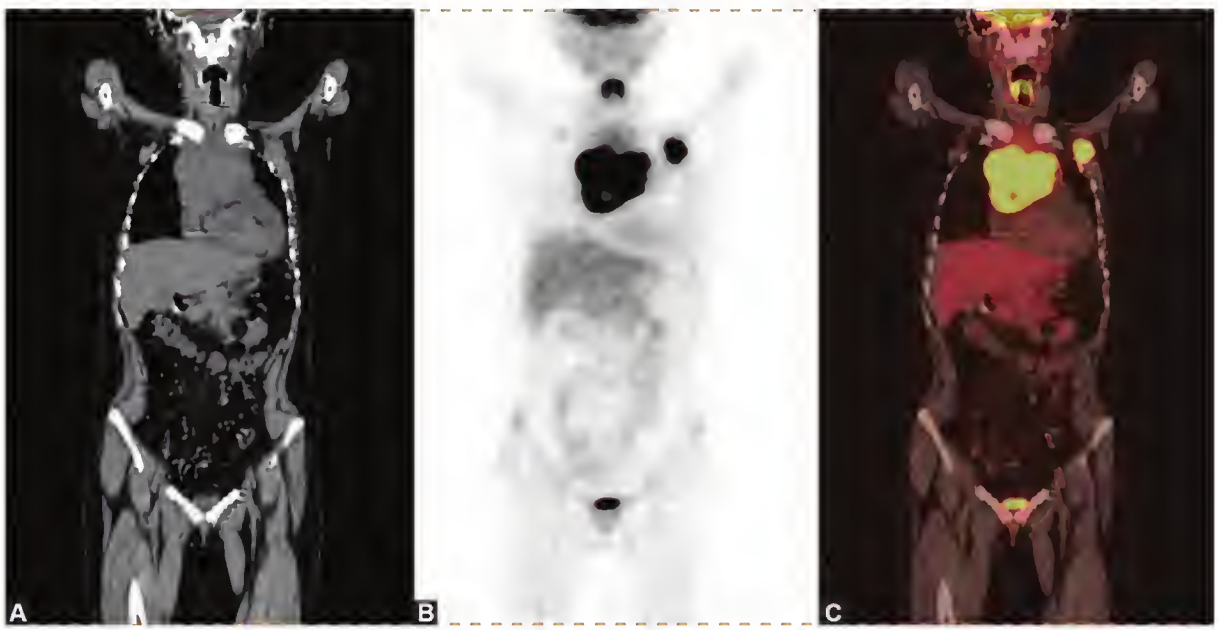
In patients with Hodgkin's disease (HD) and non-hodgkin's lymphoma (NHL), PET-CT detects more lesions which change the stage of the disease in almost 15% of patients when compared to conventional imaging like CT (**Figures 3A to C**). For histopathological examination of the lesion in HD and NHL, PET-CT can guide the biopsy from suitable and easily accessible site.

Cancer of unknown primaries and other cancers

Patients with head and neck cancers commonly present with cervical lymph node metastasis from an unknown primary. Here, PET-CT is a valuable tool in patients with an occult primary tumour in the head and neck region. PET-CT can identify primary tumour in approximately 30% patients and allow accurate tumour and lymph node staging, that is essential for treatment planning. PET-CT differentiates resectable and unresectable disease in oesophageal and gastric cancers and



Figures 2A to C: Axial sections of CT (A), PET (B) and PET-CT (C) showing focal areas of increased FDG uptake in outer quadrant of right breast in a 35-year-old female with dense breasts. Biopsy of lesion revealed intraductal breast cancer.

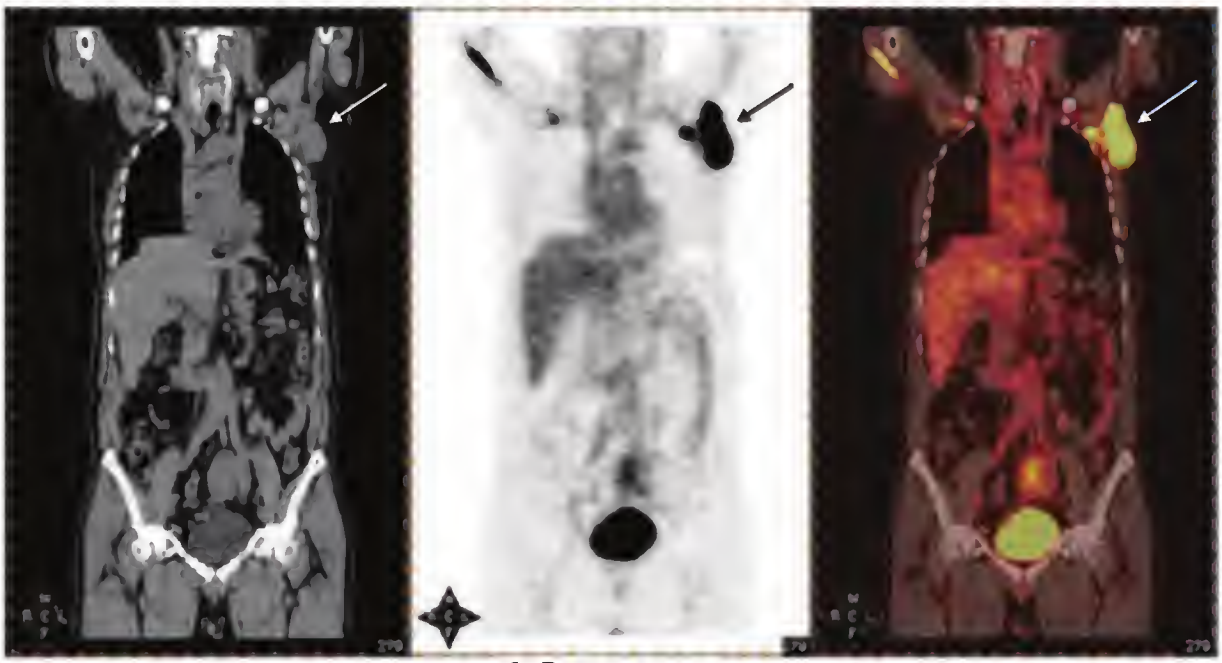


Figures 3A to C: In a known case of Hodgkin's lymphoma underwent PET-CT scan for initial staging. Coronal sections of CT (A), PET (B) and PET-CT (C) showing focal areas of increased FDG uptake in the mediastinum and left axillary lymph nodes suggestive of active disease in these regions.

helps in avoiding futile surgeries. However, the detection of regional nodal metastases is limited due to the small volume of the disease in some lymph nodes. The FDG uptake in osteosarcoma correlates well with histological grading or tumour aggressiveness. In patients with ovarian cancers having raised serum CA-125, accurate staging is very important for proper management. The PET-CT has high sensitivity and specificity as compared to conventional imaging modalities like transvaginal ultrasound (USG) and contrast enhanced computed tomography (CECT) in staging and detecting metastases. PET-CT may reveal unsuspected and occult metastases to the liver, bones, and lungs, those cannot be detected by conventional imaging, and this can change the management protocol in patients with pancreatic cancer.

Treatment Response Evaluation

PET-CT has emerged as a useful imaging modality that can evaluate the therapy response and differentiate responders from non-responders. As most of the chemotherapeutic drugs are cytostatic, conventional imaging like CT and MRI has limited value in evaluating the treatment response as they use the size criteria. However, PET-CT as functional imaging modality can show the treatment response earlier by determining the glucose uptake by tumour which decreases earlier than the size in solid tumours. PET-CT performed after 1-2 cycles of chemotherapy can differentiate progressive disease from remission better than conventional imaging modalities in lymphoma, NSCLC, etc. and can change the treatment plan accordingly (**Figures 4A and B**).



Figures 4A and B: A case of Hodgkin's lymphoma who underwent pre-chemotherapy (A) and post-chemotherapy PET/CT (B) imaging. In pre-chemotherapy scan, coronal sections of CT, PET and PET/CT are showing increased FDG uptake in multiple left axillary lymph nodes shown by arrows (upper row). In post-chemotherapy scan, coronal sections of CT, PET and PET/CT are showing resolution of FDG uptake in left axillary lymph nodes (arrows) suggestive of complete response (lower row).

In colorectal cancer patients, Delta SUVmax (absolute SUVmax change) and response index (RI), (per cent SUVmax change) are best predictive parameters in response evaluation of neoadjuvant chemotherapy.

In breast cancer patients, PET-CT detects metabolic changes much earlier than conventional imaging and clinical examination after initiation of chemotherapy. There is strong correlation between the quantitative changes in SUV and overall clinical assessment of response of skeletal metastases to therapy and changes in tumour markers in breast cancer patients. In patients with oesophageal carcinoma, PET-CT is more specific than CT and endoscopic USG for loco-regional lymph node metastasis and response evaluation to neoadjuvant chemotherapy.

Around two-third of patients with HD and 50% of patients with NHL show persistent mass lesion on conventional imaging modalities after treatment. However, PET-CT readily shows absent metabolic activity in these lesions and lower incidence of relapse in these patients proving its efficacy in treatment response monitoring in lymphoma.

CT is the imaging modality of choice in gastrointestinal stromal tumours (GIST), which can locate a mass lesion, contiguous organ invasion and distant metastases. Since the introduction of imatinib mesylate, PET-CT is being used widely in GIST. PET-CT may show significant decrease in FDG uptake early after imatinib therapy, while on conventional morphological imaging, tumour size may remain constant for a significant time. Therefore, PET-CT accurately separates responders from non-responders at an early stage, and is helpful during follow-up. However, in the assessment of the solid tumours, the role of PET-CT is yet to be determined.

Restaging/Recurrence and Prognosis

Most of the cancers relapse or recur even after the successful therapy. PET-CT is becoming standard of care in evaluating the recurrence of various cancers and in determining the prognosis. PET-CT has proven role in assessing the prognosis of NSCLC, pancreatic cancer, lymphoma, cervical cancer and other cancers as discussed below. In colorectal cancer, CT is frequently used to localise the site of possible recurrence, which has lower sensitivity and specificity. In a meta-analysis conducted on 577 patients, the sensitivity and specificity of FDG-PET for detecting recurrent colorectal cancer was found to be 97% and 76%, respectively. In head and neck cancers, PET-CT is sensitive and specific in detecting residual and recurrent lymph node metastasis and this can detect the complete metabolic response, and thus, predicting overall survival; it changed radiotherapy planning technique in 29% and altered TNM staging in 34% of the patients. PET-CT has been shown to be useful in malignant melanoma, ovarian cancer, recurrent cervical cancer, hepatocellular carcinoma (HCC), prostate and cancer of the bladder.

PET-CT IN INFECTIOUS AND INFLAMMATORY DISEASES

Infectious diseases are the major cause of morbidity and mortality in developing countries and the incidence of both community and hospital acquired infections is on the rise. Most of the times, focus of infection remains undetermined. For the successful management of patients with presumed or established inflammatory and septic diseases, the detection and localisation of infectious and non-infectious foci in soft tissues is of primary importance. Whenever, the lesions of infectious and inflammatory disease cause changes in local anatomy, capillary permeability, or tissue water content, the conventional imaging like USG, CT, and MRI are effective in detecting inflammation. Scintigraphic techniques are best used to localise inflammatory foci when normal anatomic landmarks are lost or obscured. FDG-PET-CT is also useful to detect infection and inflammatory foci. The enhanced uptake of FDG in activated inflammatory cells, such as lymphocytes or macrophages, is related to significantly increased levels of glycolysis as a result of increased numbers of cell surface glucose transporters, particularly after cellular stimulation by multiple cytokines. PET-CT is useful in the diagnosis, treatment response evaluation of infectious and inflammatory diseases, to find out recurrence/residual disease in case of chronic disorders and in pyrexia of unknown origin (PUO).

Diagnosis

PET-CT has shown its usefulness in diagnosing various difficult to diagnose infectious and inflammatory conditions. It has been successfully used in the diagnosis of tuberculosis (TB), sarcoidosis, osteomyelitis, vasculitis, human immunodeficiency virus (HIV) infection and infections in organ transplant.

Tuberculous lesions show variable FDG uptake according to the grade of inflammatory activity and they do not show any characteristic pattern. PET-CT helps in detecting unsuspected distant foci of infection (**Figure 5**). For the diagnosis of TB, biopsy and histopathological examination are essential many a times. Here, PET-CT is useful in guiding biopsy from metabolically active lesions. In another granulomatous disease sarcoidosis, although, PET-CT shows FDG uptake by sarcoid granulomas but it cannot distinguish sarcoidosis from HD or NHL and even from TB. However, PET-CT can assess the extent and degree of the disease once the diagnosis has been established.

In chronic osteomyelitis, PET-CT is highly sensitive in the detection of the disease, even in patients treated with antibiotics before FDG-PET imaging. When chronic osteomyelitis is suspected in complicated fractures, PET-CT appears to be the study of choice as FDG uptake normalises in less than 2 to 3 months whereas bones scintigraphy remains positive for longer periods following complicated fractures reducing the false positive results. Diagnosing osteomyelitis in diabetic foot using conventional imaging poses a challenge as findings of acute osteomyelitis may be similar to those of acutely evolving neuropathic osteo-arthropathy on CT, MRI which frequently coexist in diabetic patients. Here, the precise anatomic localisation of increased FDG uptake provided by PET-CT enables accurate differentiation between osteomyelitis and soft-tissue infection. In diagnosing the infected prosthesis, studies have shown variable results on the role of PET-CT. More studies are needed to confirm the role of PET-CT in the evaluation of periprosthetic infections or inflammation.

PET-CT is useful in early diagnosis and establishing the extent of the vasculitis in patients with several types of vasculitis such as giant cell arteritis, polymyalgia rheumatica, Takayasu's arteritis, periaortitis due to Wegener's granulomatosis, aortitis, unspecified large vessel vasculitis and infectious vasculitis. PET-CT is helpful in demonstrating giant cell arteritis in arteries exceeding 4 mm

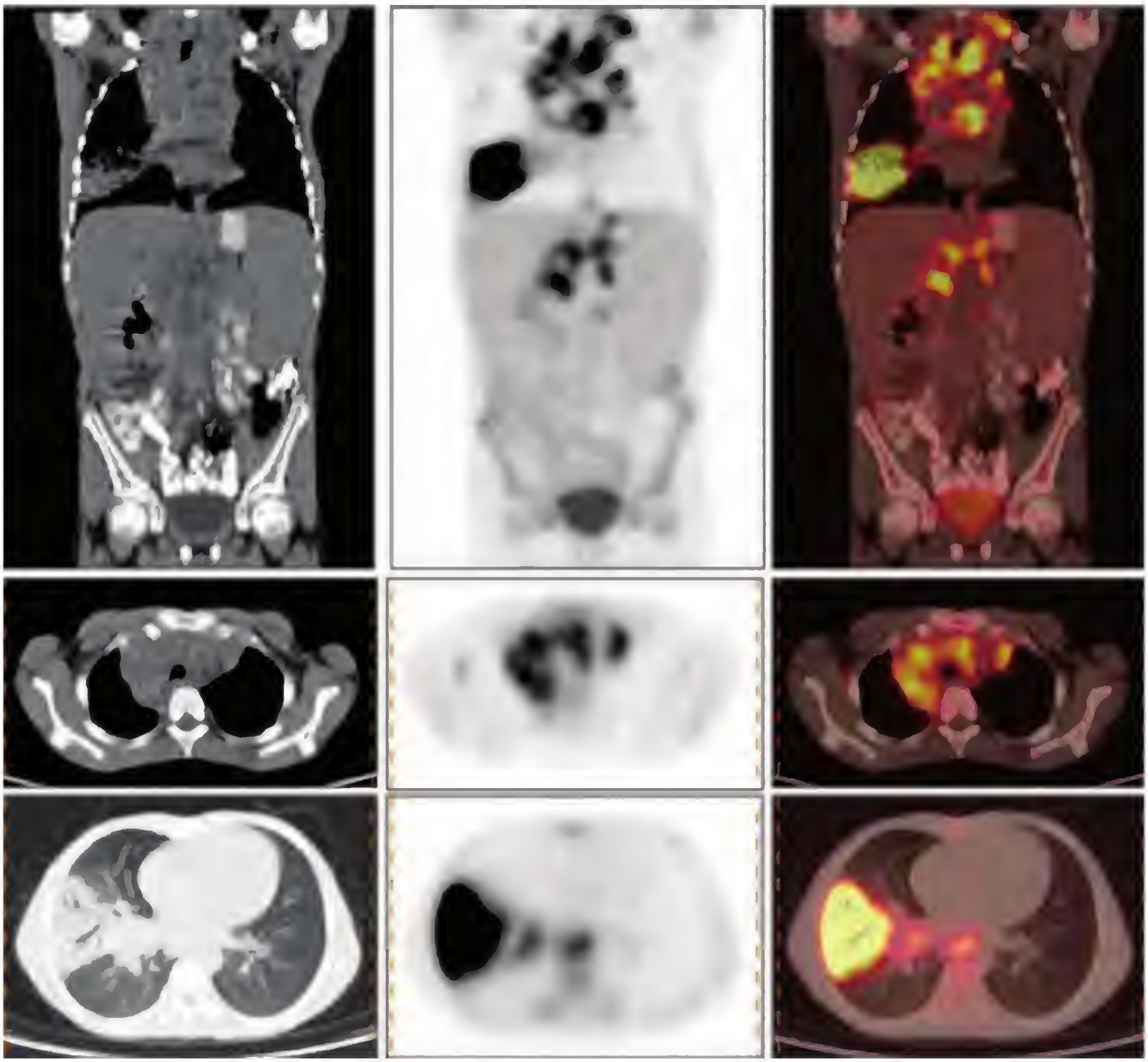


Figure 5: Patient is a case of extensive tuberculosis. Coronal (upper row) and axial sections (middle and lower row) of CT, PET and PET/CT are showing multiple focal areas of increased FDG uptake in left supraclavicular, mediastinal lymph nodes and right lung mass suggestive of active disease.

in diameter; however, in very small vessels it cannot replace the need of arterial biopsy for making the diagnosis.

In HIV-infected patients with central nervous system (CNS) lesions PET-CT has a major role in their management. PET-CT demonstrates activated lymphoid tissue in the head and neck region during acute stages, a generalised pattern of peripheral lymph node activation at the mid-stages, and abdominal lymph node involvement during the late disease. PET-CT imaging has been reported to be more accurate than CT or MRI in differentiating a malignant CNS lymphoma from non-malignant CNS aetiologies, such as toxoplasmosis, syphilis, and progressive multifocal leucoencephalopathy.

In organ transplantation cases, PET-CT can distinguish infection from rejection and hence, this non-invasive and repeatable test could reduce the number of biopsies required during the follow-up period of patients after organ transplantation. In inflammatory bowel disease (IBD), detection of disease and its extent can be assessed with PET-CT enteroclysis and good correlation has been demonstrated between the degree of inflammation and the uptake of FDG.

Pyrexia of Unknown Origin (PUO)

PUO diagnosis is still a challenge for the internists. The infections are the most common cause of PUO, followed by neoplasm and noninfectious inflammatory diseases. For improving the management in patients with PUO, the accurate localisation and characterisation of the underlying cause is of paramount importance. Because of high sensitivity of PET-CT in detecting malignant lesions, infections, and various inflammatory processes, PET-CT has the potential to play a role in the diagnostic protocol and management of patients with PUO but there are some disadvantages also in some cases. PET-CT cannot exclude cerebral disease or meningitis, because physiological uptake in the cerebral cortex in most cases

obscures any pathological uptake. Normal activity in the kidneys and the bladder severely hampers the delineation of the disease in these organs. With the development and the introduction of several new PET radiotracers, it is expected that PET-CT will secure a major role in future in the management of patients with inflammatory and other benign disorders.

Treatment Response Evaluation

In infectious and inflammatory diseases, PET-CT has the ability to monitor the response to therapy when baseline PET-CT study is available before the commencement of the therapy. It is mainly true for chronic granulomatous diseases. PET-CT can also detect residual/recurrent disease in some cases. PET-CT is useful in follow-up of patients with known TB, for monitoring response to treatment; however, more studies are needed to confirm its role, especially in spinal TB. With our own experience, we feel that PET-CT can be useful for detecting suspected recurrence and residual disease activity in patients treated previously. Similarly PET-CT will also be useful in assessing treatment response in patients with sarcoidosis. The PET-CT has been also used in IBD for the early diagnosis, assessing the extent of the disease and evaluating treatment response and disease activity in various stages of the disease.

PET-CT IN CARDIOLOGY

PET-CT has demonstrated its usefulness in patients with cardiac diseases. PET-CT quantifies the *in vivo* physiologic and pathologic processes including myocardial perfusion (coronary blood flow) and metabolism without disturbing their physiological properties. This very property of PET-CT is the basis for it being used as a clinical imaging tool for the quantitative assessment of myocardial perfusion and for the characterisation of tissue viability in patients with advanced coronary artery disease (CAD). Cardiac PET-CT helps in selecting the patients with CAD and left ventricular dysfunction that would benefit from coronary artery revascularisation. PET-CT also characterises the viability of myocardium which can prognosticate the outcome of the patients after revascularisation in patients with ischaemic cardiomyopathy and chronic left ventricular dysfunction. PET-CT also aids in assessing the presence and stability of plaques; however, it is not used routinely for the detection of any vascular disease. PET-CT is also used in the evaluation of cardiomyopathies, post-cardiac transplant evaluation and cardiac receptor evaluation for the regulation of cardiovascular functions.

PET-CT IN NEUROLOGY

The PET-CT is increasingly being used in neurology in the evaluation of epilepsy, brain tumours, dementias and movement disorders, although due to increased functional uptake of FDG by cerebral cortex the evaluation of meninges and cortical tissue is difficult. The PET-CT imaging of the brain allows non-invasive quantification of cerebral blood flow, metabolism, and receptor binding. In epilepsy, surgical removal of epileptogenic foci results in significant control of the seizures and the quality of life. Although, MRI identifies the focus of the seizure in most of the patients, but still a normal MRI has been reported in 20% to 30% of potential surgical candidates. PET-CT in ictal period shows an increase in glucose metabolism and cerebral blood flow in epileptogenic focus whereas, in post-ictal period the increased glucose uptake gradually returns to baseline. Interictally, there is hypoperfusion and decreased glucose metabolism in epileptic focus.

In brain tumours, higher FDG uptake as compared to the normal brain correlates with the higher histologic grade. PET-CT also prognosticates the shorter survival period in case of higher glucose metabolism. In disorders with dementia such as Alzheimer's disease (AD), PET-CT shows decrease in glucose metabolism in the temporoparietal lobes. In AD, a new PET tracer has been employed to target amyloid saline plaques and neurofibrillary tangles which shows prolonged retention in affected areas of the brain. Similarly newer tracers (2-carbomethoxy-3-(4-chlorophenyl)-8-(2-^{18}F-fluoroethyl) nortropane (^{18}F-FECNT) and F-DOPA) are being used in movement disorders, which allow assessment of the integrity of pre-synaptic dopaminergic neurones and are able to diagnose Parkinson's disease and other movement disorders, identify the speech and sensory-motor areas to minimise post-operative morbidity. It is also being used to measure the pharmacokinetic and pharmacodynamic effects of drugs of abuse on the human brain.

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Section 4

Clinical Pharmacology

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4.1 Introduction and Scope of Clinical Pharmacology

Ranjit Roy Choudhury, Urmilla Thatte

INTRODUCTION

Clinical pharmacology is the study of drugs in relation to clinical sciences and deals mainly with the effects of medicines in human beings. Apart from giving a scientific basis for drug use, clinical pharmacology also includes drug development, especially in man. For a physician, awareness of clinical pharmacology (and therefore the knowledge of drug behaviour in man) is necessary to guide rational therapeutics.

Although the genesis of pharmacology (Greek *pharmakos*, medicine or drug; and *logos*, study) is not very distinct, it is known that experimental demonstration of drug action began as far back in 1809, when François Magendie demonstrated, in dogs, that the spinal cord was the site of the convulsant action of *Nux vomica* (a strychnine-containing plant drug). Later in 1842, Claude Bernard discovered that curare acted at the neuromuscular junction to interrupt the stimulation of muscle by nerve impulses. However, pharmacology emerged as a separate science only in 1847, when Rudolf Buchheim was appointed as the professor of pharmacology at the University of Dorpat in Estonia. It was his student Oswald Schmiedeberg (1838–1921), who has established pharmacology as a special discipline and was also responsible for the pre-eminence of the German pharmaceutical industry up to World War II. His student, John Jacob Abel, became the first chairman of pharmacology in the USA.

The seeds of modern clinical pharmacology were sown as far back as 1937 when Harry Gold (who is considered the father of modern clinical pharmacology) described in the *JAMA*, the double-blind trial design. The formal subject 'Clinical Pharmacology and Therapeutics' was introduced in the USA only in 1960 by Gold. Then there was surge of knowledge in this field which established clinical therapeutics firmly.

SIX STEPS TO RATIONAL THERAPEUTICS

When drug treatment is rationally approached, six simple steps need to be taken. These have been summarised in **Table 1**. In this algorithm, the cornerstone for optimal therapeutics is an appreciation of the clinical pharmacology, i.e. the pharmacokinetics and pharmacodynamics of a drug.

PHARMACOKINETICS

Pharmacokinetics is the quantitative analysis of the time course of drug absorption, distribution, metabolism and excretion or to put in simple terms deals with 'what the body does to the drug'. This knowledge forms the scientific basis for deciding the dose and dosage regime of a medicine. Modifications can be made in the dosage form or in the chemical structure of a drug to influence individual pharmacokinetic parameters, thereby assisting in optimising dosing regimen (e.g. slow release formulations will delay the absorption, while modifications in lipid solubility of an injectable drug will change the distribution, metabolism and excretion, and thereby the duration of action). Knowledge of pharmacokinetic principles also assists in the development of new drugs, especially while selecting drug doses.

Information related to the absorption, distribution, metabolism and excretion of a drug allows for calculating the initial loading as well as maintenance doses to achieve and maintain target levels at the site of expected action (**Figure 1**). The route of administration (e.g. oral, ocular, inhaled, etc.) as well as several drug-related factors (including the formulation and this is where pharmaceutics plays a crucial role), and the site of drug absorption, including vascularity (e.g. muscles are very vascular and therefore allow good absorption) influence how much of a drug is absorbed into the systemic circulation. As the drug absorption is variable, an important parameter that is used to compare the availability of a drug at the site of action is bioavailability. This is defined as 'the rate and extent to which the active substance is absorbed from the pharmaceutical form and is available at the site of action'. A study of bioavailability is a useful tool to compare formulations (e.g. conventional to slow release) or generics. Comparative studies in animals or humans (clinical trials) are done only if entirely justified. When the bioavailability of two drugs, when administered in equimolar doses, is similar, these are considered to be bioequivalent and it can be assumed that their clinical effects would be comparable.

After absorption, a drug is rapidly distributed. For most drugs, distribution is characterised by a rapid mixing into one

Table 1: Six Steps to Rational Therapeutics

1. Making the correct diagnosis and defining each patient's problems.
2. Identifying the need and targets for drug therapy.
3. Understanding the clinical pharmacology of the medicines from which a rational choice can be made.
4. Selecting the appropriate medicine for that patient: Here the safety, tolerability, efficacy and price (STEP) of the drugs are good guidelines for making a choice when there is one [either between groups (e.g. alpha-blockers or ACE-inhibitors, or between drugs of the same group, e.g. enalapril or ramipril or lisinopril, or even between pharmaceutical brands of each medicine)].
5. Monitoring the treatment: Here the choice of the correct endpoint for both effect and safety is important as well as appropriate time points for modulating and individualising therapy. It is crucial to monitor for unexpected drug interactions and appropriately counselling the patient.
6. Developing a rapport with the patient to ensure complete and correct compliance.

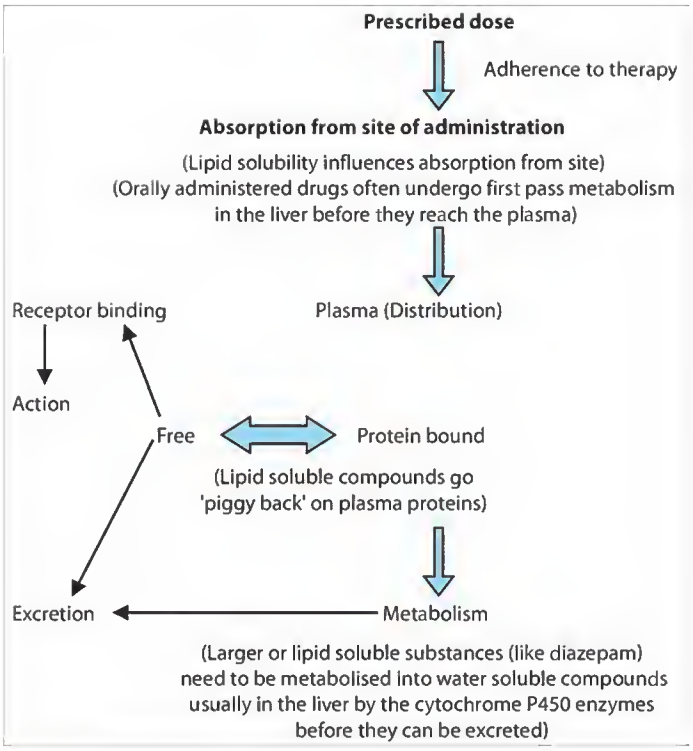


Figure 1: Fate of a drug in the body. All the parameters are influenced by various host- and drug-related factors (some of the key factors are indicated in brackets).

compartment consisting of blood volume and other tissues. This distribution depends on the molecular weight, lipid solubility, protein binding and active transport. Some other drugs (like diazepam) are initially distributed into a small central compartment [consisting of the well-perfused tissues like the brain (contributing to a rapid onset of action with minimal side-effects), blood and heart]. From this, these drugs are rapidly redistributed to a larger peripheral compartment (consisting of poorly perfused tissues like adipose) leading to a rapid reduction in the plasma concentration followed by a slower reduction which occurs due to renal clearance.

Clearance is the ability of the body to remove the drug from circulation and is clinically the most relevant in determining dosage (especially maintenance dose and intervals). The liver is responsible for biotransformation (although some drugs may be excreted via the bile) while the kidney excretes the drug or metabolites and may also be responsible for some metabolism. The hepatic microsomal enzyme system (CYP or cytochrome P450) which has been now studied in great detail is one of the major contributors to variability in drug clearance and the study of how an individual's genetic inheritance affects the body's response to drugs is called pharmacogenomics *(discussed in a subsequent chapter of sec. 6, chapter 9)*. Thirty CYP gene families have been identified in humans and the categories are based upon protein sequence homology. Most of the drug-metabolising enzymes are in the CYP 1, 2 and 3 families. The activity of CYP enzymes can be influenced by genetic and environmental factors [nutrition, alcohol, other drugs (cimetidine is an inhibitor while phenobarbitone induces these enzymes) and smoking] thus influencing drug metabolism.

Apart from this, several other factors influence clearance including many host and drug factors, influencing to a large extent, therapeutic decisions about the choice of drug and dosing regimes. *Prescribing in special conditions is discussed in chapter 4 in this section.*

A certain amount of the drug is cleared from the body in unit time. The time taken to clear 50% of a drug from the body is defined as the 'half-life' ($t_{1/2}$). Most drugs follow first order (exponential) kinetics and these drugs have a fairly constant $t_{1/2}$ (when rate of clearance depends on the concentration of the drug). However, some drugs follow zero order or saturation kinetics where the clearance processes get saturated at a point in time, thus leading to a fixed amount of the drug getting cleared rather than a fixed proportion. Thus, the $t_{1/2}$ now varies according to the concentration and can contribute to toxicity. Phenytoin is a good example, where as the dose increases, the clearance shifts from being exponential to a saturation type, making it important for close monitoring.

A useful clinical application of the knowledge of pharmacokinetics is applied in therapeutic drug monitoring (TDM) which is the measurement of drug levels in body fluids (mostly blood or plasma, and sometimes saliva, urine or cerebrospinal fluid) at intervals to minimise toxicity and maximise effect. Drugs that have a narrow therapeutic window, poor or no physiologic or therapeutic endpoints to guide dosage, and whose pharmacokinetics varies widely between individuals, are good candidates for TDM. Further, if there is a critical need to monitor adherence, TDM is a useful tool.

PHARMACODYNAMICS

Pharmacodynamics deals with 'what the drug does to the body' and is the study of the biochemical and physiological effects of drugs on the body and their mechanisms of action. Knowledge of pharmacodynamics helps in intelligent drug development and also forms the basis of rational drug therapy. Most drugs act by altering body's control systems by different mechanisms, e.g. by binding to receptors, interfering with transport processes, inhibiting enzymes, etc. Coupled with the body's homeostatic responses to the primary actions of the drug, a composite therapeutic effect occurs, which finally leads to well defined and desired clinical endpoints.

ADVERSE EFFECTS OF DRUGS

Unwanted effects are an integral part of drug use. It has been said by Mathew Prior (1664-1721) 'Cur'd yesterday of my disease, I died last of my physician!' Complete information regarding known adverse reactions as well as a knowledge of how to recognise and manage unexpected adverse reactions to medicines is an integral part of rational therapeutics. *Chapter 3 in this section deals with this important part of clinical pharmacology.*

Among the adverse reactions to drug, allergic reactions are clinically the most challenging for both diagnosis and management. Allergic reactions are generally of four types: type I (immediate, anaphylactic, e.g. penicillin), type II (antibody dependent cytotoxic reactions, penicillin induced haemolytic anaemia), type III (immune complex mediated) and type IV (lymphocyte medicated delayed reactions, contact dermatitis). Characteristically, allergic reactions do not show a correlation with the pharmacological properties of a drug, lack a linear relationship with the dose (i.e. a very small dose can precipitate a reaction), are rare and unpredictable, can recur on re-exposure,

usually disappear on withdrawal of drug and reappear on reintroduction of drug. Taking history of drug allergy is crucial before starting therapy as a rule, as allergic reactions, although common with some drugs, can occur with any medicine.

DRUG INTERACTIONS

Drug interactions are common in today's rampant practice of polypharmacy and if they go unrecognised, can lead to fatal outcomes. The true incidence of drug interactions is difficult to determine. Drug interactions can be pharmacodynamic (due to interactions at the receptor) or pharmacokinetic (related to absorption, distribution, metabolism or elimination of the drug).

Pharmacodynamic interactions occur due to additive, synergistic, or antagonistic effects from co-administration of two or more drugs (e.g. synergistic actions of antibiotics, additive effects of ethanol and benzodiazepines, or antagonistic effects, like anticholinergic effects of drugs such as amitriptyline with acetylcholinesterase inhibitors).

Pharmacokinetic interactions are also common. Interference with absorption of drugs by food is the most common example (e.g. Indinavir is rapidly absorbed in a fasted state and absorption is reduced by 80% with a high calorie/fat/protein meal while the absorption of saquinavir is increased significantly when given with a high fat meal. Chelation in the stomach (tetracycline or dairy products) is another cause for interaction. Alteration in gastrointestinal motility or pH also influences drug absorption (e.g. antacids, omeprazole, H2-blockers may decrease absorption of ketoconazole and itraconazole). Competition between drugs for protein or tissue-binding sites can increase free (unbound) concentrations leading to enhanced pharmacological effects (e.g. oral hypoglycaemic agents and nonsteroidal anti-inflammatory drugs). Drug metabolism interactions are very common and occur by co-administration with CYP inducers or inhibitors. Drugs can inhibit a specific CYP even though they are not metabolised by that isozyme, e.g. quinidine is a potent CYP2D6 inhibitor but is itself metabolised primarily by CYP3A4. Cimetidine, erythromycin, ketoconazole, ritonavir, fluoxetine, paroxetine (CYP2D6) and nefazodone (CYP3A4) are the common CYP inhibitors while drugs like rifampin, carbamazepine, phenobarbital or phenytoin induce CYP. Many medicinal plants have been shown to interact with drugs through interference of metabolism (the concentrations of indinavir are decreased in the presence of St John's Wort as it induces CYP3A4 while grapefruit, by inhibiting CYP3A4 can increase concentrations of saquinavir, benzodiazepines or calcium channel blockers).

For a clinician, recognising drug interactions is very crucial so as to manage the patient appropriately. A patient showing exaggerated toxicity or drug effects or treatment failure should trigger a high index of suspicion. When a drug interaction is suspected, the physician must study the time course of the interaction, investigate whether it is a drug class effect and assess if the interaction is clinically significant.

Understanding and applying these principles of clinical pharmacology form the basis rational therapeutics. However, an important principle of therapeutics that must be remembered is 'Drugs cannot work if patients do not take them!' When the physician reaches the decision that the patient requires medicine, a prescription results (**Table 1**). Perhaps the most crucial aspect of drug therapy is that of compliance which is defined as 'the extent to which a person's behaviour coincides with medical advice'. Noncompliance to medication can lead to serious problems for the patient as well as to the community. It is impractical to expect 'perfect' compliance, but useful to define what would be 'adequate' compliance in a given patient during therapy. Supervised therapy [as in directly observed treatment, short-course (DOTS)] assists in improving compliance. Improved communication to convince the patient of the need for compliance and simplifications of the regimes are some other methods reported to improve compliance. In fact, no drug can substitute for effective communication between a doctor and a patient.

An important aspect of drug therapy and response to medicines is the placebo effect and the physician needs to be aware of and exploit this phenomenon to the maximum. An essential part of a therapeutic decision is an assessment of the cost-benefit assessment *(see chapter on Pharmacoeconomics)*.

INTRODUCTION OF NEW DRUGS

New drugs are introduced into the market regularly by pharmaceutical companies and this is associated with aggressive marketing. After extensive preclinical and clinical research (*described in the section on drug development*), a drug is marketed for an approved condition for which it has been developed. When a drug is used for an indication or in an indication that is not approved this is called 'off-label' use and the responsibility for use rests on the physician alone. There has to be sufficient scientific justification for the off-label use. Research on the other hand for 'off-label' indications, new routes of administration or new formulations including fixed drug combinations require regulatory clearance. In India, drug choices are wide because of the variety of drugs approved. Additionally, each drug has several generics and to make a rational choice between these requires skill and a clear understanding of principles of clinical pharmacology.

An interesting feature of therapeutics in India is the widespread popularity of 'alternative' systems of medicine among patients. *Ayurveda, Siddha, Unani, Yoga,* Naturopathy and Homeopathy are officially recognised by the Government of India and most clinicians will come across patients, especially those with chronic diseases like asthma or arthritis using alternative systems of medicine. A physician must be aware and recognise that the medicines from alternative systems used by the patients may have an impact (favourable or unfavourable) on therapy including the occurrence of adverse reactions and drug interactions.

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4.2 Rational Use of Drugs

Sangeeta Sharma

The availability of essential drugs is minimal and capacity of the facilities is grossly inadequate. The private sector is the most important source of health care in India, providing approximately 80% of the services. Patients have to shell out of their pocket payments for seeking private health services at the cost of other essential expenditure. The pharmaceutical industry has witnessed tremendous transformation since the 1950s but at the same time irrational, non-essential and hazardous drugs have flooded the market.

Access to essential medicines, high expenditure on medicines and irrational combinations are the three problems people face and public systems are challenged to respond to. Other concerns are the rising health care costs, increasing medicine costs, newer products and technology, over-dependence on investigations, diseases of old age, rising incidence of heart disease, cancer, increased expectations and reducing health budgets.

DRUGS: A CRITICAL INPUT

Drug expenditure is the most critical aspect of the financing of health services. Lack of drugs can block the operation of the health care system. Credibility, effectiveness and attendance at health services, depend on a large extent on patient being able to obtain relevant drugs at the right time. A good diagnosis is not much use if the patient cannot obtain the necessary treatment.

RATIONAL USE OF MEDICINES

Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. Unfortunately, worldwide more than 50% of all medicines are prescribed, dispensed or sold inappropriately and 50% of patients fail to take their medicines correctly. Inadequate consulting time, very short dispensing time and incorrect use by patients is of great public health concern too.

Global Epidemic of Irrational Use of Medicines

Problems of irrational use of drugs and non-availability of drugs are often similar in many countries including India. Common types of irrational medicine use are:

- The use of too many medicines per patient (polypharmacy).
- Choice of more expensive drugs when less expensive drugs would be equally or more effective.
- Inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections—common cold, diarrhoea, etc.
- Overuse of injections when oral formulations would be more appropriate.
- Failure to prescribe in accordance with clinical guidelines.
- Failure to provide available, safe and effective drugs/vaccines.
- Under-use of life-extending drugs for illnesses, such as hypertension, heart disease, asthma, and other chronic illnesses.

Massive Detrimental Effects of Irrational Use of Medicines

1. Lack of access to medicines and inappropriate doses results in:
   - Serious morbidity and mortality, particularly for childhood infections and chronic diseases, such as hypertension, diabetes, epilepsy and mental disorders.
   - Overuse of medicines leading to wastage of meagre resources resulting in significant patient harm in terms of poor patient outcomes and adverse drug reactions.
2. Rising anti-microbial resistance:

   Overuse of antimicrobials is leading to increased anti-microbial resistance (AMR) and non-sterile injections to the transmission of hepatitis, HIV/AIDS and other blood-borne diseases. AMR is one of the world's most serious public health problems resulting in prolonged illness and hospitalisation, which are costly and the use of drugs other than first-line drugs may increase cost 100-fold, making them unaffordable.

   Development and spread of anti-microbial resistance is due to:
   - Overuse, misuse, and irrational use by doctors.
   - Non-compliance and self-medication by patients.
   - Non-human use of antibiotics in animal husbandry, aquaculture and agriculture.
3. Irrational overuse of medicines can stimulate inappropriate patient demand, and lead to reduced access and loss of patient confidence in the health system.

   The first step to correcting irrational use of medicines, i.e. promoting rational use of medicines, is to understand:
   - Types and amount of irrational use of medicines, so that strategies can be targeted towards changing specific problems.
   - Monitoring the reasons why medicines are used irrationally, so that appropriate, effective and feasible strategies can be chosen. People often have very rational reasons for using medicines irrationally. Causes of irrational use include lack of knowledge, skills or independent information, unrestricted availability of medicines, overwork of health personnel, inappropriate promotion of medicines and profit motives of selling medicines.

Table 1: Twelve Core Interventions to Promote More Rational Use of Medicines

1. A mandated multi-disciplinary national body—to co-ordinate medicine use policies.
2. Evidence-based clinical guidelines—to aid prescribers on how to treat patients.
3. Essential medicines list based on treatments of choice—to be followed in procurement and distribution of medicines.
4. Drugs and therapeutics committees—to monitor quality of care in the hospitals.
5. Problem-based pharmacotherapy training in undergraduate curriculum—to better equip future doctors in how to prescribe.
6. Continuing in-service medical education as a licensure requirement—in order to ensure that prescribers remain up-to-date with new treatments/guidelines.
7. Supervision of health care workers, audit of prescribing and feedback to prescribers—in order to help prescribers use medicines more appropriately.
8. Provision on independent information (drug bulletins) on medicines—in order to make sure that prescribers have sufficient unbiased information on medicines.
9. Public education about medicines to try and reduce inappropriate self-medication and demand for medicines and also to increase awareness about the importance of adherence.
10. Avoidance of perverse financial incentives such as prescribers earning money from the sales of medicines which encourage over-prescription of medicines.
11. Appropriate and enforced regulation, particularly concerning medicine promotional activities by the pharmaceutical industry, licensing of drug outlets (pharmacies, hospitals) and healthcare workers, and the availability of prescription-only medicines without prescription.
12. Sufficient government expenditure to ensure availability of medicines and staff.

Adapted from WHO, 2002.

Policies to Promote Rational Use of Medicines

Based on the available evidence, WHO has developed recommendations for twelve core national policies and structures that are needed to promote rational use of medicines (**Table 1**).

Essential medicines are those that satisfy the priority health care needs of the population. These can be selected with due regard to disease prevalence, evidence on efficacy, safety and comparative cost-effectiveness. Therefore, these should be available at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford. No public sector or health insurance system can afford to supply or reimburse all medicines that are available in the market. Lists of essential medicines also guide the procurement and supply of medicines in the public sector, schemes that reimburse medicine costs, etc. Careful selection of a limited range of essential medicines results in a higher quality of care, better management of medicines, and more cost-effective use of health resources.

Clinical Guidelines or Standard Treatment

These guidelines is consist of systematically developed statements to help prescribers make decisions about appropriate treatments for specific clinical conditions. These are an effective tool for assisting health professionals to choose the most appropriate medicine for a given condition. Essential medicines list together with standard treatment guidelines are the most powerful tools for promotion of rational use of medicines.

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4.3 Adverse Drug Reactions and Pharmacovigilance

MC Gupta

INTRODUCTION

Drugs have the potential to do good which may be trivial to lifesaving. Drugs, used appropriately, can improve both the quality and longevity of life, but drugs also have the potential to cause harm which may be trivial to death. No drug can be considered to be totally devoid of causing any harmful effects to the recipient. The principle of appropriate treatment entails making a balance between the benefit and the harm in such a way that the benefit always outweighs the harm.

ADVERSE DRUG REACTIONS

Magnitude of the Problem of Adverse Drug Reactions

In USA and Canada, adverse drug reactions (ADRs) are the fourth leading cause of death. Over one million Americans suffered from ADRs in 2009. Worldwide also, the ADRs are the sixth leading cause of death. Monetary costs involved in the management of these ADRs are astronomical, a staggering US dollar 75 to 180 billion which may almost be adequate to meet the cost of managing the cardiovascular diseases ($120 to 150 billion) or cancers ($130 to 195 billion). Responsibility of drug-induced injury raises important issues affecting medical practise, not only pertaining to development of drugs, but also of regulatory laws especially in view of the Consumer Protection Act (CPA) in India.

The overall objective of drug development is to ensure that medicinal products being produced are of acceptable quality, good efficacy and safety with a minimum possibility of causing serious adverse effects. All the hazards of drug use cannot be known before it is marketed; neither tests in animals nor clinical trials will reveal all the possible side-effects of the drug. These may only be known when the drug has been administered to a large number of patients over a considerable period of time.

Definition

Adverse drug reaction (ADR) is a response to the drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function.

ADRs have been classified into two broad categories: type A and type B. Type A (augmented) reactions are common, predictable, dose-dependent reactions that account for at least 80% of total reactions and are produced by known pharmacologic actions of the drug. Type B (bizarre) reactions, on the other hand, are uncommon and unpredictable, usually having an immunologic basis and occur only in susceptible individuals. More recently, further classes of ADRs have been defined. These include type C (continuous), which are dose related and time related, type D (delayed) which are time-related and type E (end of use) which are seen after withdrawal of a drug.

ADVERSE EVENT

1. Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.
2. An adverse event may or may not be due to the drug, while an adverse drug reaction is always due to the drug.
3. Adverse event is more relevant to the new drugs where nothing is known of the adverse drug reactions of the molecule under trial.
4. An adverse event can eventually become the ADR of the drug, if it is proven with some certainty that it is because of the drug only.

PHARMACOVIGILANCE

World Health Organization (WHO) defines pharmacovigilance as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems'.

Food and Drug Administration defines it as, 'all the post-approval scientific and data gathering activities relating to the detection, assessment and understanding of adverse events'.

Why Pharmacovigilance?

The information on the safety, collected during the premarketing phase of a medical drug, is inevitably incomplete with regard to the possibility of adverse reactions. Following are the important reasons as to why the pharmacovigilance activities should be routinely carried out.

1. Tests in animals are insufficiently predictive of human safety.
2. Limitations of the premarketing phases of clinical trials
   - Failure to detect rare and delayed adverse drug reactions.
   - Conducted in strictly controlled conditions and not in an actual clinical scenario.
   - Do not provide data
     - In children, elderly, seriously ill, pregnant and lactating patients
     - Patients with other diseases
     - Patients receiving other drugs
     - Patients from various populations
3. Aggressive marketing strategies of the pharmaceutical companies.
4. Fast changing physician and patient preferences.
5. Easy accessibility to drugs.

Pharmacovigilance is needed in every country, because there are differences between countries (and even regions within countries) in the occurrence of adverse drug reactions and other drug related problems. This may be because of differences in:

1. Disease and prescribing practices
2. Drug production distribution and use (e.g. indications, dose and availability).
3. Pharmaceutical quality and composition (excipients) of locally produced pharmaceutical products.
4. Genetics, diet and traditions of the people.
5. The use of non-orthodox drugs (e.g. herbal remedies) may pose special toxicological problems, when used alone or in combination with other drugs.

Data derived from within the country or region may have greater relevance and educational value and may encourage national regulatory decision-making. Information obtained in a certain country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may be different.

The WHO International Drug Monitoring Programme may provide information on possible safety issues which may not yet have emerged within the country's data.

Aims of Pharmacovigilance

Pharmacovigilance is needed for the prevention of drug-induced human suffering and to avoid financial risks associated with unexpected adverse effects.

Major aims of pharmacovigilance are:

1. Early detection of hitherto unknown adverse reactions and interactions.
2. Detection of an increase in frequency of known adverse reactions.
3. Identification of risk factors and possible mechanisms underlying these adverse drug reactions.
4. Estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve drug prescribing and regulation.

The ultimate goals of pharmacovigilance are:

1. The rational and safe use of medical drugs.
2. The assessment and communication of the risks and benefits of drugs in the market to the clinicians.
3. Educating and informing the patients.
4. Making the appropriate regulatory decisions as and when required.

Methods of Pharmacovigilance

A number of methods have been employed for the pharmacovigilance activities, the spontaneous reporting being the most common, effective and cheap in terms of costs. Globally also, this method has the best acceptability. The various methods which can be used for the pharmacovigilance activities are:

1. Case reports and case series.
2. Spontaneous reporting, e.g. yellow card system in UK, blue card system in Australia, Med watch in USA and National Pharmacovigilance Programme (NPP) in India.
3. Prescription event monitoring.
4. Comparative observational studies, e.g. case control and cohort studies.
5. Pharmacy based postmarketing surveillance studies.
6. Intensive hospital monitoring.
7. Record linkage schemes by computer.
8. Population statistics.
9. Meta-analysis

Spontaneous Reporting of Adverse Drug Reactions

Spontaneous reporting is currently the major source of information in pharmacovigilance. This is a sensitive, powerful and a cost-effective system. It is expected now that all the prescribing clinicians should take the professional responsibility of reporting the adverse events causing a risk to the patient to the pharmacovigilance centre of their state/region, and thus, contributing to the NPP. The advantages of the spontaneous reporting are:

1. It can cater to large population.
2. It can cover all types of medicines including the herbals.
3. It is possible to do both in hospital and outpatients.
4. It may generate rapid alerts.
5. It is least likely to influence prescribing behaviour.
6. Low set-up and recurring costs.

The system has some disadvantages also like under-reporting by the clinicians, difficulty in detecting ADRs, number of the exposed unknown patients and there may be a bias in reporting the ADRs.

Who can report?

1. Professionals working in health care are the preferred source of information in pharmacovigilance, e.g. family practitioners, medical specialists and pharmacists.
2. Dentists, midwives and nurses.
3. Pharmaceutical manufacturers should ensure that suspected ADRs must be reported to the competent authority.
4. ADRs may be reported directly by the patients to the national or local ADR monitoring centres. It is important to communicate with their physicians for additional information and data verification.

What to report?

In the early stages of any pharmacovigilance system, reports on all suspected ADRs, known or unknown, serious or non-serious are encouraged, because it is necessary to create a 'notification or reporting culture'. All serious adverse events should be reported. A serious ADR entails, hospitalisation, disability, congenital abnormalitis or death.

1. *For new drugs (up to 5 years):* All suspected reactions, including minor ones, should be reported.
2. *For established drugs:* Serious or unusual suspected adverse reactions are to be reported. If an increase in frequency of a given reaction is suspected, then this is also reported.
3. Special fields of interest are drug abuse and drug use in pregnancy and lactation.
4. Lack of efficacy and suspected pharmaceutical defects is recommended.
5. Adverse reactions to cosmetics.
6. All suspected ADRs associated with drug-drug, drug-food or drug-food supplements interactions.
7. Suspected ADRs associated with the drug withdrawals.
8. ADRs occurring from overdose or medication error.

Pharmacovigilance is primarily concerned with the pharmaceutical medicines (including radiological contrast media, vaccines and diagnostics) but adverse reactions associated with drugs used in traditional medicine (e.g. herbal remedies) should also be considered.

The pharmacovigilance programme in general has not taken off very well in most countries really because of some misconceptions on the part of the clinicians, such as:

1. All serious ADRs are documented by the time, a drug is marketed.
2. It is difficult to determine if a drug is responsible.
3. ADRs should only be reported if absolutely certain.
4. One reported case is not going to make a difference.
5. One can have legal complications if he reports an ADR.

The general attitude of the prescribers which does not really help the cause of pharmacovigilance programme is amply shown by the 'seven deadly sins', *i.e. indifference, ignorance, financial incentives, legal hurdles, complacency, diffidence and lethargy*.

Stakeholders in pharmacovigilance

The stakeholders who can help in pharmacovigilance are the users (patients), prescriber (the clinician), supplier (pharma industry) and the Government. Media can also play an important role.

Communication tools

The main reason for poor success of the pharmacovigilance programmes all over the world has been a poor communication. It is required to use well-defined tools for an effective communication within the various participants of any such programme. Following are some of the proposed tools which are likely to help:

Vehicle	Issued by
"Dear Doctor" letters	Pharmaceutical manufacturers
Medicine alerts	National health authorities
Media statements	National health authorities/ pharmacovigilance centres
Patient information leaflets	National health authorities/ pharmacovigilance centres/ pharmaceutical manufacturers
Newsletters	National pharmacovigilance centres and WHO

Pharmacovigilance Scenario in India

The status of the pharmacovigilance activities in India has been dismal. A fresh effort is being made again to revive this programme by the Government through Drug Controller General of India (DCGI). The revised National Pharmacovigilance Programme has now chosen 24 centres for this all over the country with a nodal center at New Delhi. With such a large population using the drugs and a vast amount of expertise, the National Pharmacovigilance Programme in terms of implementation and an acceptable outcome should not be a problem, if all cooperate and report.

Good pharmacovigilance practices

The pharmacovigilance is an important tool in the lifecycle of a drug starting from the beginning of the clinical trials and going into the post-marketing phase with the sole motive of making the drug treatment safe for the patient. The various ingredients of these practices are as follows:

1. Education, training and access to reliable information for the clinicians and the patient.
2. Good pharmacovigilance regulations.
3. Development of a national pharmacovigilance database.
4. Good pharmacovigilance communication.
5. Good culture of spontaneous reporting by the clinicians and the patients.
6. Proactive industry initiatives.
7. Provision of convenient system of submission and feedback on reported ADRs.
8. Better patient care through better safety information.

CONCLUSIONS

The clinicians have to be aware of the harmful potential of the drugs and to be ready to detect the ADRs at the earliest and correlate them with the drug therapy and if so to manage them as best as possible to serve the best and safe interest of the patients which will go a long way for the success of the NPP. This will surely need the active and willing participation of all the stakeholders.

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4.4 Prescribing in Special Situations

Uma Tekur

INTRODUCTION

Inter-individual and intra-individual variation in drug response is a well known phenomenon. It is, therefore, imperative that the health care providers are aware of the sources of such variations. This knowledge will help physicians prescribe drugs more effectively and safely.

The variations in the drug response may be:

1. *Pharmacokinetic variations* are chiefly due to alteration in the absorption, distribution, metabolism or excretion of drugs in an individual patient leading to an alteration in the concentration of drug available at the site of its action. These variations may be seen in malabsorption syndrome; heart failure, nephrotic syndrome (due to altered absorption); renal or hepatic impairment or in meningitis (variation in distribution, metabolism or excretion).
2. *Pharmacodynamic variations* due to difference in response to a drug. These may be seen in *Myasthenia gravis*, nephrogenic diabetes insipidus, familial hypercholesterolaemia, precocious puberty, etc.

The human body undergoes constant physiological changes throughout one's life. Definitive changes are observed in childhood, old age, and in women during pregnancy and lactation.

The present chapter will briefly discuss the drugs use: (i) at the times of physiological changes seen in pregnancy, childhood and old age, and (ii) in hepatic and renal impairment.

DRUGS IN PREGNANCY

There is a two-fold problem that should be taken care of while administering drugs during pregnancy, viz: (i) alteration in drug response due to variation in physiology, and (ii) the teratogenic effects of drugs.

A pregnant woman will require drug treatment primarily under two circumstances.

1. For the management of pregnancy related (obstetrical) conditions, and
2. For the management of medical conditions unrelated to pregnancy.

Obstetrical Conditions

The common obstetrical problems encountered during pregnancy are:

Nausea and vomiting

These symptoms are seen in early pregnancy and usually do not require any drug therapy. However, hyperemesis gravidarum may be treated with doxylamine (anti-histaminic) alone or in combination with pyridoxine. Metoclopramide should be avoided in pregnancy. Other antiemetics that may be safely used in pregnancy are, promethazine, cyclizine and prochlorperazine.

Anaemia

Due to increased demand of growing foetus anaemia occurs commonly. Folic acid and iron should be given routinely during pregnancy. Folic acid should be started as soon as pregnancy is diagnosed whereas iron may be started in second trimester. The risk of neural tube defects is significantly reduced with supplemental folic acid. This is in addition to a healthy diet that should be recommended throughout the pregnancy.

Pregnancy induced hypertension

It can present as pre-eclampsia or eclampsia. Apart from increase in blood pressure, eclmapsia manifests as seizures. Alpha methyldopa is the drug of choice for the management of hypertension whereas magnesium sulphate is used for the treatment of eclampsia.

Pre-term labour

Atosiban (oxytocin receptor antagonist), calcium channel blockers, terbutaline like drugs can be used for delaying the labour. In addition, dexamethasone can be administered to accelerate foetal lung maturation.

Placenta praevia

Drugs do not play much role in the management of this condition.

Rh isoimmunisation

To a mother with Rh negative blood group, if a baby is born with Rh positive blood group, anti-D (anti-Rh immunoglobulin) should be administered within 72 hours of delivery to prevent erythroblastosis foetalis that may occur during subsequent pregnancy.

Medical Conditions Complicating Pregnancy

General guidelines to be followed are:

1. As a general rule, drugs should be avoided during pregnancy.
2. The drugs having the best safety record over time should be used if necessary.
3. Newer drugs should be avoided unless safety is clearly established.
4. The drugs should be used at lowest effective dose and for shortest period.
5. Over-the-counter drugs cannot be assumed to be safe in pregnancy.

The following is a list of drugs that may be given during pregnancy if necessary.

1. ***Analgesics:*** Paracetamol and ibuprofen (at low doses) are safe during pregnancy. Other nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids should be avoided during pregnancy.
2. ***Anti-allergics:*** Older anti-histaminics like chlorpheniramine and promethazine are considered safe during pregnancy. Second generation agents like cetirizine should be avoided.
3. ***Anti-microbials:*** Penicillins, macrolides and cephalosporins are considered safe during pregnancy. Tetracyclines, aminoglycosides and fluoroquinolones should be avoided.
4. ***Anti-tuberculosis drugs:*** Rifampicin and isoniazid are safe during pregnancy. Streptomycin should not be used in pregnancy.
5. ***Anti-parasitic and anti-protozoal drugs:*** Diloxanide furoate (anti-amoebic) drug is safe during pregnancy whereas metronidazole should be avoided.

   Chloroquine and proguanil are safe antimalarials; and piperazine and niclosamide are preferred for worm infestations.
6. ***Anti-hypertensive drugs:*** Methyldopa, hydralazine, labetalol, clonidine and prazosin are safe during pregnancy. Angiotensin converting enzyme (ACE)-inhibitors and angiotensin receptor blockers are absolutely contra-indicated during pregnancy.
7. ***Anti-diabetic drugs:*** Insulin is safe to be used during pregnancy whereas oral anti-diabetic drugs should be avoided.
8. ***Hormones:*** Inhaled and topical corticosteroids can be safely used during pregnancy. Oral steroids like prednisolone in low doses may be given. However, high-dose and prolonged use of oral corticosteroids are not indicated. Thyroxine can be used safely for the treatment of hypothyroidism and propylthiouracil is used for hyperthyroidism.
9. ***Drugs for central nervous system (CNS) disorders:*** Haloperidol (anti-psychotic drug) is safe. Fluphenazine, clozapine should be avoided during pregnancy. Lithium is contraindicated. Amitryptyline, imipramine and fluoxetine are safe anti-depressants whereas other SSRIs should be avoided.
10. ***Anti-coagulants:*** Heparin and low molecular weight heparins are considered safe during pregnancy whereas oral anti-coagulants like warfarin should be avoided.
11. ***Asthma:*** Inhaled bronchodilators like salbutamol, and ipratropium, inhaled corticosteroids like beclomethasone and mast cell stabilisers like cromoglycate are safe drugs during pregnancy. Theophylline and oral corticosteroids should be avoided.
12. ***Laxatives:*** Dietary fibre, lactulose and Ispaghula are considered safe laxatives during pregnancy.
13. ***Anti-diarrhoeals:*** Oral rehydration salts should be used to prevent and treat the dehydration. Use of loperamide and diphenoxylate are unsafe.

Breastfeeding and Drugs

Many drugs are secreted in the breast milk. However, all the drugs do not necessarily cause harm to the baby. The clinician must determine the risk-benefit ratio of the continued breast-feeding while prescribing drugs to a lactating female. It is inappropriate to discontinue breastfeeding while on drug treatment or to continue breastfeeding while taking drugs that are contraindicated.

Two factors to be considered are:

1. Are these drugs indicated by themselves in children, e.g. penicillins?
2. Is there any risk to the infant in the concentration present in the milk?

Safety Assessment of Some Frequently Used Drugs

Analgesics

Analgesics such as paracetamol, ibuprofen, naproxen and codeine are considered to be 'safe', due to low transfer into breast milk. Aspirin is best avoided due to the theoretical risk of Reye's syndrome. Sumatriptan has a short half-life of approximately 2 hours and infant exposure can be almost completely avoided by expressing and discarding breast milk for approximately 8 hours after dosing. Tramadol has a low transfer into breast milk (insufficient data) therefore is to be avoided. Morphine is usually considered 'safe' because of low transfer into milk, and high first-pass metabolism.

Anti-helminthics

There does not appear to be any data on the transfer of mebendazole or pyrantel embonate into human breast milk although these agents are generally considered to be 'safe' due to poor absorption from the gastrointestinal tract.

Antibiotics

- Antibiotics such as penicillins, cephalosporins and macrolides are considered to be compatible with breastfeeding although there are theoretical risks of alterations to infant bowel flora and allergic sensitisation.
- The safety of metronidazole is controversial.
- The transfer of tetracyclines into breast milk is low but are avoided due to the possible risks of inhibiting bone growth or causing dental staining.
- Fluoroquinolones have been reported to cause arthropathies in immature animals and hence avoided.
- Sulphonamides such as sulphamethoxazole are avoided in infants with hyperbilirubinaemia or glucose-6-phosphate dehydrogenase deficiency.

Anti-coagulants

Heparins (unfractionated and low molecular weight) are considered 'safe' since do not cross into breast milk to a significant extent. Warfarin is also considered to be compatible with breastfeeding as transfer is low, and adverse effects and changes in prothrombin time have not been detected. However, it would be prudent to monitor the infant's prothrombin time during treatment.

Anti-convulsants

Carbamazepine, phenytoin and sodium valproate are generally considered to be compatible with breastfeeding although the infant should be observed for evidence of central nervous system depression. Lamotrigine and gabapentin are best avoided during breastfeeding.

Anti-depressants

Selective serotonin reuptake inhibitors (SSRIs) transfer into breast milk to varying extents. Paroxetine is the preferred SSRI in breastfeeding women. Fluoxetine along with its active metabolite, norfluoxetine transfers to a greater extent and, has a long half-life of one to two weeks and may accumulate in a breastfed infant. Tricyclic anti-depressants are considered to be compatible with breastfeeding. Moclobemide considered compatible with breastfeeding.

Anti-histamines

Promethazine, dexchlorpheniramine and diphenhydramine are considered to be safe although it would be prudent to monitor for evidence of sedation or irritability in the infant. Loratadine and fexofenadine are likely to be safe due to low transfer into milk.

Benzodiazepines

Sporadic use of midazolam and temazepam (short half-life) are safe. Diazepam (having long half-life) may accumulate and is associated with lethargy, poor suckling and reduced weight gain.

Recreational agents

These have particular problems because the dose and pattern of usage are uncontrolled. In addition most have relatively high infant doses. Alcohol consumption should be minimised during lactation (e.g. by withholding breastfeeding for about two hours after ingestion of a standard alcoholic drink). Caffeine exposure may lead to restlessness and irritability in infants. Smoking is best avoided by breastfeeding mothers.

DRUGS IN GERIATRICS

Ageing alters pharmacokinetics and pharmacodynamics, affecting the choice, dose, and dosing frequency of many drugs. The elderly have many chronic disorders and consequently use more drugs than any other age group. Safe, effective pharmacotherapy is one of the greatest challenges in clinical geriatrics. Appropriate use of drug requires an evaluation of potential benefits and risks.

EFFECT OF AGE ON PHARMACOKINETICS OF DRUGS

Absorption and Distribution

Absorption and distribution of drug tend to be trivial and clinically inconsequential. The relative decrease in total body water leads to higher blood (and often tissue) concentrations of some water-soluble drugs.

Hepatic Metabolism

Decreased hepatic blood flow significantly affects hepatic elimination of drugs. Hepatic cytochrome p450 enzymes is reduced. In the elderly, the initial doses of, labetalol, propranolol, verapamil should be reduced. Drugs with active metabolites lihe diazepam, chlordiazepoxide, amitriptyline, imipramine, chlorpromazine, thioridazine, risperidone, and morphine, meperidine, propoxyphene, may accumulate and have increased risk of toxicity. The maintenance doses of these drugs should be reduced.

Renal Elimination

Clinical implications depend on the contribution of renal elimination to total systemic elimination and on the drug's therapeutic index. The physiologic changes decrease renal elimination of the drugs. Creatinine clearance (measured by the Cockcroft-Gault formula) is used to guide of dose excreted by the kidneys.

$$Cl_{creat}\ (mL/min) = \frac{[140 - age\ (yr)]\ [body\ wt\ (kg)]}{(72)\ [serum\ creatinine\ (mg/dL)]}$$

For women, the calculated values are multiplied by 0.85.

EFFECT OF AGE ON PHARMACODYNAMICS OF DRUGS

Increased sensitivity due to ageing must be considered with drugs like morphine, pentazocine, warfarin, ACE-inhibitors and diazepam (especially when given parenterally) and tolbutamide, glyburide and beta-blockers should be used with caution because of serious dose-related toxicity.

For effective and safe sedation, the dose of midazolam should be decreased by 30% in elderly patients because of pharmacodynamic changes associated with age.

Principles of Drug Therapy in Elderly

Efficacy and safety are important considerations when prescribing drugs in the elderly. Therefore, use drugs with documented efficacy and lowest toxicity.

Dose must often be reduced in the elderly. In general, the starting doses of drugs are about one-third to one-half the usual adult doses.

Complexity of drug regimens (e.g. multiple drugs, frequent dosing, and variable doses) increases the risk of non-compliance. If a patient has more than one disorder, e.g. hypertension and angina then treat both conditions with a single drug like a beta-blocker or calcium channel blocker. Wherever possible choose long-acting or slow-release preparations for better compliance.

Cost of drugs can impose a major financial burden, hence least expensive drug with comparable efficacy should be considered.

Drug Therapy in Children

Children are not small adults. It cannot be assumed that a child's dose is proportional to an adult's dose (i.e. a 5 kg child requires 1/10 the dose of a 50 kg adult).

Pharmacodynamic Considerations

Children have increased risk with certain drugs because of differences in pharmacokinetics or because of drug effects on growth and development. Although the adverse effects are similar to those seen in adults, but children are at high-risk of accidental poisoning. Infants are at risk of toxicity from drugs used by adults.

Common drugs with unique or higher risk of adverse effects in children are presented in **Table 1**.

Drug dosing

In children, less than 12 years is always a function of age, body weight, or both. This approach is practical but not ideal; even within a population of similar age and weight, drug requirements may differ because of maturational differences in absorption, metabolism, and elimination. Thus, dose adjustments should be based on plasma drug concentration, wherever possible.

Table 1: Drugs Manifesting Unusual Toxicity in Children

Drug	Adverse effect
Local anaesthetics (e.g. benzocaine, mixture of lidocaine and prilocaine)	Cyanosis due to conversion of haemoglobin to methemoglobin
Sulphonamides	Kernicterus in neonates
Diphenoxylate	Respiratory depression and death as an overdose syndrome, usually in children < 2 years
Fluoroquinolones	Cartilage toxicity suspected based on animal studies, but adverse effects in humans are not proved
Chloramphenicol	Grey Baby syndrome in neonates
Prochlorperazine	Extrapyramidal effects, opisthotonus and bulging fontanelles. Febrile and dehydrated infants especially at risk
SSRIs	Increased incidence of suicidal ideation in children and adolescents
Tetracycline	Discolouration and pitting of tooth enamel. This adverse effect is restricted to children < 8 years

DRUGS AND LIVER DISEASE

Pharmacotherapy in liver disease can be discussed under two broad headings:

1. Drugs causing hepatotoxicity.
2. Hepatic disease affecting the drug pharmacokinetics and dynamics.

Drug-Induced Hepatotoxicity

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Major mechanisms of drug-induced hepatotoxicity include:

1. Interference with bilirubin transport and conjugation occurs, e.g. rifampicin.
2. Use of paracetamol and isoniazid cause cytotoxic damage.
3. Cholestasis occurs with orally active anabolic and androgenic agents and oral contraceptives, phenothiazines like chlorpromazine, trifluoperazine, promazine, pecazine, etc.
4. Mixed cytotoxic/cholestatic injury occurs with chlorpromazine. However, p-aminosalicylic acid may cause mixed hepatocellular liver injury.
5. Fatty liver (steatosis) occurs with the use of tetracycline.
6. Chronic active hepatitis, cirrhosis and subacute necrosis is seen with alpha-methyldopa, nitrofurantoin and isoniazid. Long-term administration of the antituberculosis drug (isoniazid) may lead to hepatic dysfunction.
7. *Liver tumours:* Anabolic steroids have been implicated as responsible for primary hepatocellular carcinomas and adenomas.
8. *Non-specific changes:* Certain hypotensives, vasodilators, anti-inflammatory agents and oral contraceptives cause a transient increase in transaminase levels.

List of Hepatotoxic Drugs

1. *Analgesics:* NSAIDs, acetaminophen.
2. *Anti-diabetic agents:* Acarbose, pioglitazone, sulphonylureas (e.g. Glyburide).
3. *Lipid-lowering medications:* HMG-CoA reductase inhibitors (statins) and nicotinic acid (niacin).
4. *Anti-hypertensives:* Labetalol, hydralazine, antiarrhythmics, amiodarone, procainamide.
5. *Antibiotics:* Erythromycin, estolate, isoniazid, nitrofurantoin, sulphonamides, tetracycline.
6. *Anti-fungal medications:* Fluconazole, itraconazole, ketoconazole.
7. *Anti-convulsant medications:* Valproic acid, carbamazepine.
8. *Psychotropic medications:* Bupropion.
9. *Tricyclic anti-depressants:* Chlorpromazine.
10. *Hormonal medications:* Tamoxifen, testosterone.
11. *Miscellaneous medications:* Halothane, methotrexate etretinate, protease inhibitors.

Hepatic Disease Affecting the Drug Pharmacokinetics and Dynamics

Liver is a metabolic factory of the body which controls and regulates the body physiology. A large proportion of drugs are metabolised and their pharmacological properties are regulated by the liver. In disease states of the liver, the metabolism of these drugs may significantly change and therefore these drugs may have enhanced action even bordering toxicity. Therefore, use of these drugs should either be reduced or stopped totally. Drugs excreted through the bile namely azithromycin, tetracycline, rifampicin and fusidic acid have a reduced excretion in cases of intrahepatic and extrahepatic obstruction.

Hypoalbuminaemia associated with marked liver dysfunction is associated with impaired metabolism of drugs which bind to albumin in the body. One of the examples is Phenytoin and the toxicity of such drugs is increased manifold. The effect of drugs like alcohol, opioids, sedatives or hypnotics may be prolonged and enhanced significantly in liver disorders.

Similarly, action of anti-coagulants may enhance mainfold in patients of advanced liver disease. The risk of bleeding also increases in patients with liver disease especially on NSAIDS and the bleeding may occur in areas like brain, kidney and subcutaneous tissue.

In liver disease, there are no clear cut guidelines available like that in CKD about the change in dosage schedule in cases of liver dysfunction. Therefore, the drugs may have to be reduced or stopped altogether.

DRUGS AND RENAL DISEASE

Pharmacotherapy in renal disease can be discussed under two broad headings:

1. Drugs causing nephrotoxicity.
2. Renal disease affecting the drug pharmacokinetics and dynamics.

Drugs Causing Nephrotoxicity

Many drugs can cause renal dysfunction.

Drugs causing prerenal damage

Nonsteroidal anti-inflammatory drugs (NSAIDs), even in short course, can cause acute renal failure; ACE-inhibitors can also cause a deterioration in renal function. Care should be taken when an ACE-inhibitor and NSAIDs are prescribed together as this combination may precipitate an acute deterioration in renal function.

Drugs causing intrarenal damage

Drugs that cause glomerulonephritis include penicillamine, gold, captopril, phenytoin penicillins, sulphonamides and rifampicin.

Drugs that may cause interstitial nephritis include penicillins, cephalosporins, sulphonamides, thiazide diuretics, frusemide, NSAIDs and rifampicin.

Aminoglycosides, amphotericin and cyclosporine can cause acute tubular necrosis.

Drugs causing postrenal damage (urinary tract obstruction)

High-dose sulphonamides, acetazolamide or methotrexate may cause crystalluria and could therefore cause obstruction. Tricyclic antidepressants, and alcohol may cause urinary tract obstruction due to retention of urine in the bladder.

Other nephrotoxic drugs

Cephalosporins: Cephaloridine, one of the first cephalosporins has been associated with direct renal toxicity but third generation cephalosporins, e.g. cefixime, have very rarely been reported to cause nephrotoxicity.

Analgesics: NSAIDs may cause acute renal failure. Analgesic nephropathy has been most commonly seen with combination analgesic that contain aspirin and/or paracetamol. Analgesic nephropathy is one of the few preventable causes of chronic renal failure. Discontinuation of the abused drugs often results in stabilisation or even improvement in renal function Lithium levels consistently above the therapeutic range have been associated with development of a nephrogenic diabetes insipidus.

Renal Disease Affecting Drug Pharmacokinetics and Dynamics

An accurate estimation of renal function, or glomerular filtration rate, requires sophisticated techniques. In practise, the serum creatinine concentration is used for day-to-day assessment of renal function. Creatinine clearance can be calculated using Cockcroft-Gault formula.

Dose Alteration in Renal Impairment

Generally dose adjustment is needed when the creatinine clearance is below 60 mL/min. Adjustments can be achieved by a reduction in dose, or an extension of the dosing interval, or both. List of some commonly prescribed drugs that require dose alteration in renal impairment are given in **Table 2**.

CONCLUSION

The dosage of drugs is based on the half life of the drug, age and weight of the individual. This dosage may need to be adjusted in special situations like, liver disease, kidney disease, pregnancy. This is important so that the function of that organ is not compromised further and due to poor excretion. The toxicity of drugs may ensure at therapeutic dosages due to retention in the body. In pregnancy the issue of medicine producing teratogenic effects and crossing the placental barrier may induce damage to the foetus.

Therefore this chapter has discussed some of important issues in drug usage in such situations. Adjustment of drug dosages has been highlighted. It is important for a clinician to know the pharmacology and metabolism of the drug along with the integrity of functional capacity of various organs where drug is metabolised or excreted and defects of various enzyme systems.

Table 2: Commonly Prescribed Drugs that Require Dose Adjustment in Renal Impairment

Class	Examples
Antibiotics/anti-fungals	Aminoglycosides (e.g. gentamicin), vancomycin, ceftazidime, cefepime, cephazolin, ciprofloxacin, fluconazole, piperacillin, carbapenems (e.g. meropenem), sulphamethoxazole
Anti-virals	Famciclovir, acyclovir, valacyclovir, valgancyclovir, gancyclovir
Anti-coagulants	Low molecular weight heparins (e.g. enoxaparin)
Cardiac drugs	Digoxin, sotalol, atenolol
Diuretics	If creatinine clearance is less than 30 mL/min: avoid potassium-sparing diuretics due to risk of hyperkalaemia-thiazide diuretics have limited efficacy
Opioids	Morphine, codeine, pethidine (due to risk of accumulation of active or toxic metabolites)
Psychotropics/anti-convulsants	Amisulpride, gabapentin, lithium, levetiracetam, topiramate, vigabatrin
Hypoglycaemic drugs	Metformin, glibenclamide, glimepiride, insulin
Drugs for gout	Allopurinol, colchicine
Others	Lamivudine, methotrexate, penicillamine

4.5 New Drug Development

Sadhna Joglekar

INTRODUCTION

Pharmaceutical medicine is a relatively new discipline, but is growing very rapidly. It deals with the discovery, development, evaluation and monitoring of drugs and devices, as well as with medical aspects of their commercial promotion.

THE PROCESS OF DRUG RESEARCH AND DEVELOPMENT

The research and development (R and D) process for a new drug can be subdivided into the following phases: discovery (basic chemical or structural research); preclinical R and D; clinical development and regulatory development.

In addition, two other processes contribute to the life-cycle of a drug, once it is marketed. These are pharmacovigilance and life-cycle management (which includes development of new or improved uses of the drug or new delivery systems).

DISCOVERY

In the early 50s and 60s, new drugs were discovered primarily through random screening and serendipity played a very crucial role. Structure-activity relationship (SAR) was a rudimentary science then. The 70s and 80s saw the process of pharmaceutical discovery evolve into a fine science of protein chemistry and enzyme elucidation. Combinatorial chemistry, genomics and high-throughput screening have characterised the 90s with a resultant drug discovery targeted at molecular and disease mechanism level.

Today, the starting point for the R and D activity is the identification of an unmet medical need. This is followed by the identification of specific molecular targets (e.g. cellular enzymes or receptors) with the help of protein biochemistry, immunology (antibody targeting), pharmacology and molecular biology. One of the latest entrants on the scene of target identification is the use of genomics and linkage analysis. A classic example of the success of this technique is the identification of apolipoprotein E (ApoE) as an important causative factor in Alzheimer's disease. Once a molecular target is identified, it is validated. If results of validation experiments appear promising, drug screens or assays are established to identify new chemical entities. An assay essentially integrates a biological system with chemical compounds that may become tomorrow's drugs. The sources of starting material for drug screens are chemical libraries, natural products, computationally designed drugs and drugs derived from medicinal chemistry which are modified using combinatorial chemistry.

Besides evaluation and validation of a new chemical entity, the drug discovery programme also includes cytotoxicity evaluation. Only compounds with good activity in '*in vitro*' assays with no cytotoxicity progress to animal testing.

PRE-CLINICAL/NON-CLINICAL TOXICOLOGY AND PHARMACOLOGY

Initiation of non-clinical toxicology studies marks the end of the discovery or research phase and the beginning of the development phase. Animal toxicology studies can be categorised into the following:

1. Acute toxicity: single dose and repeat dose
2. Subacute toxicity
3. Chronic toxicity
4. Special toxicological studies

Single dose studies are an important first step in establishing the safety profile of a new chemical entity, the aim being to test a range of doses, from those that produce no effect to those that produce some level of exaggerated effect. The results of these studies guide dose selection for the repeat dose studies, in which animals are provided continuous exposure to test drug to identify safe levels of the drug. Generally, animals are exposed to higher doses of the drug for longer duration than that planned in clinical studies. An important aspect of these studies is pharmacokinetic correlation called 'toxicokinetics'.

The duration of chronic studies depends to a large extent on the intended duration of therapy in clinical usage. It varies from 6 months to 9-12 months in rodent and non-rodent species.

Special studies include reproduction and teratogenicity studies, carcinogenicity studies and mutagenicity studies. It was the thalidomide disaster which highlighted the need to evaluate new drugs in reproductive toxicology studies. Carcinogenicity studies involve exposure of rodents to the new chemical entity for 18-24 months and are usually required for drugs intended to be used clinically for 6 months or more. Apart from these, special studies could also include neurotoxicity studies, metabolic studies, etc.

All preclinical studies intended to support further clinical work or marketing applications need to be conducted in compliance with good laboratory practices (GLP) and ICH (International Conference on Harmonisation) guidelines, wherever applicable. In addition, local national regulations stipulate different types of studies.

CLINICAL DEVELOPMENT

The successful culmination of *in vivo* animal data, receptor binding studies and *in vitro* functional assays, is a progression of the new chemical entity to clinical testing. The clinical development programme is divided into four phases. Although in earlier times, the testing of a drug used to progress from one phase to the next one in a step-wise manner, the temporal distinction between these phases has significantly blurred in recent times, due to evolving regulatory

environment, financial considerations and a need to expedite drug development. Definitions of phases of clinical trials are therefore purely functional and an investigational medicine is often evaluated in two or more phases simultaneously. It must be highlighted here that all clinical trials with drugs are regulated in India by the Schedule Y of the Drugs and Cosmetics Act, 1945 (http://cdsco.nic.in). Further, the Indian Council of Medical Research (ICMR) has issued guidelines for ethical conduct of biomedical research *(http://www.icmr.nic.in/human_ethics.htm)* and it is expected that all individuals conducting clinical research would follow these guidelines.

Phase I (First in Human) Studies

Phase I studies are the first opportunity for extrapolation from animal data to human exposure. These are initial safety studies, usually conducted in normal volunteers, the notable exception being oncology drugs which are evaluated in cancer patients even at Phase I level. The aim of these studies is to establish a dose range tolerated by volunteers for single and multiple doses. Additionally, pharmacokinetic studies are usually considered as Phase I studies, regardless of when these are conducted during a medicine's development.

Phase II (First in Patients) Studies

These are studies in a selected group of patients, with an aim to assess safety and identify the tolerable effective dose of the new drug. Phase IIa generally refers to pilot studies which may assess dose response, frequency of dosing, type of patient, etc. Phase IIb, also termed as 'pivotal studies', are well-controlled trials, usually representing the most rigorous demonstration of a drug's efficacy. Studies in this phase are usually exploratory in nature.

Phase III Studies

These are aimed at generating additional efficacy and safety data in relatively large number of patients in both controlled and uncontrolled trials. Special population groups such as the elderly or those with renal failure are also studied during this phase.

Phase III trials are often subdivided into IIIa (prior to regulatory submission of New Drug Application) and IIIb studies (after regulatory submission of New Drug Application but before its approval). Phase III studies are generally aimed at being confirmatory studies.

Phase IV Studies

New drug development does not stop when regulatory approval comes in. As a matter of fact, the true test of a new drug begins once it is available in the market and millions of patients are prescribed this drug in a real-world, uncontrolled environment. Specific studies are conducted after a medicine is marketed in order to provide additional information on efficacy or safety, or drug interactions or comparisons with other marketed drugs. Phase IV studies are distinct from post-marketing surveillance, which are observational or non-experimental in nature.

CLINICAL STUDY DESIGNS

While designing clinical studies, different methods are used to enhance the accuracy of the data and to reduce bias and effect of nondrug factors. Some of these techniques are given below.

Blinding

This technique is employed to reduce observer bias and patient bias by concealing the identity of the treatment being administered. If either the investigator or the patient is unaware of the treatment, the study is termed as 'single-blind' study. If both these parties are unaware, the study is termed as 'double-blind'.

Placebo-Controlled Study

In addition to the specific effects of the drug, the final patient response is often affected by non-specific factors such as patient's personality, attitude of the medical staff, appearance of the drug and the feeling of being looked after. To distinguish the pharmacological effect from non-specific effects, a pseudo drug, identical in appearance but pharmacologically inert (placebo), is administered.

Randomisation

In a comparative study, allocation of patients to different groups must be done by random assignment. Randomisation ensures random distribution of uncontrolled variability factors and ensures that patient assignment to treatment groups cannot be predicted.

Finally, one must be cognizant of the fact that the R and D process is fraught with inherent risks and is an expensive and time-consuming process. It is estimated that the end-to-end process can take upwards of 10 years and cost on an average in excess of US $800 million in the US before a chemical is marketed as a 'medicine'.

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4.6 Pharmacoeconomics

Gurudas Khilnani

INTRODUCTION

The health expenditure is increasing day-by-day due to increasing cost of medicines and other health services. The expenditure is further escalated by increased life-expectancy, technological upgradation and increased demand due to increased awareness. Therefore, there is a need for optimal allocation of limited resources. Pharmacoeconomics is a subset of health economics that identifies, measures and compares the costs of medicines/treatments with outcomes. It helps us to make therapeutic choices among the alternatives. It should not be viewed merely as cost cutting academic exercise because it is an important aspect of rational therapeutics and enhancing patient care. Pharmacoeconomic analysis is also increasingly incorporated in clinical protocols for the evaluation of new drugs.

COMMON TERMS USED IN PHARMACOECONOMIC ANALYSIS

Efficacy

It is the utility of treatment in ideal (trial conditions) settings. Clinical effectiveness is the effect of treatment in clinical settings than in ideal settings.

Incremental Analysis

It finds out the superiority and benefit of new treatment over and above existing one. This is done by calculating additional cost of new treatment for treating one extra patient or how much extra cost is needed to discharge a patient one day earlier to the existing treatment. This is called as incremental or marginal cost, which is how much cost is changed with a small change in outcome. Incremental analysis is usually done for cost-effective analysis.

Cost Effectiveness

It compares natural units of beneficial outcome (e.g. reduction in HbA1c, life years gained, etc.) with the cost of treatment. Cost of a drug may be lower than the alternative available and therefore, total cost of treatment is considered. An example is use of low molecular weight heparin (LMWH) *versus* conventional heparin (CH). The cost price of CH is less than that of LMWH, but CH use requires frequent injections (nursing charges included) and monitoring by activated partial thromboplastin time (aPTT) test, which also has some cost. Thus, LMWH may become more cost-effective in certain situations. **Figure 1** gives four possible outcomes found in such a analysis.

It is obvious that a therapy, which is less costly and more effective, should be preferred. If a newer medicine or treatment is more costly but less effective, it should be discarded. When new treatment is more effective but more costly then cost-effectiveness analysis may provide quantitative data (how many life years are gained and is it worth to spend more?) for rational selection of new therapy. If new medicine/treatment is less effective and less costly, it is to be ascertained by cost-effectiveness analysis that existing medicine/therapy be retained or not.

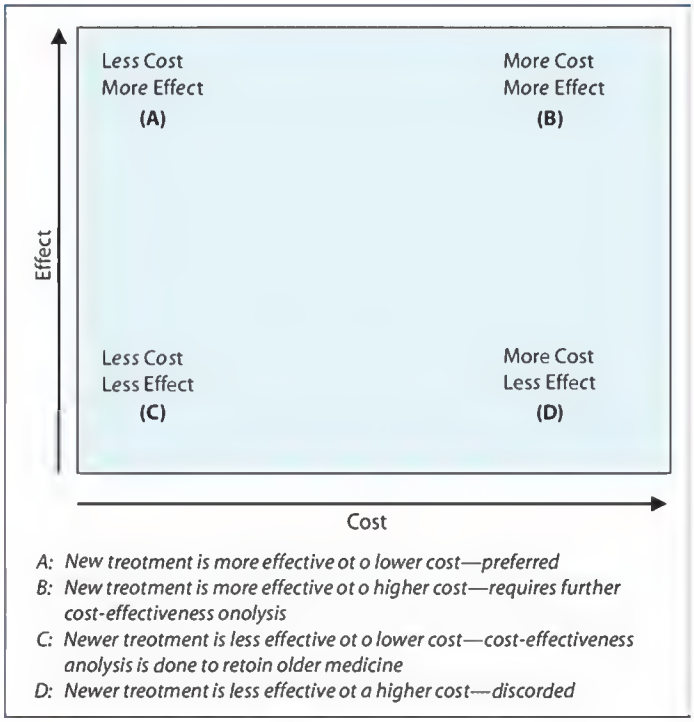


Figure 1: Cost-effectiveness analysis.

Perspective

Since overall cost reduction affects society at large, therefore societal perspective is considered in most of the pharmacoeconomic analyses.

METHODS OF PHARMACOECONOMIC EVALUATION

Utilising the basic fundamentals of economics, the cost is considered as one factor and is compared with benefit accrued from the use of medicine or treatment as another variable. Therefore, cost outcome analysis is an integral part of pharmacoeconomics. The data for analysis can be collected by prospective or retrospective studies. Another method is the use of 'modelling' such as decision analysis tree to make value based decisions.

Cost

This includes direct, indirect and intangible costs.

Direct cost

It is the cost of procurement of medicines and treatment. It includes price of medicines, nursing, hospitalisation, transportation and drug administration. These are measured easily.

Table 1: Types of Pharmacoeconomic Analysis

Type of analysis	Measurement	Example	Advantages	Disadvantages
Cost minimisation	Differences in costs with equal benefits Excess cost of branded drug	Generic versus branded drug use: Use of medicine by two different routes of administration	Simple, useful when outcomes are similar	Cannot be used when outcomes are different
Cost effectiveness	Health benefits in natural units (life years saved, heart attacks prevented, strokes prevented and costs in monetary units (rupees) Cost per (unit) patient saved	Use of heparin versus low molar heparin in acute myocardial infarction: effect on mortality	Magnitude of benefit of two treatments (defined outcome) is measured with monetary units	Cannot be used for direct comparisons of outcomes between the treatments of different conditions
Cost utility	Measures utility units, degree of well-being achieved. Measures qualitative and quantitative change Cost per QALY gained	Reduction in mortality and morbidity. Quality adjusted life years (QALYs)*	Can compare two treatments for different conditions	Utility units are not easily defined and fixed.Measured values vary with time and disease perspective
Cost benefit	Costs and benefits are measured in monetary terms (Rupees) Benefit: Cost ratio	Comparison of surgical treatment with drug treatment of chronic simple glaucoma	Dissimilar treatments (outcomes) can be compared	Difficulty in quantifying health benefit in monetary terms (Rupee value) Intangible benefits are usually ignored

** One QALY is living for one year in perfect health or living in half perfect health for two years and so on.*

Indirect cost

It is the cost of loss of work output and earnings due to patient's illness and family members' attendance during illness. These are difficult to measure.

Intangible cost

It is a cost due to pain, distress and suffering affecting quality of life. It is measured for cost-utility analysis. In addition, there is an opportunity cost which is the benefit foregone in opting for an alternative therapy or drug. For example, diversion of some of limited funds for procurement of a new anti-platelet drug may put constraint on the treatment of outdoor patients on antibiotics.

Benefit

It is the outcome which is measured in physical (natural) units such as number of strokes prevented, life years gained or it can be in utility units such as quality adjusted life years gained (QALYs) which involves quality and quantity both. The benefit may also be measured in monetary units as in cost-benefit analysis. In ascertaining benefit or outcome, one has to make assumptions and these assumptions may be varied in sensitivity analysis. There are four major types of PE analyses which are used in making decisions. **Table 1** shows the advantages and disadvantages of these types.

TYPES OF PHARMACOECONOMIC ANALYSES

The four common types of pharmacoeconomic analyses, their advantages and disadvantages are given in **Table 1**. Cost-minimisation and cost-effectiveness analyses are commonly used for evaluation of newer medicines and therapies. Cost-utility analysis requires a comprehensive analysis. Cost-benefit analysis is useful to compare the cost of different therapies in dissimilar disorders.

USES OF PHARMACOECONOMIC ANALYSIS

Pharmacoeconomic studies increase cost consciousness among the medical fraternity and health administrators. Pharmacoeconomic methods are utilised to assist hospitals, insurers, and health care professionals in making important decisions such as selecting medicines for hospital formularies, settling insurance claims of treatments from different hospitals, and formulating and implementing preventive health policy respectively. It assists clinicians to prepare standard treatment guidelines and to prescribe cost-effective medicines and therapies.

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Section 5

Immunology

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5.1 An Overview of the Immune System

Sita Naik

The immune system deals with a wide variety of organisms that are encountered in the environment, by preventing the establishment of infection and eliminating infections that gets established. The immune system has evolved to selectively destroy only foreign molecules and cells with little collateral damage to the host's own normal cells. The system is unique in its ability to retain a memory of each attack, allowing it to respond more efficiently to subsequent attacks by the same invader. Hence, individuals rarely suffer more than once from the same infectious disease such as chicken pox, mumps, or whooping cough.

The immune response consists of two broad overlapping sets of events, the early or first-line of defence that occurs within minutes to hours of encounter with foreign antigen, the innate or non-specific immunity and a delayed response, which occurs within days, called adaptive or specific immunity. The recognition of events constitute the afferent arm and the effector arm functions either through cells (cell-mediated immunity) or antibodies (humoral immunity).

CELLS AND ORGANS OF THE IMMUNE SYSTEM

Granulocytic Cells

The granulocytic cells are neutrophils, eosinophils and basophils. Neutrophils are the first cells to reach the site of infection. They engulf foreign particles in a membrane bound vacuole, the phagosome which fuses with neutrophil granules to form phagolysosomes. The enzymes within these granules digest the contents of the vacuole either by oxygen-dependent mechanism (respiratory burst) or oxygen independent mechanism. Eosinophils are phagocytic cells that participate in allergic responses. Allergens and parasites stimulate an immunoglobulin (IgE) antibody response and IgE coated antigen is recognised by the receptor for Fc portion of IgE on eosinophils. This results in release of its enzymatic contents which can destroy many parasites. Basophils are non-phagocytic cells which mediate immediate hypersensitivity responses. Mast cells are analogous to the circulating basophils and reside at various tissue sites. These cells are rich in granules containing histamine and other mediators of immediate hypersensitivity.

Mononuclear Phagocytes

These cells have a common lineage from haematopoietic precursors in bone marrow and enter the circulation as incompletely differentiated monocytes. They migrate into tissues to become mature macrophages such as microglial cells of central nervous system, Kupffer cells lining the vascular sinusoids in liver, alveolar macrophages in lung, etc. They ingest antibody coated antigens very efficiently through the large number of specialised Fc receptors they bear (**Figure 1**), a mechanism termed opsonisation. Neutrophils and other cells produce cytokines, which are low molecular weight proteins that regulate the intensity and duration of the immune response by acting on other cells and tissues. Macrophages are activated by locally produced cytokines and in turn secrete a variety of cytokines which are important for activation of the adaptive immunity. The ingested pathogen is broken down in phagolysosomes and antigenic fragments are transported to the cell surface in a form that can be recognised by antigen-specific T lymphocytes, and hence, the name 'antigen-presenting cell' (APC). These macrophages carry specialised plasma membrane glycoproteins called major histocompatibility complex (MHC) class II molecules. The density of MHC antigens on the cell surface is increased following activation, thus increasing their antigen presenting capability.

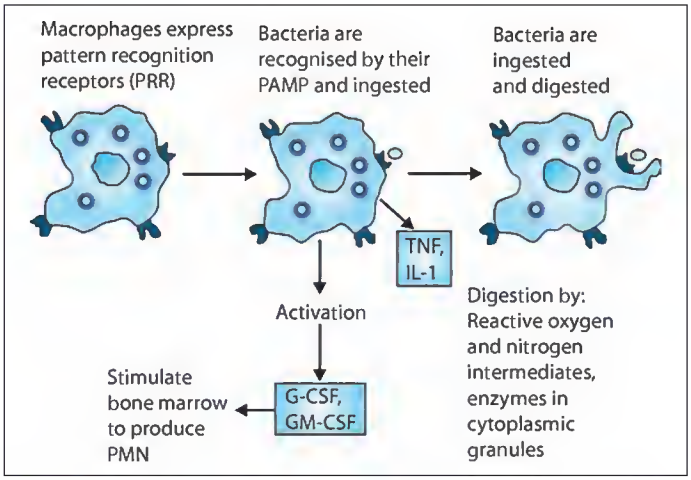


Figure 1: Macrophages bear several receptors (pattern recognition receptors or PRR) that recognise the PAMP on microbes and ingest them.

Dendritic Cells (DCs)

These are morphologically distinct cells with membranous or spine-like projections, which are located in the interstitium of most organs, except the brain, and are abundant in the T-cell-rich areas of lymph nodes and spleen. Immature DCs are efficient phagocytes and are abundant at locations where external antigens enter the body, namely skin, alveoli, gut mucosa, etc. They ingest newly entering antigens, undergo maturation, lose their phagocytic capability and become efficient APCs. Follicular dendritic cells (FDC) are located in the germinal centres of lymph nodes, spleen and mucosa-associated lymphoid tissues. These are not of bone marrow origin, are unrelated to the interdigitating DCs, do not bear cell surface MHC molecules and cannot act as APCs. They display 'trapped' antigens on their cell surface for recognition by B lymphocytes.

Lymphocytes

Lymphocytes mediate the adaptive immune responses and are of three types, T cells, B cells, and natural killer (NK) cells.

B lymphocytes (B cells)

B cells develop in the bone marrow and are characterised by the presence of membrane-bound immunoglobulin (Ig) molecules which are the receptors for antigens. Following

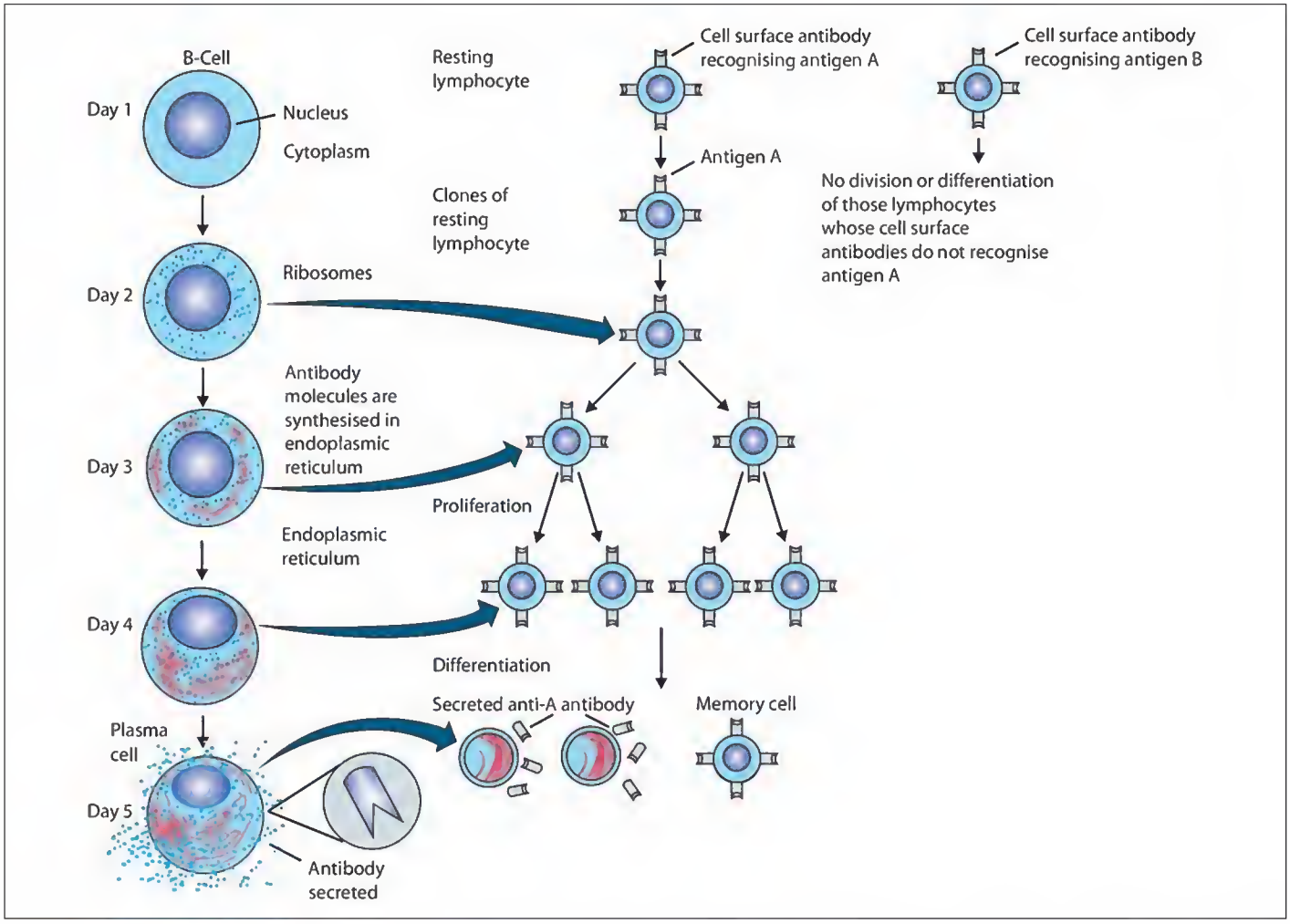


Figure 2: Maturation of B cells into plasma cell. Each B cells bears a unique surface immunoglobulin molecule, which is termed 'B cell receptor' (BCR). It arises from a population of undifferentiated stem cells and becomes committed to producing only one species of antibody molecule.

receptor binding to specific antigen, the cell divides and progeny differentiate into terminally differentiated, antibody producing plasma cells that cannot divide (**Figure 2**).

T lymphocytes (T cells)

T cells develop and mature in the thymus and acquire their specific cell surface receptor for antigen recognition, the T cell receptor (TCR). TCR recognises the modified antigenic fragments or peptides presented by the MHC antigens on APCs. MHC molecules are genetically diverse glycoproteins that are of two types, class I molecules expressed on almost all nucleated cells and class II molecules expressed on APCs. TCR engagement with MHC-peptide is followed by cell division and generation of effector T cells. These are of two types, CD4 expressing T helper cells (T_H cells) and CD8 expressing cytotoxic T lymphocytes (CTLs of T_C cells). T_H cells are activated by MHC class II bearing professional APCs leading to activation of other lymphocytes that are specific for the same antigen. CTLs recognise antigenic fragments along with class I MHC on cells infected with viruses, bacteria, yeast, protozoa, and parasites and kill them. They also are the principle mode of elimination of tumour cells. Cells are recognised by the CD nomenclature which refers to the monoclonal antibodies that react with a particular membrane molecule that are grouped together as a cluster of differentiation or CD.

Natural killer cells

These large granular lymphocytes are part of the innate immune response and do not have membrane markers of T cells (CD4 or CD8) or B cells (sIg) but bear CD16 and CD56. They can kill a wide range of tumour cells and some virus and lyse them; this is termed antibody dependent cellular cytotoxicity (ADCC). Hence, ADCC can occur only after the innate immunity is activated and antibodies are produced. NK cells have surface receptors with stimulatory and inhibitory functions (**Figure 3**). However, body's own cells are protected from NK-mediated killing because the ligands for the inhibitory receptors (killer Ig like receptor or KIRs) are MHC class I molecules which are present on all nucleated cells. Down regulation of MHC expression due to virus infections or malignant transformation makes these cells susceptible to NK cell-mediated killing through the stimulatory receptors. NK cells mediate cytotoxicity through enzymes present in their granules namely perforins that assemble within the membrane of the target cell to form transmembrane channels and granzymes that enter the perforin channels and activate caspases. Caspases are proteolytic enzymes that initiate the programmed death pathway.

The bone marrow, thymus, lymph nodes, spleen and various mucosa-associated lymphoid tissues are involved in the development of an immune response. Cells move freely

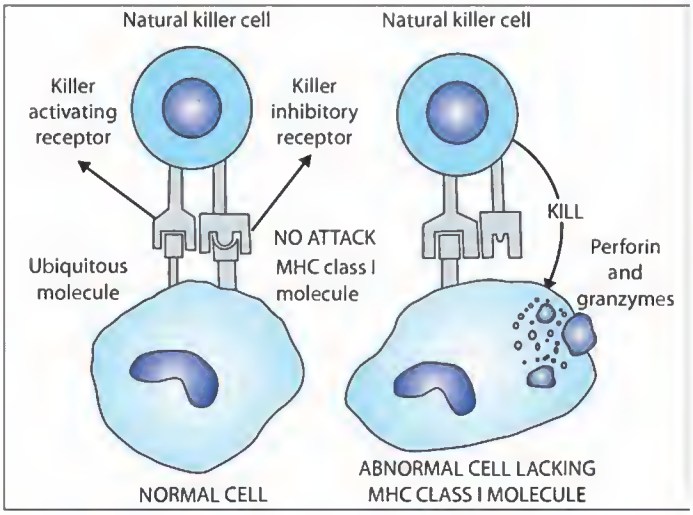


Figure 3: NK cells bearing activating and inhibitory receptors.

between organs and this permits immediate activation of the immune response at any site of entry of a foreign agent. All the cells originate in the bone marrow, except follicular dendritic cells. 'Clonal selection' of T lymphocytes, takes place in thymus resulting in the generation of mature T lymphocytes that recognise only non-self antigen.

INNATE IMMUNE RESPONSES

Unlike the adaptive immunity, innate responses lack antigen specificity and the same set of defence mechanisms acts against all pathogens. The earliest barriers to pathogen entry are physical and chemical ones such as ciliary action of bronchial mucosa, enzymes in saliva and sweat, acidity of the stomach, etc. Pathogens that breach these barriers are recognised by the innate immune system by specialised receptors that help to discriminate the invading organism as non-self. These molecular sensors that recognise broad structural, highly conserved motifs within microbial species that are not present in the host and are termed pathogen associated molecular patterns (PAMPs). These are various combinations of sugars, some proteins, particular lipid-bearing molecules and some nucleic acids, which are part of invading bacteria or viruses. The cellular receptors for PAMPs are the soluble and cell-bound pattern recognition receptors (PRRs). Soluble PRRs bind to and promote phagocytosis and complement-mediated lysis (**Table 1**).

The most important cellular PRR is the toll-like receptor (TLR) present predominantly on immature DCs and macrophages (**Table 2**). The members of this family are type 1 membrane proteins that bear a common structural element. In the extracellular domain consisting of repeating segments of 24 to 29 amino acids called leucine-rich repeats (LRR). A subset of the LRRs recognise the ligand and the cytoplasmic Toll/IL-1 (TIR) domain binds to adaptor proteins and activates signalling pathways. Each TLR detect a repertoire of conserved pathogen molecules and the complete set of TLRs can detect a wide variety of viruses, bacteria, fungi and some protozoa. Interestingly, TLRs that recognise extracellular ligands are present on the cell surface (TLR 1, TLR2, TLR4, TLR5, TLR6) while those that recognise intra-cellular ligands (TLR 3, TLR 7, TLR 8, TLR 9) are found within the cell.

Table 1: Pattern Recognition Receptors of the Innate Immune System

Receptor (location)	Target (source)	Effect
Complement (blood-stream,tissue fluids)	Microbial cell wall components	Complement activation, opsonisation, lysis
Mannose-binding lectin (blood-stream, tissue fluids)	Mannose containing microbial carbohydrates (cell wall)	Complement activation, opsonisation
C reactive protein (CRP) (blood-stream, tissue fluids)	Phosphatidylcholine, pneumococcal polysaccharide (microbial membranes)	Complement activation, opsonisation
Lipopolysaccharide (LPS) receptor, LPS-binding protein (LBP) (blood-stream, tissue fluids)	Bacterial lipopolysaccharide (Gram-negative bacterial cell walls)	Delivery to cell membranes
Toll like receptors (cell surface or internal components)	Microbial components not found in host	Induces innate responses
NOD family receptors* (intracellular)	Bacterial cell wall components	Induces innate responses
Scavenger receptors (SR) (cell membrane)	Many targets; Gram-positive and Gram-negative bacteria, apoptotic host cells	Induces phagocytosis or endocytosis

**Nucleotide-binding oligomerisation domain*

Table 2: Toll-like Receptors and their Ligands

TLRs	Ligands	Target microbes
TLR 1	Triacyl lipopeptides	Mycobacteria
TLR 2	Peptidoglycans GPI-linked proteins Lipoproteins Zymosan	Gram-positive bacteria Trypanosomes Mycobacteria Yeast and other fungi
TLR 3	Double-stranded RNA (dsRNA)	Viruses
TLR 4	LPS F-protein	Gram-negative bacteria Respiratory syncitial virus
TLR 5	Flagellin	Bacteria
TLR 6	Diacetyl lipopeptide Zymosan	Mycobacteria Yeast and fungi
TLR 7	Single-stranded RNA (ssRNA)	Viruses
TLR 8	Single-stranded RNA (ssRNA)	Viruses
TLR 9	CpG unmethylated dinucleotides Dinucleotides Herpes virus infection	Bacterial DNA Some herpes viruses
TLR 10, 11	Unknown	Unknown

Another cellular PRR, NOD (nucleotide-binding oligomerisation domain) 1 and NOD2 are present in the cytoplasm and recognises products of peptidoglycans of Gram-positive bacteria. The cell surface scavenger receptors (SR) internalise Gram-positive and Gram-negative bacteria and apoptotic cells.

TLRs are widely expressed on DCs, macrophages, neutrophils but not NK cells and are activated through a common pathway. This culminates in the production of a number of important pro-inflammatory cytokines and the important anti-viral cytokine, interferon-α. DCs are predominantly involved in acting as a link between adaptive and innate immunity while neutrophils and macrophages ingest the invading organism and destroy them.

COMPLEMENT SYSTEM

The complement system consists of about 20 serum proteins and is an important constituent of innate immunity. It is activated sequentially with amplification stages to ensure that single molecule can trigger generation of thousands of terminal effector molecules. The three pathways of complement activation are the classical pathway activated by antigen-antibody complexes, the alternate pathway activated by polysaccharides from yeasts and Gram-negative bacteria and the mannan-binding lectin pathway activated by the mannose containing proteins and carbohydrates on microbes (**Figure 4**). Activation of any of these pathways culminates in activation of C3 and generation of C3 convertase. This enzyme, via a final common pathway leads to assembly of C5-C9 complexes (membrane attack complex or MAC). The MAC forms transmembrane pore on the cell surface and death by osmotic lysis. MAC has a similar structure as perforin which is released by NK cells to mediate killing. Normal host cells also bear a number of complement regulatory proteins on their surface [complement receptor (CR) and decay accelerating factor (DAF)] which inhibit C3 convertase generation and prevent progression of complement activation. These molecules protect self cells from complement lysis while at the same time causing lysis of microbes which lack these molecules. Complement activation also leads to generation of C3a which acts as an opsonin and C5a which is an anaphylatoxin and vasodilator.

The functions of the complement system include: (i) lysis of invading bacteria, viruses and cells, (ii) opsonisation of organisms and promotion of their ingestion, (iii) clearance of immune complexes, and (iv) binding to specific complement receptors on immune cells and triggering their specific cell functions including the secretion of immunoregulatory molecules. Persons with absence of one of the alternative pathway proteins, late components (C3-C9) or one of the control proteins (H or I) are susceptible to severe infections with pyogenic organisms, particularly Gram-negative bacteria, particularly *N. meningitides*. Classical pathway deficiencies (C1, C4, and C2) are associated with increased risk of infection, though not as frequently as with the alternative pathway or late component deficiencies. Bacteria that cause recurrent infections in these patients include, but are not limited to *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*.

ACUTE INFLAMMATION

Acute inflammation is the early response of the body to invading organisms and is characterised by vasodilatation and increased local blood flow resulting in redness and warmth and extravasation of fluid into the extravascular space resulting in swelling and pain. In a few hours, leucocytes migrate into tissue spaces to phagocytose the invading organisms. These cells release pro-inflammatory cytokines, TNF-α, IL-1, IL-6, G-CSF and GM-CSF. TNF-α and IL-1 cause increased expression of E-selectin on endothelial cells and neutrophils which bear L-selectin bind to the endothelium, thus slowing their flow. The stable bond formed between LFA on the neutrophils and ICAM-1 on the

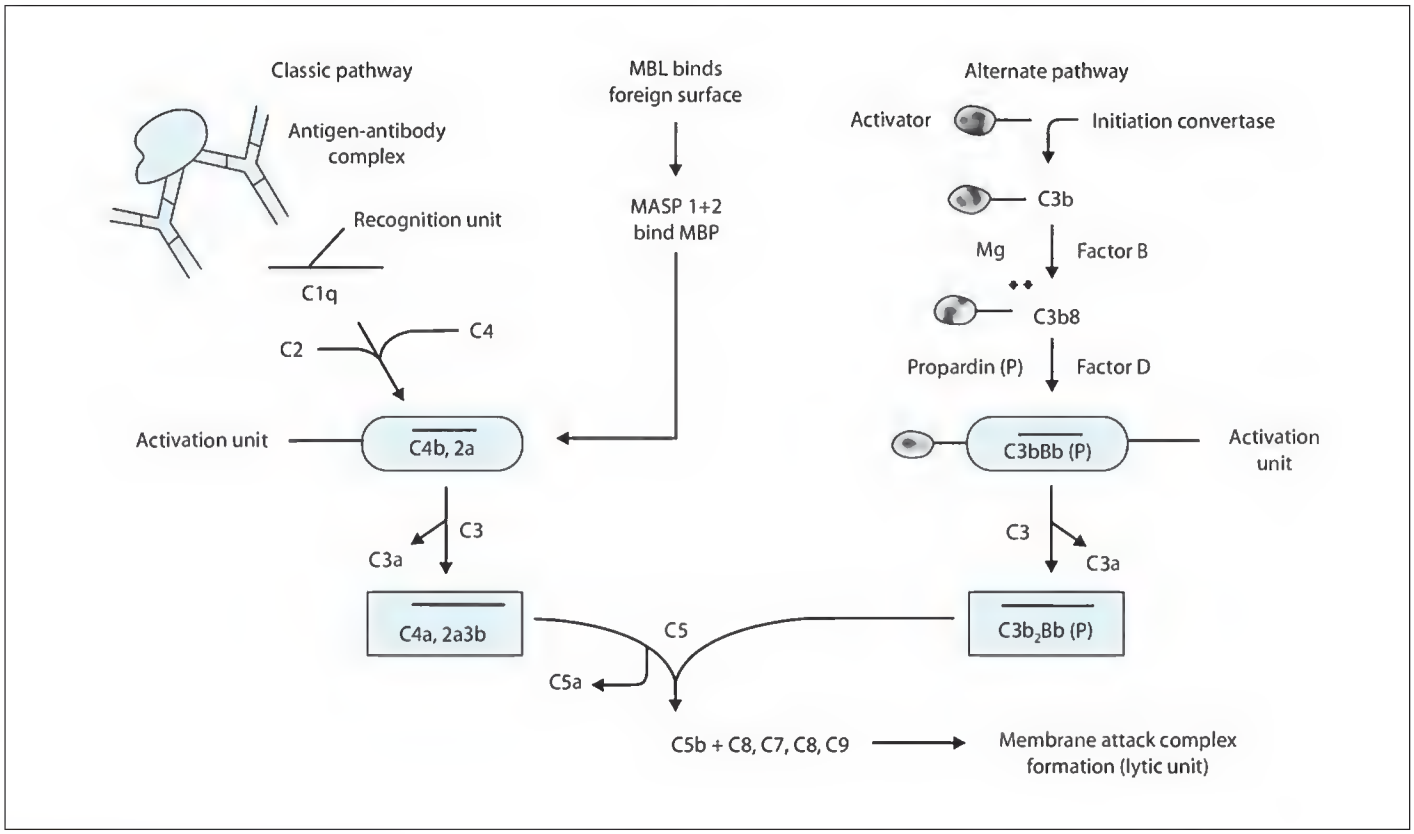


Figure 4: The complement activation pathways.

endothelium and the released chemoattractants of host (interleukin-8, leukotriene B4 and complement 5a) and bacterial origin (FMLP) helps the neutrophils to move out of the vascular compartment into spaces (**Figure 5**). These cells phagocytose and clear the pathogen. While G-CSF and GM-CSF stimulate the production of large numbers of leucocytes in the bone marrow, the vasodilators and anaphylatoxins, C3a and C5a, cause release of additional inflammatory mediators, including histamine from mast cells. The sluggish local blood flow and increased permeability of vessels allows a fresh supply of complement, coagulation and other proteins from the circulation to permeate into the inflamed tissues to maintain the inflammation. TNF-α, IL-1 and IL-6 also act at distant sites, particularly the liver, to induce synthesis of acute phase proteins such as C-reactive protein (CRP). This is widely used in clinical practice as a biomarker of the acute phase response. CRP can bind polysaccharides on the surface of pneumococci and phosphorylcholine on many other bacteria to act as an efficient opsonin.

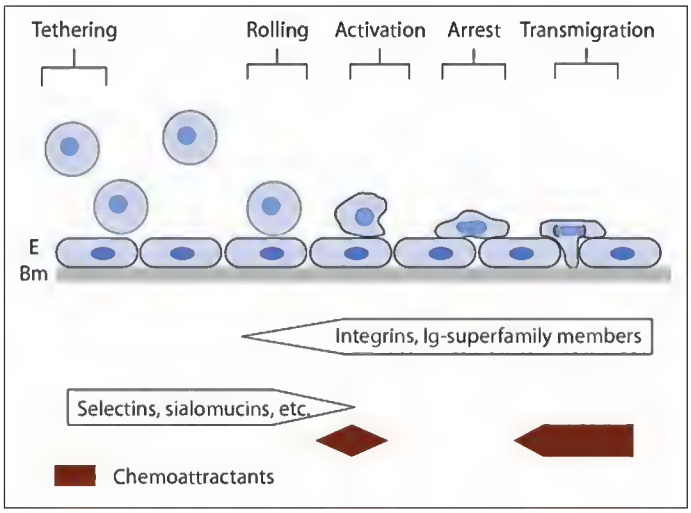


Figure 5: The multi-step cascade of leucocyte extravasation. The blood-borne cell makes transient contact with endothelial cells, which leads to the cell rolling along the vascular lining. If the cell gets activated, it subsequently adheres to the endothelium, seeks out inter-endothelial junctions and migrates through the basement membrane into the tissue.

ANTIGEN PROCESSING AND PRESENTATION

MHC class II bearing APCs process endocytosed antigens. The endocytic vesicles bearing antigen fuse with endosomes (**Figure 6**) and hydrolytic enzymes within the endosomes degrade foreign antigens into small peptide fragments of 10-20 amino acid length. These fragments bind to MHC class II molecules. MHC class II molecules are synthesised within the endoplasmic reticulum (ER) and move along the biosynthetic pathway into an endosome or lysosome. To meet the peptide and form the MHC-peptide complex. This gets transported to the cell membrane for recognition by the T cell receptor of CD4+ T cells.

Endogenous antigens that originate within the cells of the host organism also trigger immune responses. For example, cells that have become infected by a virus usually manufacture foreign proteins encoded by viral genes. Fragments derived from the viral proteins or from altered self-antigens as in the case of cancer cells (endogenous proteins) are degraded into short peptides of 8-10 residues by proteases that are part of a multimeric complex called *proteasome*. The peptides are transported into the ER where they bind to newly synthesised MHC class I molecules. The MHC–peptide complex moves through the biosynthetic pathway to reach the plasma membrane where the peptide is displayed for recognition by the TCR of CD8+ T cells (**Figure 6**).

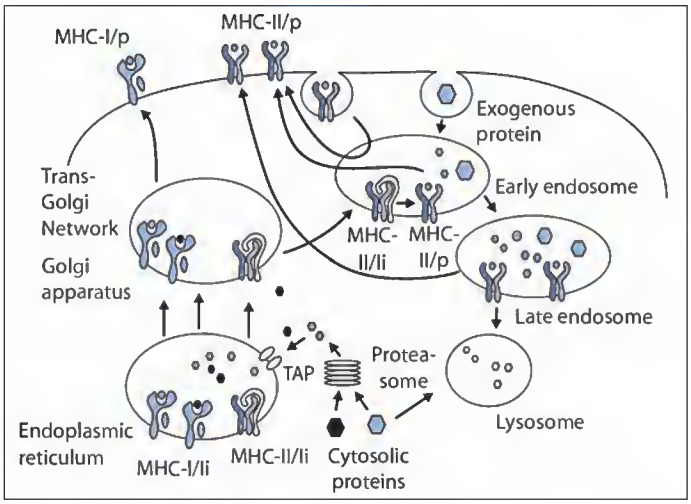


Figure 6: Processing of exogenous and endogenous antigens.

CD4 and CD8 molecules are expressed on mutually exclusive subsets of T cell and bind to a non-polymorphic site on the MHC II and MHC I molecules respectively. Thus, T helper functions of CD4+ cells is strictly dependent on recognition of the CD4 molecule by the class II molecule on APCs, a phenomenon termed 'restriction'. This stimulates antibody production, which is useful to neutralise or lyse extracellular organisms by a variety of mechanisms. The cytotoxic function of CD8+ T cells is class I 'restricted' and the endogenous pathway delivers peptides to MHC class I molecules which are recognised by cytotoxic CD8+ cells that kill the presenting cell. This is beneficial to the host since this is the only way intracellular antigens can be eliminated. Also, viruses can infect any cell in the body and it is advantageous that class I molecules are present on all nucleated cells. The distinct compartmentalisation of the exogenous and endogenous pathways for presentation of antigen to CD4 and CD8 cells respectively is a clever strategy to increase efficiency of dealing with infectious agents.

MATURATION OF T AND B LYMPHOCYTES

Autoreactive lymphocyte clones are deleted during development of T and B cells in the thymus and bone marrow respectively. Progenitor T cells from the early sites of haematopoiesis migrate to the thymus, undergo proliferation and begin to express their TCR; cells that fail to express their TCR die by the process of apoptosis. A process that is unique to T and B-lymphocytes, gene rearrangement, generates TCRs by a totally random phenomenon and has an estimated potential to produce over 10^{15} kinds of T cell receptors. Being a random process, rearrangement generates TCRs with equal frequency and affinity for foreign and self-antigen. To ensure that only T lymphocytes bearing TCRs for foreign antigens exit the thymus and all those that can react with self-antigen are eliminated (**Figure 7**), interaction of immature thymocytes with cortical epithelial cells rescues all T cells whose TCRs can recognise self-MHC molecules from apoptosis (positive selection). These cells interact with DCs and macrophages in the thymic medulla where all lymphocytes that bear TCR for self-MHC alone or self-antigen

plus self-MHC undergo apoptosis (negative selection). This is achieved by a unique arrangement in which, all self-antigens get expressed in the thymic medulla. This occurs under the control of the autoimmune regulator (AIRE) gene and genetic defects in this gene leads to the human autoimmune disease known as autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy (APECED). A third subpopulation of cells, FoxP3 positive T regulatory cells, also develop in the thymus and play an important role in maintaining the balance within the immune system.

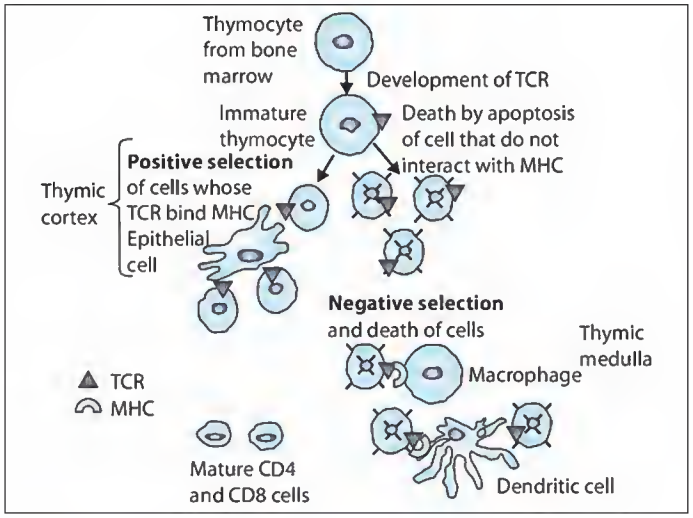


Figure 7: Thymic selection.

Thus, all T cells that leave the thymus recognise foreign antigen with self-MHC and do not recognise self-antigen. Less than 2% of the thymocytes that enter the thymus survive this rigorous selection exercise.

Unlike T lymphocytes, B lymphocytes recognise conformational epitopes on antigens through the B cell receptor (BCR); there is no antigen presentation or an MHC analogous molecule in BCR engagement. Hence, there is no requirement for a round of positive selection; however, negative selection of self-reactive B cells occurs in the bone marrow. As in the thymus, more than 90% of immature B cells are eliminated through negative selection.

Although the developmental process is aimed at providing an immune repertoire that can recognise and deal with all external antigens without any self-directed responses, many low-affinity anti-self T and B cells escape and survive. Self-reactive T cells and low titre autoantibodies can be demonstrated in most individuals if adequately sensitive methods are used and their frequency increases with age. Fortunately, autoimmune disease develop in only a small proportion of the population because peripheral tolerance mechanisms keep these autoreactive cells in an inactive state through T cell anergy. T cell activation only occurs following an initial pro-inflammatory response and upregulation of co-stimulatory molecules on APCs.

ADAPTIVE IMMUNITY

The unique features of the acquired immune response are specificity, diversity and memory. The response is specific to the structural components of complex protein, polysaccharide and other antigens termed epitopes or determinants. The unique receptors on T and B lymphocytes recognise even subtle differences between antigens. Due to the huge diversity of these receptors, the immune system can respond to an extremely wide range of antigen specificities. After each successful immune response, memory for the specific antigen is retained for long periods of time and it allows the body to respond more rapidly to subsequent encounter with the antigen.

ACTIVATION OF THE CELLULAR RESPONSE

Adaptive immunity, develops over 2-3 days, and following transport of antigens from the site of infection to the secondary lymphoid organs. Antigens are transported by DCs from the periphery to the lymph node, from blood to the spleen and from the mucosae to the mucosa-associated lymphoid tissues. As described earlier, at the site of inflammation, DCs are activated and become potent APCs bearing upregulated chemokine receptors. Lymphoid tissues constitutively express chemokines and DCs home to lymphoid tissues where they come in contact with the T lymphocytes. T lymphocytes are in continuous circulation throughout the body, taking 1-2 days to complete their sojourn. The large number of T cells that traffic through lymph nodes come in contact with the DCs bearing the processed antigen within the MHC class II. After a series of hit and trials, T cell bearing the correct TCR is found and TCR-MHC-peptide interaction, results in immediate activation of the T cell. Without interaction of the TCR with its cognate antigen, T cells remain quiescent and may recirculate through lymphoid tissues for many months or years. The TCR consists of an α and a β chain complexed with γ, δ, ε and ξ chains of the CD3 molecule (**Figure 8**). The α and β chains bind to the MHC/peptide complex and CD3ξ chain transduces intracellular signals that result in activation of a number of genes, including a variety of cytokine genes.

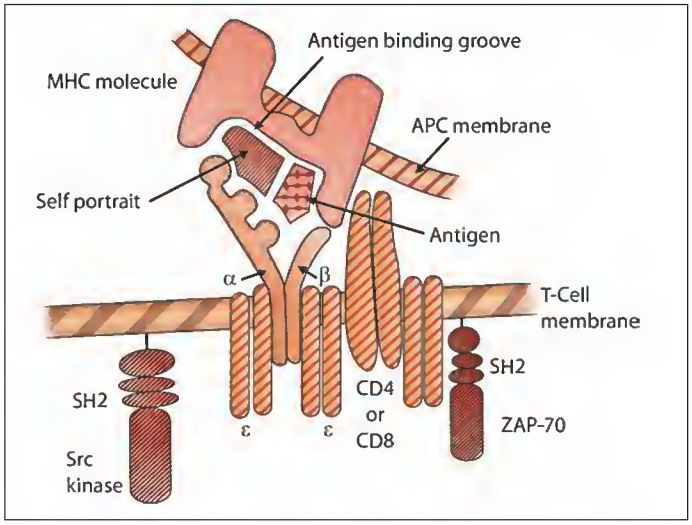


Figure 8: The T cell receptor–CD3 complex.

In addition to signalling through the TCR-CD3 complex, additional signalling through co-stimulatory molecules is required, failing which T cell activation is abortive for generating effector cells. Such T cells either get anergised or undergo programmed cell death. The most important co-stimulatory molecule is CD28, a homodimeric glycoprotein on T cells that interacts with two receptors, CD80 and CD86, expressed on APCs. While CD86 is expressed constitutively at low levels and CD80 is not expressed on professional APCs like DCs, but

get rapidly upregulated following activation by the pro-inflammatory cytokines. This is the critical role of innate immune responses, since failure to upregulate these molecules leads to anergised T cells. It also ensures that the effector arm is activated only when there is a genuine need to deal with overwhelming antigen load. CTLA4 or CD152 on T cells, is structurally related to CD28 and binds to CD80 and CD86 with higher affinity than to CD28. However, its engagement along with the TCR results in negative signalling.

Activated T cell expands clonally to produce large number of progeny which home back to the site of inflammation, guided there by tissue-specific adhesion molecules. However, all the activated cells do not leave the lymph node and some remain as central memory cells.

CELLULAR EFFECTOR RESPONSE

The effector T cells are of CD4+ helper (Th) and CD8 +cytotoxic (Tc) type and CD4 effector response diverges to either a Th1 or a Th2 type. The Th1 response is characterised by the cytokines TNFα, IL-2 and IFN-γ and Th1 expansion results in appearance of cell mediated immunity involving generation of specific CTLs and activated macrophages. Th2 cells make IL-4, IL-5 and IL-13 that are critical for induction of humoral immunity and eosinophilia. It is not clear what determines whether a particular response will be Th1 or Th2 in type. A new subset of T cells, the Th17 cells, secrete IL-17 and are involved predominantly in the maintenance of the inflammatory response. The mechanism of target cell lysis by CD8+ cells is same as NK cells, except that unlike NK cells, CTLs release these enzymes only on antigen stimulation.

THE HUMORAL RESPONSE

Immunoglobulins or antibodies neutralise toxins, prevent organisms adhering to mucosal surfaces, opsonise bacteria for phagocytosis and sensitise infected cells for lysis by antibody mediated cellular cytotoxic attack by NK cells while antigen-antibody complexes activate the classical complement cascade. B lymphocytes reside primarily in lymphoid tissues with little recirculation. They recognise native antigen, through the BCR, which is a membrane-bound immunoglobulin.

Immunoglobulins

There are five classes of immunoglobulins (Ig), namely IgG, IgM, IgA, IgE and IgD. They have a common structure consisting of two identical light (L) chains of approximately 22,000 Da and two identical heavy (H) chains of 55,000 Da or more (**Figure 9**). Each light chain is bound to a heavy chain by disulphide bonds and other non-covalent interactions and each set of H+L chains is bound to the other by similar bonds to form the four chain structure $(H\text{-}L)_2$. The numbers and position of the disulphide bonds vary among the different classes of Ig. Each H and L chain is made of variable (V) and constant (C) regions, with each light chain having one variable (VL) and one constant (CL) unit and heavy chains having one variable region (VH) and 3 to 4 constant regions (CH). The first 110 amino acids of the VH and VL chains show a great degree of variability (hypervariable regions) and form the region by which antigen is recognised. This, the antigen combining site, binds to the conformational epitopes on the antigen, which is formed by non-contiguous regions of the antigen and is dependent on its tertiary and quaternary structure. This is in contrast to the recognition of linear peptides by the TCR. The five types of H chains (γ, μ, α, ε and δ) can each combine with either of the two L chains (κ, λ) to form the molecules of IgG, IgM, IgA, IgE and IgD (**Table 3**).

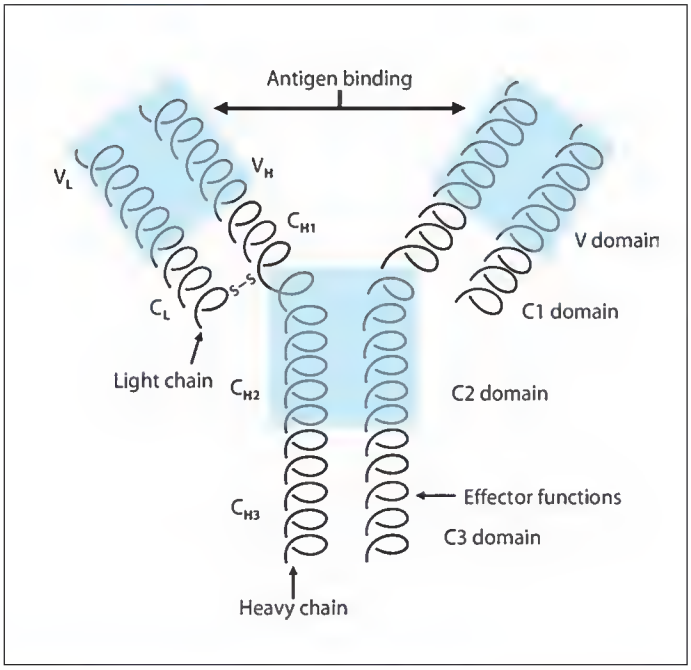


Figure 9: The arrangement of immunoglobulin.

Table 3: Immunoglobulin Classes and their Functions

	IgG	IgA	IgM	IgE	IgD
Molecular weight	150,000	150,000-600,000	900,000	190,000	150,000
Heavy chains	γ1, γ2, γ3, γ4	α1, α2	μ	ε	δ
Normal serum levels (mg/ml)	13.5	3.5	1.5	0.0003	0.03
In vivo serum half-life (days)	23	6	5	2.5	3
Activate classical complement pathway	++	–	++	–	–
Crosses placenta	+	–	–	–	–
Present on membrane of mature B cells	–	–	+	–	+
Binds to Fc receptor on phagocytes	++	–	?	–	–
Mucosal transport	–	++	+	–	–
Induces mast cell degranulation	–	–	–	+	–

Effector Functions of Antibodies

The first immunoglobulin produced during an immune response is IgM. Th2 derived IL-4, IL-5, IL-6 and IL-13 help in the antibody response. These cytokines also upregulate CD40 ligand (CD40L) on T cells which interacts with the constitutively expressed CD40 on B cells and APCs, an essential interaction to

switch the cell from IgM to IgG production. Most of the effector responses are most efficiently carried out by IgG and as the immune response matures IgG molecules undergo somatic hypermutation, a process by which the quality of the antibody to fit the antigen is improved. It is also evident that, the help provided by T cells is crucial for antibody production and most antigens are thus T-cell dependent. A few antigens especially polysaccharides, having a repeating structure can cross-link multiple BCRs and stimulate IgM response. However, this is not followed by affinity maturation or isotype switch and such responses wane rapidly. These are called T-cell-independent antigens.

REGULATION OF THE IMMUNE RESPONSE

An efficient immune response is characterised by augmentation of innate (antigen independent) response by the products of the adaptive (antigen specific) response. Pro-inflammatory cytokines, upregulate numerous cytokine receptors on T cells which bind with T-cell derived cytokines setting up paracrine and autocrine mechanisms for amplification of the immune and inflammatory processes. A Th1 response deals with intracellular pathogens while Th2 response favours antibody production (IL-4 favours class switching and IgE production, IL-5 eosinophilia); IL-4 provides stimuli for feedback amplification of the Th2 response and dampening of the Th1 response.

This cascade is exquisitely orchestrated and immune response is generated that is adequate to control this challenge. However, the expansion of the effector response is not uncontrolled; antigen elimination deprives the antigenic stimulus. The contraction occurs leaving behind long-lived memory cells for CD4, CD8 and B cell memory. These reside in secondary lymphoid organs, to be recalled for immediate and accelerated responses on subsequent exposure to the antigen.

The counter-regulatory mechanisms include negative signalling in T cells by CTLA-4, and T regulatory cells (Treg) which actively downregulate activated T cells. Tregs are CD4+ T cells that express cell surface CTLA4 and CD25 and have a characteristic transcription factor, FoxP3. Tregs are important for maintaining tolerance to self-antigens.

CONCLUSION

The immune system is an extremely fine-tuned orchestra that responds efficiently to external challenges only to the exact quantum that is required to deal with that challenge. Diseases are a consequence of failures of the development of the system (primary immunodeficiency), failures of the normal control mechanisms (autoimmunity and cancer) or excessive efforts to deal with the foreign challenge of chronic infections like tuberculosis.

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5.2 General Concepts of Immunoinflammatory Disorders

Ramnath Misra

Understanding cellular and molecular basis of inflammation and immunology has helped to develop targeted therapy in several immunoinflammatory diseases, such as rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, ankylosing-spondylitis, juvenile idiopathic arthritis, systemic lupus erythematosus (SLE), inflammatory myositis, vasculitis, etc. Immunoinflammatory diseases result from an aberrant immune response and a heightened inflammation process consequent to generation of effector T- or B-cells. Though the precise trigger for the inflammation is not understood, the cells and molecules that cause the tissue damage have been elucidated in great detail in these conditions. Therefore, biological therapy directed at inhibiting key molecules or dysregulated cells have been successful in limiting tissue damage and increase the quality of life.

While hypersensitivity is an inappropriate immune response to antigens (allergens), autoimmunity is directed against self-antigens. Both situations result in inflammation that causes tissue damage by various mediators of inflammation.

THE NORMAL IMMUNE RESPONSE AND THE IMMUNOLOGICAL BASIS OF AUTOIMMUNITY

Immune response is mediated by the T-cells causing the cellular and B-cells producing antibodies. These cells work in collaboration helping each other in a coordinated way. There is a tight control over these T- and B-cells reacting against self-antigens in cells or tissues called the *'self-tolerance'*. During the embryonic maturation of these lymphocytes, most self reacting lymphocytes are removed by apoptosis (negative selection). A protein called autoimmune regulator (AIRE), is believed to stimulate expression of several peripheral antigens to the thymic epithelial cells. Mutations in the AIRE gene can cause polyendocrinopathy in experimental animals. Those lymphocytes that escape this central deletions are kept under control by peripheral mechanisms, such as lack of B7 by (APCs) to interact with CD28, repeated stimulation by self-antigen causing activation induced cell death and suppression by CD4+, CD25+ regulatory T-cells.

HOW DOES AUTOIMMUNITY DEVELOP

Several hypothesis have been proposed.

Sequestration of Self-Antigens

During thymic development, lymphocytes are not exposed to those self-antigens which are not expressed by the thymic epithelial cells. These include, but are not limited to, the lens protein, sperms or ova or myelin basic proteins (protected by the blood-brain barrier in the central nervous system). Later, an inadvertent exposure of the antigens, leads to development of autoimmunity.

Molecular Mimicry

Several host proteins and proteins of pathogens (bacteria, virus, etc.) share structural similarity and autoimmunity is a consequence of the immune response generated against the pathogen. For example, in acute rheumatic fever, cellular and humoral responses against the *Streptococcus* M protein cross-react against myocardial tissues causing carditis. However, cross-reactive microbial antigens have not been found even after extensive search in the classical autoimmune diseases, like juvenile diabetes, RA and SLE.

Altered Self-Antigen Presentation

In animal models of autoimmune diseases, it has been shown that autoimmune response to one antigenic epitope (part of the protein seen by the antibodies or T-cells) may spread to involve other epitopes which are normally not seen by lymphocytes. These later epitopes could be self-antigens.

Polyclonal B-Cell Activation

Many infectious agents, such as gram-negative bacteria, Epstein-Barr virus and cytomegalovirus cause polyclonal activation of B-cells. A wide spectrum of antibodies is produced in patients with AIDS and infectious mononucleosis as part of the diseases process. A persistent stimulation of T lymphocytes may also lead to polyclonal stimulation of B cells. Some of these antibodies may be directed against self-antigens.

Autoimmune diseases are polygenic in nature with a number of genes contributing to the causation of the disease. They result from a multi step process, probably triggered by an environmental factor, in a genetically susceptible individual. The risk of developing autoimmune diseases is higher among monozygotic twins than dizygotic twins and familial clustering is often seen. Unaffected healthy family members of patients have higher incidence of autoantibodies than normal healthy population. The susceptibility to autoimmune disease differs between two sexes with SLE, RA, and scleroderma affecting predominantly the females. This difference has been attributed to hormonal differences and the effect of circulating foetal cells in maternal blood during pregnancy.

BASIS OF HYPERSENSITIVITY AND AUTOIMMUNE DISEASES

Autoimmune diseases are classified as organ specific and systemic non-organ-specific (**Tables 1 and 2**). The immunological basis of hypersensitivity and autoimmune diseases have been described as Types I , II, III and IV reactions by Gell and Coombs.

Hypersensitivity is the inappropriate host response to an antigen which results in tissue damage of variable severity and even death. The hypersensitivity may be 'immediate' in which symptoms manifest within minutes to hours of exposure to the antigens or 'delayed', due to delay in the onset of symptoms up to days after the exposure to antigen.

Table 1: Organ Specific Autoimmune Diseases that are Caused by Antibodies Directed against Autoantigens

Diseases	Antibodies directed against cells/tissues	Effect
Type 1 Diabetes	Beta cells	Cell lysis
Grave's disease thyrocytes	TSH receptor	Stimulating
Myasthenia gravis	Acetylcholine receptor	Blocking Ach
Autoimmune haemolytic anaemia	Red cell surface antigens	Fc receptor mediated phagocytosis
Autoimmune thrombocytopaenic purpura	Platelet GpIIb-IIIa	Fc receptor mediated phagoctyosis by splenic macrophages
Goodpasture's syndrome	Alpha 3 chain of collagen	Complement mediated inflammation of the blood vessels in kidney and lung
Wegener's granulomatosis	Serine proteinase 3	Neutrophil damage

Table 2: Systemic or Non-Organ-Specific Diseases with their Respective Target Cells/Tissues

Disease	Self-antigen
Systemic lupus erythematosus	DNA, nucleosomes, Sm, histones, RNP, Ro, La lymphocytes, platelets
Rheumatoid arthritis	IgG, cyclic citrullinated peptide, synovium, cartilage
Sjögren's syndrome	Salivary glands, epithelial cells, kidneys
Polymyositis	Myocytes

Type I Hypersensitivity Reaction

This is also known as immediate or anaphylactic hypersensitivity. IgE antibodies are generated in the first exposure to antigen (allergens) and during the subsequent exposure binds to the Fc receptor for IgE which is expressed abundantly on mast cells and basophils. A subsequent exposure to the same allergen cross-links the cell-bound IgE and triggers the release of various biologically active primary (preformed) and secondary mediators (**Table 3**). The preformed mediators are responsible for immediate reaction, such as local oedema, increased secretion and bronchospasm. The secondary mediators are responsible for delayed phase reactions, and act by recruiting inflammatory cells which amplify the reactions. Of the recruited cells, eosinophils are particularly important and are preferentially expanded under the influence of (Th)2 derived cytokines, such as IL-3, IL-5 and GM-CSF. These mediators act on the surrounding tissues and cause vasodilatation and smooth muscle contraction. The clinical picture may vary from a mild local reaction to a severe systemic anaphlyaxis, which may be fatal. Systemic anaphylaxis may result from penicillin and administration of foreign proteins, such as antisera, intravenous immunoglobulins and monoclonal antibodies of murine origin. The clinical manifestations are skin urticaria, rhinorrhoea, rhinitis, conjunctivitis, angioneurotic oedema, respiratory stridor due to laryngeal spasm, asthma due to bronchoconstriction and abdominal cramps and diarrhoea. In severe cases death occurs due to shock and vascular collapse. The reaction usually takes 15 to 30 minutes from the time of exposure to the antigen, although sometimes it may have a delayed onset (10 to 12 hours).

The diagnosis is mainly clinical and in cases confirmation is needed, intradermal challenge with allergens may be done with caution.

Type II Hypersensitivity Reaction

Type II hypersensitivity is mediated by IgG or IgM antibodies directed against cell-bound antigens. Antibodies binding to cell surface antigens, activates the complement cascade and deposits of complement products C3b and C4b facilitates their ingestion and destruction by Fc receptor bearing macrophages. Preformed antibodies may cause transfusion reactions following incompatible blood transfusion, erythroblastosis foetalis due to placental transfer of maternal antibodies to the foetus with destruction of foetal red blood cells and autoimmune haemolytic anaemia.

The diagnosis of type II hypersensitivity diseases is made by demonstration of circulating or tissue-bound antibodies to target antigens. Some examples are Coombs test for haemolytic anaemias, antibodies to Ach receptor in myasthenia gravis, antibodies to glomerular basement membrane in Goodpasture's syndrome. However, antibodies are not of clinical importance, such as antibodies to platelet glycoprotein and glutamic acid decarboxylase (GAD) in type 1 DM. Here the diagnosis is dependent upon the manifestation of organ damage, such as purpura and hyperglycaemia, respectively.

Type III Hypersensitivity Reaction

In this type, immune complexes containing antigens and antibodies to auto or bacterial antigens are deposited in the capillaries and small blood vessels, causing complement activation, neutrophil activation and release of proteolytic enzymes leading to inflammation and tissue damage. SLE is a prototype example of type III hypersensitivity disease. Circulating antibodies to anti-nuclear antibodies (**Figure 1**) which are directed against a variety of nuclear constituents

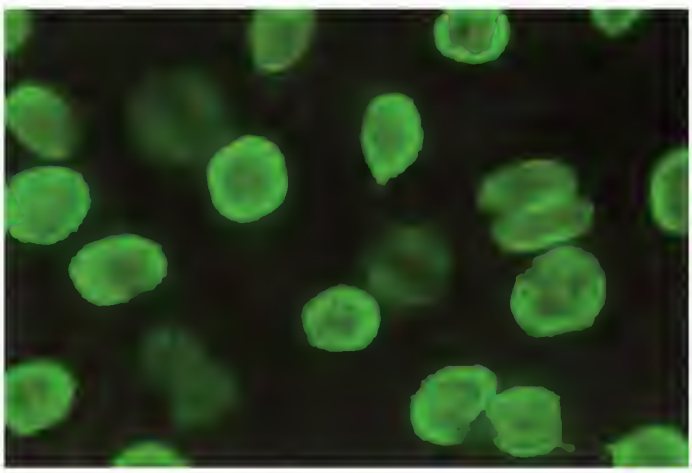


Figure 1: Anti-nuclear antibodies detected by indirect immunofluorescent assay. Circulating anti-nuclear antibodies with its antigens, such as dsDNA, nucleosomes gets deposited in the blood vessels to activate complement mediation inflammation and subsuequent damage.

Table 3: Primary and Secondary Mediators in Hypersensitivity Reaction

	Mediators	Effects
Primary (pre-formed)	Histamines	Smooth muscle constriction, vasodilatation, increased glandular secretions
	Enzymes (chymase, tryptase)	Generation of kinins and activated complement C3
Secondary mediators	Leukotrienes C4,D4	Vasoactive
Lipid mediators	Leukotrienes B4	Chemotactic for neutrophils and eosinophils
	Prostaglandin D2	Bronchospasm
	Platelet activating factor	Platelet aggregation, histamine release
Cytokines	TNF, IL-1, IL-3, IL-4, IL-5, IL-6	Mediate inflammation at the local site

(such as nucleosomes, DNA, Sm, U1RNP, Ro or SS-A, La or SS-B) get deposited at various sites giving rise to malar rash, photosensitivity, arthritis, glomerulonephritis, serositis and central nervous system involvement. Immunofluorescence microscopy of kidney biopsy reveals deposits of IgG, IgM and complement components C1q and C3. Other examples are serum sickness and primary Sjögren's syndrome.

Type IV Hypersensitivity Reaction

Also known as delayed type hypersensitivity (DTH), it is mediated by effector T-cells which have been earlier exposed to the same antigen. These cells accumulate at the site of entry of antigen, and get activated releasing cytokines that cause accumulation of monocyte/macrophage cells from the peripheral blood. A typical example is Mantoux test. This type of hypersensitivity is an important defence mechanism against parasites and intracellular organisms. When pathogen is not cleared within a week or so, a granuloma may form at the site which releases proteolytic enzymes and destroys the surrounding tissue. Such pathology of hypersensitivity is seen in sarcoidosis and other granulomatous conditions.

DTH can be measured by injecting the antigen intradermally and measuring the local reaction at 24 to 48 hours. Contact dermatitis and Bacillus-Calmette Guerin skin test are examples of DTH reaction. Histology reveals lymphocytes, monocytes, macrophages at the site of reaction. The granuloma seen in tubercular and in non-tubercular cases occurs after 21 to 28 days of antigen exposure and is also an example of DTH reaction.

CYTOKINES—KEY MEDIATORS OF INFLAMMATION

Although the triggering factor for an autoimmune disease is not known, much is understood about the sequence of events that follow. Studies in experimental models for autoimmune diseases have shown that cytokines are the key mediators of inflammation. They activate the cells from which they are produced and markedly influence the cell composition at the inflammation site and the reparative process that follow. For example, in RA, antibodies to cytokine targets have shown excellent results for controlling the signs and symptoms of the disease. The putative triggering agent in the synovial compartment activate the synovial macrophage which produce as key mediator of inflammation tumour necrosis factor TNF-alpha which has pleiotropic effect both locally as well as systemically. These include release of other proinflammatory cytokines (IL-1, IL-6, IL-18, IL-23 and GM-CSF), activation of endothelial cells and upregulation of adhesion molecules E-selectin and VCAM1, chemokine release (Rantes, MCP1, SDF1) causing leucocytes influx, induction of acute phase response in liver, chondrocytes and osteoclast activation causing cartilage and bone loss, and upregulating and maintenance of class II expression. These cytokines activate cells of the adaptive immune system, especially naive CD4+Th cells which are driven to Th1 and the recently described Th17 cells. IL17, in turn, activates synovial fibroblast to produce RANK L and in synergism with IL-1 and TNF activates osteoclast precursor cells to osteoclast causing bone resorption. IL17 has also been shown to be an important cytokine in psoriasis skin and joint lesions.

The elaboration of cytokine pathways has made it possible to develop monoclonal antibodies directed against TNF-α, IL-1, Th17, IL-6 to downregulate the proinflammatory process in RA, Crohn's disease, ankylosing spondylitis and psoriatic arthropathy with effective control of signs and symptoms of the disease.

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5.3 Immunology of Infectious Diseases

Sita Naik

The earlier chapters have discussed how the immune response has evolved to protect the host from external infectious agents. The diversity seen in the T cell and B cell receptors have probably evolved over time to deal with the diversity of the infectious agents. The organisms, however, constantly evolve mechanisms to evade immune recognition and the effector immune response. Some of these will be discussed later in this section. Each new effort by the organism is reciprocated by the host response making the required adjustments. This constant evolutionary battle has given us the system as we know it today.

For an infection to establish itself in a susceptible host, it has to overcome the combined efforts of the innate and adaptive immune systems to eliminate it. The earliest barriers, which try to prevent the establishment of the infection, includes the physical one provided by the epithelial lining itself. The epithelial layer also provides specialised barriers, such as the ciliary processes of the lining epithelium of nasal passages and production of anti-bacterial peptides at many locations. The acidic pH of the stomach forms an effective barrier for any ingested agent as do the normal flora of the gastrointestinal, genito-urinary and respiratory tracts which competitively inhibit the binding of pathogen to host cells.

Although, there has been a significant decline in the morbidity and mortality caused by infectious diseases in much of the developed world, they continue to be a major killer in our country. The understanding of the immune response to infectious agents is also important in the context of new and emerging pathogens like severe acute respiratory syndrome (SARS) and the challenges posed by the old and well established ones like influenza virus. These have not spared any region of the world. In recent times, the major challenge has been posed by an infectious disease, caused by human immunodeficiency virus (HIV) pandemic and the resultant re-emergence of tuberculosis (TB), leishmaniasis, and other opportunistic infections.

VIRAL INFECTIONS

Viruses establish infection by entering cells often through specific cell surface receptors. They use the host cell machinery for their replication and in many instances this replication machinery is error prone, allowing many mutated forms to emerge. It is beneficial to the infecting virus not to kill the host cell. Viruses adopt various survival strategies, such as prolonged latency (HIV) or rapid transmission to a new host (influenza). The innate immune response plays a crucial role in viral elimination. Viral nucleic acids are recognised by the toll like receptors leading to the activation of interferon responsive elements and production of type 1 interferons (IFN-α and IFN-β). These cytokines bind to the type 1 IFN receptors and activate the JAK-STAT pathway which in turn activates several genes including 2'-5'-oligo-adenylate synthetase. This leads to activation of a ribonulease that degrades viral RNA. Other genes that contribute to the antiviral activity are also activated, including dsRNA-dependent protein kinase (PKR), a dsDNA dependent protein kinase that causes inactivation of protein synthesis, and thus, viral replication. Many other cell types such as macrophagges, monocytes and fibroblasts produce IFNs and interleukin (IL)-12 is an important cytokine produced during the innate response. This is a potent activator of NK cells which are efficient killers of virus infected cells.

Antibodies have a limited but important role in limiting acute infection. Both humoral and cellular responses are important for viral immunity. Antibodies that neutralise viral surface molecules involved in cell entry can prevent establishment as well as cell to cell spread of the virus. Secretory immunoglobulin (IgA) has an important role in this regard as in the case of attenuated oral polio vaccine. Further in the course of infection, antibodies can also agglutinate viral particles and function as an opsonising agent to facilitate Fc or C3b-receptor mediated phagocytosis of viral particles.

Most of the vaccines against viruses that are in use act by generating neutralising antibodies (HBV, polio). Antibodies also help in activating the complemet pathway leading to virus lysis. However, once infection is established, cellular mechanisms are required and the infected cell has to be lysed. Both CD4+ and CD8+ cells play important roles in antiviral immunity. The activated CD4+ cells secrete numerous cytokines, of which IFN-γ can induce an antiviral state in the cell, IL-2 helps in the maturation of precursor CTLs to a mature effector population and both IL-2 and IFN-γ activate NK cells which are important in killing infected cells in the initial days of the infection. In established infections, CTLs are probably the most important effector mechanism with CTL activity peaking 7 to 10 days following infection. Elimination of infected cells ensures that no virus infects new cells and perpetuates infection. Failure of CTL activity results in dormancy or chronicity of the infection.

Viruses have developed a variety of mechanisms to subvert the immune effector mechanisms directed against them, and thus, ensure their survival. For instance, hepatitis C virus can overcome the anti-viral effects of type I IFNs by interfering with the action of PKR. Herpes simplex virus (HSV)-1 and HSV-2 inhibit the antigen presentation by MHC class I, thus escaping CTL mediated target lysis. CMV, HIV and measles downregulate class I expression, thus interfering with efficient antigen presentation. Vaccinia virus secretes a protein that binds to C4b and inhibits classical pathway, while herpes simplex glycoprotein binds C3b and inhibits both classical and alternate pathways. Many viruses cause a generalised immunosuppression (mumps, measles, EBV, CMV, HIV) by various mechanisms.

Viruses constantly change their antigenicity as a strategy for evasion from immune mediated elimination. The classical example is of influenza virus where this strategy leads to emergence of new strains and the failure of previously generated immunity to protect against fresh infections. HIV also uses this strategy, with an estimated mutation rate 6.5 times faster than influenza. This has led to the difficulties in generating vaccines against these infections.

BACTERIAL INFECTIONS

Most bacterial infections are extracellular and specific antibodies bind and lyse these by activating the complement cascade on the bacterial cell wall leading to membrane pore formation. Gram negative bacteria also act as opsonins and thus facilitate phagocytosis and intracellular killing within the phagocyte. Many bacteria also release harmful toxins that are neutralised by the specific antibody as in the case of diphtheria. However, cell-mediated immunity is important in the case of intracellular bacteria.

Many bacteria too have evolved strategies to evade the host immune response. Many bacteria (*Neisseria gonorrhoeae, Haemophilus influenzae, Neisseria meningitidis*) secrete proteases that cleave secretory IgA at the hinge region, and thus, abrogate their ability to agglutinate these organisms. *N. gonorrhoeae* can change its surface antigens, thus evading the neutralisation by IgA. *Streptococcus pneumoniae* surface polysaccharide can prevent phagocytosis effectively while *S. pyogenes* do so by its surface M protein. The long side chains on the lipid A moiety of the cell wall core polysaccharide of Gram negative bacteria help resist complement mediated lysis. The elastase secreted by *Pseudomonas* inactivates C3a and C5a anaphylotoxins, and hence, decreases local inflammation. In some instances, the disease and symptoms are caused by the immune response against the pathogen and not the pathogen itself. In fact, pathogen induced cytokine production, usually TNF and IL-1, is responsible for septic shock and toxic shock syndromes. It also contributes to some of the pathology seen in tuberculosis.

Intracellular bacteria can survive within the protected environment of cells for long periods. The examples are *L monocytogenes* and more importantly, *Mycobacterium tuberculosis*. The sustained antigenic stimulation results in activation of CD4+ cells and the characteristic delayed type hypersensitivity response. The activated CD4+ cells secrete cytokines which attract large number of macrophages and these differentiate into epithelioid cells and sometimes coalesce to form multinucleated giant cells. The localised accumulation of lysosomal enzymes released by the activated macrophages leads to extensive tissue necrosis, seen as the caseous material at the centre of the this accumalation of lymphocytes, epithelioid cells and giant cells. Thus, the characteristic 'granuloma' which is considered to be pathagnomonic of tuberculosis is the outcome of the intense immune response against tubercular antigens. The immune effort is successful in restricting multiplication of the bacilli in the majority of cases. Failure to contain multiplication, leads to continuing tissue necrosis with eventual rupture of the granuloma and release of mycobacteria. This leads to the miliary lesions in the lung and establishment of infection at various extrapulmonary sites.

PARASITIC INFECTIONS

Diseases caused by protozoa and helminths account for considerable part of the disease burden in developing countries. Protozoa are mainly unicellular eukaryotes that live and multiply intracellularly. Of these, malaria and leishmania are of particular relevance to our country. The host does mount an immune response to malarial parasite, and anti-malarial antibodies can be demonstrated in those who have been infected. However, the parasite has a multi-stage life cycle in which it resides within erythrocytes as sporozoites and gametocytes, and within hepatocytes as merozoites. These are antigenically distinct stages and the immune response to these stages is not well understood. This has proved a challenge for the development of a malaria vaccine.

The immune response to leishmania has been better sudied. While leishmania major causes predominantly a cutaneous disease that is not seen in India, the visceral form of the disease that is endemic in parts of eastern India is caused by *L. donovani*. Those who resist infection have a robust TH1 response, while those who develop the disease have a TH2 biased response. Although these distinctions are more clearly seen in murine models of the disease, there appears to be a role for cellular immunity in protection against this parasite. However, leishmania also has two distinct antigenic forms, the infective promastigote, and the amastigote form which resides within the protected environment of the phagosome. The protective immunity is still far from clear and a vaccine is not on the horizon.

FUNGAL INFECTIONS

These are caused by entry of the fungal organism through inhalation or through sites of injury. They are often restricted at the site of entry by the barriers provided by the innate immune system. They are also restricted by phagocytosis by neutrophils and by the activation of the complement system. The important role of the immune system is evident from the fact that non-pathogenic commensal fungi can cause disease in the immunocompromised host. The best example of this is the *Candida albicans* which can cause a serious systemic illness in acquired immunodeficiency syndrome patients.

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5.4 Primary Immunodeficiency Disorders—A Clinical Approach

Surjit Singh

The large majority of children who appear to have had 'frequent' or 'very frequent' infections in infancy are completely normal when examined clinically. A small minority, however, who need further investigations can be identified clinically. In these children, possibility of an underlying primary immunodeficiency disorder (PID) should be seriously considered. Of course, the more common secondary causes of immunodeficiency [e.g. human immunodeficiency virus (HIV) infection] and conditions which may mimic an immunodeficiency (e.g. cystic fibrosis, α-1-antitrypsin deficiency, Kartagener's syndrome and gastro-oesophageal reflux disease) should be excluded.

PIDs are a heterogenous group of conditions with the majority of cases presenting in infancy and early childhood and some conditions, e.g. common variable immunodeficiency (CVID) manifesting in late childhood or even in adult life. PIDs are not as rare as is often believed and if immunoglobulin (Ig) subclass deficiency and IgA deficiency are included, the prevalence rate may be as high as 1/250 - 1/1000 population. However, there is a spectrum of illness and majority of children with 'minor' immunodeficiencies may not develop clinically symptomatic diseases. A PID should be suspected when a child has two or more of the following signs:

1. Four or more new ear infections within a year
2. Two or more serious sinus infections within a year
3. Two or more months on antibiotics with little effect
4. Two or more cases of pneumonia per year
5. Failure of an infant to gain weight or grow normally
6. Recurrent deep skin or organ abscesses
7. Persistent thrush in the mouth or elsewhere on the skin in children more than 1 year old
8. Need of intravenous antibiotics to clear infections
9. Two or more deep-seated infections, like meningitis or cellulitis
10. A family history of immunodeficiency

CLASSIFICATION OF PIDs

PIDs are classified based on the affected component of the immune system. The International Union of Immunological Societies has suggested one such classification system which is enumerated below:

1. Severe combined immune deficiencies in which both T- and B-cells are defective, e.g. severe combined immunodeficiency (SCID)
2. Predominantly antibody deficiencies, e.g. X-linked hypogammaglobulinaemia (XLH)
3. Other well-defined immunodeficiency syndromes in which there are non-immunological features, e.g. ataxia-telangiectasia (AT)
4. Diseases of immune dysregulation, e.g. X-linked lymphoproliferative syndrome (XLPS)
5. Congenital defects of phagocytic cells, e.g. congenital neutropaenia. Affected children may present with life-threatening bacterial or fungal infections
6. Defects of innate immunity relating to monocyte and dendritic cell function
7. Autoinflammatory disorders, e.g. periodic fevers
8. Complement deficiencies. Affected children may have a clinical presentation like, that of XLH. Further, children with C2 and C4 deficiency may present with an autoimmune disease mimicking lupus

Based on the clinical experience from various centres which may not necessarily reflect the true epidemiological situation, 60% to 70% of PID cases are due to humoral immunodeficiencies, 15% to 20% due to cellular immunodeficiencies, 10% to 15% due to phagocytic cell defects and 10% to 20% due to miscellaneous causes.

APPROACH TO A CHILD WITH SUSPECTED PID

Clinical History

The age of presentation is important and earlier the age of onset in children, the more severe is the immunodeficiency. Appearance of recurrent/serious infections before the age of 6 months is suggestive of a severe combined immunodeficiency or a neutrophilic disorder. Children with XLH usually present after the first 6 months of life while the usual age of presentation of CVID is the second decade of life.

Type of Infection

The type of infection may suggest a specific immunodeficiency syndrome (**Table 1**).

Family History

The inheritance pattern provides some leads to diagnosis. For instance, ataxia telangiectasia and certain forms of chronic granulomatous disease (CGD) and SCID have an autosomal recessive inheritance while XLH, XLPS, Wiskott-Aldrich syndrome, hyper-IgM syndrome, SCID and CGD have an X-linked recessive inheritance.

Physical Examination

Generally, children with a serious immunodeficiency usually fail to thrive and conversely an underlying serious PID is unlikely in a well-looking school going child even if there is a history of – 'frequent' infections. Some PIDs have an associated syndrome which can be picked up on physical examination (**Table 2**).

Investigations

A broad diagnosis of the PID group can be made based on history and findings. Investigations should be done with a specific PID in mind since these only serve to confirm the clinical suspicion. HIV infection should be excluded before embarking on investigations for a PID.

Table 1: Type of Infection and Associated Possible Immunodeficiency Syndrome

Type of infection	Likely immunodeficiency
Viral, fungal, mycobacterial/bacterial infections starting within a few weeks of birth	SCID
Recurrent pyogenic bacterial infections (e.g. *Streptococcus pneumoniae, Haemophilus influenzae*) starting from early infancy	Humoral immunodeficiency syndrome (e.g. XLH) complement deficiency
Recurrent pyogenic bacterial infections (e.g. *Streptococcus pneumoniae, Haemophilus influenzae*) starting late in childhood	CVID
Recurrent Staphylococcal 'cold abscesses' and respiratory infections (especially with pneumatocoeles)	Hyper-IgE syndrome
Recurrent *Giardia lamblia* infection	IgA deficiency; other humoral immunodeficiencies
Cryptosporidiosis in early childhood	SCID
Recurrent (Staphylococcal) skin infections, persistent fungal pneumonia, recurrent Staphylococcal pneumonia, multiple liver abscesses	CGD
Disseminated Bacillus-Calmette Guerin (BCG) infection	SCID
Recurrent mycobacterial infections	Defect in interferon γ, interleukin-12 receptor pathway
Recurrent Neisseriae infections	Late complement deficiencies

Table 2: Symptoms and Clinical Features with Associated Immunodeficiency Syndromes

Clinical features	Likely immunodeficiency
Failure to thrive since early infancy, diarrhoea, rash, atrophic tonsils and lymph nodes	SCID
Failure to thrive, recurrent respiratory infections in a boy with onset after 6 months	XLH
Recurrent respiratory infections starting later in childhood, diarrhoea, hepatosplenomegaly	CVID
Infantile eczema (often atypical), recurrent infections since early infancy and bleeds(due to thrombocytopaenia) in a boy	Wiskott-Aldrich syndrome
Typically coarse facial features with history of recurrent Staphylococcal infections	Hyper-IgE syndrome
Slowly progressive ataxia, recurrent bacterial infections (especially pneumonia), bulbar/facial telangiectasia	Ataxia-telangiectasia

Screening Tests

Screening tests should include a complete blood count and peripheral smear examination, quantitative serum immunoglobulin assay, chest radiograph and markers for T (CD3) and B (CD19) cells (**Table 3**). Hypogammaglobulianaemia is diagnosed if the serum immunoglobulin levels are below -2 SD of the age related norms. The physiological hypogammaglobulinaemia in the first 3 to 6 months of life, may get abnormally prolonged to

Table 3: Screening Tests

Investigation	Clinical correlate
Haemogram	
Haemolytic anaemia	CVID
Lymphopaenia	Cell mediated immunodeficiency
Neutropaenia	Agranulocytosis
Marked polymorhonuclear leucocytosis	CGD, leucocyte adhesion molecule deficiency
Thrombocytopaenia	Wiskott-Aldrich syndrome, CVID
Peripheral blood smear	
Giant granules in neutrophils	Chediak-Higashi syndrome or variants
Quantitative serum IgG, IgA, IgM	Several humoral and cellular PIDs; levels to be interpreted in the context of the clinical diagnosis
Chest radiograph	
Persistent pneumonia	Chronic granulomatous disease
Pneumatocoeles	Hyper-IgE syndrome
Absent thymic shadow	SCID
T- and B-cell markers (CD3; CD19)	Absent or low T- and B-cells in SCID; B cells absent with normal T-cells in XLH

persist even at 18 to 24 months (and sometimes longer), a condition known as transient hypogammaglobulinaemia of infancy (THI).

Confirmatory Tests

If the clinical findings and screening tests suggest a PID, more detailed investigations are necessary (**Table 4**). If antibody deficiency is suspected on clinical grounds and serum immunoglobulin level is normal, an IgG subclass deficiency or a functional antibody defect should be suspected.

Table 4: Confirmatory Tests

Detailed analysis of lymphocyte subsets by	
Flow cytometry	CD3: T- cell marker CD19, CD20: B-cell marker CD16, CD56, CD57: natural killer (NK) cell marker CD4: Marker for helper-inducer subset of CD3 lymphocytes CD8: marker for suppressor cytotoxic subset of CD3 lymphocytes
Lymphocyte proliferation using mitogen, phytohaemagglutinin	Functional assessment of T- cells
Complement component assays	For complement deficiency
Nitroblue tetrazolium dye reduction test	Useful and simple test for diagnosing CGD
IgG subclasses by nephelometry or ELISA (G1, G2, G3, G4)	A child with deficiency of one subclass may have a normal level of total IgG because of compensatory over-production of other subclasses
IgE	Levels are frequently above 2000 IU/mL in the hyper-IgE syndrome

Prenatal Diagnosis

As the genetic defect is now known for several of the PIDs, many of these disorders can be diagnosed prenatally using chorionic villus sampling, cultured amniotic cells or foetal blood sampling. Prenatal diagnosis has been successfully carried out for XLH, some forms of SCID and the Wiskott-Aldrich syndrome. Further, under special circumstances sex determination by ultrasonography can be used to exclude X-linked PIDs.

TREATMENT

Prevention of infection is an integral part of the management of children with PIDs. This is achieved using prophylactic antimicrobials, judicious use of vaccines and early treatment with appropriate anti-microbials after exposure. If a blood product has to be transfused, the donor should be screened for cytomegalovirus infection. For cell-mediated immunodeficiencies, the blood should be doubly irradiated to prevent development of graft-versus-host disease.

Intravenous immunoglobulin (IVIG) given in doses of 400-600 mg/kg every 3 to 4 weeks has improved the outlook for children with humoral PID. Replacement immunoglobulin can now also be given subcutaneously (100 mg/kg weekly), but such preparations are yet to be marketed in our country. Haematopoietic cell transplantation (with peripheral blood stem cells or bone marrow) is the treatment of choice for cellular immunodeficiencies and since children with severe forms of SCID cannot reject the donor stem cells, pre-transplantation chemotherapy is not required in many cases. Gene therapy using viral vectors has been successfully used in patients with adenosine deaminase activity (ADA)-deficient SCID, X-linked SCID and in the Wiskott-Aldrich syndrome.

PROGNOSIS

With timely diagnosis and appropriate treatment, children with several of the PIDs can lead a normal life. Most patients with a humoral immunodeficiency disorder can survive to adulthood with replacement immunoglobulin. Disorders, like hyper-IgE syndrome, chronic granulomatous disease and IgG subclass deficiency can be successfully managed with prophylactic anti-microbials. In the case of ataxia-telangiectasia, the immunodeficiency is usually not severe but these patients succumb to other complications (e.g. malignancies). Haematopoietic stem cell transplantation carried out expeditiously, is the only treatment option for severe forms of cellular immunodeficiencies (e.g. SCID, Wiskott-Aldrich syndrome). Long-term survival rates of matched haematopoietic stem cell transplantation for PID are now upwards of 90%.

SPECIFIC IMMUNODEFICIENCIES

Severe Combined Immunodeficiency

This group of PIDs is characterised by the absence of T- and B-cell (and sometimes natural killer cell) function. The inheritance pattern is either autosomal recessive (e.g. ADA deficiency SCID) or X-linked recessive (e.g. X-linked SCID), the latter being the more common. Other types of autosomal recessive SCID include Janus kinase 3 deficiency (T-B+NK-) and IL-7Rá deficiency (T-B+NK+). Affected children develop severe infections with opportunistic organisms soon after the neonatal period and in the first 6 months of life. Typical presenting features include failure to thrive, rash, diarrhoea, pneumonia and oral thrush. Physical examination may show absence of tonsils and impalpable lymph nodes. Live vaccines must be avoided.

X-Linked Hypogammaglobulinaemia (XLH)

Affected boys usually remain well during the first 3 to 6 months of life due to the presence of maternally acquired IgG. After this, they present with serious and recurrent bacterial infections. Laboratory investigations reveal a panhypogammaglobulinaemia with normal numbers of T-cells but absent or very low numbers of B-cells in the peripheral circulation. The genetic defect is at the level of the tyrosine kinase gene located on the X chromosome.

Common Variable Immunodeficiency

CVID is a group of disorders characterised by hypogammaglobulinaemia and a normal B-cell number. Many patients also have a T-cell defect but this is more difficult to document and characterise. Low levels of lymphocyte proliferation following mitogen stimulation may be demonstrable. A number of mutations in different genes have been identified, all causing the same phenotype. Patients usually become symptomatic after the first decade of life and associated autoimmune features (e.g. leucopenia, haemolytic anaemia, arthritis) are commonly seen. Hepatosplenomegaly and lymphadenopathy are prominent clinical features. Patients with CVID need to be closely monitored for the development of lymphoreticular malignancies.

Immunoglobulin A Deficiency

IgA deficiency is the most common form of PID with prevalence of 1:350-1:650. IgA deficiency is diagnosed if the serum IgA level is less than 5-10 mg/dL or if the level is below -2SD of the age related normal value. While majority of the patients may remain asymptomatic throughout life, some do have an increased incidence of respiratory and gastrointestinal infections and allergic disorders. A small proportion of these patients may have an associated deficiency of one of the IgG subclasses (e.g. IgG2, IgG4). Autoimmune diseases associated with IgA deficiency include lupus, rheumatoid arthritis and chronic active hepatitis. Some patients with IgA deficiency may develop anti-IgA antibodies and this may lead to unfavourable transfusion reactions if the patient is given blood products.

IgG Subclass Deficiency

IgG subclass deficiency, a condition with undetermined clinical significance, is the most common form of PID seen in clinical practise. One may suspect the condition if a patient presents with the clinical phenotype of a humoral immunodeficiency has normal (or, at times, even elevated) levels of serum immunoglobulins. The disorder can present in early childhood or later.

Wiskott-Aldrich Syndrome (WAS)

WAS, an X-linked recessive immunodeficiency disorder, is caused by a mutation in the gene encoding a cytoplasmic protein, Wiskott-Aldrich syndrome protein. WAS is expressed in haematopoietic cell lineages and controls the assembly of actin filaments. Children present with eczema, recurrent serious

bacterial infections and thrombocytopaenia, characterised by small sized platelets. Children with WAS present in early infancy and have impaired immunological responses to the polysaccharide antigens. They are especially susceptible to infection with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*. Serum IgM levels are low, while IgE may be elevated. The clinical phenotype is variable ranging from a very fulminant course with repeated infections to milder forms in which children survive childhood. Long-term complications include development of lymphoreticular malignancy.

Ataxia-Telangiectasia

Ataxia-telangiectasia is an inherited disorder of DNA repair mechanism with characteristic susceptibility to radiation-induced chromosomal damage. Serum IgA levels are low with IgG subclass deficiency. Patients present with progressive cerebellar ataxia that becomes evident around 2 to 3 years of age. Affected children may have recurrent respiratory infections that are less severe than seen in WAS. The telangiectasia become apparent around 4 to 6 years of age and may be first noted over the lateral aspect of bulbar conjunctiva. Most children need to be supported with prophylactic antimicrobials. There is a risk of development of lymphoproliferative malignancies later in life. Bone marrow transplantation is not a treatment option in this condition.

DiGeorge Syndrome

DiGeorge syndrome is a T-cell deficiency disorder of varying severity which is associated with abnormal embryogenesis of the 3rd and 4th pharyngeal pouches. The phenotype includes severe neonatal hypocalcaemia causing tetany, hypoparathyroidism and congenital cardiac defects (e.g. truncus arteriosus, transposition of great vessels). Patients have a typical facies characterised by low-set ears, micrognathia, shortened and upturned philtrum of the upper lip and hypertelorism. Patients with milder degrees of immunodeficiency may be given only supportive management while those with more severe forms of the disease are candidates for haematopoietic stem cell transplantation.

Chronic Granulomatous Disease (CGD)

CGD is a group of disorders characterised by defects in superoxide radical generation due to reduced activity of the NADPH oxidase. Both denovo mutations, and X-linked recessive (mutations in the X-chromosome gene encoding $gp91^{phox}$) or autosomal recessive (mutations in the gene encoding $p47^{phox}$ on chromosome 7) inheritance occur, X-linked being the most frequent. Patients present with recurrent life-threatening infections often starting very early in life. Infections are caused by catalase-positive bacteria (e.g. *Staphylococcus aureus*, *Serratia spp.*) or fungi, especially *Aspergillus*. Typical clinical findings include a persistent non-resolving pneumonia, prominent lymphadenitis and multiple liver abscesses. Osteomyelitis of the small bones of hands and feet is also characteristic. Long-term prophylaxis with a combination of trimethoprim-sulphamethoxazole and itraconazole has resulted in significant reductions of morbidity and mortality in this condition.

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5.5 Laboratory Investigations in Immune-Mediated Diseases

Amita Aggarwal

Immune-mediated diseases occur either because of lack of an appropriate immune response as in immunodeficiency states or an abnormal response like in allergic diseases and autoimmune disease. Laboratory investigations play an important role in diagnosis of patients with such immune disorders. The available tests need to be used judiciously in order to provide a cost-effective and efficient approach to diagnosis.

AUTOANTIBODIES IN SYSTEMIC AUTOIMMUNE DISEASES

Autoantibodies directed against self-antigens are present in many autoimmune diseases. These may be directed to any constituent of cell, be it cell membrane, cytoplasm, deoxyribonucleic acid and other proteins in the nucleus. Although their pathogenetic role is not clear, they are good diagnostic markers due to their frequent association with specific diseases. However, the mere presence of an autoantibody is not equivalent to disease and absence of an autoantibody does not exclude a disease. The common antibodies used in clinical practise are given in **Table 1**.

Table 1: Autoantibodies that are Commonly Used and their Disease Association

Antibody	Associated disease
Rheumatoid factor	Rheumatoid arthritis, Sjögren's syndrome
Anti-nuclear antibody	Systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myositis, Sjögren's syndrome (**Figures 1A and B**)
Anti-dsDNA	SLE
Anti-proteinase 3	Wegener's granulomatosis
Anti-myeloperoxidase	Microscopic polyarteritis nodosa, Churg-Strauss syndrome
Anti-cardiolipin	Anti-phospholipid syndrome, SLE

Rheumatoid Factor

Rheumatoid factor (RF) is an antibody directed against the Fc portion of immunoglobulin (IgG) and is usually of IgM type. RF is detected by latex agglutination, nephelometry or enzyme linked immunoassay and the results should always be expressed in International Unit (IU) for ease of comparison between different laboratories or methods. Presence of RF in a patient with joint disease increases the probability of diagnosis of rheumatoid arthritis (RA). It is present in 75% to 85% of patients with RA and in 10% of children with juvenile arthritis. In a patient with established RA, its presence suggests a more aggressive disease. It is also present with lesser frequency in infections like malaria, leprosy and tuberculosis, malignancies and other autoimmune diseases like Sjögren's syndrome, SLE, etc. The prevalence of RF increases with age and geriatric population have a prevalence of approximately 20%. Thus, in elderly patients with vague joint pains, presence of RF should not lead to a diagnosis of RA. RF titres correlate poorly with activity of disease in RA, and therefore, there is no utility in repeating the test.

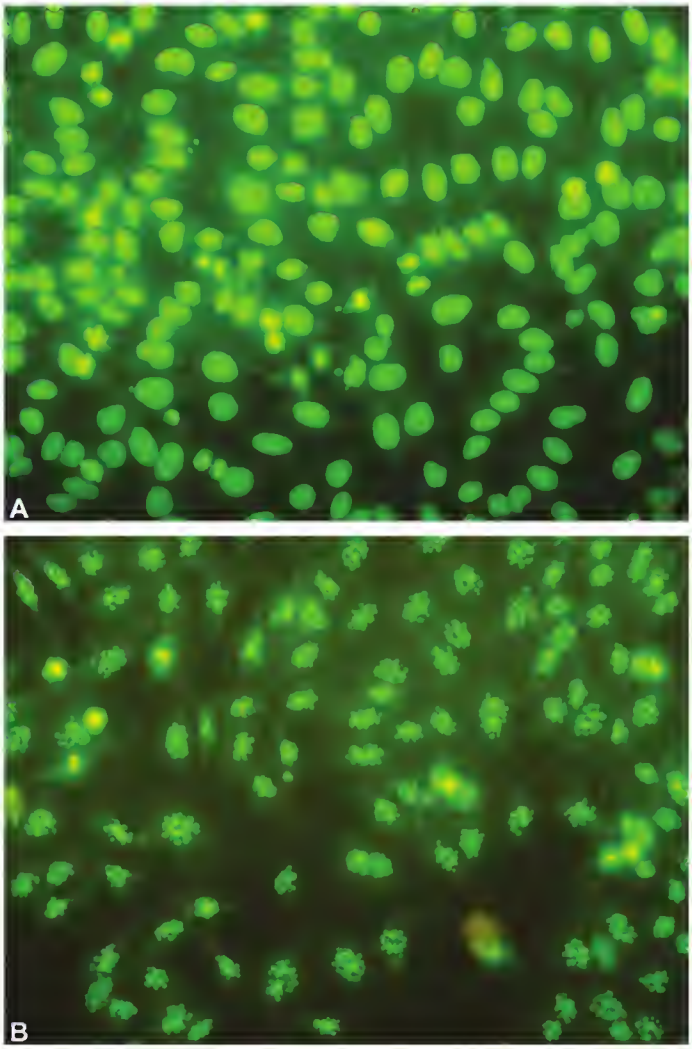
Anti Citrullinated Peptides Antibody (ACPA)

ACPA are a set of antibodies directed against citrullinated self peptides and are highly specific for a diagnosis of RA. Anti-cyclic citrullinated peptide (anti-CCP) is the most often used test and has a specificity of 95% and a sensitivity of 65-70%. In contrast to RF, it is rarely seen with other connective tissue diseases and infections. In early arthritis, presence of anti-CCP antibodies increases the likelihood of RA.

Antinuclear Antibody (ANA)

ANA is a heterogenous group of autoantibodies directed against components of nucleus including deoxyribonucleic acid, ribonucleic acid (RNA) associated proteins (nRNP, Sm, La, Ro), nucleolar proteins, centromere, etc.

The 'gold standard' for ANA detection is indirect immunofluorescence (IIF) assay using Hep2 cells (**Figures 1A and B**).



Figures 1A and B: Antinuclear antibody positivity on Hep2 cells by immunofluorescence microscopy. (A) Homogeneous pattern suggestive of antibodies to dsDNA and (B) Centromere pattern suggestive of limited systemic sclerosis.

The recently developed ELISA tests are inferior to IIF both in sensitivity and specificity. The IIF test also has the advantage that the fluorescence pattern can give an indication regarding the target antigen against which the antibody is directed. For instance, rim pattern suggests antibodies to dsDNA and is suggestive of SLE, while a centromere pattern is typical of patients with limited systemic sclerosis (**Figure 1B**). ANA is used as a screening test and its detection increases the likelihood of the diagnosis of a connective tissue disease in a patient with multisystem involvement. Further investigations, like anti-dsDNA antibodies, anti-Sm antibodies are needed to establish the specificity of the ANA present in the sera. ANA is also positive in other conditions, such as infection, malignancy, RA and juvenile idiopathic arthritis.

Antibodies to dsDNA

Antibodies to dsDNA are a hallmark of SLE. They are detected by IIF using *Crithidia luciliae*, Farr assay (liquid phase radio-immunoassay) or ELISA. *Crithidia luciliae* is a protozoan parasite of *Leishmania* family which has a prominent kinetoplast made of dsDNA. Anti-dsDNA titre is raised in about 60% of patients with SLE and has a good correlation with presence of lupus nephritis. Serial measurement can help in monitoring of the disease activity. However, a rise in the antibody titre alone does not warrant a change in the treatment which should be made in the context of clinical parameters.

Antibodies to Extractable Nuclear Antigens

Antibodies to extractable nuclear antigens (ENAs) comprise of antibodies to various RNA associated proteins. Each antibody has a specific disease phenotype associated with it and variable prevalence (**Table 2**). ENAs are detected using ELISA or immunoblotting. Since antibody titres do not correlate with disease activity, qualitative assays like immunoblot or line assays are as useful as quantitative assays like ELISA.

Table 2: Antibodies to Nuclear Target Antigens

Antibody	Disease	Prevalence
Anti-Sm	SLE	30%
Anti-nRNP	SLE	40%
	Mixed connective tissue disease	100%
	Rheumatoid arthritis	15% to 20%
Anti-Ro	Primary Sjögren's syndrome	60%
	SLE	30%
Anti-La	Primary Sjögren's syndrome	30%
	SLE	15%
Anti-centromere	Limited systemic sclerosis	50%
Anti-Scl 70	Diffuse systemic sclerosis	45%

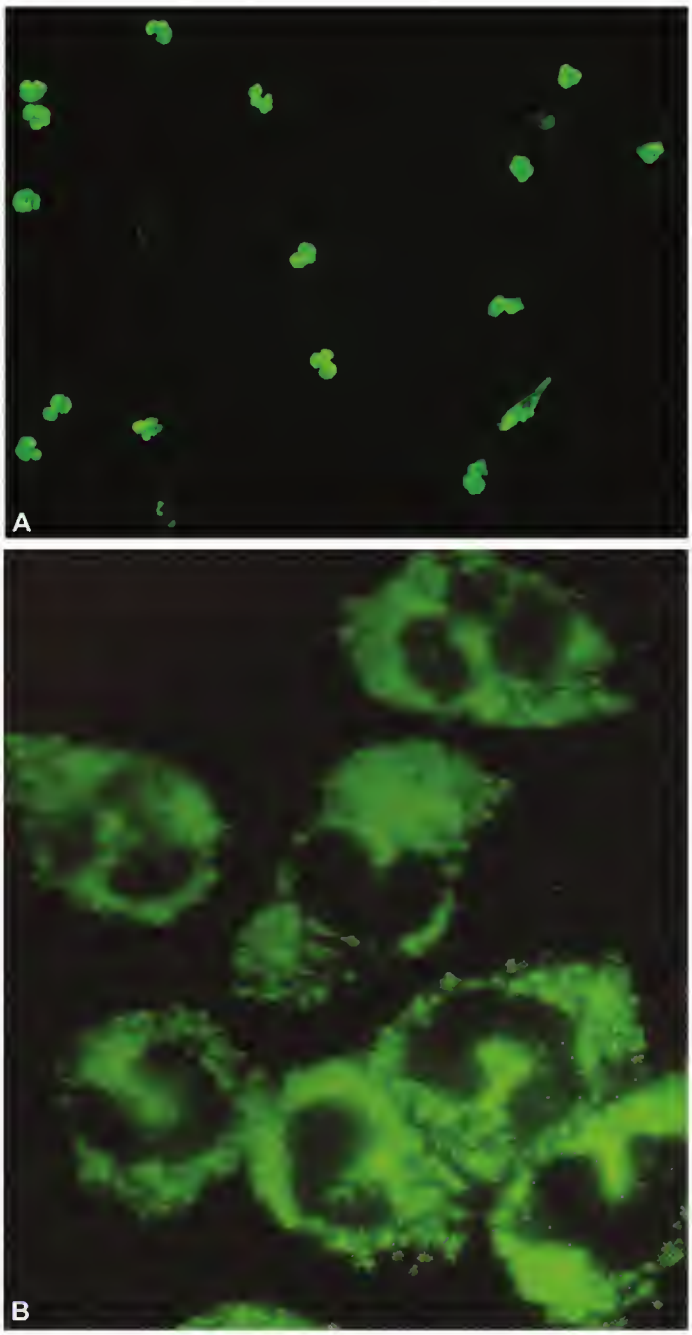
Antiphospholipid Antibodies

Presence of antibodies to phospholipids is mandatory for the diagnosis of antiphospholipid (APL) syndrome. Cardiolipin is the most commonly used substrate. IgG and IgM antibodies are measured by ELISA and the results are expressed as mild, moderate and marked elevation. IgA antibodies to cardiolipin can also be detected, but have less diagnostic value.

Anti-beta 2-glycoprotein 1 antibodies which are directed against a co-factor required for binding of cardiolipin are more specific for diagnosis and are detected by ELISA. Detection of anti-prothrombin antibodies may be used as a substitute for lupus anticoagulant assay but it has low sensitivity. Antibodies against other phospholipids, like phosphotidylserine, annexin-V, are not useful clinically.

Antibodies to Neutrophil Cytoplasmic Antigens

Anti-neutrophilic cytoplasmic antibodies (ANCAs) are serological markers of severe necrotising vasculitis affecting the small vessels and are seen in patients with Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyarteritis nodosa. ANCA is detected using IIF assay with human neutrophils as substrate. Two patterns of staining are recognised namely cytoplasmic (cANCA) and perinuclear (pANCA) (**Figures 2A and B**). The antigenic target of cANCA is proteinase 3 (PR3) which has specificity of 85-90% for diagnosis of Wegener's granulomatosis. pANCA is mainly



Figures 2A and B: ANCA positivity on neutrophil smear showing: (A) pANCA pattern; (B) cANCA pattern.

directed against myeloperoxidase (MPO) and is present in 60% of patients with microscopic PAN. pANCA or an atypical staining pattern is also positive in other diseases, like ulcerative colitis, RA, SLE, etc. However, the antigenic targets are variable (cathepsin G, lactoferritin, BPI, elastase, etc). Antibodies to MPO and PR3 are usually detected by ELISA and quantitative measurement of antibodies to PR3 is helpful in monitoring disease activity in patients with Wegener's granulomatosis. ANCA is not useful in a patient with classical polyarteritis, Takayasu's arteritis, etc.

ORGAN-SPECIFIC AUTOANTIBODIES

The characteristic autoantibodies found in the organ-specific autoimmune diseases along with their prevalence is given in **Table 3**. Most of these can be detected by IIF assays using appropriate tissue substrates or by ELISA. Quantitative titres are not useful in the management of these conditions and the IIF tests have adequate sensitivity to assist in diagnosis. In many of these diseases, detection of antibody only suggests an autoimmune aetiology and is not required for diagnosis. For instance, the diagnosis of Graves' disease is based only on clinical findings and hormone levels. Antibodies to insulin, GAD65 and IA-2 though present years before onset of type 1 diabetes mellitus are not useful in diagnosis.

Table 3: Organ-Specific Autoantibodies

Disease	Antibodies	Prevalence
Hashimoto's thyroiditis	Thyroid microsomal antibodies, antibodies to TPO	85% to 90%
Graves' disease	Antibodies to TSH receptor	90% to 95%
Type 1 diabetes mellitus	Antibodies to Islet cells, insulin, GAD65, IA2	75%
Pernicious anaemia	Antibodies to parietal cells	85% to 90%
Chronic active hepatitis	Antibodies to smooth muscle (actin) Antibodies to liver-kidney microsomes	Type I CAH Type II CAH
Primary biliary cirrhosis	Antibodies to mitochondria (pyruvate dehydrogenase)	90%
Coeliac disease	Anti-endomysial antibodies, antibodies to tissue transglutaminase	95%
Immune thrombocytopaenia	Antibodies to platelets (GpIIb/IIIa)	80% to 90%
Autoimmune haemolytic anaemia	Antibodies to RBCs (Rh antigen)	95%
Myasthenia gravis	Antibodies to acetylcholine receptor	70% to 75%
Goodpasture's syndrome	Antibodies to basement membrane	60% to 70%

INVESTIGATION FOR IMMUNODEFICIENCY DISEASES

Immunodeficiency diseases are broadly classified into T-cell defect, B-cell defect, complement deficiency or phagocytic defect. Laboratory investigation of a patient with immunodeficiency is a step-wise process:

- Exclusion of secondary causes
- Screening tests to detect common diseases
- Second level tests to confirm an immunodeficiency disease
- Advanced test for diagnosis of rare immunodeficiency diseases.

Screening Tests

These are simple, easily available tests that help in excluding a major immunodeficiency state. These include: immunoglobulin levels and B-cell count for B-lymphocyte defects; lymphocyte count and CD4/CD8 numbers by flow cytometry, delayed type hypersensitivity test with multiple antigens (PPD, tetanus toxoid, *Candida*, *Trichophyton*) and chest radiograph for thymic shadow for T-lymphocyte defects; phagocyte morphology, IgE levels and NBT reduction test for neutrophil function defects; and CH50 and serum C3, C4 levels for complement defects.

Second Level Tests

If an underlying immunodeficiency is suggested or there is high index of suspicion, additional tests are performed. The tests include iso-haemagglutinin titres, antibody response to tetanus toxoid for B-lymphocyte defects; lymphoproliferative assay to mitogen and recall antigens for T-lymphocyte defects; chemotaxis, superoxide production and bactericidal assay for neutrophil function defects; and AH_{50} for defects of complement function.

Advanced Tests

These are performed to establish the exact cause of the immunodeficiency disease. The exact genetic defect has been identified in many conditions, such as mutations in btk, CD40 and CD40L gene in B-cell defects, interleukin (IL)-2 receptor gamma chain, and TCR signalling molecules in T-cell defects. in NADPH oxidase system in neutrophil defects and serum complement C5-9 complex in complement deficiencies and gene mutation analysis can provide an exact diagnosis.

All these tests need to be performed using appropriate age-matched controls, especially for cellular assays as the immune system has different maturity at different ages. The normal reference values of immunoglobulins for all age groups should be established for each population group. **Table 4** provides a guideline for evaluating immunoglobulin results, since antibody deficiency is present in more than half the children with immunodeficiency.

Tests for Allergic Diseases

Although allergic reaction is mediated by IgE and, total IgE levels are elevated in patients with allergic diathesis, this is not of diagnostic value. Antigen-specific IgE measured by radio-allergosorbent assay helps to identify the specific offending allergens. The skin or prick test is commonly used for identification of the offending agent in allergy prone individuals. A large number of probable allergens are injected intradermally along with saline as a negative control and

histamine as a positive control. The immediate wheal and flare response is observed and allergens giving positive reaction are used for de-sensitisation programme.

Table 4: Immunoglobulin (Ig) Levels as Clue to Diagnosis of Immunodeficiency Diseases

Ig Levels	Diagnosis
Levels of all immunoglobulins reduced	X-linked agammaglobulinaemia, severe combined immunodeficiency, intestinal lymphangiectasis, common variable immunodeficiency
Only IgA reduced	Selective IgA deficiency
IgM: normal or increased IgA, IgG: reduced	X-linked hyper IgM syndrome
IgG, IgA, IgM: normal IgG subclass reduced	Selective deficiency of IgG subclass
Transient reduction in IgG, IgA	Transient hypogammaglobulinaemia of infancy

The patch test in which allergen is applied to the skin is useful for identifying cases of contact dermatitis. All provocative tests should be done under close supervision as sometimes they can aggravate the symptoms.

PRESENCE OF ABNORMAL IMMUNOGLOBULIN OR PARAPROTEIN

A malignant clone can produce hypergammaglobulinaemia in some B-cell malignancies. Serum electrophoresis, in which proteins are separated, based on their size, is helpful in their diagnosis. Normal serum shows five distinct bands, of albumin, α_1 globulin, α_2 globulins, β globulins and γ globulin of which albumin has the fastest mobility. The normal γ globulin band is replaced by a single sharp band called the M peak in multiple myeloma. Other diseases, like primary amyloidosis, Waldenstrom's macroglobulinaemia and monoclonal gammopathy of uncertain significance can also give an M band.

In 10% to 15% of cases of multiple myeloma no M peak is seen as only light chains are produced and immunofixation has to be performed. Immunofixation can also help in typing of paraprotein.

In conclusion, a wide array of tests are available for evaluation of immunological diseases. However, they should be used judiciously in the appropriate clinical setting to get best help from the tests.

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5.6 Pharmacological Manipulation of the Immune System

Mitali Chatterjee

Diseases with an immunological basis occur as a result of aberrations of the immune response. Therefore, an effective drug for these diseases should have the ability to modulate the immune response by inducing immunosuppression, tolerance or immunostimulation. Such manipulations are used to prevent allograft rejection, boost the immunosurveillance against cancers and treat allergic conditions.

INDUCTION OF IMMUNOSUPPRESSION TO LIMIT GRAFT REJECTION

Drugs that induce immunosuppression and result in an effective organ transplant can act at one or multiple steps involved in T cell activation and proliferation pathways.

Corticosteroids

The advent of corticosteroids in the 1960s revolutionised the arena of organ transplantation. Steroids are classical immunosuppressants that form the mainstay of treatment. They act to dampen antigen presentation by APCs. Steroids bind to steroid receptors, are transported to the nucleus and bind to the glucocorticoid response elements to regulate the transcription of many genes. Their effects on the immune system include blocking of T cell activation cascade, downregulation of interleukin (IL)-1 and IL-6 genes, and through indirect mechanisms IL-2 production. Glucocorticoid receptor complexes also increases Iκβ expression, curtailing NF-κβ which causes enhanced apoptosis of activated T cells. Since long-term steroids administration has serious adverse effects, which may even be life-threatening, introduction of newer agents and steroid-sparing protocols have been developed.

Azathioprine, Mizoribine and Mycophenolic Acid

Antiproliferative agents such as azathioprine inhibit *de novo* purine biosynthesis, prevent mitosis and consequently proliferation of rapidly dividing cells, including T and B lymphocytes. The purine salvage pathway in lymphocytes is less active than in other rapidly dividing cells. Hence, these cells are more dependent on the *de novo* synthesis of DNA and RNA building blocks. Inhibition of *de novo* nucleoside synthesis achieves a milder immunosuppression than with cyclosporine A (CsA) or rapamycin and it also inhibits many other cell types. Newer anti-proliferative agents are mycophenolate mofetil and rapamycin. Mycophenolate mofetil selectively prevents proliferation of activated T lymphocytes by inhibiting purine synthesis and non-competitive inhibition of the type II isomer of inosine monophosphate dehydrogenase (IMPDH). Rapamycin inhibits graft rejection by blocking IL-2 activation and phosphorylation of 70 S6 kinase inhibiting progression of cells from G to S phase.

Cyclosporine and Tacrolimus (FK 506)

The introduction of CsA, a calcineurin inhibitor which inhibits normal T cell signal transduction was a great leap forward for transplantation. However, due to the narrow therapeutic range coupled with high intra- and inter-patient variability of CsA, it was replaced by a newer calcineurin inhibitor, tacrolimus, which also inhibits IL-2 but is 10 to 100 times more potent than CsA. The antiproliferative effect of calcineurin inhibitors is mediated by its binding to an immunophilin (cyclophilin for cyclosporine and FKBP12 for tacrolimus); they block phosphatase activity, prevent induction of cytokine genes, importantly IL-2 and halt cell cycle progression of T cells. These compounds are hydrophobic in nature and easily penetrate plasma membranes. The introduction of these agents caused dramatic alterations in the outcome of renal transplantation and has brought down the frequency of acute rejection episodes from 85% to 50%. The occurrence of post-transplant diabetes mellitus, especially when combined with steroids and associated nephrotoxicity, are important complications associated with both tacrolimus and cyclosporine.

Sirolimus (Rapamycin)

This is another fungal metabolite, which is structurally related to FK-506 and binds to same proteins. However, its mechanism differs from that of FK-506, since it prevents phosphorylation of a p70 kinase in the CD-28 co-stimulatory and IL-2R signal transduction pathway. Rapamycin blocks T cell proliferation during late G1 and pre-S phase of the cell cycles. Thus, rapamycin inhibits late signals in T cell activation while cyclosporine and FK-506 inhibit an early signal in T cell receptor signal transduction pathway and these compounds have synergistic effect when given together.

Anti-Lymphocyte Globulin

More general immunosuppression is achieved by use of anti-lymphocyte globulin, which has an overall lymphocyte depleting property. This has been licensed for a long time and was widely used prior to the availability of the more specific agents like OKT3 and anti-IL 2R antibodies. A disadvantage of using polyclonal ATG is the general recommendation to administer the medication via central venous access.

BLOCKING THE T CELL RECEPTOR AND CO-RECEPTOR

The OKT3 was the first mouse antibody licensed for use in humans; it is directed against the CD3 antigen that is closely associated with the T cell receptor. The principal mechanism of action of OKT3 is inhibition of cell-mediated immunity by binding to CD3 and promoting phagocytosis or complement mediated lysis of CD3+ T cells. Anti IL-2 receptor antibody prevents T cell activation by blocking the binding of IL-2 to activated T cells. This approach would prevent T cell activation and a monoclonal murine IgG2 directed against the ε chain of the pentapeptide CD3 complex (OKT3) has been approved for human use. However, it needs to be administered in large doses to achieve effective T cell silencing and at this dose the toxicity is considerable. Hence, this drug is only used to treat acute rejection.

Another approach is the use of humanised monoclonal antibodies against the IL-2 receptor (anti-CD25), such as daclizumab and basiliximab. These target only activated T cells, while sparing resting T cells. Targeting costimulatory receptor/ligand pairs is a viable alternative for triggering immunosuppression. Antibodies to the CD40/CD40 ligand have been shown to induce long-term graft survival by inhibiting release of Th1 cytokines interferon (IFN)-gamma, IL-2 and IL-12 and concomitant up-regulation of Th2 cytokines. Inducing blockade of the B7/CD28 costimulation pathway using CTLA-4 Ig which binds to CD28 also prevents activation of T cells. A long-term goal in transplantation research is to develop therapies that would induce graft-specific tolerance for which alloreactive T cells would be targeted, leaving other T cells competent to function effectively.

ROLE OF IMMUNOTHERAPY IN CANCER

In contrast to the graft situation, immunotherapy in cancer involves stimulation of the immune system for the elimination of residual tumour. It has been proposed that cancers evolve from a chronic inflammatory environment which suppresses the cell-mediated immunity and encourages tumour angiogenesis. The immune response directed at the tumour can be enhanced by a variety of approaches including vaccines, infusion of T cells, or cytokines. These approaches either increase the number of effector cells and/or increase production of soluble mediators, such as lymphokines.

VACCINES

Specific tumour antigens can be administered as vaccines. However, the inability of these antigens to stimulate a strong T cell response limits the utility of such vaccines. The immunogenicity of these antigens can be augmented by a variety of immunological approaches that are not being discussed here. In fact dendritic cell vaccines using monocyte-derived DCs pulsed with tumour antigens have been evaluated in early clinical trials using HER-2/neu peptide in case of metastatic breast carcinomas and gp100, MART-1 and MAGE-3 antigens in stage IV melanomas. In melanomas, heat shock protein gp96, gp100, tyrosinase, and MAGE have been used as vaccines with adjuvants such as BCG. Responses have been modest with some instances of complete or partial remissions or prolongation of survival. The immunogenicity of tumours is also enhanced by infecting irradiated tumour cells with viruses transduced with genes expressing cytokines (e.g. IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF), or genes for HLA molecules or co-stimulatory molecules. These injected tumour cells undergo apoptosis or are destroyed by inflammatory responses and the shed antigens are processed by dendritic cells and presented to T cells. The disadvantage of tumour cell-based vaccines are that antigen is prepared from tumour cells extracted from surgical resection or biopsy specimens and, hence, has to be individualised for each patient.

Viral vectors and naked DNA in the form of plasmids encoding tumour antigens are administered to muscle cells. A prime boost approach has been applied where the patient is first immunised with vaccinia virus, encoding the gene for carcinoembryonic antigen (CEA), followed by CEA protein. Clinical responses have been limited, but various modifications of these strategies continue to be explored.

MONOCLONAL ANTIBODIES

Monoclonal antibodies can cause death of tumour cells both directly by apoptosis and blocking of growth factor receptors or indirectly by antibody-dependent cell-mediated cytotoxicity. An example of antibody-dependent cell-mediated cytotoxicity is that of rituximab, a chimeric antibody targeting CD20 that is expressed in B cell malignancies. The antibody binds to CD20 on B cells and to Fc receptors present on monocytes, macrophages, and natural killer cells leading to tumour cell destruction. Monoclonal antibodies may also bind complement and trigger the complement cascade, causing complement-dependent cytotoxicity. The end result is a membrane attack complex that literally perforates the cell membrane, causing cell lysis and death.

Successful therapy with monoclonal antibodies is handicapped by the qualitative and quantitative heterogeneity in distribution of antigens on malignant cells. The poor blood flow to tumours may not permit adequate concentrations of the systemically delivered antibodies to reach tumour cells. The presence of high interstitial pressure within the tumour also prevents binding of monoclonal antibodies. Since most monoclonal antibodies are of rodent origin, there exists the possibility that the host will mount an immune response to these antibodies. This response not only decreases the efficacy of monoclonal antibody therapy, but also eliminates the possibility of re-treatment. Despite these obstacles, there has been tremendous success in the clinical application of monoclonal antibodies in haematological malignancies and solid tumours (**Table 1**).

CYTOKINES

Cytokines regulate the innate immune system and function in cascades. Thus, clinical trials of individual cytokines have rarely been found effective. Some of the individual cytokines that have been tested and found to be beneficial are mainly for the treatment of haematological malignancies or immunogenic tumours and include IL-1 β, Interferon-α, IL-12 and GM-CSF.

Interferon

IFN-α is a family of molecules that up-regulate genes for MHC class I, tumour antigens, adhesion molecules and is additionally an anti-angiogenic agent. It promotes B and T cell activity, stimulates macrophages, dendritic cells and upregulates Fc receptors. The benefit of IFN-α therapy in renal cell carcinoma is small but consistent and it is now considered as second-line therapy. It is also effective in metastatic melanoma where it enhances disease-free and overall survival. However, toxicity remains a major problem and patients have to be adequately hydrated and given treatment for the associated depression and decreased energy levels.

Interleukin-2

IL-2 is a T cell growth factor that binds to a specific tripartite receptor on T cells. Patients treated with high doses of IL-2 have shown clinical responses in renal cell carcinoma and melanoma. IL-2 has also shown activity in non-Hodgkin's lymphoma, leukaemias and lymphomas, post-stem cell transplant. However, high-dose therapy with IL-2 results in severe toxicity akin to a state of septic shock. Hypotension, low systemic vascular resistance, high cardiac output, grade 3/4 haematological, hepatic and renal toxicity, and pulmonary oedema have all been

Table 1: Monoclonal Antibodies Approved for Cancer Therapy

Name	Target site	Indications
Alemtuzumab	CD52	CLL
Bevacizumab	VEGF (receptor for vascular endothelial growth factor)	Metastatic colorectal cancer; non-small cell lung cancer, pancreatic cancer, breast and ovarian cancer
Cetuximab	HER1, receptor for epidermal growth factor (EGFR)	Colorectal, head and neck cancers
Edrecolomab	Glycoprotein 17-1 A	Colorectal cancer
Epratuzumab	CD22	Indolent, aggressive non-Hodgkin's lymphoma
Gemtuzumab ozogamicin	CD33	Relapsed AML
Ibritumomab tiuxetan	CD20 (conjugated with Indium-111 or Yttrium-90)	Non-Hodgkin's lymphoma
Panitumumab	receptor for epidermal growth factor	Colorectal cancer
Pertuzumab	Inhibits dimerisation of HER-2 with EGFR	Lung cancer, metastatic breast carcinoma
Rituximab	CD20	Lymphomas
Tositumomab	CD20 (conjugated with I^{131})	Non-Hodgkin's lymphoma
Trastuzumab	HER2, receptor for epidermal growth factor	Metastatic breast carcinoma
Vitaxin	Vascular integrin α(v)beta(3)	Solid tumours

documented but are nearly always reversible. A similar scenario was recently reported in a phase I trial of the anti-CD28 MAb RGN 1412; CD28, a superagonist and activator of T cells triggered by a cytokine storm resulting in a 'systemic inflammatory response syndrome' or SIRS.

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

GM-CSF has been approved for use in stem cell and bone marrow transplantation to aid reconstitution of the myeloid series. In patients with stage III and IV melanoma, chronic, intermittent GM-CSF following surgical resection improved long-term survival and treatment was well tolerated.

Interleukin-12 (IL-12)

IL-12, a heterodimeric protein that promotes NK and T cell activity, is a growth factor for B cells. IL-12 given alone has minimal therapeutic benefit but has shown utility as a vaccine adjuvant as it can induces a strong T helper 1 response. IL-12 boosts the response to peptide vaccines in patients with resected stage III and IV melanoma.

FLt3L Ligand (FLt3L)

FLt3L stimulates progenitor cells in the bone marrow resulting in an increase in DCs. Patients with HER-2/Neu overexpressing breast or ovarian cancers were administered FLt3L which showed evidence for enhanced HER-2/Neu T cell response, indicating its immunomodulatory potential.

Immunotherapy may be the next great hope for cancer treatment. While monoclonal antibodies, cytokines, and vaccines have individually shown promise, it is likely that the best strategy to combat cancers would be a multipronged approach since cancers have multiple mechanisms of preventing the activation of and evading an immune response. Through these concerted efforts, our ultimate achievable goal may be a durable anti-tumour immune response that can be maintained over the course of a patient's life-span.

TREATMENT OF ALLERGIC DISEASES

Allergic diseases including asthma are emerging public health problems. They are characterised by an abnormal immune response to ubiquitous and generally innocuous environmental antigens which cause disease in atopic individuals. Immediate phase responses are usually followed by the development of late phase reactants and eosinophilic inflammatory processes driven by the production of Th2 lymphocytes of IL-4, IL-5, IL-9 and IL-13.

Conventional treatment of allergic conditions includes antihistaminics and anticholinergics to relieve symptoms along with corticosteroids to suppress the allergic inflammatory processes. However, while this approach effectively controls symptoms, discontinuation of these medications results in reappearance of symptoms on re-exposure to the offending allergens. Therefore, these therapies have a limited capacity to alter the natural course of allergic diseases and the underlying immunological processes remain uncorrected.

Current therapies for allergic conditions are aimed at neutralising the allergic response. Allergen-based immunotherapy aims at inducing a shift in helper T cells from Th2 cytokines (IL-4 and IL-5) towards production of Th1 cytokines, IFN-γ and IL-12, which control IgE production. It is accompanied by induction of T-regulatory cells via an enhanced release of IL-10 which induces long-term hyporesponsiveness to the allergen. The IgG blocking antibodies that develop, compete with IgE for binding to allergens and prevent aggregation of IgE complexes with the α chain of the high affinity IgE receptor on mast cells. Collectively, this prevents release of mediators of inflammation from mast cells and basophils, prevents infiltration by inflammatory cells, and decreases the number of mast cells.

Another approach is to induce allergic specific tolerance so that exposure to a particular allergen fails to produce symptoms. Immunotherapy involves administering increasing concentrations of extracts of allergens; this induces hypo-sensitisation or desensitisation and attenuates symptoms for several years even after being discontinued. The potential risk involved of fatal anaphylaxis, particularly during the up-dosing phase, necessitates that allergen immunisation should always be conducted in a hospital setting. To overcome this problem, 'hypoallergic naturally occurring' allergens prepared from plants and trees have been tested and found to be effective in

minimising the risk of anaphylaxis. An alternative approach is administration of 'recombinant' allergens, wherein the cysteine residues have been removed by site directed mutagenesis. Allergen immunisation is carried out by various approaches. By subcutaneous immunotherapy (SCIT), wherein patients are sensitised to one or more environmental allergens, for 3 to 5 years of SCIT, can give long-term remission for 3 to 5 years following discontinuation of SCIT. The alternative approach, sublingual immunotherapy (SLIT), has the advantage of route of administration but unlike SCIT, long lasting immunomodulating effects are yet to be established. SLIT simply helps to reduce incidence of rhinitis and medication usage. A third approach is DNA vaccines which induce a strong Th1 response. This can be further enhanced by administration of immunostimulatory sequence of CpG motifs, such as GACGTC, which is the ligand for Toll like receptor-9 on dendritic cells. This leads to activation of signalling pathway of MAPK, NF-kappaB, cytokines (IFN-α, IFN-β, IL-10, IL-12) along with co-stimulatory molecules (e.g. CD409, B7); collectively this helps to shift away from a Th2 pro-allergic response towards a Th1 response. Fusion proteins, e.g. IL-12 fused with the prototype allergen OVA also potentiate Th1-based immune response and reverse established allergic responses. Other alternatives include blocking IgE or its synthesis and interruption of the Th2 dependent allergic cascade. This has been achieved using omalizumab, a recombinant humanised monoclonal antibody against IgE, which not only neutralised IgE, but also inhibited IgE production in B cells and decreased expression of FceR1 on basophils. Importantly, it did not permit activation of mast cells, basophils or monocytes rendering it non-anaphylactogenic. Inhibition of IL-4 and IL-5, and treatment with soluble recombinant IL-4 receptor has been reported to improve severe atopic asthma.

IMMUNOTHERAPY FOR AUTOIMMUNE DISEASES

Conventionally, treatment for autoimmune diseases was based on therapies that reduced inflammation and induced non-specific immunosuppression. However, as autoimmune diseases are chronic, prolonged use of anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs, or corticosteroids, translates into a shorter life expectancy and a poor quality of life. The improved understanding of the immunopathogenesis of autoimmune diseases has led to a shift towards targeting specific signalling molecules associated with the adaptive immune response. The growing number of targeted therapeutics now includes monoclonal antibodies, soluble receptors and molecular mimetics. Possibly the greatest success story has been neutralising TNF-α by infliximab, the humanised monoclonal antibody against TNF-α in the treatment of rheumatoid arthritis. This principle of TNF-α blockade has also been extended for Crohn's disease, ankylosing spondylitis, psoriatic arthritis and psoriasis and has also led to the development of other TNF-α blockers (**Table 2**). Although the long-term safety is satisfactory, it must be kept in mind that anti-TNF-α treatment has been associated with an increased incidence of tuberculosis, production of anti-nuclear and anti-double stranded DNA antibodies.

Targeting B cells decreases production of autoantibodies and also depletes B cells, thereby decreasing the proportion of antigen presenting cells. Rituximab is a human-mouse chimeric antibody specific for CD20, a B cell antigen that rapidly depletes B lymphocytes. It was initially approved for the treatment of B cell lymphomas but has been effectively applied in patients with idiopathic thrombocytopaenic purpura, autoimmune

Table 2: Monoclonal Antibodies that are Approved or Being Evaluated for Use in Autoimmune Diseases

Disease	Biological effect	Antibody	Binding epitope
Rheumatoid arthritis	Auto-antibodies, immune complexes	Denosumab Infliximab Lenercept Etanercept Alemtuzumab Abatercept Anakinra Rituximab Anti-IFNg	Nuclear factor kappa B TNF Soluble TNF p55 receptor Soluble TNF p75 receptor CD52 CTLA-4Ig IL-1RA CD20 IFN-γ
Type 1 diabetes mellitus	Decreased insulin production	Anti-CD3 (OKT3)	CD3
Systemic lupus erythematosus	Auto-antibodies cause complement mediated lysis, Type-III hypersensitivity reactions	Rituximab Anakinra BG9588, IDEC 131	CD20 IL-1RA CD154 CD154
Multiple sclerosis	Myelin destruction	Alemtuzumab Natalizumab	CD52 Alpha-4 integrin
Psoriasis	Activation of T cells in dermis	Infliximab Alefacept Efalizumab	TNF LFA3-Ig CD11a
Juvenile rheumatoid arthritis	Damage of synovium	Etanercept Anakinra Tocilizumab	Soluble TNF p75 receptor IL-1RA IL-6
Crohn's disease	Damage of intestinal mucosa	Infliximab Natalizumab	TNF Alpha-4 integrin

ND = Not defined; IFN = Interferon-gamma; TNF = Tumour necrosis factor; IL = Interluekin.

haemolytic anaemia, vasculitis, dermatomyositis, rheumatoid arthritis, Sjogren's syndrome and systemic lupus erythematosus. However, there are reports of progressive multifocal leukoencephalopathy following its use. Other biologicals targeting CD20 include MAbs ocrelizumab, ofatumumab, hA20 and TRU-015 that also act by depleting B cells. An alternative approach to B cell depletion is modulation of B cell function by targeting CD22, thus, preventing B cell activation. Antibodies to CD3 are also being tried to induce immune tolerance to both allo- and autoantigens, the goal being to achieve self-tolerance. The CD3 antibodies are showing promising results in type 1 diabetes (**Table 2**).

The limitation of the targeted therapies is that despite their high selectivity for immune cell subsets or receptors, they need to be applied at multiple intervals to retain their effectiveness. The risk of excessive immunosuppression remains a concern. Therefore, it is currently recommended that for long-term improvement, targeted therapy should be coupled with conventional anti-inflammatory agents.

Taken together, our enhanced understanding of the immune system in the last two decades has led to the availability of a large number of novel treatments and strategies to tackle immune based diseases. However, our inability to date, to achieve complete success by immunotherapy indicates the complexities of the immune response that cannot be tackled by a single agent but instead by adopting a multipronged approach.

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5.7 Immunology of Organ and Haematopoietic Stem Cell Transplantation

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Transplantation is the treatment of choice for functional failure of many organs. The success of transplantation depends on the degree of histocompatibility between donor and recipient, among other factors. The genetic difference between recipient and the donor is determined by a set of immune response genes clustered together as human leucocyte antigen (HLA) system. These antigens play an important role in immune discrimination between self and non-self (foreign) molecules.

MAJOR HISTOCOMPATIBILITY COMPLEX

The blood group system (A, B, O), the major histocompatibility complex (MHC) and the minor histocompatibilty antigens (mHA) that include the male specific H-Y antigen system constitute the histocompatibility system in humans. The MHC of man, the HLA system, is located on the short arm of chromosome 6 extending over approximately 4 megabases of DNA. The MHC molecules bind peptide fragments derived from protein antigens (viruses, bacterial peptides, mismatched transplant antigens, etc.) and display them on the surface of antigen presenting cells (APCs) evoking effector responses upon recognition by the T-cell receptor (TCR).

The four inherent features of the MHC are the extraordinary high polymorphism of its genes at the population level, tight linkage among its various loci, non-random association of HLA alleles and its multi-peptide binding ability making it an important immune response control system. The major clinical role of HLA testing remains in the area of donor selection in organ and stem cell transplantation.

GENETICS OF HLA

The human MHC gene cluster contains three distinct groups of loci, a centromeric *'class II region'* which has HLA-DP, DQ and DR loci, a telomeric *'class I region'* that contains the classical HLA-A,B,C and a central 'non-HLA' or *'class III region'* which contains genes whose products are involved in the complement cascade (C2, C4 and properdin factor Bf) and various non-immunological functions (**Figure 1**). Both class I and II gene products show important differences in structure, function and tissue distribution. Matching donors and recipients for HLA-A, B and C for haematopoietic stem cell transplantation (HSCT) loci of class I and of HLA-DR/DQ loci in the class II region during organ and bone marrow transplantation is critical to the survival of a graft.

HLA Class I Genes

HLA class I molecules are expressed on all nucleated cells. Of the 35 loci that have been described so far, HLA -A, -B and -C are the most important. Using tools of molecular biology and DNA typing methods, 238 alleles have been identified in locus

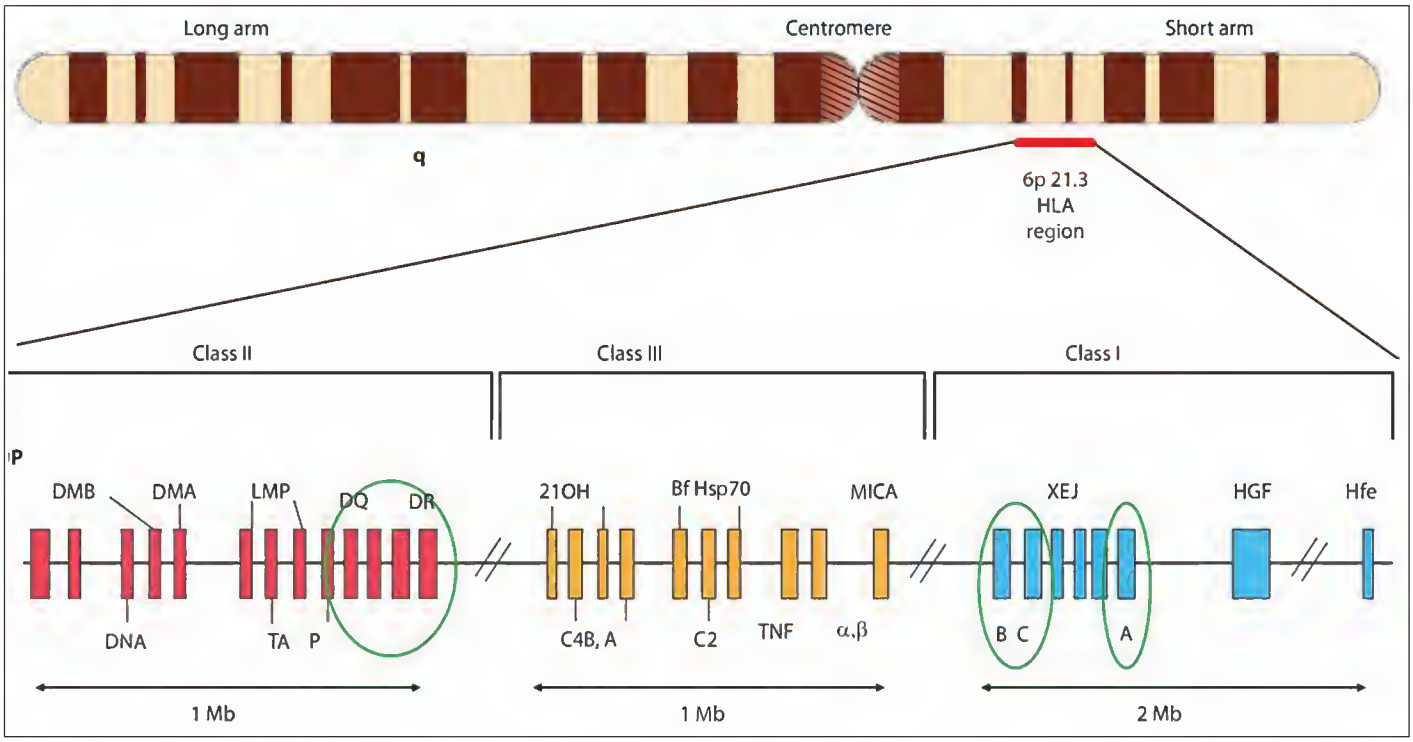


Figure 1: Human major histocompatibility complex (MHC) with chromosomal location and gene map showing multiple genes on the short arm of chromosome 6 (6p21.3). The two way array shows the genetic distance covered by the respective regions on the chromosome. The circled loci are highly polymorphic and are important for donor-recipient matching in the transplantation context. Note that MICA (MHC class I related chain A) is situated in close proximity to the HLA-B locus.

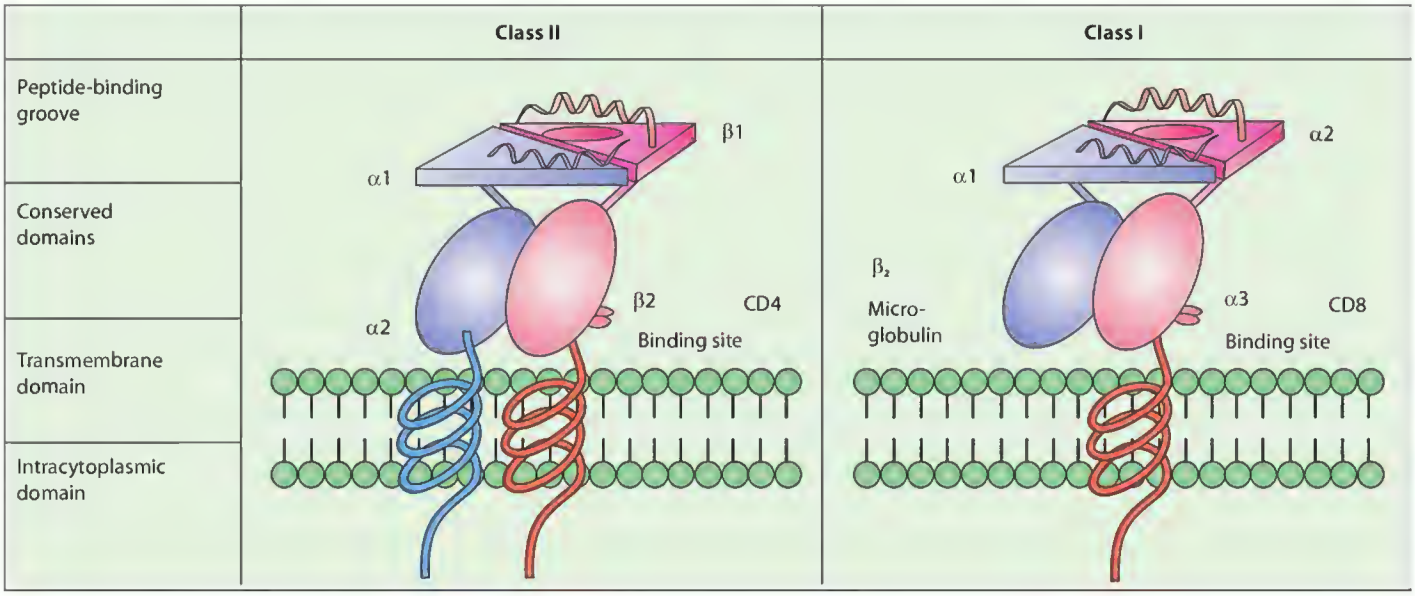


Figure 2: Schematic view of HLA class II and class I molecular structures showing the peptide binding cleft formed between α1 and β1 domains in case of class II and α1 and α2 domains in case of class I molecules. The membrane proximal domains (α2, β2 of class II and β2m and α3 of class I) are conserved and non-polymorphic.

A, 451 in locus B, and 238 in locus Cw. These molecules are heterodimeric glycoproteins consisting of an MHC encoded alpha or heavy chain and non-MHC encoded light chain (beta-2 microglobulin) (**Figure 2**). The extracellular portion of the heavy chain is folded into three globular domains, α1, α2 and α3 and associates noncovalently with the β2 microglobulin (β2m). X-ray crystallography of class I molecule has revealed that the region distal from the membrane is formed by α1 and α2 domains which take part in antigen binding. Functionally, MHC class I molecules bind to CD8 co-receptor molecules on the T-cells and therefore, present non-self-antigens to CD8+ T-cells. MHC class II molecules bind to CD4 co-receptors molecules on T-cells and hence, they present antigen to CD4+ helper T-cells.

HLA Class II Genes

The HLA-class II region of the human MHC has at least six subregions termed DR, DQ, DO, DN, DM and DP. They are expressed as heterodimers on the cell surface and are composed of an α (alpha) gene and a β (beta) chain that traverse the plasma membrane (**Figure 2**). Their tissue distribution is restricted to specific cells of the immune system involved in antigen presentation (APCs), namely B lymphocytes, macrophages, monocytes, epithelial cells, dendritic cells, Langerhan's cells and Kupffer cells. Currently, 438 DRB1, 71 DQB1 and 59 DPB1 alleles can be recognised using DNA typing methods of polymerase chain reaction and oligonucleotide probes.

Class III Genes (Central Genes)

At least 39 genes have now been located in a 1000 kb stretch of DNA within the class III region interposed between class I and class II regions. This includes the complement genes C2, C4 and Bf (factor β), the TNF-α and TNF-β genes and the Hsp 70 (heat shock protein) genes.

NOMENCLATURE OF HLA

In HLA nomenclature system colons (:) are introduced into the allele names to act as demiliters of separate fields. Thus, the allele HLA-A*02010101 is designated as HLA-A*02:01:01:01, where the first 2 digits following the star sign represent the HLA allele family, which often corresponds to broad serological HLA antigen (in this case HLA-A2). The 3rd and 4th digits correspond to the order in which the sequences were determined, 5th and 6th digits the synonymous substitutions in coding region and 7th and 8th digits the variations in introns or untranslated regions.

POLYMORPHISM AND INHERITANCE

An individual inherits two alleles of each of the above loci, one each from either parent. A complete set of alleles on the same chromosome is usually inherited (a *haplotype*) and the two HLA haplotypes in an individual derived after family testing constitute the *genotype*; the total HLA antigen profile is the *phenotype*. Siblings in a family have a 25% chance of being HLA-identical, 50% chance of being HLA-haploidentical (sharing one parental haplotype only) and 25% chance of being HLA-unidentical (**Figure 3**).

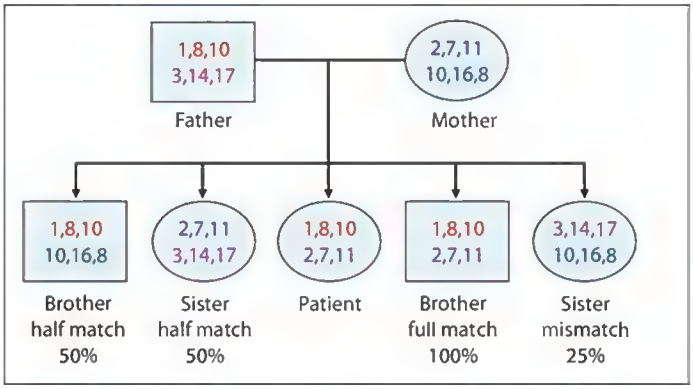


Figure 3: Segregation of HLA haplotypes in a family. The sibs inherit one haplotype from each parent and accordingly four different haplotypic combinations are possible. In this case, the patient is HLA-identical with her younger brother, HLA-unidentical with her younger sister and shares only one haplotype (haplo-identical) with her elder brother and sister.

SELECTION OF OPTIMAL DONORS

The MHC is the major barrier in selection of HLA matched donors for patients requiring solid organ or HSCT. The probability of finding a 100% matched donor is higher among the family members, because of the haplotypic inheritance pattern of the MHC. Four main donor categories are considered for HSCT: (1) HLA-identical sibling; (2) family donors other than siblings-defined by extended family testing, and who share HLA-A,B,C,DR and DQ alleles; (3) HLA-identical cord blood following antenatal testing; and (4) the unrelated HLA matched donors obtained through marrow registries.

The best HSCT results are seen in patients with a genotypically HLA-identical sibling. The probability of finding such a donor is approximtely 30% to 35%; about 30% of remaining patients are successful in finding a matched, unrelated voluntary donor through unrelated donor marrow registries. Large global, American and European registries have been established; however, Asians-Indians are poorly represented in them. An Asian-Indian Donor Marrow Registry (AIDMR) has been established at the All India Institute of Medical Sciences, New Delhi since 1994 and has close to 5000 registered voluntary Asian-Indian donors.

Matching strategies for renal transplantation consider only HLA-A, HLA-B and HLA-DR loci. In renal and other solid organ transplantation, a direct relationship exists between graft survival and the level of matching. Four types of donors are generally available for renal transplantation. Family donors include parents, siblings and offspring and their match status is determined by the parental haplotype inheritance and whether they share one, both or no HLA haplotypes (**Table 1**). In HSCT, the level of HLA matching is much more critical than solid organ transplants and is limited to *HLA-identical* sibling donors. This is because of the risk of graft versus host diseases (GVHD) where T-cells in the stem cell graft react against allogeneic host HLA molecules expressed on all tissues.

Table 1: Donor Categories for Renal Transplantation and Probability of HLA Match

Donor category	Match probability	Match designation
Family donors		
Parents	50% match or one haplotype match	Haploidentical
Siblings	25% chance of full match	HLA identical
	50% chance of one haplotype match	Haploidentical
	25% chance of no haplotype match	HLA unidentical
Offsprings	50% match or one haplotype match	Haploidentical
Cadaver donor	Generally poor	Expressed as mismatch (mm) for the number of HLA antigens shared in HLA– A, B, and DR loci: for example, full house match (0/6 mm) or grades of 1 to 6 antigen mm
Spousal donor	Generally poor	
Unrelated donor	Generally poor	

HLA = Human leucocyte antigen

Most grafts from unrelated donors are mis-matched at several HLA loci. The 10 year graft survival of 70% seen in the HLA-identical sibling grafts is significantly reduced to 50% for the HLA haploidentical parental donor grafts and < 40% for those involving poorly matched cadaver donors as is seen in the long-term renal graft survival compiled by the UCLA registry (**Figure 4**). The 'half-life' (the period at which at least half the grafts are still functioning) is 25 years for well-matched HLA-Id sibling grafts, 11.5 years for parental donors and only 7.8 years for cadaver donor grafts which are generally mis-matched. There has been no significant improvement in the half-life of grafts even following introduction of highly effective immunosuppressive agents including tacrolimus and sirolimus.

ALLORECOGNITION

Allorecognition refers to T-cell recognition of genetically encoded polymorphism between members of the same species. CD4+ recipient T-cells recognise donor alloantigens through either the *direct pathway* in which host T-lymphocytes recognise native MHC molecules expressed on graft-associated APCs or the *indirect pathway*, in which donor alloantigen-derived peptides are recognised in the context of self MHC molecules expressed on recipient APCs (**Figures 5A and B**). The direct pathway is of particular relevance during acute rejection. Donor derived APCs expressing donor alloantigens rapidly migrate from the graft and enter the secondary lymphoid tissues, where they can encounter and prime the allospecific T-cells. Cytotoxic T-lymphocytes, B-cells, macrophages and natural killer cells are recruited in a graft undergoing rejection. The main mechanisms implicated for graft destruction are cell-mediated cytotoxicity, delayed type hypersensitivity and antibody-dependent-cellular cytotoxicity.

GRAFT REJECTION

Efforts are always made to ensure that patient and donor are matched for HLA gene loci as completely as possible. However, this is difficult to achieve and immunosuppressive drugs are given to control the host immunity caused by HLA disparity. The aim is to prevent or control rejection and allow the recipient to develop long-term acceptance (or tolerance) of the graft. Rejection can be mediated by antibodies, lymphocytes or both and can manifest as hyperacute (in the early post-transplant period, within hours), acute (occur at any time) and chronic rejection (slowly developing process with progressive decline in graft function).

Hyperacute rejection is caused by preformed donor specific alloantibodies in a presensitised recipients. Humoral presensitisation may be caused by a previous transplant, blood transfusions or pregnancy. The alloantibody-mediated rejection is initiated by activation of the complement cascade leading to release of various inflammatory mediators and the initiation of the coagulation and fibrinolytic systems. Hyperacute rejection is manifested by rapid vascular constriction, oedema and thrombotic occlusion.

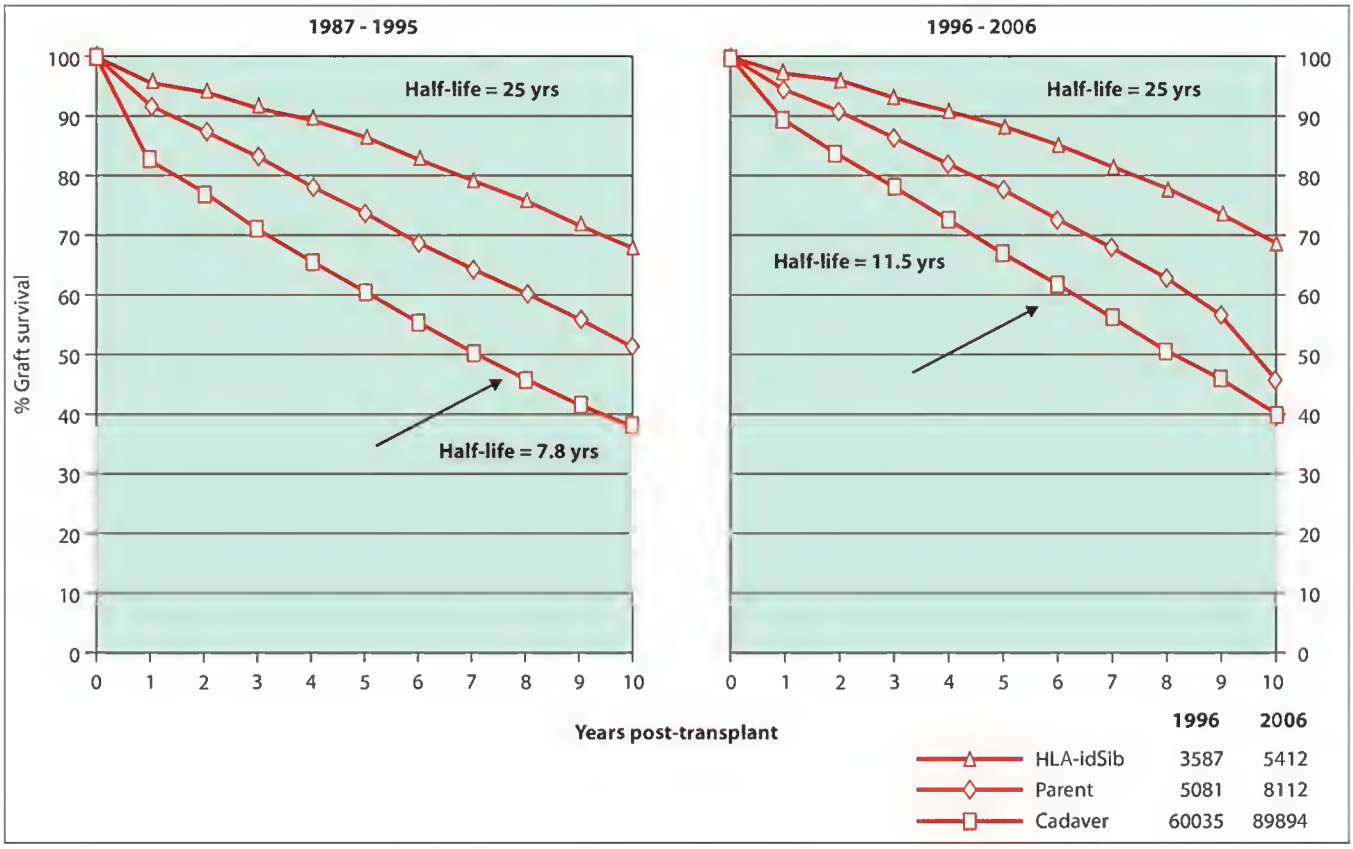
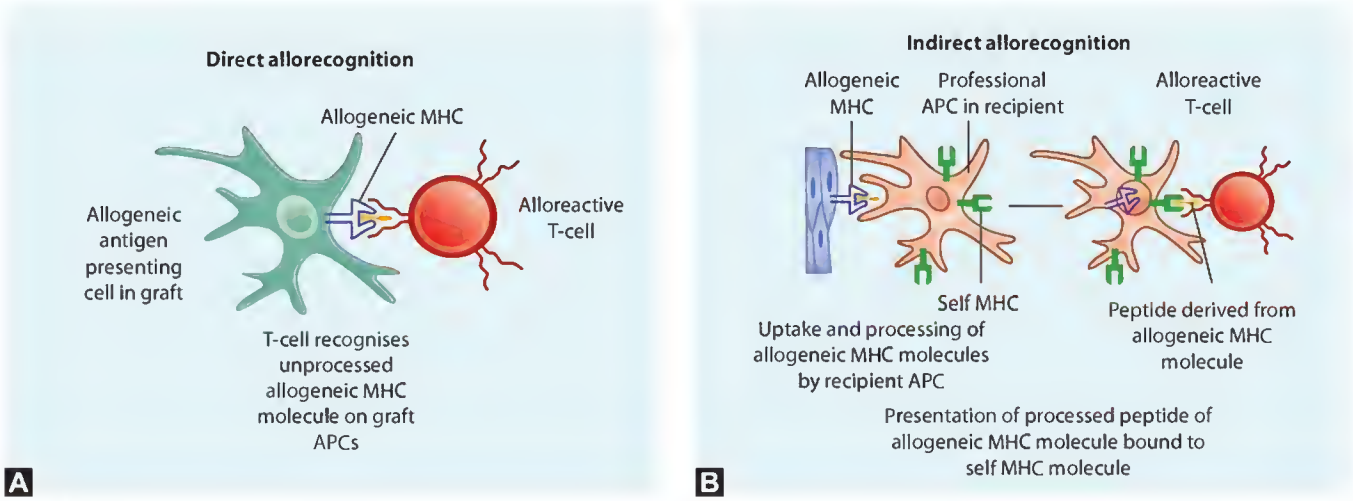


Figure 4: University of California Los Angeles (UCLA) data involving large series of kidney transplants showing the HLA matching effect followed for at least a 10-year period. The HLA-identical sibling donor transplants have 70% graft survival compared to 50% for haplo-identical parental grafts and < 40% for mismatched cadaver donor grafts. The half-life of the HLA-Id grafts is 25 years which drops significantly to 7.8 years (1987-95 block) and 9.3 years (1996-2006 block) for the cadaver donors.

Source: Kaneku et al 2006.



Figures 5A and B: The pathways of allorecognition that cause problems in organ transplantation as a result of HLA mismatching. (A) Direct pathway. The alloreactive responses of recipient T-cells to donor APC expressing incompatible antigens. (B) Indirect pathway. Allogeneic HLA antigens are taken up and processed by the recipient APCs and presented in the context of autologous (self) HLA molecules to recipient T-cells. Antigen-presenting cell trigger CD4+ and CD8+ cells, and as a result local and systemic immune response develops. Cytokine recruitment and activation of specific T-cells, NK cells and macrophage-mediated mechanisms lead to cytotoxicity and finally the allograft destruction.

MHC = Major histocompatibility complex; HLA = Human leucocyte antigen.

The injury in acute rejection (AR) is caused by T-cells (T-cell mediated rejection) and antibodies (humoral rejection), either alone or together. It typically appears during the first 1-6 weeks after transplantation and declines sharply after the first 6 months. The allograft vascular endothelium is the primary target of the initial stage of cellular rejection and lymphocytes exert a direct cytotoxic effect on graft parenchymal cells, and mediate a delayed type hypersensitivity (DTH) response.

Chronic rejection, affects most long-term transplant survivors and is characterised by vasculopathy, fibrosis and a progressive loss of the organ function. Chronic rejection is mediated by low-

grade, persistent DTH response and activated macrophages secrete mesenchymal cell growth factors leading to fibrosis. Persistent viral infections also induce cellular immune responses. The donor-specific alloreactive T-cells and the chronic ischaemia secondary to injury of the blood vessels by antibody or cell-mediated mechanisms also contribute. Vascular occlusion may occur as a result of smooth muscle cell proliferation in the intima of the arterial walls.

PRE- AND POST-TRANSPLANT ANTIBODY SCREENING

A meticulous '*crossmatch test*' for possible occurrence of anti-donor antibodies is always performed before any transplantation. This is similar to the direct crossmatch done prior to blood transfusions; donor lymphocytes instead of red cells are tested with patient serum. Several improved cross-match assays have been developed to increase the sensitivity and specificity of the test and include the anti-human globulin test (AHG), flow cytometry, and solid phase assays like enzyme linked immunosorbent assay and luminex systems. Serum treatment with dithiothreitol is used to distinguish clinically less relevant IgM type antibodies.

HLA antibodies that develop *de novo* post-transplantation and not necessarily donor specific, are associated with poor graft survival. It is, therefore, advisable to monitor routinely the post-transplant development of such antibodies, as a predictive marker for allograft function.

CONCLUSION

Recent advances in immunological techniques promise improved management of transplant patients by predicting rejection episodes before the onset of irreversible and terminal damage. HLA matching is beneficial in both short as well as long-term survival of the renal allograft and in live related as well as deceased donors. The poor match status between donor and recipient is frequently associated with more vigorous antibody response. Molecular approaches for clinical monitoring of the post-transplant immune status and identifying the best functionally matched donor before the transplant procedures are among the key areas of futuristic research in the area of clinical transplantation. Continuing progress in understanding molecular mechanisms of graft rejection may lead to the ultimate goal of long-term acceptance of organ allograft through tolerance induction.

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Section 6

Medical Genetics

Section Editor: Shyam Swarup Agarwal

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6.1 Introduction to Medical Genetics

Shyam Swarup Agarwal

DEFINITION

Genetics is the science of study of genes, a field devoted to understanding principles and mechanisms of heredity and variation. Gene—a segment of deoxyribonucleic acid (DNA) that codes one polypeptide chain—is the basic unit of inheritance that transmits characters from generation to generation. Collectively genes are responsible for uniqueness of each species as well as each individual. Studies in genetics deal with decoding the structure, function and transmission of genes that determine the development and differentiation of a single cell zygote into a whole human being, and also, the functioning of various organs and systems of the body from conception to death. In addition, genetics also includes the study of genesis and selection of variation which determines survival of the fittest, and thus, evolution. Classically, genetics had dealt with study of one gene at a time, both for sake of simplicity and lack of tools to study multiple genes or the genome as a whole. It needs to be appreciated that the normal structure (anatomy) and function (physiology) of genes that determines health (Genetics in Medicine) is as important as the study of their aberration that leads to genetic disease (Medical Genetics as a speciality).

GENETICS AND GENOMICS

With recent advances in molecular biology leading to successful completion of the Human Genome Project in 2003, and emergence of technologies enabling study of whole genome, transcriptome, proteome and metabolome of the cell, in one go, a new era of medicine has dawned. In the words of Victor McKusick, "... Biomedical research in the future would be progressively more integrated and integrative; that families of genes, not single genes, and physiologic systems, not single reactions will be the objects of study....". This approach when applied to the study of genes in health translates into "Integrated Systems Biology", and in patient care to "Genomic Medicine". Literally, genomics can be defined as the study of the 'genome' as a whole, the sum total of all the genes and non-coding genetic material as well. This includes study of gene-gene and gene-environment interaction.

HISTORY

Although occurrence of familial disorders (such as, haemophilia, colour blindness, polydactyly, etc.) and resemblance of children to their parents was known for a long time, it was Mendel's classic experiments in 1865 on transmission of *discrete* characters in sweet-pea plants that laid the foundation of genetics (the term 'genetics' was coined by William Bateson in 1906). It was remarkable that Mendel deduced the laws of inheritance much before the discovery of chromosomes. The contributions of Mendel remained unnoticed till the turn of the 19th century when they were independently rediscovered by de Vries, Tschermak and Correns. But very soon the application of Mendelian laws was found for alkaptonuria, albinism, cystinuria and pentosuria—the inborn errors of metabolism—identified by Sir Archibald Garrod in 1909. As a parallel activity, around the same time (1879 onwards), diploid nature of the chromosomes in eukaryotic cells and mitotic and meiotic cell divisions were delineated that provided the physical basis for Mendelian inheritance (Sutton 1902). The correct number of human chromosomes, however, was not known until 1956 (Tjio and Levan 1956).

Next major milestone in genetics was the study of variation in *Drosophila melanogaster*, the fruit fly, which led to identification of spontaneous mutations and their induction by radiation and chemicals (Muller and Morgan). Studies on fruit flies also led to the discovery of linear arrangement of genes on a chromosome, the linkage of closely located genes on the same chromosome, and mechanism of determination of sex and meiotic re-combination. The first inkling about the biochemical functioning of genes came from the studies of Beadle and Tatum (1941) on auxotrophy in the fungus neurospora. It led to the hypothesis of 'one gene-one enzyme (polypeptide chain)' as the basis of inheritance. The chemical nature of genetic material was discovered by Avery, Macleod and McCarty in 1944 who showed that the 'transforming principle' of pneumococcus was DNA [in some organisms the genetic material was later shown to be ribonucleic acid (RNA) instead of DNA]. Subsequently, in quick succession, the molecular structure of DNA was delineated by Watson and Crick in 1953, and the processes of DNA replication, transcription and translation were delineated leading to unravelling of the genetic code. The holy trinity of DNA-RNA-Protein became the gospel truth of life, until Baltimore and Temin discovered the enzyme 'reverse transcriptase' in onco-RNA viruses providing a mechanism for reverse transcription of RNA into DNA, that gets integrated into host genome.

A totally new chapter in the field of human/medical genetics has been written with the advent of genetic engineering in 1970s. The discovery of restriction endonucleases (Smith 1968) enabled cutting and pasting of different DNAs leading to engineering of 'new' DNA. The 'new' DNA can be cloned in plasmids giving rise to millions of copies of the desired DNA (unique single copy genes). Combined with the technique of DNA sequencing, genetic engineering has paved the way for the Human Genome Project (1995-2003) that led to mapping and sequencing of the entire human genome. The completion of the Human Genome Project in 2003 is likely to be as revolutionary as the discovery of Mendelian principles of inheritance at the turn of last century.

MAJOR DIVISIONS OF THE FIELD OF GENETICS

Genetics as a whole encompasses a wide field of study. It has many sub-divisions. On basis of tools used for the study, there are four classical sub-divisions of genetics, viz., (1) Mendelian or

pedigree genetics, (2) cytogenetics, (3) biochemical genetics, and (4) molecular genetics. To this list, another specialised area of statistical genetics, bioinformatics and computational genetics has been added in recent years which is going to dominate the scene of genomic medicine in the years to come. The above terms are self-explanatory and are covered in separate chapters under this section. With regards to the area of study, the discipline of genetics can be divided into the following categories: (1) human genetics, (2) medical genetics, (3) clinical genetics, and (4) community genetics. These are interrelated areas which run into one another. A brief description of each follows, giving some idea about the scope of each domain. In addition, there are other areas of application as well, such as developmental genetics, population genetics, evolutionary genetics, and forensic genetics, etc.

Human Genetics

Human genetics may be broadly defined as study of the role of genes in health and normal variation. While identity of all the genes has been unravelled with successful completion of the Human Genome Project, their detailed function—giving rise to the ultimate phenotype—still remains to be delineated to a large extent (Functional genomics and Phenomics). Even more importantly, we need to understand regulation of temporal and spatial expression of genes, gene-gene interaction and gene-environment interaction. Some examples include production of different haemoglobins during embryonal, foetal and adult life; regulated secretion of insulin and other hormones to achieve glucose homoeostasis—after and in-between meals; regulation of reproductive cycles from puberty to menopause; senescence and even life span, characteristic of each species. It needs to be realised that the basis of life has now been reduced from cell to molecule, and we have to understand the entire anatomy, physiology, pathology and pharmacology at the molecular level—the so called "Molecular Medicine".

Human genetics deals with not only understanding of normal structure and function, but also of normal variation such as height, weight, colour of the skin and eyes, intelligence, etc. Unravelling of the human genome sequence has led to identification of millions of SNPs, CNVs and STRs among normal healthy individuals, some of which may contribute to quantitative variation—giving rise to characteristic Gaussian distribution curve for these genetic traits.

Human genetics is as relevant to medicine, as anatomy, physiology and biochemistry are.

Medical Genetics

Medical genetics is an extension of human genetics. It deals with the study of the role of genes in causation of the disease. In this context, genes play a dual role. On one side chromosomes, genes and DNA constitute the 'genetic system' in anatomical sense that is the site of lesion for genetic disease, and on the other, the gene acts as an aetiological agent contributing to causation of disease. In the latter context, genetic make-up of the individual determines susceptibility/resistance to environmental pathogens, giving rise to complex, multifactorial polygenic disorders. The defects of nuclear DNA, because of their presence in gametes, follow Mendelian segregation, whereas mitochondrial DNA defects follow maternal inheritance. More than 3,000 genetic disorders are listed in the *Online Mendelian Inheritance in Man* (OMIM) database which collectively affect approximately 2% to 3% of all births (excluding congenital malformations which account for another 1.5% to 2.5% of all live births). The genetic defect acquired in somatic cells may give rise to malignant transformation (leading to cancer), or senescence, without being transmitted to the next generation.

The studies in medical genetics include understanding of the pathophysiology of genetic diseases, i.e. how the abnormal gene gives rise to disease. The most classical example is of sickle cell disease where substitution by 'T' for 'A' at codon 6 of beta globin gene leads to substitution of glutamic acid by valine resulting in formation of a slow-moving haemoglobin (Hb S). The latter, under hypoxic conditions, gives rise to sickling of red cells which are responsible for all the manifestations of sickle cell disease. This knowledge allows for definitive diagnosis of the disease, antenatal diagnosis, as well as screening of the disorder in newborns for better prevention of various complications. Efforts are also being made to correct the defect by gene therapy, and designing of pharmacophores for treatment of genetic diseases.

Besides causation of disease, the genetic make-up of an individual may also modify its response to drugs – both safety and efficacy (Pharmacogenomics), toxins (Toxicogenomics) and nutrients (Nutrigenomics). This information can be used for personalising therapy as well as for prevention of disease.

Clinical Genetics

Clinical genetics deals with application of the knowledge of genetics to patients with genetic disorders in the clinic and at the bedside. It includes diagnosis, management and prevention of genetic disorders. To begin with, the role of genetic clinic was limited to genetic counselling. With the development of the technique of amniocentesis in the 1960s to obtain foetal cells, antenatal diagnosis could become possible, providing the couple an opportunity to choose reproductive options in a child at risk of genetic disorder. Simultaneously, the development of Guthrie's technique for newborn screening of phenylketonuria and other inborn errors of metabolism on one hand, and diets for treatment of these disorders on the other, has revolutionised the treatment of genetic disorders to the extent that screening of newborns has been made mandatory by law in a number of countries in the developed world. With the advent of DNA diagnostic tests, the scope of antenatal diagnosis has expanded to cover several hundred disorders. In addition to antenatal diagnosis and newborn screening, several other interventions have been developed for management of patients with genetic disorders. This includes replacement therapy such as AHG in haemophilia, high-dose vitamin therapy in homocystinuria, bone marrow transplantation for thalassaemia and others. More recently, recombinant DNA technology has allowed large scale manufacture of enzymes for enzyme replacement therapy for lysosomal storage disorders, though the cost of treatment remains high. There is also a ray of hope that gene therapy and other forms of molecular and cellular therapies may develop for some genetic disorders in the future. All theses developments have necessitated that the speciality of clinical genetics be developed for the benefit of patients with genetic disorders and primary care physicians (PCPs) be knowledgeable to suspect, counsel and refer these patients to speciality centres.

The core competencies required by PCPs have been published by the National Coalition for Health Professional Education in Genetics.

Community Genetics

Community genetics is an extension of clinical genetics for the public at large. One of the earliest examples was the screening of Ashkenazi Jews for Tay-Sachs disease carrier state and the offer of antenatal diagnosis to the couple at risk. Application of the same principle to thalassaemia screening in the Cyprus island has virtually eliminated the birth of even a single thalassaemic child in that country. It is one of the most radical and successful implementation of primary prevention of genetic disorders. In more recent years, periconceptional folic acid supplementation has led to marked reduction in the birth of children with open neural tube defect. Likewise, identification of several high-risk markers for Down's syndrome and other chromosomal disorders has led to universal counselling and screening of all pregnancies (irrespective of maternal age) with triple/quadruple test. For many of the strategies of antenatal diagnosis, it is desirable that the couples at risk should seek genetic advice before conception. It is strongly recommended that obstetric care should commence with preconception clinics. Cost-benefit analyses have shown that many of the screening programmes deserve to be taken up as national public health programmes. One of the new areas that are emerging is that of cancer genetics. Association of BRCA1/BRCA2 gene mutations with familial breast-ovarian cancer, and APC/MSH mutations with familial colon cancer have shown the utility of predictive screening for prevention of cancer. With increasing recognition of genetic markers for various polygenic-multifactorial disorders, such as diabetes, hypertension, coronary artery disease, etc., community genetics is bound to become a major component of public health programmes.

CURRENT STATUS AND FUTURE PROSPECTS: INDIAN SCENARIO

It needs to be considered under 3 headings, viz., teaching, practice and research. As far as teaching is concerned, most medical colleges in India do not have any teaching-training programme in human and medical genetics at present, mainly because of lack of trained medical faculty in this discipline. As mentioned above, we now need to tune ourselves to the molecular basis of health and disease. As far as clinical practice is concerned, there has been some introduction of services in this area as a by-product of clinical research programmes in this field. However, its penetration is limited mainly due to absence of adequate diagnostic laboratory facilities. There is an urgent need to establish quality assured laboratories, with adequate counselling support, to provide to our people (at least to those who can afford) what is already available elsewhere. Since clinical genetics is still largely a preventable programme, it would be better to take it up in the public health, national programme mode. As far as research is concerned, we are better than the other two areas. Most of our biomedical research labs have adequate infrastructure and expertise to be competitive in this field. What is needed is innovation in our approach and competition in spirit to make use of the opportunity. This will, however, require well-defined clinical material for exploration as well as validation which also needs to be addressed.

RECOMMENDED READINGS

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6.2 Mendel and Beyond

Ratna Dua Puri

INTRODUCTION

The roots of understanding of genetics can be traced back to 1865 when the Augustinian monk Gregor Mendel described the principles of inheritance based on his meticulous and painstaking cross-breeding experiments with the sweet pea *(Pisum sativum)* plants which he grew in his monastery garden in Brno. After 8 years of tedious experimental work with hybrid plants, Mendel proposed the basic principles of inheritance which are enumerated in **Table 1**.

Table 1: Basic Principles of Mendelian Inheritance

- Each individual inherited trait, including its alternate form, is determined by a pair of factors, later called genes by Wilhelm Johannsen in 1909.
- Each member of the pair of factors is inherited from one parent (the members of the pair segregate during gametogenesis—so that each gamete contains only one factor).
- The gene determining the alternative form of the trait is called 'allele'. The genes may be dominant or recessive, depending on their expression in the hybrid state. In the F1 hybrid only the dominant form is expressed. The recessive gene is neither lost, nor blended. It remanifests in the F2 generation in a ratio of 3:1.
- Genes determining different traits (now identified to be located on different chromosomes) segregate independently of each other.

The observations of Mendel are summarised in two laws which form the basis of inheritance of unifactorial traits.

The Law of Segregation

For any particular trait, the pair of alleles of each parent separate during meiosis so that the gamete receives only one allele. Only one allele passes from each parent to an offspring.

Principle of Independent Assortment

This law states that different pairs of alleles determining different traits are passed to offspring independently of each other. Today, we know this is true only for those genes which are located on different chromosomes, or quite far from each other if located on the same chromosome. The genes located close to each other are inherited together (linkage).

A Mendelian trait is one which is controlled by a single gene, follows Mendel's laws of inheritance, and mutation in the gene leads to altered/diseased phenotype.

Life is not simple, and so is the relationship of phenotype to the genotype. Heterogeneity of genetic disorders, both intra-family and inter-family, is the rule rather than an exception. This led to invocation of the phenomenon of 'penetrance' and 'expression'. The next challenge was to account for anticipation and various anomalous patterns of inheritance. At first, the very validity of the Mendelian laws was challenged, but with better understanding of the molecular basis of gene function, such as genomic imprinting, instability of triplet repeats, mitochondrial gene structure, function and phenomenon of homo-heteroplasmy, uniparental disomy, epigenetic modulation of gene expression, etc. our appreciation of the Mendelian principles of inheritance has enhanced rather than diminished. The next challenge is to unravel and understand the phenomenon of polygenic inheritance. Interestingly, even the monogenic disorders are greatly influenced by multiple genes-so called modifier genes. There is a growing realisation that no gene functions in isolation. The effect of every gene may be influenced by gene-gene interaction and gene-environment interaction. The fuzziness will give way to more clarity as we know more.

As a clinician, to identify individuals at risk for a genetic disorder, and to counsel the families with a child suffering from genetic disease, it is important to ascertain the mode of inheritance. This requires recording of the family history. The following discussion of the art of pedigree drawing and then its analysis to deduce the pattern of inheritance of the disease under consideration is of great importance.

PEDIGREE DRAWING

The initial step in any genetic consultation is the collection of relevant family data. A pedigree or a family tree is a diagrammatic representation of the relationships amongst family members and record of relevant medical information about each of them by employing a combination of internationally accepted symbols and lines. The index case, or proband, is the affected person who brings the family to notice and his position in the pedigree is depicted by an arrow. From this start point the brothers/sisters, parents, offspring and maternal and paternal relatives are recorded using the symbols as shown in **Figure 1**.

By convention, a three-generation pedigree is used in clinical practice. More extended family trees may be drawn if needed.

The importance of the pedigree chart is to record concisely and pictorially complete family history with names and dates of birth, their health and disease status, etc. from which the mode of inheritance of the disorder can be deduced. For example, limb girdle muscular dystrophy can be inherited as an autosomal dominant or recessive trait and this can be differentiated by pedigree analysis. It can also be used to identify the risk of transmitting an inherited condition to the offspring, to identify family members at risk of the disorder, or carriers of the disorder.

MENDELIAN INHERITANCE/SINGLE GENE DISORDERS

This refers to a group of disorders occurring as a result of a defect/mutation in one or both alleles of a gene. Autosomal pattern of inheritance is due to a mutation of a gene on an autosome and in sex-linked inheritance/trait, the relevant gene

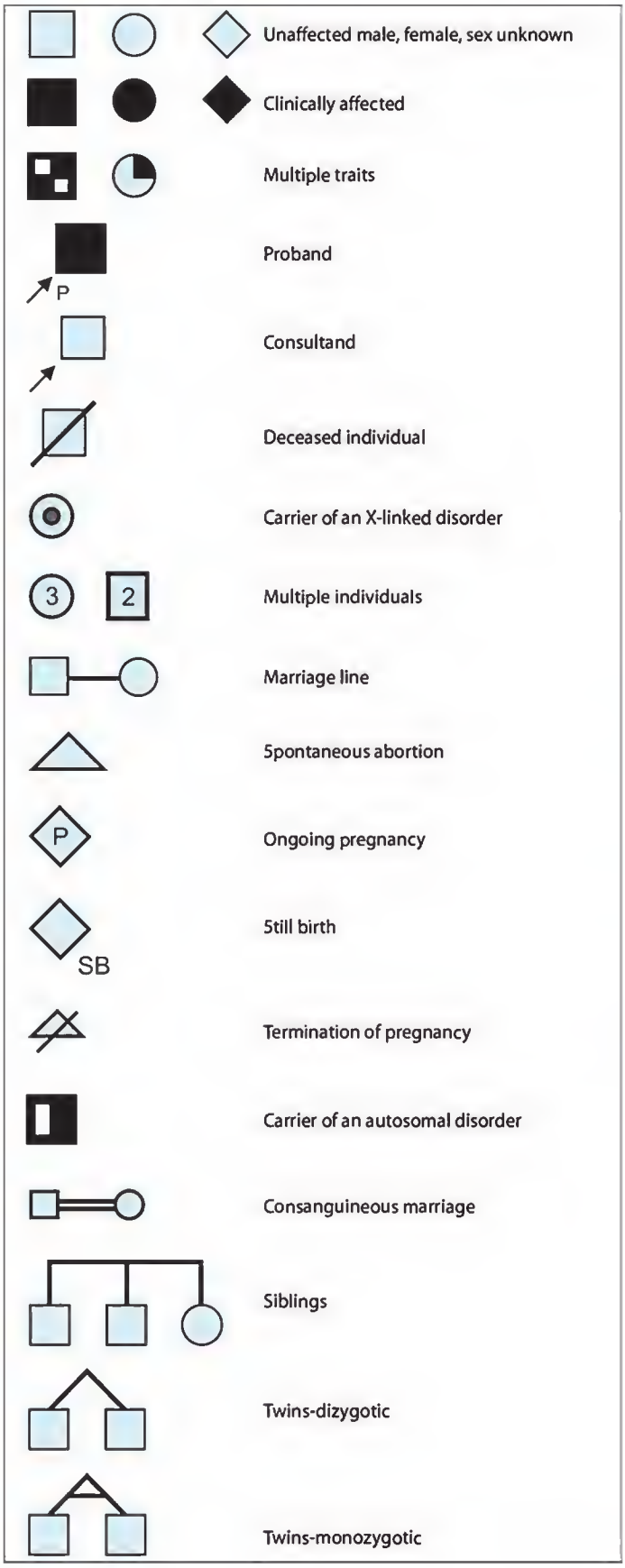


Figure 1: Pedigree symbols.

is on the X or Y chromosome. An individual with identical alleles of the gene is homozygous, and one whose alleles are not identical is heterozygous.

CONCEPT OF DOMINANCE AND RECESSIVENESS

Dominance is defined in terms of expression of the gene (disease or trait) in the heterozygous state. This occurs as a result of gain of function mutation where the abnormal gene product (even in the presence of normal product of the other gene) is sufficient to lead to altered state, e.g. Huntington chorea, Charcot-Marie-Tooth disease. Oncogenes are classical example of dominant genes. On the other hand, a recessive gene manifests as loss of function. It gives rise to disease/trait only when both the copies of the gene are knocked out, i.e. in homozygous state, e.g. thalassaemia. A dominant negative mutation results in a gene product that is non-functional, but it interferes with the function of the normal allele, so that it manifests even in the heterozygous state, e.g. osteogenesis imperfecta.

Autosomal Dominant Inheritance

The disorder occurs due to a mutation in one copy of a gene present on autosomes. Hence, these disorders manifest in the heterozygous state where the affected individual has one abnormal (mutated) and one normal allele (**Figures 2 and 3**). The characteristics of autosomal dominant inheritance are listed in **Table 2**.

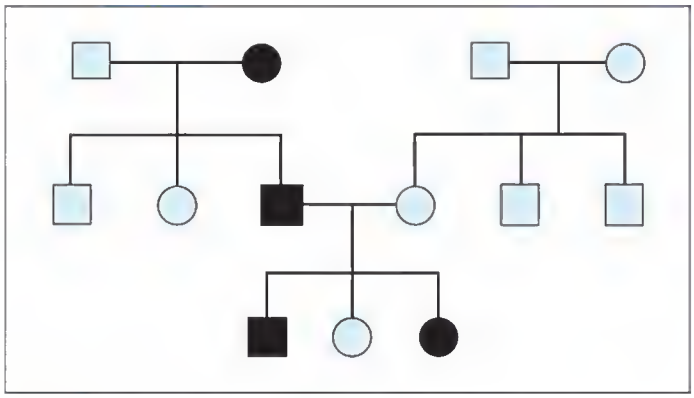


Figure 2: Autosomal dominant inheritance.

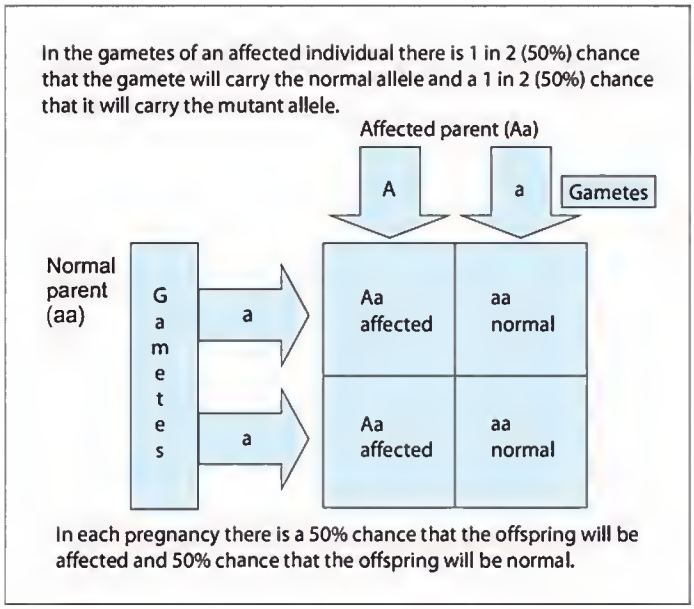


Figure 3: Punnett square showing segregation of alleles in a family with an autosomal dominant disorder.

Table 2: Characteristics of Autosomal Dominant Inheritance

- Vertical mode of transmission with expression in more than one generation
- Males and females are equally affected
- Father to son transmission present
- The risk to the offspring of an affected individual is 50% in each pregnancy
- Family members, who are unaffected, themselves do not transmit the disorder

Examples: Huntington disease, achondroplasia, autosomal dominant polycystic kidney disease, facioscapulohumeral dystrophy, neurofibromatosis I and II, tuberous sclerosis.

It is not unusual to see deviations from the typical characteristics of autosomal dominant pattern of inheritance described above. These have significance while counselling families.

Penetrance

In some disorders, the individual who carries the mutant gene does not manifest any sign or symptom of the disease, i.e. the gene is non-penetrant. This phenomenon may result in skipped generation in the pedigree chart (**Figure 4**). For disorders that show incomplete penetrance, the unaffected individual cannot be completely reassured that his or her children will not be affected unless molecular tests are done, e.g. hereditary non-polyposis colorectal cancer, acute intermittent porphyria.

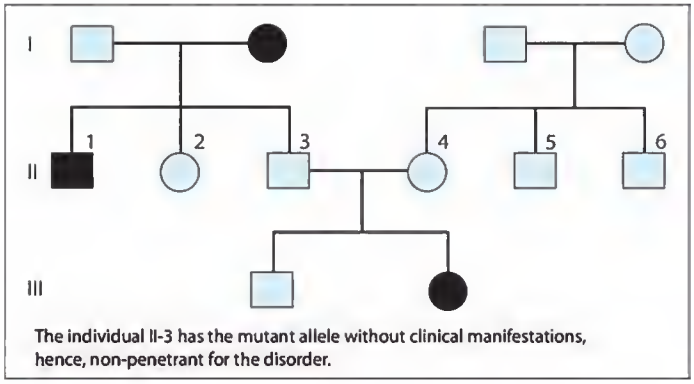


Figure 4: Autosomal dominant inheritance with non-penetrance.

Variable expression and pleiotropy

Individuals in the same family who carry an identical mutation can have varying clinical features and severity of the disorder, e.g. tuberous sclerosis—a mildly affected parent with only minor skin lesions can have a child with severe infantile spasms and mental retardation. Such intra-familial variability is difficult to explain on the basis of monogenic inheritance, as all the affected members in the family carry the same mutation. But now it is understood that no gene functions in isolation and the disease manifestations may be modified by interaction with other genes and the environment. Now, more and more information about genes which modify the phenotype of so-called monogenic disorders is becoming available. The phenomenon of gene-gene interaction is known as epistasis. Pleiotropy refers to multiple effects of a single gene/mutation in several tissues or organs of the body, e.g. neurofibromatosis type 1 can cause skin pigmentary changes, neurofibromas, short stature, mental subnormality and Lisch nodules in the eyes.

Onset

The onset of genetic disorders can be variable, e.g. Huntington chorea, spinocerebellar ataxias, etc. In these disorders, it is difficult to counsel at what age a person will develop the disease, or the quantum of risk of transmitting the disorder to the offspring if the person has not developed symptoms yet. In majority of these diseases, this dilemma may be overcome by the availability of DNA diagnostic tests.

New mutations

In some autosomal disorders, an affected person may be born to normal parents and there may be no history of similar disease in previous generations. In this clinical situation a new change in the gene (*de novo* mutation during gametogenesis) is responsible for the disease phenotype. The affected offspring would have 50% risk of transmitting the disease gene, but the risk to siblings will be nil, e.g. achondroplasia, Marfan's syndrome. It is important to exclude variable expression/non-penetrance and non-paternity as other possible reasons for an apparent new dominant mutation. In some cases there may be gonadal mosaicism—where the risk of recurrence cannot be excluded. *De novo* mutations are more likely to occur if paternal age is more than 45 years.

Homozygosity in an autosomal dominant disorder

In some autosomal dominant disorders, the severity of the disease increases in homozygotes, e.g. homozygosity for mutation causing achondroplasia may result in severe skeletal dysplasia that is lethal in the intrauterine or perinatal period. There is a 25% risk of lethal achondroplasia in the offspring if both the parents are affected with achondroplasia.

Recurrence risks

If one parent is affected by an autosomal dominant disorder and the other is normal, the risk of recurrence for their offspring in each pregnancy is 50%. Each pregnancy is an independent event and the probability remains the same with every conception, independent of the disease status of any previous children (**Figure 3**).

If both parents are affected by an autosomal dominant trait, then the risk of an affected child is 75% in each pregnancy. There is a 25% chance that they will have a child with both alleles mutated, e.g. achondroplasia.

Autosomal Recessive Inheritance

These disorders manifest when both alleles of a gene present at a locus are mutated. This disorder manifests only in the homozygous state. Most metabolic disorders due to enzyme deficiency follow the autosomal recessive mode of inheritance. This is because; being a catalyst, even half the product in a person with mutation in only one copy of the gene (carrier) is sufficient for the normal functioning of the cell (**Figures 5 and 6**). The characteristics of autosomal recessive inheritance are summarised in **Table 3**.

Recurrence risks

In each pregnancy, carrier parents have a 25% risk of having an affected child.

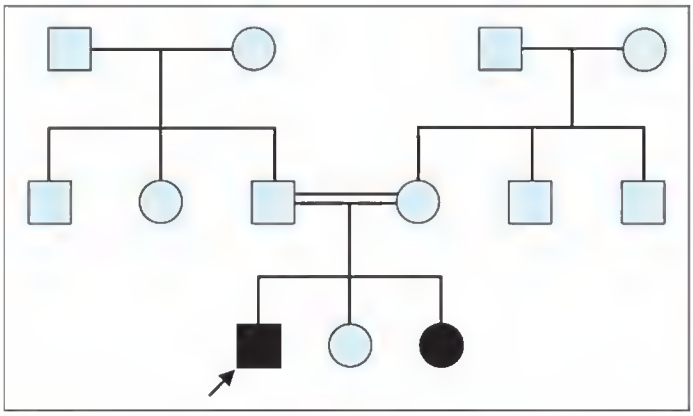


Figure 5: Autosomal recessive inheritance.

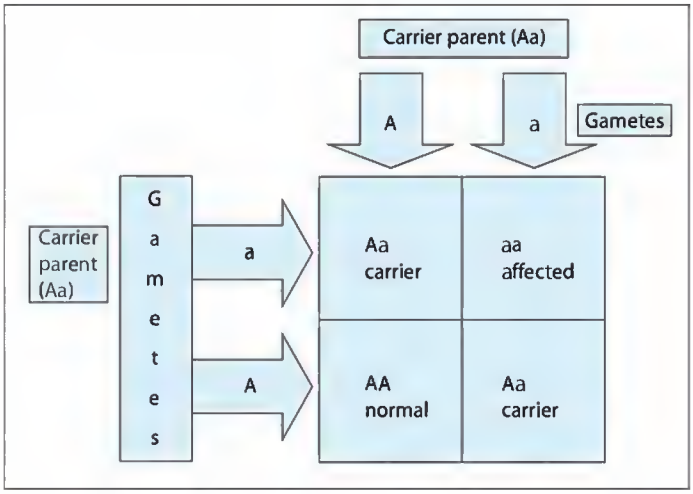


Figure 6: Punnett square of gametes and offspring for autosomal recessive inheritance.

Table 3: Characteristics of Autosomal Recessive Disorders

- Horizontal mode of transmission. All affected individuals are in one generation
- Parents of an affected individual are obligate, unaffected carriers
- The risk of recurrence to the siblings of an affected individual with carrier parents is 25% in each pregnancy
- Healthy siblings of an affected individual have a two-third risk of being a carrier
- Consanguinity among parents is more common in these disorders

Examples include beta-thalassaemia, sickle cell anaemia, Wilson's disease, cystic fibrosis, Fanconis anaemia, autosomal recessive polycystic kidney disease, oculocutaneous albinism.

X-linked Disorders

These disorders occur due to mutations in genes present on the X chromosome. X-linked disorders can be recessive with expression only in males, or dominant with expression in both the sexes. The characteristics of X-linked disorders are listed in **Table 4**.

X-linked recessive inheritance

Only males manifest the disease and it is transmitted through healthy female carriers (**Figure 7**).

Rarely, manifestations in a carrier female of an X-linked recessive disorder can occur in the following situations: Turner's syndrome with 45, X karyotype and mutation in a gene on the X chromosome, carrier female marrying an affected male giving birth to a daughter with mutation on her both X chromosomes, skewed inactivation of the X chromosome, and X-autosome translocation.

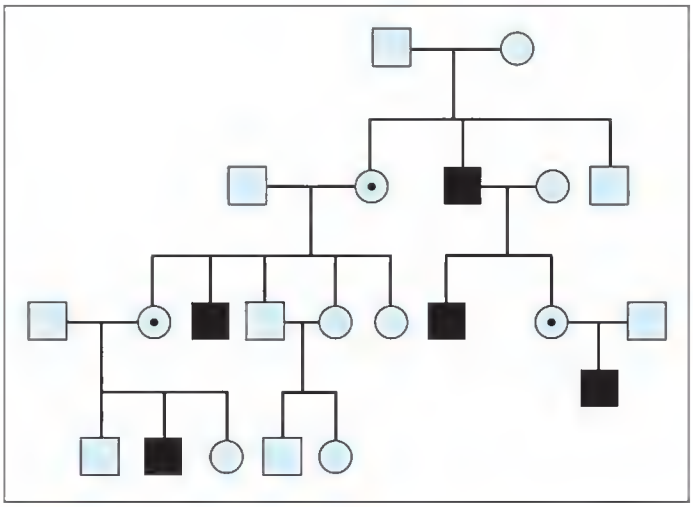


Figure 7: X-linked recessive inheritance.

Table 4: Characteristics of X-linked Disorders

- No father to son transmission
- All daughters of an affected male have the mutant gene, hence, are carriers
- Unaffected males never transmit the disease to their offspring
- Carrier women will transmit the disease to 50% of their sons
- Carrier women transmit the mutant allele to 50% of their daughters

Examples: Haemophilia A and B, Duchenne's muscular dystrophy, G6PD deficiency, X-linked ichthyosis, X-linked agammaglobulinaemia.

There are some X-linked recessive disorders where a heterozygous female can manifest a mild phenotype in the absence of above situations, e.g. Fabry's disease, X-linked hereditary nephrogenic diabetes insipidus, fragile-X mental retardation.

Recurrence risks

In each pregnancy, a woman with a mutation in one X chromosome has a 50:50 chance of having an affected son, and a 50:50 chance to have a daughter who carries the mutation. In the situation of marriage between an affected father and a non-carrier spouse, all sons are normal whereas all daughters are carriers.

In mating between a carrier female with an affected male, 50% daughters are affected, and 50% are carriers; whereas 50% sons are affected and 50% are normal.

X-linked dominant inheritance

Looks similar to an autosomal dominant pedigree with both males and females affected (**Figure 8**). Differences are summarised in **Table 5**.

Y-linked Inheritance

Only males are affected as these disorders are due to genes on the Y chromosome. An affected male will transmit the trait to all his sons but none to his daughters, e.g. hairy ears. Genes involved in spermatogenesis are present on the Y chromosome, but as they are associated with infertility, the inheritance

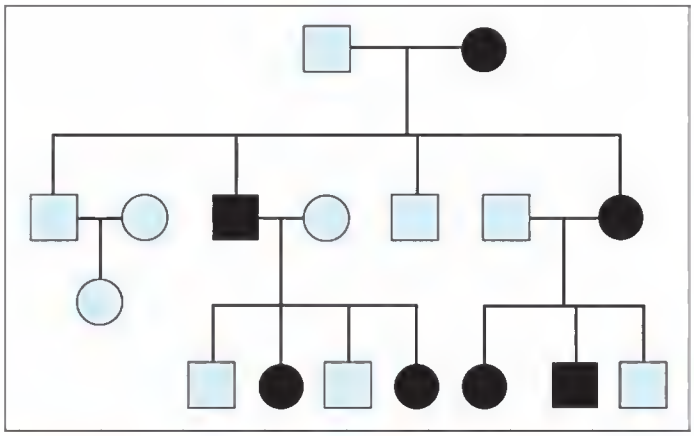


Figure 8: X-linked dominant inheritance.

Table 5: Differences of X-linked Dominant Inheritance

- Affected males transmit the disorder to all daughters but none to their sons
- Some of these disorders are lethal in males (hemizygous state), thus showing false predominance of affected females
- No direct father to son transmission
- Females (being heterozygotes) may be less severely affected

Examples of X-linked dominant disorders are Rett syndrome, X-linked hypophosphataemic rickets, incontinentia pigmentii.

pattern, may only come to light with the use of modern assisted reproductive techniques like intracytoplasmic sperm injection.

NON-MENDELIAN PATTERNS OF INHERITANCE

These are disorders due to mutations in single genes but they do not conform to the above Mendelian patterns of inheritance.

Mitochondrial Inheritance

Each cell has several copies of mitochondrial DNA which is capable of replicating independently of the nuclear genome. Mutations in the mitochondrial genome, and some nuclear genes controlling mitochondrial function, result in mitochondrial disorders (**Figure 9**). The pedigree of mitochondrial disorders is peculiar—both sexes are affected but the disease is exclusively transmitted through females. The division of mitochondria from parent to daughter cells during cell division is random, giving rise to wide variations in wild type and mutant type mitochondria in different cells, different tissues, and at different times (heteroplasmy). Due to this unique behaviour of mitochondria, these diseases display extensive phenotypic variability (**Table 6**).

Epigenetics

Epigenetics refers to modifications in the genetic material that do not change the nucleotide sequence, but result in functional changes in the DNA molecule. It is a heritable change, as far as somatic cells are concerned, and may lead to alterations in gene expression. As a result of this, the phenotype can vary even though the nucleotide sequence does not differ. The common epigenetic changes occur as a consequence of cytosine methylation of DNA and histone modifications. DNA methylation occurs in the cytosine residue of the CpG islands which are most commonly located in the promoter region of protein coding genes. This process causes alteration in gene transcription.

A special category of genes called imprinted genes are subject to epigenetic re-programming during gametogenesis or during

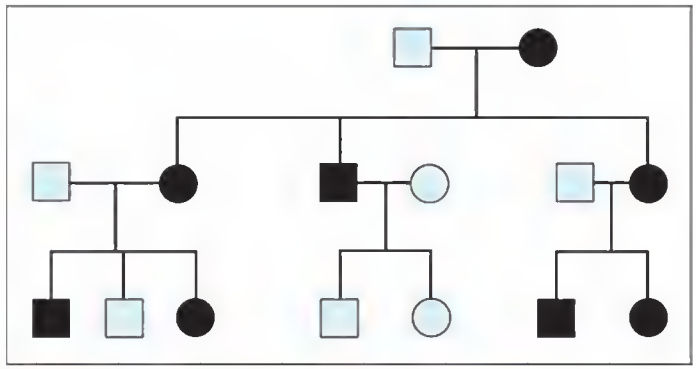


Figure 9: Mitochondrial inheritance.

Table 6: Characteristics of Mitochondrial Disorders

- Maternal transmission as mitochondria are exclusively maternal in origin
- Both males and females are affected
- Offspring of affected male will not manifest the disorder
- All offspring of the affected female have the risk of being affected
- Homoplasmy and heteroplasmy: In a cell with two populations of mitochondria, with wild type DNA and mutant mitochondrial DNA, during cell division the proportion of wild type and mutant type mitochondria may drift towards a pure type, either wild or mutant (homoplasmy), or may remain mixed (heteroplasmy)
- Threshold expression: When the mutant mitochondrial DNA crosses a threshold level, phenotypic expression results. This accounts for the variability in the clinical manifestations of mitochondrial disorders in different individuals and also the tissues affected in one individual

Examples of mitochondrially inherited disorders are Leber hereditary optic neuropathy, Leigh disease, MELAS (mitochondrial encephalopathy, lactic acidosis, stroke), MERRF (myoclonic epilepsy, ragged red fibres), Kearns-Sayre syndrome.

early embryogenesis in a predetermined fashion. Lyonisation of one of the two X chromosomes in females is an example of the same.

Genomic Imprinting and Uniparental Disomy (Table 7)

Parent-of-origin-dependent transmission of some diseases, such as Prader-Willi and Angelman syndrome was first described in the 1980s.

Table 7: Genomic Imprinting

Salient features of the imprinting are:

- It occurs before fertilisation
- It confers transcriptional silencing
- It is stably transmitted through mitosis in somatic cells
- It is a reversible process during passage though the opposite parental germline so that the sex appropriate imprint can be established

For every gene on a chromosome there are two copies, one inherited from the father and the other from the mother. Usually both copies are active and used for protein synthesis. However for some genes, their expression in the cells depends on the parent of origin. This is referred to as genomic imprinting whereby the parent of origin of the gene is stamped on it and the phenotype of the disorder depends on the parent of origin of the allele. For this group of genes, a functional hemizygous state is normal, with expression of only the paternal or maternal allele. A gene is maternally imprinted if the allele derived from

the mother is inactive, and paternally imprinted if the allele from the father is inactive. Best examples of imprinting are Prader-Willi syndrome and Angelman syndrome which can also occur due to deletion of chromosome 15q11-13 region, or uniparental disomy (UPD).

Uniparental disomy is the condition where both copies of a particular chromosome are inherited from one parent and none from the other. Usually UPD has no clinical consequence unless the involved chromosome has one or more imprinted genes. The disease phenotype in UPD occurs as a result of loss of the normally functioning gene where both chromosomes are inherited from the parent where the gene is imprinted, and hence, non-functional. In Prader-Willi syndrome (hypotonia, mental retardation, obesity, hyperphagia, and characteristic facies), the paternal allele is the active gene and the maternal counterpart is normally inactive. Any condition resulting in the absence of the active paternal allele results in the disease. This could occur as a result of microdeletion of the gene on the paternally inherited chromosome, or both chromosomes being inherited from the mother (maternal uniparental disomy). The reverse situation occurs in Angelman syndrome characterised by hypertonia, inappropriate laughter, mental retardation and seizures. The active allele in this case is present on the maternal chromosome, hence maternal 15q 11 deletion, or paternal uniparental disomy results in the disorder (**Figures 10A and B**).

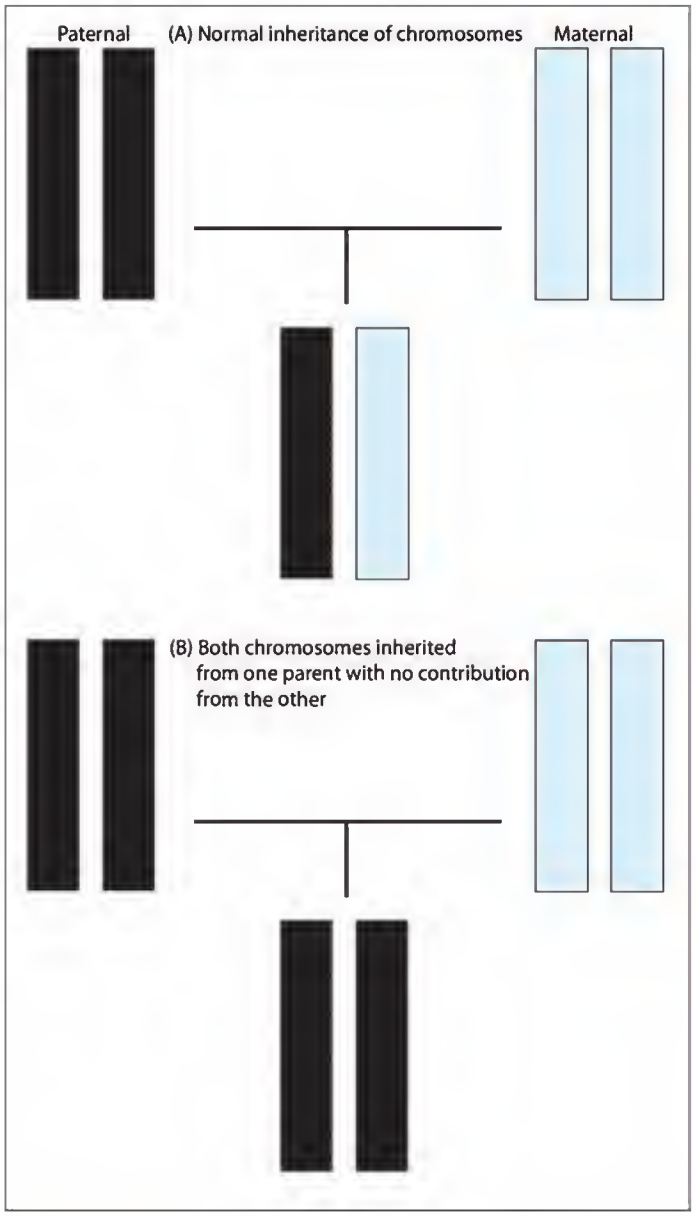
Other disorders due to genomic imprinting are Beckwith-Wiedemann syndrome, Russell-Silver syndrome, neonatal diabetes mellitus, etc. Majority of these disorders are sporadic with negligible risk of recurrence.

Dynamic Inheritance/Trinucleotide Repeat Sequence Mutation–Anticipation

Some genetic disorders express a more severe phenotype, and an earlier age of onset in successive generations. This phenomenon is called anticipation. It is observed in many autosomal dominant neurological disorders like myotonic dystrophy, spinocerebellar ataxias, and Huntington disease, etc. Spinobulbar muscular dystrophy and fragile-X mental retardation are X-linked triplet repeat disorders.

Genes of the above disorders carry trinucleotide repeats (e.g. CGG, CAG) in them. When the number of repeats increases beyond a critical size threshold, the repeat sequence becomes unstable with a tendency for repeat numbers to increase in each successive generation. This phenomenon is known as dynamic mutations. Premutation(s) are intermediate sized alleles, between alleles with normal range of trinucleotides and larger ones (mutation) which is associated with the disease phenotype. The premutation is the harbinger of full mutation during meiosis.

For some disorders the sex of the transmitting parent influences the degree of expansion of the repeat, and thus, the occurrence of the disease in the offspring, e.g. fragile-X mental retardation is usually transmitted through a female with mutation developing during oogenesis, whereas Huntington disease is more often severe if transmitted through an affected father.



Figures 10A and B: Uniparental disomy and genomic imprinting.

In myotonic dystrophy, an autosomal dominant disorder, the mildest form manifests as cataract in late life, but as the repeat number increases in successive generations, neuromuscular manifestations like myotonia and dystrophic features occur at an early age. At the most severe end of the spectrum, the disease manifests at birth and presents with respiratory distress, hypotonia and mental retardation. This usually occurs when the mutation is transmitted from an affected mother.

Somatic/Gonadal Mosaicism

The presence of two genetically different cell lines, derived from a single zygote in an individual is called mosaicism. This can be present in somatic, gonadal, or both cells. Somatic mosaicism usually results in a milder and partial phenotype. Gonadal mosaicism does not lead to any phenotypic abnormalities in the individual, but may be responsible for a clinically unaffected individual to have two or more affected offspring, e.g. facioscapulohumeral dystrophy, Duchenne's muscular dystrophy, osteogenesis imperfecta type II.

Digenic Inheritance

In digenic inheritance mutations in two different genes together give rise to the affected phenotype. Disease does not occur when the individual carries mutation only in one gene, e.g. Bardet-Biedl syndrome, retinitis pigmentosa, sensorineural hearing loss, Hirschsprung disease.

Polygenic-Multifactorial Inheritance

This includes conditions where multiple genes, and also the environment, play a role in expression of the disease phenotype. In these disorders the pedigree chart usually shows familial aggregation but the disease phenotype does not segregate in Mendelian proportions. The risk of recurrence in these disorders is derived empirically from population studies, and is influenced by the number of affected individuals in the family. Also, closer the relation of the individual at risk to the proband, higher is the risk of recurrence. It has to be kept in mind that familial aggregation may also occur simply due to sharing of the same environment.

Examples of polygenic inheritance: congenital malformations like neural tube defects, pyloric stenosis, etc., and complex multifactorial disorders like hypertension and coronary artery disease, etc.

CONCLUSION

Pedigree analysis is a very useful tool for elucidation and interpretation of family history. It should be incorporated as a standard practice in clinical medicine and should be learned by all clinicians. Besides its role in genetic counselling, it can greatly help in making the diagnosis, e.g. haemophilia in a child with bleeding, and also as a tool for risk assessment in familial disorders, like diabetes, hypertension, autoimmune disorders, etc.

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6.3 Clinical and Molecular Cytogenetics

Ashutosh Halder

INTRODUCTION

Cytogenetics is a branch of genetics that is devoted to the study of structure and function of cellular constituents concerned with heredity. A chromosome, as seen at metaphase, consists of two identical strands of chromatids. The chromatids are joined at the centromere, which appears as a constriction. The centromere divides the chromosome into a short arm (p), and a long arm (q). Individual chromosomes differ in size. Depending on the position of the centromere, chromosomes are categorised as metacentric (at the centre), submetacentric (slightly away from the centre), acrocentric (near the end) and telocentric (at the end). Human chromosomes are classified into different groups, viz., Group A (chromosome 1-3), Group B (chromosome 4-5), Group C (chromosome 6-12, X), Group D (chromosome 13-15), Group E (chromosome 16-18), Group F (chromosome 19-20) and Group G (chromosome 21-22,Y). Chromosomes of Groups D and G are acrocentric and their p arms do not contain important genes. Chromosomes 1-22 are in pairs (autosomes). Chromosome X and Y are sex chromosomes. A karyotype is a full set of chromosomes from an individual (**Figures 1A and B**). Homologous chromosomes (members of each pair) in meiosis (cell division during gametogenesis) exchange (recombine) DNA segment at crossing-over. It is responsible for genetic variation.

Chromosomal study is carried-out from living nucleated cells through *in vitro* culture methods using cell culture medium containing growth-stimulating agents. A mitotic inhibitor (colchicine) is added to stop cell division at mitosis. The cells are then treated with a hypotonic solution to swell the cells and then fixed in Carnoy's fixative (3:1 methanol to acetic acid). The cell suspension is then dropped onto slides, air-dried and banded using trypsin and Giemsa stain. Other chromosome-banding techniques practiced are quinacrine banding, reverse banding, C-banding, nucleolar organising region staining, etc. High-resolution banding involves analysing chromosomes during prophase or early metaphase (prometaphase), wherein the number of bands increases from about 300 to 800. Analysis of banded chromosomes is done under a microscope by a trained cytogeneticist. Generally, 20 metaphases are analysed from each individual (enough to rule-out mosaicism at clinical significance). The results are reported as per the guidelines of an International System for Cytogenetic Nomenclature (ISCN).

NUMERICAL ABNORMALITY

Normal chromosome complement of 46 (46, XX in female and 46, XY in male) is known as diploid, while one set of 23 chromosomes seen in gametes (23, X in female or 23,Y and 23, X in male) is known as haploid. Error in segregation of chromosomes during cell division leads to gain or loss of chromosome, which is called aneuploidy. It includes missing of a member of the pair (monosomy) or presence of more than two chromosomes in a pair (trisomy for 3 numbers, tetrasomy for 4 numbers, etc). Errors in mitosis result in mosaicism, i.e. two types of cells originated from single cell. Sometimes an individual may have an additional set of haploid (triploidy; 69) or diploid (tetraploidy; 92) chromosomes.

STRUCTURAL ABNORMALITIES

In structural abnormality, the appearance (morphology) of the chromosome is altered. Structural anomalies are classified into the following types:

Deletion

A portion of the chromosome is missing, resulting in loss of genetic material.



Figure 1A: Metaphase cell.

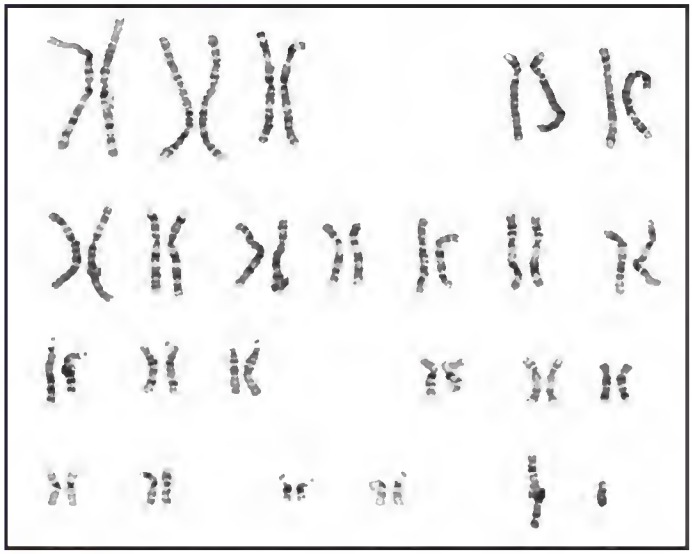


Figure 1B: Karyotyped chromosomes.

Duplication

A portion of the chromosome is duplicated, resulting in extra genetic material.

Translocation

A portion of one chromosome is transferred to another chromosome. There are two main types of translocations, i.e. reciprocal and Robertsonian. In reciprocal translocation, segments from two (or more) different chromosomes are exchanged. In Robertsonian translocation, the long arm of one acrocentric chromosome is translocated to the long arm of another acrocentric chromosome with loss of short arms of both the chromosomes, resulting in one chromosome, derived from two chromosomes. Translocations can be balanced (no gain or loss of genetic material) or unbalanced.

Inversion

A portion of the chromosome breaks, flips around and rejoins, resulting in change of orientation (physical position) of the genetic material.

Ring

Chromosomal ends break (near the tip) and rejoin each other to form a ring. This can happen with or without the loss of genetic material.

Isochromosome

Isochromosome is an abnormal chromosome with two identical arms, i.e. either two short (p), or two long (q) arms. It is formed by faulty chromatid separation during segregation.

Polymorphism

Chromosome polymorphism is a normal variation in appearance (heterochromatin, satellite, etc.) which occurs frequently (5%). It does not give rise to any phenotypic or reproductive problems.

OTHER ABNORMALITIES

Chromosomal Breakage/Instability/Fragility

It is characterised by spontaneous/induced chromosomal instability, breakage, constriction or fragility.

Uniparental Origin

Normally, each member of the pair of chromosomes is derived from each parent. Sometimes, both members of the pair (part or whole) of chromosome may be derived from one parent. Occasionally the entire set of chromosomes may derive from one parent as in molar pregnancy.

CLINICAL EFFECTS OF CHROMOSOMAL ABNORMALITY

The phenotype due to chromosomal abnormality depends on gain or loss, fusion, rearrangement, or altered parental inheritance of genes located on the chromosome. Most aneuploidies of autosomes, unbalanced structural abnormalities of autosomes, triploidies, tetraploidies and other polyploidies are spontaneously aborted. Remaining aneuploidies and unbalanced structural abnormalities of autosomes produce mental retardation and varying degree of dysmorphism. Sex chromosome aneuploidies often produce hypogonadism.

Trisomy 21 Down's Syndrome (DS)

Trisomy 21 is the commonest autosomal aneuploidy in live births (1 in 800 to 1000). It is caused by presence of all or part (21q21-22) of extra chromosome 21 leading to over expression of chromosome 21 genes (amyloid beta A4 precursor protein, microRNAs, etc). It is characterised by mental sub-normality, developmental disability, facial dysmorphism (round face, epicanthic fold, up-slanting palpebral fissures and macroglossia; **Figure 2**), cardiac malformations, and often duodenal atresia, thyroid dysfunction and early onset of Alzheimer's disease. Fertility is reduced; males are usually unable to father children. Majority of cases of DS are due to trisomy 21 where the risk of recurrence in the siblings is negligible. About 4% cases are due to translocation. The risk of recurrence in translocation cases varies depending on the chromosomes involved and sex of the carrier parent (more if mother is the carrier and may be up to 100% with chromosome 21:21 translocation). Birth of a child with DS is preventable through maternal serum screening, prenatal diagnosis and selective termination of pregnancy. Parental age at conception, in particular maternal age above 35 years, increases the risk of DS.



Figure 2: Facial profile in Down's syndrome.

Trisomy 18 (Edward Syndrome)

It is the second most common autosomal trisomy in live births (1 in 3,000). It is more in female births. The incidence increases with maternal age. The affected newborns have a low rate of survival. The syndrome is characterised by multiple congenital malformations of heart, kidneys, central nervous system (CNS), gastrointestinal tract (GIT), etc. besides low-set malformed ears, hypertelorism, cleft lip/palate, clenched hands, underdeveloped thumbs, Rocker bottom feet and joint contractures.

Trisomy 13 (Patau Syndrome)

It affects approximately one in 10,000 live births. It is associated with severe growth retardation and major congenital anomalies. The typical features are holoprosencephaly, microcephaly, microphthalmia, spinal defect, omphalocoele, cleft palate, polydactyly, overlapping of fingers and rocker-bottom feet. Trisomy 13 cases usually do not survive beyond a few months of life.

47, XXY Male (Klinefelter Syndrome)

It is seen in one out of every 1,000 males. The patient is usually tall, and presents with small testicles, reduced fertility and gynaecomastia. About 50% cases of Klinefelter syndrome have mosaicism, where 47, XXY cell line is present along with 46, XX; 46, XY; 48, XXYY or 48, XXXY cell lines.

Other Trisomy of Sex Chromosomes (47, XYY male and 47, XXX Female)

About 1 in 1,000 boys are born with a 47, XYY karyotype. 47, XYY boys may have increased growth velocity, learning difficulty and acne at puberty. Testosterone levels are normal with normal sexual development and fertility. 47, XXX female (triple X syndrome) occurs one in 1,000 girls. It does not cause any unusual features due to lyonisation of the extra X chromosome (leaving only one X chromosome active). However, females with this condition may have menstrual irregularities, including early onset of menarche and early menopause.

Monosomy X (Turner Syndrome; 45, X)

Turner syndrome occurs once in 2,500 female births. Approximately 98% of Turner syndrome conceptuses end up with miscarriage (**Figure 3**). Turner syndrome cases present with short stature, broad chest, low hairline, low-set ears, webbed neck, increased carrying angle of the elbow and gonadal dysfunction. Major systemic problems are also frequently present, including congenital heart defect (bicuspid aortic valve, coarctation of the aorta), kidney defect (horse shoe kidney), hypothyroidism, diabetes mellitus, vision problems, hearing defect, etc.



Figure 3: Turner syndrome abortus with cystic hygroma.

Translocations and Disease

Translocation is caused by rearrangement between parts of nonhomologous (usually) chromosomes. In the process, a fusion gene may be created by joining of two separated genes. This is a common event in cancer, infertility and congenital malformation. Reciprocal translocations are usually harmless. However, if a gene is disrupted or disregulated at the breakpoint, it is likely to cause symptoms like autism, intellectual disability, congenital anomalies, etc. Besides, it can give rise to gametes with unbalanced chromosomes leading to miscarriages or malformations. Robertsonian translocations also increase risk of unbalanced gametes.

Triploidy/Polyploidy Syndrome

Triploidy accounts for 2% of all conceptions, but only one in 50,000 are live births. Triploid newborns die immediately after birth. They present with growth retardation, relative macrocephaly, cleft lip, low-set ears, agenesis of corpus callosum, heart defects, dysgenetic kidney and omphalocoele. The polyploidies generally lead to miscarriage, still birth or partial hydatidiform mole and are often associated with cancer.

Chromosomal Breakage/Instability/Fragile Syndrome

Chromosomal breakages may occur either spontaneously, or be induced by DNA damaging agents like radiation, ultraviolet light or alkylating agents. The examples include Fanconi anaemia, Bloom syndrome, ataxia telangiectasia, xeroderma pigmentosum, etc. These diseases are caused by the defects in DNA repair genes, and have a high-risk of developing malignancies.

Sometimes chromosomal fragility/stricture occurs at defined sites known as fragile sites. One of the common abnormalities is Fragile-X syndrome. These patients have characteristic facial appearance, mental retardation, and may have large testes.

MICRODELETION/MICRODUPLICATION SYNDROMES

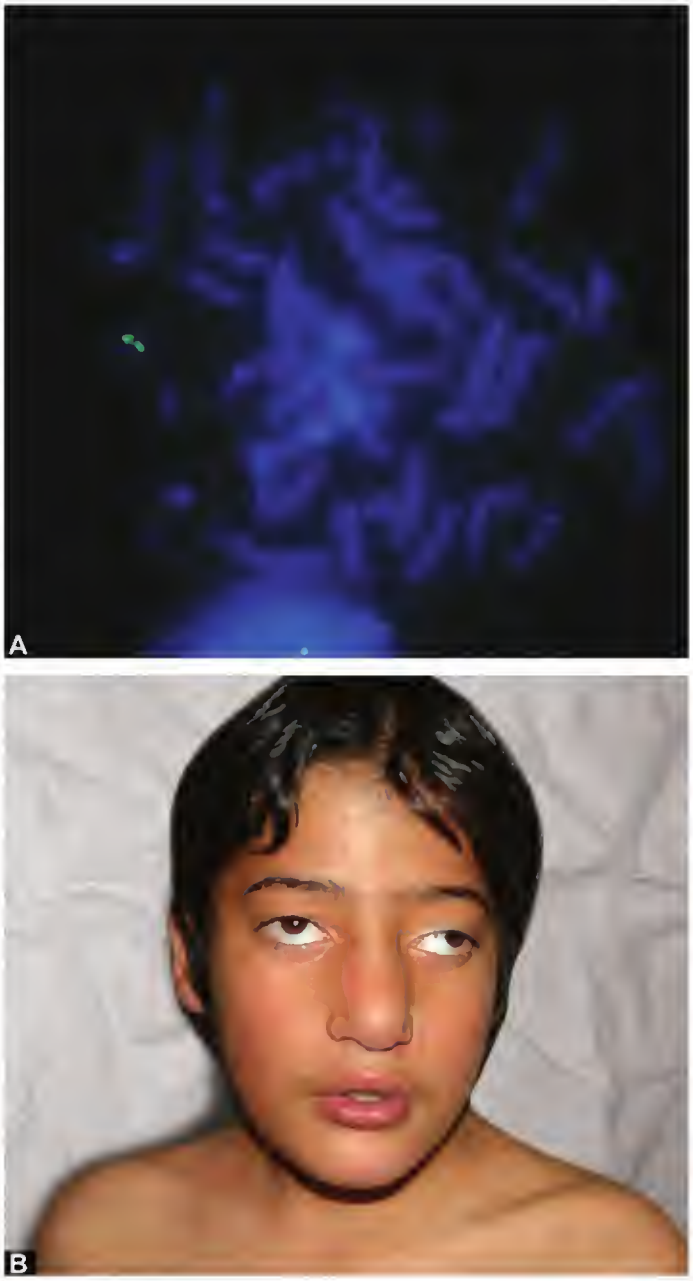
Microdeletion/microduplication syndromes are characterised by small (< 5Mb) chromosomal deletions/duplications in which one or more genes are involved. They are frequently associated with multiple congenital anomalies or neuropsychiatric disease. The phenotype is the result of haploinsufficiency/over-expression of genes in the critical interval. The examples of microdeletion syndromes are Velocardiofacial syndrome (22q11.2), Prader-Willi syndrome/Angelman syndrome (15q11-13), Williams syndrome (7q11.23), Smith-Magenis syndrome (17p11.2), Cri-du-chat syndrome (5p15.2), Miller-Dicker syndrome (17p13.3), WAGR syndrome (11p13), Hereditary neuropathy with pressure palsy (17p12), Wolff Hirschhorn syndrome (4p 16.3), Tricho-rhino-pharyngeal syndrome (8q 24.1) and ATR 16 (16 p 13.3). The examples of microduplication syndromes are Charcot-Marie-tooth neuropathy 1A (17p 12), Alzheimer disease (21q 21.3), Spinocerebellar ataxia type 20 (11q 12), Pelizaeus-Merzbacher disease (Xq 21-22), Parkinson disease (4q 21), etc.

Velocardiofacial/DiGeorge Syndrome

It is the commonest microdeletion syndrome. It is seen with a frequency of 1 in 4,000 births. Almost all cases have 22q11.2 microdeletion (involving *COMT*, *TBX1*, *UFD1L*, *HIRA*, etc. genes; **Figure 4A**). Most deletions are the result of a *de novo* event, though 5% to 10% cases are inherited. The major clinical features are facial dysmorphism (long broad nose with bulbous tip, hypertelorism, low-set ears, etc. **Figure 4B**), palatal abnormalities (velopharyngeal incompetence, submucous cleft palate, etc.), hypocalcaemia, T-cell immunodeficiency, cono-truncal heart defects (tetralogy of fallot, truncus arteriosus, etc.) and learning disabilities.

William Syndrome

Its prevalence is estimated to be one in 7,500-10,000 births. Individuals with this syndrome have periorbital fullness, long philtrum and prominent lips (**Figure 5A**). Cardiovascular anomalies like supravalvular aortic stenosis and pulmonic



Figures 4A and B: Velcardiofacial syndrome: hemizygous deletion of 22q11.2 (A) and facial profile (B).

valvular stenosis are common. Other symptoms include dental malocclusion, hypercalcaemia, hyperacusis and a hoarse voice. Over 90% cases of William syndrome are due to microdeletion of 1.6 Mb size in 7q11.23 locus involving elastin gene.

Prader-Willi and Angelman Syndromes

These are seen with prevalence between 1 in 10,000 to 25,000 births. Prader-Willi syndrome is recognised by almond-shaped eyes and inverted V-shaped upper lip (**Figure 5B**). Neonates present with hypotonia, weak cry, poor sucking and hypothermia. Children present with voracious appetite, obesity, decreased pain, disturbed thermoregulation, psychomotor retardation, and impulsivity. Adolescence cases present with absence of pubertal growth spurt, hypogonadism, small hands and feet, diabetes mellitus and hypercholesterolaemia. Many symptoms of Prader-Willi syndrome are related to hypothalamic dysfunction. The clinical features of Angelman syndrome are microcephaly, large mouth, mandibular prognathism, hypopigmentation and mental retardation (**Figure 5C**). Patients later show truncal ataxia and hypertonia of limbs. Episodes of prolonged laughter, hyperactivity, sleep disorder and seizure are also common. Both Prader-Willi and Angelman disorders result from loss of 15q11-13 (SNRPN, MKRN3, MAGEL2, necdin, UBE3A, etc. genes) – the difference being that Prader-Willi syndrome is of paternal origin while Agelman syndrome AS is of maternal origin in 70% to 75% cases.



Figures 5A to C: Facial profile of William syndrome (A); Prader-Willi syndrome (B); and Angelman syndrome (C).

Charcot-Marie-Tooth Disease Type 1A (CMT 1A)

This is one of the most common inherited neurological disorder that affects one in 3,000 individuals. It is associated with

duplication (in 90%) of 17p11.2 *(PMP22;* **Figure 6***)*. Clinical presentation comprises of toe walking, pes cavus, claw hand, slapping gait, foot drop, absent or decreased deep tendon reflexes, nerve hypertrophy and loss of touch sensation predominantly in feet and legs.

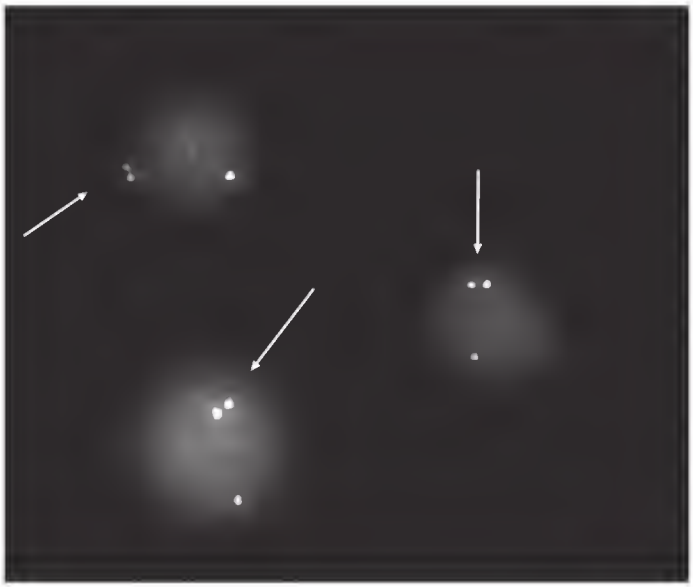


Figure 6: Hemizygous duplication (arrow) of 17p11.2 locus in a case of Charcot-Marie-Tooth disease Type 1A *(Courtesy: Prof. Mariano Rocchi, Uniba Biologia, Italy)*.

GENOMIC DISORDERS

Genomic disorders are a group of diseases that result from genomic rearrangements, such as insertions, deletions, duplications, inversions, etc. Human genome is a highly dynamic structure. Approximately 5% (~800 genes) of the human genome is structurally variable in the normal population. Genome architecture makes the genome susceptible to rearrangements through recombination mechanisms. Non-allelic recombination between low-copy repeats (LCRs) results in loss or gain of genomic segments. LCR DNA spans 10-400 kb, shares ~97% sequence homology and provides the substrate for recombination, thus predisposing the region to rearrangements. The mechanisms by which rearrangements contribute to various phenotypes (such as diversity, traits, susceptibility, behaviour or disease like microdeletion/duplication syndromes, schizophrenia, autism, etc.) are diverse and include gene dosage alterations, gene disruption, gene fusion, position effects, mutations, etc. Rearrangements introduce variation into our genome and serve as evolutionary function.

FLUORESCENCE *IN SITU* HYBRIDISATION (FISH)

FISH is a molecular cytogenetic technique used to detect and localise presence or absence of specific DNA sequence on chromosomal/nuclear DNA. It uses fluorescent probes (labelled nucleic acid sequence) that bind to DNA that have sequence homology. There are two types of FISH techniques—direct and indirect. In the direct method (**Figure 7**), fluorescent molecules (FITC, Cy3, etc.) are directly attached (enzymatically or non-enzymatically) to the probe so that probe-target hybrid can be visualised under fluorescent microscope immediately after hybridisation. In the indirect method, reporter molecules (biotin or digoxigenin) are attached to the probe and the probe is detected by either affinity cytochemistry with fluorescent dyes (indirect FISH) or chromogenic dyes (chromogenic *in situ* hybridisation or CISH). The probe can be cloned DNA sequence, or generated by polymerase chain reaction (PCR) from flow-sorted chromosomes, micro-dissected chromosomes or even whole genome. Probes may be from alphoid sequence of centromeres (150-250 bp repeats), telomeric/subtelomeric sequence (5-6 bp repeats), or unique sequence (100-500 Kb), etc. FISH is highly sensitive and can detect cell-cell heterogeneity and mosaicism. Further, FISH has been modified to spectral karyotyping, Rx FISH, or Multiplex FISH to identify all 24 chromosomes in one experiment; fibre FISH to characterise break points or Padlock probe FISH to improve resolution to single nucleotide level.

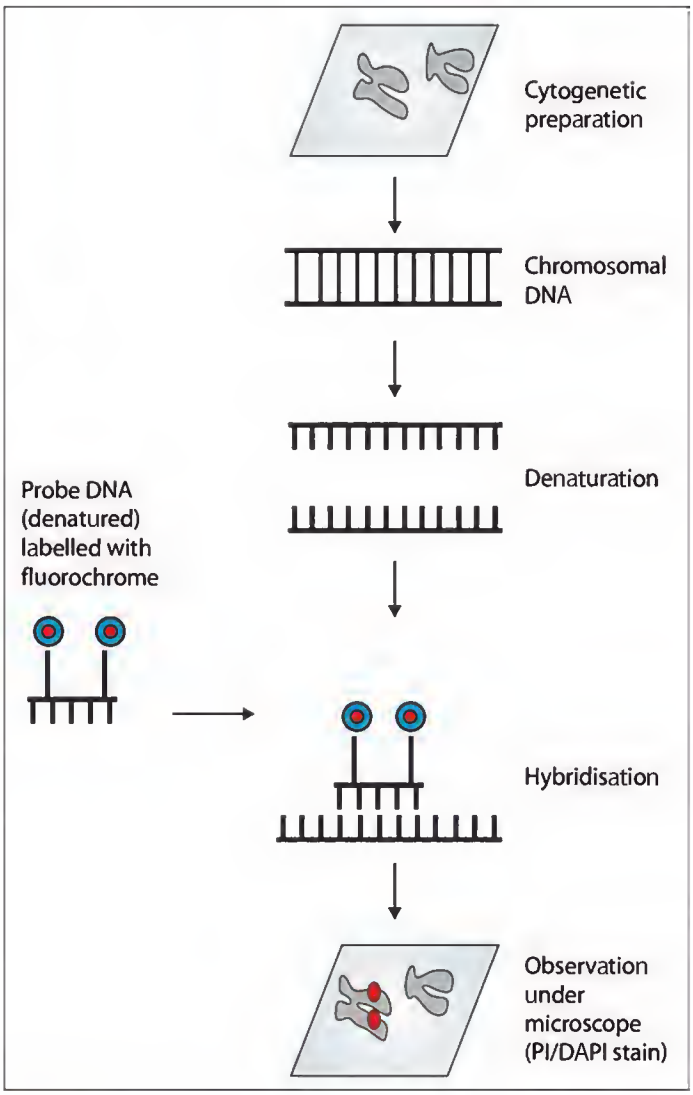
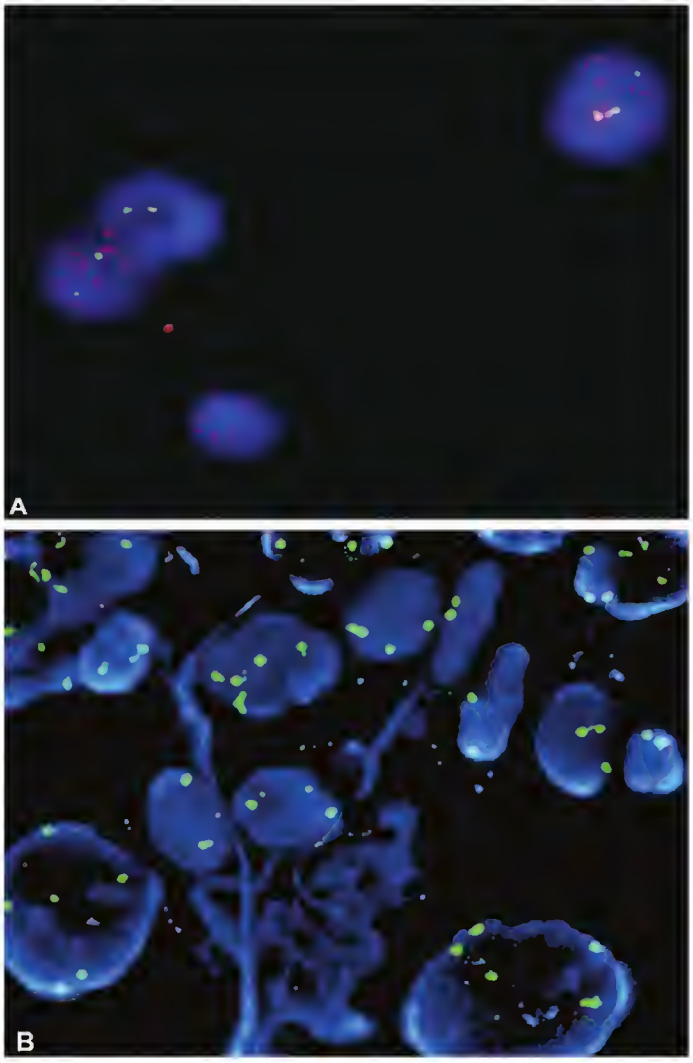


Figure 7: Various steps of FISH procedure.

The major application of FISH is in the field of cancer (**Figures 8A and B**) followed by prenatal diagnosis (PND), preimplantation diagnosis (PGD), microdeletion-microduplication syndrome diagnosis, specific postnatal diagnosis and meiotic segregation error study. Detection of cancer-specific chromosome abnormality such as Philadelphia chromosome (bcr-abl fusion gene) assists in diagnosis/sub-classification of disease and selecting appropriate treatment besides monitoring of minimal residual disease, early relapse and engraftment of sex-mismatched allogenic bone marrow transplant. Rapid prenatal diagnosis can be made using FISH (**Figures 9A and B**) that

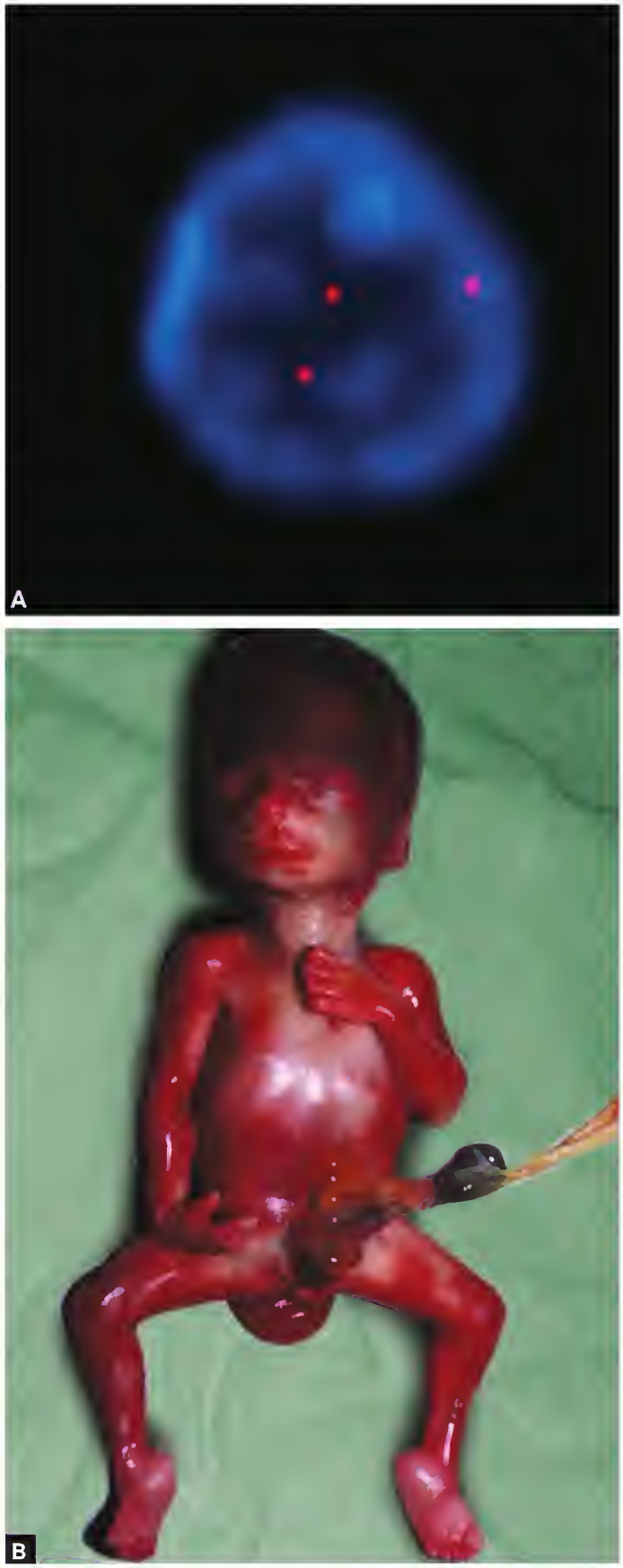


Figures 8A and B: Interphase FISH on tumour cells showing gene amplifications C MYC and cells-to-cells heterogeneity (A); copy numbers 1 to 6 with chromosome 1 FISH (B).

reduce parental anxiety and guide obstetric management quickly. In PGD, typically one or two blastomeres are biopsied from embryo and subjected to FISH for aneuploidy screening or specific translocation identification. FISH is capable of doing rapid sexing in a situation like ambiguous genitalia at birth where immediate assignment of sex is required for not only social reason but also for appropriate management. It has similar value in an acutely sick baby with congenital malformation syndrome suggestive of aneuploidy or microdeletion syndrome requiring urgent intensive care. FISH is the main modality of chromosome analysis for meiotic chromosome segregation and microdeletion syndrome besides the study of chromosome function and behaviour in interphase cells.

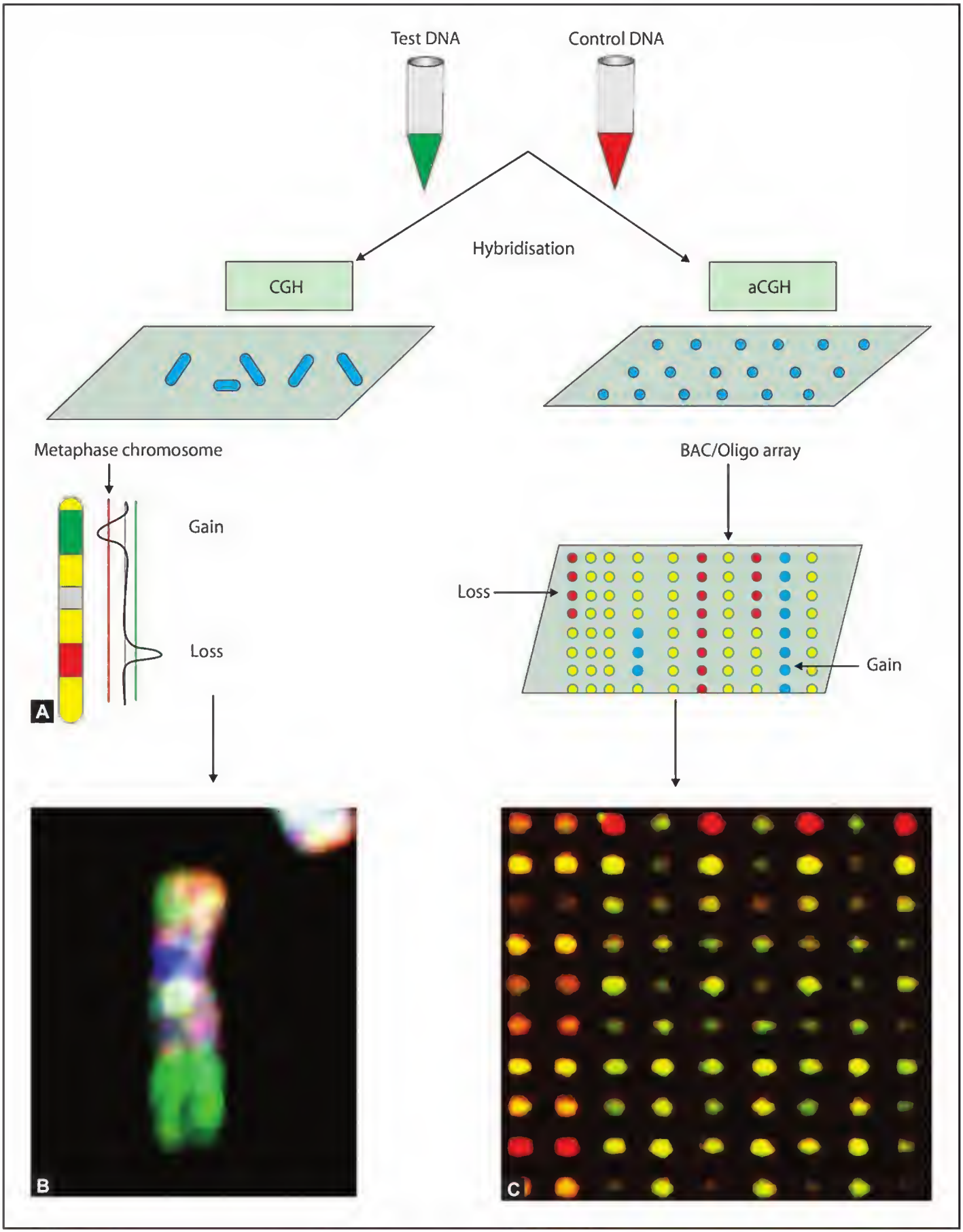
COMPARATIVE GENOMIC HYBRIDISATION (CGH)

CGH is a FISH technique that allows comprehensive analysis of chromosomal imbalance (relative copy number) in entire genome (molecular karyotyping at cytogenetic resolution; ~5 Mb) by single test without metaphase preparation and cell culture of the test samples. The strategy of CGH is based on co-hybridisation of differentially labelled whole genomic test and control DNA in equal ratio on normal metaphase spread, like dual FISH (**Figures 10A to C**). The slide is visualised using epifluorescence microscope. Image processing along with



Figures 9A and B: Interphase FISH on amniotic fluid cells showing 3 copies of chromosome 18 (A); leading to termination of pregnancy with trisomy 18 foetus (B).

quantification of fluorescence intensities of each karyotyped chromosome is done by computer software. Hybridisation results into general staining of all chromosomes. If the test DNA

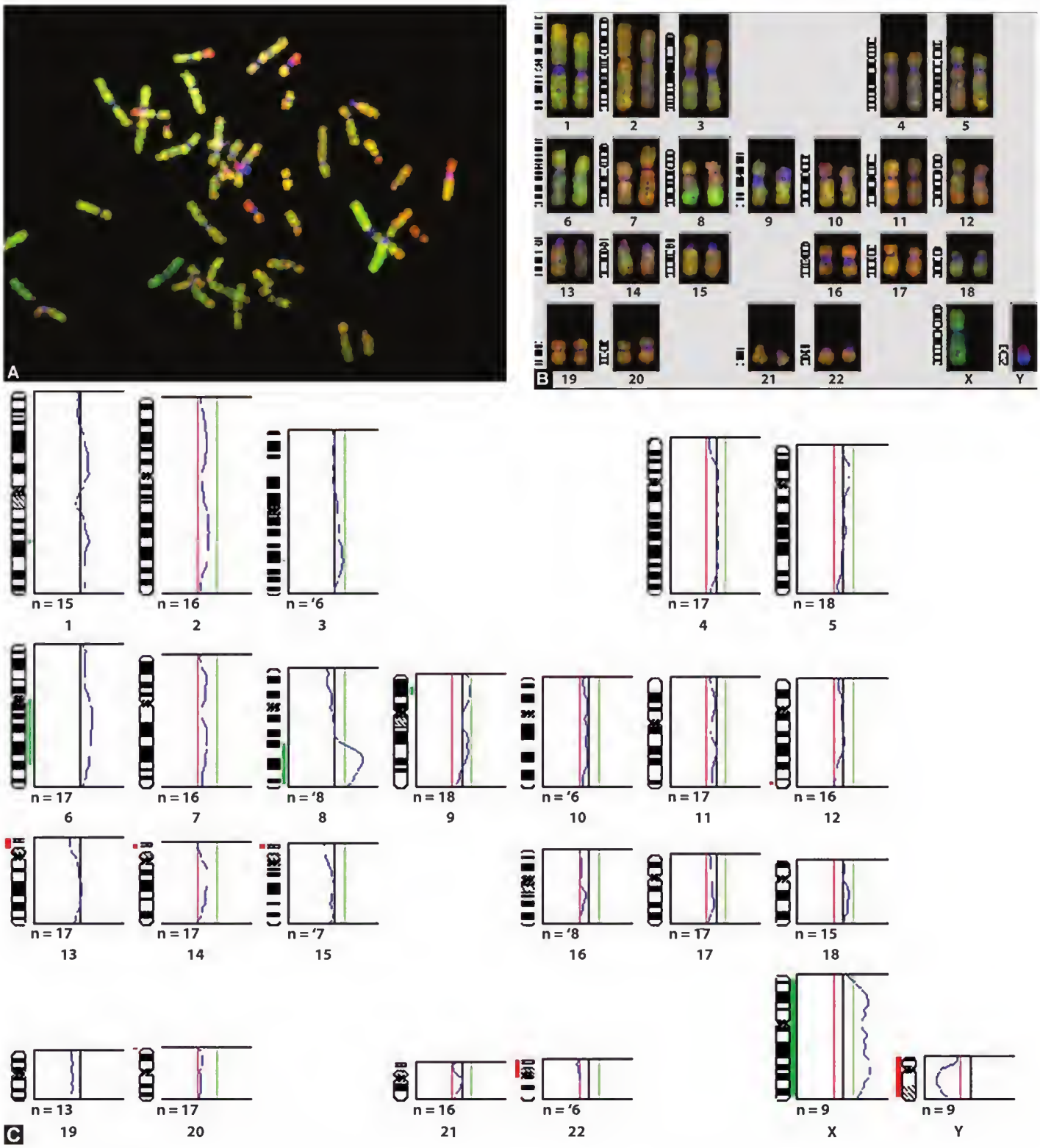


Figures 10A to C: Showing principles of CGH and high resolution molecular karyotyping (aCGH) procedure (A); CGH binned view of chromosome 8 showing C MYC amplification (B); and magnified view (C) of array showing DNA amplifications (green spots), deletion (red spots) and no change in copy numbers (yellow spots).

contains additional copies of DNA material, hybridisation will reveal higher signal intensity of test DNA (if labelled with green, then more green) at the corresponding target region of the hybridised chromosome. Similarly, deletion/monosomy will give rise to lower signal intensities (**Figures 11A to C**). The CGH cannot detect mosaicism of less than 40%, balanced translocation and tetraploidy. CGH is labour intensive, difficult (karyotyping of DAPI banded chromosome) and time consuming. This technique is getting replaced by high resolution molecular karyotyping.

HIGH RESOLUTION MOLECULAR KARYOTYPING (ARRAY CGH)

High resolution molecular karyotyping is an extension of CGH. It is carried-out on the principle of CGH (**Figures 10A to C**), though with some modifications (co-hybridisation is carried out on DNA spots/arrays rather than metaphase chromosomes). Following hybridisation of differentially labelled test and reference genomic DNA to the target sequences on the microarray, the slide is scanned to measure



Figures 11A to C: Showing CGH metaphase (A) green as amplification, red as deletion, yellow as no change in copy numbers and blue as heterochromatin karyotype (B); and profile/analysis (C) from tumour samples (green amplification and red deletion).

fluorescence intensities at each target on the array. The fluorescent ratio for the test and reference DNA is then plotted against the position of the sequence along with the chromosomes. Gains or losses across the genome are shown by values higher or lower than normal 1:1 ratio (as in CGH). The resolution depends on the size, number of targets and position of targets on the genome. It also depends on the platform used (BAC based arrays have lower resolution than SNP based arrays). The molecular karyotyping result is presented using the ISCN, along with a written description and interpretation of the result. Molecular karyotyping (aCGH) procedure is rapid (24-36 hours). It provides whole genome view at a very high resolution (up to 100 Kb), and does not depend on live cell, or cell culture. It detects majority of microscopic as well as sub-microscopic chromosomal changes from any DNA source in a single experiment without prior knowledge of abnormalities. The only limitation is its inability to detect polyploidy or balanced chromosome abnormalities. It has the potential of diagnostic application in the evaluation of multiple malformations, mental retardation, prenatal diagnosis and cancer. Now disease-specific (microdeletion syndrome), chromosome-specific, or other (sub-telomeric) arrays are available for specific applications.

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6.4 Genetic Tests

Ashwin Dalal

Advances in the field of genetics have made it possible to detect genetic abnormalities in increasing number of genetic disorders. This has brought the field of medical genetics to the forefront of clinical practice.

DEFINITION

Genetic testing is defined as 'the analysis of human DNA, RNA, chromosomes, proteins, and metabolites to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes'. It includes a broad range of techniques that can be used for diverse applications, including diagnosis of genetic disease in foetuses, newborns, children, and adults; identification of future health risks to the individual; and prediction of drug responses, etc.

HISTORY

Genetic testing before 1959 was limited to biochemical tests like G6PD test, sickle cell test, etc. since necessary tools for direct genetic analysis were not available. Lejeune for the first time discovered the chromosomal cause of Down's Syndrome in 1959 which led to application of genetic testing in humans. Since then the field of cytogenetics has blossomed to cover a wide range of disorders, particularly genetic syndromes, mental retardation, congenital malformations and cancer *(see chapter on cytogenetics)*. Direct detection of genetic mutations in humans had to wait till the 1970s when discovery of restriction endo-nucleases, cloning of human genes and blotting techniques made it possible to amplify and probe human DNA. The completion of Human Genome Project in 2003 has heralded a new era of 'molecular genetics'. The number of genetic tests for human diseases has increased to several thousand in the last 20 years.

CLASSIFICATION OF GENETIC TESTS

Genetic tests can be classified into the following categories based on the purpose for which these are conducted:

1. Diagnosis including prenatal diagnosis (PND) of human genetic diseases
2. Predictive testing for genetic markers associated with polygenic disorders, and presymptomatic diagnosis; and
3. Forensic testing for establishment of identity, paternity testing, and zygosity testing, etc.

Diagnosis and Prenatal Diagnosis of Human Genetic Disease

Genetic tests are commonly employed for the diagnosis and prenatal diagnosis of human single gene disorders. Many of the single gene disorders can be diagnosed based on typical clinical features (tuberous sclerosis, neurofibromatosis), or investigations like muscle biopsy and immunohistochemistry (Duchenne muscular dystrophy), haemoglobin electrophoresis (beta thalassaemia), factor VIII level determination (haemophilia A), etc. In these cases, however, knowledge of genetic mutations is a prerequisite for prenatal diagnosis. Presence of DNA from at least one affected member in the family can be of great assistance in identifying the mutation in the family for counselling and PND. In contrast, there is another group of diseases where genetic testing is the only way to conclusively diagnose the disease condition as there is no other diagnostic test available, e.g. Huntington disease, spinocerebellar ataxias, Friedreich's ataxia, etc. This also includes use of genetic tests for carrier testing and preimplantation genetic diagnosis (PGD). Genetic tests can also be used for diagnosis and classification of tumours, prognostic prediction and diagnosis of cancer predisposing conditions, e.g. familial adenomatous polyposis *(see chapter on Cancer Genetics)*.

Predictive Testing

Predictive testing is done where the person is not having any signs or symptoms of the disease but is likely to develop the condition in future. This information can be used to prevent or delay onset of the disease, if appropriate medical or lifestyle interventions are available. Predictive testing includes pre-symptomatic and predisposition testing.

In pre-symptomatic genetic testing, a healthy person is tested for diseases with delayed onset. A positive result indicates that the patient will develop the condition but does not indicate when this will occur. Evaluating a healthy person with a family history of Huntington disease is an example of pre-symptomatic genetic testing. Although there is no cure for this disease, a positive result can be used for life planning, including reproductive planning, etc. However, it is essential to provide adequate and appropriate pre-test and post-test counselling to the patient in these cases.

Predisposition genetic testing informs individuals of increased or decreased risk of developing a particular disease, however, the degree of certainty is unknown. This most often applies to cancer predisposition testing (e.g. BRCA1, BRCA2 in breast-ovarian cancer families, etc.) in which a positive result indicates need for increased surveillance, while a negative result implies risk similar to the general population. Eventually, this area is likely to include risk estimates for a wide range of common disorders like hypertension, diabetes mellitus, coronary artery disease, etc. and response to drugs and other treatments (pharmacogenetics).

TECHNIQUES IN GENETIC TESTING

Genetic testing by molecular genetic methods involves various techniques designed to amplify and probe the DNA so that meaningful information can be obtained. All molecular DNA tests need DNA to be extracted from a patient's sample containing some nucleated cells. DNA is commonly extracted from peripheral blood leukocytes or tissue samples in cases of cancer. The DNA once extracted can be stored for long

periods in a stable condition and subjected to various tests as required.

Southern Blotting

Southern blotting is a method of detection of mutations in which genomic DNA is isolated from peripheral blood leucocytes or solid tissue samples and digested with a restriction endonuclease. Restriction endonucleases are nucleolytic enzymes which cut the DNA at a specific sequence. This is followed by size separation by electrophoresis. The size-fractionated DNA is transferred to a solid membrane support by means of capillary action and target sequences are detected by hybridisation with sequence-specific probes labelled with radioisotopes. Although, Southern blotting remains a useful technique for detecting large deletions or genomic rearrangements, it is seldom used in clinical laboratories due to its labour intensive and cumbersome nature. Southern blotting is rapidly being replaced by assays based on fluorescent dyes which eliminate the risk of radiation. However, Southern blotting still remains the gold standard in testing for certain diseases like triplet repeat disorders, e.g. fragile-X syndrome.

Polymerase Chain Reaction and Its Applications

Polymerase chain reaction (PCR) was discovered by Kary Mullis in 1983. This technique allows selective amplification of specific target nucleic acid sequences from total DNA using a pair of 15-25 nucleotide long forward and reverse primers specific for the target region to be amplified. The main components of a PCR reaction include a heat stable DNA polymerase, four nucleotide triphosphates (dATP, dGTP, dCTP and dTTP) and a suitable buffer containing magnesium ions. The basic steps of a PCR cycle are shown in **Figure 1**. They include the following:

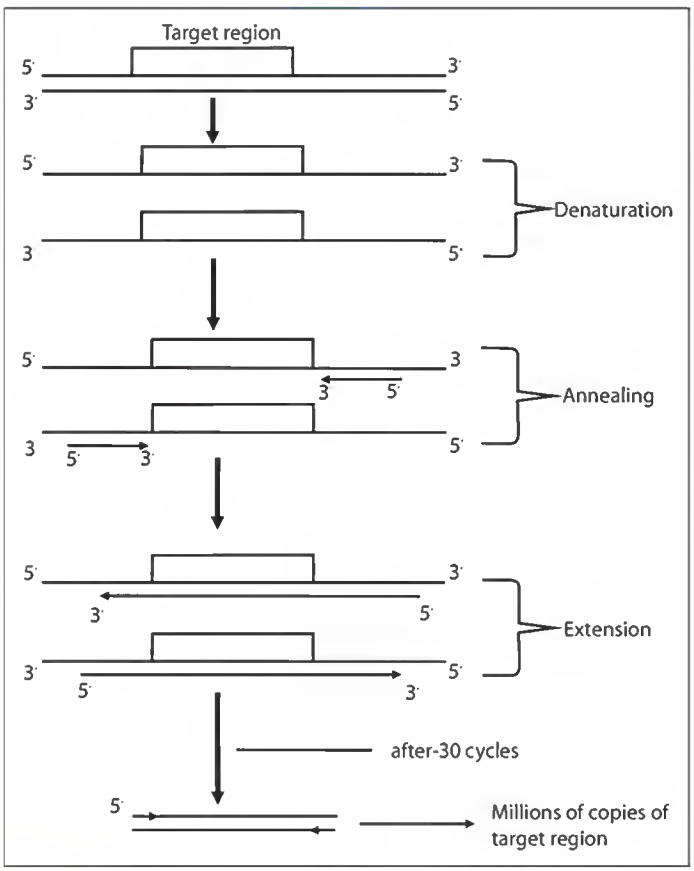


Figure 1: Principle of polymerase chain reaction.

1. *Denaturation:* The template DNA which is double-stranded is separated to single strands at a temperature of around 92-96°C;
2. *Annealing:* Primers bind to the specific target regions of the single-stranded DNA at a temperature of around 50-65°C (exact temperature is specific for each primer pair); and
3. *Extension:* The primers are extended at a temperature of around 68-78°C in the presence of DNA polymerase, dNTPs and Mg^{2+} ions. The concentration of Mg^{2+} ions is critical for each PCR reaction. It is determined empirically.

The newly synthesised DNA strand acts as a template for the next cycle, which is repeated around 25 to 30 times, leading to formation of millions of copies of the specific target DNA. In order to retain the activity of DNA polymerase enzyme at such high denaturation temperature, *Taq* DNA polymerase, extracted from a micro-organism called *Thermus aquaticus* is used in the PCR reaction. This particular enzyme has an optimum working temperature around 80°C.

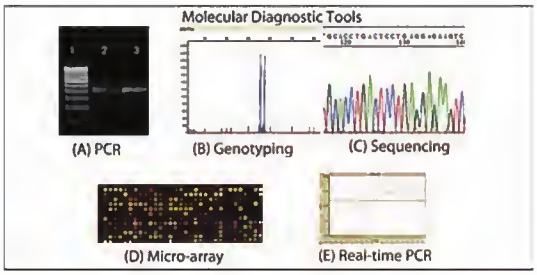
Applications of PCR

PCR is the starting point in most of the molecular genetic tests. Some important clinical applications of PCR are as follows (**Figures 2A to E**):

1. *Mutation detection for genetic disorders:* Genetic mutations can be detected by PCR alone (e.g. Huntington disease), PCR followed by digestion with restriction endonucleases (for detection of restriction fragment length polymorphism) (e.g. diagnosis of spinal muscular atrophy), PCR followed by dot-blot hybridisation (e.g. thalassaemia mutation detection), PCR followed by capillary electrophoresis for genotyping (e.g. detection of triplet repeat disorders), etc.
2. *Sequencing:* PCR is used as first step for DNA amplification for all methods of DNA sequencing.
3. *Detection of pathogens:* PCR is used to detect small quantities of pathogen DNA in human samples, e.g. PCR for *Mycobacterium tuberculosis*. PCR can also be used to detect viruses, including use of reverse transcriptase enzyme for RNA viruses, and real-time PCR (RT-PCR) for quantification of viral load in diseases like hepatitis B and C, human immunodeficiency virus (HIV), etc.
4. *Forensic genetics:* PCR is used in forensic laboratories to identify DNA sequences that are unique to each individual.

Real-time PCR and its applications

The RT-PCR is a type of PCR which allows quantification of the PCR product in 'real-time'. It is used to quantify the amount/number of copies of input DNA/RNA. The method utilises 5'-exonuclease activity of *Taq* polymerase, and a dual-labelled internal non-extendable probe with reporter dye at one end and quencher dye at the other end. The probe emits fluorescence signal on cleavage, based on the principle of fluorescence resonance energy transfer (FRET). To start with, the primer binds to the DNA and is extended by *Taq* polymerase. As the extended end of the primer approaches the probe already bound to specific region of the template DNA, the 5'-exonuclease activity of the polymerase enzyme cleaves the reporter dye present at 5' end of the probe resulting in increase of reporter fluorescence emission (e.g. FAM at 518 nm) in



Figures 2A to E: Molecular diagnostic tools used in the molecular genetics laboratory. Agarose gel electrophoresis showing 100 bp ladder in lane 1 and PCR product (450 bp) in lanes 2, and 3 (A); Capillary electrophoresis for genotyping showing 2 alleles (blue peaks) and sizing ladder (red peaks) (B); Electropherogram showing sequence of nucleotides (C); Micro-array slide showing dots corresponding to amplification (green dots), deletion (red dots) and normal (yellow dots) (D); Real-time PCR showing exponential increase in PCR product (red line) followed by plateau formation (E).

every cycle. The RT-PCR is used for a broad range of applications including quantitative gene expression analysis, single nucleotide polymorphism (SNP) genotyping, point mutation detection, copy number analysis, quantification of viral load, and drug target validation, etc.

DNA Sequencing

DNA sequencing is a PCR-based technique in which sequence of the DNA can be determined at single nucleotide level. Various methods employed in the past used radioactivity for detection of sequences. More recent methods are based on fluorescent dyes. Some of these methods include:

1. *Chain termination method:* It was developed by Sanger in the 1970s. In this method, PCR is carried out in presence of small amounts of dideoxynucleotides (ddNTPs), in addition to usual constituents of the reaction mixture. Each ddNTP is labelled with a different fluorescent probe. Incorporation of ddNTP, which lacks the 32-hydroxyl group on the ribose sugar, required for continuation of the polymerisation process, blocks further elongation of the DNA chain. For example incorporation of ddATP in place of dATP at sites where thymine is present in the template DNA will lead to formation of DNA fragments of different sizes ending with ddATP. Correspondingly, DNA fragments of different sizes ending with ddTTP, ddCTP and ddGTP are produced. All the different sized fragments are then resolved by capillary electrophoresis and resulting electropherogram is analysed by software, such as Chromas 2.0, etc. which calls the sequence of individual bases in the DNA.
2. *Micro-array:* In this method small oligonucleotides with varying combination of nucleotides are used and the sequence is detected based on hybridisation of the template DNA with the immobilised oligonucleotides.
3. *Next generation sequencing:* The present methods of sequencing using capillary electrophoresis can be used for sequencing of limited number of base pairs at a time. These are being replaced by high throughput sequencing methods called next generation sequencing methods which can sequence the entire human genome of 3 billion base pairs for less than $5,000. It is hoped that the newer technologies will bring down the cost to less than $1,000 in the near future.

Forensic Genetic Testing

Forensic testing uses DNA sequences to identify an individual for legal purposes. This type of testing can identify crime or catastrophe victims, rule-out or implicate a crime suspect, or establish biological relationships between people (for example, paternity).

Association Studies in Complex Disorders

Complex disorders or multifactorial disorders are conditions resulting from interplay of genetic susceptibility and environmental influences. Very little is known about the genetics of these disorders. Traditional genetic methods like linkage analysis cannot be used for deciphering the genetic factors in these disorders. Hence, we have to resort to association studies, similar to the ones conducted for deciphering the environmental factors involved in these diseases, e.g. smoking and lung cancer. Genetic association studies look at the association of SNPs with occurrence of a particular disease, using a set of cases and controls from specific ethnic populations. When such a study is conducted by looking at thousands of SNPs throughout the genome, these studies are termed as Genome Wide Association Studies (GWAS). These types of studies need high throughput methods which can detect multiple SNPs in a single assay. This type of high throughput data can be generated using micro-arrays which can detect millions of SNPs in a single assay.

Microarrays

Microarray is a collection of small oligonucleotides spotted on to a glass slide or silicon chip. The micro-array technique is based on complementary hybridisation of nucleic acids. In this technique, sequence complementarity leads to the hybridisation between two single-stranded nucleic acid molecules, one of which is immobilised on a matrix like glass slide or silicon chip. There are two types of the chips: cDNA micro-arrays and oligonucleotide arrays. They differ in the size of the arrayed nucleic acids. In cDNA micro-arrays, relatively long DNA molecules are immobilised on a solid surface such as membranes, glass or silicon chips. These types of arrays are used for large-scale screening and expression studies. The oligonucleotide arrays are spotted with short nucleic acids (oligonucleotides up to 25 nucleotides) and are useful for the detection of mutations and expression monitoring, gene discovery and mapping.

Applications of cDNA arrays: expression profiling

cDNA arrays are used for expression profiling by hybridising cDNA obtained from specific samples/tissues to look for up-regulation or down-regulation of genes in disease states so that this knowledge can be used to develop new biomarkers and treatment strategies. Expression profiling has been used extensively for various cancers and has resulted in development of novel drugs for treatment of various cancers, e.g. monoclonal antibody (trastuzumab) treatment in cases of breast cancers with HER2/neu gene amplification.

Applications of oligonucleotide microarrays

Oligonucleotide microarrays are used for typing of alleles at different loci throughout the genome. They can be used for:

1. Detection of mutations in human genetic disorders
2. Detection of microdeletions/microduplications and copy number changes throughout the genome.

3. Genotyping of SNPs: The data obtained from typing of these polymorphisms can be used for genome-wide association studies in multifactorial disorders like hypertension, diabetes mellitus, etc. and mapping of genes for single gene disorders by linkage analysis.

SPECIAL CONSIDERATIONS IN HUMAN GENETIC TESTING

Genetic test results not only apply to the individual across his/her entire lifespan, but have implications to other family members as well. Hence, special considerations need to be kept in mind while ordering a genetic test.

1. *Confidentiality:* It is very important to maintain confidentiality regarding the results of genetic tests since they have a bearing on various issues like insurance, job security, etc.
2. *Quality assurance:* As newer and newer methods and assays are available for genetic testing, proper quality control needs to be maintained by the testing laboratories. Accreditation of laboratories and practice of internationally recognised standards and guidelines needs to be ensured.

LIMITATIONS OF GENETIC TESTING

The patient needs to be counselled regarding limitations of genetic tests before conducting the test. Some limitations of genetic tests include:

Multiple Mutations

Different types of mutations can result in a single phenotype/disease, e.g. Duchenne muscular dystrophy can be caused due to deletion of any/some of the 79 exons in dystrophin gene or due to point mutations in the same gene. Thus, we have to use different genetic methods to look for deletions and point mutations to establish the genetic basis of this disorder.

Errors in Genetic Testing

Various errors can occur during genetic testing either due to human errors, machine related errors, reagent related errors, etc. All precautions need to be taken to prevent errors during genetic testing. It is recommended always to use a positive and negative control during assays like PCR so that errors due to contamination of foreign DNA can be avoided.

Limited Information

The genetic basis of some disorders is not completely understood and hence genetic testing in these diseases will give limited information regarding genetic etiology, e.g. retinitis pigmentosa, deafness, etc.

DIRECT-TO-CONSUMER TESTING

Direct-to-consumer (DTC) genetic testing is advertised and offered directly to the consumer without having to go through a health care professional. In this case the test can be ordered by the patient, family member at risk, or anyone from the population on-line themselves. While on one hand it offers the advantage of privacy and confidentiality, on the other it suffers from the danger of creating confusion due to misinterpretation of genetic information. A variety of DTC tests are being offered by different companies, ranging from testing for breast cancer risk, macular degeneration risk, adverse drug reaction risk, etc. to ancestry analysis. The DTC testing is not under any regulation regarding marketing claims, and quality of services provided. Advertising of DTC has been criticised for conveying exaggerated and inaccurate messages about connection of genetic test result and disease risk, utilising emotions as a selling factor. Truly speaking, we still do not have enough data to quantify the risks conferred by the risk alleles towards occurrence of various disease phenotypes. It would be advisable to defer the application of DTC tests until such data and knowledge is available.

Properly designed educational programmes are urgently needed to aid the medical fraternity and general public in understanding implications of molecular diagnostic studies. Judicious application of molecular genetic testing can go a long way in improving the health of populations in future.

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6.5 Inborn Errors of Metabolism

Madhulika Kabra

Traditionally, management of patients with inborn errors of metabolism (IEM) has been a concern of paediatricians. Most of these disorders present exclusively in infancy and childhood, and due to their severity patients may succumb early in life. Paediatric forms of the disease are more severe, hence, more easily recognisable. Newborn screening programmes for several of these disorders exist in developed countries, and have helped in early diagnosis and prompt management. Early diagnosis, strict dietary management, biochemical interventions, and careful medical care have led to increasing number of patients with inherited biochemical defects surviving into adulthood.

In addition to increasing age of survival of children with early-onset biochemical disorders, some milder variants first present late as adult-onset disease. It is now clear that potentially every disorder has a milder form with a later onset and there is a distinct possibility that diagnosis in adults may be missed due to lack of awareness among physicians. Examples include adults with organic acidaemia and movement disorders, urea cycle disorders, late onset lysosomal storage disorders, etc. The age of onset is determined by the presence of variable activity of the defective enzyme that results from different genetic mutations. Adult female carriers of the X-linked ornithine transcarbamylase deficiency may have variable manifestations of hyperammonaemia after protein ingestion—confusion, ataxia, migraine headache, or even frank coma. Internists not only need to assume responsibility of taking care of surviving patients, but should also be competent to diagnose and manage adult-onset IEM.

DEFINITION AND EPIDEMIOLOGY

IEM are conditions caused due to a genetic defect related to synthesis, metabolism, transport or storage of various biochemical compounds. The genetic defect usually causes deficiency of one or more enzymes or transport proteins.

Worldwide incidence of IEM has been estimated to be about 3-4 per 1,000 live births. More than 300 such defects are known. Most IEM are inherited in an autosomal recessive manner, some are X-linked. Exact incidence of IEM in India is not known as no population based data is available. In one study, 5% of the cases of mental retardation due to genetic cause were due to IEM [Indian Council of Medical Research (ICMR) multicentric study]. In other studies from India, 0.5% to 2.4% of mentally retarded children have been reported to have an amino acid metabolism disorder.

AETIOPATHOGENESIS

IEM are disorders which are caused by deficiency of an enzyme that leads to a block in the metabolic pathway. This leads to: (i) deficiency of the end product, (ii) accumulation of the substrate, and (iii) generation of secondary metabolites through some alternate pathway. Symptoms are caused both due to deficiency of the product and accumulation of the substrate/alternate metabolite. **Figure 1** illustrates the mechanism.

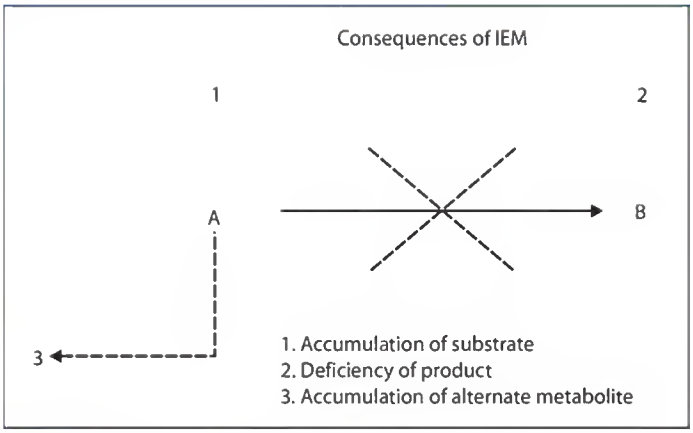


Figure 1: Consequences of enzyme deficiency in a metabolic pathway.

CLASSIFICATION

IEM are classified in two major groups—small molecule diseases and large molecule diseases (**Table 1**).

Table 1: Clinical Classification of Inborn Errors of Metabolism

Acute (generally present in infancy)	Intermittent (Precipitated by stress, infection, starvation, diet)	Chronic (generally present late in childhood/adults)
Due to small molecule defect (amino acids, organic acids, simple sugars, etc)	Caused due to milder metabolic derangement	Due to large molecule defect (storage disorders) (energy deficiency)
Poor feeding, vomiting, lethargy Convulsion, hypotonia Cataract Abnormal body odour Negative septic screen in a sick infant	Repeated episodes of Reduced level of consciousness Acidosis or ketosis or hypoglycaemia Weakness Ataxia/spasticity vomiting, Reye syndrome like episodes	Progressive central nervous system degeneration manifested as seizures, development delay or failure to thrive, mental retardation Hypotonia/spasticity, muscular weakness Associated organomegaly, abnormal fundus, coarse facies

The major categories of IEM which can present as an acute emergency include—organic acidurias (OA), fatty acid oxidation (FAO) defects, mitochondrial encephalomyelopathies, aminoacid disorders [phenylketonuria (PKU), maple syrup urine disease (MSUD), non-ketotic hyperglycinemia (NKH), tyrosinaemia], urea cycle defects (UCD) and disorders of carbohydrate metabolism (galactosaemia)].

CLINICAL PRESENTATION AND SUSPICION OF IEM

Infants and Children

The classical presentation in newborns is of an initial period of normalcy, followed by symptoms, usually getting precipitated

by feeding which resemble sepsis. In infants and older children, symptoms may get precipitated by intercurrent illness or dietary factors and may be intermittent. If untreated, patients may rapidly deteriorate and slip into encephalopathy. History of consanguinity, family history of developmental delay or sudden infant death syndrome, onset of symptoms with institution of feeds, unexplained growth disturbances, recurrent vomiting, poor feeding, seizures, apnoea, breathlessness may be important clues.

Physical findings

Clinical findings are non-specific and include tachypnoea, apnoea, lethargy, hypertonia, hypotonia, hepatosplenomegaly, ambiguous genitalia, jaundice, dysmorphic or coarse facial features, rashes or patchy hypopigmentation, ocular findings (cataracts, lens dislocation or pigmentary retinopathy), intracranial haemorrhage, and unusual odours. **Table 2** gives some important clinical markers for IEM.

Table 2 : Clinical Pointers to Specific Disorders

Cutaneous abnormality: Perioral eruption (multiple carboxylase deficiency), increased pigmentation (adrenoleukodystrophy), decreased pigmentation (phenylketonuria)

Abnormal urinary or body odour: Musty (phenylketonuria), maple syrup (maple syrup urine disease), sweaty feet (isovaleric acidaemia, glutaric acidaemia type II), cat urine (multiple carboxylase deficiency), sulphurous (homocystinuria)

Hair abnormalities: Alopecia (multiple carboxylase deficiency), kinky hair (Menkes disease), arginosuccemic aciduria, multiple carboxylase deficiency)

Dysmorphic features: Zellweger syndrome, glutaric acidaemia type II

Ocular abnormalities: Cataract (galactosaemia, Zellweger, homocystinuria), iris heterochromia/retinitis pigmentosa (Zellweger syndrome), KF ring (Wilson's disease)

Hepatomegaly: Galactosaemia, glycogen storage disease, tyrosinaemia

Hepatosplenomegaly: Storage disorders – Niemann-Pick, Gaucher disease, mucopolysaccharidosis

Renal enlargement: Zellweger, GSD I, tyrosinaemia

Laboratory findings

Laboratory findings which should raise a suspicion of IEM include metabolic acidosis with increased anion gap, primary respiratory alkalosis, hyperammonaemia, hypoglycaemia, ketosis or ketonuria, lactic acidosis, non-glucose reducing substance in urine, abnormal liver functions, unexplained neutropaenia and thrombocytopaenia. In general, IEM can have one of the following presentations:

1. *Neurologic syndromes:* These can present as acute encephalopathy, chronic encephalopathy, movement disorders, myopathy, and psychiatric problems.
   (a) Acute encephalopathy: Encephalopathy in acutely presenting IEM has certain characteristics. It usually occurs with little warning in a previously healthy individual and early signs may be taken as a behavioural problem. The condition often progresses rapidly and consciousness may fluctuate. History of recurrent similar episodes may be present.
   (b) Chronic encephalopathy: Psychomotor retardation/developmental delay are the commonest manifestation of IEM. The retardation tends to be global and progressive. History of regression of milestones may be present. Irritability, aggressiveness, hyperactivity and lack of night sleep are commonly associated. In addition, retardation is often associated with objective neurological signs, like tone changes, pyramidal or extra-pyramidal deficits. Seizures, visual failure, extra-pyramidal disturbances are signs of grey matter disease. Involvement of non-neural organs like hepato-splenomegaly gives important clues to diagnosis.
   (c) Movement disorders: In patients with IEM can be seen in a large variety of disorders and are usually associated with other neurologic signs. Movement abnormalities can be intermittent or progressive. These may occur in the form of ataxias, dystonia, choreoathetosis and Parkinsonism. Common examples of IEM presenting as movement disorder are organic acidurias, neuronal ceroid lipofuscinosis (late onset forms), lysosomal storage disorders and urea cycle disorders, etc.
   (d) Myopathy: IEM presenting with myopathy are usually due to defects in energy metabolism. The myopathy can be progressive, e.g. glycogen storage disease, mitochondrial disorders.
2. *Hepatic syndromes:* Liver involvement is seen in a number of IEM. There are four possible presentations: (i) Jaundice (unconjugated—G6PD deficiency, Gilbert, Crigler-Najjar, and conjugated—galactosaemia, tyrosinemia, fructose intolerance); (ii) Hepatomegaly (asymptomatic hepatomegaly is common, e.g. GSD); (iii) Hypoglycaemia galactosaemia, GSD); and (iv) Hepatocellular dysfunction galactosaemia, GSD (IV and III), Niemann-Pick type B, α_1 antitrypsin deficiency, etc.
3. *Cardiac syndromes:* Serious cardiac disease has been found to be associated particularly with fatty acid oxidation defects, mitochondrial disorders, GSD II, Fabry's disease and MPS.

Clinical Presentation in Adults

A history of intermittent attacks triggered by feeding or fasting or some stress may suggest milder intermittent forms of small molecule diseases like disorders of urea cycle, amino acid metabolism, or fatty acid oxidation. A slow progressive course may suggest a lysosomal storage disease or a peroxisomal disorder. Often detailed questioning may disclose evidence of problems in childhood or adolescence. A positive family history may also give a clue. A detailed enquiry for mild clinical symptoms at an early age is warranted as those symptoms may be passed off as non-specific and unrelated. These features often remain unrecognised, as they may be mild and often intermittent in nature. Specific neurological findings such as vertical supranuclear ophthalmoplegia or a cherry red spot may suggest a lysosomal storage disorder. Alternatively, there may be abnormalities affecting other organ systems. The internist may confront a group of disorders caused by mutations in mitochondrial DNA that express themselves as disorders of cellular energy metabolism secondary to electron transport chain defects. The manifestations may involve single organ system or may be these disorders may mimic an idiopathic,

organ-specific, degenerative disease. Affected persons may present at any age with variable features of myopathy, ophthalmoplegias, encephalopathy, strokes and cardiac manifestations. The cardinal biochemical feature is lactic acidaemia; lactic acid elevation in the cerebrospinal fluid may be the sole abnormality. **Table 3** gives brief information about inherited metabolic disorders with adult onset forms.

Table 3: IEM with Adult Onset

Disease	Presentation
Lysosomal storage diseases	
Pompe's disease	Muscle weakness, cardiomyopathy
Fabry's disease	Peripheral nerve pain, renal failure, angiokeratoma, cardiomyopathy, stroke-like episodes
Gaucher's disease type III	Horizontal supranuclear gaze defect, developmental delay, skeletal abnormalities, psychosis, organomegaly
Gaucher's disease type I	Anaemia, splenomegaly, thrombocytopaenia
GM1 gangliosidosis	Extrapyramidal signs, sometimes with psychosis
Krabbe's leukodystrophy	Pes-cavus, spastic tetraparesis, leukodystrophy, visual problems
Metachromatic leukodystrophy	Loss of cognitive function or behavioural abnormalities, neuromuscular weakness with impaired nerve conduction, leukodystrophy
Niemann-Pick's disease type C	Psychomotor retardation, ataxia, dystonia
Amino acid disorders	
Arginase deficiency	Disorientation, coma
Citrullinaemia	Disorientation, coma, restlessness
Hartnup's disease	Dementia, ataxia ± skin lesions
Homocystinuria	Occlusive cerebrovascular disease, dislocated lenses, osteoporosis, psychiatric disturbances
Hyperornithinaemia	Gyrate atrophy of the retina and choroid
Ornithine transcarbamylase deficiency	Behavioural disturbances, coma episodes, sleep disorders
Fatty acid oxidation defects	Muscle weakness, easy fatigability ± liver disease ± cardiomyopathy ± hypoglycaemia
Organic acid disorders	
Glutaric aciduria type 1	Dystonia ± hypoglycaemia, may present with Reye-like syndrome
Propionic acidaemia	Chorea, dementia, recurrent vomiting
Peroxisomal disorders – X-linked ALD	Onset at 20-30 yrs in males, gait disturbance, spastic paraparesis, intellectual function usually intact, impotence ± Addison's disease, occasionally cerebral symptoms
Mitochondrial disorders	Encephalopathy, stroke-like episodes, muscle weakness, multisystem disease (NARP, MELAS, MERRF, Kearns-Sayre syndrome, LHON)
Glycogen storage diseases	Muscle weakness, cardiomyopathy, hepatomegaly, hypoglycaemia, myopathy
Homocystinuria and methylmalonic aciduria	Megaloblastic anaemia, dystonia, stroke
Juvenile Batten's disease	Seizures, visual loss, dementia
Porphyrias	Limb, neck, and chest pain, muscle weakness, sensory loss, seizures, behavioural abnormalities
Refsum's disease	Retinitis pigmentosa, peripheral polyneuropathy, cerebellar ataxia, abdominal symptoms, photosensitivity
Segawa disease	Cyclical dystonia
Wilson's disease	Dystonia, pseudobulbar palsy, Parkinsonian features, liver disease
Lesch-Nyhan syndrome	Choreiform movements, dysarthria ± renal problems

LABORATORY APPROACH TO SUSPECTED IEM

Screening and Definitive Diagnosis

Based on history and suspicious clinical course, an investigational plan for IEM should be followed. Initial screening investigations will help in disease classification and instituting presumptive therapy. **Figure 2** gives step-wise approach to a suspected IEM. **Figures 3A and B** give details of evaluating a child with metabolic acidosis and **Figures 4A and B** give differential diagnosis of hyperammonaemia. **Figure 5** gives details of evaluation of a patient presenting with hypoglycaemia. For definitive diagnosis a combination of investigations is required. These include tandem mass spectrometry (TMS), gas chromatography mass spectroscopy (GCMS, primarily for organic acidurias) and high performance liquid chromatography (HPLC for amino-acidopathies). Enzyme assays are required for the diagnosis of lysosomal storage disorders. DNA-based diagnosis for causative mutations is the most reliable diagnostic modality but is difficult due to limited availability and heterogeneity in different populations.

Definitive diagnosis may not be available promptly; hence, treatment has to be started empirically in most situations. **Table 4** gives details of workup which is required for acutely presenting IEM. Routine tests such as blood sugar, serum calcium, liver function tests, blood counts and urine tests (**Table 5**) may give some clues to diagnosis. Four laboratory tests are particularly useful in broad classification of IEM and instituting empirical therapy—arterial blood gas analysis, blood lactate, blood ammonia, and urine ketosis (**Table 6**).

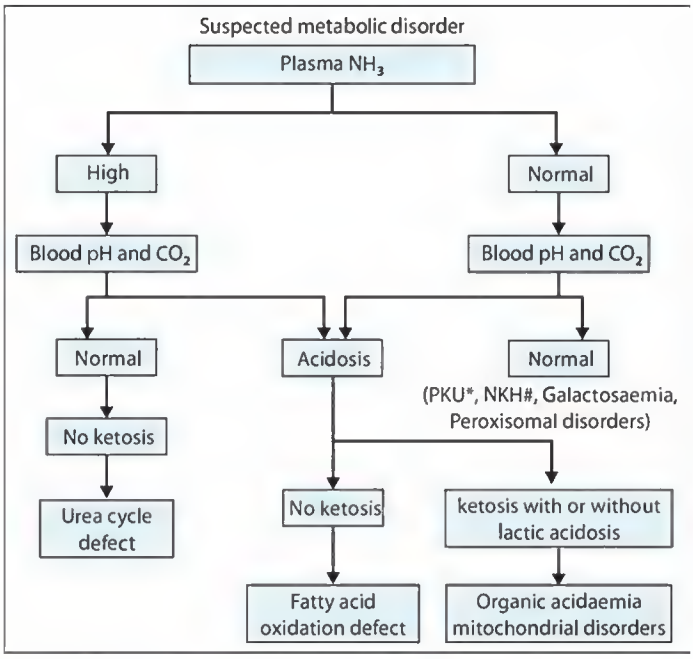


Figure 2: Approach to a case of suspected IEM.
**Phenylketonuria, # Non-ketotic hyperglycinaemia*

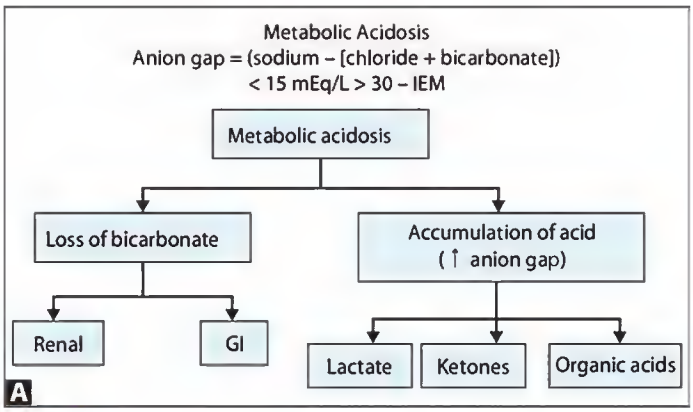
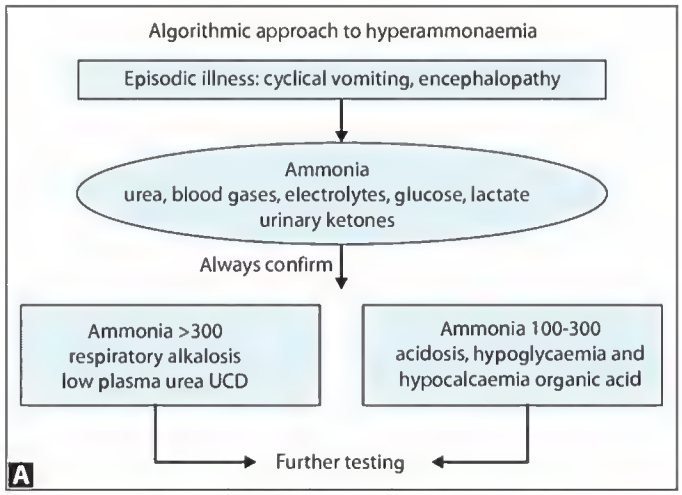


Figure 3A: Approach to a patient with metabolic acidosis.



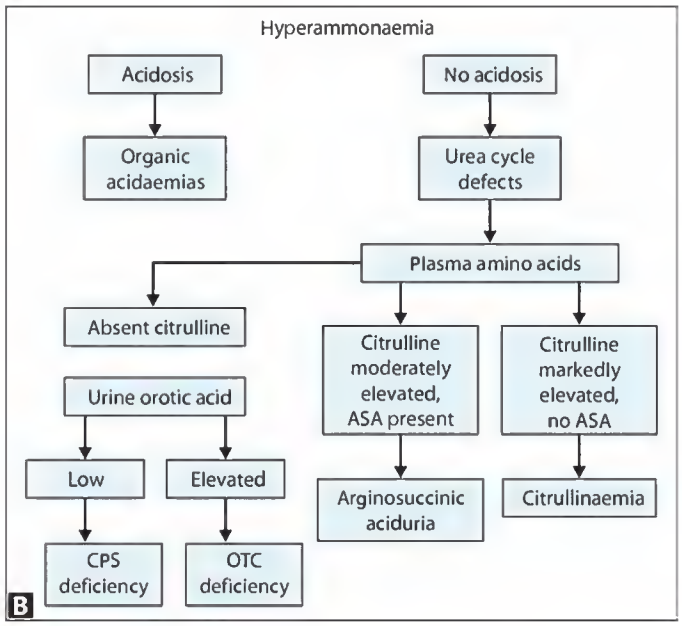


Figure 4A and B: Approach to a patient with hyperammonaemia.

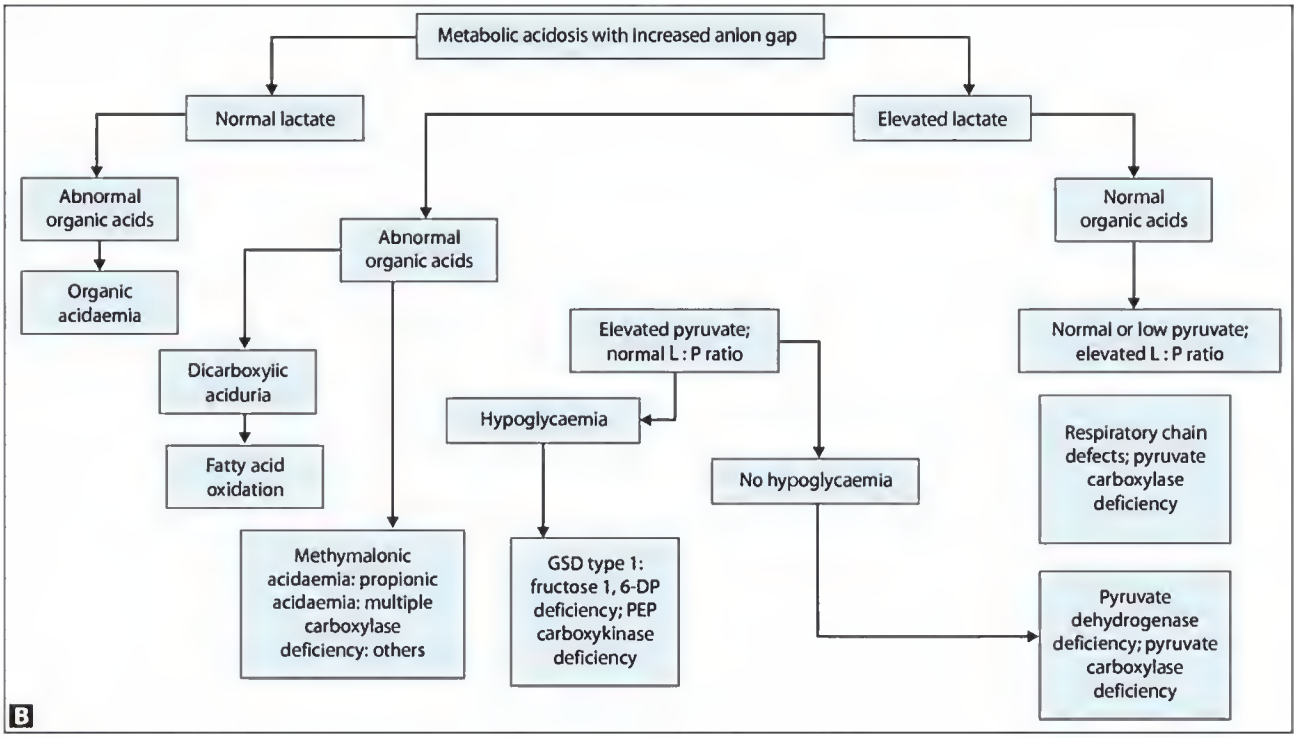


Figure 3B: Approach to a patient with metabolic acidosis.

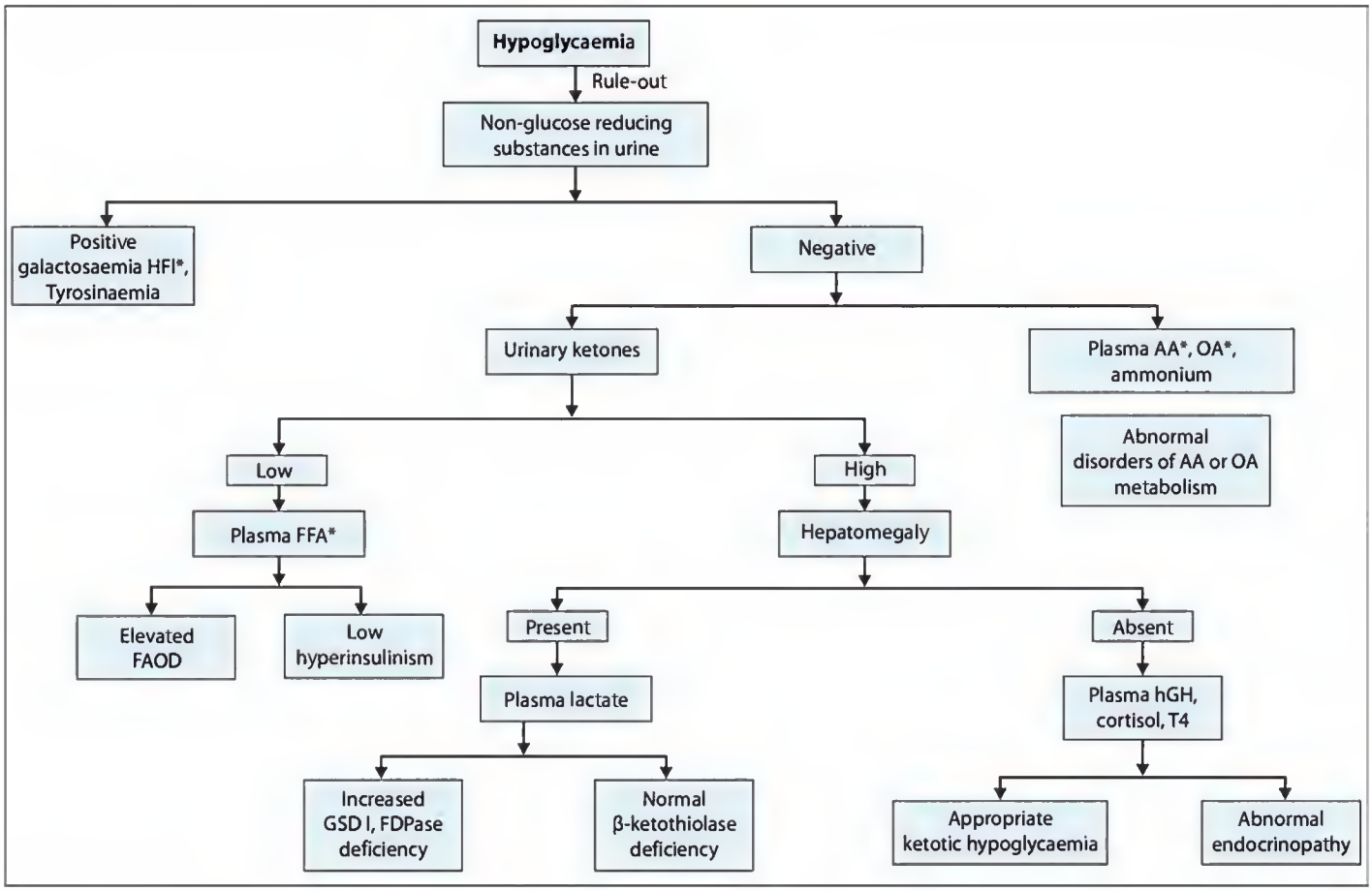


Figure 5: Approach to a patient with hypoglycaemia.

** HFI = Hereditary fructose intolerance; AA = Amino acids; OA = Organic acids; FAOD = Fatty acid oxidation defects; FFA = Free fatty acids.*

Table 4: Investigations for Acutely Presenting IEM

	Investigations	Sample storage for specific investigations
Urine	Smell (special odour)	*Urine collection:* Collect each fresh micturition
	Look (special colour)	separately and put it in the refrigerator
	Acetone (acetest, ames)	*Freezing:* Freeze at -20 °C, samples collected
	Reducing substances (clinitest, ames)	before treatment and, afterward, an aliquot
	Keto acids (DNPH)	of 24-hour collection on treatment
Blood	Blood cell count	Plasma, heparinised, 5 mL at -20 °C
	Electrolytes (for anion gap)	Blood on filter paper (as 'Guthrie test')
	Glucose, calcium	Whole blood 10 to 15 mL collected in EDTA vial
	Blood gases	(for molecular biology/enzyme studies)
	Uric acid	
	Prothrombin time	
	Transaminases (and other liver tests)	
	Ammonia	
	Lactic and pyruvic acids	Arterial blood sample
Miscellaneous	Lumbar puncture	Skin biopsy (fibroblast culture)
	Chest radiograph	Cerebrospinal fluid, 1 mL frozen
	Echocardiography, EMG	*Post-mortem:* Liver, muscle biopsies
	Cerebral ultrasound	(macroscopic fragment frozen at -70 °C)
	CT, MRI, EEG	
Specialised investigations	HPLC, GCMS, TMS	

Table 5: Urine Metabolic Screen

Disorder	Ferric Chloride	DNPH*	Reducing Substances	Nitroprusside	MPS Spot Test**
Phenylketonuria	+	+	–	–	–
Galactosaemia	–	–	+	–	–
Organic aciduria	+	+	–	–	–
Amino aciduria	–	+	–	–	–
Homocystinuria	–	–	–	+	–
Mucopolysaccharidosis	–	–	–	–	+

** DNPH = Dinitrophenyl hydrazine ** MPS spot test = Mucopolysaccharidoses spot test*

Table 6: Four Basic Tests for Inherited Metabolic Disorders

Group	Acidosis	Ketosis	Lactate	Ammonia	Diagnosis
I	–	+	–	–	MSUD
II	+	+	–	–	Organic aciduria
III	+	+	+	–	Lactic acidosis
IV	–	–	–	+	Urea cycle disorder
V	–	–	–	–	NKH, sulfite oxidase, Peroxisomal, PKU galactosaemia

Points to Remember when Collecting Samples

Samples should be collected before specific treatment is started or feeds are stopped, as tests may be falsely normal if the child is off feeds. Samples like serum ammonia and lactate should be immediately tested. Lactate level should be arterial and collected after 2 hours fast. For children ammonia sample is to be collected approximately after 4–6 hours while in adults it should be collected after a longer period of fasting. Detailed history including drug details should be provided to the laboratory.

Investigation for a Dying Child (Biochemical Autopsy)/Post-mortem Investigations

If a child (suddenly) dies of an unknown, possibly metabolic disease, it is essential to collect representative post-mortem samples and discuss the analysis with a metabolic specialist. Without diagnosis, genetic counselling of the parents and reliable risk assessment for future children is not possible. The following should be collected for post-mortem analysis if a metabolic disorder is suspected but specific investigations have not yet been performed:

1. Serum and plasma (centrifuge several millilitres immediately, freeze in separate fractions).
2. Guthrie-card (dried blood spot on filter paper).
3. Urine (10-20 mL, freeze immediately, consider bladder wash with NaCl).
4. DNA (3-10 mL EDTA blood, freeze without centrifuging), and
5. Consider CSF (several 1 mL fractions, freeze immediately, if possible at -70°C).

Consider fibroblasts (skin biopsy may be stored 1 to 2 days at 4°C in culture fluid).

Biopsies

The acquisition of organ biopsies depends on the clinical picture and should be discussed with the laboratory/metabolic specialist (samples are usually frozen immediately in liquid nitrogen): muscle (skeletal, consider heart), liver, kidney and brain.

TREATMENT

Immediate Management of Acutely Presenting Disorders

Initial emergency treatment should be started empirically even on suspicion of IEM, and even without knowledge of the specific metabolic diagnosis or disease category.

1. General measures:
   (a) Airway, breathing and circulation should be established,
   (b) Treat precipitating/associated conditions like septicaemia.
   (c) Seizures: These should be managed as per the protocols. Pyridoxine should be given to neonates with seizures unresponsive to conventional anticonvulsants. Valproate and phenobarbitone are preferably avoided as they interfere with mitochondrial metabolism.
2. Correction of metabolic abnormalities
3. All oral intake should be stopped to reduce levels of potentially harmful proteins and sugars. Treat hypoglycaemia and prevent catabolism. Maintain fluid and electrolyte balance. Treat acidosis. For intractable acidosis, haemodialysis/peritoneal dialysis is required.
4. Removal of toxic metabolites: Abnormal metabolites are removed by restricting intake of the offending substrate, or by promoting renal excretion of toxic metabolites. In severe cases, dialysis (preferably haemodialysis) is required. Although haemodialysis has advantages over peritoneal dialysis (PD), vascular access remains the primary technical problem and PD is, therefore, usually offered.

SPECIFIC MANAGEMENT

Hyperammonaemia

Kidneys clear ammonia poorly. Its removal is hastened by formation of compounds other than urea, hence, decreasing load on the urea cycle. Compounds used are sodium benzoate, phenyl

acetate and arginine. Intravenous preparations of sodium benzoate and phenyl acetate are not available in India. Oral sodium benzoate is available and can be used in the same dose.

Ammonia level more than 200 µmol/L to 350 mg/dL

Protein intake is to be stopped, and catabolic state is interrupted by high-calorie infusion (>120 kcal/kg/day). Arginine hydrochloride 360 mg/kg, carnitine 50 mg/kg, Na-benzoate 350 mg/kg and Na-phenylbutyrate or Na-phenylacetate 250 mg/kg should be started. The patient should be transferred to a referral centre. Citrulline may be used in the dose of 170 mg/kg per day in CPS and OTC deficiency. Anticonvulsants like sodium valproate should be avoided.

NH_3 level more than 400 µmol/L

In addition to the above measures, extracorporeal detoxification should be started as soon as possible. Use haemodialysis, if possible; otherwise, peritoneal dialysis.

Long-term treatment of urea cycle defects

Start low-protein diet containing essential amino acids early. Na-benzoate orally in a dose of 250-400 mg/kg/day and Na-phenyl-butyrate orally in a dose of 250-500 mg/kg/day is also to be administered. Supplement vitamins (e.g. folic acid 500 µg/day) and trace elements. If carnitine is low, supplement carnitine in the dose of 30-50 mg/kg. Consider lactulose as it binds intestinal ammonia due to acid pH. The target value of NH_3 is less than 80. Essential amino acids should be in the normal range.

Organic Acid Disorders

Emergency treatment in the hospital includes the following:

(a) *Interrupt catabolic state:* High-dose energy substitution, usually glucose intravenous (exceptionally via nasogastric tube), if necessary with intravenous insulin.

(b) *Stop protein intake:* In some disorders, the accumulation of toxic metabolites can be reduced by intestinal antibiotic treatment (metronidazole, colistin).

(c) *Ensure adequate fluid and electrolyte intake:* Aim for a sodium concentration >140 mmol/L to reduce the risk of cerebral oedema.

(d) *Carry-out detoxifying measures depending on the disease and laboratory findings:* Increased diuresis, dialysis, haemofiltration.

(e) *Consider specific drug treatment* (vitamins, carnitine, etc.) depending on the disease and laboratory findings.

Long-term treatment includes the following: (a) Diet: protein restriction, (b) If indicated give specific vitamins or co-factors, (c) Carnitine (50-100 mg/kg/day), and (d) Regular laboratory monitoring (depending on the disease).

Disorders of Fatty Acid Oxidation

The main therapy is prevention of fasting and catabolic states. In acute situations, intravenous glucose infusion (8-10 mg/kg/min) should be started without delay. In contrast, in patients with defects in LCAD metabolism, low fat diet supplemented with medium chain triglycerides may be beneficial. Avoid valproate as an antiepileptic drug if possible.

Mitochondrial Disorders

Most approaches used for the treatment of mitochondriopathies have not been scientifically evaluated, and success is limited. General measures include avoidance of drugs that inhibit the respiratory chain, e.g. valproate, barbiturates, tetracyclines, chloramphenicol. L-Carnitine 50-100 (up to 200) mg/kg/day in 4 doses; avoid lactic acidosis by limiting excessive physical exercise, controlling fever, early and efficiently, and early treatment of seizures.

Treatment regimen in acute lactic acidosis and suspected mitochondriopathy includes: coenzyme Q_{10} + riboflavin (in the neonate: 100 mg/day), vitamin C, carnitine, biotin (20 mg/day), phylloquinone or menadione and thiamine.

Specific long-term treatment, though of uncertain efficacy, includes: coenzyme Q_{10} 4-5 mg/kg/day in 2 doses, riboflavin 3-20 mg/kg/day in 4 doses, thiamine 25-100 mg/kg/day, tocopherol (vitamin E) 100-300 (up to 1,000) mg/day and Creatine 4-10 g/day (stop every 4th month), e.g. in mitochondrial myopathy. Corticosteroids are not indicated.

Vitamin/Cofactor Therapy

In certain IEM, enhancement of the activity of a mutant enzyme can be achieved by giving mega-doses of a vitamin cofactor required for enzyme's action. One-third of the cases of homocystinuria due to cystathionine b-synthetase deficiency are pyridoxine responsive. Deficiency of multiple biotin-dependent carboxylases responds to 10 mg of biotin given daily. Some cases of methylmalonic acidaemia respond to pharmacological supplementation of intramuscular hydroxycobalamin in a dose of 1 mg per day. A diet low in fat and protein together with a trial of oral riboflavin (200-300 mg per day) and carnitine may be helpful in some patients with glutaric aciduria type I and II.

Dietary Therapy and Enzyme Replacement

Specific therapy will depend on the final diagnosis. Dietary therapy is required for PKU, MSUD, galactosaemia, homocystinuria, etc. Cost of the special diets is high and critical monitoring is required for effective management. Enzyme replacement therapy is available for many lysosomal storage (e.g. Gaucher's, MPSI, MPSII, GSDII, Fabry's, MPSVII) disorders with excellent results. Bone marrow/stem cell transplantation is another option for lysosomal storage disorders.

Newborn Screening

Newborn screening is a well-tested strategy for secondary prevention of IEM. Most developed countries test for IEM using TMS in addition to screening for congenital hypothyroidism and congenital adrenal hyperplasia. Samples are collected by heal prick 48 to 72 hours after birth. Early diagnosis and timely management prevents neurological sequelae and mortality. India does not have a national newborn screening programme presently. The ICMR has initiated a multicentric pilot project for newborn screening of 100,000 babies for congenital

hypothyroidism and congenital adrenal hyperplasia to study the incidence of these disorders and also the feasibility of introducing such a programme in India. The Governments of Chandigarh and Goa, India have also initiated newborn screening programmes recently.

Genetic Counselling and Prenatal Diagnosis

As most IEM are autosomal recessive, the risk of recurrence in subsequent pregnancies is 25%. For X-linked disorders recurrence risk is 50% for male offspring. Prenatal diagnosis is possible by enzyme assay in chorionic villous biopsy or amniotic fluid cells. Mutation analysis on DNA extracted from chorionic villous sample or amniotic fluid cells is a more robust and preferred modality if causative mutations are known.

RECOMMENDED READINGS

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6.6 Molecular Genetics, Human Genome Project and Genomic Medicine

Girisha KM

The understanding of the structure, function, regulation and variations in DNA is the key to the understanding of human health and disease. This chapter discusses the molecular basis of life, gives insight into genetic variation between individuals and its clinical implications.

STRUCTURE OF DNA

Deoxyribonucleic acid (DNA) is a long polymer of nucleotides. Each nucleotide is made up of a nitrogenous base [purines: adenine (A) and guanine (G); and pyrimidines: cytosine (C) and thymine (T)], a deoxyribose sugar, and a phosphate group. Ribonucleic acid (RNA) differs from DNA in having a ribose sugar in place of deoxyribose, and pyrimidine uracil (U) in place of thymine. Watson and Crick (1953) demonstrated how deoxynucleotides are assembled to form the double stranded helical structure of DNA, where sugar and phosphate molecules form two sides of the ladder that are held by strong phosphodiester bonds, and rungs of the ladder are formed by nitrogenous bases facing inside, being held together by hydrogen bonds that are weaker and separate during replication and transcription. The two strands run anti-parellel to each other with one strand having the orientation of 5′ to 3′ direction and the other of 3′ to 5′ direction (**Figure 1**).

In human nucleated cells, approximately 2 metres of DNA is condensed about 10,000 times and packaged into chromosomes. The DNA is first wound around a histone protein core to form a nucleosome, which in turn forms a helical solenoid. The solenoids are organised into chromatin loops, which are attached to a protein scaffold and further packaged into chromosomes.

DNA REPLICATION

Replication of DNA is the key event for transmission of genetic information from parent cell to its progeny. The process leads to formation of two identical copies of the original DNA that get segregated into two daughter cells during cell division. The replication begins with uncoiling and separation of two strands of the DNA molecule by the enzyme helicase. Each strand of the DNA directs synthesis of its complementary copy through complementary base pairing (adenine pairs with thymine and cytosine pairs with guanine) resulting in formation of two DNA molecules (semi-conservative synthesis) identical to the original parent molecule. This process conserves the genetic information, and transmits it unchanged to each daughter cell. The key enzyme that carries out DNA synthesis is DNA polymerase. The process initiates at several sites simultaneously during the S (synthetic) phase of cell cycle. The synthesis of a new DNA strand proceeds in 5′ to 3′ direction. This leads to formation of one continuous strand (leading strand) which is the copy of the 3′ to 5′ strand; and the other strand is synthesised in parts (Okazaki fragments) that are later joined together by the enzyme DNA ligase.

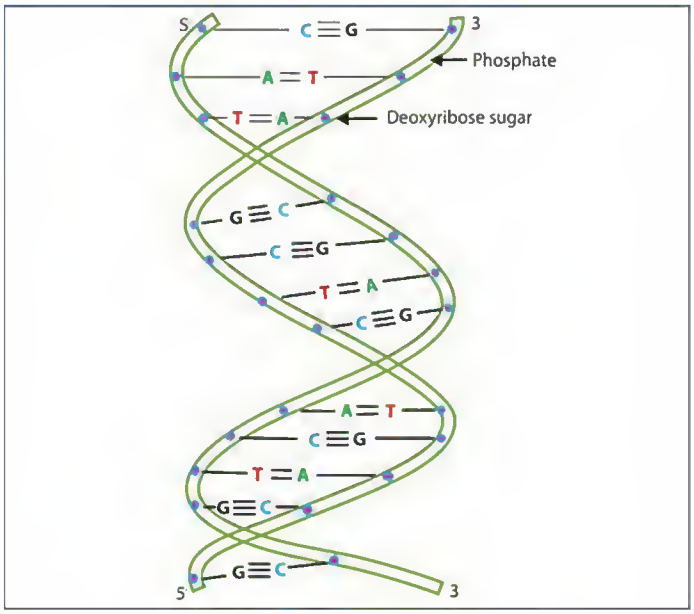


Figure 1: Helical structure of the DNA showing the sugar-phosphate backbone and the nitrogenous bases. The DNA resembles a ladder with the sides formed by the phosphodiester bond between phosphoric acid and deoxyribose sugar and the rings formed by hydrogen bonds in-between the nitrogenous bases. Two hydrogen bonds are formed between adenine (A) and thymine (T) and three hydrogen bonds between guanine (G) and cytosine (C).

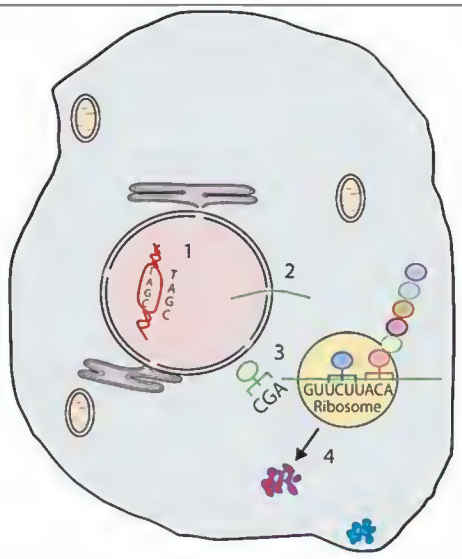
TRANSCRIPTION AND RNA PROCESSING

Transcription is the process whereby genetic information stored in DNA is utilised for gene function. It leads to formation of RNA which migrates to cytoplasm for synthesis of proteins. The transcript of the coding DNA is known as messenger RNA. The mRNA is single stranded. It is synthesised by the enzyme RNA polymerase that adds complementary ribonucleotides to the RNA chain (uracil replaces thymine in mRNA). The particular strand of DNA that acts as a template for synthesis of mRNA is called 'antisense strand' so that the new molecule of mRNA is the copy of the other 'sense strand'.

The mRNA leaves the nucleus to cytoplasm after several processing events. The RNA processing includes removal of introns at specific splice sites in mRNA (splicing), addition of a methylated guanine nucleotide to the 5′ end of the molecule (5′ capping) and addition of about 200 adenylate residues at the 3′ end (polyadenylation). Now the mRNA molecule is ready to be translated.

THE GENETIC CODE

The 20 different amino acids in proteins are coded by the four different nucleotides (bases) in DNA (**Figure 2**). The sequence of triplet nucleotide bases in the DNA molecule that specifies the sequence of amino acids in the protein molecule is called the genetic code. The genetic code from DNA is transmitted to



1. DNA replicates to produce more copies so that it can be equally distributed to both the daughter cells.
2. Genetic information in the DNA is transcribed into the mRNA through the process of transcription. mRNA is then translocated into the cytoplasm.
3. In the cytoplasm, the information carried by the mRNA is translated into proteins by ribosomes and tRNA.
4. The protein then formed carries out various intracellular and extracellular functions and, thus, carrying out the complex functions pertaining to life.

Figure 2: Central dogma of molecular biology.

	U	C	A	G	
U	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr STOP STOP	Phe Phe STOP Leu	U C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

Figure 3: The genetic code: Triplet nucleotides in the mRNA form codons and code for specific amino acids. An amino acid may be coded by more than one codon and three codons stop the elongation of polypeptide chain.

codons of the mRNA during transcription which is then decoded into specific amino acids during translation.

The codons on mRNA are non-overlapping, and are read as per translational reading frame. Among 64 possible triplet codons from 4 nucleotides, some code for same amino acid (degeneracy, since there are only 20 amino acids). Three codons code for termination of the polypeptide synthesis (stop codons). The process of transfer of genetic information from DNA to RNA to protein is sometimes referred to as 'central dogma' or 'holy trinity' of molecular biology (**Figure 3**).

TRANSLATION

The genetic code in the DNA (of a gene) is transmitted on to the codons of mRNA and these direct the synthesis of polypeptide chain by incorporating specific amino acids during the process of translation. In the ribosomes, the site of protein synthesis, the mRNA molecules with the help of specific transfer RNAs (tRNA) carrying the 'anticodons' for individual amino acids synthesise the polypeptide chain, originally directed by the genetic code in the gene. The polypeptide chains, thus synthesised, undergo several post-translational modifications (hydroxylation, methylation, glycosylation, proteolytic cleavage, etc.) to become functional proteins that are transported to their specific cellular locations.

REVERSE TRANSCRIPTION

In most situations, the genetic information flows from DNA to RNA. However, in certain types of viruses (retroviruses) genetic information can flow in reverse direction from RNA to DNA. This is termed reverse transcription or RNA-directed DNA synthesis and involves the enzyme reverse transcriptase. Some regions of the DNA serve as templates for synthesis of RNA, which in turn act as templates for synthesis of DNA. This DNA may get integrated into nuclear DNA of other cells.

GENE: THE FUNCTIONAL UNIT OF DNA

A 'gene' may be conceptualised as the sequence of DNA that contains the information required for a functional product (**Figure 4**). The product encoded may be a polypeptide or RNA molecule. Previously, it was thought that the coding sequence of a gene lies in continuity, which is now known to be a rarity. Now, the 'gene' has been shown to consist of amino acid coding exons, intervening non-coding introns, promoter sequences at 5' region that initiate transcription and other regulatory elements like enhancers, silencers, and locus control regions. Genes may overlap, may be found within another gene, or even the same sequence may be transcribed in reverse direction to produce another product.

REGULATION OF GENE EXPRESSION

The estimated 23,000 genes in each human cell control all the cellular processes in the living being. Their expression varies at different stages of development, and depending on the type of the cell/tissue. Several complex pathways are involved in controlling temporal and spatial expression of genes.

Signalling molecules called transcription factors bind to regulatory sequences of DNA, nuclear receptors (hormones) or even specific ligands located at the cell surface for signal transduction. The transcription factors may bind to promoter elements (TATA, GC and CAAT boxes) of the specific genes located adjacent to the coding region (cis-acting) to regulate the pace of protein synthesis, or to enhancer or silencer elements located at a distance and act on both copies of the gene (transacting) to enhance or suppress the transcription. Transcription factors themselves are coded by genes and bind to DNA to regulate gene expression.

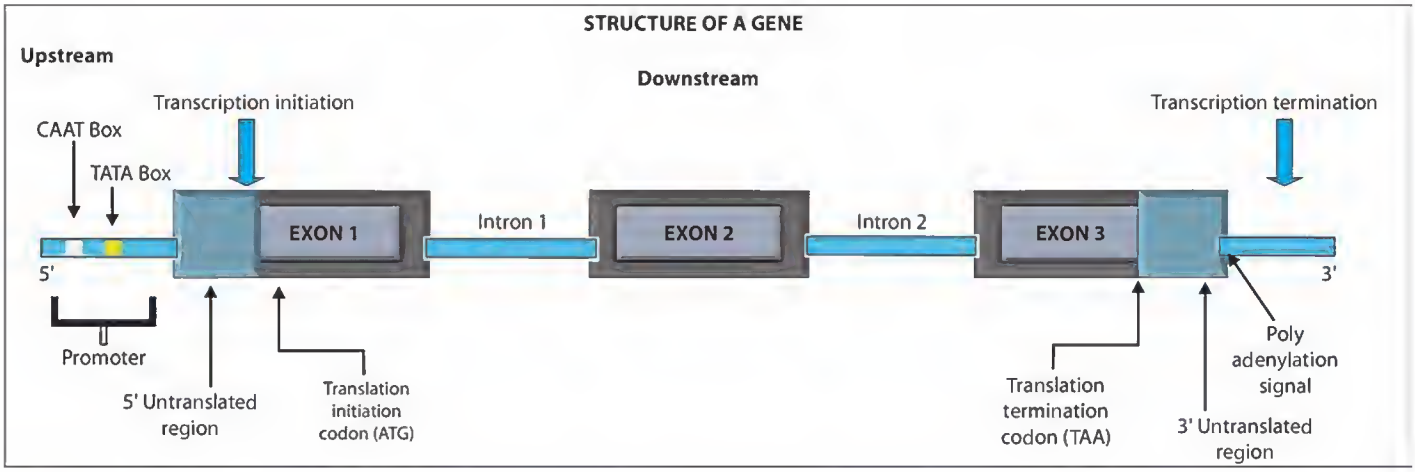


Figure 4: Structure of a gene: A typical gene is made up of a promoter, a transcriptional start site, exons, introns, translational stop site and a Poly A signal. The promoter facilitates the binding of RNA polymerase to the gene during transcription; the transcriptional start site contains the initiation codon ATG, which marks the start of transcription. Exons encode the information for a functional protein. The 5' and 3' untranslated sequences play a role in gene regulation.

Gene activity may also be related to patterns of chromatin condensation. Heterochromatin is usually highly condensed and is characterised by histone modification that makes it inaccessible to transcription factors, whereas euchromatin is decondensed and transcriptionally more active.

Though regulation of expression of most of the genes is mediated by transcription factors, regulation can also occur at various stages of protein synthesis, viz. RNA processing, transport, and translation. Alternative splicing is a mechanism where a gene can code for more than one protein or at varying rates.

STRUCTURE AND ORGANISATION OF THE HUMAN GENOME

The 'human genome' refers to the total genetic information in human cells. In simple terms, genome refers to the entire DNA content of the cell. It consists of the larger nuclear genome ($3x10^9$ bp) and the very small mitochondrial genome (16.6 kb). The nuclear genome encodes bulk of genetic information, most of which specifies synthesis of proteins of the body. Mitochondrial genome encodes its own transfer RNA, ribosomal RNA and few of its own polypeptides.

Nuclear Genes

It is estimated that there are about 23,000 genes in the entire nuclear genome. The size of the genes varies greatly, with small genes comprising of one to three exons (e.g. beta globin gene) and large genes with up to 79 exons (dystrophin gene, ~2.5 Mb).

Unique single-copy genes are present in single copy (in the haploid set of chromosomes). These encode the polypeptides that are involved in a wide variety of cellular functions: enzymes, receptors, regulators, etc. Some others are members of *multigene families*. These arise through gene duplication events during evolution. These may be found in physically close clusters like alpha and beta globin genes on chromosome 16 and 11, respectively or dispersed throughout the genome like the HOX gene family, which are important developmental genes. The genes which encode the ribosomal RNAs are clustered as tandem arrays at the short arms of the acrocentric chromosomes and those encoding the transfer RNAs occur in numerous clusters throughout the genome. These constitute *classic gene families*. Genes encoding the human leukocyte antigens (HLA) and the T-cell receptor genes belong to the immunoglobulin *gene superfamily*. *Pseudogenes* closely resemble known structural genes but do not express. They are thought to have arisen either by duplication of genes that have lost function due to mutations or by insertion of complementary DNA sequences lacking promoter sequences.

Extragenic DNA

The sequences that represent all the genes of the human body constitute around 1.5% of the genome. The rest of the human genome is made up of repetitive DNA sequences that are predominantly inactive. These have also been referred to as junk DNA, but have some uncertain regulatory role.

Tandem repeats

The non-coding DNA may occur in tandem repeats or may be interspersed in the genome. *Satellite DNA* is clustered around the centromeres of certain chromosomes and contains very large series of tandemly repeated sequences that are transcriptionally inactive. *Mini-satellites* consist of repetitive sequences found at the telomeres of chromosomes. Highly polymorphic short tandem repeats of core units made up of 10-100 base pairs are used in DNA fingerprinting. *Micro-satellite DNA* consists of tandem repeats of 1-4 base pair sequences located throughout the genome.

Highly repeated interspersed repetitive DNA

Approximately one-third of the human genome is made up of two main classes of short and long repetitive DNA sequences that are interspersed throughout the human genome. These include several lakhs of copies of short interspersed nuclear elements (SINEs) and the long interspersed nuclear elements (LINEs).

Mitochondrial DNA

Mitochondria contain their own 16.6 kb circular DNA (mtDNA). It encodes for 37 genes including 2 for ribosomal RNA, 22 for transfer RNA and 13 for polypeptide sequences. It may be noted that most of the protein component of mitochondria are product of nuclear genes.

DNA CLONING

Cloning refers to selective amplification of a specific DNA fragment of interest to produce it in a large quantity for further analysis. This can be done by either one cell based *in vivo* amplification, or via polymerase chain reaction *in vitro*.

To clone a segment of DNA, the first step is to generate DNA fragments. This can be done by various methods, the most popular being digestion with restriction enzymes that cleave the DNA into fragments at recognition sites specific to the enzyme. Enzymes that produce staggered (sticky) ends are used for DNA cloning. Next, a suitable vector (plasmid, bacteriophage, cosmid, bacterial or yeast artificial chromosome) is also digested with the same restriction enzyme. The sticky ends of the DNA fragment and the DNA of the vector are attached by the enzyme DNA ligase to generate a recombinant DNA molecule. The recombinant vector is then introduced into especially modified bacterial or yeast host cell that gets transformed. When the host cell multiplies, large quantities of DNA of interest or clones are also synthesised. The transfected cells are then screened for antibiotic resistance or sensitivity genes incorporated in the transforming vector or for the product of gene of interest. Specific clones containing the desired DNA inserts are then selected and cultured separately. This clone serves as the source of amplified DNA fragment of interest for further analysis.

DNA Libraries

DNA libraries contain a large number of clones representing entire repertoire of DNA/RNA derived from a given source. When whole DNA from nucleated cell is used as the source, the resultant product is called genomic DNA library. It may also be chromosome specific library if clones are prepared from sorted chromosomes. When mRNA is used to synthesise the DNA (complementary DNA (cDNAJ) and library is created from it, it is termed cDNA library. The cDNA library contains DNA sequences that are copies of transcribed mRNA. Specific clones from the library may be used for different purposes.

VARIATIONS IN HUMAN GENOME

Humans display a remarkable degree of genetic variation. The most obvious traits include height, blood pressure and skin colour. This also encompasses variation in disease traits and susceptibility to diseases, etc. Even though the sequence of human nuclear DNA is 99.9% similar between any 2 individuals; only 0.1% is sufficient for no. 2 individual to be alike.

Mutations and Polymorphism

Genetic variations originate from 'mutation' that is defined as a change in DNA sequence that is heritable. As a result of mutations, DNA sequences and genes may vary from person-to-person. Different sequences on a particular location (locus) of the chromosome are referred to as alleles. A homozygote has the same allele on both members of a chromosome pair, but alleles differ in a heterozygote. The genotype refers to the alleles present at a given locus.

If a locus has 2 or more alleles where the frequency of minor allele exceeds 1% in population, the locus is said to be polymorphic. Usually such alleles do not produce significant phenotypic effect (i.e. these are neutral in effect), but are presumed to be selected/maintained in the population. These can serve as a useful genetic marker.

Types of Mutations

The variations in the human genome may be at the genomic level as in aneuploidy, chromosomal level as in translocations, or at the gene level as in point mutations. A germline mutation affects cells that produce gametes and is transmitted from generation to generation, whereas a somatic mutation (that can lead to cancer) is confined to somatic cells.

Mutations in individual genes are classified on basis of sequence change and its consequence on protein product and its function. Substitution refers to replacement of a single nucleotide by another, and is the most common type of mutation. Transition refers to substitution of the same type of nucleotide (i.e. purine by purine, or pyrimidine by pyrimidine nucleotide). The reverse is transversion. Substitutions can result in a synonymous change (silent, with same amino acid retained in the protein product), or a non-synonymous change of amino acid. Non-synonymous mutations are missense when the altered amino acid affects protein function or stability, and nonsense when it leads to creation of a stop codon. A substitution may also affect the splice site leading to aberrant splicing of mRNA, or the promoter that leads to altered gene expression.

Deletions involve the loss of one or more nucleotides. If it occurs in the coding sequence, it may disrupt the reading frame (frame shift mutation), unless the deletion affects nucleotides that are a multiple of three (in frame). Larger deletions involving a part or whole of the gene also occur.

Insertion refers to addition of one or more nucleotides into a gene. Depending on the number of nucleotides inserted, the mutation may cause a shift in the reading frame. Expansion of triplet repeats is a form of insertion. It is described elsewhere in this section.

Substitution, insertion and deletion may affect the splice site, either by activating a cryptic splice site or by abolition of a regular splice site. This may result in exon skipping, retention of intronic sequences and frame shift.

Functionally, a mutation can lead to loss of function of a protein [deletion of dystrophin gene (some exons) in Duchenne muscular dystrophy], haploinsufficiency (50% of the protein product is insufficient for normal cellular function as in familial hypercholesterolaemia) or gain of function (as in achondroplasia), or rarely a dominant-negative effect where product of mutant gene in heterozygous state results in loss of activity of normal gene product of the corresponding allele as well.

Single Nucleotide Polymorphisms

Single nucleotide polymorphisms (SNPs, also pronounced as SNIPS) refer to single base differences in the DNA sequence, found throughout the human genome with a frequency of about 1 per 1000 bp, in more than 1% of the population. These are mostly biallelic and occur in both coding and non-coding regions of the genome. It is easy, fast and inexpensive to assay SNPs, and many sites can be assayed simultaneously and automated. They are almost always found near the genes of interest. Combination of SNPs can be used to construct haplotypes, or SNP profiles which serve as powerful tools to study linkage, genetic predisposition to multifactorial diseases, detection of submicroscopic chromosomal imbalances, pharmacogenetics, etc. More recently SNP microarrays have been extensively used for genome wide association studies.

Copy Number Variations

Being diploid, humans have two copies for any particular segment of DNA. However, in some areas, the number of copies of the particular segment varies between two human genomes (of two individuals). This phenomenon has now been termed

copy number variation (CNV) and more and more such copy number variants are being uncovered by the use of array comparative genomic hybridisation technique that is being used widely. A CNV may vary in size from 1 kb to several mega bases and can occur anywhere in the genome. Usually they result from deletion-duplication events and are heritable. It is estimated that approximately 0.4% of the genome of unrelated people typically differs with respect to copy number. Like any other genetic variation, CNVs have been found to be associated with disease susceptibility and resistance. CNVs encompass more DNA than SNPs. CNVs can be limited to a single gene or include contiguous set of genes. CNVs can result in having either too many or too few of the dosage sensitive genes, which may be responsible for substantial amount of human phenotypic variability, complex behavioural traits, and disease susceptibility. It is often difficult to determine whether a particular CNV that is uncovered in a chromosomal array is pathogenic or not. A CNV that arose *de novo* in an individual with abnormal phenotype is likely to be pathogenic whereas a CNV that is inherited from an asymptomatic parent or a CNV that is found in other unaffected individual is likely to be a polymorphism.

HUMAN GENOME PROJECT

It has been one of the most ambitious undertakings in the history of biomedical research. The Human Genome Project (HGP) began in 1991 and produced the first draft sequence of the human genome by 2001, well ahead of its scheduled date of completion. A completed, highly accurate sequence was unveiled in 2003. The entire data is now available in the public domain. In addition to sequencing of the entire human genome, the project had set several other objectives and areas of work as well: human gene maps and mapping of human inherited diseases, maps of model organisms, development of new DNA technologies, development of bioinformatics, comparative genomics and functional genomics. The project also had an ethical component to look into various issues arising out of genome research. The project has provided a map of genetic markers using many thousands of polymorphisms (variations) distributed throughout the genome. Additionally, more than 4 million SNPs have been identified in the human genome.

In addition to the human genome, genomes of several other organisms like *Escherichia coli*, *Haemophilus influenzae*, *Saccharomyces cerevisiae* (yeast), *Caenorhabditis elegans*, *Drosophila melanogaster* (fruit fly), mouse, rat, and zebra fish have also been sequenced. The genes in these organisms show significant homology to genes in humans and provide an opportunity to study candidate genes for human diseases *(comparative genomics)*. These model organisms are also invaluable tools to study expression of genes and function of their protein products in normal development as well as their dysfunction in inherited disorders. Developments in molecular techniques and computational abilities have made gene mapping easier and faster. But it has also thrown many ethical, legal and social challenges. Completion of HGP project represents the beginning of an era of scientifically exciting, but socially complex, biomedical research and molecular medicine.

POST-GENOMIC ERA OF 'OMICS'

The major goal of HGP was to provide entire structure of human genome *(structural genomics)*. But this is of limited use without knowing function of the genome. The emphasis has now shifted to methods suitable for study of functions of different genes identified in the genome. Functional genomics aims to study functions of a gene at biochemical, cellular and organismal level, including gene-gene interactions and gene-environmental interactions. The approach also takes into consideration the role of conserved genes in model organisms and human homologues. Transgenic (those which carry the gene of interest) and knock-out (where the gene of interest is absent or mutated) models provide invaluable insight into function of genes. *Transcriptomics* (study of total mRNA transcript of the cell) provides more scope for linking genes and their products into functional pathways and networks. Expression pattern also reveals how changes in gene expression coordinate the biochemical activities of the cell in health and disease. Development of microarray technology has provided useful means to study expression of thousands of genes at a time. The field of *proteomics* encompasses the analysis of protein expression, protein structure and protein interactions to understand the functions and interactions of genes. *Metabolomics* refers to the study of metabolites and metabolic networks (pathways).

GENOMIC MEDICINE

Each person has a unique genome, except for monozygotic twins, and hence different phenotype (physical traits). Its needs and responses with respect to nutrition, disease susceptibility, preventive care, disease phenotype, complications, treatment, response to drugs, are likely to be unique. All physicians will soon need to understand the concept of genetic variability, its interactions with the environment, and its implications for patient care. With sequence of the human genome now available and technology making it possible to sequence the whole genome of any individual, the practice of medicine will enter into a new era in which an individual patient's genome will help determine the optimal approach to care, be it preventive, diagnostic, or therapeutic.

With rapid progress in technologies to unravel the genome, proteome and even metabolome, there is a paradigm shift in the research focus from disease causing genes to modifier genes, structure to function, aetiology to pathogenesis, and disease diagnosis to susceptibility recognition. Though stem cell therapy and gene therapy still remain a dream despite over two decades of research, we are likely to see major discoveries demystifying human health and disease at an astonishing pace in the coming years. All the monogenic disorders and the underlying defects will be characterised enabling molecular diagnosis of all and prenatal diagnosis whenever indicated. This will open up new treatment options based on innovative strategies. Predictive testing is already possible for some disorders and the number is likely to increase in case of multifactorial diseases. The ultimate aim of understanding the human genome is to offer genomic medicine where the genetic make-up of an individual paves the way for a healthy lifestyle, prevention of disease, and optimal treatment of medical conditions. Simultaneously, progress in the medical field, in all likelihood will increase the debate on social and ethical issues involved.

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6.7 Gene Therapy

Rita Mulherkar

INTRODUCTION

There are more than 3000 genetic disorders caused by single gene defects. In addition, there are many other multifactorial disorders where genetic variation plays a significant role in the aetiology of the disease. The strategies of conventional treatment for genetic disorders often require life-long treatment and are expensive. Besides, for many disorders there is nothing to offer. The possibility of curing the genetic disorder by replacing the defective gene or repairing the mutation *in-situ* appears to be much more logical. Recent advances in molecular biology have made gene therapy an achievable goal.

Gene therapy, as yet, is an experimental modality of treatment where a functional gene is introduced into a cell to take over the function of the defective gene. The first gene therapy trial in humans was approved in 1989. Since then more than 1500 trials in various conditions have been carried out. These studies have provided the 'proof of principle' but safe and effective gene therapy for genetic disorders is still a long way to go. In addition to monogenic disorders, clinical trials using gene therapy are also being carried out for disorders like cardiovascular disease, diabetes mellitus, cancer and infectious diseases like human immunodeficiency virus (HIV).

Gene therapy can be carried out to correct the genetic defect in a fertilised egg (Germline Gene Therapy), or in somatic cells (Somatic Gene Therapy). Due to fear of possible adverse effect on future generations and other social, ethical and legal issues, germline gene therapy is not permitted in any country at present. For somatic gene therapy, special guidelines for clinical trial protocols and permission of ethics committee and other regulatory bodies of the country may be essential.

REQUIREMENTS FOR GENE THERAPY

The prerequisites of successful human gene therapy (HGT), include selecting a therapeutically suitable gene (with a proven role in the pathophysiology of the disease), appropriate gene delivery system (e.g. viral and non-viral vectors to transfer the gene into the cells), efficacy and safety studies in appropriate animal models, and suitable manufacturing and analytical processes to produce well-defined HGT products for clinical investigations. It is only after successful pre-clinical trials for gene therapy in cell culture and animal models, that the therapeutic gene be tested in clinical trials.

In monogenic disorders, addition of the wild type gene has shown some promise in several clinical trials. The first successful gene therapy trial for severe combined immunodeficiency syndrome (SCID) due to adenosine deaminase (ADA) deficiency was carried out in 1990. In this disorder, the wild type ADA gene was introduced in T-cells of the patient and the transduced cells were transferred back to the patient. This resulted in dramatic improvement in immune competence of the patient, so much so that she could attend the normal school. Once the therapeutic gene is selected, the sequences which regulate expression of the gene, i.e. the promoter sequences also need to be selected. A tissue-specific promoter would regulate expression of the therapeutic gene in that particular tissue. A ubiquitous promoter, on the other hand, would express the gene in most tissues, e.g. a viral promoter such as cytomegalovirus (CMV) promoter. The choice of vector is equally important. Most efficient vectors are viral vectors which are modified in the lab to become non-pathogenic. Viruses have evolved over a period of time to efficiently utilise the cellular machinery for its own advantage and make numerous copies of itself in the cell. Thus a gene cloned in a viral vector also replicates itself along with the virus and either gets integrated in the host genome or remains in the nucleus as an episomal body. Adenoviral and adeno-associated virus vectors have been the most widely used vectors in clinical trials so far.

IN VIVO AND *EX VIVO* DELIVERY OF A THERAPEUTIC GENE

The therapeutic gene along with its regulatory sequences can be introduced into the patient either directly as naked deoxyribonucleic acid (DNA) or through a vector, which is injected intramuscularly or systemically. This is known as *in vivo* gene delivery. On the other hand, the therapeutic gene can be introduced into cells removed from patient's body and manipulated *in vitro* before injecting them back into the humans. This is called as *ex vivo* gene delivery. In *ex vivo* gene delivery, there is scope for selectively expanding the cells carrying the transgene, and carry-out quality assurance procedures before administering it to the patient. Stem cells, because of their capacity to survive indefinitely, are good candidates for *ex vivo* gene therapy.

Methods of Gene Delivery

Techniques for gene (DNA) delivery into cells in culture have been the crux of success of recombinant (DNA) technology. Various chemical and physical methods have been used to introduce DNA into cells *in vitro*, the process being called transfection of cells. The cheapest and most widely used method in the laboratory is transfection via calcium phosphate precipitation where DNA is trapped in a fine precipitate and layered onto cells in culture. The DNA enters the cell via endocytosis. Other chemical methods include the use of cationic (positively charged) molecules, such as liposomes, which bind both to the negatively charged DNA on one hand and the negatively charged cell membrane on the other, thereby, facilitating DNA entry into the cell. Physical method, such as electroporation, is another commonly used method for introducing DNA into cells in culture. It is a technique where cells are mixed with the DNA construct and then briefly exposed to pulses of high electrical voltage. This creates transient, reversible pores on the cell surface allowing foreign DNA to enter the host cell. However, the most efficient method for DNA delivery is the use of viral vectors. These include retroviruses,

such as Moloney murine leukaemia virus and adenoviruses which are the common cold viruses. Some important properties desired of an ideal vector are as follows: (a) should protect and deliver DNA into the cell without any alteration, (b) transit easily through cell membrane and from cytoplasm to nucleus, (c) persist in host cell nucleus, (d) be non-toxic (non-pathogenic, if viral) and non-immunogenic, and (e) be easy to produce in large quantities.

Depending on tropism, selected retroviruses can infect all dividing mammalian cells. They carry ribonucleic acid (RNA) as their genome which is converted to cDNA by the enzyme reverse transcriptase inside the infected cell. The cDNA of the virus along with the therapeutic gene, under appropriate regulatory sequences, gets incorporated in the host genome. Thereafter, the virus uses the host cellular machinery to make the therapeutic gene product. Adenoviruses, on the other hand, are DNA viruses; they enter the cell via membrane receptors and remain episomal (unintegrated in the host DNA) in the nucleus. The transduction efficiency (infectivity) of adenoviruses is much greater than that of retroviruses in human tissues. They also have the advantage of transfecting non-dividing cells. But they are immunogenic and do not last for long. Recently, vectors based on HIV lentivirus are being tested as they are the most efficient vectors. Viruses are made non-pathogenic by removing some structural genes from its genome.

STRATEGIES FOR GENE THERAPY

Gene therapy strategy for different diseases varies depending on the genetic information available for a particular disease. Various strategies employed for gene therapy are described below.

Gene Augmentation Therapy

For a disease caused by a mutation leading to loss of function, introduction of a functional copy of the gene into the patient's cells will restore normal function of the cell. However, sustained, long-term expression of the therapeutic gene in an adequate and regulated amount is a major problem. For diseases like severe combined immunodeficiency syndrome (SCID) due to adenosine deaminase deficiency, and haemophilias, expression of even a small amount of protein is sufficient to ameliorate the symptoms. Such diseases are good candidates for gene therapy.

Targeted Mutation Correction

If a mutated gene produces a defective protein which by itself has the harmful effect, i.e. dominant negative effect, then the mutation has to be repaired. In this situation, introduction of a normal copy of the gene will not be effective. For this purpose, a normal copy of the gene is required to be targeted to the same location as the defective gene by homologous recombination. This approach has not yet been possible, although much research is continuing in this area.

RNA Interference (RNAi) for Inhibiting Gene Expression

RNA interference is the technology by which expression of the gene can be inhibited, so that the protein it codes for is not made. The system depends on introduction of double-stranded RNA (dsRNA) inside the cell which activates a cascade of events leading to destruction of the specific RNA molecule. The dsRNA may be in the form of silencing RNA (siRNA) or short hairpin RNA, (shRNA) which is made synthetically and introduced into cells, like DNA, for gene therapy. The sequence of the dsRNA molecule is the same as the sequence of the RNA that is targeted to be destroyed. This approach could be of great benefit in diseases such as cancer, where proteins known to play a role in cell proliferation and anti-apoptosis can be manipulated by this technique. Also, knocking down of the genes which confer resistance to chemotherapy/radiotherapy could sensitise tumour cells to treatment. Numerous trials blocking gene expression at RNA level are in progress and have shown promise.

Gene Therapy for SCID

In 1990, the first genetic disorder to be treated by gene therapy was ADA-SCID. The ADA mini gene was transferred by retroviral vector *ex-vivo* into peripheral blood lymphocytes from 2 patients undergoing enzyme replacement therapy. Long-term survival of transfected T- and B-lymphocytes, marrow cells, and granulocytes expressing the transferred ADA gene was demonstrated and resulted in restoration of cellular and humoral immunity. Although the haemopoietic stem cell would have been the ideal target cell for somatic cell gene therapy of the haematopoietic system, the use of T-lymphocytes as gene therapy vehicle was chosen since they represent the affected cells and known to be long survivors. Subsequently, 8 out of 10 children with ADA deficiency have been successfully treated following infusion of autologous CD34+ cells transduced with the ADA gene.

More recently children with X-linked SCID have shown almost complete reconstitution of their immune system after receiving retrovirally transduced autologous $CD34^+$ haematopoietic stem cells carrying a functional gamma chain of multiple cytokine receptor genes. These children are able to lead a normal life, have responded to several childhood immunisations and have shown good antibody response to infections. However, five of the 20 treated children subsequently developed a leukaemia-like disease after 3.5 years, probably due to the undesired activation of an oncogene by retroviral integration in the host genome.

Gene Therapy for Lysosomal Storage Disorders

Gene therapy is an attractive alternative in many lysosomal storage disorder patients who have responded poorly to bone marrow transplantation or enzyme replacement therapy. The primary goal is to introduce a normal copy of the gene for the lysosomal enzyme into a depot organ such as liver or muscle, so that there is sustained production and reconstitution of therapeutic levels of the enzyme in the affected tissues. A mouse model of Gaucher disease has been developed. In this model, chemically induced deficiency of glucocerebrosidase (GC) is created which results in accumulation of elevated levels of glucosylceramide (GL-1) in lysosomes of Kupffer cells. When these animals were administered mannose-terminated GC (cerezyme) there was reduction of GL-1 levels in liver. Gene transduction of hepatocytes with a plasmid DNA vector encoding human GC (pGZB-GC) achieved similar results. Based on pre-clinical studies, clinical trials are being carried-out where gene coding for GC is transferred to the haematopoietic cells. In one of the clinical trials, the GC gene was targeted via retroviral vector to CD34+ progenitor cells. Preliminary results indicate engraftment of genetically corrected cells in the patient. Further results are awaited.

GENE THERAPY IN CANCER

The largest number of gene therapy trials have been done in patients with cancer (about 65%). It may be not only because cancer is a genetic disease at somatic cell level, but more so out of desperation. Several approaches have been tried for this purpose, viz. (a) introduction of a gene to convert a prodrug to active cytocidal drug in tumour cells causing selective tumour cell destruction, (b) introduction of a multidrug resistant (MDR) gene in normal bone marrow cells to protect them from toxic effects of chemotherapy, (c) introduction of genes for enhancing antitumour immune responses, and (d) introduction of tumour suppressor gene, such as p53, mutation of which is related to several cancers. The latter therapy has even been approved in China for the treatment of head and neck cancer.

FUTURE OF GENE THERAPY

So far four patients have died related to gene therapy. In addition, the occurrence of leukaemia in successfully treated children with X-SCID has been a big dampner. Generally, reaction of the scientific community has been to go back to the bench. This has also served as an impetus to improve vectors and lay greater emphasis on *in situ* gene correction. Successes continue to be achieved in experimental models. Recently, it has been possible to cure sickle-cell disease in an experimental animal using transduced induced pleuripotent stem cells. The unbridled enthusiasm of the nineties has given way to more sober and more realistic expectations. So far the promise continues and the efforts are on. The success in treating SCID, and understanding the molecular basis of leukaemogenesis indicates that the dream may still come true.

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6.8 Genetic Counselling and Prenatal Diagnosis

Shubha R Phadke

For most of the genetic disorders there is no curative treatment at present, or the treatment is cumbersome, costly and associated with risks. Also, many genetic disorders are associated with decreased life expectancy, and mental or physical handicap. Due to these reasons, families with a genetic disorder or those at risk of having an offspring with a genetic disorder, need information about the disease to help them cope with the problem and ways to prevent the occurrence or recurrence of the disorder. The process of communication of this information is genetic counselling. It is aimed to answer the questions of the family, viz. 'Why did this happen to me?", and "Will it recur in my family?' As genetic disorders can involve any system of the body, it is important that clinicians in all specialities are able to identify clinical presentations which are due to, or can possibly be due to, genetic disorders, counsel them and refer them to a geneticist for appropriate investigations and advice where available. In this chapter the importance of genetic counselling in the management of genetic disorders is stressed and basic principles of genetic counselling are discussed.

DEFINITION OF GENETIC COUNSELLING

The American Society of Human Genetics defined genetic counselling as 'a communicative process which deals with human problems associated with the occurrence and/or recurrence of a genetic disorder in a family'. This process involves an attempt by one or more appropriately trained persons to help an individual or a family to: (i) comprehend the medical facts, including the diagnosis, probable course of the disorder and available management; (ii) understand the manner in which heredity contributes to the disorder, and the risk of recurrence in the family; (iii) understand the alternatives for dealing with the risk of occurrence or recurrence; (iv) choose a course of action which seems to them appropriate in view of this risk, their family goals, ethical and religious standards and to act in accordance with the decision; and (v) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

It is clear from the above definition that the primary goal of the genetic counselling is to educate the concerned persons about the medical aspects of the genetic disorder in their family. The family can use the information in a meaningful way to cope with the disorder and the risk of recurrence in accordance with their psychosocial and religious background.

A person who seeks genetic counselling is called consultand or 'counsellee', and the person who gives the advice is called the counsellor. In association with a medical specialist, persons with various backgrounds such as nursing, sociology, psychology or genetics can be trained as genetic counsellor.

INDICATIONS FOR GENETIC COUNSELLING

The following clinical presentations indicate the need for referral to a clinical geneticist and genetic counselling:

1. Congenital malformation: Lethal or non-lethal, isolated or multiple, prenatal or postnatal.
2. Still births/perinatal deaths with or without malformation.
3. Developmental delay or mental retardation with or without malformations, facial dysmorphism and/or neurological deficit.
4. Neurodegenerative diseases presenting as focal neurological deficit, ataxia, spasticity, hypotonia, seizures or psychomotor regression.
5. Mypopathies and muscular dystrophies.
6. A neonate or an infant with acute sickness, or failure to thrive or has recurrent episodes of vomiting, acidosis and/or convulsions.
7. Ambiguous genitalia or abnormalities of sexual development like primary amenorrhoea and delayed puberty.
8. Infertility and poor obstetric history like recurrent spontaneous abortions and foetal losses.
9. Proportionate or disproportionate short stature.
10. Childhood deafness.
11. Known monogenic disorders like thalassaemia, Wilson disease, haemophilia A, mucopolysaccharidosis, etc.
12. Down's Syndrome and other chromosomal disorders.
13. Familial cancers or cancer prone disorders.
14. Relatives of an individual having a structural abnormality of a chromosome or chromosomes.
15. Any unusual disease of the skin, eyes, bones or unusual facial features.
16. Any disease which is familial.
17. Exposure to a known or possible teratogen during pregnancy.
18. Consanguineous marriage.
19. Advanced maternal age.
20. Carrier of a genetic disorder.
21. Positive screening test for a genetic disorder.

STEPS IN GENETIC COUNSELLING

The process of genetic counselling is quite complex. It requires correct diagnosis and latest information about medical and genetic aspects of the disorder. The steps of genetic counselling are as follows:

1. Accurate diagnosis of the proband
   (a) History taking
   (b) Pedigree drawing

(c) Clinical examination
(d) Biochemical, haematological, imaging and other necessary investigations.

2. Chromosomal or DNA tests, as needed.
3. Latest information about pathophysiology of the disease, available treatment, risk of recurrence, and availability of prenatal diagnostic test.
4. Communicating the information in simple, layman's language to the consultand and family members concerned.
5. Giving the consult and a written or typed case summary which includes the case details, diagnosis and details of genetic counselling.
6. Follow-up sessions may be needed to support the family, communicate new information, and observe any progression of the disease in the proband.

In addition to accurate diagnosis, consideration of many other issues like psychosocial, religious, educational and ethical are of paramount importance for effective genetic counselling. Success of genetic counselling depends on whether the consultand feels benefited by genetic counselling or not. Hence, it is important to assess the expectations of the consultand and to tailor the counselling accordingly, keeping in mind the psychosocial, religious and educational backgrounds of the consultand.

Genetic counselling for some common genetic disorders is discussed below. This is to illustrate the principles of genetic counselling and various issues involved in the process.

CASE-I

Down's Syndrome: A Common Chromosomal Syndrome and the Commonest Genetic Cause of Mental Retardation

A 3-month-old infant was brought to the clinic with rapid breathing, feeding difficulty and excessive crying. The child had a pansystolic murmur in the left parasternal region and typical facial features like flat face, hypertelorism, upslant of eyes and Simian crease on both hands. The diagnosis was Down's syndrome with ventricular septal defect with congestive cardiac failure.

In addition to echocardiography and treatment of cardiac failure, the karyotype from blood was recommended. Karyotype is needed not only to confirm the diagnosis of Down's syndrome but also to know the type of chromosomal abnormality. Ninety-five per cent of Down's syndrome cases are due to free trisomy 21 (47,+21) (**Figure 1**), and the risk of recurrence in siblings of such a child is 1%. Four per cent of Down's Syndrome cases are because of translocation of chromosome 21 to 14, 15, 21 or 22 (**Figure 2**). Karyotypes of both parents of such a case are essential. The risk of recurrence varies depending on the chromosome involved and sex of the carrier parent (**Table 1**). The karyotyping of parents of a child with free trisomy 21 is not indicated.

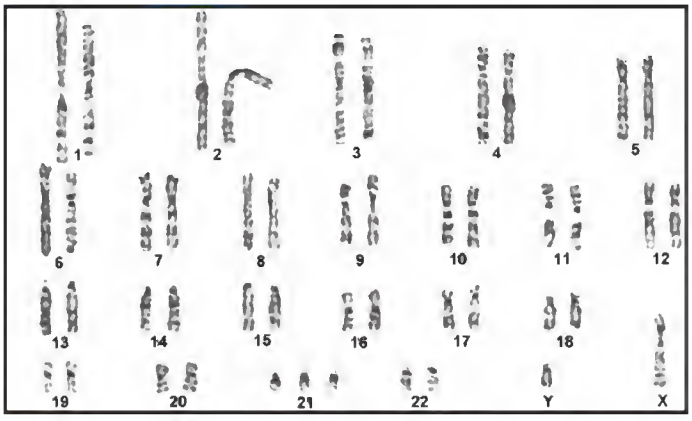


Figure 1: Karyotype showing free trisomy 21.

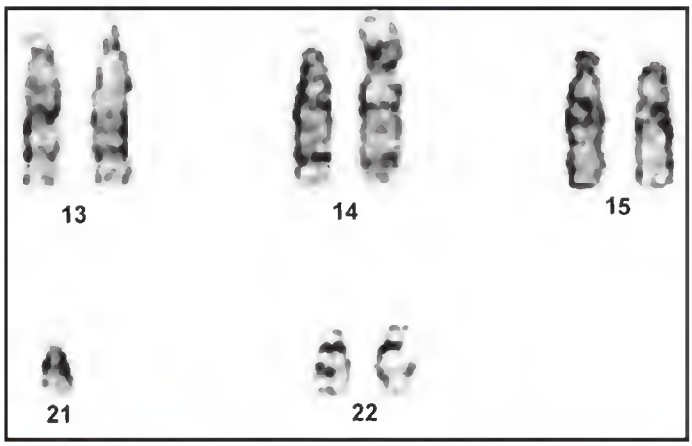


Figure 2: Partial karyotypes showing balanced translocation between chromosomes 14 and 21.

Table 1: Risk of Recurrence of Down's Syndrome in the Offspring of a Parent with a Balanced Translocation

Translocation	Carrier Father	Carrier Mother
t(14;21)	1% to 5%	15%
t(21;22)	1% to 5%	15%
t(21;21)	100%	100%

Genetic counselling

The challenge in this case is to break the news of the diagnosis of Down's syndrome to the parents. Further, the parents are to be advised regarding the need for surgical treatment of the cardiac defect, and associated problem of mental sub-normality and developmental delay which would become more pronounced as the child grows. Realistic information about mental abilities is essential. Though the intelligent quotient (IQ) of Down's syndrome cases varies from 40 to 70 or more, most of the cases with Down's syndrome are moderately retarded. Though late, they learn to walk, talk, carry-out self-care activities, and can also be taught to do simple repetitive tasks. They can work in a supervised and sheltered workplace. They can lead a loving, useful and happy life but need lifelong supervision. Importance of regular surveillance for hypothyroidism and hearing and ophthalmological problems needs to be stressed, but increased risk of leukaemia and atlanto-axial dislocation need not be told in the first visit as the risk of these conditions is very small. Risk of recurrence of Down's syndrome in any subsequent pregnancy should be discussed after the karyotype report is available. Prenatal diagnosis in the next pregnancy can prevent recurrence and the family should be provided the information before planning the next pregnancy.

Messages

1. The diagnosis of Down's syndrome is obvious at birth and should be communicated to the family soon after birth. This helps in screening for major malformations immediately

after birth and timely treatment. Of course giving the bad news of the birth of a child with mental sub-normality to the family, happy with the childbirth and an apparently normal looking neonate is a challenge to the paediatrician and obstetrician.

2. Chromosomal analysis of all children with Down's syndrome is important to provide the risk of recurrence and prenatal diagnosis.
3. Prenatal diagnosis of Down's syndrome is possible by doing karyotype analysis from chorionic villi or an amniotic fluid sample.
4. The primary care physician or a paediatrician can take up the responsibility of providing regular follow-up needed for children with Down's syndrome. This includes clinical examination for associated abnormalities, investigations for iron deficiency anaemia, hypothyroidism and ophthalmologic and ear examinations.

CASE-II

Prenatally Detected Mild Ventriculomegaly at 20 Weeks of Gestation on Routine Ultrasound Examination

A 32-year-old lady married for 8 years, who conceived after treatment for infertility, came for routine ultrasonography (USG) at 20 weeks of gestation. In the first year of her marriage, she had two spontaneous abortions at 10 weeks of gestation. The USG showed mild ventriculomegaly. Hence, she was referred for genetic counselling.

The first step of genetic counselling was to get a targeted ultrasonographic examination done to look for associated malformations. It showed mild dilatation of the lateral ventricles of the brain with open spinal defect and a large sac in the thoracolumbar region. There was no talipes equinovarus deformity or any major malformation of the heart, kidneys, abdominal wall, face, etc.

Genetic counselling

Meningomyelocoele is a major malformation which is often associated with Arnold-Chiari malformation and obstructive hydrocephalus. These defects are surgically treatable. But in spite of surgery after birth, many (50% or more) of the operated cases may have residual neurological defects including paraplegia, bladder-bowel incontinence and cognitive defects due to ventriculomegaly. In some cases hydrocephalus progresses rapidly, which may need destructive surgery for large head causing obstructed labour or may lead to stillbirth. The mother should be asked about the history of taking teratogenic drugs like anticonvulsants, and investigated for diabetes mellitus, as these are common risk factors for neural tube defect. Though the chance of chromosomal abnormality with isolated neural tube defect is low, prenatal chromosomal analysis by amniocentesis is recommended for proper counselling. If the family opts to continue the pregnancy regular follow-up USG examination, delivery at a good centre with good neonatal facilities, consultation with a paediatric surgeon or a neurosurgeon needs to be arranged.

If the family opts for termination of pregnancy, foetal autopsy, or after delivery detailed clinical and radiological examination of the baby is essential for counselling regarding risk of recurrence in a subsequent pregnancy. The risk of recurrence of isolated neural tube defect in the next pregnancy after the birth of one affected child is 5% and can be reduced by intake of folic acid by the mother during periconceptional period. If the meningocoele/meningomyelocoele is a part of a multiple malformation syndrome like spondylothoracic dysplasia or Meckel-Gruber syndrome then the risk of recurrence is 25%. Accurate diagnosis is also important to provide prenatal diagnosis during the next pregnancy which can be done ultrasonographically, as early as at 14 weeks. One USG at 16 to 18 weeks by an ultrasonographer with specialisation in prenatal diagnosis will be able to detect open neural tube defect with almost 100% sensitivity.

Messages

1. One routine USG examination should be offered at 16 to 18 weeks of gestation for prenatal diagnosis of malformations.
2. Accurate diagnosis of associated malformations and foetal chromosomal analysis is important for giving information about prognosis of malformation.
3. The information about possible outcomes of the malformation, especially if the malformation is treatable, will help the family in deciding about continuation or termination of pregnancy.
4. The uncertainties in providing exact outcome in each case should be truthfully shared with the family.
5. The genetic counselling should be non-directive. Possibilities of good and bad outcomes should be told with their likelihood. Many other factors like presence of previous normal or similarly affected children, age of mother, history of infertility may affect the family's decision. In this case, due to long period of infertility and two spontaneous abortions, the family may not take up the option of amniocentesis for karyotyping as it is an invasive procedure and associated with a small risk of abortion.
6. Autopsy of foetuses terminated after prenatal diagnosis of malformations is important not only for confirmation of prenatal diagnosis but also to look for associated malformations which may have been missed on USG, or may not be detectable on USG. Autopsy may change the diagnosis in about 30 to 50% foetuses, hence, essential for genetic counselling.

CASE-III

Pre-pregnancy Counselling for Family History of Huntington Chorea

A couple married for 2 years and planning to raise a family came for genetic counselling. The husband was 32-year-old and the wife was 27-year-old. The husband's brother who is 40-year-old had developed abnormal movements since the last 4 years and was diagnosed to have Huntington chorea. His father died at the age of 65 years, who suffered from similar problems for 10 years and had become bed-ridden. The couple wanted to know whether their child could have the same disease and whether it could be avoided.

Genetic counselling

The first step of genetic counselling is to draw a pedigree chart and confirm the diagnosis. A 3-generation pedigree chart was

drawn which showed that two of the uncles of the consultand (husband in this case) were similarly affected and one of them was seen as an out-patient at the Department of Genetics. The family was asked to get the medical records of the affected uncle with his permission. The records confirmed the diagnosis of Huntington chorea by a neurologist as well as by DNA-based mutation analysis. The DNA test showed that the uncle with Huntington disease had 44 CAG repeats in HD gene and the other copy was normal (20 CAG repeats). This confirmed the presence of mutated HD gene in the family.

Now, the question: What is the risk of Huntington disease mutation in the offspring of the couple? This will depend on whether the consultand himself is carrying the mutation or not. As Huntington disease usually manifests after 40 years of age, many individuals who carry the mutation will be clinically normal at 32 years of age. Hence, it is essential to test the husband's DNA for HD mutation. If he is not the carrier of the mutation, he will not develop the disease in future and also there is no risk of Huntington disease in the offspring of the couple and prenatal diagnosis is not indicated. But if he is a carrier of mutation, then there is 50% chance that the offspring may inherit the mutated copy of the gene from him and develop the disease in future. The age of onset of symptoms depends on the number of CAG repeats and the number of repeats may increase when the mutation is transmitted from one generation to the next. The individuals with repeats around 80 may develop the disease in childhood. The birth of a child with HD mutation can be avoided by prenatally testing the mutation in chorionic villi at 10 to 12 weeks of gestation providing the couple an option for reproductive planning. All DNA-based tests have some error rate, usually around 1%.

This opens a lot of issues for the family. First, pre-symptomatic diagnosis in the husband may cause major psychological problems as there is no treatment for the disease. Also, if this information if not kept private and confidential it may cause problems at the job, and for medical insurance, etc. Hence, the couple should be given time before opting for DNA testing. If after adequate counselling and careful deliberation the consultand wants to go for a DNA test, then it should be ordered. After the results are available, the couple should be explained the results, and post-test counselling should be provided. Continued psychological support may be needed. If the husband is the carrier of mutation, there is 50% risk of transmitting the mutation to the offspring. Many laboratories and also families are not comfortable with the idea of termination of a affected pregnancy as the foetus will not manifest the disease until 3 to 4 decades. This is ethically debatable, especially with the present pace of developments in the field of genetics, where new treatments for many genetic diseases are expected in the future. After discussing all these issues in a non-directive manner, the family may take their reproductive decision. The whole process may take many sessions to understand difficult scientific information and various complexities of the situation.

Messages

1. DNA-based diagnosis is available for many single gene disorders and is useful for diagnosis of patient and prenatal diagnosis.
2. The confirmation of diagnosis in the proband or affected member of the family is an important first step before providing genetic counselling.
3. Mutation detection is essential for prenatal diagnosis based on DNA analysis.
4. The counselling should be non-directive and the family should make their own reproductive decisions.
5. The genetic counselling involves providing a lot of scientific information and probabilities, which may be a difficult task, for which very good communication skills are needed to be a good genetic counsellor.
6. The information provided during genetic counselling may be psychologically disturbing and adequate pre-test and post-test counselling is necessary.
7. Pre-symptomatic and prenatal diagnosis of late onset genetic disorders pose a lot of ethical, legal and social dilemmas and need to be dealt with sensitivity.
8. Pre-pregnancy counselling plays an important role in genetic disorders and is the most appropriate time for genetic counselling, as it provides time for organising investigations, understanding the situation and making appropriate decisions.

CASE-IV

Counselling for Familial Breast Cancer

A 28-year-old married woman comes for genetic counselling as her 35-year-old sister is diagnosed to have carcinoma breast and her mother died of carcinoma breast at the age of 50 years. Pedigree chart showed that one sister of her mother had carcinoma of ovary. Her maternal uncle's wife also had carcinoma breast.

Genetic counselling

Presence of three blood relatives with carcinoma breast and ovarian carcinoma suggests familial breast cancer. Note that the wife of her maternal uncle is not her blood relative and medical ailments in her do not influence the risk of genetic disorders in the consultand. Such an individual needs to be offered surveillance for carcinoma breast and ovaries as early detection may help in better treatment and improve outcome. This is the case where mutation detection in carcinoma breast related genes, namely, BRCA1 and BRCA2 is indicated. The BRCA1 and BRCA2 account for 50% and 30% of familial breast cancers, respectively. First the mutation has to be tested in one of the individuals with carcinoma breast (it can be done on the operated breast cancer tissue), and if the mutation is detected then DNA testing of the consultand and other probable carriers in the family (who are more than 18 years of age) needs to be discussed. The individuals who have the mutation need to be kept under close surveillance for carcinoma breast and ovaries as per accepted guidelines. The confirmed carriers of BRCA gene mutations can be offered even radical measures like prophylactic mastectomy or oophorectomy.

Messages

1. Three or more family members with one type of cancer or related cancers should alert the clinician for the possibility of familial cancers and refer the family for genetic counselling.

2. The pointers towards the possibility of familial cancer include cancer at young age, co-occurrence of multiple primary cancers and bilateral cancers in paired organs, associated clinical features like hyperpigmentation of lips (Peutz-Jeghers syndrome), adenomatous polyposis colon, neurofibromatosis, etc.
3. Mutation detection in the individual with the cancer is important before the mutation-based screening can be offered to the unaffected family members.
4. Mutation testing for carcinoma breast and other familial cancers is technically demanding, costly and not easily available. Even if mutation detections not done, continued surveillance for early diagnosis can be offered to individuals with familial cancer.

CASE-V

A Couple with Three Recurrent Spontaneous Abortions in the First Trimester

A non-consanguineous couple with three spontaneous abortions was referred for genetic testing. The chromosomal analysis from peripheral blood was done for both the spouses. The karyotype of the wife showed a balanced translocation between chromosomes 7 and 11 (**Figure 3**).

Genetic counselling

The balanced translocation in this case is likely to be the cause of recurrent spontaneous abortions in this case. The gametes of an individual with a balanced rearrangement may have unbalanced karyotype and the conceptus with a major chromosomal imbalance may not be compatible with life and abort spontaneously. As such individuals also have gametes with normal chromosomal complement, or balanced chromosomal complement, so they can have normal offspring as well. The risk of repeated abortions is about 30% but may vary depending on the chromosomes involved and their breakpoints. There is no treatment to prevent formation of unbalanced gametes or to prevent abortion. Some of the chromosomal imbalances may be small and such foetuses may not be aborted but may have malformations or a mental handicap. Hence, this couple should be offered prenatal karyotyping by amniocentesis if the pregnancy continues beyond the first trimester.

The other options are use of donor ova (or sperms, if husband is the carrier of a balanced chromosomal rearrangement), or preimplantation diagnosis. The latter involves *in vitro* fertilisation and single cell genetic test which in addition to being costly is also not easily available.

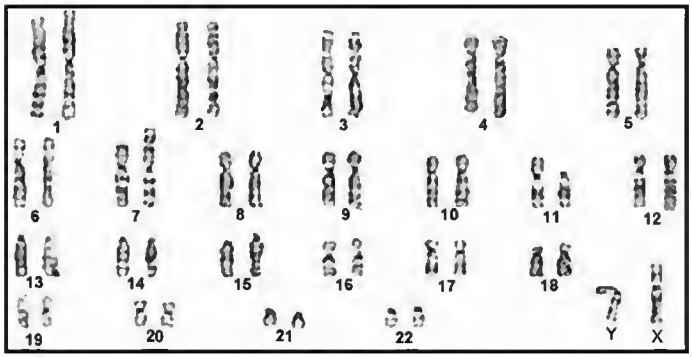


Figure 3: A karyotype showing a balanced translocation between chromosomes 7 and 11.

The other treatable causes of recurrent abortion should also be simultaneously investigated as more than one cause may coexist. Investigations for toxoplasmosis, rubella and cytomegalovirus infections are not indicated as they do not cause recurrent abortions.

Messages

1. About 5% of the couples with recurrent spontaneous abortions have one spouse with balanced chromosomal rearrangement.
2. If the karyotype is abnormal, there is no treatment but counselling, and prenatal diagnosis is needed.
3. One in 500 normal people have a balanced chromosomal translocation, and such carriers are usually phenotypically normal.
4. The individual with balanced translocation is not at any risk of medical ailment due to chromosomal abnormality.
5. All attempts should be made while counselling such a couple to protect from blame or guilt in the family.
6. Chromosomal variants, such as long 'Y' chromosome, pericentric inversion of chromosome 9, etc. are not known to be associated with recurrent spontaneous abortions.

CASE-VI

A Family with a Two-year-old Child with Metachromatic Leukodystrophy

A couple came with a 2-year-old son who was diagnosed as a case of cerebral palsy. The mother of the child was 6 weeks pregnant. The family wanted to know the risk of recurrence of a similar problem in the next child.

The pedigree chart showed that the parents were cousins and their first child had a similar problem and had died at two-and-a-half years of age. The proband (the affected child) was normally developing till about one year of age and was able to stand without support. Then he lost the milestones, and developed scissoring of lower limbs (**Figure 4**). There was hypertonia of limbs with exaggerated knee reflexes and absent ankle reflex. The deterioration continued. Magnetic resonance imaging (MRI) brain showed changes indicative of white matter involvement. The enzyme assay for metachromatic leukodystrophy showed deficiency of aryl sulphatase A which confirmed the diagnosis of metachromatic leukodystrophy.

Genetic counselling

Metachromatic leukodystrophy is an autosomal recessive disorder and the risk of recurrence to a subsequent child of these parents is 25%, i.e. 1 in 4. The prenatal diagnosis can be carried out by assaying the enzyme in chorionic villi at 11 weeks of gestation. If the foetus is found to be deficient in the enzyme, the family can take an appropriate decision according to their convictions.

If by DNA sequencing of the aryl sulphatase A gene (ARSA) mutations can be identified in the proband or his parents then prenatal diagnosis by mutation detection can be done. DNA-based prenatal diagnosis is more accurate than that by biochemical test (enzyme assay).



Figure 4: A child with metachromatic leukodystrophy. Note the scissoring of lower limbs.

Messages

1. All children with developmental neurological problems should not be labelled as cerebral palsy without evaluation, as many genetic disorders may manifest as developmental delay or mental retardation which superficially mimics cerebral palsy.
2. Presence of normal development followed by regression of milestones is characteristic of metabolic disorders.
3. Presence of consanguinity, or similarly affected 2 or more siblings, suggests the possibility of an autosomal recessive disorder.
4. Confirmation of genetic metabolic disorder by enzyme assay of involved metabolic pathway is essential for diagnosis, genetic counselling and prenatal diagnosis.

PRENATAL DIAGNOSIS

The availability of prenatal diagnosis for a number of genetic disorders has made counselling and decision-making easier. A variety of tissues can be collected from the foetus for chromosomal, DNA and biochemical analysis. These include chorionic villi (11-12 weeks of gestation) and amniotic fluid (16-20 weeks). Rarely, foetal skin, muscle, liver biopsy or blood sample may be collected for biochemical or tissue analysis. Analysis of foetal cells and foetal DNA from mother's blood has become technically possible and can be used for foetal Rh typing. Prenatal diagnosis based on free foetal DNA in mother's plasma is used not only for single gene disorders but also for aneuploidy detection. Preimplantation diagnosis is a good option for families who do not approve of termination of pregnancy.

High resolution ultrasonography can detect a number of structural malformations of the central nervous system, gut, kidneys, limbs, spine and heart. Detection of associated malformations and chromosomal analysis is useful for providing counselling in a case with prenatally detected malformation. But for counselling regarding next pregnancy, examination of baby or foetus after delivery or termination (foetal autopsy) is important, because in 30% to 40% cases associated malformations may be missed or may not be detectable on ultrasonography.

CONCLUSION

All cases in which a genetic disorder is diagnosed or suspected, a complete evaluation of the affected individual and genetic investigations are important. Genetic counselling is an integral part of management of a case with genetic disorder. It is the responsibility of the primary care physician to suspect cases with a probable genetic disorder and refer them to a clinical genetics centre. As the clinical geneticists are few in number, paediatricians, obstetricians and physicians may have to take up the responsibility of providing diagnosis and counselling for common genetic disorders.

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6.9 Pharmacogenomics and Personalised Medicine

C Adithan

Optimal therapy for major illnesses is still elusive. The drug therapy of psychiatric illnesses, cancer, hypertension and many other common diseases is associated with unsatisfactory response and undesirable adverse effects. Many approaches have been adopted to improve this condition. Among them the role of genetic factors in drug response is very important.

PHARMACOGENETICS AND PHARMACOGENOMICS

The action of a drug is regulated by several factors, namely drug metabolising enzymes, transporter proteins, receptors and several other mediators. These enzymes and proteins are encoded by genes in the deoxyribonucleic acid (DNA). A number of variations have been identified in the structure of genes encoding these factors. This can result in varying drug responses in each individual depending upon their genetic make-up. A genetic variation occurring in more than 1% of the population is termed as genetic polymorphism. The study of the effect of a single gene or genetic polymorphism on drug response is called pharmacogenetics. Study of the effect of variations in multiple genes, including whole genome approach, on drug response is called pharmacogenomics. It is predicted that application of pharmacogenomics in clinical practice may lead to individualised drug therapy (personalised medicine), thus, paving the way for improved effectiveness and reduced adverse drug reactions.

PERSONALISED MEDICINE

Personalised medicine is the science concerned with providing medical care tailored to the genomic and molecular profile of an individual patient. The physician selects the drug and its dosage using detailed information about the patient including clinical data, genotype or level of gene expression, drug profile, as well as genetic details of the causative organism, if any. The important pre-requisites for success of personalised medicine are valid biomarkers and availability of reliable, simple and affordable genetic tests.

CLINICAL APPLICATIONS

The clinical practice of personalised medicine has started to receive attention with more drugs being discovered using methods of pharmacogenetics. For a drug to be used clinically based on pharmacogenetic data, identification and establishment of a valid pharmacogenetic biomarker is necessary. Some of the drugs for which a valid pharmacogenetic biomarker has been identified are warfarin, irinotecan, carbamazepine, abacavir, azathioprine, trastuzumab, imatinib, maraviroc, rituximab, omeprazole, and clopidogrel.

Oral Anticoagulant Drugs

Warfarin, an oral anticoagulant is used in patients with cardiovascular disorders. The most common complication of warfarin includes bleeding manifestations. It is metabolised by the enzyme CYP2C9 encoded by the gene CYP2C9. Further, its activity depends on the enzyme epoxide reductase complex 1 encoded by the gene *VKORC1*. Variations in the nucleotide sequences of the coding region of these enzymes result in altered metabolism and activity of warfarin. Patients with the variant genotypes, such as *CYP2C9 *1/*3* and *VKORC1 AA* have six-times lower dose requirement compared to the common genotypes of *CYP2C9 *1/*1* and *VKORC1 GG*. The United States Food and Drug Administration (US-FDA) has made label changes in warfarin and recommended genetic testing for these two genes before initiation of warfarin therapy. Based on the genotype of the patient, the dose has to be adjusted to an optimum level of international normalised ratio (INR).

Anticancer Drugs

Irinotecan, an inhibitor of the enzyme topoisomerase 1 is used as an anticancer agent. It is a pro-drug and gets converted to an active form SN 38 which inactivates topoisomerase 1, and thus, inhibits DNA replication. The SN 38 gets inactivate by the process of glucuronidation by the enzyme UGT1A1. This enzyme is encoded by the gene *UGT1A1*. It was found that the variant genotype *UGT1A1 *28/*28* was associated with impaired conjugation, and hence, results in higher plasma levels of SN38. This genotype was associated with greater haematological toxicity. This led to changes in the label of irinotecan by the US-FDA which also recommended genetic testing for patients who are to be started on treatment with irinotecan.

Anticancer agents such, as azathioprine and 6-mercaptopurine are metabolised by the enzyme thiopurine methyl transferase enzyme (TPMT) encoded by the gene *TPMT*. Individuals with variant genotype of *TPMT* have reduced or absent enzyme resulting in high drug levels and greater myelo-toxicity. It is recommended to do a genotype or phenotype test for TPMT before starting thiopurine therapy.

Other drugs where genetic testing is preferred, include trastuzumab, rituximab, imatinib and maraviroc. Trastuzumab, a monoclonal antibody targeting the HER2 protein is used in breast cancer patients who are over-expressing HER2/neu protein. It is more effective in the treatment of early stage HER2 positive breast cancer patients. Rituximab, a monoclonal antibody directed against the CD-20 protein in B-cell lymphocytes is approved for use in B-cell non-Hodgkin lymphoma and rheumatoid arthritis. The patients may be tested for expression of CD-20 protein by the B-cells for initiation of therapy with rituximab. Imatinib mesylate is used for treatment of chronic myeloid leukaemia which is associated with the chromosomal abnormality termed as 'Philadelphia chromosome' which produces mutant protein responsible for cell proliferation. Imatinib inactivates this overactive protein BCR-ABL-tyrosine kinase. Thus, testing for this genetic abnormality is necessary for treatment with imatinib mesylate.

Antiretroviral Drugs

Abacavir, the antiretroviral drug was found to have higher incidence of hypersensitivity reactions associated with patients having human leucocyte antigen (HLA)*5701. The development of high resolution HLA typing enabled identification of patients at risk for abacavir hypersensitivity and avoided adverse drug reactions. After the publication of PREDICT1 and SHAPE studies, there has been an increased demand for HLA typing tests for patients with human immunodeficiency virus (HIV) infection.

Maraviroc, an antiretroviral drug, prevents entry of HIV into the host cell by binding the CCR5 protein on cell surface. The virus requires binding to CCR5 protein for cell membrane fusion and entry into host cell. Thus, the entry of CCR5 tropic viruses is inhibited. However, the viruses which are CXCR4 tropic do not respond to maraviroc and result in dominance of CXCR4 tropic strains. It is recommended to test for tropism of the virus strain in a patient before initiation of therapy with maraviroc.

Omeprazole and Clopidogrel

The proton pump inhibitor omeprazole is metabolised by CYP2C19 enzyme. Patients with variant genotype *CYP2C19 *2/*2* have markedly reduced metabolism of omeprazole. This has been found to result in higher cure rates with anti-*Helicobacter pylori* regimen in such patients. For a patient with similar variant genotype *CYP2C19 *2/*2*, the anti-platelet drug clopidogrel can have reduced therapeutic effect due to reduced conversion to its active metabolite by the enzyme CYP2C19. In such patients, genotyping for CYP2C19 polymorphism would enable selection of a suitable alternative anti-platelet drug.

Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS), a severe form of dermatological manifestation of hypersensitivity reaction to drugs, was found to occur with the anti-epileptic drugs, carbamazepine. Studies have shown a strong association between the HLA-B*1502 and occurrence of SJS in patients receiving this drug. This variant gene was found to occur at higher frequency in Hans Chinese, Malays and Thais. Based on strong association demonstrated, the US-FDA made label changes in carbamazepine and recommended testing for HLA-B*1502 in Asian populations before starting therapy with carbamazepine. This would help in identifying patients who are at risk of developing SJS with carbamazepine, and thus, avoid drug-induced morbidity.

BARRIERS FOR PHARMACOGENETIC TESTING

Although extensive studies are being done in the field of pharmacogenomics, the concept of personalised medicine is yet to be incorporated in clinical practice to a large extent. This can be attributed to factors, such as increase in cost of therapy due to inclusion of pharmacogenetic testing as part of drug therapy and difficulty in imparting the pharmacogenetic knowledge to clinicians on a wider scale. Further, availability of laboratory facilities to do pharmacogenetic tests is necessary for the widespread use of pharmacogenetics in clinical practice. Most clinicians prefer to rely on clinical and biochemical parameters for dose selection and empiric dose titration rather than testing for genetic make-up of the individual.

The cost of genotyping could be a major limiting factor in application of pharmacogenetics on a larger scale in clinical practice. One alternative is to do bulk testing. The cost of genotyping 1000 DNA samples is approximately 0.3 to 0.5 USD (US Dollors) per genotype compared to 130 USD for testing of a single sample. This difference is due to the fixed price of the set-up of assay marker. Hence, patient samples can be analysed only when collected in large numbers.

Several ethical issues arise with the application of pharmacogenetic methods. Categorisation of populations based on genotypes may result in exclusion of smaller groups of people from usage of drugs which are brought into the market based on pharmacogenetic tests. Further, revelation of genetic risk factors for late onset diseases and variation in drug response for such diseases may have profound psychological impact on the patient and affect the quality of life. This information can also lead to denial or increased cost of insurance policy coverage for such people.

Pharmacogenomics and personalised medicine have many promising features but there are issues in their application on a larger scale for clinical practice. They can be solved only by further refining of the process involved in it and policy decision making by the government.

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6.10 Cancer Genetics

Rajiv Sarin

CANCER IS A GENETIC DISEASE

Cancer is a 'genetic disease', as gene mutation/s and chromosomal alterations are the hallmark of all cancer cells. The term 'genetic' in this context refers to molecular pathology of the disease and not to transmission from generation to generation, as is often the case for hereditary diseases. It shall be noted that while all cancers are characterised by genetic alterations, only 2% to 5% of human cancers are hereditary. It is because the genetic alterations in cancers are acquired, and remain restricted to the somatic cell. The origin of hereditary cancers is discussed separately.

The genes associated with causation of cancer are broadly classified into two types, viz. 'tumour suppressor genes' (TSGs) and 'proto-oncogenes', based on their normal cellular function and mechanism of causation of cancer. Knowledge of specific genetic alteration/s which gives rise to a particular cancer has been of immense use in improving prognostic classification, and development of targeted therapy for several cancers. In case of hereditary cancers it can be used for detection of carrier status, genetic counselling and cancer prevention.

MULTI-STEP CARCINOGENESIS AND CLONAL ORIGIN OF CANCER

The process of carcinogenesis is characterised by three steps - initiation, promotion and progression. Accumulation of 5-10 mutations in specific genes is invariably required for a normal cell to transform into a malignant phenotype as shown for the colon cancer model by Vogelstein (**Figure 1**). According to the clonal theory of cancer, cancer initiates from a single cell. It progresses through a series of mutations at successive cell divisions, with selection at each step, resulting in the establishment of an autonomous, malignant clone with selective growth advantage which leads to formation of a tumour mass. During their long natural history, most cancers develop molecular heterogeneity due to development of sub-clones, ultimately leading to development of the 'metastatic clone' which eventually kills the individual.

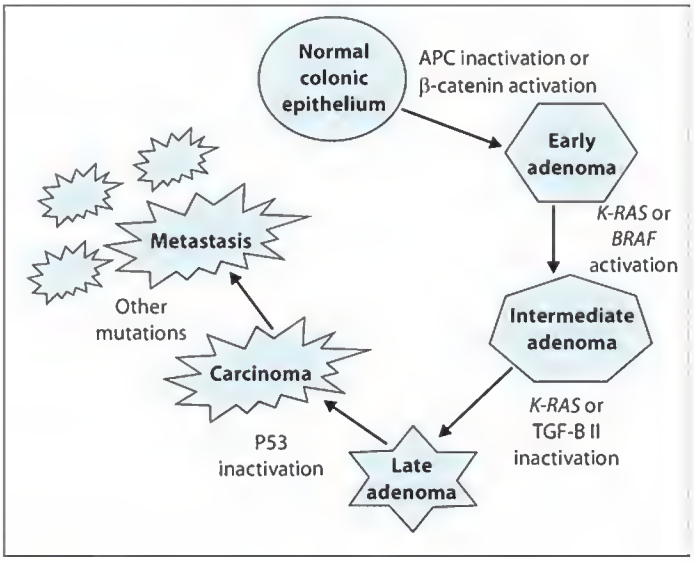


Figure 1: Multi-step carcinogenesis (Vogelstein's colon cancer model).

GENOMIC INSTABILITY

Genomic instability is a cardinal feature of cancer. In certain hereditary cancer syndromes, the underlying defect mismatch repair pathway, as seen in hereditary non-polyposis colon cancer (HNPCC), or neucleotide excision repair pathway (NERP) as seen in xeroderma pigmentosa (XP), which results in genomic instability and cancer. In sporadic cancers, the genomic instability is often the result of accumulation of several mutational events during malignant transformation and progression.

ONCOGENES AND TUMOUR SUPPRESSOR GENES

Oncogene, the activated form of proto-oncogene, is the 'accelerator switch' of cell division while tumour suppressor gene (TSG) is the 'natural brake' of cell division (**Table 1**). Mutations in specific domains of proto-oncogenes, their amplification or translocation, sometimes leading to formation of fusion genes, result in gain of function and constitutive activation of mechanisms controlling cell proliferation. Germline point mutation in the cysteine rich extracellular domain or intracellular tyrosine kinase domain of RET proto-oncogene resulting in multiple endocrine neoplasia (MEN-2) syndrome is a classical example of oncogene driven hereditary cancer. A somatic mutation, or over-expression of oncogenes, is a common mechanism of sustained growth stimulus in sporadic cancers. Some clinically relevant examples include point mutations in phosphate binding loop of K-RAS in pancreatic, colon and lung cancer; catalytic kinase domain of epidermal growth factor receptor (EGFR) in head, neck, lung and pancreatic cancers; over-expression of C-ERBB2 in breast cancer and the BCR-ABL fusion gene in chronic mylogenous leukaemia (CML). In contrast to gain-in-function mutations of oncogenes, TSGs undergo loss-of-function when certain mutations or chromosomal alterations lead to diminution in normal activity of proteins controlling apoptosis (p53 protein); cell cycle regulation (RB protein), or DNA damage repair (BRCA1 or XP proteins), etc. Somatic mutation in p53 gene is one of the most frequently occurring genetic alterations in human cancers.

TSGs are broadly classified as *Gatekeeper* or *Caretaker* genes based on their normal cellular function. As the names imply, the gatekeeper genes control critical events and check points in the cell cycle (RB, TP53, APC, etc.), while the caretaker genes maintain genomic integrity through their critical role in DNA repair (mismatch repair genes, nucleotide excision repair genes, BRCA1, etc).

Table 1: Comparison Between Oncogenes and Tumour Suppressor Genes

Oncogene (Activated Proto-oncogene)	Tumour Suppressor Gene
Encode components of a signalling pathway that regulate cell proliferation and control the machinery of cell cycle (e.g. MYC, RAS or EGFR, etc).	Regulate cell cycle progression (e.g. RB), apoptosis (e.g. p53) and DNA damage repair (e.g. BRCA1/2)
Mutation or over-expression of a single allele results in gain of function which drives cell proliferation and malignant transformation	Mutation or deletion of both alleles results in loss of tumour suppressor function thereby allowing malignant transformation
Examples	**Examples**
Point mutations (missense) KRAS in pancreatic and colon cancers RET in multiple endocrine neoplasia (MEN-2) syndrome	Point mutations (missense, nonsense, frameshift) TP53 in Li-Fraumeni syndrome RB1 gene in retinoblastoma BRCA1 and 2 in HBOC syndrome APC genes in familial adenomatous polyposis Mismatch repair genes in HNPCC
Gene amplification/over-expression NMYC in neuroblastomas C-ERBB2/HER2neu in breast cancer	Large genomic rearrangements BRCA1 and 2 in HBOC Mismatch repair genes in HNPCC
Chromosomal translocation ABL (9q34) to BCR (22q11) in CML MYC (8q24) to IgH (14q32) in Burkitt's lymphoma FLI1 (11q24) to EWS (22q12) in Ewing's sarcoma	Deletion WT1 in Wilm's tumour SMAD4 in pancreatic and colon cancers
Aneuploidy Loss of chromosome 10 (PTEN) in glioblastomas	

KNUDSON'S TWO HIT HYPOTHESIS FOR TUMOUR SUPPRESSOR GENE (RETINOBLASTOMA PARADIGM)

Knudson proposed the "two hit hypothesis" to explain genesis of retinoblastoma, a childhood malignant tumour of the eye, and clinical features distinguishing hereditary from sporadic retinoblastoma. Hereditary form of retinoblastoma occurs at a younger age, generally in the first year of life and sometimes at birth; frequently arises in both eyes; and could be multifocal within each eye. In this form, first hit is the inherited germline mutation in one of the two alleles of RB genes present in all cells of the body and second-hit is the somatic mutation in second of RB gene in one of the retinal cells, resulting in development of retinoblastoma (**Figure 2**). This hypothesis explains why both alleles of a tumour suppressor gene are to be inactivated for development of cancer and why most forms of hereditary cancer occur at a younger age, are frequently bilateral, and multiple as compared to their sporadic counterparts. It is important to note that while the mutation is recessive at cellular level (requiring both alleles to be inactivated), the inheritance pattern for cancer risk is autosomal dominant. Progeny of germline mutation carriers have 50% probability of inheriting the germline mutation (one mutated allele in each cell of the body). Subsequently a very high proportion of these carriers acquire the second inactivating mutation in one of the target organ cells (somatic mutation) resulting in 70% to 100% penetrance for cancer development in mutation carriers.

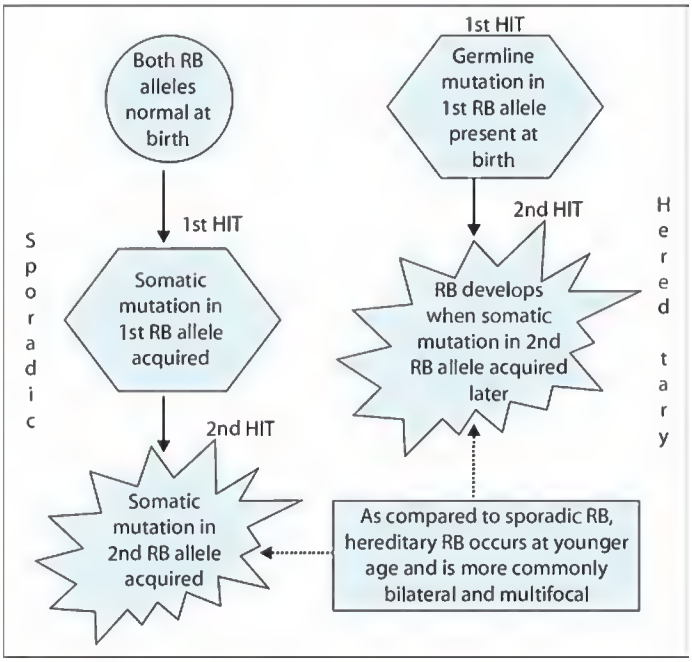


Figure 2: Kundson's two hit hypothesis in retinoblastoma.

EPIGENETIC REGULATION IN CANCER

Epigenetic alteration refers to the change in genome (or gene expression), which is inherited by the daughter cells without any alteration in the DNA sequence. Common epigenetic modifications include DNA methylation of CpG islands (cytosine precedes Guanine) in the promoter region of a gene, thereby controlling gene expression, and acetylation of histones that could silence TSGs. Global genomic hypomethylation in the CpG islands of TSGs and specific histone modifications are commonly seen in many human cancers. Being reversible, these epigenetic changes are attractive drug targets with various drugs like histone deacetylase inhibitors undergoing evaluation in clinical trials. Analysis of epigenetic silencing of the MGMT gene by promoter methylation is now in clinical use to predict response to temozolamide chemotherapy for glioblastoma.

HEREDITARY CANCER SYNDROMES AND GENETIC TESTING

It is estimated that 2% to 5% of all cancers are hereditary, occurring as a result of germline mutation in one of the several TSGs (BRCA1, BRCA2, TP53, NF1, etc), or proto-oncogene. Vast majority of hereditary cancer syndromes are autosomal dominant (**Table 2**) with few rare syndromes associated with DNA repair defects being autosomal recessive (**Table 3**).

Table 2: Autosomal Dominant Hereditary Cancer Syndromes and Their Phenotypic Features

Genetic Syndrome	Malignancy (Lifetime Risk of a Cancer)	Phenotypic/Tumour Features
Hereditary breast ovarian cancer (HBOC) syndrome Incidence: 1 in 1000 Genes: BRCA1 (17q); BRCA2 (13q)	Breast cancer (70% to 80%), Ovarian cancer (40% to 60%) Male breast cancer, prostate, pancreas, colon, etc. (especially in BRCA2 carriers)	Cancer presents at young age, frequently bilateral and same person may develop breast and ovarian primaries BRCA1 associated breast tumours are generally ER, PR and C-ERBB2 negative (Triple –ve) and poorly differentiated
Hereditary non-polyposis colon cancer (HNPCC) syndrome Incidence: 1 in 400 Genes: One of the mismatch repair genes MSH2 (2p)	All cancers (70% to 90%) Colorectal cancer (30% to 75%) Endometrial cancer (20% to 40%) Other cancers: Gastric, brain, small bowel, pelvi-ureteric, hepatobilliary	Colon polyps in 30% cases but unlike FAP polyps in HNPCC rarely exceed few dozen Compared to sporadic cases, HNPCC associated colon cancer is generally right-sided (ascending or transverse colon) and at younger age **Amsterdam -II Criteria for HNPCC**
MLH1 (3p) MSH6 (2p) PMS2 (7p) PMS1 (2q)	**Lynch-I syndrome:** HNPCC with only colorectal cancers in the family **Lynch-II syndrome:** Extracolonic cancers of HNPCC in the family **Turcot's syndrome:** Person with colon cancer and brain tumour	– At least 3 first degree relatives with colon, endometrial, small bowel or pelvi-ureteric carcinoma – At least 2 generations affected – At least one affected person <50 years age – FAP should be excluded
Familial adenomatous polyposis (FAP) Incidence: 1 in 1,000 Gene: APC (5q)	Colorectal carcinoma (100%) Upper gastrointestinal (duodenum) cancer Periampullary cancer Papillary thyroid cancer Brain tumours Hepatoblastoma Desmoid tumour	Hundreds to thousands of polyps by 2nd decade leading to cancer by 4th decade **Attenuated FAP:** Fewer polyps (10-100) **Gardners syndrome:** FAP variant with extracolonic lesions like desmoid tumours, osteoma, epidermoid cysts, dental abnormalities, fibroma, and congenital hypertrophy of retinal pigment epithelium
Peutz-Jeghers syndrome Incidence: 1 in 250,000 Gene: STK11 (19p)	All cancers (50%) Common cancers are colorectal, pancreatic, breast, ovarian, testicular, endometrial and melanomas	May present with intussuseption in childhood due to hamartomatous jejunal/gastrointestinal polyps Mucocutaneous melanocytic macules in lips and buccal mucosa (95%) Multiple and sometimes atypical naevi
Hereditary retinoblastoma Incidence: 1 in 25,000 Gene: RB1 (13q)	Bilateral retinoblastoma (90%) Rarely trilateral retinoblastoma Osteosarcoma in adolescence	Childhood tumour which presents at an average age of 1 year for bilateral and 1.5 years for unilateral cases and 90% cases by 3 years age
Li-Fraumeni syndrome (LFS) Incidence: 1 in 50,000 Gene: TP53 (17p)	All cancers (90%) Breast cancer, soft tissue sarcoma or bone sarcoma, brain tumours, leukaemia, adrenocortical tumours	**LFS:** Sarcoma before 45 years of age in proband with one 1st degree relative with cancer before 45 years of age and one 1st or 2nd degree relative with cancer before 45 years of age or sarcoma at any age.
Multiple endocrine neoplasia 2A and 2B (MEN2A and MEN2B) Incidence:1 in 30,000 Gene: RET (10q)	Medullary carcinoma thyroid (MTC) develops in (70% to 100%) parathyroid adenoma RET mutation carriers and penetrance depends on location of mutation Bilateral phaeochromocytoma (50%)	**MEN2A:** MTC, phaeochromocytoma and **MEN2B:** MTC, phaeochromocytoma, mucosal neuromas over tongue and lips (Blubbery lips), corneal nerve thickening, skeletal anomalies, gastrointestinal (GI) gangloneuromatosis but parathyroid is normal
Neurofibromatosis Type 1 (NF1) Incidence: 1 in 2500 Gene: NF1 (17q)	Cutaneous neurofibroma (100%) Plexiform neurofibroma (20%) Childhood optic glioma (15% to 20%) Malignant peripheral nerve sheath Tumour – MPNST (5% to 15%)	Cutaneous stigmata (widespread neurofibromas, *Café-au-lait* spots, axillary freckling) and Lisch nodules (hamartomas) in iris are diagnostic. Learning disabilities in 50% Hypertension is common Scoliosis and pseudoarthrosis in 10%
Neurofibromatosis Type 2 (NF2) Incidence: 1 in 25,000 Gene: NF2 (22q)	Bilateral acoustic neuroma (85%) Spinal schwannoma (65%) Skin schwannoma (65%) Meningiomas (45% to 50%) Other gliomas	Cutaneous stigmata of NF1 generally absent but few (< 6) Café-Au-lait spots in some Acoustic neuromas present with unilateral or bilateral deafness Posterior subcapsular cataract and retinal hamartomas in 1/3rd cases
Cowden syndrome Incidence: 1 in 200,000 Gene: PTEN (10q)	Early onset breast cancer (30% to 50%) Bowel cancer (20%) Follicular thyroid cancer (3% to 10%)	Mucocutaneous stigmata by 3rd decade *Diagnostic criteria:* Cobblestone-like papules of the gingiva and buccal mucosa. Facial trichilemmomas, acral keratosis Other features in 40% cases (GI polyps and macrocephaly)

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von Hippel-lindau syndrome (VHL) Incidence: 1 in 36,000 Gene: VHL (3p)	All tumours (80% to 90% penetrance) Cerebellar and spinal haemangioblastoma (35% to 85%) Renal cell cancer (25% to 48%), phaeochromocytoma (15%)	Retinal angioma are the earliest lesions detected at a mean age of 25 years in 40% to 70% cases. Renal, liver and pancreatic cysts are common
Tuberous sclerosis (TS) (Type 1 and 2) Incidence: 1 in 10,000 Gene: TSC1 (9q) TSC2 (16p)	Sub-ependymal giant cell astrocytomas (SEGA) is a characteristic benign tumour of TS, Ependymoma Renal cell carcinoma	Characteristic facial angiofibroma (adenoma sebaceum), hypopigmented ash leaf spots and leathery Shagreen patches over neck or back Renal angiomyolipoma is very common which may bleed or cause renal failure by compression Cardiac rhabdomyoma are common Characteristic CNS hamartomas (sub-ependymal nodules and cortical tubers) which causes epilepsy, autism and common learning difficulties

Table 3: Autosomal Recessive Hereditary Cancer Syndromes and Their Phenotypic Features

Genetic Syndrome	Malignancy (Percentage Lifetime Risk)	Other Phenotypic Features
Bloom syndrome Incidence: Very rare Gene: BLM (15q26)	All cancer (penetrance 80%) Prone for all cancers (except prostate cancer) at unusually young age (mean 25 years) Multiple primary cancers are common Particularly prone for AML	Low birth weight, physical and mental growth retardation. Characteristic facial appearance (narrow skull, malar hypoplasia, small mandible); characteristic voice, photosensitive skin, telangiectasia and hypo/hyperpigmented patches Immunodeficiency and infertility are common
Ataxia telangiectasia Incidence: 1 in 100,000 Gene: ATM (11q22)	Breast cancer Lymphoma (B-CLL) Leukaemia (T-CLL)	Cerebellar ataxia, telangiectases, immune defects, gonadal dysfunction, thymic hypoplasia Increased sensitivity to X-rays Serum AFP is elevated in 95%
Xeroderma pigmentosum Incidence: 1 in 250,000 Gene: XPA-G and V (9q,2q,3p,19q,11p, 6p, 13q and 6p)	Skin cancer (basal cell carcinoma commonest followed by squamous carcinoma and melanoma) in tropical countries most patients develop skin cancer by adulthood	All forms of XP have extreme UV sensitivity which results in actinic keratosis, freckling and finally skin and conjunctival/corneal cancers Neurologic abnormalities and mental retardation are commonly seen in XP-B, XP-D, XP-A
Fanconi anaemia Incidence:1 in 350,000 14 Genes in 16p FANC 'A' to FANC 'G' FANC 'I'-'J' and FANC 'L' to FANC 'O'	Almost all patients develop bone marrow failure or haematological malignancy (commonly AML) if they live long enough If cured of the haematological condition, most patients will develop solid tumours	Commonly present with progressive bone marrow failure starting from childhood Pigmentary changes in skin, malformations of the heart, kidney and limbs (aplasia of the radius, thumb deformity) Endocrinopathy and growth retardation
Recessive hereditary colon cancer Gene: Mut YH (1p34)	Colon cancer	Adenomatous colon polyps seen in most cases which could vary from as few as 5 polyps to frank polyposis Extracolonic features of FAP/ Gardener's syndrome not seen and extra-colonic cancers not seen

While many hereditary cancer syndromes such as hereditary breast ovarian cancer (HBOC) syndrome or Li-Fraumeni syndrome do not have any specific phenotypic feature before the occurrence of cancer, some cancer predisposition syndromes have characteristic phenotypic features that predate cancer diagnosis by many years or decades. These phenotypic features include cutaneous signs in NF1, XP, tuberous sclerosis, Peutz-Jegher's syndrome or characteristic benign hamartomatous lesions or cysts in internal organs or eye as seen in FAP, NF1, tuberous sclerosis, VHL, etc. In syndromes without characteristic external or internal phenotypic features, the diagnosis of a hereditary cancer syndrome is based on detailed family history of types of cancers, age at cancer diagnosis, or bilateral, multifocal or multiple primary cancers in an individual. Based on detailed family history and clinical examination of the proband if a cancer predisposition syndrome is evident or suspected, further radiological or laboratory investigations are performed to look for other associated phenotypic features or cancers. Mutation analysis of the gene(s) likely to be implicated in the suspected syndrome helps in confirmation of the syndromic diagnosis, risk estimation and genetic counselling of the family.

The gold standard for mutation analysis is automated DNA sequencing but it is expensive, may detect sequence changes of unknown clinical significance and may fail to detect large genomic rearrangements. In addition to these technical and interpretive issues, genetic testing has several other ethical, legal and social implications (ELSI) and is, therefore, advisable only when inherited cancer predisposition is suspected and genetic testing is likely to modify or aid clinical management for patients or high risk cases in that family. Genetic testing is generally done first for the cancer affected member of the family on a gene which is most likely to be involved (e.g. BRCA1 and BRCA2 for HBOC). With the small likelihood of a false negative or false positive result due to technical errors, the four possible results

of mutation analysis are: (1) Known deleterious mutation identified; (2) Known polymorphism identified; (3) Sequence variation of unknown clinical significance identified; and (4) No mutation or sequence variation identified. A counsellor has to be well versed with the interpretation of all the alternatives to provide effective counselling.

CANCER SCREENING AND PREVENTION IN HIGH RISK INDIVIDUALS/MUTATION CARRIERS

Healthy members of families with specific hereditary cancer syndromes would be considered to be at a high-risk for developing cancer based on their relationship with the affected members and in families where a specific mutation is known all those who are found to be mutation carriers are considered at high-risk. There are well established guidelines for screening of such high-risk individuals from families with common hereditary cancer syndromes with organ specificity (HBOC, HNPCC, FAP, MEN-2). High-risk women from HBOC families are recommended to have monthly breast self examination, six-monthly clinical breast examinations by a trained oncologist, surgeon or a gynaecologist. Annual breast imaging is recommended using mammography and/or breast MRI in young women with dense breasts. Breast screening should start between 25 to 30 years of age or five years before the age of earliest cancer in the family. The sensitivity of ovarian cancer screening in detecting early stage ovarian cancer in such high-risk women is not well established but annual transvaginal ultrasound and CA-125 tumour marker starting at 35 years of age may be considered.

Preventive strategies in high-risk women from HBOC families vary from non-invasive chemoprevention with antiestrogens to prophylactic bilateral mastectomy with breast reconstruction or prophylactic oopherectomy. Prophylactic oopherectomy reduces the risk of ovarian cancer by almost 100% (rare occurrence of primary peritoneal carcinoma still exists) and reduce the risk of breast cancer by 50%. While bilateral prophylactic nipple sparing mastectomy with reconstruction can reduce breast cancer risk by almost 100%, the psychosexual issues of such surgery in healthy young women have to be discussed in detail during counselling.

MOLECULAR SIGNATURES OF CANCER FOR DIAGNOSIS, PROGNOSIS AND GUIDING TARGETED THERAPY

Classification of various tumours has evolved from conventional morphology based histopathology to immuno-histochemistry and finally to molecular pathology in which tumour specific gene mutations, over-expression, chromosomal rearrangements and global gene expression profile is characterised and used in clinical management of certain cancers. Molecular sub-classification of tumours helps in refining diagnosis, prognostification and predicting response to specific targeted therapies based on the molecular pathology. The common examples include accurate diagnosis of Ewing's sarcoma (EWS-FLI1 translocation) and lymphomas (CD markers); prognostication of neuroblastoma (N-MYC amplification) and breast cancer (gene expression profile) and guiding targeted therapy for breast cancer with HER2/Neu over-expression (Herceptin) and CD-20 positive lymphoma (rituximab). The classical t(9;22) (q34.1;q11.2) translocation of CML which results in BCR-ABL fusion gene which drives oncogenesis is targeted through tyrosine kinase inhibitors (imatinib) as shown in **Figure 3**. Imatinib is now the standard of care in patients of CML who test positive for this translocation.

MOLECULAR DIAGNOSTIC TECHNIQUES IN CANCER

A greater variety of high throughput tests are becoming available which also have greater sensitivity and specificity to study chromosomal alterations, gene over-expression, gene mutation and global gene expression profile. These technologies which were instrumental in making major discoveries of molecular and genetic basis of cancer are now being routinely used in molecular diagnosis of cancer. Some of the key diagnostic methods are outlined below.

Fluorescent *In Situ* Hybridisation (FISH)

Characterises chromosomal aberration using DNA probes, specific for a gene, chromosome segment or whole chromosome. FISH has the advantage of directly obtaining the position of the probes in relation to chromosome bands or to other previously mapped reference probes and visualise cytogenetic aberration on interphase nuclei without the need for having metaphase preparation. FISH is particularly useful for translocations in paediatric tumours and haematolymphoid malignancies and more quantitative study of over-expression of Her2Neu in breast cancer.

Microsatellite Instability Test

Microsatellites are small repetitive DNA sequences that undergo expansion or contraction of the repeat sequences during DNA replication. The mismatch repair (MMR) genes survey the newly replicated DNA for possible errors and repair the mismatched bases. Defect in MMR genes as seen in HNPCC would result in microsatellite instability (MSI) which is characterised by change of length of the microsatellite (insertion or deletion of repeats) within the colonic tumour as compared to the DNA from normal tissue. For HNPCC, a panel of five microsatellite markers recommended by National Cancer Institute (Bethesda Panel) is used for detection of MSI. If two or more microsatellite markers are unstable, it suggests HNPCC which can be confirmed through germline mutation analysis using automated DNA sequencing of hMLH1, hMSH2 and hMSH6 genes.

Gene Expression Profiling

In addition to a large number of genetic pathways involved in the multi-step carcinogenesis, there is underlying genetic instability and epigenetic modifications of gene expression. Newer techniques such as RNA microarrays are now used to study the differential expression profile of thousands of genes in the neoplastic cells as compared to the normal cells of the same tissue origin. Such studies have led to molecular classification of breast cancers, lymphomas and few other tumours and allowed better understanding of the pathways relevant to development of particular cancer type and in identifying molecular targets for cancer diagnosis and therapy.

Automated DNA Sequencing

DNA sequencing using automated capillary sequencer is the gold standard for gene mutation analysis. In the commonly used Sangers method which is frequently done by dideoxy- chain

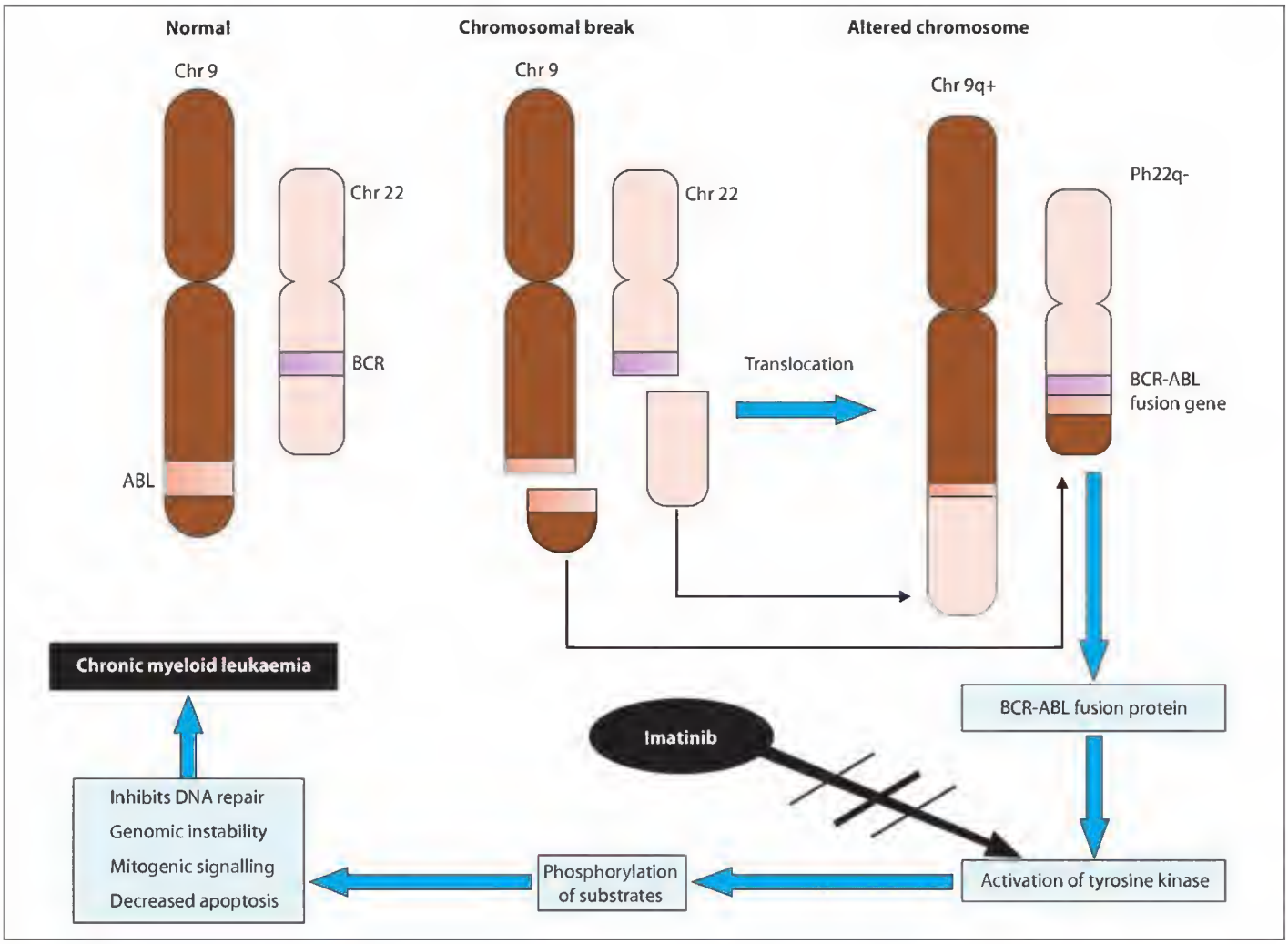


Figure 3: Chromosomal translocation: BCR-ABL fusion gene in CML has increased tyrosine kinase activity is down-regulated by imatinib.

termination, the DNA template which is to be sequenced is prepared as a PCR amplicon product. Sequencing is achieved by utilising fluorescent labelled nucleotides incorporated into the DNA copy. The DNA sequence can then be derived by the positions of the fluorescent labelled nucleotides. Laser stimulated fluorescent emissions are read directly by an optical detector as the DNA fragment passes past it. The sequencing data are stored, analysed and converted to complete DNA sequence by special software and compared with normal reference DNA sequence. A major advantage of the automated sequencing is the speed of detection and the information it gives about the nature of the change found. Capillary sequencers are also used for estimating the fragment length polymorphisms for microsatellite analysis, haplotype analysis and DNA fingerprinting. The possible results of DNA sequencing of a gene and certain caveats are described earlier in the Genetic testing section.

CONCLUSION

Cancer genetics has undergone a revolutionary change in the past two decades. This knowledge of molecular mechanisms underlying cancer initiation, promotion and progression has brought about a major change in the way we diagnose and manage certain cancers. Presently, a greater emphasis is being laid on developing specific diagnostic tests and novel therapies targeting the molecular signatures resulting in a shift in the way we practice medicine, from generalised therapy to a more tailor-made individualised therapy. For hereditary cancers, genetic testing has helped in precise risk estimation, counselling, with appropriate surveillance and cancer prevention strategies.

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Section 7

Critical Care Medicine

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7.1 Basic Considerations in Critical Care

RK Mani

CRITICAL VERSUS NON-CRITICAL CARE

Critical care is not merely an extension of patient care to an acute setting. The urgency of acute illness in critical care has led to a departure from traditional approaches. The usual linear method of history, physical examination, investigations, diagnosis and treatment has given way to an iterative approach in critical care (**Figure 1**). Owing to the emergent nature of presentations the correction of life-threatening physiological derangements receives first priority that translates as the CAB (circulation, airway and breathing) after eliciting brief historical information and conducting rapid physical examination. This is followed by close monitoring to stabilise the patient (electrocardiogram, mean arterial pressure, oxymetry, central venous pressure, urine output, sensorium, intracranial pressure, etc.) that is the hallmark of critical care. The next step involves detailed history-taking and physical examination towards formulation of a working diagnosis and management strategy.

Inherent to critical care is the early recognition of organ system dysfunction and prompt institution of appropriate support. At any point in such evaluation, one may need to return to the initial steps to ensure that physiological targets are being achieved.

TIMELINESS OF INTERVENTIONS

The concept of the 'golden hour' that mandates timely and appropriately aggressive intervention is of essence in critical care. Therapeutic efficacy that translates to favourable outcome has been proven to be a function of how early the therapy was instituted from the time of presentation. Notable examples of this principle are the early goal-directed therapy for septic shock, timing of the 1st dose of antibiotic and antifungal therapy, thrombolysis and revascularisation procedures for acute myocardial infarction, surgical source control, thrombolytic therapy for acute ischaemic stroke and adjuvant therapies such as activated protein C for severe sepsis and septic shock, to

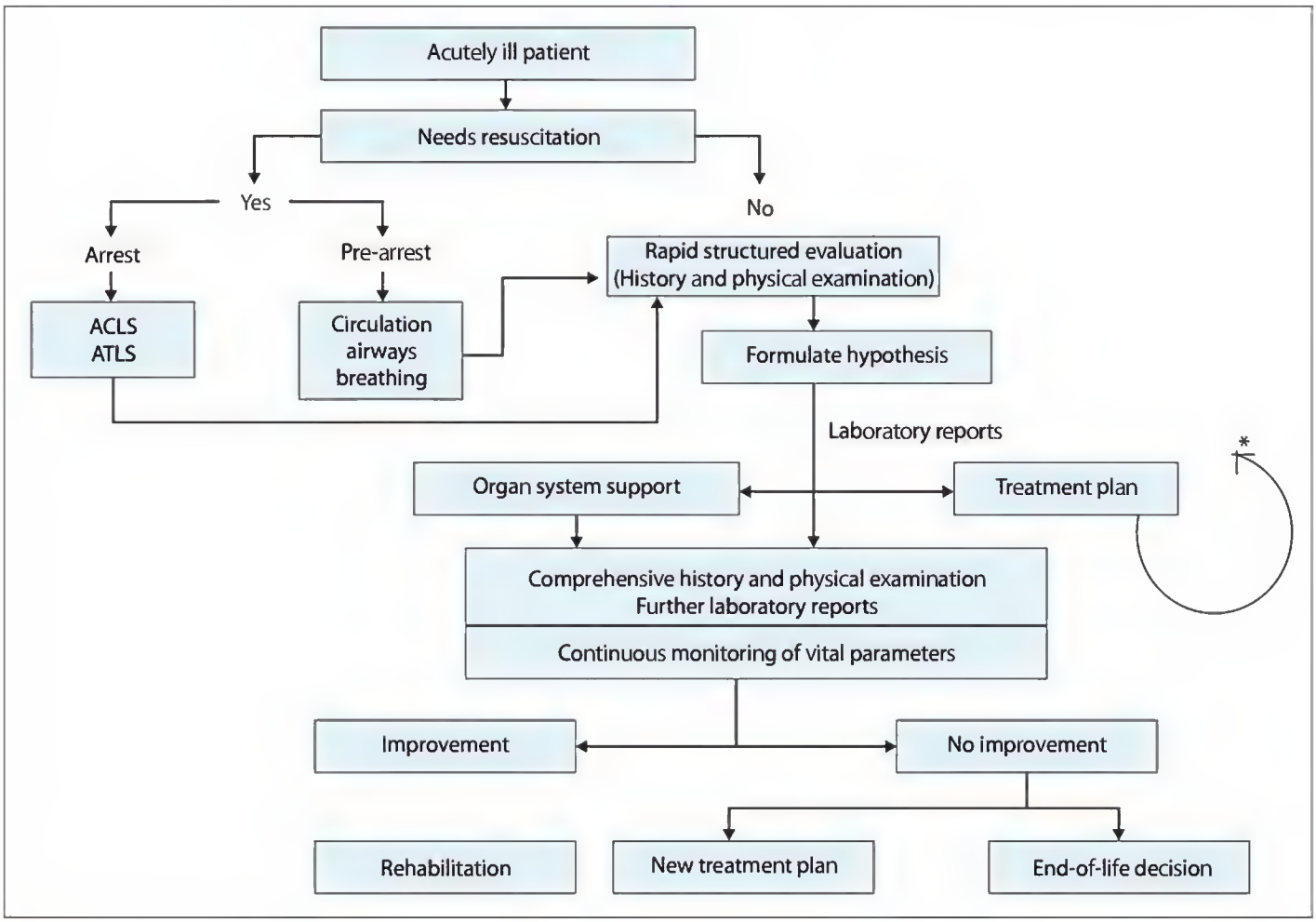


Figure 1: General approach to the management of the critically ill patient.

**The curved arrow represents the iterative approach in the management of the critically ill patient.*

ACLS = Advanced cardiac life support; ATLS = Advanced trauma life support.

name a few. Thus, it is also crucial to institute early support to organ systems in the form of oxygen supplementation, non-invasive (NIV) and invasive mechanical ventilatory support, circulatory support through fluids and vasopressors, haemodialysis and renal replacement therapy, and nutritional support. A sense of urgency is vital to minimise the eventual mortality and morbidity as well as the cost of treatment.

MINIMISING RISKS OF ORGAN SUPPORT

Mechanical ventilation (MV) is one of the primary interventions that saves lives. However, safe ventilatory strategies that minimise mechanical complications (barotrauma) as well as microstructural trauma called ventilator-associated lung injury (VALI) is an essential tenet of critical care. Non-invasive ventilation has obviated the need for more potentially injurious MV in a sizeable number of patients especially in the setting of exacerbation of chronic obstructive pulmonary disease (COPD). The concept of 'protective ventilation' is a widely accepted concept that finds practical application in the form of low tidal volume and positive end expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS), permissive hypercarbia for ARDS, bronchial asthma and COPD, and recruitment manoeuvres, such as prone positioning. The need to protect the lungs has also led to the search for supports such as extra-corporeal membrane oxygenation (ECMO) and other extra-corporeal lung-assist devices.

The risks of aggressive fluid resuscitation are minimised by improved monitoring of haemodynamic variables and the emerging awareness of the need to monitor intra-abdominal pressure.

The adverse effects of sedation and neuromuscular blocking agents have been reduced by setting specific therapeutic targets and by the practice of daily sedation interruption.

INFECTION CONTROL

The critical care unit is well recognised as the epicentre for the development of multiple drug-resistant flora. One of the key responsibilities of the intensivist is to adopt practices that minimise the incidence of nosocomial infections, prevent horizontal transmission and limit the emergence of resistant pathogens. This includes attention to hand hygiene and handling of intravenous (IV) cannulae and airways, aseptic measures for bedside procedures and imaging, head-up positioning and general housekeeping. Refining antibiotic prescribing practices are vitally important for optimising therapy, reducing the incidence of bacterial resistance and minimising costs. Protocols and policies are essential to regulate these processes.

PREVENTION OF COMPLICATIONS AND GENERAL CARE

Careful attention to detail includes pharmacological and/or mechanical measures to prevent deep venous thrombosis, eye care to protect against exposure keratitis, mouth care to reduce bacterial colonisation, skin care to prevent pressure sores and bowel care to prevent constipation.

ETHICS, END-OF-LIFE CARE AND PALLIATION

The increasing efficacy of modern critical care has raised its expectations often to unrealistic levels. The aging population, the increasing complexity of surgical interventions, the frequent use of immunosuppressive medications and implanted devices and organ transplantation all have added to the challenges of critical care. However, when critical care fails, it greatly escalates the emotional, social and financial burdens of the family. Most interventions also carry significant risks and costs requiring an informed consent from the patient or his/her family. Therefore ethical considerations weigh heavily on clinical decision-making. The physician must integrate the ethical principles of respect to patient's autonomy, beneficence, non-malefiscence and social justice in his practice.

As a corollary to ethical decision-making, it behoves the physician to disclose early and honestly poor prognosis, and offer palliative end-of-life care options to the family. Since death is a common occurrence in the intensive care unit (ICU), appropriate care of the dying is an important tenet of critical care. Ethical, social, humanitarian and legal factors impact on issues relating to voluntary foregoing of life-supporting therapies. A pathway to end-of-life care decisions has been suggested by the Indian Society of Critical Care Medicine (ISCCM) (**Figure 2**). Palliative care aimed at ensuring patient comfort starts from the time of initial care and gradually assumes centre stage as therapeutic strategies shift from the 'cure' to the 'care' mode when attempts at cure are deemed to have failed.

FAMILY NEEDS

As opposed to non-critical conditions where care is said to be patient-centric, critical care is patient- and family-centric. This is because more than 95% of critically ill patients lose the capacity to decide for themselves. It is of utmost importance that the intensivist communicates daily with the family for prognostication, emotional support, decision-making and informed consent, cost estimations and where appropriate, end-of-life decision-making. This is best done by the senior staff of the unit along with primary physicians and senior nurses.

CRITICAL CARE ORGANISATION

The ICU constitutes a team of doctors, nurses, technicians, therapists and other support staff. Most of the staff needs to work in shifts to provide uninterrupted round-the-clock cover. Adequacy of staffing is vital to ensure efficiency, infection control, patient and family satisfaction and avoidance of caregiver fatigue and attrition. Ongoing education, training and clinical research activities are integral to constant upgradation and search for excellence.

'OPEN' VERSUS 'CLOSED' INTENSIVE CARE UNITS

In the 'open model' of critical care units consultant physicians direct the care of their individual patients with the assistance of house staff that provides round-the-clock on-the-spot patient care. An intensivist, if available, is not involved directly in the care of most of the patients. Because the primary physician often does not have the time or the skills required to provide comprehensive care to the patient, he often apportions management to several single organ specialists.

A 'closed' system implies that patient care is either directed or co-managed by an intensivist. In this model, the intensivist assumes full responsibility for treatment planning and integrates the inputs from several sub specialists. He provides

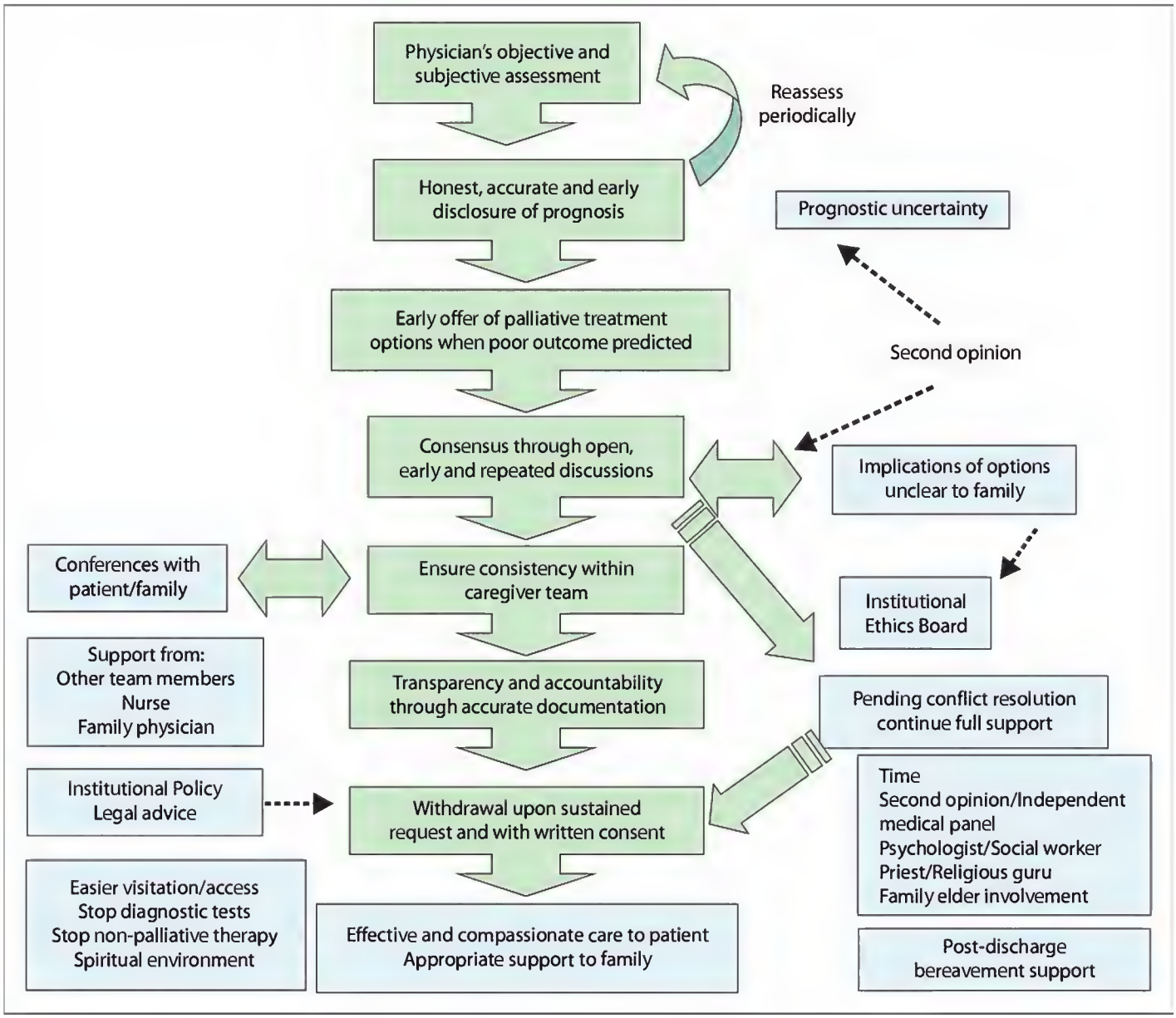


Figure 2: Pathway to end-of-life decision.

leadership in the management of individual patients, organises 'on call' cover, puts in place infection and quality control practices, staff training and clinical research. In an open structure, an 'open-door' policy may exist for admission and discharges.

Several retrospective and prospective studies showed improved outcomes in terms of mortality, morbidity and cost especially in seriously sick patients, when ICUs adopted the closed model. This model also facilitates early end-of-life decisions and appropriate reduction of futile care that minimise the escalation of costly interventions in terminally ill patients. The limitation of this model is the scarcity of trained and experienced intensivists. Currently 'open' and 'semi closed' models pre-dominate in India and true 'closed' units are a miniscule minority.

ORGAN RETRIEVAL

With expanding scope and expertise of organ transplantation the critical care specialist has a new role to play. In the foreseeable future he will be called upon to identify the potential organ donor early and notify the nearest organ procurement organisation.

QUALITY AND SAFETY

Patient safety requires that systems are in place to evaluate the quality and safety issues of the ICU. This includes data collection and monitoring to audit parameters such as mortality, length of stay, ventilator-associated pneumonia and blood stream infection rates, critical incidents and sentinel events, medication errors, etc. With training and experience, the complications of ICU procedures can be minimised. A culture that promotes safety, a team spirit that believes in constructive self-criticisms, setting protocols and standard operating procedures are essential for reducing errors and adverse events.

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7.2 Monitoring of Critically Ill Patients

M Hanumantha Rao

Monitoring is one of the primary duties of an intensivist or critical care specialist. Effective vigilance is helpful in assessing the severity of organ dysfunction and suitably assist the organs by different methods. In order to ensure optimal care of these patients, it is vital to understand the technology of advanced and sophisticated monitoring equipment including the cost-benefit issues. Vigilance and anticipation of complications are the important issues in the intensive care unit (ICU). All critically ill patients need different types of monitoring, because they are likely to develop dysfunction of different organ systems during their stay in critical care unit. By proper monitoring one can assess the severity of dysfunction of each of these organs and then choose suitable therapeutic interventions and artificial support for the failing organs like heart, kidney and lung. Many physiological measurements are necessary to convey the patient's condition. To assess all the aspects of patient's condition many physiologic measurements or group of measurements are required. This chapter briefly reviews the indications, contraindications, techniques and complications of frequently used monitors in critical care units.

Many monitoring techniques are available in clinical practice (**Table 1**) and specific monitoring is required for different systemic diseases. However, many patients need monitoring of all systems. Some variables are monitored continuously and some intermittently. The variables that are monitored continuously include heart rate, arterial blood pressure, pulse oximetry (**Figure 1**). Arterial blood gases and some laboratory tests are monitored intermittently.

VITAL SIGNS

Simple, basic, economical and the most frequently used non-invasive method of monitoring the patient includes heart rate, blood pressure, respiratory rate, and temperature.

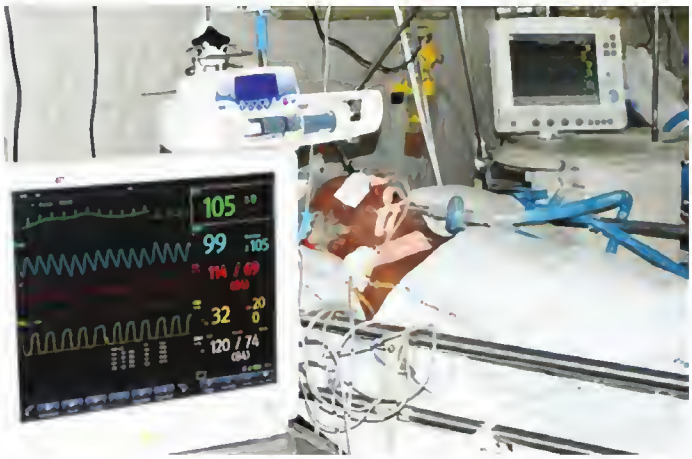


Figure 1: A 4-channel monitor connected to a critically ill patient showing ECG (green), SaO_2 (blue), IBP (red), $ETCO_2$ (yellow) and NIBP (white).

ECG = Electrocardiography; SaO_2 = Oxygen saturation; IBP = Invasive blood pressure; $ETCO_2$ = end-tidal CO_2; NIBP = Non-invasive blood pressure.

Table 1: Physiologic Variables that are Frequently Monitored in Critically ill Patients

Electrocardiogram
Heart rate
Systemic arterial blood pressure
Temperature
Haemoglobin
Haematocrit
Pulmonary capillary wedge pressure
Urine output
Arterial blood gas analysis
Blood volume
Plasma volume
Central venous pressure
Intracranial pressure
Cardiac output
Oxygen saturation
End-tidal carbon dioxide
Coagulation profile
Central venous oxygen saturation
Airway pressures
Scalars and loops
Blood urea nitrogen
Serum creatinine
Liver function tests
Serum electrolytes
Blood glucose
Intake and output chart

CARDIOVASCULAR MONITORING

Heart rate per minute is routinely monitored in all critically ill patients. It is clinically counted by manual palpation of the radial artery just above the wrist joint for one full minute. It can be automatically calculated by either electrocardiogram (ECG) wave or arterial pulse wave. It is a non-specific, haemodynamic variable. A slow heart rate less than 50 beats per minute is defined as bradycardia and heart rate more than 100 beats per minute is defined as tachycardia.

Electrocardiogram

It has become a routine to monitor ECG in all the critically ill patients. Most of the patients have cardiac activity monitored by a 3-lead system or a 5-lead system. Monitoring heart rate and rhythm is a standard practice. It detects dysrhythmias, myocardial ischaemia and function of pace-maker. To receive the maximum signal of ECG, electrodes need to be placed properly after de-greasing and cleaning the area with spirit. Lead II is routinely used to monitor the rhythm and lead V5 for ischaemia. ST segment analysis is crucial in suspecting ischaemia. It is a routine practice to monitor two leads simultaneously to assess both rhythm and ischaemia. Alternatively, one can use modified chest leads CM_5 or CS_5 which detect both ischaemia and dysrhythmia. The factors that may interfere with the signal is skin movement, muscle artifact,

respiration and shivering. The leads used for ECG monitoring are disposable and for single use only. Signals are usually sent to central monitoring station by a small radio transmitter.

Haemodynamic Monitoring

Arterial blood pressure

Systemic arterial blood pressure is proportional to cardiac output, when peripheral vascular resistance is constant. It is maintained by physiological compensation when there are changes in cardiac output and blood volume. It is affected by cardiac output, vasomotor tone and volume status of a patient.

Blood pressure may be normal despite grossly impaired cardiac function and so is a crude indicator of the state of the circulation. But if blood pressure is inadequate, tissue perfusion suffers. In critically ill patients auto-regulatory mechanisms in vascular beds of vital organs, like brain, kidney and liver become impaired and perfusion to these organs will be pressure dependent. Blood flow to tissues and perfusion is dependent on mean blood pressure. Mean pressure is not an arithmetic average of systolic and diastolic pressures. It is one-third the sum of systolic plus twice the diastolic pressure.

Non-invasive blood pressure

Systemic blood pressure can be monitored non-invasively (NIBP) or invasively (IBP). The use of conventional sphygmomanometer can be simple and reliable. Other indirect methods of measuring blood pressure include palpation, auscultation and oscillotonometry. The NIBP monitors have a pneumatic cuff which is programmed to inflate and deflate periodically depending on the programme. During this the phasic oscillations in the pneumatic cuff pressure produced by arterial pulsation are sensed and detects the systolic and diastolic pressures. The mean pressure is calculated by the pre-programmed computer device. This is a simple, basic and reliable monitor when the pressure is normal or high. But in hypotensive patients these are often inaccurate.

Invasive blood pressure

The most accurate and beat to beat variation of blood pressure is recorded by introducing a catheter into an artery and measuring the invasive blood pressure (IBP). This is an invasive procedure and should be used only for selected patients where it is indicated. Most frequently, radial artery of the non-dominant hand is used. Alternatively, femoral, dorsalis pedis, ulnar arteries can be used. The catheter introduced into artery is connected to a pressure monitoring line filled with heparinised saline which is connected to an electronic pressure transducer. The transducer needs to be zeroed to atmospheric pressure now and then. The fluid in the pressure monitoring line transmits pressure from the artery to pressure sensitive diaphragm of the transducer, which is connected to a monitor. The arterial pressure wave-form is displayed on the monitor and the digital values of systolic, diastolic and mean pressures. The readings are reliable and highly accurate if the transducer is zeroed and calibrated correctly. There is risk of infection and many complications are reported because of its invasive nature.

Dysrhythmia

Different types of dysrhythmias are not uncommon in critically ill patients. Therefore, it is important to monitor and record the initiation and termination of dysrhythmia in the ECG monitoring. Rhythm should be documented on admission and the change of each shift of the intensive care unit (ICU). Rhythm is better monitored in lead II or MCL_1 which is a modified chest lead.

Pulmonary Capillary Wedge Pressure

Pulmonary capillary wedge pressure (PCWP) is frequently used to assess the pre-load of the left ventricle and cardiac output by thermodilution technique. The pulmonary artery catheter, named after Swan and Ganz , is a balloon tipped, flow directed triple-lumen catheter introduced through right internal jugular vein or subclavian vein and then the balloon is inflated and passed till wedging occurs in the pulmonary capillary. After proper wedging one can record PCWP tracing and digital values of pressures.

Cardiac Output

Fick's principle is usually used to monitor cardiac output (CO) using thermodilution technique. The Swan-Ganz catheter has a temperature measuring device (thermistor). Bolus of cold saline is injected into right atrium through the proximal lumen. As the bolus reaches the thermistor, the change in temperature is used to calculate the cardiac output. The injection of cold saline can be done intermittently to calculate the cardiac output. The latest methods of monitoring the cardiac output are lithium dilution technique (LIDCO), pulse contour counter pulsation (PICCO) and ECG.

Oxygen Delivery

Tissue perfusion and delivery of oxygen is important for the survival of organs. It is deranged in different types of shocks. The delivery addresses three main issues in the supply of oxygen to the tissues, namely (i) cardiac output (CO), (ii) haemoglobin (Hb), and (iii) oxygen saturation (SaO_2). It can be calculated by using the formula.

Delivery of oxygen = Hb (g/dL) × SaO_2% × CO (L/min)
(ml/minute) × 1.34 x 10/100

Mixed Venous Oxygen Saturation

The blood from superior vena cava and inferior vena cava mixes in the right atrium and passes to pulmonary artery through the right ventricle. This sample is called mixed venous blood and it can be obtained from the distal port of pulmonary artery catheter (PAC) and some catheters have fibreoptic sensors embedded in them which directly measure SVO_2. When there is inadequate delivery of oxygen to tissues, they compensate by extracting more oxygen from arterial blood leading onto decrease in SVO_2.

RESPIRATORY SYSTEM

The monitoring of the respiratory system is very important and crucial in the management of patients who are critically ill. It is less advanced technologically compared to cardiovascular monitoring. Respiratory rate, tidal volume and minute volume can be assessed by bed-side portable hand-held spirometers. All the parameters are displayed on the monitoring screen of any latest ICU ventilator, if the patient is intubated and ventilated (**Figure 2**). Tachycardia, excessive sweating, use of accessory muscles of respiration can be monitored clinically to indicate impending respiratory failure.

Oxygen Saturation

A simple and non-invasive way of monitoring SaO_2 is by pulse oximeter (**Figure 3**). Oxyhaemoglobin and reduced haemoglobin

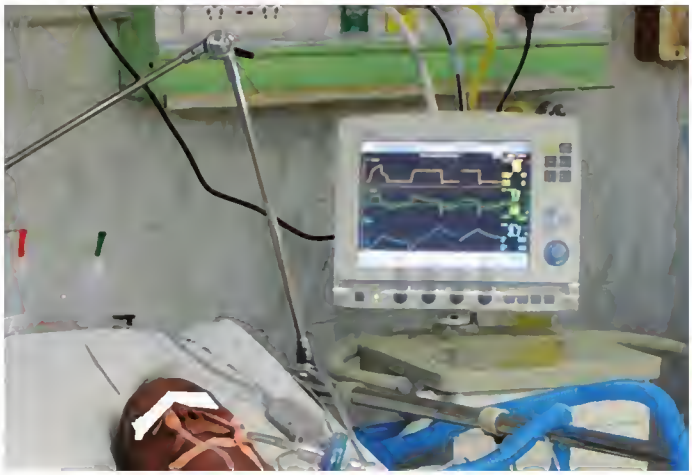


Figure 2: An intensive care unit ventilator showing the trace of airway pressure scaler (yellow), flow scaler (green) and volume scaler (blue).

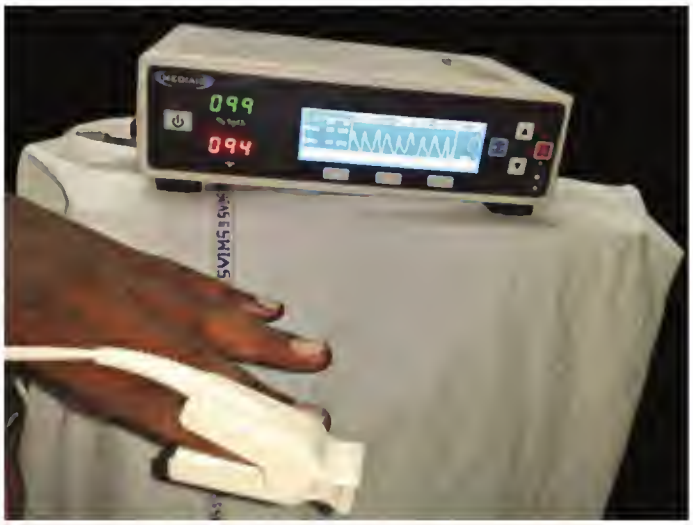


Figure 3: A pulse oximeter showing saturation wave and digital values of SaO_2 (green) and heart rate (red).

absorb light in the visible and near infrared regions at different wavelengths. In majority of patients measurement of SpO_2 by pulse oximeter reflects arterial saturation and partial pressure of oxygen (PaO_2) can be estimated by oxyhaemoglobin dissociation curve. However, in critically ill patients, peripheral perfusion is often reduced where saturation measurements are not reliable. The sensor probe can be applied to the tip of finger, toes, or lobule of ear. Oxygen saturation and heart rate can be continuously monitored. In hypothermia the SpO_2 is not accurately recorded. It is advisable to cover the probe from the ambient light, which affects the signal.

Capnography

Capnography is the technique of displaying carbon dioxide concentration changes during the respiratory cycle. Capnography provides a non-invasive means of rapidly identifying the problems, such as oesophageal intubation, inadvertent bronchial intubation and apnoea. Overall it provides a means to evaluate the integrity of the airway and the quality of patient's cardio-pulmonary functions.

Arterial Blood Gas Analysis

The analysis of arterial blood gases (ABG) helps to differentiate type I and type II respiratory failure and the severity as well. ABG analysis can be done intermittently. However, continuous monitoring can be done using a arterial catheter with fibreoptic electrode. From the analysis of ABG sample, PaO_2, partial pressure of carbon dioxide ($PaCO_2$), pH, HCO_3, absolute and standard base excess can be assessed. Proper anticoagulation of arterial blood with heparin and quick transport in ice slush to the nearest ABG analyser (**Figure 4**) is very important to get accurate values. PaO_2 should always be interpreted in relation the fraction of inspired oxygen (FiO_2). The ratio of PaO_2 to FiO_2 of inspired air (PaO_2/FiO_2) gives adequacy of gas exchange. In acute respiratory distress syndrome (ARDS) the ratio is less than 200. Serum electrolytes, lactate, blood glucose can also be measured in an ABG sample. Serial ABG analysis gives very useful information during mechanical ventilation and weaning process as well.



Figure 4: Arterial blood gas analyser.

NEUROMUSCULAR MONITORING

Central Nervous System

Clinical examination of the central nervous system is simple and non-invasive way of evaluating the brain. However, the requirement of opioids, sedation, propofol and muscle relaxants make the clinical exam extremely difficult in critically ill patients. Glasgow Coma scale score (**Table 2**) is an another simple way to assess the neurological status in the management of these patients.

Table 2: Glasgow Coma Scale Score

Eyes (E)	Open	Spontaneously	4
		To command	3
		To pain	2
		No response	1
Best verbal response (V)	–	Oriented	5
		Disoriented	4
		Inappropriate words	3
		Incomprehensible	2
		No response	1
Best motor response (M)	To command	Obeys	6
	To pain	Localises to pain	5
		Flexion—withdrawal	4
		Decorticate rigidity	3
		Decerebrate rigidity	2
		No response	1
		Total	15

Intracranial Pressure

Sterile catheter can be placed in the ventricle of a patient in supine posture and by connecting it to a transducer system can give us the intracranial pressure (ICP) and trace. The normal ICP is 10 to 15 cm H_2O. The indications of ICP monitoring are head injury, subarachnoid haemorrhage and post-operative neurosurgical patients. Continuous measurement of ICP can be done by a number of devices placed within the cranium through a small burr hole made in parietal or frontal bone on non-dominant side. Subdural catheter, extradural or subdural bolt and intra-ventricular catheter can be connected to fluid filled system, which are connected to conventional pressure transducer and recording systems. Catheter block and infection are important and serious complications of these systems. Fibreoptic system can introduce a miniature pressure transducer into parenchyma to record the ICP. The transcranial Doppler is a non-invasive technique which calculates blood flow in the arteries and detects cerebral ischaemia.

Cerebral Function Monitor (CFM)

This is a compact form of electroencephalogram, where unwanted frequencies are filtered and summated. It uses only 3 electrodes and monitors electrical activity continuously. It is used in patients who develop seizures in ICU.

Jugular Venous Oxygen Saturation

Jugular venous oxygen saturation measurement and difference of cerebral arterio-venous oxygen content have been used in neuro ICU to indicate global cerebral ischaemia and to investigate hypotension. Indwelling catheters enable to record the jugular bulb oxygen saturation continuously and they reflect global changes in cerebral functions.

Peripheral Nervous System and Peripheral Neuropathy

The damage of the peripheral nerves may result in peripheral neuropathy. It is caused by diabetes mellitus, uremia, human immunodeficiency virus or nutritional deficiency. Other causes include mechanical pressure, such as compression or entrapment, direct trauma, injuries and contusion. Diagnosis of neuropathy is based on symptoms and physical examination. Examination of muscle strength, reflexes and sensitivity to position, vibration, temperature and light touch are to be assessed. Vibration perception is more sensitive than touch and pressure.

RENAL FUNCTION

A very useful guide indicating adequacy of cardiac output, splanchnic perfusion and renal function is hourly urine output monitoring. Specific gravity and osmolality of the urine are useful monitoring tools to differentiate pre-renal and renal failure.

Blood Urea and Serum Creatinine

Blood urea, serum creatinine and electrolyte trends are useful in evaluation of the progress of renal function. A rise in blood urea can occur in the absence of renal dysfunction in gastrointestinal bleeding, high protein intake and increase catabolism. Estimation of the concentration ability of the kidneys can be derived by comparing the blood and urine sodium, potassium and urea. Urine/plasma osmolality ratio of <1.2, urea ratio of <10 and a urinary sodium of >40 mmol/L indicates acute renal failure.

HEPATIC SYSTEM

Even though the damage to liver may not affect its activity because of its tremendous functional reserve, it is routine to monitor the function because it performs important functions of synthesis, storage, metabolism and excretion of toxic products. The tests of liver function alone are poor indicators of the degree of liver disease, and therefore, indicators of cell damage are frequently used instead, for instance hepatic enzymes. Albumin, because of long half-life is not a sensitive indicator of liver function. Disorders of clotting factors and prothrombin time are useful indicators of monitoring liver function.

HAEMATOLOGICAL MONITORING

Acquired coagulopathies and haemostasis abnormalities are not uncommon in critically ill patients. Clotting function assessment is monitored by platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen concentration and fibrin degradation products (FDP) or D-dimer.

Oxygen delivery to the tissues is important and haemoglobin plays a crucial role and should be monitored frequently. Monitoring total leukocyte count and differential count is important to differentiate infective or non-infective causes and may give a clue of acute or chronic type of infection.

GASTROINTESTINAL SYSTEM

Bleeding from gastrointestinal system can occur in critically ill patients and simple periodic naso-gastric tube suction confirms the diagnosis. Paralytic ileus needs to be diagnosed promptly and treated. The important function of gastrointestinal system is nutrition. Naso-gastric tube feeding or enteral feeding should be considered, if there are no contraindications.

Gastric Tonometry

In critically ill patients development of acidosis in gastric mucosa may be a significant factor contributing to stress ulceration and consequent gastrointestinal bleeding. The acidosis is possibly due to mucosal ischaemia. Gastric tonometry detects ischaemia. The mucosal pH may be measured indirectly as tissues are highly permeable to CO_2, and hence, the PCO_2 of fluid within the lumen of the gut is equilibrated with that of the cells in the superficial layers of gut wall. The measurement of intra-luminal PCO_2 is made using a silicone balloon of approximately 3 ml capacity which is permeable to CO_2 and is positioned at the distal end of the nasogastric tube.

NUTRITION

Critically ill patients offer an exceptional challenge with regard to metabolism and nutrition and it is often neglected. So metabolic status needs to be monitored repeatedly. The intake of calories, lipids, proteins, fluids, electrolytes and minerals administered by enteral and parenteral routes are documented and monitored at regular intervals.

Electrolytes

Measurement of serum electrolytes is particularly important in critically ill patients. ECG helps in monitoring hypokalaemia and hyperkalaemia. Tall peaked 'T' waves are seen in hyperkalaemia. Decreased T wave amplitude and 'U' waves are seen in hypokalaemia. Syndrome of inappropriate antidiuretic

hormone (SIADH) results from inappropriate secretion of antidiuretic hormone (ADH) and result in retention of ingested or infused water. Monitoring of serum osmolarity, serum sodium, and urine sodium and urine osmolarity are to be done.

Endocrine and Metabolic Monitoring

Different endocrine abnoramalities can occur in critically ill patients. Serial blood glucose and ABG analysis are important monitoring tools for hyperglycaemia, diabetic ketoacidosis and volume depletion. An elevated ACTH levels and decreased cortisol levels occur in primary adrenal insufficiency.

Deep Venous Thrombosis

Deep venous thrombosis (DVT) is mostly asymptomatic except for mild discomfort and swelling. The incidence of venous thrombosis is high in patients with cancer, varicose veins, obesity and long period of lying down. DVT produces severe swelling of the extremity and without treatment can lead to long-term complications, like pulmonary embolism. Soleal veins of the lower leg are the most frequent sites of DVT. They are mostly asymptomatic, but may have mild calf tenderness (Homans sign). This condition is diagnosed by venography, Doppler ultrasound and impedance plethysmography.

Monitoring of Infection

Clinical and laboratory evaluation is required for monitoring of infections in critically ill patients. Patients may have the clinical signs like raised body temperature (>38°C) or hypothermia (<36°C), heart rate more than 90 beats per minute, increased respiratory rate (>20 breaths per minute). Laboratory investigations show raised total leucocyte count (>12000 cells/mm^3 or presence of 10% immature forms) or leucopaenia (<4000 cells/mm^3). Neutrophilia is seen in acute bacterial infections. Neutropaenia is seen in viral infections, brucellosis. Lymphocytosis is seen in brucellosis and tuberculosis. Monitoring of acute phase reactants like C-reactive protein is also raised in acute infections. Microbiological culture profiles of blood, sputum, urine, central venous pressure catheter tip and urinary catheter are important monitors of the infection and for institution of appropriate antibiotic.

SUMMARY

Critically ill patients have different physiological reserves and respond to insults in different ways. Monitoring is focused to examine the components of different systems including cardiac output, oxygenation of blood, etc. It may be difficult to monitor all the variables in all the patients. Different modalities of monitoring needs different monitors which are expensive. Cost benefit ratio should always be kept in mind. Invasive monitoring is used only in patients when indicated and analyse whether information obtained can modify the treatment. No amount of monitoring can cure a patient. However, successful management of critically ill patients requires the use of monitors to allow formulation of appropriate management. Monitoring is not only expensive but can also produce complications, which outweigh the benefits some times. One should strike a balance in managing the monitoring modalities of a patient who is critically ill.

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7.3 Fluid and Electrolyte Balance in Health and Disease

Sanjay Jain

INTRODUCTION

A thorough understanding of the homeostatic mechanisms, that controls fluid and electrolyte balance, is essential for the accurate assessment and treatment of the wide variety of disorders. These homeostatic mechanisms function via carefully regulated mechanisms in the kidneys, lungs and the skin to maintain specific tonicity, volume and ionic composition of the body fluids.

DISTRIBUTION OF TOTAL BODY WATER

Water is the most abundant fluid in the body comprising 60% of total body weight in males and 50% in females. Two-third of this is distributed intra-cellularly and one-third is present extra-cellularly. Out of the extra-cellular compartment, three-fourth is present in the interstitium and the remaining one-fourth is distributed intra-vascularly. Another small compartment of fluid, the transcellular compartment, includes fluid in the synovial, peritoneal, pericardial and intraocular spaces, as well as the cerebrospinal fluid. The ionic composition of the extra-cellular and the intra-cellular fluids is different. The plasma and interstitial fluid are similar in composition being separated by only a thin, highly permeable capillary membrane. The only significant difference lies in the much higher protein concentration of the plasma due to the lower permeability of the capillaries to the plasma proteins. Due to a net negative charge of the proteins, they tend to hold a slightly higher concentration of sodium in the plasma. For the same reason, the concentration of anions is higher in the interstitium.

Radioactive water (tritium, $3H_2O$) and heavy water (deuterium, $2H_2O$) mix well with total body water and can be used to measure the same using the dilution principle. Extra-cellular fluid (ECF) volume can be measured using radioactive sodium, chloride, iothalamate and inulin. The presence of higher concentration of albumin in the plasma can be used to determine plasma volume (I^{125} tagged albumin). Interstitial fluid volume and intra-cellular fluid volume are indirect measurements and cannot be measured directly.

Plasma osmolality is determined by the following formula:

$$(Na^+ \times 2) + (\text{glucose}/18) + (\text{BUN}/2.8)$$

The Na^+ concentration is expressed in mEq/L while glucose and blood urea nitrogen (BUN) in mg/dL. The normal osmolality is 290 to 310 mosm/L. All fluids, with sodium and potassium concentration equal to 150 mEq/L, are considered to be isotonic.

HYPONATRAEMIA

Hyponatraemia is defined as a serum sodium less than 136 mmol/L and is the most frequent electrolyte abnormality in clinical medicine.

Pseudohyponatraemia is a rare situation in which serum Na^+ is low but the ECF osmolality and tonicity are normal. It is an artifact due to accumulation of other plasma constituents, viz. triglycerides or plasma proteins.

Causes of Hyponatraemia

Causes of hyponatraemia are discussed in **Table 1**. In hyperglycaemia, relative insulin deficiency causes myocytes to become impermeable to glucose which in turn acts as an osmole drawing water into the cell. For every 100 mg/dL rise in plasma glucose concentration, there is a 1.4 mEq/L fall in sodium.

Table 1: Causes of Hyponatraemia

Isotonic hyponatraemia
Following transuretheral resection of prostate: Isosmotic (mannitol) or hyposmotic (glycine/sorbitol) irrigation of the bladder
Hyperlipidaemia
Hyperproteinaemia
Hypertonic hyponatraemia
Hyperglycaemia
Intravenous administration of mannitol
Hypotonic hyponatraemia
Hypovolemic hyponatraemia, i.e. primary Na^+ loss (secondary water gain)
Renal loss, e.g. diuretics (almost always thiazides), post-obstructive diuresis, osmotic diuresis
Extrarenal loss, e.g. gastrointestinal loss (diarrhoea, vomiting), integumentary loss (sweating), third space loss (burns, pancreatitis, muscle trauma)
Euvolemic hyponatraemia, i.e. primary water gain (secondary Na^+ loss)
Primary polydipsia
SIADH
Hypothyroidism
Adrenal insufficiency
Chronic kidney disease
Abnormal arginine vasopressin secretion
Malignancy: Pulmonary and mediastinal tumours
CNS: Acute psychosis, stroke, haemorrhage
Miscellaneous: Beer potomania, severe nausea, HIV infection and post-operative state
Hypervolemic hyponatraemia: Primary Na^+ gain (secondary excess water gain)
Congestive heart failure
Nephrotic syndrome
Cirrhosis
Acute and chronic kidney disease
Pregnancy

SIADH = Syndrome of inappropriate antidiuretic hormone; CNS = Central nervous system; HIV = Human immunodeficiency virus

Clinical Features

The signs and symptoms depend on the degree of hyponatraemia and the rate of decline of sodium. Nausea and

malaise are the earliest findings, and may be seen when the plasma sodium concentration falls below 125 to 130 mEq/L acutely. This may be followed by headache, lethargy, muscle cramps, confusion, disorientation and obtundation, and eventually seizures, coma and respiratory arrest, if the plasma sodium concentration falls below 115 to 120 mEq/L.

The cerebral adaptation permits patients with chronic hyponatraemia to appear to be asymptomatic despite a plasma sodium concentration that is persistently as low as 115 to 120 mEq/L. Symptomatic chronic hyponatraemia is rarely, if ever, associated with cerebral oedema severe enough to cause herniation of the brain. During hyponatraemia, brain cells that have been exposed to hypotonic plasma swell, because of intracellular fluid shift. The early adaptive response of the brain cells to hyponatraemia is by loss of water into the cerebrospinal fluid (CSF) followed by extrusion of sodium and potassium from the brain cells. The late adaptive response occurs with the extrusion of organic osmolytes such as myoinositol, glycerophosphatylcholine, glutamate, glutamine, creatinine and taurine. If adaptation of the brain is incomplete, raised intracranial tension develops which may eventually lead to death.

Diagnosis

The diagnostic approach to the patient with hyponatraemia consists of a directed history and physical examination, appropriate laboratory tests, and in selected patients, assessing the response to volume expansion with isotonic saline.

Laboratory work-up includes serum osmolality, urine osmolality and urine Na^+. The plasma osmolality, which normally ranges from 275 mOsm/kg to 290 mOsm/kg, is reduced in most hyponatraemic patients, because it is primarily determined by the plasma sodium concentration and accompanying anions. In patients with hyponatraemia and a low plasma osmolality, the urine osmolality can be used to distinguish between impaired water excretion (which is present in almost all cases) and primary polydipsia, in which water excretion is normal but intake is so high that it exceeds excretory capacity. The normal response to hyponatraemia (which is maintained in primary polydipsia) is to completely suppress antidiuretic hormone (ADH) secretion, resulting in the excretion of maximally dilute urine with an osmolality below 100 mOsm/kg and a specific gravity ≤ 1.003. Values above this level indicate an inability to normally excrete free water, most commonly because of continued secretion of ADH.

In patients with hyponatraemia, hypo-osmolality and inappropriately concentrated urine, the urine sodium concentration can be used to distinguish between hyponatraemia caused by a decreased effective arterial blood volume and euvolaemic hyponatraemia. The urine sodium concentration is usually below 25 mEq/L in hypovolaemia, unless there is renal salt wasting while it is more than 40 mEq/L in syndrome of inappropriate antidiuretic hormone hyper-secretion (SIADH). Later is also associated with increased uric acid excretion.

Management

The two primary goals of therapy are: to initiate treatment of the underlying condition and to restore the normal serum osmolality without causing an iatrogenic complication. The following methods of increasing the serum sodium concentration and to restore serum osmolality can be used:

1. Restricting water intake

Water restriction to below the level of output is the primary therapy for hyponatraemia in oedematous states (such as heart failure and cirrhosis), SIADH, primary polydipsia and advanced renal failure.

2. Giving oral or intravenous sodium chloride

Sodium chloride, usually as isotonic saline or increased dietary salt, is given to patients with true volume depletion and adrenal insufficiency, and to some patients with SIADH. Administration of hypertonic saline is limited to patients with symptomatic or severe hyponatraemia or, occasionally to patients with SIADH and highly concentrated urine.

3. Giving vasopressin antagonist

Conivaptan is an intra-venous formulation that blocks V2 and V1a receptors while lixivaptan, tolvaptan and satavaptan are oral formulations that are exclusively V2 receptor antagonists.

Osmotic demyelination syndrome (ODS) is associated with rapid correction of hyponatraemia. A rapid increase in the plasma sodium concentration can lead to ODS, previously known as central pontine myelinolysis. This rapid cellular dehydration originally was identified in the pons, but has now been identified in other areas of the brain.

HYPERNATRAEMIA

Hypernatraemia is defined as elevation of serum sodium concentration to a value exceeding 145 mEq/L.

Causes of Hypernatraemia

It can be caused by either a net water loss or rarely by a gain of hypertonic sodium solution. Net water loss can occur in the absence of a sodium deficit (free water deficit) or in its presence (hypotonic fluid loss). Various causes of hypernatraemia are described in **Table 2**. Thirst is the most important protective mechanism against sustained hypernatraemia, thus the highest risk exists in those with altered mentation, intubated patients, infants and elderly patients. The other protective mechanism is ADH secretion stimulated by hyperosmolality caused by hypernatraemia.

Clinical Manifestations

The primary manifestation of hypernatraemia reflects central nervous system dysfunction, which in turn, is a consequence of cellular dehydration in the brain. Signs and symptoms vary with the degree, rapidity of onset of hypernatraemia and the age of the patient. Elderly patients generally have few symptoms until the serum sodium concentration exceeds 160 mmol/L. Intense thirst may be present initially, but it dissipates as the disorder progresses and is absent in patients with hypodipsia. Convulsions are rare except during inadvertent sodium loading, rehydration or in the presence of intracranial bleed. Values above 180 mEq/L are associated with a high mortality rate, particularly in adults.

Diagnosis

The history should include a review of recent and current medication use and questions regarding exercise, heat exposure, sweating, vomiting, diarrhoea, urine output, recent fluid intake and the presence of thirst. Physical examination should include an assessment of ECF volume and a complete

Table 2: Causes of Hypernatraemia

- Net water loss
- Pure water loss: Euvolaemic hypernatraemia
  - Insensible water losses
  - Hypothalamic lesions impairing thirst or osmoreceptor function
  - Central diabetes insipidus
  - Congenital nephrogenic diabetes insipidus
  - Acquired diabetes insipidus
- Hypotonic fluid: Hypovolaemic hypernatraemia
  - Renal causes
    - Loop diuretics
    - Osmotic diuretics
    - Post-obstructive diuresis
    - ATN-diuretic phase
    - Intrinsic renal disease
  - Gastrointestinal causes
    - Vomiting
    - Nasogastric drainage
    - Enterocutaneous fistula
    - Diarrhoea
  - Cutaneous causes
    - Burns
    - Excessive sweating
    - Pemphigus
- Hypertonic sodium gain: Hypervolaemic hypernatraemia
  - Hypertonic sodium bicarbonate infusion
  - Ingestion of sodium chloride
  - Hypertonic saline enemas
  - Hypertonic dialysis
  - Cushing's syndrome
  - Primary hyperaldosteronism

neurologic evaluation. Urine volume should be monitored, urine osmolality should be measured in several spot urine samples and 24-hour urine osmolar excretion should also be measured if polyuria is present. In the less common situation of hypervolemic hypernatraemia, there is often an antecedent history of medical intervention that includes the administration of sodium-containing solutions. The findings on physical examination are consistent with ECF volume expansion, whereas the cause of hypernatraemia is usually apparent (e.g. diarrhoea), the urine osmolality may be useful in clarifying the cause in patients without obvious gastrointestinal or insensible water losses. During hypernatraemia caused by extrarenal water losses, the renal response should be to generate hypertonic urine with an osmolality of 700 to 800 mOsm/kg.

If the urine osmolality (U_{osm}) is less than 300 mOsm/kg, then water loss is occurring via the kidneys, secondary to decreased hypothalamic release of ADH (central diabetes insipidus) or impaired sensation in the cortical collecting tubule (nephrogenic diabetes insipidus). In central diabetes insipidus, provision of ADH results in an increase in U_{osm}, whereas in nephrogenic diabetes insipidus, it results in little to no increase in U_{osm}.

If U_{osm} is between 300 mOsm/kg and 800 mOsm/kg, patients might have partial forms of nephrogenic or central diabetes insipidus or an osmotic diuresis from urea or glucose. In patients believed to have diabetes insipidus, a water deprivation test can be performed to assess the integrity of pituitary release and renal response to ADH.

Management

For treating acute hypernatraemia, normal saline solutions are initially given intravenously. In the highly volume-contracted patient with severe hypernatraemia, administering isotonic saline solutions has two advantages. It provides fluid resuscitation in impending cardiovascular collapse. Moreover, the isotonic salt solution, which is hypotonic with respect to the hypertonic patient, avoids an unnecessary rapid fall in the serum sodium level.

Amount of the water deficit and ideal rate of correction must be considered while correcting the water deficit in the hypernatraemic patient. The maximum safe rate at which the plasma sodium concentration should be lowered, is by ≤ 0.5 mEq/L per hour and no more than by 12 mEq/L per day. The preferred route for administering fluids is the oral route or a feeding tube. If neither is feasible, fluids should be given intravenously. Only hypotonic fluids are appropriate including pure water, 5% dextrose, 0.2% sodium chloride (referred to as one-quarter isotonic saline) and 0.45% sodium chloride (one-half isotonic saline).

HYPOKALAEMIA

It is one of the most common electrolyte abnormalities in clinical practice. Hypokalaemia is defined as serum potassium (K^+) less than 3.6 mEq/L.

Spurious hypokalaemia is an entity when serum K^+ levels are low but total body K^+ stores are normal. It may be seen in marked leucocytosis (TLC >1,00,000) where white blood cells take-up K^+, if the serum sample is stored at room temperature. It may be seen in the setting of an insulin dose being given just prior to taking a serum sample due to intracellular shift of K^+.

Causes of Hypokalaemia

The causes of hypokalaemia may be classified into reduced K^+ intake and increased K^+ losses **(Table 3)**. Decreased intake of K^+ rarely causes hypokalaemia. The daily requirement is 40 to 120 mEq/L; however, the normal kidney is able to decrease the daily excretion of K^+ in the presence of low intake.

Clinical Manifestations

The clinical manifestations tend to be proportionate to the degree of hypokalaemia. Patients are asymptomatic above the K^+ level of 3.0 mEq/L. However, rapidly falling K^+ levels or other conditions predisposing to arrhythmias can give rise to symptoms at a much higher level. The usual manifestations are described below:

1. Muscle weakness

Hypokalaemia is one of the causes of acute flaccid paralysis starting in the lower limbs and progressing upwards. It can also lead to respiratory muscle involvement to cause respiratory failure or affect gastrointestinal muscles resulting in ileus. Other muscular manifestations include cramps, paresthesias and tetany.

2. Cardiac arrhythmias

Various types of cardiac arrhythmias can be induced by hypokalaemia including atrial pre-mature complexes, ventricular pre-mature complexes, sinus bradycardia, paroxysmal atrial tachycardia, atrioventricular block and

ventricular tachycardia (VT)/ventricular fibrillation (VF). Presence of concomitant coronary ischaemia, digitalis, increased beta adrenergic activity and hypomagnesemia increases the risk of arrhythmias.

3. Renal abnormalities

Hypokalaemia can induce impaired urinary concentrating ability, increased ammonia production, increased renal bicarbonate production and hypokalaemic nephropathy.

4. Rhabdomyolysis

Severe hypokalaemia (< 2.5 mEq/L) may induce rhabdomyolysis and myoglobinuria.

Table 3: Causes of Hypokalaemia

- Decreased potassium intake
- Increased transcellular shift
  - Metabolic alkalosis
  - Insulin administration
  - Beta-2 adrenergic agonists
- Increased potassium loss
  - Renal
    - Diuretics, especially loop diuretics
    - Primary mineralocorticoid excess
    - Metabolic acidosis
    - Hypomagnesemia
    - Amphotericin B
    - Salt wasting nephropathy
    - Polyuria
    - Non-reabsorbable ions
  - Extra-renal loss
  - Excessive sweating: Generally insignificant, may be seen after heavy exercise when sweating is > 10 L per day
  - Gastrointestinal losses, e.g. diarrhoea, nasogastric aspiration, vomiting
  - Dialysis or plasmapheresis

Diagnosis

Total body K^+ depletion may result from renal or extrarenal causes. Most of the times, a good history and examination reveals the source of K^+ loss (renal *versus* extrarenal). If the source is unclear, a 24-hour urinary K^+ excretion may be of benefit. A 24-hour urinary K^+ >20 mEq/L implies that renal potassium loss is the cause of hypokalaemia. The presence of metabolic acidosis is most often due to diabetic ketoacidosis or renal tubular acidosis type 1 or type 2. The transtubular potassium concentration gradient (TTKG) is used to evaluate the force for K^+ secretion in the cortical collecting duct in the kidney.

The electrocardiographic changes of hypokalaemia include flattening or inversion of T waves (early), prominent U waves, ST-segment depression, prolonged PR interval and widening of QRS complex. These changes do not correlate well with plasma K^+ levels.

Treatment

In the absence of an independent factor, causing transcellular K^+ shifts, the magnitude of the deficit in body stores of K^+ correlates with the degree of hypokalaemia. On an average, serum K^+ decreases by 0.3 mmol/L for each 100 mmol reduction in total body stores, but the response is extremely variable.

Oral correction is recommended in all non-urgent settings where patient does not have any arrhythmias or paralysis and does not have any contraindication to oral supplementation. Intravenous K^+ supplementation is used for profound, life-threatening hypokalaemia and in patients who do not tolerate oral solution. Electrocardiogram (ECG) monitoring should be done with supplementation rates >20 mEq/hr. The concentration of administered potassium should be no more than 40 mEq/L in a peripheral vein or 60 mEq/L in a central vein. Infusion rates should be limited to <20 mEq/hr with peripheral cannula and >40 mEq/hr via central line. In all cases, serum K^+ should be checked after 2 to 4 hours of ongoing replacement. Serum Mg^{2+} levels should be checked if hypokalaemia is refractory to correction.

HYPERKALAEMIA

Hyperkalaemia is a common and life-threatening electrolyte imbalance. Early recognition of this condition can allow for the initiation of corrective measures. Hyperkalaemia is defined as a serum K^+ concentration of larger than 5.0 mEq/L. The normal concentration of K^+ depends on the K^+ intake, its excretion by the kidney, and by the balance between extra-cellular and intra-cellular spaces.

Causes of Hyperkalaemia

The causes of hyperkalaemia may be divided into two major groups as described in **Table 4**.

In normal individuals, a phenomenon referred to as K^+ adaptation ensures a proportionate rise in K^+ secretion by the kidney in response to an increase in ingested K^+. Hence, in the presence of normal renal function, hyperkalaemia due to excess intake is rare. Of these metabolic acidosis is a frequently seen cause. In response to every 0.1 unit reduction in extra-cellular pH, the plasma K^+ concentration will rise by 0.6 mEq/L (range 0.2-1.7 mEq/L).

Table 4: Classification of Causes of Hyperkalaemia

- **Hyperkalaemia due to excess release of intracellular potassium**
- Metabolic acidosis
- Insulin deficiency and hypertonicity
- Tissue catabolism
- Exercise
- Beta-adrenergic blockade
- Drugs, e.g. succinylcholine, digitalis overdose
- Hyperkalaemic periodic paralysis
- Pseudohyperkalaemia
- **Hyperkalaemia due to reduced renal clearance**
- Renal failure
- Decreased effective circulating volume
- Impaired sodium reabsorption, e.g. primary hypoaldosteronism, adrenal insufficiency, secondary hypoaldosteronism, renal tubular acidosis, drugs (angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, potassium sparing diuretics)
- Increased chloride reabsorption, e.g. Gordon's syndrome, cyclosporine
- Ureterojejunostomy

Clinical Manifestations

Hyperkalaemia is associated with very few overt symptoms and signs, and these manifests only at very high levels or when the rise is rapid. Severe muscle weakness and paralysis may be seen in some cases. The primary cause of mortality in hyperkalaemia

is cardiac rhythm disturbances. As a result, hyperkalaemia can be recognised by some typical ECG abnormalities.

A tall and symmetrical T-wave is the first sign of hyperkalaemia. T-waves are usually taller than half of the preceding QRS complexes when considered significant and may appear tented in severe cases. Due to slowing of cardiac conduction, other subsequent changes ensue, including progressive lengthening of the PR interval and QRS duration, atrioventricular conduction delay and loss of P-waves, progressive widening of the QRS complex and merging of the T- and U-waves resulting in a 'sine wave' pattern. The terminal event is ventricular fibrillation or asystole. The level of K^+ does not correlate with the degree and progression of ECG changes.

Diagnosis

The most common causes of hyperkalaemia, such as renal failure, drugs and transcellular K^+ shift, are relatively simple to identify. Chronic hyperkalaemia not related to these aetiologies is usually due to impaired secretion of K^+. Assessment of the TTKG is helpful to differentiate between decreased effective circulating volume (TTKG >10) and other causes (TTKG <5). In cases where TTKG is < 5, the presence of kaliuresis in response to administration of mineralocorticoid indicates hypo-aldosteronism.

Management

Hyperkalaemia requires emergent treatment. Severe arrhythmias can occur at K^+ levels >7.5 mEq/L but may also occur at lower levels. The goals of therapy are to decrease membrane excitability; thereby preventing arrhythmias, shifting K^+ to the intra-cellular space and promoting K^+ loss and removal of exogenous source of K^+.

1. Membrane excitability is controlled by the infusion of 1000 mg (10 ml of a 10% solution) of calcium gluconate over 2 to 3 minutes. The effect begins within minutes but is short lived (only 30 to 60 minutes). The dose can be repeated if no change in ECG is noted within the next 5 to 10 minutes. This does not affect the levels of K^+.
2. Insulin causes a shift of extra-cellular K^+ into the cells by enhancing the effect of the Na^+-K^+ ATPase pump. An infusion of 10 to 20 units of regular insulin in 20 to 50 g of dextrose can result in the fall of K^+ by 0.5 to 1.5 mEq/L in 15 to 30 minutes. This effect peaks at 30 minutes and lasts several hours. Diabetic patients with hyperglycaemia may be given insulin alone.
3. Sodium bicarbonate is effective in shifting K^+ into the intra-cellular space when given in hyperkalaemia associated with metabolic acidosis. The action begins within 30 to 60 minutes and persists for several hours.
4. Beta-2-adrenergic agonists promote the cellular uptake of K^+. The onset of action is within 30 minutes and lasts for 2 to 4 hours. These drugs can be effectively used in the treatment of acute hyperkalaemia, lowering the plasma K^+ concentration by 0.5 to 1.5 mEq/L.
5. Removal of potassium can be achieved using loop or thiazide diuretics if renal function is adequate. Potassium binding resins, like sodium polystyrene sulfonates, are useful in binding dietary potassium in the gut and preventing its absorption. One gram of resin binds 1 mEq of K^+ and releases 2 to 3 mEq of sodium. The usual dose is 25 to 50 g mixed in 20% sorbitol to prevent constipation. It lowers plasma K^+ concentration by 0.5 to 1.5 mEq/L. A retention enema may also be used.
6. The most effective way of lowering K^+ is by haemodialysis. Severe hyperkalaemia, not responding to conservative management, is an indication for haemodialysis. Peritoneal dialysis may be done in hypotensive patients but is only 15% to 20% effective.

CALCIUM METABOLISM

Calcium plays a vital role in body homeostasis. Diverse physiologic processes in body like muscle contraction, neuromuscular signaling, blood coagulation and hormone secretion take place because of calcium. Total body calcium is around 1 to 2 kg of which 99% is in the bones. The normal total levels of calcium in body are 8.5 to 10.5 mg/dL of which 50% is ionised. The remainder is ionically bound to negatively charged proteins (albumin and immunoglobulins) or loosely complexed with phosphate, citrate, sulphate or other anions. Intra-cellular calcium concentrations are 10,000 folds lower than extra-cellular levels. The levels are maintained by feedback mechanism involving parathyroid hormone and active vitamin D. Liver, kidneys, intestines and bones are the principle sites of metabolism.

Causes of Hypocalcaemia

The causes of hypocalcaemia can be classified according to the activity of parathyroid hormone (PTH) **(Table 5)**.

Table 5: Causes of Hypocalcaemia

Low or absent parathyroid hormone (PTH)	
Parathyroid agenesis:	Isolated/DiGeorge syndrome
Parathyroid destruction:	Radiation/surgical/infiltration by metastases/autoimmune process
Decreased PTH release:	Hypomagnesemia, activating calcium sensing receptor (CaSR) mutations
High or ineffective PTH	
Chronic renal failure	
Vitamin D deficiency/resistance	
Pseudohypoparathyroidism	
Drugs: Calcium chelators, bisphosphonates, phenytoin, ketoconazole	
Severe acute hyperphosphataemia: Tumour lysis, rhabdomyolysis	
Miscellaneous	
Acute pancreatitis	
Hungry bone disease (after parathyroidectomy)	
Severe burns, sepsis, acute renal failure, extensive transfusions with citrated blood (transient)	

Clinical Manifestations

Hypocalcaemia may be asymptomatic if the decrease in serum calcium are relatively mild and chronic. Moderate-to-severe hypocalcaemia is associated with paresthesias, usually of the fingers and toes, and circumoral region. Tapping the inferior portion of zygoma produces twitching of perioral muscles (Chvostek's sign). Carpal spasm can be induced by inflation of blood pressure cuff to 20 mmHg above the patient's systolic blood pressure for 3 minutes (Trousseau's sign). Life-threatening complications, like cardiac arrhythmias, bronchospasm, laryngospasm and seizures, may occur due to severe hypo-calcaemia.

Diagnosis

Besides measuring serum calcium, it is useful to determine albumin, phosphorus and magnesium levels. Each 1 g/dL reduction in the serum albumin concentration lowers the total calcium concentration by approximately 0.8 mg/dL (0.2 mmol/L) without affecting the ionised calcium concentration. Serum intact PTH measurements provide critical information in patients with hypocalcaemia, but can be interpreted correctly only when serum calcium is measured simultaneously. Suppressed PTH levels along with hypocalcaemia suggests absent or reduced PTH secretion as the cause of hypocalcaemia. Elevated PTH levels should direct to search for secondary hyperparathyroidism. Levels of 25-hydroxy vitamin D should be done if nutritional cause of hypocalcaemia is suspected. 1, 25 dihydroxy vitamin D levels are useful in patients with renal dysfunction and hypocalcaemia.

Management

The treatment depends on the severity of hypocalcaemia, the rapidity with which it develops and accompanying complications. Acute symptomatic hypocalcaemia is treated with intravenous calcium gluconate 10 ml 10% wt/vol (90 mg) diluted in 50 ml of 5% dextrose or 0.9%; normal saline is given over 5 minutes. It may be followed by a continuous infusion of 5 ampules of calcium gluconate (450 mg) in dextrose 5% or normal saline 500 ml over 12 hours. Intra-muscular or subcutaneous route should be avoided due to chances of necrosis. Associated magnesium deficiency should also be corrected.

Asymptomatic chronic hypocalcaemia can be treated with oral formulations containing calcium (1 to 2 g/day) and vitamin D2 or D3 (25,000 to 1,00,000 U daily) or calcitriol (1,25 dihydroxy vitamin D) 0.25 to 2 µg/day. Vitamin D deficiency is treated with oral supplementation of vitamin D (50,000 U 2 to 3 times per week for several months).

HYPERCALCAEMIA

It is a very common problem in day-to-day practice. It could be an incidental finding on laboratory testing or reflection of some serious underlying disease.

Causes of Hypercalcaemia

Broadly, the aetiology can be classified on the basis of either related to or unrelated to PTH **(Table 6)**.

Table 6: Classification of Aetiology of Hypercalcaemia

Parathyroid hormone (PTH) related
Primary hyperparathyroidism: Solitary adenomas/multiple endocrine neoplasia (MEN)
Tertiary hyperparathyroidism (CKD with long-term stimulation of PTH)
Lithium therapy
Familial hypercalciuric hypercalcaemia
PTH unrelated
Malignancy associated: Solid tumours (breast, lung, kidney), blood disorders (myeloma)
Vitamin D associated: Vitamin D intoxication, granulomatous disease like sarcoidosis, lymphomas
High bone turnover: Hyperthyroidism, immobilisation, thiazides, vitamin A intoxication
Excessive calcium intake: Milk alkali syndrome, total parenteral nutrition

Clinical Manifestations

Hypercalcaemia is largely asymptomatic in half of the patients. Mild hypercalcaemia (upto 11 to 11.5 mg/dL) may present with vague symptoms like difficulty in concentration, personality changes or depression. Groans (constipation), moans (psychotic noise), bones (bone pain, especially if PTH is elevated), stones (kidney stones) and psychiatric overtones (including depression and confusion) are a common mnemonic for hypercalcaemic symptoms. Symptoms are common at calcium levels of 12 to 13 mg/dL, especially if they develop acutely and may include lethargy, stupor or coma, as well as gastrointestinal tract symptoms like anorexia, nausea, constipation or pancreatitis. Bone pains, pathologic fractures, polyuria or polydipsia may also occur. ECG changes in the form of short QT interval, widened T-waves and atrioventricular conduction disturbances may also occur. Severe hypercalcaemia (> 15 mg/dL) is life-threatening and coma or cardiac arrest could occur. Immediate measures should be taken to decrease the levels.

Management

The treatment of hypercalcaemia depends on the serum calcium levels, symptom presentation or rapidity with which it develops. Mild asymptomatic hypercalcaemia does not require immediate treatment. The steps in the treatment include hydration, diuretics like furosemide, bisphosphonates, calcitonin and glucocorticoids. Use of oral or parenteral phosphate is not recommended due to systemic toxicity of calcium-phosphate complex. Dialysis can be used as a useful therapy in emergency conditions where severe hypercalcaemia is associated with renal failure and is difficult to manage medically.

MAGNESIUM

Magnesium is a critical co-factor in more than 300 enzymatic reactions in the human body and is essential to the normal functioning of the human body. The average daily intake of magnesium is 360 mg, out of which approximately one-third is absorbed through the small bowel. It is mainly excreted through the kidneys; with 15% to 25% ultrafiltrate magnesium reabsorption through the proximal tubule and 5% to 10% in the distal tubule. Approximately 1% of total body magnesium is present in the serum and interstitial space with the normal plasma magnesium concentration of 1.4 to 2.2 mEq/L. Magnesium is found in various dietary sources, best being green leafy vegetables. It is also found in nuts, soybean and whole grain foods.

Hypermagnesemia

Under normal physiological conditions, magnesium is excreted in the urine. Hypermagnesemia is seen when either the renal function is impaired or there is excess of magnesium load.

Causes of hypermagnesemia

Causes of hypermagnesemia are listed in **Table 7**.

Clinical manifestations

Depends on the serum magnesium concentration, symptoms can range from asymptomatic (<3 mEq/L) to life-threatening cardiac and neuromuscular effects (>4 mEq/L). Magnesium concentration of 4 to 6 mEq/L leads to nausea, headache, lethargy and sluggish deep tendon reflexes. Concentration of 6 to 10 mEq/L leads to somnolence, hypocalcaemia, hypotension and absent reflexes. Levels more than 10 mEq/L

Table 7: Causes of Hypermagnesemia

Renal failure: Hypermagnesemia up to 2 to 3 mEq/L is seen in end-stage kidney disease. Severe hypermagnesemia is seen only if excess exogeneous magnesium load is given.
Magnesium infusion: Parenteral infusion like treatment for pre-eclampsia, eclampsia
Magnesium enemas and oral ingestion which exceeds the renal excretory capacity
Hormonal: Primary hyperparathyroidism, diabetic ketoacidosis, adrenal insufficiency
Tumour lysis syndrome
Milk alkali syndrome

causes muscle paralysis, complete heart block, respiratory and cardiac arrest.

Management

Prevention is by avoiding magnesium loading in patients with impaired renal functions. Cessation of magnesium supplements in patients with normal renal function will allow restoration to normal levels. Intravenous calcium gluconate can be given as a magnesium antagonist. Haemodialysis may be required in patients with renal failure or with severe life-threatening hypermagnesemia.

Hypomagnesemia

Hypomagnesemia is especially common in intensive care unit settings with nutrition, diuretics, etc. In the presence of hypomagnesemia, kidney can decrease the renal excretion. Hypomagnesemia can occur in the setting of gastrointestinal or renal losses. However, it is often associated with other metabolic abnormalities like hypokalaemia, hypocalcaemia and metabolic acidosis.

Causes of hypomagnesemia

Causes of hypomagnesemia are listed in **Table 8**.

Table 8: Causes of Hypomagnesemia

Gastrointestinal losses: Chronic diarrhoea especially if associated with dietary deficiency, malabsorption, steatorrhoea and small bowel resection
Acute pancreatitis, alcoholic patients
Renal losses: Loop and thiazide type diuretics, primary defect in renal tubular magnesium handling, Bartter's and Gitelman's syndrome
Hormonal: Primary aldosteronism
Hypercalcaemia: Resulting from increased reabsorption of calcium in the loop of Henle leading to hypomagnesemia
Drugs: Aminoglycosides, amphotericin B, cisplatin, cyclosporine, pentamidine, proton pump inhibitors
Hungry bone syndrome following parathyroidectomy

Clinical manifestations

The clinical features of hypomagnesemia include tetany, positive Chvostek's and Trousseau's signs and generalised convulsion. ECG changes include widening of QRS complex, peaking of the T-waves, prolongation of PR interval and diminution of T-wave and ventricular arrhythmias, especially during myocardial ischaemia. hypomagnesemia can also present along with hypocalcaemia. Mild hypomagnesemia can lower the plasma concentration of calcium. Vitamin D deficiency is also noted in hypocalcaemic and hypomagnesemic patients.

Management

It is important to correct the underlying cause of hypomagnesemia, e.g. stopping the offending drug. Magnesium is replaced by oral route in asymptomatic patients or those with mild deficiency by sustained release formulations, dose being 2 to 4 tablets per day. Intravenous magnesium replacement is required in conditions like ventricular arrhythmias and tetany.

7.4 Acid Base Disorders

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INTRODUCTION

In critical care practice, a wide range of disorders affecting the acid-base balance are encountered. In addition to diseases that cause primary acid-base disorders, a number of disease states either predispose patients to develop these conditions or require the use of medications that alter renal, gastrointestinal, or pulmonary function and secondarily alter acid-base balance. The history and physical examination and measurement of blood and urinary indices allow identification of the underlying cause of these disorders in most cases. Arterial blood gas (ABG) analysis, considered to be one of the most precise measurements in medicine, is a crucial investigation that is frequently employed in the critical care setting. It provides valuable precise information regarding the acid-base, ventilation and oxygenation status of the patient.

BASIC PHYSIOLOGICAL AND CHEMICAL CONCEPTS

Interpretation of the ABG report requires a clear understanding of the basic concepts and physiological principles underlying the disorders of acid-base homeostasis, oxygenation and ventilation. A brief overview regarding the essential fundamental physiological concepts is provided and a practical approach for the bed-side interpretation of ABG results is described.

Acid-Base Chemistry

pH

The concept of pH was put forward by the Danish chemist, Soren Peter Sorensen in 1909 to refer to the negative logarithm of hydrogen ion (H^+) concentration.

$$pH = -\log [H^+]$$

The pH is a 'dimensionless representation' of the H^+ concentration, it has no units and is just a number. There are several advantages of the expression pH compared to H^+. Measured by the pH electrode, pH is related to the logarithm of H^+ 'activity' rather than 'concentration' of H^+ and this seems physiologically more appropriate. The relationship between pH and H^+ is shown in **Table 1**. For each 0.1 pH unit increment, H^+ falls by 20%; by remembering this relationship, the intermediate values can be derived accurately.

Overview of Acid-Base Balance in the Human Body

The normal extracellular fluid (ECF) H^+ concentration is 40 nmol/L. Under normal physiological conditions, the H^+ concentration varies little from its normal value due to the processes of acid-base regulation as maintenance of H^+ concentration at this level is considered to be essential for normal cellular processes. In order to achieve this, close interaction between three physiological systems of the body, namely, the chemical buffers of the body namely kidneys and the lungs is considered essential.

Table 1: Relationship between pH and $[H^+]$

pH	$[H^+]$ (nmol/L)
6.8	158
6.9	125
7.0	100
7.1	79
7.2	63
7.3	50
7.4	40
7.5	31
7.6	25
7.7	20
7.8	15

Dissolved carbon dioxide (CO_2) is in equilibrium with carbonic acid

$$CO_2 + H_2O \underset{\longleftarrow}{\xrightarrow{\text{Carbonic anhydrase}}} H_2CO_3^-$$

Carbonic acid ionizes according to the equation

$$H_2CO_3 \xrightarrow{\text{Carbonic anhydrase}} H^+ + HCO_3^-$$

By the law of mass action

$$\frac{[H^+]\,[HCO_3^-]}{[H_2CO_3]} = K'$$

Taking logarithm on both sides, we have

$$\log \frac{[H^+]\,[HCO_3^-]}{[H_2CO_3]} = \log K'$$

Therefore,

$$\log [H^+] + \log \frac{[HCO_3^-]}{[H_2CO_3]} = \log K'$$

and

$$\log [H^+] = \log K' - \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

By changing signs on both sides of the equation, we have

$$-\log [H^+] = -\log K' + \log \frac{[H_2CO_3^-]}{[H_2CO_3]}$$

Since $-\log [H^+]$ is called pH and $-\log K'$ is called pK, the equation can be re-written as

$$pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

This has been called the 'Henderson-Hasselbalch' equation.

The pK represents the pH at which maximum buffering capacity can be achieved for that reaction. Since the carbonic acid concentration is dependent on the amount of dissolved CO_2 which in turn is dependent on its solubility and the partial pressure of carbon dioxide ($PaCO_2$) in the arterial blood. Therefore, in this equation, H_2CO_3 can be substituted by s x $PaCO_2$, where, s = solubility coefficient. In the clinical setting, pK = 6.1; s = 0.0301.

Therefore,

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.0301 \times PaCO_2}$$

The body responds to the perturbations in the acid-base balance by buffering, which is the immediate response followed by respiratory (alteration in ventilation) and renal (alteration in bicarbonate excretion) responses.

The major buffer system in the ECF is the CO_2-bicarbonate buffer system. Other buffer systems that play a role in buffering are protein and phosphate buffer systems. In the blood, concentration of phosphate is very low and it is quantitatively unimportant. Protein buffers in blood include haemoglobin and plasma proteins. Haemoglobin is an important blood buffer particularly for buffering CO_2. According to the 'isohydric principle', at a given moment, all buffer systems which participate in defense of acid-base changes are in equilibrium with each other. It is important to remember that the carbonate and phosphate salts in bone act as a long-term supply of buffer, especially during prolonged metabolic acidosis.

NOMENCLATURE FOR CLINICAL INTERPRETATION OF ARTERIAL BLOOD GAS MEASUREMENTS

The nomenclature for clinical interpretation of ABG measurements are listed in **Table 2**. Normal laboratory values and acceptable therapeutic ranges for pH and $PaCO_2$ are shown in **Table 3**. The typical alterations in the ABG results and the expected compensatory mechanisms in simple acid-base disorders are listed in **Tables 4A and B**.

Table 2: Nomenclature for Clinical Interpretation of ABG Measurements: Acid-Base Status

Acidosis is an abnormal process or condition which would lower arterial pH if there were no secondary changes in response to the primary aetiological factor

Alkalosis is an abnormal process or condition which would raise arterial pH if there were no secondary changes in response to the primary aetiological factor

Acidaemia = Arterial pH < 7.36

Alkalaemia = Arterial pH > 7.44

Simple acid-base disorders are those in which there is a single primary aetiological acid-base disorder

Mixed acid-base disorders are those in which two or more primary aetiological disorders are present simultaneously

Respiratory disorders are caused by abnormal processes which tend to alter pH because of a primary change in $PaCO_2$ levels

Metabolic disorders are caused by abnormal processes which tend to alter pH because of a primary change in HCO_3^-

ABG = Arterial blood gas; $PaCO_2$ = Partial pressure of carbon dioxide; HCO_3^- = Bicarbonate

Table 3: Normal Laboratory Values and Acceptable Therapeutic Ranges for pH and $PaCO_2$

Variable	Mean	1SD	2SD	Acceptable Therapeutic Range
pH	7.40	7.38-7.42	7.35-7.45	7.30-7.50
$PaCO_2$ (mmHg)	40	38-42	35-45	30-50

SD = Standard deviation; $PaCO_2$ = Partial pressure of carbon dioxide

Table 4A: Expected Compensatory Mechanisms in Respiratory Acid-Base Disorders

Acid-base Disorder	Initial Change	Compensatory Response	Equations for Expected Range of Compensation
Respiratory acidosis	↑$PaCO_2$	↑HCO_3^-	
Acute			For every 10 mmHg↑ in $PaCO_2$, pH decreases by 0.08 units Expected pH = 7.4 – [0.008 × ($PaCO_2$ – 40)]
Chronic			For every 10 mmHg↑ in $PaCO_2$, pH decreases by 0.03 units Expected pH = 7.4 – [0.003 × ($PaCO_2$ – 40)]
Respiratory alkalosis	↓$PaCO_2$	↓HCO_3^-	
Acute			For every 10 mmHg↓ in $PaCO_2$, pH increases by 0.08 units Expected pH = 7.4 + [0.008 × (40 – $PaCO_2$)]
Chronic			For every 10 mmHg↓ in $PaCO_2$, pH increases by 0.03 units Expected pH = 7.4 + [0.003 × (40 – $PaCO_2$)]

Table 4B: Expected Compensatory Mechanisms in Metabolic Acid-Base Disorders

Acid-base Disorder	Initial Change	Compensatory Response	Equations for Expected Range of Compensation
Metabolic acidosis	↓HCO_3^-	↓$PaCO_2$	↓$PaCO_2$ = 1.2 × △ (HCO_3^-) Expected $PaCO_2$ = [1.5 × (HCO_3^-) + 8] ± 2 (Winter's formula)
Metabolic alkalosis	↑HCO_3^-	↑$PaCO_2$	↑$PaCO_2$ = 0.7 × △ (HCO_3^-) Expected $PaCO_2$ = [0.7 × (HCO_3^-) + 21] ± 2

Indices for Acid-Base Balance

Indices for acid-base balance include $PaCO_2$, actual bicarbonate, standard bicarbonate and buffer base. *Standard bicarbonate* is the measurement made in the clinical laboratory after the blood has been equilibrated at 37°C with a $PaCO_2$ of 40 mmHg. *Actual bicarbonate* is calculated from $PaCO_2$ and pH using Henderson-Hasselbalch equation. Base excess is defined as the number of mEq of acid or base needed to titrate 1 L of blood to a pH of 7.40 at 37°C while $PaCO_2$ is held constant. For quick bed-side calculation, it can be assumed that at $PaCO_2$ held constant at 40 mmHg, 7 mEq of acid or base are required to change pH by 1 unit (0.10). *Base excess (or deficit),* which is a true reflection of non-respiratory component of acid-base balance, is an estimate and not an actual measurement. Therefore, it will be reliable only if the measurements used to derive it, the pH and $PaCO_2$ are estimated accurately. Base excess is determined as follows:

Calculating $PaCO_2$ Variance

First, the $PaCO_2$ variance is determined by calculating the difference between the measured $PaCO_2$ and 40; then, the decimal point is shifted two places to the left.

Example:

pH 7.06, $PaCO_2$ = 74
74 – 40 = 34
$PaCO_2$ variance = 0.34
pH 7.48, $PaCO_2$ = 20
40 – 20 = 20
$PaCO_2$ variance = 0.20

Calculating Predicted pH

Predicted respiratory pH is calculated as follows. If the $PaCO_2$ is greater than 40, half the $PaCO_2$ variance is subtracted from 7.40. If $PaCO_2$ is less than 40, the $PaCO_2$ variance is added to 7.40.

Examples:

1. pH 7.06, $PaCO_2$ = 74
   74 – 40 = 34
   $PaCO_2$ variance = 0.34
   0.34 × ½ = 0.17
   Predicted respiratory pH = 7.40 – 0.17 = 7.23
2. pH 7.48, $PaCO_2$ = 20
   40 – 20 = 20
   $PaCO_2$ variance = 0.20
   Predicted respiratory pH = 7.40 + 0.20 = 7.60

Estimate of Base Excess/Deficit

The difference between the predicted respiratory pH and the measured pH reflects the metabolic pH change. Normally, a 10 mEq/L variance from normal buffer baseline represents a pH change of 0.15. If the pH decimal point is moved two places to the right, a 10 (10 mEq/L) to 15 (0.15) relationship will be evident and this has been expressed as "⅔ relationship". By determining the difference between the measured pH and the predicted respiratory pH, moving the decimal point two places to the right and multiplying by ⅔, base excess/deficit can be calculated.

When the measured pH is greater than the predicted pH, it is termed as *base excess*. When the measured pH is less than the predicted pH, it is termed as *base deficit*.

Examples:

1. pH 7.06, $PaCO_2$ = 74, predicted pH = 7.23
   Difference between predicted and measured pH = 7.23 – 7.06 = 0.17
   Applying ⅔ rule, 0.17 × ⅔ = 0.11
   Base deficit = 11 mEq/L
2. pH 7.48, $PaCO_2$ = 20, predicted pH = 7.60
   Difference between predicted and measured pH = 7.6 – 7.48 = 0.12
   Applying ⅔ rule, 0.12 × ⅔ = 0.08
   Base deficit = 8 mEq/L
3. pH 7.20, $PaCO_2$ = 90
   90 – 40 = 50
   $PaCO_2$ variance = 0.50
   0.50 × ½ = 0.25
   Predicted respiratory pH = 7.40 – 0.25 = 7.15
   Difference between predicted and measured pH = 7.20 – 7.15 = 0.05
   Applying ⅔ rule, 0.05 × ⅔ = 0.033
   Base excess = 3 mEq/L
   Base excess/deficit calculation serves as a useful guide for bicarbonate administration.

Anion Gap

Anion gap (AG) represents the concentration of all the unmeasured anions in the plasma (**Table 5**) and is calculated by the following formula:

$$AG = [Na^+] - [Cl^-] + [HCO_3^-]$$

Normal AG is 12 ± 4 mEq/L. Conditions resulting in metabolic acidosis other than hydrochloric acidosis usually lead to a decrease in the serum bicarbonate concentration without a concomitant rise in serum chloride thereby increasing the AG.

Table 5: Unmeasured Anions and Cations Contributing to the Anion Gap

Unmeasured Anions	Unmeasured Cations
Serum proteins, mostly serum albumin (15 mEq/L)	Calcium (5 mEq/L)
Organic acids (5 mEq/L)	Potassium (4.5 mEq/L)
Phosphates (2 mEq/L)	Magnesium (1.5 mEq/L)
Sulphates (1 mEq/L)	
Total = 23 mEq/L	**Total = 11 mEq/L**

Delta Ratio

Delta ratio is related to the AG and buffering, and is defined as:

Delta ratio = increase in AG/decrease in bicarbonate

A high delta ratio can occur when the bicarbonate levels are already elevated at the onset of the metabolic acidosis either due to a pre-existing metabolic alkalosis, or as a compensation for pre-existing respiratory acidosis. A low delta ratio occurs with hyperchloraemic normal AG acidosis (**Table 6**).

DIAGNOSIS OF ACID-BASE DISORDERS

Clinical Assessment

Patients with acid-base disturbances (**Tables 7A and B**) may present with symptoms due to the aetiological causes that

Table 6: Utility of Delta Ratio when Assessing Metabolic Acid-Base Disorders

Delta Ratio	Interpretation
<0.4	Hyperchloraemic normal AG acidosis
<1	High AG and normal AG acidosis
1 to 2	Usual for uncomplicated high AG acidosis Lactic acidosis: average value 1.6 DKA more likely to have a ratio closer to 1 due to urine ketone loss
>2	High AG acidosis and a concurrent metabolic alkalosis or a pre-existing compensated respiratory acidosis

AG = Anion gap; DKA = Diabetic ketoacidosis

resulted in the disturbance. They may also present with manifestations that develop as a consequence of the disturbance as well as with symptoms that have nothing to do with the acid-base disturbance. Therefore, a carefully obtained history and a thorough physical examination are essential for the interpretation of ABG report. The following sequence may be followed to interpret the ABG report to diagnose acid-base disturbances (**Figure 1**).

Step 1: Validity of the ABG report

First, whether pH, $PaCO_2$ and HCO_3^- are compatible should be confirmed using the Henderson-Hasselbach equation which can also be expressed as:

$$H^+ = 24 \times \frac{PaCO_2}{[HCO_3^-]}$$

Step 2: Acidosis or alkalosis?

Net deviation in the arterial pH will indicate whether an acidosis or an alkalosis is present (**Table 2**). If pH is normal, either no acid-base disorder is present or compensating disorders are present.

Step 3: Identifying the primary disturbance: respiratory or metabolic?

Simple acid-base disorders result in a predictable change in the $PaCO_2$ and HCO_3^- (**Tables 4A and B**). Low $PaCO_2$ and HCO_3^- indicate respiratory alkalosis or metabolic acidosis; but a mixed disorder cannot be excluded. Elevated $PaCO_2$ and HCO_3^- indicate respiratory acidosis or metabolic alkalosis; but a mixed disorder cannot be excluded. If $PaCO_2$ and HCO_3^- show a change in opposite directions, it is indicative of a mixed disorder.

Table 7A: Causes of Metabolic Acid-Base Disorders

Metabolic Acidosis	Metabolic Alkalosis
Elevated AG	**Alkali load**
Endogenous	Milk-alkali syndrome
Ketoacidosis	Bicarbonate administration
Diabetes mellitus	Excess bicarbonate-precursor administration
Starvation	**Contraction alkalosis**
Alcohol-induced	Gastric causes
L-Lactic acidosis	Vomiting
Hypoxic (e.g., shock, hypoxaemia, severe anaemia, cyanide poisoning,carbon monoxide poisoning)	Gastric aspiration
Non-hypoxic (e.g., diabetes mellitus, liver failure, kidney failure, sepsis, drugs [ethanol, ethylene glycol, methanol, salicylates, phenformin], neoplasms)	Renal alkalosis
D-Lactic acid acidosis (associated with jejuno-ileal bypass, short bowel syndrome or intestinal obstruction; due to formation of D-lactate by gut bacteria) Uraemic acidosis	Diuretics
Exogeneous	Post-hypercapnoeic metabolic alkalosis
Methanol	Diarrhoea states
Ethylene glycol	Villous adenoma
Salicylates	Hereditary chloride-losing diarrhoea of infancy
Paraldehyde	**Metabolic alkalosis without volume contraction**
Normal AG	Steroid excess (primary)
Non-renal	Primary mineralocorticoid excess [e.g. adrenal adenoma (Conn's syndrome); bilateral adrenal hyperplasia (pseudo-Conn's syndrome); adrenal carcinoma]
Diarrhoea	Cushing's syndrome
Pancreatic fistula	Indeterminate hyperaldosteronism
Urinary diversion	Dexamethasone-suppressible hyperaldosteronism
Acid ingestion	Secondary aldosterone excess
Renal	Renovascular disease
Uraemia	Renin-secreting tumours
Proximal RTA	Errors of steroid metabolism
Hypokalaemic distal RTA (e.g. classic, amphotericin-induced)	11-hydroxylase deficiency
Hyperkalaemic distal RTA (e.g. short-circuit distal RTA, such as, urinary tract obstruction; sickle cell disease; drug-induced)	11- dehydrogenase deficiency
Mineralocorticoid deficiency (e.g. Addison's disease; selective aldosterone deficiency; hyporeninemic hypoaldosteronism)	17- hydroxylase deficiency
	Terminal steroid metabolism defect
Others	Liddle's syndrome
Pyroglutamic acidaemia (acetaminophen induced)	Bartter's syndrome (loss of function mutations in TALH)
	Gittleman's syndrome (loss of function mutation in Na^+-Cl^- cotransporter in DCT)
	Iatrogenic hypermineralocorticoidism
	Exogenous corticosteroids
	Glycyrrhizic acid
	Carbenoxolone fludrocortisone

AG = Anion gap; RTA = Renal tubular acidosis; TALH = Thick ascending limb of Henle's loop; DCT = Distal convoluted tubule.

Table 7B: Causes of Respiratory Acid-Base Disorders

Respiratory Acidosis	Respiratory Alkalosis
Neurological causes	**Pregnancy**
Poliomyelitis	**Pulmonary receptor stimulation**
Excessive sedative, hypnotic drug use	Pneumonia
Spinal cord injury with quadriparesis	Pulmonary embolism
Phrenic nerve palsy	Bronchial asthma
Guillain-Barré syndrome	**Hypoxia**
Myasthenia gravis	High altitude
Eaton-Lambert syndrome	Left to right shunts
Paralytic agents	Congestive heart failure
Botulism	**Pulmonary oedema**
Myopathies, muscular dystrophies, myositis	**Psychogenic Drugs**
Motor neuron disease	Theophylline
Electrolyte abnormalities	Catecholamines
Hypokalaemia	Salicylates
Hypocalcaemia, Hypophosphataemia	Progesterone
Chest-wall disease	Doxapram
Scoliosis	**Central nervous system**
Flail chest	Subarachnoid haemorrhage
Pleural disease	Respiratory centre disease
Pneumothorax	Cheyne-Stokes respiration
Massive pleural effusion	**Cirrhosis of liver**
Obstructive airway disease	**Fever**
Acute tracheal, laryngeal, bronchial obstruction	**Sepsis**
Obstructive sleep apnoea	**Errors of ventilator management**
Diffuse (small-airway) obstruction	Excessive tidal volume
Errors of ventilator management	Excessive ventilation rate
Excessive dead space	
Insufficient tidal volume	
Insufficient ventilation rate	
Others	
Myxoedema (idiopathic alveolar hypoventilation)	
Oxygen therapy in chronic hypoxia	

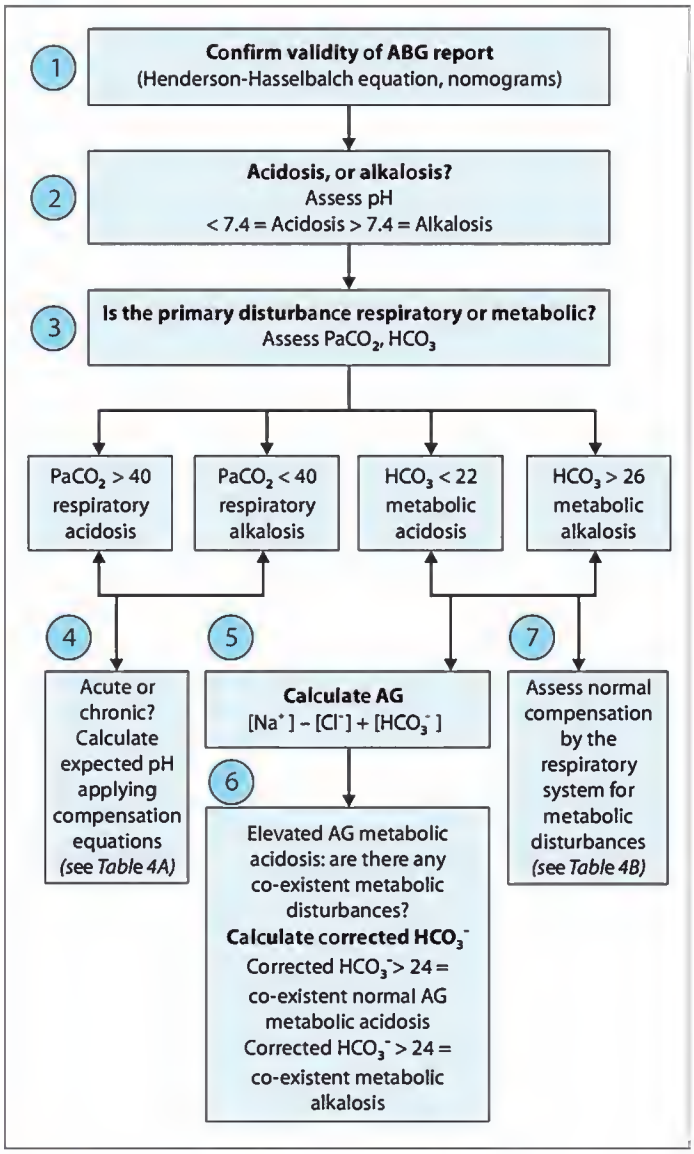


Figure 1: Stepwise approach for interpretation of an arterial blood gas (ABG) analysis report and assessment of acid-base status.

AG = Anion gap; $PaCO_2$ (mmHg); HCO_3^- (mEq/L)

Step 4: For respiratory disturbance: acute or chronic?

In acute respiratory disturbances, a $PaCO_2$ variation from normal by 10 mmHg is accompanied by a pH shift of approximately 0.08 units. In chronic respiratory disturbances, renal compensation and bicarbonate shift requires several hours to develop and is likely to be maximal after 4 days. Thus, during chronic respiratory disturbances, a $PaCO_2$ variation from normal by 10 mmHg is accompanied by a pH shift of only 0.03 (**Table 4A**). If the expected values and the actual values match, a mixed disorder is unlikely. If the expected values and the actual values differ, a mixed disorder is present.

Step 5: For metabolic acidosis, calculating the anion gap

The AG should be measure in all patients with metabolic acidosis. For the purposes of routine clinical use, AG greater than 12 is considered to be elevated AG. Causes of *elevated AG* metabolic acidosis can be remembered with the mnemonic **MULEPAKIR** [**M** = methanol poisoning; **U** = uraemia; **L** = lactic acidosis; **E** = ethylene glycol poisoning; **P** = paraldehyde ingestion; **A** = aspirin overdosage; **K** = ketoacidosis (diabetic keotacidosis; alcoholic ketoacidosis and starvation); **I** = isoniazid overdosage; and **R** = rhabdomyolysis].

Serum albumin level has important bearing while calculating the AG. Albumin has a negative charge on its surface and accounts for a significant proportion of the unmeasured anions (**Table 5**). A 50% reduction in the serum albumin concentration will result in a 75% reduction in the AG. In patients with severe hypoalbuminaemia, eventhough elevated AG metabolic acidosis is actually present, the measured AG may be less than or equal to 12. So, in a patient with severe hypoalbuminaemia if the AG increases and approaches 12, an additional metabolic cause for the increased AG must be suspected and looked for.

Two methods are used to correct the AG for the influence of albumin in patients with hypoalbuminaemia. The expected AG is calculated using the serum albumin and phosphate concentrations, as follows:

$$\text{Expected AG (mEq/L)} = (2 \times \text{albumin [g/dL]}) + (0.5 \times PO_4 \text{ [mg/dL]})$$

The expected AG is then compared with the AG calculated using the formula ($Na^+ - [Cl^- + HCO_3^-]$). If the calculated AG is found to be more than the expected AG, the difference is attributed to unmeasured anions from non-volatile acids.

Alternatively, adjusted AG can be calculated using the formula:

$$\text{Adjusted AG} = \text{Calculated AG} + 2.5 \times [4.5 - \text{measured albumin (g/dL)}]$$

Conditions causing normal AG acidosis (≤12) can be remembered by the acronym **ACCRUED** (**A** = acid infusion; **C** = compensation for respiratory alkalosis; **C** = carbonic anhydrase inhibitors; **R** = renal tubular acidosis; **U** = ureteral diversion; **E** = extra-alimentation or hyper-alimentation; **D** = diarrhoea). Normal AG metabolic acidosis can also be grouped as per the serum potassium levels. Causes of normal AG acidosis with a normal to high potassium include hyperaldosteronism, type IV renal tubular acidosis (RTA), moderate degree of renal failure, administration of hydrochloric acid and post-hypocapnia. Normal AG acidosis with a low potassium level can be seen in proximal type II RTA and distal type I RTA.

When urine electrolytes are available, assuming a urine pH of less than 6.1 and euvolaemia, urinary AG, [calculated as urinary $(Na^+ + K^+) - Cl^-$] can help in distinguishing renal from non-renal causes. A negative urinary anion gap indicates a non-renal cause of acidosis (e.g. diarrhoea).

Others

Delta ratio is also useful in the assessment of elevated anion gap metabolic acidosis to determine if a mixed acid-base disorder is present. *Osmolar gap* is also useful in differentiating the causes of elevated AG metabolic acidosis. Osmolar gap is calculated by subtracting the calculated serum osmolality from measured osmolality using the formula shown below:

$$\text{Calculated osmolality} = 2[Na^+ \text{ (mEq/L)}] + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{Blood urea nitrogen (mg/dL)}}{2.8}$$

$$\text{Osmolar gap} = \text{Measured osmolality} - \text{Calculated osmolality}$$

Osmolar gap > 10 mOsm/L is considered abnormal when calculated using this formula. Conditions causing increased osmolar gap metabolic acidosis include ethanol, ethylene glycol, methanol, acetone and propylene glycol poisoning. While a high AG, high osmolar gap metabolic acidosis is seen in methanol and ethylene glycol poisoning, normal AG, high osmolar gap metabolic acidosis is seen in isopropyl alcohol poisoning.

Step 6: Determining whether other metabolic disturbances co-exist with an elevated anion gap acidosis

A normal AG acidosis or a metabolic alkalosis may exist concurrently with an elevated AG acidosis. In this situation, corrected bicarbonate should be calculated as follows:

$$\text{Corrected } HCO_3^- = \text{measured } HCO_3^- + (AG - 12)$$

where, AG = anion gap

If the corrected HCO_3^- is greater than 24, a metabolic alkalosis co-exists; if it is less than 24, then a normal AG metabolic acidosis co-exists.

Step 7: Assessing the normal compensation by the respiratory system for a metabolic disturbance

In simple metabolic acidosis, the measured $PaCO_2$ will fall within the range predicted by Winter's formula (**Table 4B**). If a concurrent respiratory disturbance is also concurrently present, it would be defined by the direction the $PaCO_2$ varies beyond the range predicted by Winter's formula rather than the $PaCO_2$ variation from the normal value of 40.

In metabolic alkalosis, the magnitude of respiratory compensatory response is not easily predictable because degree of $PaCO_2$ increase does not exhibit an exactly linear relationship with the HCO_3^-. However, for practical purposes, the following equation has been found to be useful to calculate the expected:

$$PaCO_2 = [0.7 \times (HCO_3^-) + 21] \pm 2$$

In compensated metabolic alkalosis, the measured $PaCO_2$ is equivalent to the expected $PaCO_2$. If the measured $PaCO_2$ is higher than the expected $PaCO_2$, the respiratory compensation is not adequate, and the condition is termed as a primary metabolic alkalosis with a superimposed respiratory acidosis. In primary metabolic alkalosis with a superimposed respiratory alkalosis, the $PaCO_2$ is lower than the expected.

TREATMENT

The aetiological causes responsible for acid-base disturbances largely determine the status and prognosis in patients with acid-base disorders. Therefore, it is essential to recognise the underlying cause responsible for the disturbance so that specific treatment can be instituted.

Metabolic Acidosis

Metabolic acidosis may induce a wide range of adverse clinical effects, some of which may be life-threatening. In life-threatening metabolic acidosis, exogeneous alkali therapy aims to prevent or reverse the detrimental consequences of severe acidaemia affecting the cerebral, respiratory, metabolic and cardiovascular systems. Intravenous sodium bicarbonate is the mainstay of alkali therapy and should be given judiciously in amounts that will return blood pH to a safer level of about 7.20. The distribution of HCO_3^- being 40% of the body weight, the amount of HCO_3^- required to return the serum concentration to normal can be calculated as follows:

$$HCO_3^- \text{ deficit} = \text{Body weight (kg)} \times 0.4 \times (\text{desired } HCO_3^- - \text{measured } HCO_3^-)$$

Except in situations of extreme acidaemia, sodium bicarbonate should be administered as an infusion rather than a bolus; about 30 minutes must elapse following the completion of the infusion before its clinical effect can be judged. One-half of the calculated deficit can be replaced in 3 to 4 hours, if severe heart failure is not present. Subsequently, monitoring of the patient's acid-base status will determine additional alkali requirements. Alterations in respiratory function, dyselectrolytaemia (especially hypokalaemia) and hypo-tension must be recognised and treated. Specific therapy is required in the setting of poisoning and overdosage. Chronic metabolic acidosis (e.g. chronic kidney disease) is treated with oral sodium bicarbonate.

Metabolic Alkalosis

Metabolic alkalosis is usually mild; when severe (pH >7.6) or rapidly developing it may be life-threatening. The chloride-responsive metabolic alkalosis can be treated with intravenous

saline administration. When alkalosis is severe, or there is a risk of volume overload, 1N hydrochloric acid administration may be required. Chloride-unresponsive alkaloses are more difficult to treat and treatment is directed at the underlying cause.

Respiratory Acidosis

Treatment of respiratory acidosis is directed at improving ventilation using non-invasive or invasive ventilatory strategies; administration of bicarbonate can be harmful and should be avoided.

Respiratory Alkalosis

Treatment of respiratory alkalosis should be directed towards the underlying cause, identification and correction of electrolyte abnormalities that usually co-exist. Usually, re-assurance, re-breathing from a bag or treating the underlying psychological stress is enough to alleviate respiratory alkalosis. Controlling fever, seizure activity and sepsis will also help.

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7.5 Enteral and Parenteral Nutrition in Critically Ill Patients

Shilpa S Joshi

Feeding is not considered medical therapy under ordinary circumstances. But when patients are critically ill and cannot eat themselves food takes the form of medical therapy.

The incidence of hospitalised malnutrition is well documented, especially in critically ill patients. Despite the advances in medicine, definitive indications for the use of nutritional support are unclear. Use of enteral and parenteral therapies should be widespread for various reasons:

1. Protein calorie malnutrition is common in a variety of hospitalised patients.
2. Documented association between malnutrition and increased morbidity and mortality.
3. It seems intuitive that well-nourished patients would respond more favourably to therapeutic interventions than malnourished patients.
4. Nutritional support can be provided safely to a wide variety of patients.
5. Several randomised prospective clinical trials showed that nutritional support benefits the patients.

Therefore, there is a clear-cut evidence base for the role of enteral and parenteral therapies in hospitalised as well as critically ill patients.

Nutritional support is a delivery of formulated enteral or parenteral nutrients to appropriate patients for the purpose of maintaining/restoring nutritional status.

ENTERAL NUTRITION

By definition, enteral nutrition means 'within or by the way of gastrointestinal (GI) tract'. In practice, enteral nutrition is generally considered tube feeding. The consensus of nutritional experts is that the GI tract is more physiologically and metabolically effective than the intravenous route for nutrient utilisation. Any disease process that adversely affects oral intake may ultimately lead to significant nutritional deprivation and depletion. Patients who cannot eat, will not eat, or should not eat, yet who have adequate function of the GI tract, are candidates for enteral tube feeding.

Once the patient has been assessed and found to be a good candidate for enteral nutrition, the clinician selects the appropriate tube and route of access for tube placement. Enteral access selection depends on several factors as given below:

1. Anticipated length of time for which enteral feeding will be required
2. Degree of risk for aspiration or tube displacement
3. Presence or absence of normal digestion and absorption
4. Whether or not there is a planned surgical intervention
5. Administration issues such as formula viscosity and volume.

Advantages of Enteral Feeding

Various advantages of enteral feeding are: (i) it is a preferred route of nutrition support as it is more physiologic, (ii) cost-effective, (iii) safe, (iv) fewer side-effects as compared to parenteral nutrition, (v) maintenance of GI immune barrier, (vi) avoidance of central catheter related complications. The indications for enteral feeding are listed in **Table 1**.

Table 1: Indications of Enteral Feeding

Oral intake inadequate or contraindicated	Mechanical: stroke, central nervous system Disorders, coma, oropharyngeal and oesophageal disorders, partial or complete oesophageal or gastric obstruction Poor appetite: chemotherapy, radiation therapy, drug effect, nausea Transitional feeding: advance from parenteral to oral intake Psychological: anorexia nervosa, depression, Alzheimer's disease
Increased nutritional requirements	Burns, trauma, sepsis, surgical or medical stress
Digestive and absorptive disorders	Inflammatory bowel disease, short bowel syndrome, pancreatitis, irradiated bowel, proximal and distal intestinal fistulae, immunocompromised syndromes
Metabolic and excretory disorders	Glycogen storage disease, hepatic encephalopathy, renal disease

Contraindications of Enteral Feeding

Enteral feeding is contraindicated in patients with peritonitis, distal intestinal obstruction, intractable vomiting or severe diarrhoea.

ASSESSMENT OF NUTRITIONAL NEEDS OF A PATIENT

Before initiation of feedings, assessment of nutritional status of every patient is fundamental and includes some key components: nutritional history, anthropometric procedure, clinical examination, biochemical data, evaluation of weight loss and previous nutrient intake before admission, level of disease severity, co-morbid conditions, and function of the GI tract.

Assessment of these parameters will help to document presence of malnutrition and will help clinician to select best method for providing nutrients and allows objective monitoring of nutritional efforts. These assessment are also needed to estimate caloric protein, micronutrient requirement and also help to select/make right kind of formula.

FORMULA COMPOSITION

Energy

The target goal of enteral nutrition (defined by energy requirements) should be determined and clearly identified at

the time of initiation of nutritional support therapy. Energy requirements may be calculated by Harris Benedict equation, which is as follows:

Males (kJ/day): REE = 278 + 58 (Wt) + 21 (H) -28.5 (Af) x SF

Females (kJ/day): REE = 2734 + 40 (Wt) + 7.7 (H) -19.7 (Af) x SF

where, kJ = Kilo Joules; REE = Required energy requirement; Wt = Weight in kilograms; H = Height in meters, Af = Activity factor, and SF = Stress factor

Values for activity factor and stress factor for various diseases to be considered as standard are given below:

Activity factor (AF)	**Stress factor (SF)**
Bed rest = 1.0	*Post-operative with complication = 1.24*
Ambulatory = 1.1	*Skeletal trauma = 1.1-1.3*
Active = 1.2-1.3	*Sepsis = 1.3-1.6*
	Cancer = 1.2

where, 1 calorie is about 4.185 kJ.

Efforts to provide more than 50% to 65% of goal calories should be made to achieve the clinical benefit of enteral nutrition over the first week of hospitalisation. Studies suggest that more than 50% to 65% of goal calories may be required to prevent increases in intestinal permeability in burn and bone-marrow transplant patients, to promote faster return of cognitive function in head injury patients and to improve outcome from immune modulating enteral formulations in critically ill patients.

If unable to meet energy requirements (100% of target goal calories) after 7 to 10 days by the enteral route alone, consider initiating supplemental parenteral nutrition. Initiating supplemental parenteral nutrition before this 7 to 10 days period in the patients already on enteral nutrition does not improve outcome and may be detrimental to the patient.

Proteins

Proteins in the diet serve as a source of amino acids that body cannot make (essential amino acids) and provide nitrogen for the synthesis of other amino acid (non-essential amino acids). Insufficient protein intake can potentially affect all aspects of a patient's care, for example, it can lead to muscle atrophy and can make it difficult to wean off the patient from ventilator. In addition to the importance of adequate amounts of protein is the quality of protein.

Proteins can be modified in various ways in enteral formulation, for example intact protein, hydrolysed protein, amino acids. Intact proteins and protein isolates requires normal pancreatic enzymes to catabolise them into small polypeptides and free amino acids.

Hydrolysed protein formulas can be directly absorbed into the blood stream. These feeds can be administered when the feeds are administered via jejunum and where only absorption of proteins takes place.

IMMUNOMODULATORY AGENTS

Glutamine and Branched Chain Amino Acids

Glutamine and branched chain amino acids are amino acids found in skeletal muscles. These have been identified as key amino acids in preserving nitrogen balance during stress and injury. Numerous studies have indicated that glutamine is necessary to maintain integrity of intestinal mucosa, immune function of lymphocytes to preserve muscle glutamine pool and to improve overall nitrogen balance.

Arginine

Arginine is a conditionally essential amino acid, i.e. it can be conditionally essential after injury. Human and animal studies have shown that increased intake of arginine after trauma decreases nitrogen losses and accelerate wound healing.

Standard formulas contain arginine in the amount of 1 g and 2 g/L. Arginine enriched formulas contain 14 to 15 g/L.

Nucleotides

Nucleotides are added to some formulas as immunity enhancers. In animals, dietary supplementation of nucleotides has shown to facilitate growth and maturation of developing gut.

Agents such as ribonucleic acid (RNA) nucleotides increase total lymphocyte count, lymphocyte proliferation and thymus function.

Taurine

Taurine is conditionally essential nutrient since it can be synthesised by dietary cysteine or methionine.

EPA-DHA

Omega-3 fatty acids eicosapentaenoic acid and docosohexaenoic acid displace omega-6 fatty acids from the cell membranes of immune cells. This effect reduces systemic inflammation through the production of alternative biologically less active prostaglandins and leukotrienes.

Patients with acute respiratory distress syndrome and severe acute lung injury should be placed on an enteral formulation characterised by an anti-inflammatory lipid profile (i.e. omega-3 fish oils, borage oil) and antioxidants.

High Nitrogen Products

These have increased proportions of branched chain amino acids. These products are used for patients with catabolic stress.

Most of formulas contain a non-protein kcal: nitrogen ratio of 150:1 (with ranges between 100:1–200:1) which is thought to be optimal for patients.

Most of the enteral formulations offer high nitrogen products. Patients who do not need high nitrogen formulas are likely to use amino acids for energy and increase urea production. As a result this formula should be given carefully to renal patients.

Carbohydrates

Carbohydrates (CHO) provide 30% to 90% of total calories of enteral formulas and in most of the formulas these are the principle source of energy. The main difference among the formulas is the form and composition of CHO. In general, the longer carbohydrate molecule are less osmotic, taste less sweet are require more digestion than the shorter ones.

Lactase deficiency is most prevalent disaccharide deficiency and hence, most of the enteral formulas are lactose free.

Fibre

Enteral formulas containing fibre may have potentially clinical applications including ameliorating constipation and tube feeding-associated diarrhoea, improving mucosal healing in inflammatory bowel disease, supporting gut barrier of critical ill patient and increasing intestinal adaptation in short bowel

syndrome. Predominant source of fibre of enteral formula is soya derived polysaccharides.

Soluble fibre may be beneficial for the fully resuscitated, haemodynamically stable critically ill patient receiving enteral nutrition who develops diarrhoea. Insoluble fibre should be avoided in all critically ill patients. Both soluble and insoluble fibre should be avoided in patients at high-risk for bowel ischaemia or severe dysmotility.

Lipids

Fat is a dense source of energy and also serves as a vehicle for fat soluble vitamins and essential fatty acids. Most of the enteral formulas contain vegetable oil as primary source of fat. Vegetable oil is also a good source of essential fatty acids. Fat does not contribute to osmolality of enteral formula.

Long Chain Triglycerides

Vegetable oils are predominant source of fat in enteral formulas. Long chain triglycerides are slowly cleared from blood stream and require carnitine for its absorption.

Medium Chain Triglycerides (MCTs)

MCTs are 6 to 12 carbon long and are usually prepared from palm kernel or coconut oil. They offer many advantages over long chain triglycerides, as they are absorbed intact without appreciable pancreatic or biliary function and are subjected to more rapid clearance from blood stream. They are transported to the liver principally via portal venous system where they cross mitochondrial membrane and can be oxidised independent of carnitine. These should not be used in patients who are prone to high ketone levels as they produce ketone.

Vitamins, Minerals and Trace Elements

A combination of antioxidant vitamins and trace minerals should be provided to all critically ill patients receiving specialised nutritional therapy.

Supplemental vitamins and minerals should be given when quantity of formula does not fulfil the requirement.

Water

Fluid balance in patients receiving enteral nutrition should be monitored. The daily water requirement for a healthy adult is 1 mL/kcal taken for approximately 30 to 32 mL/kg. Minimum of 30 mL of water every 6 hours is recommended as a flush for tube patency alone.

Probiotics

Administration of probiotic agents has been shown to improve outcome (most consistently by decreasing infection) in specific critically ill patient populations involving transplantation, major abdominal surgery, and severe trauma. No recommendations can currently be made for use of probiotics in the general intensive care unit population because of a lack of consistent outcome effect.

PHYSICAL CHARACTERISTICS OF A FORMULA

Osmolality

Osmolality is a physical phenomenon of net permeability resulting in equilibrium across the cell membrane. It is a measure of concentration of free particles, molecule or ions in a given solution in water. These particles include electrolytes, minerals, carbohydrates, proteins or amino acids and are expressed in milli osmoles per kilogram of water. All nutrients and dietary components except water contribute to osmolality solution. It has been widely thought that isotonic formulas (osmolality ranging from 280 to 320 milli osmoles/kg) are tolerated well than hyper or hypotonic formulas.

Renal Solute Load

Renal solute load refers to the constituents in the formula that must be excreted by the kidneys. Protein, sodium, potassium, and chloride are the major constituents of enteral formulas that contribute to the renal solute load. It is important, as there is obligatory water loss with each unit of solute.

Nutritional Formulations

A wide variety of commercially prepared formulas with variable sources and concentrations of protein, carbohydrate and fat are currently available.

Polymeric Formulas

Polymeric formulas are composed of intact proteins, disaccharides and polysaccharides and variable amount of fat. The osmolality of polymeric formula is usually lower than that of elemental formulas. These formulas require a functioning GI tract for digestion and absorption of nutrients. Polymeric formulas can be further subdivided into hypercaloric formulas, normocaloric formulas, etc.

Pre-Digested Formulas

Pre-digested formulas are composed of low molecular nutrients, have minimal residue and are thought to lead less stimulations of pancreatic and GI secretion and are less allergic than other formulas. These formulas have greater osmolalities than the polymeric formulas because of the small molecule weight of nutrients.

Modular Products

Individual macro-nutrients modules, such as glucose polymers, proteins, and lipids, are available as additives to foods and enteral formulas to change overall fuel composition.

Disease Specific Formulas

These products are designed for patients who have specific medical conditions that may require nutrient modifications.

Formula Selections

Selection of appropriate formulas is based on patient's medical and nutritional status, digestive and absorptive capabilities indicate whether pre-digested or polymeric formulas can be used.

Administration of Tube Feeding

Proper administration of enteral formulas ensures safe delivery of desired nutrients, enhanced patient tolerance and optimal nutritional support. There are various methods of feeding the patients. Choice of technique depends upon GI function, feeding site, and ultimately patient's response.

1. ***Bolus feeding***

   Bolus feeding is rapid administration of large volumes of formula over a short period of time usually by syringe. This form of feeding is least cumbersome but is associated with

increased possibility of aspiration, regurgitation and GI side-effect. A rate of 30 mL/min or a volume of 500 to 750 mL per feed appears to mark physical tolerance limit.

2. ***Continuous feeding***

   Continuous infusion is controlled delivery of prescribed volume of formula at a constant rate over a continuous period of time using infusion pumps or gravity assisted sets. This method is considered advantageous since gastric cooling is minimised and few GI tract side effects are experienced. Continuous infusion into jejunum is more analogous to normal gastric emptying.

3. ***Intermediate infusions***

   In intermediate feeding, total quantity of formula needed for 24 hours is divided into equal portions and required fractions are administered in 3 to 6 feedings. Each feeding is administered over 30 to 90 minutes period.

Techniques of Feeding

1. Selection of appropriate formulas.
2. Elevate the head of the patient's bed to at least 30 degree to horizontal levels before feeding begins.
3. Aspirate through nasogastric or gastrostomy tube before initiating feeding to determine whether retained gastric secretions are present.
4. Begin feeding schedule of 100 to 150 mL of isotonic or slightly hypertonic formulas every 4 hours.
5. Increase formula amount by 50 mL every 1 or 2 feeding up to 450 mL every 4 hours.
6. Flush the tube at least with 30 mL of water after feeding and every 4 hours to maintain patency.

Complications of enteral feeding are shown in **Table 2**.

Table 2: Complications of Enteral Feeding

Mechanical complications	Blockage of tube Dislocation of tube Aspiration pneumonia
Gastrointestinal complications	Delayed gastric emptying Constipation Malabsorption

PARENTERAL NUTRITION

Parenteral nutrition is a form of intravenous therapy that provides opportunity to replenish or maintain nutritional status. Parenteral nutritional was originally developed to nourish those whose GI tract was not capable of digesting and absorbing nutrients.

Central parenteral nutrition is delivery of nutrients through the large diameter vein usually subclavian or superior vena cava. Peripheral parenteral nutrition is usually delivered through small veins usually in the forearm. Central parenteral nutrition is indicated when volume and concentration of solution preclude peripheral administration and when anticipated duration of therapy is greater than 7 days to 2 weeks and when substantial depletion of body fat and protein has occurred. Peripheral parenteral nutrition is preferred when solution concentration is less than 1000 mOsm/L and duration of therapy is less than 10 days.

RATIONAL OF PARENTERAL NUTRITION

1. The patient is well nourished before admission but after 7 days of hospitalisation enteral nutrition has not been feasible or target goal calories have not been met consistently by enteral alone.
2. On admission, the patient is malnourished and enteral nutrition is not feasible.

   A major surgical procedure is planned, the pre-operative assessment indicates that enteral nutrition is not feasible through the peri-operative period and the patient is malnourished.
3. Indications: The basic indications for the use of parenteral nutrition are required for nutrition when the GI tract is either not working or not available or not appropriate (**Table 3**).

Table 3: Indications for Parenteral Nutrition

Non functioning gut, e.g. paralytic ileus
Malnourished patients after major abdominal surgery
Severe mucositis systemic chemotherapy, upper gastrointestinal strictures or fistulae and acute pancreatitis
Patients with major resections of the small intestine (short bowel syndrome) before compensatory adaptation occurs
Patients in the intensive care unit with systemic inflammatory response syndrome or multiple organ dysfunction syndromes.

PARENTERAL MACRONUTRIENTS

Proteins/Amino Acids

The primary function of protein in parenteral nutrition is to maintain nitrogen balance, thus, preventing skeletal muscle from being degraded from gluconeogenesis. Protein requirement can be very high during intensely catabolic state. A positive nitrogen balance may not be feasible during the first few days of the catabolic stress. A positive caloric balance is necessary to establish a positive nitrogen balance. For delivered amino acids to be incorporated into new protein rather than catabolise the ratio of non-protein calories to gram of nitrogen should approach 150:1. This ratio is based on the fact that 10% to 15% or more of required calories during catabolism are derived from protein breakdown.

Commercial amino acids are available. Dilute solutions are most often used for peripheral administration. Amino acid profiles of parenteral solutions are based on Food and Agriculture Organisation – World Health Organisation (FAO-WHO) recommendations for optimal proportion of essential amino acids.

Carbohydrates

Primary function of parenteral carbohydrate is to serve as energy source. Optimum carbohydrate is an amount adequate to spare protein without exacerbating hyperglycaemia. Commercial carbohydrates consist of N-hydrate, dextrose monohydrate in sterile water.

Fats

Parenteral lipids provide as a source of essential fatty acids and calories. These can be substituted for dextrose calories for patients with glucose intolerance or used as concentrated caloric source for patients who require volume restriction. Fats

have lower respiratory quotient than carbohydrates, which is a rational for use of lipids to provide large proportion of non-protein calories in patients with respiratory failure. Because fat emulsions are isotonic, these can be administered through peripheral vein. Alternatively these may be directly added to parenteral nutritional solution.

Electrolytes

Electrolytes requirement for patients receiving total parenteral nutrition may vary depending on body weight, presence of malnutrition or catabolism, the degree of electrolyte depletion, change in organ function, ongoing electrolyte losses and disease process.

Vitamins

Vitamin requirements during parenteral nutrition therapy are uncertain because these are not based on balanced studies. Recommendations for parenteral nutritional therapy have been made by American Medical Association—Nutrition Advisory Group.

Water

Water requirements vary depending on the capacity of patient to excrete an osmotic load. Usually requirements are 30 ml/kg in normal adult or approximately 1 ml/kcal delivered. An additional 360 ml per day is recommended for each centigrade of temperature elevation. Also 300 to 400 ml of water per day may be necessary for new intra-celluloid fluid, if anabolism is being induced.

Restriction of water is necessary during volume overload and presence of hyponatraemia. Patients who become hyperosmotic may need additional free water on daily basis.

Trace Elements

Trace elements are those nutrients that make-up less than 4 g or 0.01% of total body content. Individual trace elements may be supplemented in appropriate dose as specific patients deficiency dictates.

Osmolality and Osmolarity

While osmolality is most often used in reference to enteral feeding, osmolarity is preferred term for parenteral solutions. Body maintains serum osmolality between 280-300 mOsm/kL. To avoid the irritation to veins, solutions with osmolarity greater than 900 mOsm/L are not usually administered peripherally.

Initiation of Parenteral Nutrition

Prior to initiation of parenteral nutrition, a baseline biochemistry profile should be checked and fluid and electrolyte abnormalities should be corrected.

Monitoring

During the first week of parenteral nutrition (and subsequently if patient is unstable with respect to fluid and electrolyte or metabolic issues) the patient should be monitored intensively.

Reintroduction of Diet

Diet should be reintroduced in a graded fashion.

COMPLICATIONS

The complications of parenteral therapy can be divided into three categories: (i) *technical*—pneumothorax, malposition, subclavian artery puncture, air embolism etc; (ii) *septic*—catheter related sepsis, septic thrombosis; and (iii) *metabolic* – hyperglycaemia, hypoglycaemia, hyperkalaemia, hypophosphataemia, etc. With proper patient monitoring, most of these complications can be minimised.

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7.6 Acute Respiratory Failure

Ashit M Bhagwati

INTRODUCTION

Respiratory system is responsible for gas exchange in the human body. Inability to maintain a normal state of gas exchange leads to respiratory failure. Disorders involving the respiratory centre in the brain, peripheral nerves, respiratory muscles, airways, pleura, lung parenchyma and the chest wall can lead to compromise of gas exchange; thereby leading to a clinical scenario of acute respiratory failure (ARF). ARF is one of the most common life-threatening disorders encountered in the intensive care unit (ICU) and is associated with poor prognosis.

DEFINITION

Clinically, respiratory failure occurs when hypoxaemia (PaO_2 is less than 60 mmHg), i.e. inadequate oxygenation of the blood or hypercarbia (arterial PCO_2 is >50 mmHg), i.e. excess content of circulating carbon dioxide; or frequently, a combination of both types of gas exchange abnormalities occur.

CLASSIFICATION

ARF is classified as hypoxaemic respiratory failure (type 1), hypercapnic respiratory failure (type 2), post-operative/peri-operative respiratory failure (type 3) and shock-related respiratory failure (type 4).

Respiratory failure is also classified as per its onset; acute or chronic respiratory failure. ARF refers to disorders of recent onset (hours to days). It suggests that respiratory failure has developed too rapidly for physiologic compensation to occur; therefore, pH is less than 7.3. Chronic respiratory failure develops overmonths to years, allowing compensatory mechanisms to improve oxygen transport and to buffer respiratory acidaemia; therefore the pH is slightly decreased. Sometimes, ARF may be superimposed on chronic respiratory failure.

HYPOXAEMIC (TYPE 1) RESPIRATORY FAILURE

Hypoxaemic respiratory failure (type 1) is defined as a condition in which the respiratory system exhibits a failure in its gas exchange function of oxygenation, PaO_2/FiO_2 <200, respiratory rate >35 breaths/min and with active use of accessory muscles of respiration. It is also associated with a normal or low $PaCO_2$. The underlying physiologic aberration results from a disease process that involves the lung itself such as a ventilation-perfusion (V/Q) mismatch, shunting or diffusion impairment. The classic example of acute hypoxaemic respiratory failure is acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).

Aetiology

Type 1 ARF is usually seen in diseases of the lung parenchyma, cardiovascular system and lower airways. The causes are due to low inspired concentration of oxygen (alveolar hypoventilation), impairment of diffusion, VA/Q mismatch, intrapulmonary shunting and low mixed venous oxygen content (**Table 1**).

Table 1: Aetiology of Type 1 Respiratory Failure

Respiratory System

Airway disease: Asthma, COPD

Parenchymal:

Airspace: Pneumonia (bacterial, viral, mycoplasmal, fungal), atelectasis, bronchiectasis, and tumours

Vascular: Pulmonary embolism, fat embolism, pulmonary arterial hypertension

Pleura: Pneumothorax

Chest Wall: Flail chest

Cardiovascular System

Pulmonary oedema (cardiac failure), cyanotic congenital heart disease

Miscellaneous: Obesity

Physiology

The process of gas exchange has two components: the flow of gas between the atmosphere and the terminal airways; and the diffusion of gases between the terminal lung regions and the pulmonary capillary blood. The efficiency of gas exchange can be evaluated clinically by measuring the PA_{O_2}, $PaCO_2$ and the alveolar-arterial (A-a) PO_2 gradient. Thus, patients with hypoxaemia may be divided into those with a normal gradient and those with an increased gradient (**Table 2**). The alveolar PO_2 can be calculated from the alveolar air equation:

$$PA_{O_2} = (PB - PH_2O)\, FiO_2 - (PaCO_2/R)$$

here, PA_{O_2} is alveolar PO_2; FiO_2 is fraction of inspired oxygen;

PB is barometric pressure (760 mmHg at sea level), PH_2O is water vapour pressure (47 mmHg at sea level), and R is respiratory exchange ratio (assumed to be 0.8).

Ventilation-perfusion mismatch and intrapulmonary shunting are the clinically important causes of hypoxaemia in ARF.

Ventilation-Perfusion Mismatch

In the presence of disease, the V/Q units vary. The low V/Q units contribute to hypoxaemia and hypercapnia as compared to high units where wastage of ventilation may occur without affecting the blood gases unless quite severe. If the patient is given 100% oxygen to breathe, there is a dramatic increase in the PaO_2 as it eliminates low V/Q units, thereby correcting the hypoxaemia.

Intrapulmonary Shunts

Normally in health some degree of intrapulmonary shunting does occur, i.e. referred to as anatomical shunt accounting for 2% of the shunt. In addition, cyanotic congenital heart diseases or A-V malformations in the lungs cause right-to-left shunt.

When the deoxygenated blood bypasses the ventilated alveoli and mixes with the oxygenated blood that has perfused the ventilated alveoli, reduction in the arterial content of oxygen occurs, i.e. hypoxaemia (PaO_2 level decreases). Such situation

occurs in conditions such as pneumonia, atelectasis and severe pulmonary oedema of either cardiac or non-cardiac origin. Hypercapnia occurs when the shunt exceeds > 60%.

In low V/Q mismatch and intrapulmonary shunting, the decreased PaO_2 is always associated with an elevated P (A-a) oxygen gradient. In patients with low V/Q mismatch, the PaO_2 has a dramatic rise in response to 100% oxygen, whereas in patients with intrapulmonary shunting, it shows a much smaller response. Differentiating between these causes of hypoxaemia is important clinically (**Table 2**).

Table 2: Physiological Conditions Causing Type 1 Respiratory Failure

Pathophysiology of Hypoxaemia	P (A-a) O_2 Gradient	$PaCO_2$
Low partial pressure of inspired oxygen	Normal	Normal or decreased
Low ventilation-perfusion mismatch	Increased	Normal or decreased
Right-to-left shunt	Increased	Normal or decreased
Diffusion impairment	Increased	Normal or decreased

ARDS is the classic example of severe hypoxaemic respiratory failure. The European American Consensus Conference on ARDS defined ALI and ARDS. ALI is a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic and physiologic abnormalities that cannot be explained by, but may co-exist with, left atrial or pulmonary capillary hypertension. The clinical criteria for ALI include: (i) acute onset of pulmonary failure, (ii) hypoxia with a PaO_2/FiO_2 ratio ≤300 mmHg, (iii) bilateral chest infiltrates visible on chest radiograph, and (iv) a pulmonary artery occlusion pressure ≤18 mmHg or no clinical evidence of increased left atrial pressure on the basis of chest radiograph and other clinical data.

On the other hand, ARDS is defined as a more severe form of ALI with a PaO_2/FiO_2 ≤200, regardless of the level of positive end-expiratory pressure (PEEP) used on the ventilator.

Clinical Manifestations

Manifestations of hypoxaemic respiratory failure are due to a combination of features of arterial hypoxaemia and tissue hypoxia. Arterial hypoxaemia causes hyperventilation due to stimulation of carotid body chemoreceptors, leading to dyspnoea, tachypnoea and hyperpnoea. There may be cyanosis; degree of cyanosis depends on the concentration of the haemoglobin and the patient's perfusion. Other features include generation of lactic acid due to anaerobic metabolism. Increased blood lactate levels may further stimulate ventilation. Mild hypoxia may also lead to impaired mental performance. With the progression of hypoxia alteration in the sensorium, somnolence, coma, seizures can occur leading to permanent brain damage.

Patient develops tachycardia, diaphoresis, and systemic vasoconstriction leading to hypertension. Severe hypoxia can lead to bradycardia, vasodilation, hypotension, myocardial ischaemia, infarction, arrhythmias and cardiac failure. The manifestations of hypoxia are further amplified in the presence of tissue hypoxia. Symptoms and signs also reflect not just acute hypoxaemia, but also the underlying cause of respiratory failure.

Chest radiograph may be normal initially but later on (in established cases) may show bilateral infiltration (interstitial, airspace or both). Arterial blood gas analysis is central to diagnosis and reveals hypoxaemia with normal, but usually a low PCO_2.

Criteria for Diagnosis of Acute Respiratory Distress Syndrome (ARDS)

1. Predisposing factors for ARDS, viz. sepsis, burns, pancreatitis, aspiration, malaria, leptospira, etc.
2. Tachypnoea, breathlessness, tachycardia, crackles on auscultation.
3. Progressive infiltrates in both the lung fields.
4. Normal pulmonary capillary wedge pressure.
5. Refractory hypoxaemia with PaO_2/FiO_2 ≤200.
6. Decreased lung compliance ≤40 mL/cm water.

HYPERCAPNIC (TYPE 2) RESPIRATORY FAILURE

Aetiology

Type 2 respiratory failure can result from abnormalities in any one component of the respiratory system including the brain, spinal cord, neuromuscular system, thorax, pleura and upper airways. Diseases of the lower airways (alveoli) or circulatory system are rare causes of type 2 respiratory failure (**Table 3**).

Table 3: Aetiology of Type 2 Respiratory Failure

Brain

Drugs: narcotics, barbiturates, sedatives, poisons, general anaesthetics

Metabolic: hyponatraemia, hypocalcaemia, hypercapnia, severe alkalosis, myxoedema

Infections: meningitis, encephalitis, bulbar polio, cerebral abscess

Neoplasms

Trauma

Central alveolar hypoventilation, obstructive sleep apnoea

Occult status epilepticus

Spinal Cord

Traumatic transection, compressive tumours, poliomyelitis

Neuromuscular

Drugs: neuromuscular blockers, aminoglycosides

Metabolic: hypokalaemia, hypophosphataemia, hypomagnesemia

Infections: tetanus, Guillain-Barré syndrome, sepsis

Trauma

Neoplasm

Myasthenia gravis

Others: critical illness neuropathy, muscular dystrophies, respiratory muscle fatigue

Upper Airways

Upper airway mass: adenoid hyperplasia, goiter, polyps, malignant tumours

Infections: epiglottitis, laryngotracheitis

Trauma

Others: bilateral vocal cord palsy, tracheomalacia, laryngeal oedema

Chest Wall

Trauma: Flail chest

Others: kyphoscoliosis, scleroderma and massive pneumothorax or pleural effusion

Physiology

The hallmark of acute hypercapnic respiratory failure is an elevated $PaCO_2$. Three processes, alone or in combination, can produce acute hypercapnic respiratory failure: a reduction in minute ventilation, an increase in CO_2 production and alveolar hypoventilation.

Reduction in minute ventilation can be affected by processes affecting the central nervous system, peripheral nervous system, neuromuscular junction, respiratory muscles, chest wall abnormalities, metabolic and electrolyte abnormalities, and upper airway obstruction. In these disorders alveolar-arterial oxygen pressure difference ($A\text{-}aDO_2$) is usually normal unless lung disease is present.

Excessive CO_2 production is usually due to fever, burns, sepsis, high carbohydrate diet, burns and hyperthyroidism. Agitation, myoclonus, or other causes of muscle activity can increase VCO_2 and contribute to type 2 respiratory failure. Increase in the respiratory quotient, which is normally 0.8-2.0 doubles VCO_2. Reduced CO_2 elimination also occurs due to decreased alveolar ventilation.

Alveolar hypoventilation may result from VA/Q mismatch (high VA/Q, increased physiological dead-space and wasted ventilation) as in pulmonary embolic diseases, intrinsic lung diseases (e.g. emphysema, asthma, cystic fibrosis or pulmonary fibrosis) and in chest wall disorders (e.g., scoliosis). Hypoventilation is characterised by hypercapnia and hypoxaemia. As minute ventilation reduces to less than 4 L/min, the $PaCO_2$ rises dramatically. Usually these patients have normal $A\text{-}aDO_2$ gradients.

Patients at risk of hypercapnic respiratory failure may also be divided into two major categories: those with normal lungs (e.g., sedative overdose, neuromuscular disorders or chest wall abnormalities) and those with intrinsic lung disease (e.g., emphysema, chronic bronchitis or asthma) where maldistribution of ventilation and perfusion results in an increase in dead space. The final result is inadequate CO_2 clearance despite normal or increased minute ventilation.

Clinical Manifestations

Patients with acute hypercapnic respiratory failure largely present with central nervous system (CNS) disturbances. Hypercapnia is a CNS depressant leading to lethargy, somnolence, coma, asterixis, restlessness, tremors, slurred speech, headache and papilloedema.

Symptoms of hypercapnia may overlap those of hypoxaemia. Basically, hypercapnic patients may have either decreased or increased minute ventilation depending on the primary disorder. As a result these patients have dyspnoea, tachypnoea, hyperpnoea with tachycardia and uncompensated respiratory acidosis.

Diagnosis

History is most important in diagnosis of ARF. It should aim at eliciting relevant information about possible predisposing factors, co-morbid conditions and identifying processes that affect prognosis. The clinical signs and symptoms of ARF reflect the underlying disease process and the associated hypoxaemia and hypercapnia. Diagnosis of respiratory failure requires arterial blood gas study, not only to determine the presence and severity of respiratory failure but also to differentiate between type 1 and type 2 respiratory failure.

POST-OPERATIVE/PERI-OPERATIVE (TYPE 3) RESPIRATORY FAILURE

Post-operative/peri-operative respiratory failure can be defined as the need for intubation and mechanical ventilation (MV) within the 48 hours after surgery. In the post-operative/peri-operative period, surgical patients following general anaesthesia often develop reduction in functional residual capacity leading to atelectasis in the dependent lung units. This leads to respiratory failure referred to as post-operative/peri-operative respiratory failure (**Table 4**). To avoid this situation, a proper pre-operative assessment is mandatory to identify the patients who are at increased risk after non-thoracic and thoracic surgery. These subgroup of patients are best managed with frequent change of posture, chest physiotherapy, adequate analgesia for post-operative pain relief. Non-invasive ventilation (NIV) also may be used to tide over the crises. However, evidence-based studies on the usefulness of respiratory physiotherapy, incentive spirometry and NIV to prevent respiratory complications are lacking.

Table 4: Aetiology of Type 3 Respiratory Failure

Intra-pulmonary Causes
Atelectasis, aspiration, pneumonia
Acute lung injury/acute respiratory distress syndrome
Volume overload/congestive heart failure
Pulmonary embolism
Asthma/Chronic obstructive pulmonary disease
Pneumothorax
Extra-pulmonary Causes
Upper airway obstruction
Obstructive sleep apnoea syndrome
Diaphragmatic dysfunction/phrenic nerve injury

SHOCK-RELATED (TYPE 4) RESPIRATORY FAILURE

Respiratory muscles consume less than 5% of the total cardiac output and oxygen delivery. Shock leads to increase in dead-space ventilation and pulmonary inflammation. The increase in dead-space ventilation is an early accompaniment of shock. It leads to hypoperfusion of the respiratory muscles, leading to respiratory muscle fatigue, causing a combined metabolic (lactic acidosis) and respiratory acidosis. Under this situation, more than 40% of the cardiac output is distributed to the respiratory muscles.

Intubation and MV help redistribution of the cardiac output to the vital organs while shock is being treated.

MANAGEMENT

The general principles of support are similar regardless of the type of respiratory failure. The priorities in the management of ARF vary according to the aetiology. However, the primary aim in all the cases are the same: (i) to maintain a patent airway and ensure adequate ventilation and oxygenation; and (ii) to treat, if possible, the primary condition. This includes removal of excessive secretions to maintain clear airway, use of aerosolised bronchodilators, antibiotics, viz. aminoglycoside (tobramycin),

colistin according to sensitivity pattern and effective systemic antimicrobials for the treatment of infections.

Hypoxaemic Respiratory Failure (Type 1)

Patients with acute hypoxaemic respiratory failure are best managed in the ICU. The management of these patients involves both supportive and specific strategies that are generally performed simultaneously. Supportive therapy is aimed at stabilising the clinical condition of the patient by improving gas exchange and includes airway management and correction of hypoxaemia. Hypoxaemia is corrected by oxygen administration and use of ventilatory support (non-invasive and invasive mechanical ventilatory support). Measures are also directed towards specific therapy for identifying and reversing the underlying pathophysiologic mechanisms. Specific therapy varies depending on the underlying disease (e.g. use of antibiotics to treat patients with pneumonia and diuretics for pulmonary oedema).

Oxygen therapy

Oxygen supplementation is the most important therapy for hypoxaemic respiratory failure. After the airway is secured, attention is directed to the management of hypoxaemia. The treatment goal is to provide adequate oxygen delivery to the tissues (SaO_2 >90% and PaO_2 ≥60 mmHg). Oxygen can be delivered by different means (nasal cannula for flow rates ≤ 5 L/min, face mask for flow rates ≥6 L/min or use of air entrainment devices, (i.e. venturi masks for higher flow rates). If the patient's condition does not improve with high-flow oxygen: MV, either invasive or non-invasive, should be considered.

Non-invasive ventilation

In last few years, substantial data has emerged on the use of NIV in patients with acute hypoxaemic respiratory failure to avoid endotracheal intubation and ventilator-associated pneumonia, thereby reducing mortality. However, despite emerging studies regarding NIV as an adjunct in the management of hypoxaemic respiratory failure, its safety and efficiency remains unanswered. This is mainly due to varied aetiologies in subgroups of patients causing respiratory failure. Recently, a few studies have focused on some of the individual diagnoses within the large category. It has been found to be very effective in cardiogenic pulmonary oedema. NIV may also be useful when some components or degree of cardiac decompensation participates in the clinical feature, even if it is not the main or only cause of episode of respiratory failure.

It should be noted that patients with hypoxaemic respiratory failure should preferably be ventilated with a full face mask during acute phase and may be shifted to nasal mask, once the condition stabilises.

Mechanical ventilation

The two major goals of therapy are to maintain alveolar ventilation and correct hypoxaemia. In cases where NIV fails to correct hypoxaemia, invasive MV is used. Patients with severe ARF and a large intrapulmonary shunting may require high FiO_2 while on the ventilator. MV increases alveolar ventilation, eliminates CO_2 and corrects acidaemia. Due to the danger of oxygen toxicity, patients should be treated with the lowest concentration of oxygen that provides adequate oxygenation.

Hypercapnic Respiratory Failure (Type 2)

Oxygen therapy

Hypoxaemia secondary to hypoventilation can be easily treated with by supplemental oxygen (increasing FiO_2). Failure of PaO_2 to improve should alert to the possibility of an unsuspected concomitant lung disease producing a shunt effect (e.g. pneumonia, atelectasis). In many patients with chronic ventilatory failure, especially chronic obstructive pulmonary disease (COPD), oxygen therapy can cause acute worsening of hypercapnia. Three mechanisms have been proposed to explain this phenomenon. These patients may have a 'blunted' CO_2 drive to breathe and the hypoxaemic drive is suppressed by supplemental oxygen. Oxygen may increase V/Q inequality by inhibition of hypoxic pulmonary vasoconstriction or by changing bronchomotor tone. Finally, haemoglobin affinity for CO_2 decreases with increasing oxygen saturation (Haldane effect), which may further contribute to hypercapnia. Therefore, supplemental oxygen therapy for ventilatory failure aims at maintenance of PaO_2 in a 'safe' range that does not compromise systemic oxygen delivery but minimises the possibility of worsening hypercapnia (SaO_2 of 90% to 92%).

Air entrainment oxygen masks (venturi masks) can be used to deliver precise doses of oxygen. If venturi masks are unavailable or are not feasible, a nasal cannula at flow rates of 0.5-2.0 L/min may be used to treat hypoxaemia (low-flow oxygen therapy). However, despite therapy, progressive hypercapnia and acidosis may develop in some patients and lead to confusion, stupor or coma, even when the FiO_2 is increased only moderately. Such patients may require tracheal intubation and MV.

Therapy in patients with asthma or COPD consists of oxygenation, hydration and aggressive treatment of the underlying aggravating factor with bronchodilators (theophyllin, anticholinergics and beta-agonists) and corticosteroids. Infection needs to be treated with appropriate antibiotics and any electrolyte abnormality must be corrected. In patients who progress to respiratory muscle fatigue, elective intubation and MV may be necessary to prevent respiratory arrest.

Non-invasive ventilation (NIV)

NIV is most commonly applied in acute hypercapnic respiratory failure commonly associated with COPD, where the ventilatory response to raised $PaCO_2$ is decreased.

Administration of NIV in patients with COPD with respiratory failure helps to increase the neural output to the diaphragm and other respiratory muscles, and thus, resets the respiratory control centre making it more responsive to an increased $PaCO_2$. These patients are then able to maintain a normal $PaCO_2$ throughout the daylight hours without the need for MV.

The use of NIV in patients with acute exacerbations of COPD is considered the ventilatory mode of choice. It helps by reducing the rate of endotracheal intubation. It also improves the vital signs, gas exchange, thereby reducing dyspnoea.

There is also reduction in the in-hospital mortality, with reduction in the complications like nosocomial pneumonia.

NIV may also be used in patients with acute exacerbations of bronchial asthma. Uncontrolled studies have reported improvements in gas exchange and low rates of intubation after

the initiation of NIV in patients with severe asthma. In another randomised trial, no benefit of NIV in asthma was demonstrated.

Although the use of NIV in asthma is inconclusive, a trial of NIV in selected patients is justified, particularly in patients who fail to respond promptly to medical treatment and have no contraindications.

It has also been suggested that aerosolised medicines may be delivered more effectively by NIV. However, NIV is not recommended for routine use in patient with asthma exacerbation.

Mechanical ventilation

Some patients with ventilatory failure may respond to early and aggressive management of the primary disorder. Others, with progressive pathology or whose loads are not rapidly reduced may require MV. Although no $PaCO_2$ absolutely mandates MV, if the pH is < 7.20 and if rapid reversal with therapy is not expected, or failure of NIV occurs or NIV is contraindicated, then prompt MV is initiated. Delayed MV in these patients increases the risk of circulatory collapse and other complications.

A common error in MV of a patient with acute on chronic respiratory failure is to reduce the $PaCO_2$ to normal (40 mmHg), which leads to a compensatory reduction in bicarbonate. On resumption of spontaneous breathing, patients who are chronically hypercapnic will retain CO_2 rapidly (to their previous pre-morbid level). As the kidneys require more time (24 to 48 hours) to compensate, an acute respiratory acidosis may ensue and impede liberation from MV. Accordingly, the ventilatory goal in patients with acute on chronic respiratory failure is not a normal $PaCO_2$ but rather a $PaCO_2$ approximating their baseline value when they are not acutely decompensated, at which the pH is normal range.

RECOMMENDED READINGS

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7.7 Sepsis and Acute Respiratory Distress Syndrome

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SEPSIS

Sepsis (derived from the Greek word *sepo* meaning "decay or putrefaction"), severe sepsis (acute organ dysfunction secondary to infection) and septic shock (derived from the French word *choquer* meaning 'to collide with'), are major health care problems world over. The incidence of sepsis and related syndromes is increasing and the conditions affect millions of individuals around each year.

DEFINITION OF SEPSIS AND RELATED SYNDROMES

Though the existence of sepsis and related disorders were known since time immemorial, formal definitions for the same were laid by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) Consensus Conference in 1991. With advances in the understanding of the pathophysiological aspects of septic shock and the dissatisfaction in several quarters regarding these definitions, a Consensus Sepsis Definitions Conference was convened in 2001 under the auspices of ACCP, SCCM, the European Society of Intensive Care Medicine, and the Surgical Infection Societies to re-visit the definitions of sepsis and related conditions. The key change was regarding the definition of systemic inflammatory response syndrome (SIRS) [manifested by (but not limited to) 2 or more of the following conditions: temperature > 38 °C or, < 36 °C; heart rate > 90 beats/min; respiratory rate > 20/min or ($PaCO_2$) < 32 mmHg; white blood cell count >12.0 × 10^9/L, < 4:0 × 10^9/L, or > 10% immature (band) forms] which was expanded to include longer list of possible signs of sepsis (**Table 1**).

As per the new guidelines, sepsis is defined as infection plus systemic manifestations of infection (**Table 1**). *Severe sepsis* is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (**Table 1**). *Septic shock* is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation.

Staging System for Sepsis

Since the definitions of sepsis and related syndromes does not allow for precise characterisation and staging of patients with this condition, staging systems have been proposed to stratify these patients by both their baseline risk of an adverse outcome and their potential to respond to therapy. In line with the tumour, node, metastasis in vogue for cancer, a classification scheme for sepsis that will stratify patients basing on their *predisposing* conditions, the nature and extent of the *infection*, the nature and magnitude of the host *response*, and the degree of concomitant *organ dysfunction*, termed PIRO staging system has been described (**Table 2**). Several attempts are underway to apply the PIRO system clinically with promising results.

Aetiology

Gram-negative bacterial infection is the most common cause of sepsis and related syndromes. However, septic shock can be caused by Gram-positive bacteria and fungi also. Polymicrobial aetiology of sepsis has also been described. In India, septic shock can occur due to falciparum malaria, enteric fever, dengue fever and other infections.

Pathogenesis

The pathophysiological hallmark of sepsis and related syndromes is the mismatch of the host response to the intensity of the pathogenic stimuli, ultimately leading to organ injury or

Table 1: Diagnostic Criteria for Sepsis in Patients with Documented or Suspected Infection

General variables
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C)
Heart rate >90/min or >2 SD above the normal value for age
Tachypnoea
Altered mental status
Significant oedema or positive fluid balance (>20 mL/kg over 24 hours)
Hyperglycaemia (plasma glucose >120 mg/dL) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count >12,000 /mL)
Leukopaenia (WBC count <4000/mL)
Normal WBC count with >10% immature forms
Plasma C-reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Haemodynamic variables
Arterial hypotension (SBP <90 mmHg, MAP <70, or an SBP decrease >40 mmHg) or <2 SD below normal for age)
SvO_2 >70%
Cardiac index >3.5 L/min/m^2
Organ dysfunction variables
Arterial hypoxaemia (PaO_2/FiO_2 <300)
Acute oliguria (urine output <0.5 mL/kg/h for at least 2 hours)
Creatinine increase >0.5 mg/dL
Coagulation abnormalities (INR >1.5 or aPTT >60 sec)
Ileus (absent bowel sounds)
Thrombocytopaenia (platelet count <100,000/µL)
Hyperbilirubinaemia (plasma total bilirubin >4 mg/dL)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

SD = Standard deviation; WBC = White blood cell; SvO_2 = Central venous oxygen saturation; INR = International normalisation ratio; MAP = Mean arterial pressure; SBP = Systolic blood pressure; PaO_2 = Partial pressure of arterial oxygen; FiO_2 = Fraction of inspired oxygen; aPTT = Activated partial thromboplastin time

Adapted from: Crit Care Med 2003; 31: 1250-6.

Table 2: Some Clinical and Laboratory Variables Being Evaluated for the PIRO Staging System for Sepsis in Adults

Variable	Clinical Parameters	Laboratory Parameters
Predisposing conditions	Age, co-morbid conditions (e.g. alcoholism, diabetes, cirrhosis of liver), gender, corticosteroid use, immunosuppressive state, religious and cultural beliefs	Genetic polymorphisms in components of inflammatory response (e.g. TLR, TNF, IL-1, CD14)
Infection	Site of infection (e.g. pneumonia, peritonitis, catheter), Type of infection (hospital acquired *versus* community acquired)	Virulence of the infecting organism, antimicrobial sensitivity, assay of microbial products (e.g. LPS, bacterial DNA), gene transcript profiles
Response	SIRS, other signs of sepsis, shock, CRP	White blood cell count, prothrombin time, APTT, blood lactate levels, biomarkers (e.g. CRP, PCT)
Organ dysfunction	Blood pressure, urine output, Glasgow coma scale, organ dysfunction as number of failing organs or composite score (e.g. MODS, SOFA, LODS)	PaO_2/FiO_2, serum creatinine, serum bilirubin, platelet count

TLR = Toll-like receptor; TNF = Tumour necrosis factor; IL-1 = Interleukin-1; LPS = Lipopolysaccharide; DNA = Deoxyribonucleic acid; SIRS = Systemic inflammatory response syndrome; APTT = Augmented partial thromboplastin time; CRP = C-reactive protein; PCT = Procalcitonin; PaO_2 = Partial pressure of arterial oxygen; FiO_2 = Fraction of inspired oxygen; MODS = Multiple organ dysfunction syndrome; SOFA = Sepsis-related organ failure assessment; LODS = Logistic organ dysfunction system. Adapted from: Crit Care Med 2003; 31: 1250-6.

dysfunction with or without hypotension. This results in a predominantly proinflammatory (SIRS), mixed [mixed antagonistic response syndrome (MARS)], or predominantly anti-inflammatory compensatory anti-inflammatory syndrome. The current concepts underlying the molecular pathogenesis of sepsis are shown in **Figure 1**. The major complications of septic shock are listed in **Table 3**.

Table 3: Major Complications of Sepsis

- Cardiopulmonary
  - Acute lung injury, acute respiratory distress syndrome
  - Depression of myocardial function
- Renal
  - Acute kidney injury
  - Drug-induced renal damage
- Disseminated intravascular coagulation
- Neurological
  - Critical illness polyneuropathy
- Multiorgan dysfunction syndrome

Clinical Manifestations

The clinical manifestations of sepsis result as a consequence of the complex interplay among the immune, coagulation, and neuroendocrine systems in response to severe infection. These manifestations overlap the signs and symptoms due to the underlying medical conditions and primary site of infection. Septic shock should be suspected whenever, a patient with fever or hypothermia, tachycardia and tachypnoea and evidence of decreased organ perfusion develops hypotension. It is not strictly necessary that tachycardia, tachypnoea or fever be present to make the diagnosis. Generally, there is predisposition to infections such as a patient on cytotoxic or immuno-suppressive drugs, chronic debilitating disease such as diabetes mellitus, cirrhosis of liver, etc. Haemtogenous seeding of the skin or underlying soft tissue can manifest as cellulitis, pustules, bullae, or haemorrhagic lesions. Other features that help in pointing towards a diagnosis of septic shock include evidence of impaired organ perfusion, altered mental status, jaundice, gastrointestinal bleed due to stress ulceration, disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS). Acrocyanosis and ischaemic necrosis of

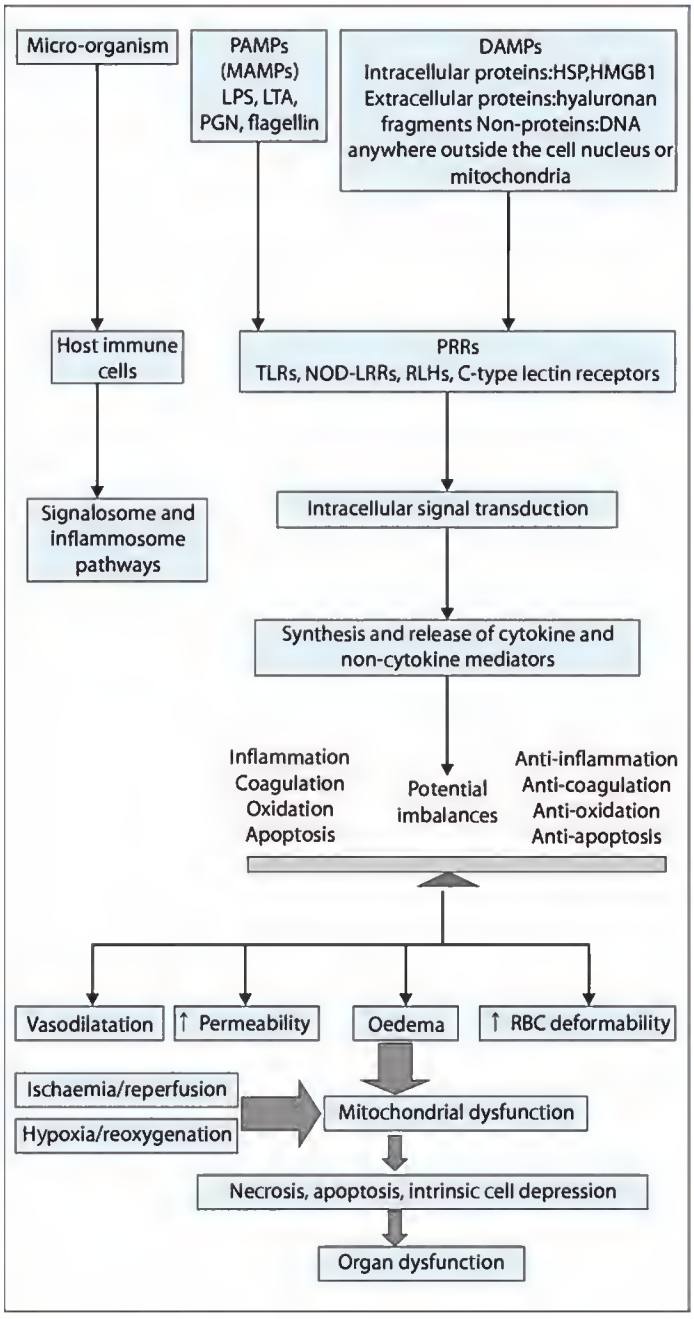


Figure 1: *Overview of the molecular pathogenesis of sepsis.*

peripheral tissues, usually digits, may be evident due to hypotension and DIC.

Principles of Management

The basic principles of initial resuscitation (fluid therapy, vasopressors, inotropic support, infection issues (source identification and control, appropriate antibiotic therapy), blood product administration and haemodynamic support described in the updated Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock 2008 must be followed meticulously (**Figure 2**).

Broad-spectrum, site-specific appropriate intravenous antibiotics (monotherapy or combination therapy as appropriate) should be started as early as possible, and always within the first hour of recognising severe sepsis and septic shock. The antimicrobial regimen must be assessed daily to optimise efficacy, prevent resistance, avoid toxicity and minimise costs. The antibiotic therapy must be administered for 7 to 10 days. The duration may be longer if the response is slow, the foci of infection are undrainable, or if immunodeficiency is present. Low doses of corticosteroids and recombinant human activated protein C may be considered as useful adjunctive therapies in selected sub-groups of patients. The optimal timing for initiating these modalities of treatments appears to be 6 to 24 hours from onset of shock. Patients receiving these treatments should systematically be monitored for superinfection and serious bleeding complications. Principles of mechanical ventilation (MV) are described under ARDS. Factors indicating poor prognosis in septic shock are shown in **Table 4**.

Table 4: Factors Indicating Poor Prognosis in Septic Shock

Pre-existing factors
Old age
Nature of co-existing illness (e.g. leukaemia)
Number of failed organs
Cardiovascular
Lack of ventricular dilatation
Persistence of tachycardia and raised cardiac output
Others
Delay in institution of treatment
Acute respiratory distress syndrome
Disseminated intravascular coagulation
Hypothermia
Leucopaenia
Hyperglycaemia
Metabolic acidosis
Renal failure
Polymicrobial infection

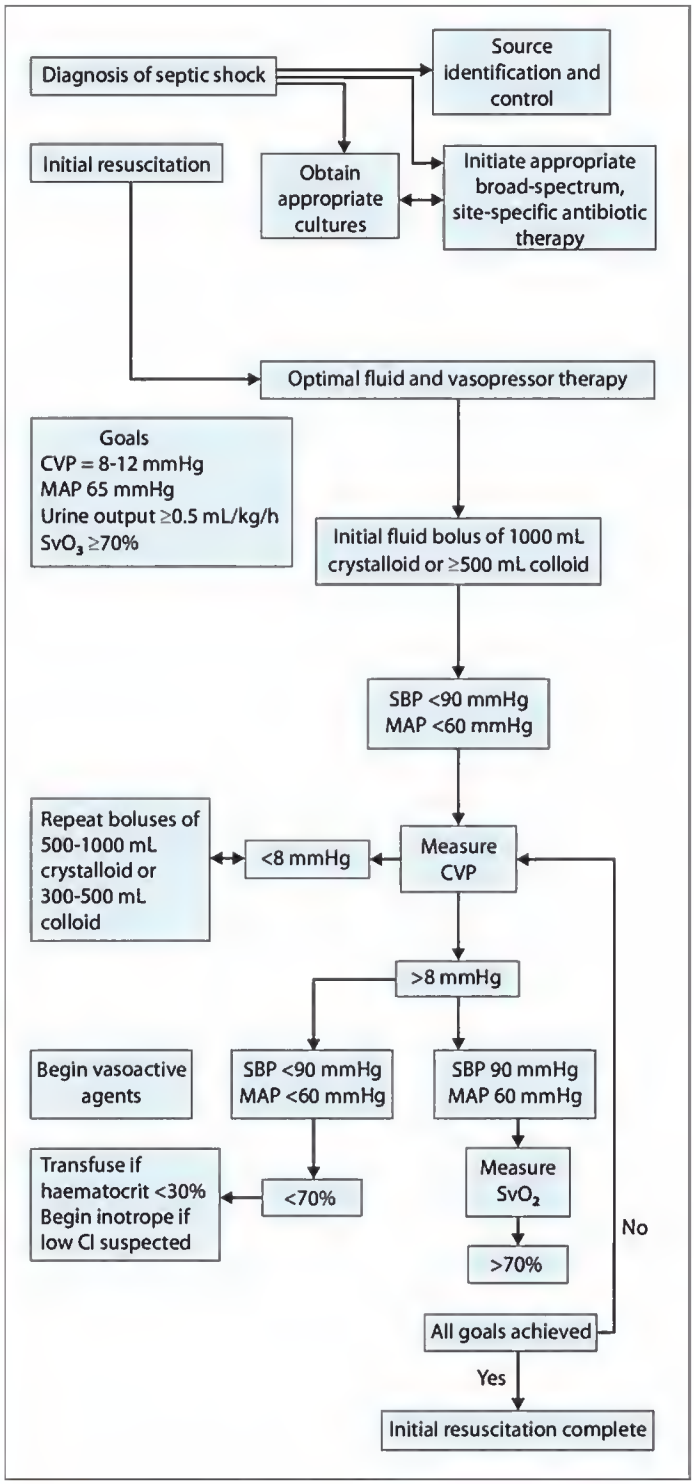


Figure 2: Initial resuscitation with goal-directed therapy in severe sepsis and septic shock.

CVP = Central venous pressure; MAP = Mean arterial pressure; SvO_2 = Central venous oxygen saturation; SBP = Systolic blood pressure; CI = Cardiac index.

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is defined as an acute lung injury (ALI) resulting in extensive bilateral pulmonary infiltrates, severe refractory arterial hypoxaemia and stiff lungs. It is a common cause of ICU admission world over.

Aetiology

Bacterial sepsis is the single most important cause of ARDS in hospitalised patients. Other common causes of ARDS are listed in **Table 5**.

Definition

The American-European Consensus Conference definitions of ALI and ARDS are simple to apply in the clinical setting and also recognise that the severity of clinical lung injury varies according to the severity of arterial hypoxaemia. Recently, pulse oximetric saturation (SpO_2) to fraction of inspired oxygen (FiO_2) ratio (S/F ratio) has been found to correspond to the arterial oxygen tension (PaO_2) to FiO_2 ratio (P/F) (**Table 6**). These non-invasive substitutes for assessing oxygenation can

Table 5: Causes of Acute Respiratory Distress Syndrome

Common Causes

Infections

- Gram-negative and Gram-positive bacterial sepsis
- Pneumonia (bacterial, viral, mycoplasma, pneumocystis)
- Pancreatitis
- Burns
- Gastric aspiration
- Bilateral lung contusion
- Cardiopulmonary bypass

Uncommon Causes

- Multiple blood transfusions
- Inhalational injuries (ammonia, chlorine, nitrogen dioxide, phosgene, smoke, sulphur dioxide)
- Fat embolism
- Raised intracranial pressure
- Infections (pulmonary and miliary tuberculosis, falciparum malaria, enteric fever, leptospirosis)
- Drugs (e.g. thiazides, methadone, barbiturates, narcotics, lidocaine, cytosine arabinoside, phenytoin, salicylates)
- Heat stroke
- High altitude pulmonary oedema

Table 6: Definitions of Acute Lung Injury and Acute Respiratory Distress Syndrome

Acute lung injury	Acute respiratory distress syndrome
Acute onset	Acute onset
$PaO_2/FiO_2 \leq 300$*	$PaO_2/FiO_2 \leq 200$*
$SpO_2/FiO_2 \leq 315$*†	$SpO_2/FiO_2 \leq 235$‡
Bilateral infiltrates on the frontal chest radiograph	Bilateral infiltrates on the frontal chest radiograph
PCWP ≤18 mmHg, or no clinical evidence of left atrial hypertension	PCWP ≤18 mmHg, or no clinical evidence of left atrial hypertension

** Irrespective of level of positive end-expiratory pressure;*
† The sensitivity of 91% and specificity of 56% for identifying acute lung injury;
‡ The sensitivity of 85% and specificity of 85% for identifying acute respiratory distress syndrome.
Adapted from: Am J Respir Crit Care Med 1994; 149:818-24; Chest 2007; 132:410-7.

be useful in the settings where arterial blood gas (ABG) analysis is not available and facilitate the monitoring of the course of the disease.

Clinicopathological Stages of ARDS

Irrespective of the precipitating factors ARDS usually evolves along a stereotypic common pathway with characteristic clinical, pathological and radiological changes as exudative phase, proliferative phase, fibrotic phase and phase of healing and repair. These changes are usually described by the term *diffuse alveolar damage*.

Clinical Features

ARDS is acute and rapid onset of respiratory failure, dyspnoea, dry cough, disorientation and agitation that usually develops 24 to 72 hours after the precipitating event marking the exudative phase. Tachypnoea, tachycardia, cyanosis, crepitations and rhonchi may also be present. Arterial hypoxaemia that is refractory to treatment with supplemental oxygen which may eventually warrant tracheal intubation and assisted MV is a characteristic feature of ARDS.

Diagnostic Work-up

The patient should be carefully evaluated for an underlying cause keeping in mind the possibility of treatable infections, such as sepsis, pneumonia, tuberculosis (TB), malaria among others. Other useful investigations include:

Arterial blood gas analysis

The ABG analysis usually reveals severe refractory hypoxaemia, hypocapnia and alkalosis if the patient is breathing spontaneously. Hypercapnia usually does not occur unless chronic lung disease co-exists.

Chest radiograph

In patients with ARDS, the radiographic changes become evident by about 12 hours after the clinical onset of respiratory failure. Initially, patchy, ill-defined opacities may become apparent through out the lungs. They rapidly coalesce and diffuse massive air-space consolidation becomes evident. In contrast to cardiogenic pulmonary oedema of cardiogenic origin, air-bronchogram is frequently visible. After about a week, the lungs remain diffusely abnormal, but the pattern gradually becomes 'reticular' or 'bubbly' suggestive of a diffuse interstitial and air-space fibrosis.

Computed tomography

Computed tomography (CT) of the chest also facilitates the identification of some causes of ARDS, such as, pneumonia and lung abscess. The CT of the chest reveals diffusely distributed, non-uniform, ground-glass opacification or consolidation which may not conform to the gravity distribution early in the exudative phase. Susbequently in the exudative phase, the consolidation becomes more homogeneous and gravity dependent. As the proliferative and fibrotic stages evolve, there is a decrease in the overall lung density and the appearance of an interstitial reticular pattern. Complications of ARDS, such as pneumothorax, pneumomediastinum and interstitial emphysema may also be evident on CT of the chest.

Echocardiography

Echocardiography is useful in differentiating ARDS from cardiogenic pulmonary oedema.

Swan-Ganz catheterisation

Swan-Ganz catheterisation facilitates measurement of pulmonary capillary wedge pressure (PCWP). A PCWP less than 18 mmHg and cardiac index more than 2.1 L/min/m^2 is altered in ARDS.

Fibreoptic bronchoscopy and bronchoalveolar lavage

Fibreoptic bronchoscopy and bronchoalveolar lavage (BAL) are employed to exclude infectious causes of ARDS. Most prominent finding on BAL in patients with ARDS (though non-specific) include increased number of polymorphonuclear leukocytes (making up to nearly 80% of the total cell population; normal value <5%). Eosinophilia in the BAL fluid, when it occurs, has therapeutic implications.

Differential Diagnosis

Several conditions mimic ARDS clinically, but, alveolar inflammatory changes are characteristic of ARDS. These conditions include:

Haemodynamic pulmonary oedema

In haemodynamic pulmonary oedema, PCWP is elevated (> 18 mmHg), and echocardiographic abnormalities may be evident. Once PCWP is brought to normal, infiltrates on the chest radiograph may clear.

Diffuse alveolar haemorrhage

The initial clinical presentation of diffuse alveolar haemorrhage may resemble ARDS and is accompanied by a dramatic fall in the haematocrit, occurrence of haemoptysis, and the presence of frothy red fluid on bronchoscopy. Haemosiderin-laden macrophages may be demonstrable in the BAL fluid.

Idiopathic acute eosinophilic pneumonia

Patients with idiopathic acute eosinophilic pneumoia may be previously healthy and present with cough, dyspnoea, fever, and occasionally chest pain. Peripheral blood and BAL fluid eosinophilia is present. This condition rapidly responds to corticosteroid treatment, usually within 48 hours.

Metastatic malignancy

When malignancy presents as ARDS it is uniformly fatal. Cytologic examination of blood drawn from pulmonary circulation through the Swan-Ganz catheter keeping the balloon inflated, or BAL fluid is usually helpful in confirming the diagnosis. More invasive procedures such as transbronchial lung biopsy, open lung biopsy may have to be undertaken at times to ascertain the diagnosis. These procedures are, however, associated with increased risk of complications.

Management

In the appropriate clinical setting, a high index of clinical suspicion is necessary to diagnose ARDS early. Efforts directed at establishing the cause of ARDS must be actively pursued to facilitate institution of specific treatment.

General therapeutic measures

Patients with ARDS should be admitted in an ICU equipped with facilities for invasive monitoring and providing assisted MV. Ideally, pulmonary and systemic arterial lines should be inserted for haemodynamic monitoring and rational fluid replacement therapy. SpO_2 monitoring by pulse oximetry, periodic ABG analysis must also be done. Adequate nutrition should be ensured; enteral route is preferred to the parenteral route as it does not cause the serious risk of catheter induced sepsis. If sepsis is presumed to be the cause of ARDS, empirical antibiotic treatment may be started in the early phase of the disease as detailed above.

Haemodynamic stabilisation

The fundamental principles remain same as in **Figure 2**.

Ventilatory support

While some patients with ARDS can be managed with conservative measures and non-invasive ventilation, tracheal intubation and assisted MV are required in a majority of the patients. Aim of MV is to maintain gas exchange with minimal complications. Initially, spontaneous ventilation using a face mask with a high flow gas delivery system can be used to deliver a FiO_2 of up to 0.5 to 0.6. Continuous positive airway pressure (CPAP) may be added to improve PaO_2 without increasing FiO_2. If a FiO_2 of more than 0.6 and CPAP of more than 10 cm H_2O are needed to achieve a PaO_2 of more than 60 mmHg, tracheal intubation and MV must be considered. The maximal clinical benefit is likely to occur if MV is initiated early, i.e. within 96 hours of the onset of ARDS, a time when alveolar recruitment potential is the greatest.

Recent evidence suggests that, whatever mode of ventilation is used, tidal volume should be set in the region of 6 mL/kg ('lung protective ventilation') and the peak pressure should be limited to 30 to 35 cm H_2O to prevent lung overdistension. Presently, in the absence of routine static pressure-volume curve measurement, positive end expiratory pressure (PEEP) is set at a relatively high level such as 15 cm H_2O in patients with ARDS. It is also a common practice to increase the I:E ratio to 1:1 or 2:1 (inverse ratio ventilation) with close monitoring of intrinsic PEEP and haemodynamics during pressure control ventilation (**Table 7**). The usefulness of recruitment manoeuvres such as the high function where intermittent breaths of larger tidal volume are administered either via the mechanical ventilators or by hand, sustained inflation or CPAP aimed at increasing alveolar recruitment are also being studied.

Other ventilatory strategies

Other alternative approaches to conventional MV include prone positioning of the patient, high frequency ventilation (HFV, rate

Table 7: Protective Lung Ventilation Protocol from the 'ARDSNet Study'

Variable	Setting	
Ventilator mode	Volume assist-control	
Tidal volume (initial)	6 mL/kg of predicted body weight* initially	
Plateau pressure	< 30 cm H_2O	
Rate of respiration	6 – 35 breaths/min	
Ratio of the duration of inspiration to the duration of expiration	1:1 – 1:3	
Oxygenation target		
PaO_2	7.3 – 10.7 kPa (55 – 80 mmHg)	
SaO_2	88 – 95 (%)	
FiO_2 and PEEP†	FiO_2	PEEP
	0.3	5
	0.4	5 – 8
	0.5	8 – 10
	0.6	10
	0.7	10 – 14
	0.8	14
	0.9	14 – 18
	1.0	18 – 24

** Predicted body weight of mole potients = 50 + 0.91 [height (cm) – 152.4]; predicted body weight of female potients = 45.5 + 0.91 [height (cm) – 152.4]*
† Set according to pre-determined combinations (PEEP ronge 5 – 24 cm H_2O)
PEEP = Positive end-expirotory pressure; FiO_2 = Fraction of inspired oxygen

> 60/min) techniques such as high frequency jet ventilation (HFJV) and high frequency oscillatory ventilation (HFOV), and liquid ventilation, among others. The relative merits of these alternative methods of MV must be critically weighed against the potential side-effects in every setting.

Extracorporeal respiratory support

In extracorporeal membrane oxygenation (ECMO), venous blood is removed via a cannula in the inferior vena cava or right atrium, passed through a heart/lung machine, and is returned to either the right atrium (veno-venous bypass) or aorta (veno-arterial bypass). Extracorporeal carbon dioxide (CO_2) removal (ECCOR) involves use of an extracorporeal veno-venous circuit with lower blood flow and oxygenation still occurring via the patient's lungs. These modalities may be useful in selected patients and, studies with a large sample size are required to clarify their role in the management of ARDS.

Pharmacological therapies

Though various pharmacological therapies are directed at the pathophysiologic mechanisms of ARDS. These include neuromuscular blockade, inhaled nitric oxide, vasoactive agents (intravenous phenylephrine, inhaled prostacyclins, almitrine, among others. The therapeutic potential of these strategies needs further study.

Corticosteroids

The role of corticosteroid treatment in the management of ARDS is controversial. The studies published in the 1980s had employed high-dose corticosteroids (1 to 8 doses of 30 mg/kg methylprednisolone) for short durations (< 48 hours). Compared with placebo, corticosteroid treatment resulted in either no difference or increased the incidence of ARDS. In more recent studies, low-to-moderate doses of corticosteroids (methylprednisolone 1 to 2 mg/kg per day to start) for longer duration (mean 25 to 32 days), with gradual tapering has been evaluated. Presently, corticosteroid therapy is not considered to be beneficial before the onset of ARDS or early in its course. A difference of opinion exists among experts regarding the efficacy of corticosteroids for late-stage ARDS. Even though low-dose corticosteroid therapy improves lung function and shortens the duration of MV in persistent ARDS, the impact on long-term mortality is unclear. More data are required from clinical trials before they can be recommended for routine use in patients with unresolved ARDS.

Nutritional supplementation

Enteral feeding with omega-3 fatty acids, such as, eicosapentanoic acid, γ-linolenic acid, and antioxidants was shown to facilitate improvement in oxygenation and reduction in mortality in earlier trials. However, this benefit has not been replicated in more recent clinical trials.

Figure 3 outline algorithm for the management of ARDS.

ARDS in the Tropics

Infectious causes such as pulmonary and miliary tuberculosis TB, falciparum malaria, enteric fever, and leptospirosis are rare but treatable causes of ARDS. When the cause of ARDS is not clear, especially in endemic areas, these aetiological causes should be kept in mind and active efforts directed at establishing this diagnosis must be pursued to facilitate early institution of specific therapy.

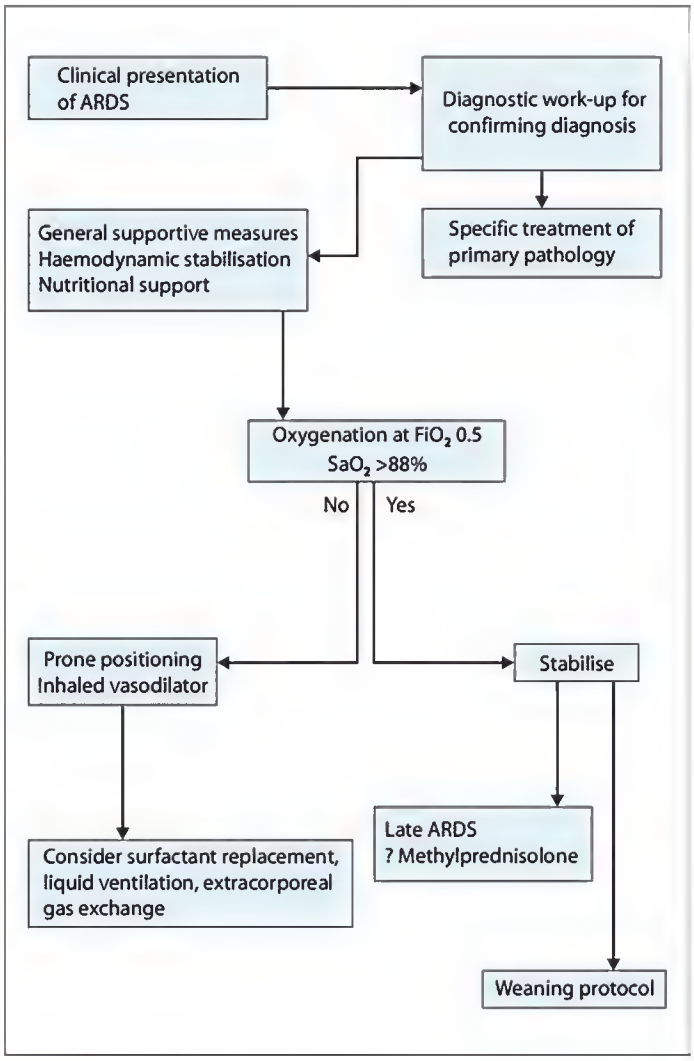


Figure 3: Treatment algorithm for the management of ARDS.

FiO_2 = Fraction of inspired oxygen; SaO_2 = Arterial oxygen saturation

Outcome

Interestingly, initial indices of oxygenation and ventilation have not been found to be useful in predicting the outcome in ARDS. Majority of deaths in patients with ARDS are attributable to sepsis or multi-organ dysfunction rather than primary respiratory disease. Certain prognostic factors have been identified to predict risk of death at the time of diagnosis of ARDS (**Table 8**).

Table 8: Predictors of Mortality in Patients with ARDS

Advanced age
Chronic liver disease
Non-pulmonary organ dysfunction
Sepsis
Organ transplantation
Human immunodeficiency virus infection
Active malignancy
Failure of pulmonary function to improve during the first week of treatment

Prevention

No form of therapy is known to prevent the occurrence of ARDS. Corticosteroid therapy, routine administration of antibiotics in the absence of evidence of infection, and use of prophylactic PEEP have not been shown to prevent ARDS in patients at risk.

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7.8 Mechanical Ventilation

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Mechanical ventilation (MV) of the lungs is defined as assisting or substituting spontaneous respiration of the patient with artificial respiration with a lung ventilator or manual resuscitator bag. Application of positive airway pressure overcomes the increased airway resistance (asthma, chronic obstructive pulmonary disease [COPD]) and inflates less compliant alveoli (acute respiratory distress syndrome [ARDS], pneumonias), improves functional residual capacity (FRC) and improves oxygenation by recruitment of atelactic lung units. Positive pressure counteracts the hydrostatic pressure in capillaries and redistributes (decreases) extracellular lung water. However, MV is associated with a number of complications which are discussed briefly in the following sections.

COMMONLY USED TERMS

It is important to know the jargon of terms used in context to ventilation for better understanding of this subject. The commonly used terms are as under:

Cycling

The mechanism used to terminate inspiration and switch over to exhalation is called cycling. It is also used to classify ventilators.

Pressure Cycling

Inspiration is terminated after desired airway pressure (P_{AW}) is achieved. The tidal volume (V_T) is directly proportional to P_{AW} and inversely proportional to airway resistance, e.g. in bronchospasm.

Volume Cycling

Inspiration stops after delivering the set V_T. Airway pressure increases with airway resistance (bronchospasm) or low compliance (pulmonary oedema).

Flow Cycling

Inspiration is terminated after the flow rate falls to a particular level e.g. 25% of peak flow rate.

Time Cycling

Inspiration is terminated after the set inspiratory time. Modern ventilators use a combination of these cycling mechanisms.

Trigger

Trigger is the signal used to start ventilator breaths. Ventilator itself triggers breaths at a set respiratory rate (RR). Alternatively, ventilator senses patient's inspiratory pressure (pressure trigger) or inspiratory flow (Flow trigger) for triggering breaths. Recently, electrophysiological activity of diaphragm is being used as trigger (*see* NAVA).

Breathing Circuit

The arrangement of corrugated tubings designed to deliver gas to the patient is called breathing circuit. It requires periodical and between-patients cleaning and sterilisation. Most components are re-usable, expensive and include corrugated tubings, humidifier or (HME), flow sensor, Y-piece, water traps and exhalation valve.

Gas Flow

Flow of the air (enriched with oxygen) in the breathing circuit is called gas flow. A number of ventilators use a continuous basal flow of 5 to 10 L which is used for sensing patient's effort and is called basal flow or bias flow.

Diagnostic Functions

Newer ventilators can measure changes in compliance, resistance, positive end-expiratory pressure (PEEP) and air trapping, etc. Auto-PEEP is measured by 'end-exipratory hold' or occlusion for 5 to 10 seconds whereas similar manoeuvre after end-inspiration 'inspiratory hold' depicts plateau/alveolar pressure ($P_{PLAT/ALV}$). These diagnostic functions are helpful in making rational ventilator adjustments.

Nebulisation

Some of the ventilators have programmable nebulisers to allow aerosol therapy without interruption, or modification of ventilation.

MODES OF VENTILATION

Mode of ventilation specifies the method and type of ventilatory assistance being provided by the ventilator. Commonly used modes for ventilating the lungs are as under:

Manual Ventilation

It refers to the hand delivered ventilation using ambu bag-mask or bag-tracheal tube technique with or without oxygen supplementation. Manual ventilation is quite effective, and controlled or assisted ventilation can be given until a ventilator becomes available.

Spontaneous Mode

Ventilator does not give breaths, but delivers the set fraction of inspired oxygen (FIO_2), continous positive airway pressure (CPAP) and pressure support.

Controlled Mechanical Ventilation (CMV)

The ventilator is set to deliver fixed breath rate and V_T (CMV-V) or inspiratory pressure (CMV-P). Spontaneous respiration is abolished with deep sedation or neuromuscular blocking drugs. CMV is used in initial phase of ventilation.

Assist-Control

Respiratory rate, V_T and trigger sensitivity level are set in this mode and the patient triggered breaths are assisted by the ventilator, otherwise it works CMV mode. Common assisted modes are as follows:

Synchronised Intermittent Mandatory Ventilation (SIMV)

Ventilator delivers the set breath rate and V_T (SIMV-V) or inspiratory pressure (SIMV-P) using patient trigger. SIMV

improves patient comfort and allows spontaneous breathing between synchronised ventilator breaths.

Pressure Support Ventilation (PSV)

Inspiratory efforts of the patient trigger the ventilator to augment gas flow to achieve the desired airway pressure. PSV helps the patient to overcome increased airway resistance and decreased compliance and thus it "off loads" the inspiratory muscles.

Proportionate Assisted Ventilation (PAV)

Proportion of assisted ventilation is directly proportional to the effort of the patient. The proportion to be assisted is set as percentage, but the assistance decreases with decreasing patient's effort (exhaustion) and hypoventilation can occur.

Adaptive Support Ventilation (ASV)

The clinician determines minute ventilation and ventilator algorithm manages the RR/V_T relationship with changing lung dynamics. If the patient fails to trigger, controlled breaths are delivered automatically to avoid hypoventilation.

Neurally Adjusted Ventilatory Assistance (NAVA)

This under-investigation mode senses the electrical activity of diaphragm (through oesophageal electrode) to trigger ventilator-assisted breaths and aims at enhanced patient comfort by neuro-ventilatory coupling. The mode is not yet available in most of the available ventilators.

Positive End-Expiratory Pressure (PEEP)

PEEP is achieved by adding resistance to the exhalation. It prevents complete emptying of alveoli, airway closure and increases the duration for gas exchange. Application of PEEP in ARDS protects the alveoli from shearing stress due to repeated collapse and expansion. However, inap-propriately high PEEP increases the risk of barotrauma and hypotension.

Continuous Positive Airway Pressure

PEEP during spontaneous respiration is called CPAP. In addition to the effects of PEEP, it decreases the inspiratory work required for opening up of closed airways.

Biphasic Positive Airway Pressure (BiPAP)

Two distinct phases of positive pressure are applied during inspiration and expiration. Inspiratory PAP (iPAP) resembles PSV whereas expiratory PAP (ePAP) resembles CPAP. Apart from intensive care unit (ICU) ventilators, separate BiPAP machines are also available. S-PAP and DuoPAP are equivalents of BiPAP.

Volume Assured Pressure Support; Volume Support; Variable Pressure Support; and Pressure Augmentation

In addition to ventilator support, e.g. PSV, these modes ensure delivery of the desired V_T in spontaneously breathing patient. Ventilator monitors the inspiratory flow and if the patient is unlikely to inhale desired V_T, the ventilator augments the gas flow and delivers the set V_T.

Inverse Ratio Ventilation (IRV)

IRV is sometimes used in severe cases of ARDS by setting an inspiration longer than exhalation during CMV. It can improve oxygenation with increased risk of cardiopulmonary complications.

Airway Pressure Release Ventilation (APRV)

APRV has been tried in place of IRV with mixed results. The lungs are kept continuously inflated with brief periods of relief for exhalation without formal breath cycles. Spontaneous breathing is possible with considerable effort. Airway pressures and circulatory effects are less pronounced than IRV.

Apnoea Back-up Ventilation

It is a safeguard CMV mode and starts automatically in case patient stops breathing or triggering breaths. Parameters for back-up ventilation should be adjusted for individual patient while starting the ventilation.

TYPES OF VENTILATORS

Different types of mechanical ventilators are available for use in the hospitals (ICU ventilators), for transport of the patient (transport ventilators), for use at home (domiciliary ventilators) and (anaesthesia ventilators) for anaesthetic applications. A simple but effective form of multi-purpose ventilator is manual resuscitator bag (Ambu bag).

INDICATIONS FOR MECHANICAL VENTILATION

Main indications for MV include respiratory failure associated with hypoxia, hypercapnoea or both, compromised circulatory status and pulmonary oedema.

Clinical Indications

Clinical indications include ARDS, acute severe asthma, COPD with acute exacerbation, Landre Guillain Barré syndrome, poliomyelitis, head injury with diffuse brain oedema, pulmonary oedema and after major surgical operations. Severe tetanus (opisthotonus) and recently bird flu and swine flu have become indications for mechanical ventilation. Only those patients who are likely to recover completely from underlying disease are selected for ventilation. Brain dead patients may require ventilation until organ harvesting. Objective indications for mechanical ventilation are given in **Table 1**.

Table 1: Objective Indications for Mechanical Ventilation

Blood gas values	PaO_2 <60 mmHg despite FiO_2 0.6 $PaCO_2$ >50 mmHg HCO_3 is also raised and pH <7.3 Alveolar-arterial O_2 gradient >400 mmHg on 100% oxygen
Bedside measurements	Respiration rate >35 breaths/min; Rapid shallow breathing index, i.e. RR/ V_T (L) >100
Spirometric values	Tidal volume <5 mL/kg Minute ventilation >10 L/min Vital capacity <15 mL/kg Peak inspiratory pressure (> –25 cm H_2O or 0 to 24 cm H_2O

PaO_2 = Arterial oxygen tension; $PaCO_2$ = Arterial CO_2 tension; HCO_3 = Plasma bicarbonate

Note: All these parameters may not be available in every patient; hence, clinical judgement is important.

PROCESS OF MECHANICAL VENTILATION

Initiation of Mechanical Ventilation

Initiating MV has inherent risks and requires meticulous preparation, which should be based on **ABCDE. A = Airway:**

Maintenance of patient airway and tracheal intubation is necessary. **B = Breathing:** Patient requires ventilation with oxygen and bag mask technique during tracheal intubation. **C = Cardiovascular instability** or even cardiac arrest may occur in sick patients. An intravenous line must be secured with 18G or 16G cannula and normal saline or Ringers' lactate should be running unless contraindicated. **D = A number of drugs** are needed; midazolam, or anaesthetic like thiopentone, muscle relaxants usually succinylcholine are used to calm and relax the patient for tracheal intubation. Adrenaline and atropine should be ready for immediate use. **E = Equipment** must be checked in advance and includes laryngoscopes, oropharyngeal airways, tracheal tubes, manual resuscitator (Ambu bag), ventilator and a patient monitor.

Management of Ventilation

Airway is secured with oral or nasal tracheal tube and ventilation of both the lungs is ensured with careful auscultation. Orotracheal tubes require deeper levels of sedation and cause excessive salivation whereas nasotracheal tubes are tolerated better, require less sedation, but there is increased risk of epistaxis, bacteraemia and sinusitis. The V_T, RR and airway pressure should be appropriate for the size of the patient and lung pathology. It is safe to use 100% oxygen during first few minutes followed by gradual reduction to a level necessary to maintain pulse oximetric saturation (SpO_2) more than 90%. Humidification of inhaled gases is essential for optimal mucociliary function and is achieved with a heated humidifier (e.g. Fischer Paykel humidifier) or a disposable heat and moisture exchanger (HME). Blood gas analysis should be done 1 to 2 hours after starting ventilation make further adjustments in ventilation. Lung physiotherapy with chest wall percussion, postural drainage of lungs and tracheobronchial suctioning is done through tracheal tube intermittently.

CARE OF THE PATIENTS ON MECHANICAL VENTILATION

General Care

The patients on ventilator are totally dependant on nursing staff and meticulous maintenance of hygiene is essential for control of infection and optimal outcome of the patients. General measures include dressing of hair, cleaning of eyes and use of lubricant eye ointment, oral hygiene with brush or small pea-nut gauge soaked in chlorhexidine 2% and oral suctioning, catheterisation of bladder, and diapers for prevention of soiling with faecal matter. Skin is kept clean with daily sponge bath, change of wet clothing or linen, talcum powder and wrinkle free sheets. Use of pneumatic mattresses combined with change of posture every 2 hours reduces the risk of bedsores. These patients are susceptible to stress induced gastrointestinal bleeding and an H_2 blocker, proton pump inhibitor or mucosal barrier like sucralfate should be administered regularly.

Sedation and Analgesia

In the initial phase of ventilation, sedation with narcotics, midazolam or propofol, etc. is required to suppress respiratory efforts of the patient and fighting with ventilator. In post-operative, traumatised and other painful conditions, adequate analgesia is required. Muscle relaxants may cause myopathy, complicate weaning and are avoided, except in neurosurgical patients. Sedatives and muscle relaxants interfere with neurological assessment of the patient. Sedation is reduced gradually as the patient recovers and weaning from the ventilator is started. The sedatives may be with held in the morning to allow the patients to wake up (daily sedation vacation).

Nutrition

Maintenance of proper nutrition with sufficient calorie content is mandatory in patients on MV. ESPEN 2004 guidelines state that enternal nutrition should be started within 24 hours in hemodynamically stable patient's. Enteral feeding is preferred because it is natural, emotionally satisfying and prevents sepsis by maintaining integrity of gut mucosa. Diet should be adequate in calorific value which should be maintained at 25-30k cal/kg body weight per day for the patients. These calories are distributed as 50% carbohydrate, protein at 1g/kg per day and rest comprises of fat. Excessive carbohydrates increase carbon dioxide production and respiratory workload which may be harmful in COPD patients. Dietary composition in diabetics and hepatorenal disease requires additional considerations. Patients on ventilator start tolerating Ryle's nasogastric tube (RT) feed after 24 to 48 hours and require insertion of RT. RT feed is started at 3 to 4 hourly intervals with volumes of 4-5 ml/kg. RT feeds are not available in a number of hospitals in our country (especially, after H_1N_1 epidemic, ventilators have been installed in district hospitals), and therefore, relatives may have to be trained to prepare RT feed using common ingredients.

Communication with Patient

Most patients undergoing MV are conscious, they should be re-assured and informed about their progress, explained about the procedures to be done on them and taught to co-operate, especially during weaning. Intubated patients cannot speak and often use tapping of bed rails or may sometimes write. Their calls should always be attended with sympathetic and re-assuring attitude.

Monitoring of Vital Signs

Continuous monitoring of vital signs like, electrocardiogram (ECG), SpO_2, and non-invasive blood pressure is required. Arterial blood gas analysis and electrolyte status is needed in metabolic disorders, like diabetes. Unstable patients require monitoring of intra-arterial pressure, central venous pressure and cardiac output. Non-invasive technology has largely replaced pulmonary artery catheterisation. Neurological patients may require monitoring of electroencephalogram or intracranial pressure. Urine output is recorded at hourly intervals in case of renal dysfunction otherwise at 3 to 4 hourly intervals.

Monitoring of Ventilation

Most of the modern ventilators monitor and display parameters like exhaled V_T, minute volume, waveforms breath rate and peak airway pressure and display simple pressure/time or volume/time waveforms on screen (**Figure 1**). Small variations (± 10%; read user manual of ventilator) from set values are acceptable and, therefore, alarms limits should be set accordingly.

Sophisticated ventilators display real time pressure, volume and flow graphics in the form of waveforms or as loops, which are utilised for diagnosing changes in resistance (resistive load, e.g. in asthma), compliance (elastance load, e.g. ARDS, pulmonary oedema), air trapping and auto-PEEP (e.g. COPD). Basic waveforms (open and loop) illustrating important findings are shown in **Figures 2A and B**.

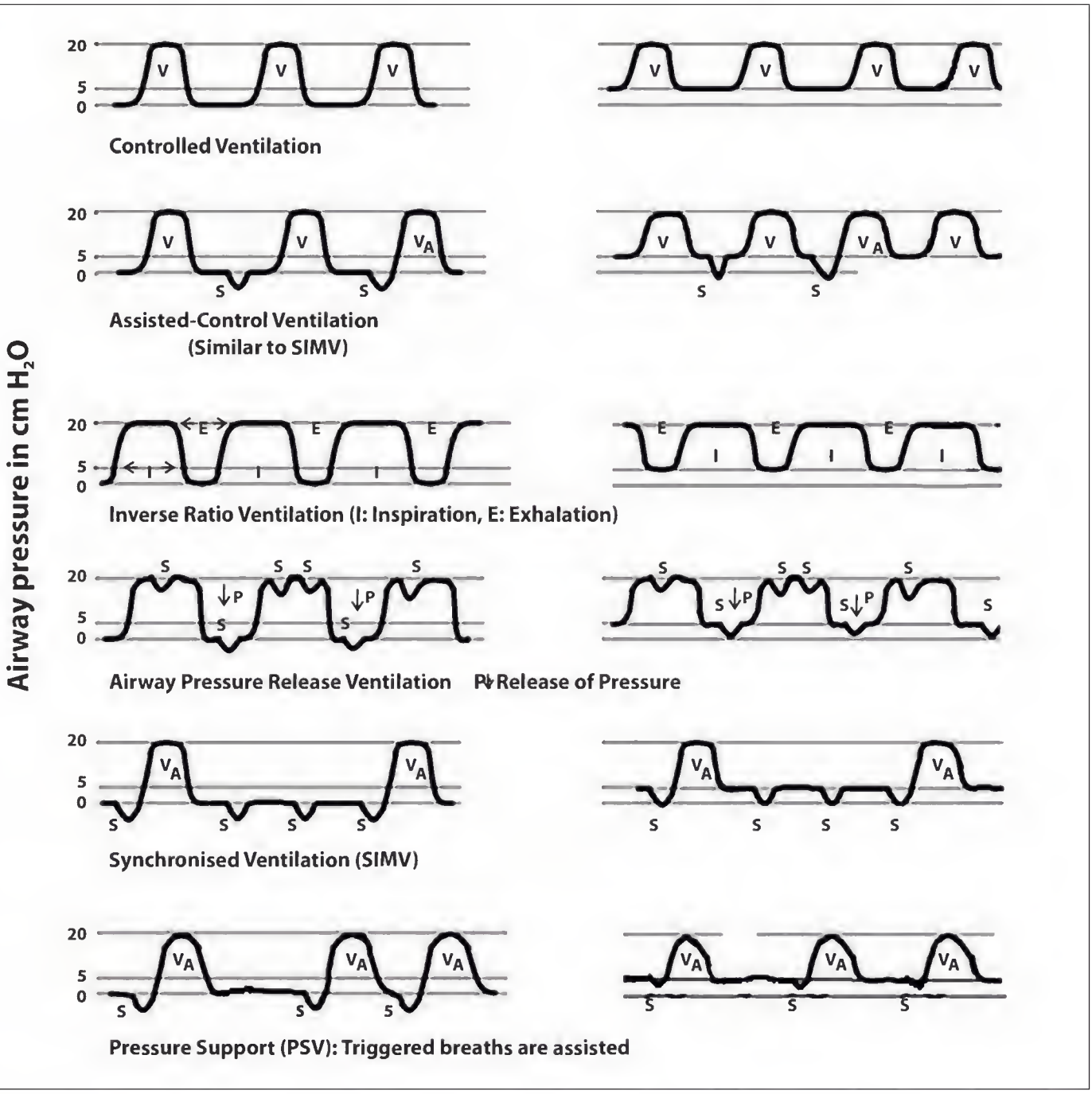


Figure 1: Airway pressure waveforms with different modes of ventilation left panel, right panel shows waveforms with 5 cm PEEP/CPAP.

V_A = Assisted breath; S = Spontaneous breath

Hysteresis

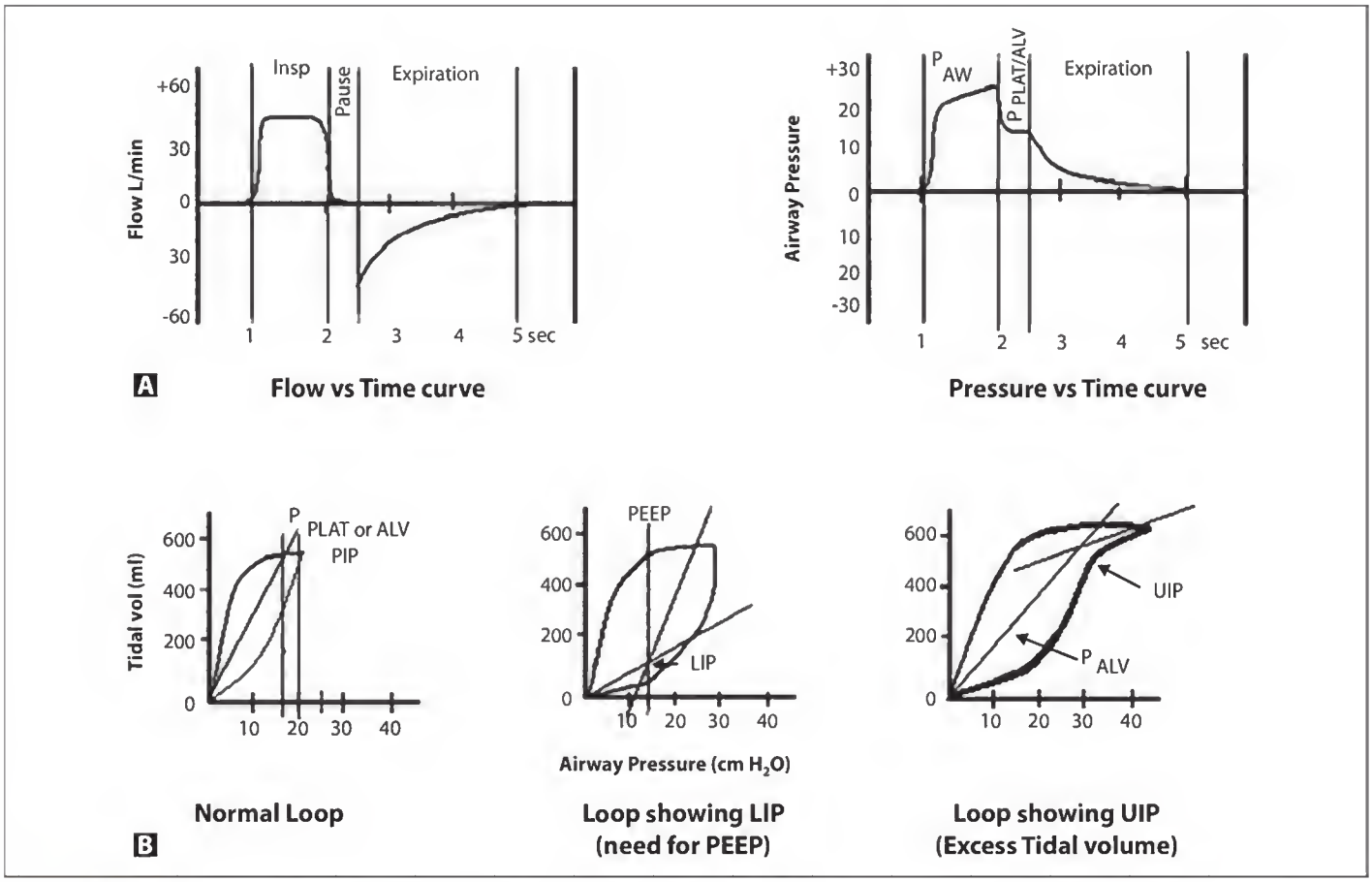
The pressure and volume curves are not linear due to variable resistive and elastic properties of the lungs and chest wall. As a result inspiratory curve assumes sigmoid shape and the lung volume is always higher during expiratory phase at any given pressure.

Upper inflection point (UIP)

Over filling of alveoli leads to abrupt rise in pressure and the upper part of inspiratory pressure curve deviates the curve to the right (pressure axis). The upper part of pressure volume curve assumes a 'duck-bill' shape. UIP is an abnormal finding and V_T needs to be decreased so that the shape of the curve/loop becomes normal.

Lower inflection point (LIP)

Pressure volume curve deviates towards pressure axis due to resistance of closed airways and after opening up of airways the curve becomes steep owing to the compliance of alveoli. This shift creates a distinct point on the axis of airway pressure called LIP or initial point of inflection (iPI). It denotes excessive airway closure and requires application of external PEEP (ePEEP). It has been recommended earlier that ePEEP value should be 2 to 3 cm more than the airway pressure corresponding to LIP, but recognition of air trapping has led to recommendation of lower value of ePEEP based on detection of airway closure or autoPEEP on expiratory curve.



Figures 2A and B: (A) Typical flow and pressure waveforms. (B) Loops showing points of inflection.

Insp = Inspiration; PIP = Peak inspiratory pressure; LIP = Lower inflection point; PEEP = Positive end-expiratory pressure

Titration of applied PEEP or ePEEP

There is no fixed method to determine the value of 'best PEEP or optimal PEEP' which would provide maximum gas exchange without side effects, like air trapping and haemodynamic compromise. Airway closure and iPEEP, both occur during expiration and the fact, that lung volume (at corresponding point on expiratory curve) at any given value of pressure on inspiratory curve is much higher. Application of PEEP/ CPAP the basis of LIP may lead to the worsening of air-trapping (iPEEP) particularly in COPD patients. The recent trend is to set ePEEP value up to 70-85% of iPEEP. A number of methods like monitoring of oesophageal pressure, monitoring airway pressure and expiratory flow/ volumes, haemodyanamic status, computed tomography and trans-thoracic-electric impedance and values of PaO_2, FiO_2/PaO_2 ratio etc are being used with reasonable success. Transthoracic impedance is directly proportional to the lung volume and its monitoring is somewhat similar to ECG monitoring. This non-invasive method may become a useful tool for monitoring and real time display of resting lung volume in future.

Pressure and flow volume loops

Advanced ventilators display these curves in the form of pressure/volume or flow/volume loops, which are very useful in diagnosing various problems.

Schedule for Investigations or Tests

A bi-weekly or as per protocols of the hospital, schedule for clinical tests like haemogram, cell counts, cultures and radiography, etc. should be followed. Appearance of new signs and invasive procedures should be appropriately investigated.

WEANING FROM MECHANICAL VENTILATION

The process of discontinuation of lung ventilation is called 'weaning from ventilation' and can take several hours to days. The patient should have substantially recovered from respiratory distress, underlying disease and haemodynamically stable with minimal cardio-respiratory support. Objective assessment of readiness for weaning a patient from ventilator is based on a number of criteria given in **Table 2**. Common methods used for weaning from ventilation are as under:

Table 2: Criteria to Assess Readiness for Weaning a Patient from Mechanical Ventilation

Clinical parameters	RR: ≤35 per minute with RSBI: <100 Stable haemodynamic state
Spirometric values	Tidal volume: ≥5 mL/kg Vital capacity: ≥10 mL/kg Minute ventilation ≤10 L/min Inspiratory pressure: < –25 cm H_2O (e.g. –26 to –50 cm H_2O)
Blood gas values	SpO_2: ≥ 90% with FiO_2: ≤0.5 Alveolar-arterial O_2 gradient: <400 mmHg on 100% oxygen

T-Piece Trial

After short duration of ventilation, the ventilator is stopped abruptly and oxygen (4 to 5 L/min) is administered through a T-piece attached to tracheal tube and after a successful trial of 90 min to 2 hours, trachea is extubated.

Spontaneous Mode

Instead of attaching a T-piece, the ventilator is switched over to spontaneous mode, PSV value is reduced to 5-6 cm H_2O (to overcome the resistance of breathing circuit) and FiO_2 30% to 40% and extubation can be done after 90 min to 2 hours trial.

Gradual Weaning

Patients after prolonged ventilation are weaned by gradually decreasing ventilatory support. Sustained tolerance of SIMV rate ≤4, PSV or iPAP level <8 and PEEP ≤5 alongwith FiO_2 of less than 50%, is followed by spontaneous mode or T-piece trial and extubation of trachea. Weaning is not always straight forward and on several occasions it becomes difficult to wean. Risk factors include advancing age, COPD, malnutrition, sepsis, electrolyte imbalance and neuro-muscular diseases. Strategies like more gradual weaning, optimisation of nutrition and electrolyte balance, intermittent nocturnal ventilation, non-invasive CPAP or BiPAP may be helpful. Ventilator dependence is both physical and psychological and should be treated accordingly.

Post-Ventilation Care

After termination of ventilation, the patient should be monitored in ICU or in high dependency unit for next 24 to 48 hours to rule-out recurrence of respiratory distress.

NON-INVASIVE VENTILATION

Non-invasive ventilation (NIV) is accomplished with an airtight interface, e.g. facemask, nasal mask or NIV helmet and invasive airways like tracheal tubes are not used. Two methods of NIV are available, one employs positive airway pressure and the other applies negative pressure to the chest wall (for complete review, refer to the chapter on NIV).

OTHER METHODS OF VENTILATION

High Frequency Jet Ventilation

High frequency jet ventilation employs a jet of gas into the upper airway with air entrainment and is based on Bernoulli's principle.

High Frequency Positive Pressure Ventilation

High frequency positive pressure ventilation delivers RR between 60 to 180 per minute and $V_T \geq$ anatomical dead space (V_D).

High Frequency Oscillations

High frequency oscillations deliver RR 180 to 3000 per minute and $V_T \leq V_D$.

The above three are un-conventional modes, require different types of ventilators and mechanism of gas exchange is not clear. Various mechanisms, like Taylor dispersal, gas velocity, convection, pendelluft, mass diffusion, and mixing due to cardiac pulsations may be responsible for gas exchange. Successful oxygenation has been reported in some patients where conventional ventilation proved ineffective.

VENTILATOR SETTINGS FOR COMMON CLINICAL CONDITIONS

Acute Respiratory Distress Syndrome

Initial ventilator settings for these patients should be high FiO_2, V_T 6 to 8 mL/kg, RR 12 to 15 per minute and a PEEP of 5 to 7 cm H_2O. Further ventilator adjustments should be done on the basis of blood gas analysis after about one hour of ventilation. PaO_2 ≥60 mmHg, permissive hypercapnoea with $PaCO_2$ ≥50 mmHg and a pH ≥7.2 should be the objective. Acute rise in $PaCO_2$ can cause ventricular arrhythmias, therefore, careful monitoring of ECG is essential. Since ARDS is one of the most complex lung conditions, all modes, e.g. APRV, IRV and non-conventional modes have been used with variable success. Neuromuscular blockers should be considered for first 48 hours.

Acute Severe Asthma

These patients have hyper-reactive airways and tracheal intubation further worsens the bronchospasm. Intravenous ketamine (2 mg/kg) is the drug of choice due to its sympathomimetic and bronchodilator properties. Intravenous lignocaine 1.5 to 2 mg/kg, administered 90 to 120 seconds before intubation may also be effective (evidence weak) in controlling the bronchospasm. Initial ventilator settings include V_T 6 to 8 mL/kg, RR 8-10 per minute, higher flow rate (80-100 L/min), plateau pressure of 25-30 cm H_2O and peak inspiratory pressure 30-35 cm H_2O. Although higher flow rate decreases inspiratory time, it might increase peak inspiratory pressure. Alternatively, pressure control mode with cycling pressure up to 40 cm H_2O may be used. Permissive hypercapnoea ($PaCO_2$ ≤50 mmHg and a pH >7.2 may also be allowed. Since these patients are likely to receive high doses of steroids, therefore muscle relaxants should be avoided unless absolutely necessary due to increased risk of myopathy. Ventilator with in-built nebuliser should be preferred, otherwise provision for attaching a nebuliser should be made.

Chronic Obstructive Pulmonary Disease

COPD patients are better managed with NIPPV using CPAP or BiPAP modes. ePEEP should be 75% to 80% of auto-PEEP or 6 to 8 cm H_2O. Since these patients are accustomed to hypercapnoea, $PaCO_2$ ≤ 90 mmHg with a pH ≥7.2 may be allowed with vigil for CO_2 narcosis and cardiac arrhythmias. Ketamine and lignocaine as described above should be preferred for laryngoscopy and tracheal intubation. The V_T of 8 to 10 mL/kg and RR of 10 to 12 per minute with moderate FiO_2 is usually sufficient. Ventilator is disconnected briefly in case of hypotension. Improvement in pulse volume and blood pressure indicates air trapping and the need for reduction of PEEP, V_T or RR to prolong exhalation.

Cardiogenic Pulmonary Oedema (CPO)

Administer high FiO_2, morphine and keep the patient propped up during transport, intubation and ventilation. Initial ventilator settings should include V_T of 8 to 10 mL/kg, RR of 12 to 15 per minute, high FiO_2 usually 100% and PEEP of 10 cm. Bladder catheterisation should precede administration of diuretics and aggressive treatment of underlying cardiac defect should commence along with. Role of NIPPV continues to be controversial in CPO despite certain reports of successful oxygenation.

Interstitial Fibrosis

These patients have fast time constants for inflation and emptying of lungs along with severe diffusion block. Ventilator

should include V_T of 5 to 6 mL/kg, RR of ≥ 16 per minute (I:E ratio 1:1 and IRV is well tolerated) and high FiO_2 are required along with PEEP of 5 to 10 cm. Treatment of interstitial fibrosis comprises of immunosuppressants and steroid administration. Muscle relaxants should be avoided and strict aseptic precautions are needed.

Normal Lungs

This group of patients includes poisoning, snake bite, tetanus, head injury and Guillain-Barré syndrome, etc. These patients have normal lung mechanics and maintain oxygenation with FiO_2 of 30% to 40%. $PaCO_2$ of 35 to 40 mmHg (30 to 35 mmHg in head injury patients) and a basal PEEP of 5 cm is usually sufficient. High FiO_2 reduces the half-life of carboxyhaemoglobin, therefore, CO poisoning should be treated with FiO_2 of 100% oxygen the first few hours (6 to 8 hours).

Progressive Neurological Diseases

Motor neuron disease and lateral sclerosis patients develop nocturnal dyspnoea due to decreased muscle tone and fatigue. These patients are managed with night time NIPPV using CPAP or BiPAP modes. Ventilation eventually needs to be terminated by observing 'care of the dying patient' protocols.

SPECIAL SITUATIONS

Pregnancy

Institution of MV imposes stress and may result in premature expulsion of foetus. Obstetrician and paediatrician should also be involved in the management. Viable foetus may require surgical extraction.

Paediatric Patients

Paediatric patients are more vulnerable to ventilator-induced lung injury. Usually pressure cycled ventilators are used and pediatric breathing circuits should be used below 25 kg body weight. Neonates and infants require different types of ventilators.

COMPLICATIONS OF MECHANICAL VENTILATION

MV can result in or contribute to a number of complications. Major complications are listed in **Table 3** and discussed below.

Respiratory System

The diseased lung units have low compliance and or high resistance. MV is preferentially delivered to normal lung units, which may be damaged by excessive pressure or volume delivered by mechanical ventilators. Rupture of alveoli can lead to life-threatening conditions, like tension pneumothorax and pneumomediastinum. Surfactant depletion and oxygen toxicity have also been implicated as reasons for lung damage. Prolonged ventilation leads to disuse atrophy of respiratory muscles and may contribute to ventilator dependence.

Cardiovascular System

Positive intrathoracic pressure impairs the venous return, increases right ventricular afterload and may cause left ventricular dysfunction leading to reduced cardiac output and hypotension. Institution of MV relieves the respiratory distress and levels of circulating catecholamines fall rapidly, leading to further hypotension and sometimes cardiac arrest. These cardiac effects are directly related to the mean airway pressure, and therefore, modes like PEEP/CPAP and IRV have more pronounced effect. This compromised haemodynamic state with decreased cardiac output and low perfusion pressure results in decreased delivery of oxygen and nutritional substrates to vital organs and contributes to multi-organ failure.

Table 3: Complications of Mechanical Ventilation

Organ System	Complications	Prevention/Treatment
Respiratory system	Volume trauma, tension pneumothorax, deterioration of blood gas status	Use appropriate ventilator modes and settings Optimise PEEP, flow rate, FiO_2 and I:E ratio
Cardiovascular system	Hypotension, cardiac arrest	Optimise volume status, adjust ventilator settings, PEEP
Psychological	Acute stress and post-traumatic stress disorder (PTSD)	Sedation, communication and reassurance
Immunological	Infection, sepsis	Use of VAP bundle approach handwashing, aseptic precautions, good hygienic status, avoid re-use of disposable items
Aspiration of gastric contents	Pneumonia, gastric acid aspiration syndrome	Early securing of airway, regularly check tracheal tube cuff leakage, observe NPO before change of tracheal tubes, regularly check Ryle's tube position Use of PPIs/ H2 Blockers/ sucralfate, Head end elevation to 30-45°
	Long-term complications	
Prolonged intubation	Vocal cord polyps and granulomas	Use appropriate size tracheal tubes, early tracheostomy
Tracheostomy	Tracheal stenosis	Decanulation with gradually decreasing diameter of tracheostomy tubes (while in hospital), tracheal dilatation or resection of affected segment
Psychological	PTSD	Psychologist/Psychiatrist consultation

PEEP = Positive end-expiratory pressure; FiO_2 = Fraction of inspired oxygen; NPO = Nil per os

Psychological

Artificial airways, mechanical breaths and suctioning are both physically and emotionally distressing. Sleep deprivation, invasive procedures, tones and alarms of monitors, inability to communicate and isolation from family impose additional stress. A state of post-traumatic stress disorder may follow even after discharge from hospital.

Infection

Nosocomial infections and ventilator-induced pneumonia are well known. Patients are vulnerable to infection due to invasive procedures, indwelling lines and catheters and stress.

Aspiration

Despite tracheal intubation, the patients remain at high-risk for aspiration of gastric contents. Checking of nasogastric tube position and residual gastric residual volume (GRV) before administration of feed or enteral drugs is important. Positive pressure NIV may cause gastric inflation especially in debilitated and comatose patients.

Long-Term Complications

Prolonged intubation and tracheostomy may cause tracheal stenosis, vocal cord polyps and granulomas in the long run. There is no consensus as to whether tracheal intubation or tracheostomy is better. However, tracheostomy should be done early if ventilation or airway protection is anticipated for longer than 3 weeks.

CONCLUSION

In critical situations it is important to secure the airways at first possible opportunity to prevent aspiration and its associated complications. Oxygen should be given till the time of start of ventilation. Use high (100%) concentration of oxygen before tracheal intubation. Once the ventilation has started, send ABG after 1 hour. Strictly avoid using the same catheter for suction and its size be appropriate. Time of suction should preferably be not beyond 5-10 second each time. Nasogastric suction should be done before emergency interventions. In case of ventilation malfunction use manual ventilation. Patient should be kept NPO for 4-6 hours before change of tubes.

Maintain and constantly monitor all pulmonary and circulatory parameters.

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7.9 Non-Invasive Ventilation

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INTRODUCTION

Non-invasive ventilation (NIV) is the delivery of the mechanical ventilation to the lungs using techniques that do not require an endotracheal airway. Three basic methods of applying NIV are: negative pressure ventilation, abdominal displacement ventilation and positive pressure ventilation (PPV). However, for practical purposes, NIV now refers to PPV administered via mask or interface that directs pressurised gas into the upper airway.

The use of PPV goes back as far as 1780, when the first bag-mask apparatus was designed for resuscitative efforts. Over the years, it has evolved as being used as a means to deliver aerosolised medications periodically, to being used in patients with acute respiratory failure (ARF) due to chronic obstructive pulmonary disease (COPD) and asthma. Today NIV is used in both acute and chronic care settings, like COPD, asthma, neuromuscular diseases, heart failure, obstructive sleep apnoea, etc.

EQUIPMENT FOR NON-INVASIVE POSITIVE PRESSURE VENTILATION (NPPV)

The equipment needed for NPPV generally includes ventilators, humidifiers and the interfaces or masks.

Types of Ventilators

NPPV has been successfully applied using portable volume ventilators, adult intensive care ventilators and portable pressure support (pressure-targeted) ventilators. The choice of ventilator depends on the level of support required and the advantages and disadvantages of the appropriate machines.

Pressure targeted ventilators

Portable pressure-targeted ventilators (PTVs) are also known as continuous positive airways pressure (CPAP) ventilators, pressure support ventilators or bilevel pressure ventilators. These ventilators are microprocessor controlled, electrically powered units that use a blower to regulate gas flow into the patient's circuit to maintain the preset pressure at the patient's connection. PTVs have a single circuit gas delivery system that uses an intentional leak port for patient exhalation instead of a true exhalation valve.

PTVs are pressure limited, flow and time triggered, flow and time cycled ventilators. These are designed to increase minute ventilation and improve gas exchange capabilities with the delivery of an inspiratory positive airway pressure (IPAP), and an expiratory positive airway pressure (EPAP). Most portable PTVs offer the CPAP, assist mode, assist/control (A/C), control (or timed) mode of ventilatory support.

In CPAP mode, the patient breathes spontaneously at a set baseline pressure and controls both the rate and depth of breathing. Flow sensors and pressure transducers respond to patient's inspiratory and expiratory efforts, and increased or decreased flow through circuit to maintain a stable pressure.

In the assist mode, a change in the set IPAP occurs in response to the patient's inspiratory efforts. In A/C mode, all respiratory efforts initiated by the patient are supported to the IPAP level, as in the assist mode, but a minimum breathing rate may also be set. If a patient fails to make an inspiratory effort within a set interval, the machine triggers inspiration to set the IPAP.

The control mode delivers pressure support breaths based on control settings, not patient's efforts. The clinician sets the IPAP and EPAP, the number of breaths per minute and the inspiratory time percentage. The breaths are time triggered to the IPAP, based on the rate set. IPAP then cycles to EPAP based on the IPAP percentage. In all modes, delivered tidal volume (V_T) depends on the gradient between the IPAP and the EPAP, the inspiratory time, patient's inspiratory effort, and the patient's lung characteristics. PTVs ability to deliver flow in response to patient demand is the same as or superior to that of intensive care unit (ICU) adult ventilators and portable volume ventilators. PTV's also allow adjustment of the amount of time required to reach the IPAP. Two other comfort features of PTVs include RAMP and delay time controls. RAMP allows positive pressure to increase gradually over a set interval (delay time) of time. The RAMP rate generally can be set in increments of 1, 2, or 3 cm H_2O, and delay time can be set in 5 minutes increments from 5 to 30 minutes.

Portable PTVs have certain limitations that may restrict their use in ARF. The oxygen delivery is not standard on most portable PTVs. Therefore, fraction of inspired oxygen (FiO_2) can vary and is affected by flow rate, type of leak port in the system, site where oxygen is bled into the circuit, and IPAP and EPAP. Higher oxygen flow rate results in higher oxygen concentrations. Lower IPAP and EPAP levels also yield higher oxygen concentrations. If leak port is in the circuit, higher oxygen concentrations can be obtained, if the oxygen is bled into the patient's mask.

Rebreathing of carbon dioxide (CO_2) is a concern with any type of PTVs that use a single circuit gas delivery system. The flow of gas through the leak port depends upon the EPAP settings and the patient's inspiratory to expiratory ratio. At low EPAP settings (< 4 cm H_2O) and at a high respiratory rate, flow may not be adequate to flush CO_2 from the circuit.

Portable volume ventilators

Portable volume ventilators were designed originally for invasive ventilation in home and extended care facility. These are patient or time triggered, pressure limited and volume cycled.

The newer generation of these ventilators has both volume and pressure targeted modes with positive end-expiratory pressure (PEEP) capabilities. These ventilators are more responsive to patient flow needs and can be used for either invasive or NIV. These are not equipped with an internal blender, hence precise oxygen concentrations are not possible and like portable PTVs

oxygen must bled into the system through an adaptor from a separate oxygen source. As such they are ideal for achieving a seamless transition from the extended care facility to the home.

Adult acute care ventilators

Ventilators used in adult critical care settings offer more ventilator support options, more alarms, a precise FiO_2 and more monitoring features than portable PTVs. Although pressure support mode is the most commonly used to administer NPPV, volume or pressure controlled modes combined with PEEP can also be administered via mask interface.

The most significant disadvantage of these ventilators is the inability of some machines to compensate for leaks. Although studies have demonstrated no significant differences in gas exchange between volume and pressure targeted modes, volume control modes are seldom used to deliver NPPV in acute care settings. However, volume control modes are more likely to be used in the chronic care settings in patients with neuromuscular disorders.

Humidification during Non-Invasive Pressure Ventilation

Excessive drying of the nasal mucosa with the administration of nasal CPAP or NPPV has been associated with nasal congestion and increased resistance. This is a leading cause of patient's discomfort and non-compliance. Humidification can prevent and improve mucosal dehydration. A passover type of heated humidifier should be used because heated bubble humidifiers, and heat and moisture exchangers, increase airway resistance in the ventilator circuit and may also interfere with patient triggering.

Interfaces

The effectiveness of NPPV is greatly influenced by the interface chosen to deliver the PPV. Various commonly used interfaces are described in **Table 1**.

RATIONALE OF VENTILATION

In ARF, NPPV is considered a life-saving application that offers a number of benefits over invasive ventilation (**Table 2**). The most significant is the avoidance of intubation. The physiological goal of NPPV in ARF is to improve gas exchange by resting respiratory muscles and increasing alveolar ventilation. NPPV reduces diaphragmatic swings, which suggests that respiratory muscles are being rested. In addition, when PEEP is applied during the pressure support ventilation, it helps offset intrinsic PEEP (PEEPi), thereby reducing the work to initiate inspiration. Like-wise pressure support facilitates inspiration, thus increasing V_T. Resting of respiratory muscles and improved V_T lead to a lower arterial partial pressure of CO_2 ($PaCO_2$), better oxygenation and decreased respiratory rate (**Figures 1 and 2**).

Table 2: Benefits of Non-invasive over Invasive Ventilation

Acute care
Reduces need for intubation
Reduces incidence of hospital acquired pneumonia
Shortens ICU and hospital stay
Reduces mortality
Preserves airway defenses
Improves patient comfort
Reduces need for sedation
Chronic care
Alleviates symptoms of hypoventilation
Improves sleep quality
Improves functional capacity
Prolongs survival

INDICATIONS AND CONTRAINDICATIONS OF NON-INVASIVE VENTILATION

The goals of NPPV and the indications for its use are based upon decades of clinical expertise and systemic research. The various

Table 1: Various Interfaces in Non-Invasive Positive Pressure Ventilation

Interface	Advantages	Disadvantages
Nasal mask	Easy to fit Less feeling of claustrophobia Low-risk of aspiration Allows patient to cough and clear secretions Maintains ability to speak and eat Less mechanical dead space More useful for chronic lung conditions	Mouth leaks Eye irritation Facial skin irritation Ulceration over nose bridge Oral dryness Nasal congestion Increased resistance through nasal passages Not used in acute lung conditions
Full face (oronasal) mask	Reduces air leakage through the mouth Less airway resistance Used in acute lung conditions	Increased risk of aspiration Increased risk of asphyxia Increased dead space Claustrophobia Difficult to secure and fit Facial skin irritation Ulceration over nasal bridge Patient must remove mask to eat, speak, or expectorate secretions
Nasal pillows or seals	Same as for nasal mask	Pressure sores around nares
Mouth piece	Facilitates communication Less feeling of claustrophobia Low-risk of aspiration Allows patient to cough and clear secretions Low-risk of carbon dioxide rebreathing No head gear requirements	Nasal air leakage Hypersalivation Possibility of orthodontic deformity

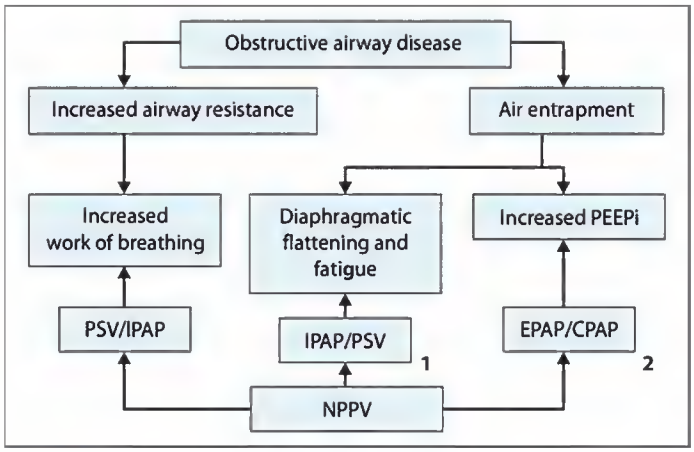


Figure 1: Mechanism of action of NPPV in obstructive airway disease.

1. Augments tidal volume; 2. Decreases inspiratory threshold
PEEPi: Intrinsic Positive end-expirotory pressure; IPAP = Inspiratory positive airwoy pressure; EPAP = Expirotory positive airway pressure; CPAP = Continous positive oirway pressure; NPPV = Non-invosive positive pressure ventilation

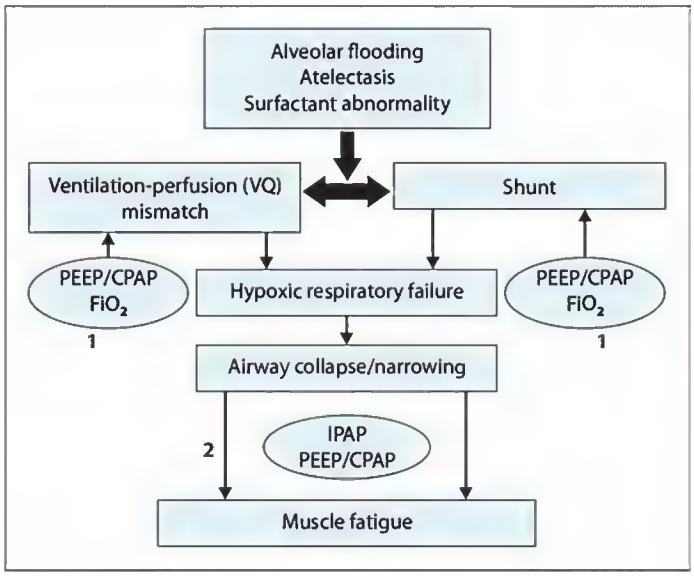


Figure 2: Mechanism of action of NPPV in hypoxaemic respiratory failure.

1. Improves FRC/Oxygenation; 2. Decreases work of breathing, rests muscles, decreoses CO_2

indications both in acute as well as chronic respiratory failure are mentioned in **Table 3**.

Table 3: Indications for Non-Invasive Ventilation

Obstructive Diseases	Hypoxaemic Respiratory Failure
COPD (A)	Acute pulmonary oedema (A)
Asthma (B)	Pneumonia (B)
Cystic fibrosis (C)	ARDS (C)
Upper airway obstruction (C)	Trauma (C)
Restrictive diseases (mainly long-term setting)	**Categories of acute respiratory failure**
Kyphoscoliosis (C)	Facilitation of weaning (A)
Neuromuscular disease (C)	Immunocompromised patients (A)
Obesity-hypoventilation syndrome (C)	Post-operative respiratory failure (B)
	Extubation failure (B)
	Do not intubate patients (C)

Letter in parenthesis indicote level of evidence: A = Multiple controlled trials; B = A single supportive controlled trial; C = Uncontrolled triols, case reports
COPD = Chronic obstructive pulmonary disease; ARDS = Acute respirotory distress syndrome

SPECIFIC INDICATIONS

Acute Indications

Chronic obstructive pulmonary disease

The main objective of NIV in acute exacerbation of COPD is not only to relieve symptoms of the disease but also to reduce associated mortality and morbidity. During an acute exacerbation, there is an increase in airway resistance and an increased respiratory rate which together lead to hyperinflation and development of PEEPi. As hyperinflation increases, respiratory muscle activity also increases leading to an increase in the work of breathing, and hence, oxygen consumption. This together with impaired diaphragmatic mechanics leads to a vicious cycle of hypoventilation, air trapping and muscle fatigue. By combining high inspiratory pressure with low expiratory pressure, NIV effectively reduces the diaphragmatic work of breathing, and hence, benefit the patient during acute exacerbations by acting as a crutch to support the patient while medical treatment is given time to work.

Unless contraindicated, NIV is to be preferably given to patients with acute exacerbations having respiratory distress and respiratory failure instead of conventional therapy alone, as NIV has been shown to reduce respiratory rate, improve dyspnoea and gas exchange, cause improvement of arterial blood gas levels, shortens duration of hospital and ICU stay, reduces intubation rate by three-fourth as well as complication and mortality rates. The indications of NPPV are mentioned in **Table 4**.

Table 4: Indications of Initiating NPPV in Acute Exacerbations of Chronic Obstructive Pulmonary Disease*

Respiratory distress with moderate-to-severe dyspnoea
Use of accessory muscles of respiration
Abdominal paradox
Respiratory rate > 30/min
pH <7.35; $PaCO_2$ >45 mmHg; PaO_2 <60 mmHg

** Any two of the above if present, NPPV should be initiated.*

NIV can also facilitate early weaning in those intubated patients with COPD who could not be extubated due to multiple failed "T" piece breathing trials. By facilitating early extubation in such patients, NIV reduces occurrence of nosocomial pneumonias, improves breathing rates, and shortens duration of ventilator use, NIV cap prevent re-intubation when used immediately after extubation for COPD patients at high risk of extubation failure and also reduce hospital stay and mortality.

Acute cardiogenic pulmonary oedema

CPAP has been in use to treat acute cardiogenic pulmonary oedema (CPE) since 1930s. The increased intrathoracic pressure reduces transmyocardial pressure, as well as the pre-load and after-load; thereby enhancing cardiac function in patients with left ventricle dysfunction who are dependent on after-load. CPAP leads to an increase in functional residual capacity, secondary to opening of collapsed alveoli and rapidly improves compliance and oxygenation. It is highly effective in improving oxygenation, lowering respiratory rate, decreasing sensation of dyspnoea, and thereby, helps in avoiding intubation.

Studies comparing NPPV with CPAP demonstrated more rapid improvement in $PaCO_2$ and pH in the former, but the mortality and intubation rates were almost similar. A disconcerting finding

was a higher incidence of myocardial infarction in NPPV group (71% *versus* 31%). The current recommendation is to use CPAP (10-12 cm H_2O) initially for the treatment of CPE and that NPPV be used only in patients who continue to be hypercapnic and dyspnoeic thereafter.

Hypoxaemic respiratory failure

Evidence of the efficacy of NPPV in the treatment of hypoxic respiratory failure has been inconsistent. Various studies comparing NPPV plus usual medical care have shown better gas exchange, reduced need for ventilation and decreased mortality rate. On the other hand, some studies found no significant improvement in the patients' overall outcomes unless the patients were also hypercapnic. Due to heterogeneity of disorders in this group, these findings cannot be applied to individual patients and need further studies for application of NPPV in these patients.

Acute respiratory distress syndrome

Mixed success has been reported in patients with acute respiratory distress syndrome treated with NIV. It can be tried in patients with mild oxygenation defects, but otherwise stable with only a single organ dysfunction. NIV should be started only in carefully selected patients within this group and intubation should be contemplated if there is no substantial improvement in oxygenation within the first hour.

Pneumonia

Use of NIV in community-acquired pneumonia is becoming more common. Various studies have outlined significant benefits of early use of NIV in patients with severe community-acquired pneumonia which include reducing the need for intubation, shortening stay in ICU and decreasing nosocomial infections. However, the advantages of NIV in community-acquired pneumonia are seen mostly in patients with underlying COPD. Further studies are needed to define the optimal mode of ventilation and the specific patient population (especially, patients without COPD) who might benefit the most.

Chest trauma

Rapid improvement in gas exchange and low intubation rates are expected among patients with chest trauma. NIV can also be used to facilitate extubation in such patients.

Post-operative patients

NIV in post-operative patients has the potential to improve many physiological parameters without apparent serious side-effects. After high-risk surgeries, especially of thorax and upper abdomen, NIV can be used to prevent complications like hypoxaemia, pneumonia and atelectasis, and reduces the rate of intubation. NIV can also be used to treat frank respiratory failure in these patients.

Difficult to wean/facilitation of weaning

NIV can be used to facilitate weaning as well as in supporting patients who develop ARF after extubation. Current data support the use of NIV in patients with risk factors for extubation failure, particularly if they have co-existing COPD, congestive heart failure and/or hypercapnia. However, early indiscriminate use of NIV in patients who have risk factors for extubation failure, but do not meet standard criteria for initiation of NIV should be discouraged. Patients with extubation failure treated with NIV should be monitored closely and if intubation is needed, delay should be avoided.

Do not intubate

The argument in favour of NPPV with "do not intubate status" is that NPPV may relive severe dyspnoea and preserve patient comfort. It may also reverse the acute process in disorders, such as COPD or pulmonary oedema, and allow the patient to live longer. The argument against NPPV is that it could actually prolong the dying process, adds to patient discomfort and consume valuable resources, and may be deemed unethical. It is necessary for patients' family and care-givers to understand these goals and to cease promptly if the goals are not being accomplished.

Long-Term Indications

Chronic respiratory failure due to restrictive thoracic diseases

Patients with restrictive thoracic diseases presenting with features of chronic respiratory failure like symptoms of hypoventilation such as morning headache or day-time hypersomnolence, severe pulmonary dysfunction may benefit from NIV. NIV ameliorates decline in lung function and improves gas exchange, cognitive function and overall survival in such patients.

Guidelines for initiating NIV in patients with chronic respiratory failure due to restrictive thoracic diseases are mentioned in **Table 5**.

Table 5: Guidelines for Non-Invasive Positive Pressure Ventilation Therapy in Restrictive Lung Disease on Long-term Basis*

1. Symptomatic despite optimal medical therapy AND
2. Severe pulmonary dysfunction OR
   - FVC ≤50% predicted
   - MIP ≥60 cm H_2O
3. Gas exchange disturbance
   - Chronic CO_2 retention ($PaCO_2$ >45) or
   - Nocturnal hypoventilation (as evidenced by O_2 saturation <88% for ≥5 consecutive minutes while breathing room air)

** 1 plus any of 2 or 3 if present, NPPV is indicated*

Patients with chronic hypoventilation syndromes due to neuromuscular diseases, chest wall or spinal deformity and obesity hypoventilation syndrome also respond gradually over a few weeks after initiation of mechanical NIV. Amelioration of nocturnal hypoventilation and improvement of sleep quality are the major consequences of this therapy and probably the major reasons for daytime improvement.

Chronic respiratory failure due to chronic obstructive pulmonary disease

Evidence of the efficacy of long-term nocturnal NPPV is vague and often contradictory in patients with severe stable COPD. Although evidence is inconclusive, the current professional consensus and guidelines recommend that patients with severe day-time CO_2 retention ($PaCO_2$ >52 mmHg) and nocturnal hypoventilation despite nocturnal oxygen therapy should be considered for NPPV therapy.

Obstructive sleep apnoea

Obstructive sleep apnoea is a life-threatening condition where nasal CPAP is the treatment of choice. Positive pressure may

provide a mechanical stent to the upper airway in such patients and prevent apnoea in all sleep stages, preferably in supine and lateral positions. As higher pressure can be uncomfortable for sleep, the minimal pressure that reasonably eliminates most respiratory disturbances like snoring and arousal together with elimination of oxygen desaturation is recommended. The American Academy of Sleep Medicine guidelines for CPAP recommend its use in patients who have apnoea-hypopnoea index (AHI) greater than 20 and for symptomatic patients who have an AHI or respiratory arousal index greater than 10.

CONTRAINDICATIONS

NIV should not be used in unconscious patients or in patients unable to protect upper airways, intractable hypotension and facial burns (**Table 6**).

Table 6: Contraindications of Non-Invasive Positive Pressure Ventilation

Respiratory arrest or need for intubation
Haemodynamic instability
Inability to protect the airway
Excessive secretions
Agitated and confused patient
Facial deformities or conditions that prevent mask from fitting
Uncooperative or unmotivated patient
Brain injury with unstable respiratory drive
Severe respiratory acidosis
Facial trauma or burn

INITIATION OF NON-INVASIVE VENTILATION

After selecting the ventilator and interface, the physician is responsible for initiating NPPV. Steps for initiation of NIV have been described in **Table 7**. The initial ventilator settings usually consist of an IPAP of 10 cm H_2O and an EPAP of about 4 to 5 cm H_2O. The difference between the IPAP and EPAP is the level of inspiratory support. IPAP augments the tidal volume and hence alveolar ventilation, increases airway pressures and decreases fatigue. EPAP prevents airway and alveolar collapse, prevents atelectasis and maintains functional residual capacity at increased level and maintains oxygenation. Slowly increasing IPAP to maintain an exhaled V_T at 5 to 7 mL/kg or higher may result in decrease in the respiratory rate. If EPAP is increased, IPAP may also need to be increased to maintain the same gradient between IPAP and EPAP, and thus ensure adequate V_T delivery.

Table 7: Steps for Initiating Non-Invasive Positive Pressure Ventilation

1. Place the patient in an upright or sitting position. Carefully explain the procedure for NPPV, including goals and possible complications.
2. Using a sizing gauge, make sure a mask is chosen that is the proper size and fit.
3. Attach the interface and circuit to the ventilator. Turn on the ventilator and adjust it initially to low pressure settings (e.g. IPAP 10 cm H_2O/ EPAP 4 cm H_2O).
4. Hold or allow the patient to hold the mask gently to the face until the patient becomes comfortable. Encourage the patient to use proper breathing technique.
5. Monitor oxygen saturation; adjust the FiO_2 to maintain saturation above 90%.
6. Secure the mask to the patient
7. Titrate the IPAP and EPAP to achieve patient comfort, adequate exhaled tidal volume. Do not allow peak pressures above 20 cm H_2O.
8. Check for leaks and adjust the straps, if needed.
9. Monitor heart rate, respiratory arte, level of dyspnoea, minute ventilation and exhaled tidal volume.
10. Obtain blood gas within 1 hour.

Monitoring during Non-Invasive Positive Pressure Ventilation

Several studies have identified possible indicators of success of NPPV in both the acute and chronic care settings (**Table 8**). A patient of ARF must be closely monitored in ICU/emergency department so that if NPPV is unsuccessful, patient can be immediately intubated (**Table 9**). The indications of intubation and termination of NPPV in favour of invasive ventilation are mentioned in **Table 10**.

Table 8: Indicators of Successful Non-Invasive Positive Pressure Ventilation

Higher level of consciousness
Younger age
Less severe illness
Less severe gas exchange abnormalities (pH 7.10–7.35; $PaCO_2$ < 92 mmHg)
Minimal air leakage around interface
Intact dentition
Synchronous breathing efforts with ventilator
Lower quantity of secretions
Absence of pneumonia
Positive response to NPPV within 1 to 2 hours
Correction of pH
Decreased respiratory rate
Reduced $PaCO_2$

Table 9: Parameters to be Monitored during Non-Invasive Positive Pressure Ventilation

Subjective responses
Patient comfort
Discomfort related to the mask
Respiratory distress
Vital signs and physical findings
Respiratory rate
Blood pressure
Ability to cough and raise secretions
Accessory muscle use
Ventilator function
Patient-ventilator synchrony
Tidal volume ≥ 6 ml/kg
Air leaking
Waveforms (if available)
Gas exchange
Continuous oximetry
Change in $PaCO_2$ if hypercapnic
Change in pH

Table 10: Indicators to Terminate Non-Invasive Positive Pressure Ventilation and Switching to Invasive Ventilation

Worsening pH and $PaCO_2$
Tachypnoea (> 30/min)
Haemodynamic instability
Oxygen saturation > 90%
Decreased level of consciousness
Inability to clear secretions
Inability to tolerate interface

Complications

NPPV is considered much safer than invasive ventilation. Complications with NPPV usually are related to mask discomfort, air pressures or gas flows (**Table 11**).

Table 11: Complications Associated with NPPV/CPAP Therapy

Complications	Corrective Action
Mask discomfort	Check mask for correct size and fit
Excessive leak around mask	Minimise headgear tension
Pressure sores	Use spacers or change to another style of mask Use wound care dressing over nasal bridge
Nasal and oral dryness or nasal congestion	Add or increase humidification Irrigate nasal passages with saline Use chin strap to keep mouth closed Apply topical decongestants Change to full face mask
Mouthpiece/lip seal leakage	Use nose clips Use custom made oral appliances
Aerophagia, gastric distention	Use lowest effective pressures for adequate tidal volume delivery Use simethicone agents
Aspiration	Make sure patients are able to protect the airway
Mucous plugging	Ensure adequate patient hydration Ensure adequate humidification Avoid excessive oxygen flow rates (>20 L/min) Allow short breaks from NPPV to permit directed coughing techniques
Hypotension	Avoid excessively high peak pressures ($\leq$ 20 cm H_2O)

Patient Weaning and Discontinuation of Non-Invasive Positive Pressure Ventilation

The duration of ventilator assistance with NPPV depends on how quickly the cause of respiratory failure can be reversed. The most common approach involves increasing periods of time off mask ventilation. If signs of respiratory distress occur, the patient is placed back on mask ventilation immediately. Prolonging the periods of ventilator interruption, when the patient is experiencing respiratory distress, may lead to rapid decompensation and need for emergency intubation. Another approach to wean is to gradually reduce the level of pressure support to a minimum level, allowing the patient to assume more of the work of breathing. Regardless of the method of weaning, the reversibility of the disease process that caused respiratory failure is the most important factor for successful weaning.

CONCLUSION

Evidence supports the use of NPPV in the treatment of respiratory failure secondary to COPD, CPE, immunocompromised state in acute care settings and weaning in COPD. Evidence is weak for use of NPPV in other indications and should not be used routinely, patients should be selected carefully. NPPV is used to avoid intubations and not replace it. Therefore, threshold for intubation should be low in acute care settings. It should be avoided in patients having multiple organ dysfunction syndrome, unconscious patients and patients with burn and facial trauma; whereas in chronic care, NPPV is the modality of choice in managing respiratory failure in patients having thoracic disorders and neuromuscular disorders.

Proper fitting of interface is essential for the success of NPPV. Proper ventilator settings and mask are more important than ventilation for patient comfort and compliance.

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7.10 Hypotension and Shock

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DEFINITION

Definition of shock includes the following haemodynamic parameters to be identified:

1. Persistent hypotension [systolic blood pressure (SBP) <80 to 90 mmHg or mean arterial pressure (MAP) 30 mmHg lower than baseline].
2. Severe reduction in cardiac index (CI) <1.8 L/min/m^2 without support or <2.0 to 2.2 L/min/m^2 with support.
3. Adequate or elevated filling pressure [(e.g. left ventricular (LV) end-diastolic pressure >18 mmHg or right ventricular (RV) end-diastolic pressure >10 to 15 mmHg].

The diagnosis is usually made with the help of pulmonary artery catheterisation; however, echocardiography may also be used to confirm elevation of LV filling pressures. The clinical manifestations are due to hypoperfusion such as cold extremities, decreased urine output, and/or alteration in mental status.

CLASSIFICATION

Hinshaw and Cox classification based on cardiovascular characteristics, is the most practical classification of shock. It divides the syndrome into four major categories: hypovolaemic, cardiogenic, extracardiac obstructive, and distributive (**Table 1**).

Hypovolaemic Shock

It is characterised by a loss in circulatory volume which results in decreased venous return, decreased filling of the cardiac chambers, and decreased cardiac output (CO) which leads to increase in the systemic vascular resistance (SVR). The haemodynamic profile on monitoring of flow pressure variables shows low central venous pressure (CVP), a low pulmonary capillary wedge pressure (PCWP), low CO and CI, and high SVR. The arterial blood pressure may be normal or low.

Cardiogenic Shock

This is primarily dependent on poor pump function. Cardiogenic shock (CS) due to acute catastrophic failure of LV pump function is characterised by high PCWP, low CO and CI, and generally a high SVR.

Distributive or Vasogenic Shock

This type of shock is associated with not only poor vascular tone in the peripheral circulation but maldistribution of blood flow to organs within the body also. The CO varies, but is usually raised. A common haemodynamic profile is a low or normal PCWP, a high CO, a low arterial blood pressure, and a low SVR.

Extracardiac Obstructive Shock

It is associated with reduced forward circulatory flow involving mechanisms different than primary myocardial or valvular dysfunction. The haemodynamic patterns observed, depend on the cause, from significant decrease in filling pressures (as in mediastinal compression of great veins); to equalisation of pressures as in cardiac tamponade; or to increased RV filling pressures with low PCWP in the case of pulmonary embolism. CO is usually decreased with an increase in SVR.

Table 1: Classification of Shock

Hypovolaemic (Oligaemic)
Haemorrhagic
Fluid Depletion (Non-haemorrhagic)
Extensive fluid loss (dehydration)
Vomiting
Diarrhoea
Polyuria
Interstitial Fluid Redistribution
Thermal injury
Trauma
Anaphylaxis
Cardiogenic
Myopathic:
Myocardial infarction
Myocarditis
Cardiomyopathy
Septicaemia
Mechanical:
Valvular
VSD
Arrhythmia:
Severe bradycardia
Marked prolonged tachycardia
Extracardiac Obstructive
Cardiac tamponade
Constrictive pericarditis
Post-MI rupture of ventricular wall
Vena caval obstruction
Acute pulmonary hypertension
Impaired Systolic Contraction
Pulmonary embolism
Aortic dissection
Distributive
Septic shock
Anaphylaxis
Neural spinal shock
Adrenal crisis
Toxic

MI = Myocardial infarction; VSD = Ventricular septal defect

Parameters in various types of shock are shown in **Table 2**.

Table 2: Haemodynamic Parameters in Various Types of Shock

	CO	PCWP	ABP	SVR
Hypovolaemic	↓	↓	↓	↑
Cardiogenic	↓	↑	↓	↑
Vasogenic	Nor ↑	Nor ↓	↓	↓
Extracardiac	↓	Nor ↓	↓	↑

CO = Cardiac output; PCWP = Pulmonary capillary wedge pressure; ABP = Arterial blood pressure; SVR = Systemic vascular resistance; Nor = Normal.

PATHOPHYSIOLOGY

Shock of all forms involve common pathophysiological mechanisms that end in cell injury, organ failure and death. The pathogenesis of shock involves multiple inter-related factors including cellular ischaemia, circulating or local inflammatory mediators, and free radical injury.

1. Hypoperfusion decreases the delivery of nutrients to the cells leading to diminished ATP production. Essential ATP dependent intracellular metabolic processes that may be affected include maintenance of transmembrane potential, mitochondrial function and other energy-dependent enzyme reactions.

   Liver and kidney are particularly sensitive as intracellular levels of ATP fall and ATP-dependent processes are impaired.

2. The effect of inflammatory mediators on cellular metabolism is of prime importance in organ dysfunction resulting from sepsis and septic shock and also haemorrhagic shock associated with extensive trauma. Generally, it is the endotoxin from Gram-negative bacteria that triggers the inflammatory cascade but bacterial antigens and cell injury itself can also initiate the cascade. Macrophage production of cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β) appear to be the prime mediators. Other substances involved in the inflammatory process include IL-2, IL-6, interferon-γ, endothelin-1, leukotrienes, thromboxanes, prostaglandins and complement fragments C3a and C5a. Two other mediators, i.e. circulating myocardial depressant substance and nitric oxide have a role to play in septic shock.

3. Free radical injury induced by reperfusion or neutrophil activity is another mechanism by which cell and organs suffer a damage. Tissue ischaemia leads to accumulation of adenosine, inosine and hypoxanthine. With resuscitation, reperfusion of ischaemic areas occurs.

The availability of O_2 generates superoxide (O_2-) by xanthine oxidase which is converted to hydrogen peroxide (H_2O_2) which further reacts to produce the highly reactive tissue damaging hydroxyl radicals. These in turn interact with critical cell targets resulting in cell lysis and tissue injury. Oxidant activity, directly and through endothelial damage attracts and activates neutrophils causing amplification of superoxide generation and further tissue damage due to neutrophil protease release.

Other microvascular pathologic processes occurring in shock include disruption of integrity of endothelial cell barrier leading to loss of plasma proteins, decrease in plasma oncotic pressure, interstitial oedema and fall in circulating volume. In addition, there is microvascular clotting and microthrombi leading to further inadequate distribution of perfusion within tissue.

COMPENSATORY RESPONSES TO SHOCK

Various compensatory mechanisms are detailed in **Table 3**. With the onset of haemodynamic dysfunction, hemostatic compensatory mechanisms engage to maintain adequate tissue perfusion. These responses are similar for varying classes of shock and are divided into four categories: (a) maintenance of mean circulatory pressure, (b) maximising cardiac function, (c) redistributing perfusion to vital organs, and (d) optimising unloading of oxygen at tissues.

Table 3: Compensatory Responses to Shock

Volume
Fluid redistribution to vascular space
From interstitium (Starling effect)
From intracellular space (Osmotic effect)
Decreased renal fluid losses
Decreased glomerular filtration rate (GFR)
Increased aldosterone
Increased vasopressin
Pressure
Decreased venous capacitance
Increased sympathetic activity
Increased circulating (adrenal) epinephrine
Increased angiotensin
Increased vasopressin
Maximise Cardiac Performance
Increased contractility
Sympathetic stimulation
Adrenal stimulation
Redistribution of Perfusion
Extrinsic regulation of systemic arterial tone
Dominant autoregulation of vital organs (heart, brain)
Optimise Oxygen Unloading
Increased RBC 2, 3 DPG
Tissue acidosis
Pyrexia
Decreased tissue PaO_2

Diagnostic Approach and Evaluation

It is imperative, that clinicians recognise the early stages of shock at a time when it is more responsive to treatment. A monitored physiologic approach to therapy provides the best opportunity for successful outcome and avoidance of organ dysfunction. Not only is the initial resuscitative technique important but also continuous evaluation of the patient's condition.

Clinical Presentation

This varies with the previous level of organ function, compensatory mechanisms, severity of organ dysfunctions and the cause of shock syndrome. Impending shock is characterised by the typical compensatory response to cardiovascular stress. Tachycardia, tachypnoea and oliguria are the hallmark. Cold extremities are seen in hypodynamic shock. With progression, blood pressure falls and frank hypotension (MAP < 60 to 65 mmHg) ensues. With further progression, anuria, mottled, dusky extremities and altered sensorium occurs. (Detailed in **Table 4**).

Laboratory Studies

These are used not only for the confirmation of diagnosis of shock but also to know the aetiologic factors. Initial laboratory tests should include a complete blood count. Leucocyte count is frequently elevated early in shock and leucopaenia is found in sepsis and late shock. Haemoglobin level varies with the type of shock. Stress of circulatory shock increases platelet count initially, but with progression thrombocytopaenia occurs. Complete chemistry profile with serum electrolytes, creatinine, blood urea nitrogen (BUN), liver function tests, calcium, magnesium and phosphate levels, serum lactate levels, prothrombin and activated partial thromboplastin times, urinalysis with a detailed sediment analysis, serum amylase level, and arterial blood gases (ABG) must be done. BUN and creatinine

Table 4: Organ System Dysfunction in Shock

Central Nervous System: Encephalopathy (ischaemic or septic), cortical necrosis
Cardiovascular System: (Heart) tachycardia, bradycardia, supraventricular tachycardia, ventricular ectopy, myocardial depression
Pulmonary: Acute respiratory failure, adult respiratory distress syndrome
Kidney: Prerenal failure, acute tubular necrosis
Gastrointestinal: Ileus, erosive gastritis, pancreatitis, acalculous cholecystitis, colonic submucosal haemorrhage
Liver: Ischaemic hepatitis'Shock' liver, intrahepatic cholestasis
Haematologic: Disseminated intravascular coagulation, dilutional thrombocytopaenia
Metabolic: Hyperglycaemia, glycogenolysis, gluconeogenesis, hypoglycaemia (late), hypertriglyceridaemia
Immune System: Gut barrier function depression, cellular immune depression, humoral immune depression

rarely change after the acute onset of shock, even if renal injury is present. ABG determines the adequacy of oxygenation and acid-base status. Serial serum lactate levels are used in the assessment of prognosis and levels of > 2 mEq/L represent tissue ischaemia. A 12-lead electrocardiogram (ECG) is critical for diagnosis of ischaemic cardiac injury. Chest radiograph is also a must. Other studies should be considered in specific conditions and may include detailed imaging studies like computed tomography (CT), abdominal radiographs or ultrasound, surface or transoesophageal echocardiography, ventilation/perfusion scan, angiograms and cardiac isoenzymes may be ordered for as and when required.

Invasive Haemodynamic Monitoring

Arterial pressure line is a must for all patients. Marked peripheral vasoconstriction makes the assessment of pressure by manual or non-invasive techniques inaccurate. Flow directed balloon-tipped pulmonary artery catheter with thermodilution cardiac output determination capability have become the standard practice for the haemodynamic assessment of circulatory shock. Continuous monitoring of central venous and pulmonary artery waveforms and pressures is also provided by them. Mixed venous oxygen saturation provides an assessment of adequacy of resuscitation of low output states before the presence of anaerobic metabolism. Oxygen delivery and oxygen consumption variables can also be determined using pulmonary artery catheter-derived data. But, the utility of this data is controversial when applied to individual patients.

Ancillary Monitoring Techniques

Echocardiography in the intensive care unit (ICU) not only detects the anatomic lesions but also allows direct measurement of cardiac output, stroke volume, pre-load, systolic contractility, diastolic function and regional motion abnormalities. There are other promising non-invasive monitoring devices, i.e. near-infrared spectroscopy to detect oxygen availability and utilisation at tissue level.

Management and Therapy

Patients in shock should be managed in an ICU with continuous ECG monitoring and close nursing support. Invasive haemodynamic monitoring with arterial and pulmonary artery catheters should be instituted in those indicated, laboratory tests as mentioned before should be performed at the earliest possible. Management of shock can be divided into specific therapy for triggering injury and general therapy of the shock syndrome.

Therapeutic Goals

1. Haemodynamic MAP >60 to 65 mmHg (higher in the presence of coronary artery disease or chronic hypertension)
2. PCWP = 12 to 18 mmHg (may be higher for cardiogenic shock)
3. CI >2.1 L/min/m^2 for cardiogenic and obstructive shock >3.0 to 3.5 L/min/m^2 for septic and resuscitated traumatic/haemorrhagic
4. Optimisation of haemoglobin >8 g/dL
5. Oxygen delivery arterial saturation >92%, SvO_2 > 60%
6. Normalisation of serum lactate (<2.2 mEq/L)
7. Maintain urine output >0.5 mL/kg/hr

The basic goal of circulatory shock therapy is the restoration of effective perfusion and oxygen supply to vital organs and tissues before the onset of cellular injury.

Airway management and mechanical ventilation

A critical first step in the treatment of shock is to ensure adequate alveolar ventilation and oxygenation. Most patients with the fully developed shock syndrome require tracheal intubation and mechanical ventilatory support, even if acute respiratory failure has not yet occurred. Mechanical ventilation allows blood flow to be redistributed, tends to reverse lactic acidosis and supports the patient until other therapeutic measures can be effective. Tracheal intubation also is indicated if mental status changes make airway unprotected or for inadequate respiratory compensation for metabolic acidosis. Positive-pressure ventilation and positive-end expiratory pressure (PEEP) may produce further haemodynamic compromise, if volume status of the patient is not maintained. PEEP may also be desirable in patients with acute respiratory distress syndrome (ARDS) or pulmonary oedema to ensure adequate oxygenation.

Acid-base balance

The previous standard practice of administering bicarbonate to patients with shock and lactic acidosis has been revised. The optimal approach to the management of lactic acidosis is to improve organ and systemic perfusion so that anaerobic metabolism is limited and the liver as well as kidneys can clear the accumulated lactate. If not effective, it has been suggested to restrict the use of sodium bicarbonate to situations with pH less than 7.1 to 7.15.

Fluids

Common to all aetiologies of haemodynamic instability and shock is the need to provide optimal intravascular volume to ensure adequacy of pre-load. Thus, it is appropriate to begin fluid administration in all shock patients who lack signs of pulmonary oedema and LV overload. Substantial controversy exists regarding the appropriate use of crystalloid and colloid fluids for resuscitation. What is most important when either type of fluid is used is to determine responses to these fluid

challenges. Optimal therapy generally means administering the quantity of fluid that maximises DO_2 while avoiding LV overload and pulmonary oedema. Also, sufficient preload should be there before or during institution of pharmacologic therapy for hypoperfusion.

Vasopressor agents

The term pressor refers to any substance that raises blood pressure (BP). These agents are divided into 3 categories: (i) Inotropes/chronotropes (i.e. drugs that increase CO by increasing cardiac contractility and heart rate); (ii) vasoconstrictors (i.e. agents that raise BP by increasing systemic vascular resistance); (iii) mixed pressor agents (i.e. drugs that act through both mechanisms).

1. Inotropic/chronotropic agents:

   Dobutamine hydrochloride, a synthetic β1, β2 receptor agonist is often used for inotropic support in cardiogenic shock. It increases myocardial contractility and CO, reduces afterload through peripheral vasodilatation and decreases LV filling pressures with improvement in diastolic coronary blood flow. It also prevents increase in infarct size in patients with acute myocardial infarction by improved collateral blood flow and balance between oxygen supply and demand. Because of β2-mediated vasodilatation caution should be observed if it is administered to hypotensive patients, especially with coexistent hypovolaemia. Milrinone lactate, a selective phosphodiesterase III inhibitor increases ionotropy and decreases systemic vascular resistance by preventing the degradation of cyclic adenosine monophosphate. The haemodynamic effects are similar to those of dobutamine. Amrinone, is rarely used because of excessive vasodilatation and thrombocytopaenia following long-term use. Dopexamine, a synthetic catecholamine, augments cardiac performance through both β2-mediated afterload reduction and baroreceptor reflex-mediated inotropy. Also, added benefit is its dopaminergic-mediated increase in renal blood flow. Isoproterenol hydrochloride, a pure β receptor agonist produces CO augmentation by increasing both heart rate and contractility. Dysrhythmias and increased myocardial oxygen requirement limit the use. Digitalis has limited use in treating acute states of hypoperfusion due to its slow onset of action and lower potency.

2. Vasoconstrictor agents:

   Phenylephrine is a pure adrenergic agonist. It causes vasoconstriction, thereby increasing BP, generally decreasing CO and often reflex slowing of heart rate. It should be used as a first-line agent in neurogenic shock. It can also be useful in patients who, despite maximal fluid and ionotropic support, remain hypotensive with evidence of organ hypoperfusion. Pure vasoconstrictors may compromise flow and perfusion, thus attention to renal function, acid-base balance, serum lactate and DO_2 is imperative. Vasopressin is used as an alternative therapy for vasodilator shock especially where a stimulation does not produce a satisfactory vasoconstrictor response. Most studies have used doses between 0.01 and 0.1U per minute. Other vasoconstrictor is noradrenaline (norepinephrine).

3. Mixed pressor agents:

   Dopamine, a precursor of norepinephrine, is commonly used as an initial pressor agent, acting at several receptors in a dose-related manner. It can be titrated towards achieving different aims of therapy: dopaminergic effects at less than 4 to 5 mcg/kg/min (e.g. vasodilatation of renal and splanchnic vascular beds), β effect at 5 to 10 mcg/kg/min (e.g. augmentation of cardiac contractility and heart rate) and α effects at more than 10 mcg/kg/min (e.g. vasoconstriction). There has been a decreased enthusiasm for its routine use to protect the kidneys from hypoperfusion insults or as a means to promote urine output in post-hypoperfusion oliguria. However, at a dose of 2 to 3 mcg/kg/min, it can reverse vasoconstrictor—induced increases in renal vascular resistance during vasoconstrictor infusion. Norepinephrine exerts both powerful inotropic (cardiac α and β1 adrenoreceptors) and peripheral vasoconstriction effects (α adrenoceptors). It can be used for persistent hypotension despite high-dose dopamine during septic and obstructive shock. It may also improve splanchnic oxygen dynamics in patients with sepsis. Epinephrine is occasionally used when other inotropes/vasopressors have failed to support blood pressure and/or cardiac output in circulatory shock. It is the first-line agent for management of anaphylactic shock. All currently used vasopressor agents ultimately produce their effects by increasing intracellular ionised calcium concentration. Thus, normal ionised calcium concentration should be maintained in patients who are on vasopressor support.

   The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend norepinephrine for more severe hypotension because of its high potency. Although both dopamine and norepinephrine have inotropic properties, dobutamine is often needed in addition. Pharmacological treatments that warrant further investigation include vasopressin, levosimendan —a calcium-sensitising agent that has so far shown little additional value in randomised heart failure trials, and/or activated protein C, which has been tried in conjunction with mechanical support in myocarditis patients.

Vasodilator agents

These drugs reduce afterload and improve CO in acute and chronic ventricular failure. For acute vasodilatation and preload reduction, nitroglycerin is the agent of choice; for afterload reduction, sodium nitroprusside, nitroglycerin, hydralazine hydrochloride, angiotensin converting enzyme inhibitors and fenoldopam are preferable. Patients with right-sided heart failure may benefit from pulmonary vasodilators, i.e. prostacyclin, prostaglandin E1 and inhaled nitric oxide.

Steroids

Prospective, double-blind, randomised, multicentre studies have demonstrated no benefit of steroid administration in hyperdynamic/septic shock. Thus, the practice of routine administration of high-dose steroids was abandoned. Stress doses of glucocorticoids are appropriate for treating shock when it is associated with adrenal insufficiency, hypothyroidism, in patients with impaired adrenal pituitary axis, or in those who

require steroids for treatment of an underlying immunologic disease (e.g. vasculitis). Conversely, steroids are relatively contraindicated in patients with cardiogenic shock as they alter the healing process of the myocardium and predispose to myocardial rupture. But recent reports also suggest a decrease in the endogeneous production of stress steroids in sepsis, causing vasopressor dependence and failure to respond to therapy. Administration of 50 mg of hydrocortisone 6 hourly indicates benefit. The mechanism for benefit may be reversal of catecholamine receptor down regulation or prevention of inflammatory mediated induction of nitric oxide synthase. Patients with shock, who require increasing doses of vasopressors or do not respond within 24 hours of therapy, may be administered steroids. However, this topic still remains controversial.

Mechanical support: intra-aortic balloon pump (IABP)

Intra-aortic balloon counterpulsation has long been the mainstay of mechanical therapy for cardiogenic shock. Use of an IABP improves coronary and peripheral perfusion via diastolic balloon inflation and augments LV performance via systolic balloon deflation with an acute decrease in afterload. Accurate timing of inflation and deflation provides optimal support. Not every patient has a haemodynamic response to IABP; response predicts better outcome. IABP support should be instituted as quickly as possible, even before any transfer for revascularisation if a skilled operator is available and insertion can be performed quickly. In the large US National Registry of Myocardial Infarction, IABP use was independently associated with survival at centres with higher rates of IABP use—whether PCI, fibrinolytic therapy, or no reperfusion had been used; however, no completed trials demonstrate benefit. Complications associated with IABP are less common in the modern era; in the largest series, the overall and major complication rates were 7.2% and 2.8%, respectively. Risk factors for complications include female sex, small body size, and peripheral vascular disease.

Reperfusion

The survival benefit of early revascularisation in CS, reported in several observational studies, was shown convincingly in the randomised SHOCK trial, which found a 13% absolute increase in 1-year survival in patients assigned to early revascularisation. This corresponds to a number needed to treat 8 patients to save 1 life. The benefit was similar in the incomplete, randomised Swiss Multicenter Study of Angioplasty for Shock. Numerous registry studies have confirmed the survival advantage of early revascularisation, whether percutaneous or surgical, in the young and the elderly. Thrombolytic therapy is less effective but is indicated when PCI is impossible or if a delay has occurred in transport for PCI and when myocardial infarction and CS onset were within 3 hours.

Timing of PCI

As in myocardial infarction without shock, earlier revascularisation is better in cardiogenic shock. Presentation 0 to 6 hours after symptom onset was associated with the lowest mortality among CS patients undergoing primary PCI in the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK) registry, in which door-to-angiography times was 90 minutes in approximately three-fourths of patients. In the SHOCK trial, there appeared to be increasing long-term mortality as time to revascularisation increased from 0 to 8 hours. However, there is a survival benefit as long as 48 hours after myocardial infarction and 18 hours after shock onset.

Total Circulatory Support: LV Assist Devices and Extracorporeal Life Support

Temporary mechanical circulatory support with LV assist devices (LVADs) is theoretically appealing to interrupt the vicious spiral of ischaemia, hypotension and myocardial dysfunction, allowing for recovery of stunned and hibernating myocardium and reversal of neurohormonal derangements. Device-related complications and irreversible organ failure remain major limitations. LVAD support involve circulation of oxygenated blood through a device that drains blood from the left-side of the heart and returns blood to the systemic arteries with pulsatile or continuous flow. Surgically implanted LVADs remove blood through a cannula placed at the LV apex and return blood to the ascending aorta. Percutaneous LVADs are also available. Extracorporeal life support involves extracorporeal circulation of blood through a membrane oxygenator, which relieves both the right and left heart and the lungs of part of their workload. Anticoagulation is required for extracorporeal life support and for percutaneous LVADs but may be optional with surgically placed LVADs. Extracorporeal life support and LVADs have been used sequentially in CS patients, usually as a bridge to heart transplantation. In the largest reported LVADs series to date, 74% of 49 patients survived to transplantation, and 87% of transplanted patients survived to hospital discharge after receiving a variety of surgical LVADs. These devices need further large trials for different use.

RECOMMENDED READINGS

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7.11 Cardiopulmonary Resuscitation

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INTRODUCTION

Sudden cardiac arrest is a leading cause of death worldwide. Recognition of this emergency is imperative to initiate prompt resuscitation of the victim. It was in the 19th Century, Doctor HR Silvester described a method (The Silvester Method) of artificial respiration in which the patient was laid on his back, with arms raised above the head to aid inhalation and then pressed against the chest to aid exhalation. The procedure was repeated 16 times per minute. A second technique, called the Holger-Neilson technique, was described in the first edition of the *Boy Scout Handbook* in the United States (US) in 1911. It is essentially the Silvester Method with the patient flipped over. This form was well used into the 1950s. The technique was later banned from first-aid manuals in the United Kingdom.

However, it was not until the middle of the 20th Century that artificial respiration combined with chest compressions as a key part of resuscitation following cardiac arrest was recognised. In 1957, Peter Safar wrote the book *ABC of Resuscitation*. In USA, it was first promoted as a technique for the public to learn in the 1970s.

Artificial respiration was combined with chest compressions based on the assumption that active ventilation is necessary to keep circulating blood oxygenated, and the combination was accepted without comparing its effectiveness with chest compressions alone. However, research over the past decade has shown that assumption to be faulty, resulting in the American Heart Association's (AHA) acknowledgement of the effectiveness of chest compressions alone.

PATHOPHYSIOLOGY

Most of the cardiac arrest cases occur as a result of ventricular fibrillation (VF) precipitated by an acute coronary event. Needless to say that timely recognition and defibrillation of the victim leads to excellent survival results. However, it needs to be realised that the goal of CPR is not just a functioning heart, but a functioning heart in a functioning person, i.e. revival of heartbeat with intact neurological function. It has been observed that outcome of the victim is better with VF than asystole or pulseless electrical activity (PEA), which in turn is influenced by the cause of the arrest and the promptness in the availability of resuscitation.

MANAGEMENT

Survival of the victim depends on the chain of interlinked processes referred to as 'chain of survival'. The 2010 AHA guidelines emphasise the importance of post-cardiac care, and hence, a fifth chain has been added to the chain of survival. The chain of survival for adults is now given below in **Figure 1**.

When these links are implemented, survival rates can approach 50% following witnessed out of hospital VF arrest.

The 2010 AHA guidelines for CPR and emergency cardiovascular care (ECC) are based on an extensive international evidence evaluation process. The ILCOR 2010 International Consensus on CPR and ECC Science with treatment recommendations summarises the international consensus after interpreting a vast number of peer reviewed resuscitation studies. The modifications recommended are for both BLS and ACLS to provide effective resuscitation outcomes.

The modifications in the protocols and resuscitation in children and infants, including current modifications, will not be discussed in this chapter.

Adult Life Support

Adult life support involves two sequences, viz. adult basic life support and adult advance life support. Here, the discussion will be restricted to techniques meant for healthcare personnel only.

Adult basic life support

This involves resuscitation of the victim without any specialised equipment or complex understanding of the pathophysiology of cardiac arrest. The objective is to maintain adequate circulation and ventilation of vital organs until specialised assistance is available. This minimises anoxic damage to the vital organs.

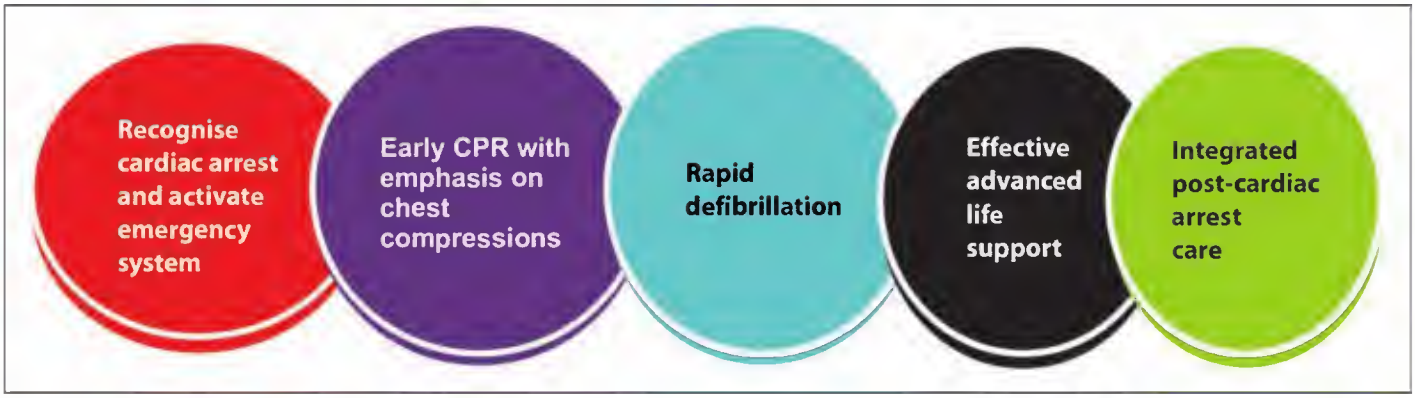


Figure 1: AHA ECC adult chain of survival.

Prompt Recognition of Arrest

Before approaching the victim the rescuer should ensure scene safety. Thereafter, the rescuer should check for response. Tap the victim on the shoulder and shout 'Are you alright'. The healthcare provider should also check for no breathing or abnormal breathing (i.e. only gasps) while checking for responsiveness. If unresponsive, then activate emergency medical system, get AED/defibrillator or ask second rescuer (if available to get it).

Circulation

Pulse check

The 2010 AHA guidelines for CPR and ECC do not emphasise the pulse check as a mechanism to identify cardiac arrest. This is because studies have shown that both lay person and healthcare providers have difficulty in detecting a pulse. Healthcare providers may take too long to appreciate a pulse, thereby delay in initiating chest compressions. To avoid this, healthcare provider should not take more than 10 seconds. If no pulse is felt during that period then proceed to closed chest compression immediately.

The ABC approach has been replaced by CAB approach, i.e. initiation of chest compressions before ventilation, since setting up of airway equipment takes time.

Closed chest compression

The process involves effective application of closed chest compression to maximise the quality of CPR. If done properly and cyclically, nearly 25% to 30% cardiac output is maintained. Closed chest compressions cause forward flow by direct pressure on the cardiac chambers (cardiac pump) or by the cyclical evacuation of the pulmonary vasculature (thoracic pump). The low flow that is generated provides protective circulation to the brain for a brief period and enhances coronary perfusion. The adequacy of the latter is the best predictor of successful restoration of spontaneous cardiac activity and circulation. Properly performed closed chest compression can produce systolic arterial pressure of 60 to 80 mmHg, diastolic pressure is low and mean arterial pressure in the carotid artery seldom exceeds 40 mmHg.

Changes from 2005 guidelines regarding compression stipulates that the compression rate should be at least 100 per minute and not 'approximately' 100 per minute. The compression depth should be at least 2 inches (5 cm) in adults and not 1½ to 2 inches as was being practised earlier for adults. Allow complete chest recoil after each compression. Minimise interruptions in chest compressions, i.e. continuous chest compressions for effective outcomes. Also, there is need to avoid excessive ventilation.

Method

To give effective chest compressions, push hard and push fast. Compress the adult chest at a rate of at least 100 compressions per minute, with a depth of 2 inches (5 cm). Allow the chest to recoil completely after each compression, and allow approximately equal compression and relaxation times. Please minimise/avoid interruptions in chest compressions and avoid excessive ventilation. Healthcare providers should interrupt chest compressions as infrequently as possible and try to limit it to no longer than 10 seconds, except for insertion of advanced airway or use of a defibrillator. When two or more rescuers are present switch chest compressors approximately every 2 minutes or after 5 cycles of compressions and ventilations at a ratio of 30:2. This is done to avoid rescuer fatigue. This switch should be accomplished in less than 5 seconds.

Managing the airway

Also the 2010 AHA guidelines regarding airway management has eliminated 'Look, Listen and Feel' from BLS algorithm.

Open airway

The healthcare rescuer should open airway using head-tilt chin lift manoeuvre after ruling out head and neck trauma. If cervical spine injury is suspected then open airway using 'jaw thrust without head extension'. If this method fails to open the airway, then use head-tilt chin lift method. Maintaining a patent airway and providing adequate ventilation is a priority in CPR.

Rescue breathing

Rescue breaths can be given through either mouth-to-mouth, mouth-to-barrier device, mouth-to-nose and mouth-to-stoma ventilation with bag and mask. Each rescue breath should ensure the following:

1. Deliver each rescue breath over 1 second.
2. Give sufficient tidal volume to produce visible chest rise.
3. Use compression to ventilation ratio of 30:2.
4. When advance airway is in place, during two person CPR, give 1 breath every 6 to 8 seconds without attempting to synchronise breaths between compressions (i.e. delivery of 8 to 10 breaths/min). There should be no pause in chest compressions for delivery of ventilations.

The algorithms presented in **Figure 2** summarise the adult BLS sequence.

Defibrillation

Early defibrillation is critical for survival in sudden cardiac arrest (SCA) victims for several reasons: (1) most frequent rhythm in SCA is VF, (2) treatment for VF is defibrillation, (3) probability of successful defibrillation diminishes rapidly with passage of time, and (4) VF tends to deteriorate to asystole within a few minutes. The success of defibrillation is time-dependent, with rates of failure increasing by about 10% for every minute of delay after the cardiac arrest.

Defibrillation works by depolarising all the myocardium and eliminating fibrillatory activity. This enables the patient's intrinsic pacemaker to take over and establish a stable rhythm. Also, the current has to be delivered in a mode that minimises trans-thoracic impedance, which can be achieved by: (a) applying firm pressure to assure contact with the skin (8 kg in adults), and (b) using a conducting gel to minimise resistance at the skin interface (Avoid ultrasound gel as it has poor conductance).

Appropriate size of the defibrillator paddle (12 cm diameter is ideal for adults) and shaving of the chest if possible, without delaying the initial shocks. Alternately, electrode pads should be placed. Alternately electrode pads should be placed on the exposed chest in an antero-lateral position. Alternate acceptable positions are antero-posterior, anterior-left infrascapular, and anterior-right infrascapular.

Conventional defibrillators deliver the current as a monophasic waveform (current flows in one direction between electrodes),

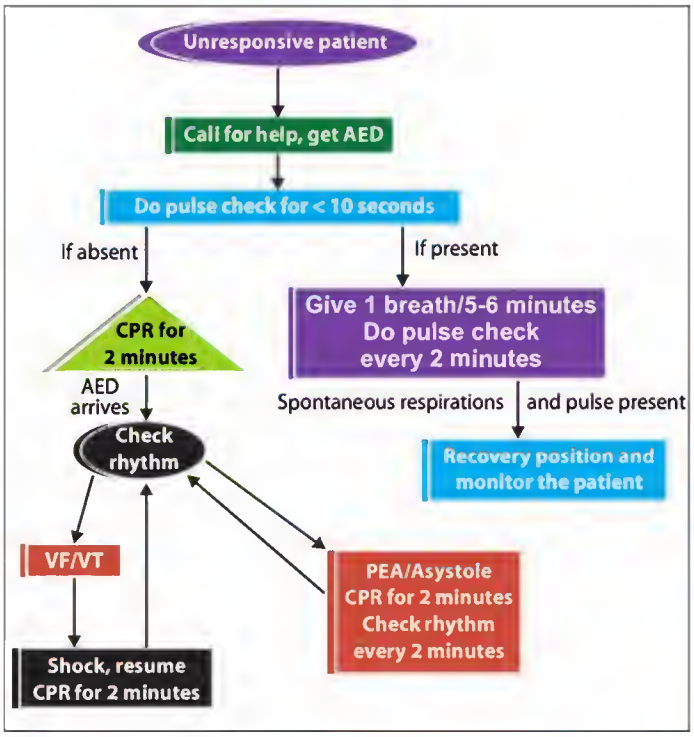


Figure 2: Adult basic life support (BLS) algorithm with AED.

VF = Ventricular fibrillotion; VT = Ventricular tochycardio; PEA = Pulseless electrical octivity

but biphasic currents (flowing first in one direction between paddles and then returning in the reverse direction) are more effective at cardioversion using much lower levels of energy. The resulting reduction in myocardial injury is of benefit.

In the absence of biphasic defibrillators, use of monophasic defibrillators can be permitted. For monophasic defibrillators, recommended energy is 360 Joules. However, the ideal recommendation is to use a biphasic defibrillator. The energy recommendation as per manufacturer is 120 to 200 Joules; if unknown then to use maximum available. Second and subsequent doses should be equivalent.

Recovery Position

The recovery position is used for unresponsive adult victims who clearly have normal breathing and effective circulation. This position is designed to maintain a patent airway and reduce the risk of aspiration. The victim is placed on his or her side with the lower arm in front of the body. Unfortunately no single position is perfect for all victims. As there are several variations of the recovery position, the goal is to see that the patient should be stable, near a true lateral position, with the head dependent and no pressure on the chest to impair breathing.

Advance Cardiac Life Support

Cardiac arrest can be caused by four rhythms; VF, pulseless ventricular tachycardia (VT), PEA, and asystole. Neither of these rhythms generate cardiac output. For a victim to survive this catastrophe a well coordinated BLS and a system of advanced cardiovascular support (ACLS) with integrated post-cardiac arrest care is essential. ACLS interventions are based on the foundation of efficient BLS intervention, namely, immediate recognition and activation of the emergency response system, early CPR, rapid defibrillation to further increase the likelihood of return of spontaneous circulation (ROSC) with drug therapy, advance airway management, and physiological monitoring. It is essentially a team-work carried out by trained healthcare workers/providers in ACLS and not by a single individual.

Various steps in ACLS process as per the guidelines of AHA 2010 are shown in **Figure 3** and described below.

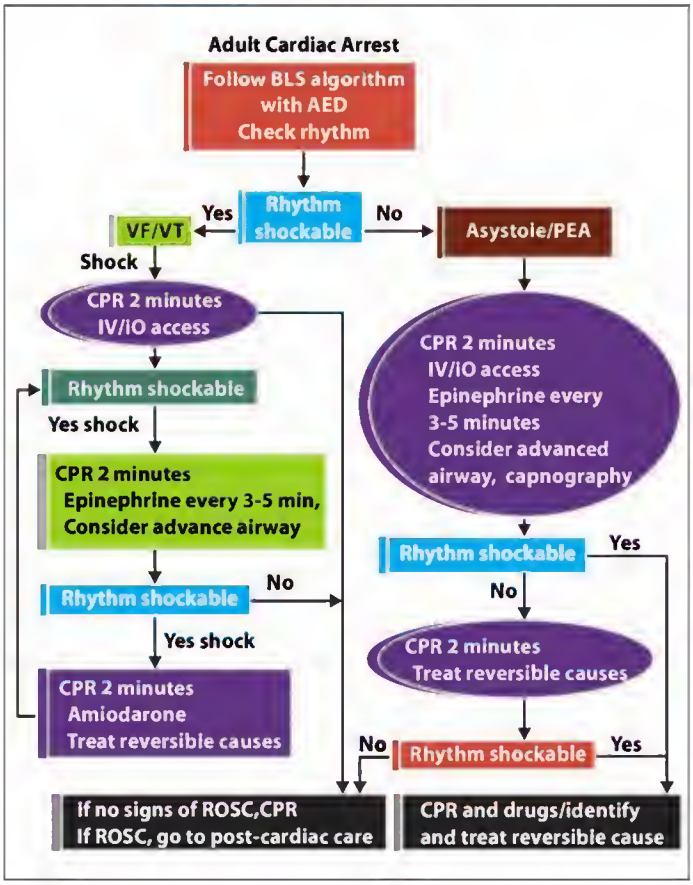


Figure 3: Advanced cardiovascular support pulseless arrest algorithm.

BLS = Bosic life support; AED = Automated externol defibrillotion; VF = Ventricular fibrillotion; VT = Ventricular tochycordio; PEA = Pulseless electricol activity; CPR = Cordiopulmonory resuscitotion; IV = Introvenous; IO = Introosseous; ROSC = Return of spontoneous circulation

Effective Steps as Recommended in BLS

1. After defibrillator is attached, check cardiac rhythm.
2. Rhythm: VF/VT or PEA or asystole.
3. If VT/VF, treatment of choice is defibrillation with continuous CPR. For refractory VF/VT use amiodarone. Drug therapy prior to amiodarone during CPR includes epinephrine every 3 to 5 minutes with vasopressin to replace 1st or 2nd dose of epinephrine.
4. For PEA/asystole shock is not indicated. Only drug therapy, i.e. epinephrine every 3 to 5 minutes with vasopressin to replace 1st or 2nd dose of epinephrine is indicated.
5. Check for any treatable/reversible causes of cardiac arrest (**Table 1**).
6. During CPR it is important to check rhythm after every 2 minutes to analyse whether the rhythm is shockable or non-shockable.
7. Consider after 2 minutes of CPR, advance airway management and physiological monitoring of the patient.

Table 1: Treatable Causes of Cardiac Arrest: The Hs and Ts

Hs	Ts
Hypoxia	Toxins
Hypovolaemia	Tamponade (Cardiac)
Hydrogen ion (Acidosis)	Tension pneumothorax
Hypo- or Hyperkalaemia	Thrombosis – Pulmonary
Hypothermia	Thrombosis – Coronary

Adult Cardiac Arrest

Advance airways

During CPR, breathing is normally maintained with bag-mask ventilation as a part of BLS algorithm, which during ACLS advance invasive airway placement is done to deliver effective oxygenation. The problem with this is interruption of chest compressions and the need for the healthcare provider to be sufficiently trained in insertion of the advance airway. Also the choice of the airway depends on the skill of the healthcare provider and the condition of the victim. Accordingly, there are two types of advance airways as descried below:

(a) Supraglottic airways
(b) Endotracheal intubation

Supraglotic airways: Insertion of supraglottic airways is easier, as it does not require direct visualisation of the glottis and can be done without interruption of chest compressions. These are very effective in maintaining an open airway, thereby facilitating ventilation. The commonly used supraglottic airways are laryngeal mask airway, oesophageal-tracheal tube (combitube), and the laryngeal tube.

Endotracheal intubation: This is ideal for a variety of reasons including to keep the airway patent, permits effective respiratory toilet, and effective for providing invasive ventilation and an alternative route for cardiac arrest drug administration. However, the drawback is in the hands of untrained healthcare worker who could cause complications like oropharyngeal trauma, prolonged interruptions in chest compressions or oesophageal intubation.

Clinical confirmation of the tube placement can be done by visual confirmation during intubation by noticing the tube passing through the vocal cords and bilateral chest expansion following bagging the victim by attaching an Amboss bag to the ET, 5 point auscultation (presence of air over the chest bilaterally and absence over the epigastric region). Various devices are used for tube placement confirmation, viz. oesophageal detector device and non-wave-form exhaled carbon dioxide (CO_2) detector if waveform capnography is not available.

Once advance airway is in place with confirmation, the two healthcare providers should no longer follow cycles of CPR, but provide continuous chest compressions at the rate of 100 per minute. Ventilation should continue at the rate of 1 breath every 6 to 8 seconds, i.e. 8 to 10 breaths per minute with the same criteria to avoid excessive ventilation. To avoid fatigue of the compressor and subsequent deterioration of CPR quality, the two healthcare providers should rotate the compressor role every 2 minutes.

Medications for Cardiac Arrest Rhythms

Drugs Routinely Administered in CPR

Vasopressors

Vasopressors are the only drugs routinely indicated in prolonged arrests irrespective of the rhythm. They enhance coronary perfusion by raising aortic root pressures and help in restoration of spontaneous circulation. However, till date no placebo-controlled trials have shown that administration of any vasopressor agent at any stage during management of VF/PVT, PEA, or asystole increases the rate of neurological integrity and survival leading to hospital discharge. However, there is evidence that they are associated with an increased rate of ROSC.

Epinephrine hydrochloride: Epinephrine hydrochloride produces beneficial effect due to its alpha-adrenergic receptor stimulating (i.e. vasoconstrictor) effect. This effect increases coronary and cerebral perfusion pressure during CPR. However, the value and safety of the β- adrenergic effects of epinephrine are controversial as it may increase myocardial work and reduce subendocardial perfusion.

The recommended dose is 1 mg intravenous/intraosseous (IV/IO) every 3 to 5 minutes during adult cardiac arrest until ROSC is achieved. Endotracheal route at a dose of 2 to 2.5 mg is used if IV/IO access is delayed or cannot be established.

Vasopressin: Vasopressin is a non-adrenergic peripheral vasoconstrictor that acts on smooth muscle V-1 receptors and increases cerebral and coronary perfusion without increasing myocardial oxygen demand. Despite its seeming benefit, current evidence is inadequate to support its use as an alternative to epinephrine in CPR. A recent meta-analysis showed no statistically significant differences between vasopressin over epinephrine for return of spontaneous circulation, 24-hour survival, or survival to hospital discharge.

One randomised controlled trial (RCT) found that repeated doses of vasopressin during cardiac arrest did not improve survival rates compared with repeated doses of epinephrine. Since effects of vasopressin have not been shown to differ from those of epinephrine in cardiac arrest, it is recommended that one dose of vasopressin 40 U IV/IO can replace either the first dose or second dose of epinephrine in the treatment of cardiac arrest.

Other vasopressors: There are no alternative vasopressors (norepinephrine, phenylephrine) with proven survival benefit compared with epinephrine.

Antiarrhythmics

There is no evidence that any antiarrhythmic drugs given during cardiac arrest can increase survival to hospital discharge. However, amiodarone has been shown to increase short-term survival to hospital admission when compared to placebo and lidocaine.

Amiodarone: Amiodarone is a membrane-stabilising drug that significantly slows conduction over the AV nodal and accessory pathways. It has complex actions on sodium, potassium, and calcium channels along with effects on alpha and beta-adrenergic receptors. It produces both hypotension and bradycardia. It is effective in enhancing responses to defibrillation in refractory VF/PVT.

Amiodarone is administered for VF or PVT unresponsive to CPR, defibrillation, and vasopressors at initial dose of 300 mg IV/IO bolus followed by an additional 1 dose of 150 mg IV/IO only.

Lidocaine: Initial animal studies did support the use of lidocaine for ventricular arrhythmias, however subsequent studies showed that compared with amiodarone; amiodarone was superior to lidocaine in restoring spontaneous circulation with improved rate of survival to hospital admission and that lidocaine was associated with more asystole after defibrillation.

Lidocaine should be considered as an alternative to amiodarone only, if amiodarone is not available. The initial dose is 1 to 1.5 mg/kg IV. If VF/pulseless VT persists, additional doses of 0.5 to 0.75 mg/kg IV push may be given at an interval of 5 to 10 minute to a maximum dose of 3 mg/kg.

Magnesium: Use of magnesium sulphate is considered only in refractory VF, *torsades de pointes*, in chronic alcoholics with unresponsive VF/pulses VT and digoxin toxicity.

Interventions and Drugs Not Recommended for Routine Use during Cardiac Arrest

Atropine

The drug reverses cholinergic-mediated decrease in heart rate, systemic vascular resistance and blood pressure. Lower level clinical studies provide conflicting evidence regarding the benefit of routine use of atropine in cardiac arrest. In fact as per available evidence, routine use of the drug during PEA and asystole is unlikely to have a therapeutic benefit. Therefore, atropine has been removed from the cardiac arrest algorithm.

Sodium bicarbonate

During cardiac arrest and resuscitation tissue acidosis with resulting acidaemia occur due to absence of blood flow during arrest with low blood flow during CPR. ROSC following high quality CPR restores acid-base balance. Except for two studies, majority of the studies have shown no benefit or found to have poor outcomes with the use of sodium bicarbonate during CPR. However, use of it can be made in special resuscitation circumstances, like pre-existing metabolic acidosis, hypothermia, hyperkalaemia, or tricyclic antidepressant overdosage.

Calcium

Routine use of calcium for the treatment of in-hospital and out-of-hospital cardiac arrest is not recommended, as routine use of calcium has not been proved to be of beneficial value in survival in any trials.

Intravenous fluids

Administration of normothermic fluid, hypertonic and chilled fluids during CPR has no advantage in survival benefit of the victim, as observed in various animal and small human studies. However, volume administration should be promptly given, if cardiac arrest is associated with severe volume losses because these patients develop signs of circulatory shock advancing to PEA.

Pacing

No studies have shown survival benefits from pacing in cardiac arrest. Existing evidence suggests that pacing by transcutaneous, transvenous, or transmyocardial means in cardiac arrest victims does not improve the likelihood of ROSC or survival outcomes regardless of the timing of pacing administration or location of arrest. As a result, electrical pacing is not recommended for routine use in cardiac arrest.

Monitoring during CPR

Physiological monitoring to optimise CPR quality and detect ROSC now plays an important role in the new 2010 AHA guidelines. Needless to say with ROSC the victim is shifted to intensive care unit (ICU) or if the event has occurred in the ICU setting monitoring of physiological parameters is done aggressively, using clinical parameters and sophisticated equipments. The age-old arterial pulse palpation, manual or intra-arterial BP monitoring, 12-lead ECG including rhythm monitoring on bedside monitor cannot be ignored.

The 2010 AHA guidelines emphasise particularly the use of $PETCO_2$ for monitoring in ACLS once advance airway placement has been done. Other parameters include coronary perfusion pressure (CPP), central venous oxygen saturation (SVO_2), SpO_2 monitoring, and arterial blood gas analysis (ABG).

Continuous Quantitative Waveform Capnography

The 2005 AHA guidelines laid emphasis on 5 points auscultation for ET placement and confirmation with an exhaled CO_2 detector or an oesophageal detector device to confirm placement of ET. The continuous quantitative waveform capnography monitoring was being referred to as a useful non-invasive indicator of cardiac output that is generated during CPR. The 2010 AHA guidelines for CPR and ECC now recommend continuous quantitative waveform capnography monitoring for confirmation and monitoring of endotracheal tube placement include in algorithm for ACLS once advance airway placement is done. The advantage of $PETCO_2$ monitoring is also for monitoring quality of CPR and detection of ROSC based on $ETCO_2$ values.

The rationale is that $PETCO_2$ provides a continuous waveform with ventilation to confirm the presence of ET. Also, it serves to play a major role in the 5th chain of survival, i.e. in post-cardiac arrest care. It plays a vital role in detecting the effectiveness of chest compressions and cardiac output in the recovery phase. Falling $PETCO_2$ during chest compressions indicate ineffective chest compressions and during ROSC may indicate falling cardiac output or rearrest.

Central Venous Oxygen Saturation (SVO_2)

Measurement of SVO_2 is done by placing oximetric tipped central venous catheters in the superior vena cava. The normal values are 60% to 80%. It is an effective tool for assessing the adequacy of blood flow during cardiac arrest, because during cardiac arrest the SVO_2 is between 25% to 35% indicating poor blood flow. The advantage of SVO_2 during cardiac arrest is to detect ROSC as it is a useful indicator of cardiac output and oxygen delivery without interruption of chest compressions for pulse and rhythm checks. If during CPR, SVO_2 is > 30% it indicates the need to improve CPR quality by improving the chest compressions. Limitations in the use of SVO_2 monitoring is the availability of the catheter and knowledge of use in all ICUs, and particularly its accuracy depends on oxygen consumption, SaO_2 values and haemoglobin levels.

Coronary Perfusion Pressure and Arterial Relaxation Pressure

Coronary perfusion pressure (CPP) is defined as aortic relaxation pressure minus right atrial relaxation pressure. Measured during CPR it correlates well with myocardial blood flow and ROSC. It requires simultaneous recording, measurement and calculation of both aortic and central venous pressures. Unfortunately, in our set-up its availability is a problem. Alternatively intra-arterial pressure monitoring is preferred to detect ROSC during chest compression or when organised rhythm is restored.

Post-Cardiac Arrest Care

A healthy brain and a functional patient are the primary goals of CPR. Post-effective CPR, significant haemodynamic instability as well as laboratory abnormalities can occur. Every organ system is at risk during this time and patients may develop multi-organ dysfunction. Therefore, optimise cardiopulmonary function to provide effective systemic perfusion, particularly perfusion to the brain. This is best achieved in critical care unit. Therefore, transport the victim to the hospital in the ICU for monitoring and management. Post-admission management measures include the following:

1. Identify the precipitating cause of arrest.
2. Adopt measures to prevent recurrence of arrest.
3. Institute measures to treat neurological complications and measures to improve long-term neurological function including control of body temperature to optimise survival and neurological recovery.
4. Do serial 12-lead ECG and cardiac biomarkers for the detection of acute coronary syndromes.
5. Do serial ABGs. Provide adequate mechanical ventilation to minimise lung injury.
6. Assess acid-base and fluid electrolyte imbalances and correct the same.
7. Monitor HGT/blood glucose levels to prevent hypoglycaemia. If hypoglycaemia is present, correct it. Maintain HGT around 140 to 180 mg/dL.
8. Avoid hypotension. Monitor central venous pressure (CVP). If low, give fluid challenge. If CVP normal and low blood pressure, start vasoactive/inotropic/inodilator drugs as the case may be, dose titrated to optimise BP, cardiac output and systemic perfusion (**Table 2**).
9. Adopt measures to reduce the risk of multi-organ injury by assessing routine biochemical parameters.
10. Assess prognosis for recovery.
11. Provide rehabilitation services to survivors.

Brain injury is a common cause of morbidity and mortality of post-cardiac arrest victims. Studies have shown that brain injury accounts for around 68% deaths of victims in out-of-hospital cardiac arrest and around 23% deaths in in-hospital cardiac arrest. Presentations of post-cardiac arrest brain injury include coma, seizures, myoclonus, various degrees of neurocognitive dysfunction (ranging from memory deficits to persistent vegetative state) and brain death.

Management of seizures involves prompt EEG with interpretation and frequent EEG monitoring or continuous monitoring in comatose patients. Treatment regimens for post-cardiac arrest seizures follow the same pattern as with seizures due to other causes. However, no studies have shown that anticonvulsant therapy improves the outcome after cardiac arrest; with several studies showing that post-cardiac arrest seizures were refractory to traditional anticonvulsant therapy.

Unfortunately, large clinical studies of brain resuscitation (BRCT trials) have shown that administration of barbiturates (thiopental), steroids (glucocorticoids) or calcium channel blockers (lidoflazine, nimodipine), diazepam and magnesium sulphate during the resuscitation have no effect on neurological recovery. One trial using coenzyme Q10 in patients receiving hypothermia failed to show improved survival with good neurological outcomes. Hence, routine use of it in patients with hypothermia is uncertain.

PROGNOSIS

While ACLS can result in the restoration of circulation in over 40% of victims, less than 5% of pre-hospital arrests and about 15% of in-hospital sudden cardiac arrest (SCA) survive to be discharged alive from the hospital. Survival-to-discharge is strongly correlated with recovery of neurological function and prognostication of such recovery is a major concern after CPR. Though this is predominantly a clinical exercise, a few diagnostic tests have been added, with little impact on predicting good outcomes. In general, it is difficult to predict good neurological outcomes after CPR, but poor outcomes can be identified by clinical/investigational features.

A recent meta-analysis of 11 studies involving 1,914 patients documented 5 clinical signs that were found to strongly predict

Table 2: Drugs for Management of Hypotension

Drug	Dose	Remarks
Epinephrine	0.1 mcg/kg/min	Used in severe hypotension
Norepinephrine	0.1 to 0.5 mcg/kg/min	Used in severe hypotension, contraindicated in hypovolaemia (low CVP)
Phenylephrine	0.5 to 2 mcg/kg/min	Used in severe hypotension and low total peripheral resistance
Dopamine	5 to 20 mcg/kg/min	Used in hypotension particularly with symptomatic bradycardia. Avoid in patients with low CVP
Dobutamine	5 to 20 mcg/kg/min	Used in hypotension with cardiogenic shock
Milrinone	50 mcg/kg over 10 minutes as loading dose then infuse at a rate of 0.375 mcg/kg/min	Used for low cardiac output states. Causes less tachycardia than dobutamine

death or poor outcomes, with 4 out of 5 predictors detectable at 24 hours after resuscitation, as given below:

1. Absent corneal reflex at 24 hours.
2. Absent pupillary response at 24 hours.
3. Absent withdrawal response to pain at 24 hours.
4. Absent motor response at 24 hours.
5. Absent motor response at 72 hours.

In another meta-analysis, it was observed that bilateral absence of cortical responses to median nerve somato-sensory evoked potentials was associated with a poor outcome in normothermic patients who were comatose for at least 72 hours.

CONCLUSION

The primary aim of CPR is to rigidly follow the chain of survival, prompt CPR with defibrillation, rapid transport of the victim to hospital emergency department for advanced support. Proper intensive care management with proper post-cardiac arrest care can contribute to restoration of a healthy brain and a functional patient which are the primary goals of CPR. Therefore, the comprehensive treatment of diverse problems after cardiac arrest involves multi-disciplinary aspects of critical care, cardiology, and neurology. It is for this reason it is mandatory to manage such victims in fully equipped critical care units.

RECOMMENDED READINGS

1. American Heart Association 2010. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122 (Suppl 3): S640-S656, S685-S705, S706-S719,S729-S767,S768-S786.
2. European Resuscitation Council Guidelines for Resuscitation 2010. www.erc.edu, www.CPRguidelines.eu
3. Fang Gao Smith, Joyce Yeung. Post-resuscitation care, Garvin Perkins. *Core Topics in Critical Care Medicine* 2010; 22: 170-5.

7.12 Brain Death and Support of the Brain-Dead Organ Donor

Rajesh Chawla, Guneet Singh

INTRODUCTION

Recent advances in resuscitative and life support techniques have led to the definition of death and its concept. The progress in organ transplantation and the increasing number of patients who have a living body but non-functioning brain, which is a consequence of discoveries in resuscitative and life support techniques, has led to study brain death more precisely. Such refinements in critical care medicine mean that neurologists, neurosurgeons, and anaesthesiologists must be able to make an appropriate diagnosis of death. The cultural and religious diversity may lead to great differences in attitudes toward brain death and there is no global consensus in diagnostic criteria. The concept of brain death as defining the death of an individual is widely accepted, and many countries have published recommendations or legal requirements for the diagnosis of brain death as a necessary pre-requisite for organ donation.

DEFINING BRAIN DEATH

Brain death has been traditionally defined as irreversible cessation of all brain functions including brainstem. The advent of effective artificial cardiopulmonary support for severely brain injured persons, however, created some confusion about the determination of death. Loss of heart and lung function was an easily observable and sufficient basis for the diagnosis of death. However, with availability of measures to support circulation and respiration by a mechanical respirator and other medical interventions, it is important to diagnose individuals who have lost all brain functions, i.e. have a dead brain in an otherwise living body. This diagnosis of determining neurological death is also important in view of the developments in transplant surgery raising ethical and legal attention on the desirability of agreeing on the medical criteria of brain death.

CRITERIA FOR CLINICAL DETERMINATION OF BRAIN DEATH

Determination of brain death clinically should include the following:

1. Eliminate error in classifying a living individual as dead.
2. Allow as few errors as possible in classifying a dead body as alive.
3. Allow a determination to be made without unreasonable delay.
4. Be acceptable to a variety of clinical situations.
5. Be explicit and accessible to verification.

Pre-Requisites for Clinical Determination

1. Clinical or neuroimaging evidence of an acute catastrophic cerebral event consistent with clinical diagnosis of cerebral death.
2. Exclusion of conditions that may confound clinical assessment of brain death, e.g. acute metabolic or endocrine derangements, hypothermia and shock.
3. Confirmation of absence of drug intoxication or poisoning.
4. Core body temperature ≥32°C (90°F)

Testing of brainstem function can proceed only after these pre-requisites have been fulfilled.

Cardinal findings in brain death which need to be established are: coma or unresponsiveness, absence of brainstem reflexes, and apnoea. **Figure 1** gives the algorithm for evaluation of coma and brainstem function.

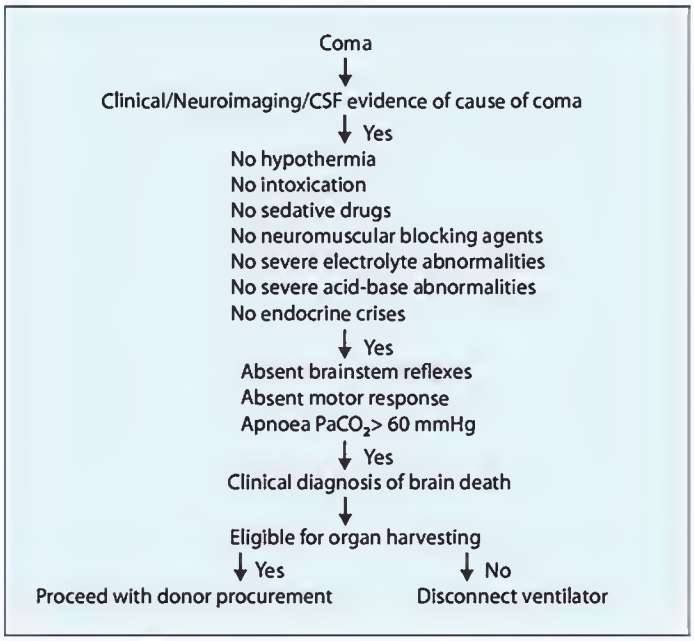


Figure 1: Testing algorithm for evaluation of coma and brainstem function.

CSF = Cerebrospinal fluid; PCO_2 = Partial pressure of carbon dioxide

Coma or Unresponsiveness

Motor responses of the limbs

Testing: Motor responses of the limbs to painful stimuli should be absent after supraorbital pressure and nail-bed pressure stimulus.

Pitfalls: Motor responses ("Lazarus sign") may occur spontaneously during apnoea testing, often during hypoxic or hypotensive episodes, and are of spinal origin. Neuromuscular blocking agents can produce prolonged weakness. If neuromuscular blocking agents have recently been administered, examination with a bedside peripheral nerve stimulator is needed. A train of – four stimuli should result in four thumb twitches.

Absence of Brainstem Reflexes

Pupils

Testing: The response to bright light should be absent in both eyes.

Round, oval or irregularly shaped pupils are compatible with brain death.

Most pupils in brain death are in middle position (4 mm to 6 mm), but the size of the pupils may vary from 4 mm to 9 mm. Dilated pupils are compatible with brain death.

Pitfalls: Many drugs can influence pupil size, but light response remains intact. In conventional doses, atropine given intravenously has no marked influence on pupillary response. Because nicotine receptors are absent in the iris, neuromuscular blocking drugs do not noticeably influence pupil size. Topical ocular instillation of drugs and trauma to the cornea or bulbous oculi may cause abnormalities in pupil size and can produce non-reactive pupils. Pre-existing anatomic abnormalities of the iris or effects of previous surgeries should be excluded.

Ocular Movements

Testing

Ocular movements are absent after head - turning and caloric testing with ice water (testing is done only when no fracture or instability of the cervical spine is apparent, and in patients with head injury, the cervical spine must be imaged to exclude potential fractures or instability or both) the oculocephalic reflex, elicited by fast and vigorous turning of the head from middle position to 90° on both sides, normally results in eye deviation to the opposite side of the head-turning. Vertical eye movements, should be tested with brisk neck flexion. Eyelid opening and vertical and horizontal eye movements must be absent in brain death.

Caloric testing

It should be done with the head elevated to 30° during irrigation of the tympanum on each side with 50 mL of ice water. Tympanum irrigation can be best accomplished by inserting a small suction catheter into the external auditory canal and connecting it to a 50 mL syringe filled with ice water. Tonic deviation of the eyes directed to the cold caloric stimulus is absent. The investigator should allow up to one minute after injection and the time between stimulation each side should be at least five minutes.

Pitfalls

Drugs that can diminish or completely abolish the caloric response are sedatives, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, and chemotherapeutic agents. After closed head injury or facial trauma, lid oedema and chemosis of the conjunctiva may restrict movement of the globes. Clotted blood or cerumen may diminish the caloric response, and repeat testing is required after direct inspection of the tympanum. Basal fracture of the petrous bone abolishes the caloric response only unilaterally and may be identified by an ecchymotic mastoid process.

Facial Sensation and Facial Motor Response

Testing

Corneal reflexes should be tested with a cotton swab. Corneal reflex and jaw reflex should be absent. Grimacing to pain can be tested by applying deep pressure with a blunt object on the nail beds, pressure on the supraorbital ridge, or deep pressure on both condyles at the level of the temporomandibular joint.

Pitfall

Severe facial trauma may limit interpretation of all brainstem reflexes.

Pharyngeal and Tracheal Reflexes

Testing

The gag response, tested by stimulation of the posterior pharynx with a tongue blade, should be absent. Lack of cough response to bronchial suctioning should be demonstrated.

Pitfall

In orally intubated patients, the gag response may be difficult to interpret.

Apnoea

Apnoea test (guidelines for the test)

Pre-requisites: Important changes in vital signs (e.g. marked hypotension, severe cardiac arrhythmias) during the apnoea test may be related to lack of adequate precautions. Therefore, the following pre-requisites are suggested:

1. Core temperature greater than or equal to 36.5°C (4.5°C higher than the required 32 °C for clinical diagnosis of brain death).
2. Systolic blood pressure greater than or equal to 90 mmHg.
3. Euvolaemia (option: preferably positive fluid balance in the previous 6 hours).
4. Eucapnia (option: arterial $PCO_2 \geq 40$ mmHg).
5. Normoxaemia (option: arterial $PO_2 \geq 200$ mmHg). A pulse oximeter is connected to the patient.

Testing (Figure 2)

1. Ventilate with FiO_2 of 100% for 10 minutes.
2. Disconnect the ventilator.
3. Deliver 100% oxygen at a rate of 6 L/min by placing a cannula at the level of the carina.
4. Look closely for respiratory movements. Respiration is defined as abdominal or chest excursions that produce

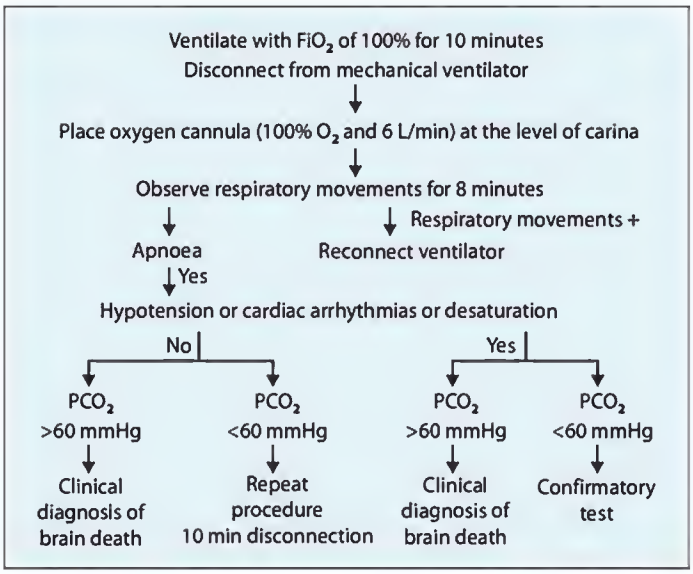


Figure 2: Procedure for the apnoea test in brain death.

FiO_2 = Fraction of inspired oxygen; PCO_2 = Partial pressure of carbon dioxide

adequate tidal volumes. If present, respiration can be expected early in the apnoea test. When the result is in doubt, a spirometry can be connected to the patient to confirm that tidal volumes are absent.

5. Measure arterial PO_2, PCO_2 and pH after approximately 8 minutes and reconnect the ventilator.
6. If respiratory movements are absent and arterial $PCO_2 \geq 60$ mmHg (option: 20 mmHg increase in PCO_2 over a baseline normal PCO_2), the apnoea test result is positive (i.e. it supports the clinical diagnosis or brain death).
7. If respiratory movements are observed, the apnoea test result in negative (i.e. it does not support the clinical diagnosis of brain death).
8. If during apnoea testing, systolic blood pressure becomes <90 mmHg, the pulse oximeter indicates marked desaturation, and cardiac arrhythmias occur, immediately draw a sample, connect the ventilator, and analyse arterial blood gas. The apnoea test result is positive if arterial PCO_2 is ≥60 mmHg or PCO_2 increase is equal ≥20 mmHg above baseline normal PCO_2. If arterial PCO_2 is < 60 mmHg or PCO_2 increase is <20 mmHg over baseline normal PCO_2, the result is indeterminate.
9. If no respiratory movements are observed, PCO_2 is <60 mmHg and no significant cardiac arrhythmia or hypotension is observed, the test may be repeated with 10 minutes of apnoea.

DURATION OF OBSERVATION

Brain death is a clinical diagnosis and irreversibility should be documented by an extended period of observation. The patient must undergo two brain death determinations at least 6 hours apart. However, this internal decision is arbitrary. The two examinations must be performed by different licensed physicians.

CONFIRMATORY LABORATORY TESTS

A repeat clinical evaluation 6 hours later is advised (option), but a firm recommendation cannot be given and the interval is arbitrary. A confirmatory test is not mandatory in most situations. All clinical tests are needed to declare brain death and are likely equally essential. A confirmatory test is needed for patients in whom specific components of clinical testing cannot be reliably evaluated. Clinical experience with confirmatory tests other than EEG, transcranial Doppler ultrasonography, and conventional angiography is limited. Many tests need costly equipment and well-trained technicians.

Conventional Angiography

Technique

A selective four-vessel angiogram is done in the radiology suite. Iodinated contrast medium is injected under high pressure in both the anterior and the posterior circulations.

Result

Intra-cerebral filling is absent at the level of carotid bifurcation or circle of willis. The external carotid circulation is patent, and at times delayed filling of the superior longitudinal sinus is seen.

Electroencephalography (EEG)

Technique

Usually a 16- or 18-channel instrument is used with guidelines developed by the American Electroencephalo-graphic society for recording brain death.

Result

No electrical activity occurs above 2 μV at a sensitivity of 2 μV/mm with filter setting at 0.1 or 0.3 second and 70 Hz. Recording should continue for at least 30 minutes.

EEG

Nevertheless in one consecutive series of patients fulfilling the clinical diagnosis of brain death, 20% of 56 patients had residual EEG activity that lasted up to 168 hours.

Disadvantage

Considerable artifacts in the intensive care unit can limit interpretation.

Isotope Angiography

Technique: Rapid intravenous injection of serum albumin labeled with technetium 99^m is followed by bedside imaging with portable gamma camera.

Results: Intracranial radioisotope activity is absent. Filling of saggittal and transverse sinuses may occur in delayed images from connections between the extracranial circulation and venous system.

Technetium 99^m Hexamethylpropylenamineoxime (99^m TcHMPAO)

Technique

The procedure can be performed at the bedside and takes approximately 15 minutes. The isotope should be injected within 30 minutes of reconstitution. A portable gamma camera produces planar views within 5 to 10 minutes. Correct intravenous injection can be checked by taking additional chest and abdominal images.

Result

No uptake occurs in brain parenchyma.

Disadvantage

The tracer should be injected immediately. Because the costs are currently high and technique is not widely available, experience is limited.

Transcranial Doppler Ultrasonography

Technique

A portable 2 MHz pulsed Doppler instrument can be used at bedside. Intra-cranial arteries should be insonated bilaterally (e.g. main carotid artery through the temporal bone above zygomatic arch and vertebral or basilar arteries through the suboccipital transcranial window). Alternatively a combination of one ophthalmic artery through transorbital window and the MCA can be tried.

Results

Transcranial Doppler signals that have been reported in brain death are as follows:

1. Absent diastolic or reverbating flow that indicates flow only through systole or retrograde diastolic flow. This pattern is caused by contractive forces of the arteries.
2. Small systolic peaks in early systole indicate very high resistance. This pattern is associated with greatly increased intracranial pressure. Lack of transcranial Doppler signals cannot be interpreted as confirmatory of brain death, because 10% of patients may not have temporal insonation

windows. An exception possibly can be made in patients who had transcranial Doppler signals during admission that disappeared at the time of brain death.

Disadvantage

Transcranial Doppler velocities can be affected by marked changes in PCO_2, hematocrit and cardiac output. Transcranial Doppler ultrasonography requires practice and skill.

Somatosensory Evoked Potentials

Technique

A portable instrument can be used at bedside. Median nerve stimulation is performed on both sides.

Result

N20-P22 response is bilaterally absent.

Miscellaneous Tests

Many of these tests have been done in small series of patients only and are not widely adopted as confirmatory tests.

Contrast computed tomograph with bolus of meglumine diatrizoate, 1 mL/kg of body weight, does not visualise intra-cranial vessels. A good correlation with cerebral angiography has been demonstrated in a few anecdotal reports.

Many other confirmatory tests are variants or modifications. Experience is limited, as these tests produce similar results in patients with neurological catastrophes who do not fulfil the clinical criteria for brain death.

COMMUNICATION WITH THE FAMILY

Critical care nurses and resident doctors should become familiar with the concept of brain death and its medical and legal criteria, because they may need to explain brain death to family members who are confused and in crisis. Sometimes the use of certain terminology appears to conflict with reality when the terminology is applied to cases in which patients are pronounced dead on the basis of neurological criteria. In order to avoid confusion, it is more helpful to tell family that their loved one is 'dead' because use of this word can help the family understand that neurological death has occurred. A clear definition of brain death must be given and reinforced.

SUPPORT OF THE POTENTIAL ORGAN DONOR

Once established, a brain dead case who is a potential donor is to be handled very carefully so as to prevent any organ damage before procuring them. After brain death since central regulation to circulation is lost, invasive haemodynamic monitoring is mandatory to avoid fluctuations and help guide fluid and vasopressor therapy.

Circulation

Inotropes and vasopressors both can be used to maintain haemodynamic parameters. Vasodilator infusion should be avoided in hypertension; rather short-acting beta blockers can be used. In patients with decreased left ventricle function and acute respiratory distress syndrome, pulmonary artery catheter is advocated. Targets to be maintained are: (i) systolic blood pressue >90 mmHg; mean arterial pressure >65 mmHg; (iii) central venous pressure 8 cm to 12 cm H_2O; pulmonary capillary wedge pressure <12 mmHg.

Respiratory Support

Ventilatory support should continue to maintain a normal blood gas picture. Intravenous steroids should be given in case lung transplant is planned. Lung protective strategy in ventilation to maintain P/F ratio is advisable. A minimum SpO_2 of 95% should be maintained.

Endocrinal Support

Injury to the hypothalamic-pituitary axis impairs the release of arginine vasopressin. The sequelae of this damage leads to occurrence of *Diabetes Insipidus* as most common abnormality.

The evaluation of the organ donor should be carried out in a step-wise approach as depicted in **Figure 3**.

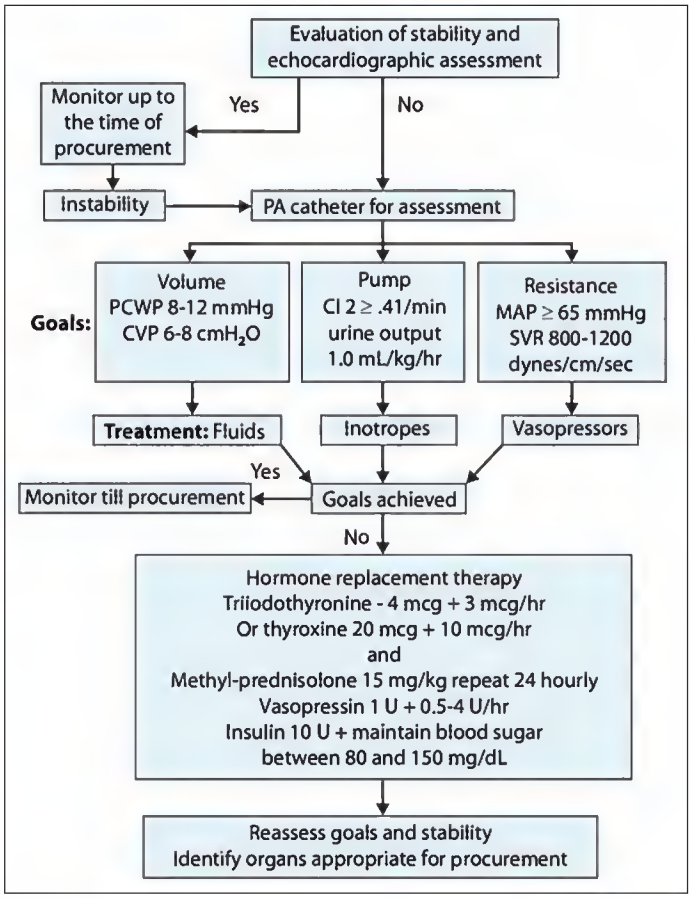


Figure 3: Stepwise approach for evaluation of organ donor patient.

PA = Pulmonary artery; PCWP = Pulmonary capillary wedge pressure; CVP = Central venous pressure; CI = Cardiac index; MAP = Mean arterial pressure; SVR = Systemic vascular resistance

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Section 8

Bone Disorders

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8.1 Bone and Mineral Metabolism in Health and Disease

Deepak Khandelwal, Ravinder Goswami

PHYSIOLOGY OF THE BONE

Bone is a special form of connective tissue with a collagen framework impregnated mineralized matrix in the form of hydroxyapatite crystals and also small, but highly active cellular fraction. Bone is involved in overall Ca^{2+} and PO_4^{3-} homeostasis. It also protects vital organs, permits locomotion with its rigidity, involved in acid-base balance, and provides the environment for hematopoiesis within the marrow spaces. Bone is of two types: compact or cortical bone, and trabecular or spongy bones. Cortical bone is the dense bone that is found in the shafts of long bones, whereas trabecular bone is composed of a honeycomb like network interspersed in the bone marrow compartment. The adult human skeleton is composed of 80% cortical bone and 20% trabecular bone. Bone is composed of 50% to 70% mineral, 20% to 40% organic matrix, 5% to 10% water and less than 3% lipids. The mineral content of bone is mostly hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$. Approximately 85% to 90% of bone protein is composed of collagenous proteins and the noncollagenous proteins is composed of rest 10% to 15%.

There are three cell types in bone: (1) bone forming osteoblasts, (2) osteocytes, and (3) bone resorbing osteoclasts. Osteoblasts are derived from mesenchymal cells, whereas osteoclasts are derived from mononuclear precursor cells of the monocyte-macrophage lineage. Bone undergoes modelling and remodelling during life. Longitudinal and radial growth occurs during childhood and adolescence. Modelling is the process by which bones change their overall shape in response to physiologic influences or mechanical forces, leading to gradual adjustment of the skeleton to the stress that it has to face. During bone modeling, bone formation and resorption are not tightly coupled. Bone remodelling is the process by which bone is renewed to maintain bone strength and mineral homeostasis. The bone remodelling units (BRUs) or bone multicellular units (BMUs) are composed of a tightly coupled group of osteoclasts and osteoblasts that sequentially carry out continuous removal of discrete packets of old bone and replacement of these packets with newly synthesised proteinaceous matrix and subsequent mineralisation of the matrix to form new bone. The remodelling cycle can be divided into four steps: (1) activation, (2) resorption, (3) reversal, and (4) formation.

The process of bone remodelling is highly regulated by mechanical forces, hormones and cytokines. One of the most important cytokine in osteoclastogenesis is receptor activator of nuclear factor-κB ligand (RANKL), which is a member of the tumor necrosis factor (TNF) family and is expressed in the bone-lining cells or osteoblast precursors that support osteoclast recruitment. Interaction of RANKL with its receptor (RANK) on osteoclast progenitors and osteoclasts then stimulates their recruitment and activation, and delays their degradation. Measurement of product of osteoblast and osteoclast activity can be helpful in diagnosis and management of metabolic bone diseases. These biochemical markers of bone remodelling are summarised in **Table 1**.

Table 1: Biochemical Markers of Bone Formation and Resorption

Bone formation markers	Serum bone specific alkaline phosphatase Serum osteocalcin Serum propeptide of type 1 procollagen
Bone resorption markers	Urine and serum cross linked N-telopeptides Urine and serum cross linked C-telopeptides Urine deoxypyridinoline

CALCIUM PHYSIOLOGY

Calcium is involved in important cellular functions like cell division, cell adhesion, integrity of plasma membrane, muscle contraction, neuronal excitability, secretion of proteins and coagulation cascade. A normal adult body contains about 1 kg of calcium, of which approximately 99% is present in the skeleton as hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$ and 1% in soft tissues and extracellular fluids. A normal calcium balance is summarised in **Figure 1**.

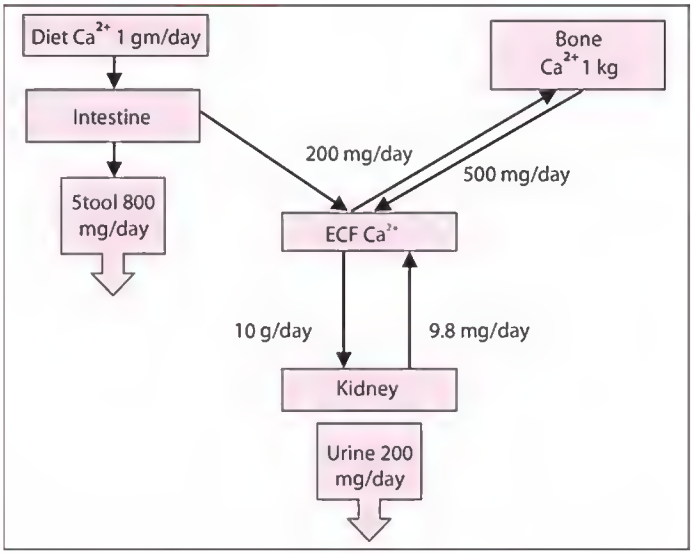


Figure 1: Normal calcium balance.

In spite of large movements of calcium between body compartments, serum calcium is maintained constant at about 10 mg/dl (2.5 mgm). The essential fraction is the biologically active free, ionized one which equals 50% of the total serum calcium (1.3 mgm). Forty percent of total serum calcium is protein-bound, principally to albumin, and the remaining 10% of calcium is complexed with various anions such as citrate, sulfate, bicarbonate, lactate and phosphate. A decrease in serum albumin of 1 g/dl results in a decrease in total serum calcium of 0.8 mg/dl without affecting the ionized fraction significantly.

As calcium is bound to carboxyl groups on albumin, pH changes affect ionised calcium. Acidosis decreases binding and increases ionized calcium, whereas alkalosis increases binding and decreases ionised calcium. The constancy of extracellular fluid concentration of calcium is maintained by hormonal regula-tion of the absorption of calcium from the gastrointestinal tract, the mobilization of skeletal calcium and the reabsorption of filtered calcium in kidney tubules. Vitamin D, parathyroid hormone (PTH) and calcitonin are the regulators of these processes.

Intestinal Calcium Absorption

Intestinal calcium absorption occurs through both an active transcellular pathway and a passive paracellular pathway. The paracellular pathway is dependent on calcium moving through tight junctions in the intestinal epithelium, which is a passive, nonsaturable process and is favored during states of high calcium intake. However, transcellular pathway, an active transport, is particularly important at low and normal calcium intake. It is summarised in **Figure 2**.

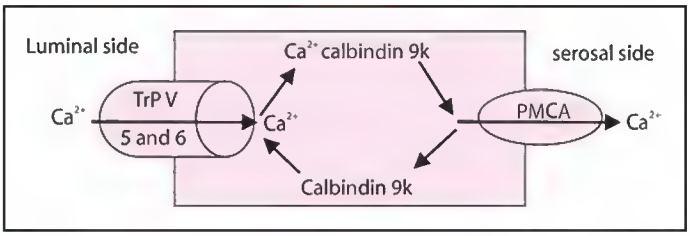


Figure 2: Intestinal absorption of Ca^{2+} via the transcellular pathway. Ca^{2+} enters through Ca^{2+} channel TrPV5 or TrPV6, in the luminal membrane of the enterocyte. Once absorbed, the transcellular movement of calcium to the basolateral membrane is dependent on binding to an intracellular protein known as calbindin-D_{9k}. The egress of calcium from the intestinal epithelium occurs through the actions of the plasma membrane calcium-dependent ATPase (PMCA1b). This transcellular movement of calcium is closely regulated by $1,25(OH)_2D_3$, which regulates the gene transcription of TRPV6, calbindin and PMCA1b.

Renal Handling of Calcium

Approximately 98% to 99% of the filtered Ca^{2+} is reabsorbed in kidney. About 60% of the reabsorption occurs in the proximal tubules via a passive, paracellular route, which follows sodium reabsorption. Rest of active calcium reabsorption takes place in the thick ascending limb of the loop of Henle and in the distal convoluted tubule and the connecting tubule. About 20% to 25% of the filtered calcium is reabsorbed in the loop of Henle through both transcellular and paracellular routes. The primary site for PTH regulation of renal calcium reabsorption is the distal nephron, which normally reabsorbs nearly all of the remaining 10% of filtered calcium by a unique transcellular active transport mechanism.

PHOSPHORUS PHYSIOLOGY

Phosphate, comprises 1% approximately of total body weight, is widely distributed in the soft tissues of the body. It is both in inorganic form and as a component of organic molecules including nucleic acids, membrane phospholipids and other phosphoproteins. However, 85% of body phosphate is stored in the bone matrix. Calcium and phosphorus are regulated by the controlled interactions of the intestine, renal tubules and bone. However, there are several important differences between phosphorus and calcium balance. Dietary phosphorus is present in abundance in most foods. This is in contrast to calcium, which is restricted to a few dietary items. Also, dietary phosphorus is absorbed almost twice as efficiently as dietary calcium. Thus, phosphorus absorption, unlike calcium, is rarely a nutritional problem. The normal range for serum phosphate level in adults is 2.5 to 4.5 mgm/dL. In children, serum phosphate levels are higher and decrease with age. Unlike plasma calcium, phosphorus is not protein bound and is filtered almost completely at the glomerulus.

Intestinal Phosphate Absorption

The average adult ingests approximately 1,000 mg/day of phosphorus, with 80% being absorbed by the intestine and the remaining 20% being excreted directly into the stool. Intestinal absorption of phosphorus can be either through paracellular or transcellular pathways. Paracellular absorption is largely dependent on the luminal concentration of phosphorus and does not appear to be saturable. Transcellular absorption occurs through the sodium-phosphate type IIb cotransporters, which have been shown to be upregulated by increasing $1,25(OH)_2D$.

Renal Handling of Phosphate

Approximately 70% of filtered phosphate is reabsorbed within the proximal tubule, which involves uptake across the brush border membrane, translocation across the cell and efflux at the basolateral membrane. The overall rate-limiting step in the reabsorptive process is phosphate uptake at the apical membrane; where the sodium-phosphate cotransporters (NPT) IIa and IIc actively transport phosphate from the lumens of nephrons into proximal tubular cells. Parathyroid hormone decreases the expression of the NPT IIa and IIc and decreases phosphate reabsorption. There are several other recently identified factors, termed phosphotonins like fibroblast growth factor 23 (FGF23), which induce renal phosphorus wasting by decreasing the expression of the NPT IIa and IIc. Human disorders associated with increased circulating concentrations of FGF23 are characterised by hypophosphataemia, and disorders associated with reduced FGF23 bioactivity, like tumoral calcinosis, are characterised by hyperphosphataemia.

PARATHYROID HORMONE

Structure and Biosynthesis

The parathyroid glands develop from the endodermal lining of the third and fourth branchial pouches. There are usually four parathyroid glands in man, two superior and two inferior each weighing about 40 mg, and located behind the thyroid gland. The predominant cell type in the parathyroid gland is the chief (also called principal) cell, which are primary endocrine cell. The primary function of parathyroid hormone (PTH) is to maintain extracellular calcium concentration in a narrow normal range. The hormone acts directly on bone and kidney and indirectly on intestine, by increasing the synthesis of $1,25(OH)_2D$ to increase serum calcium concentration. Rapid feedback effect on PTH secretion and production along with biological actions in multiple target tissues makes PTH as most important regulator for minute-to-minute control of extracellular calcium. In contrast, vitamin D is of importance in long-term, day-to-day, and week-to-week regulation of calcium balance.

PTH is synthesised as a part of the larger precursor protein containing a 25-amino acid hydrophobic residue-rich signal sequence and a 6-amino acid prosequence preceding the

amino terminus of PTH. These portions of the precursor are sequentially removed within the cell and mature 84-amino acid PTH is secreted from storage granules. A portion of the PTH secreted from parathyroid glands consists of carboxy-terminal PTH fragments. The carboxy-terminal fragments of PTH do not activate the PTH/PTHrP (parathyroid hormone-related protein) receptor and might even block bone resorption. Secreted intact PTH (1-84) is metabolised by liver and kidney and disappears from the circulation with a half-life of 2 minutes. However, rate of clearance of carboxy-terminal fragments occurs principally by glomerular filtration and much slower, with a half life of 20-40 minutes and these fragments accumulate in patients with renal failure. Older assays for PTH detected both intact 1-84 PTH and also carboxy-terminal fragments and therefore detected unreliably high levels of PTH, especially in patients with renal failure. These problems largely circumvented by use of current assays which utilise two antibodies recognising epitopes from both ends of the molecule, reliably measuring only intact PTH.

Biological Effects

PTH/PTHrP-receptor (PTHR1) binds both PTH and parathyroid hormone-related protein (PTHrP) and is primarily coupled to G_s, and via this heterotrimeric G protein activates adenylyl cyclase. PTHR1 is expressed on osteoblasts in bone and proximal and distal tubules of the kidney. A second PTH receptor, which can be activated by PTH but not by PTHrP, called the PTH2 receptor (PTH2R), is expressed in multiple tissues including brain, vascular endothelium and smooth muscle, endocrine cells of the gastrointestinal tract, and sperm. The functional role of the PTH2R is not clearly known.

PTH has multiple actions on bone, some direct and some indirect. PTHR1 is expressed on osteoblasts, but not on osteoclasts. Therefore, PTH stimulates osteoblast activity directly, whereas osteoclasts are stimulated indirectly through paracrine factors secreted by osteoblasts. PTH-mediated bone calcium release can occur within minutes. The chronic effects of PTH are to increase number of osteoblasts and osteoclasts, and to increase in bone remodelling. As PTH can increase both bone formation and bone resorption, net effect on bone mass varies according to whether PTH is administered continuously or intermittently, and also on type of bone. When PTH concentrations are persistently elevated like in primary hyperparathyroidism, significant bone loss occurs mainly in cortical bone with subperiosteal resorption, formation of bone cysts and spontaneous fractures. However, intermittent administration of low doses of PTH causes net increase in bone formation and increase in trabecular bone mass, with little effect on cortical bone mass and this concept has been utilised as use of PTH as anabolic therapy in patient with osteoporosis.

PTH has two major effects on the kidney: to increase calcium reabsorption in the distal nephron and to decrease proximal tubular reabsorption of phosphate. Calcium excretion depends both on the amount of calcium which reaches the distal tubule and on the concentration of circulating PTH. In hypercalcaemia, the filtered load of calcium increases so that more calcium is delivered to the distal tubule. In hyperparathyroidism, PTH increases fractional reabsorption of calcium, but because of the large calcium load delivered, hypercalciuria results. PTH decreases proximal tubular reabsorption of phosphate, so that increased urinary excretion of phosphate occurs. Sustained elevations in PTH thus result in hypophosphataemia in addition to hypercalcaemia. Both PTH and hypophosphataemia stimulate l α-hydroxylase activity to increase formation of $l,25(OH)_2D$.

Regulation of Synthesis and Secretion

The parathyroid gland has multiple methods for adaptation to change in extracellular calcium. Most rapid is secretion of preformed hormone, which occurs within minutes. Second, intracellular degradation of newly synthesised PTH provides an important regulatory mechanism by increasing the fraction of biologically inactive carboxy-terminal fragments of PTH. Third, PTH production is also regulated at the level of gene transcription and lastly, prolonged hypocalcaemia also elicits an increase in both the size and number of parathyroid cells. Secretion of PTH is primarily regulated by the concentration of ionized calcium in serum. Critically important to the process of calcium homeostasis is the G-protein-coupled calcium sensing receptor (CaSR), which is located on the surface of parathyroid chief cells. Increased serum ionised calcium leads to activation of CaSR causing activation of downstream signaling pathway leading to decrease in PTH secretion. Heterozygous and homozygous inactivating mutations in CaSR cause familial hypocalciuric hypercalcaemia (FHH) and neonatal severe hyperparathyroidism respectively. In these patients, CaSR fails to inhibit PTH secretion in hypercalcaemia because of defective calcium sensing in parathyroid and also inappropriate hypocalciuria occurs in presence of hypercalcaemia because of defective calcium sensing at renal level. Conversely, activating mutations in CaSR cause familial hypoparathyroidism with hypercalciuria. $1,25(OH)_2D$ has no direct effect on PTH secretion, but it dramatically suppresses PTH gene transcription. In hypomagnesaemia, in addition to impaired responsiveness of target tissues to PTH action, PTH secretion is decreased.

Parathyroid Hormone-Related Protein

Parathyroid hormone-related protein (PTHrP) is peptide with PTH like activity. PTHrP and PTH have marked homology at their amino terminal ends and they both bind to the PTH1R, yet their physiologic effects are very different. PTHrP is primarily an autocrine or paracrine factor, acting close to where it is produced. Other than important function during breast development and systemic calcium metabolism during lactation, it is also involved in Ca^{2+} transport in the placenta. Normally it appears to have little influence on calcium-phosphate homeostasis in an adult. However, secretion of PTHrP by a wide variety of tumors contributes to the humoral hypercalcaemia of malignancy by mimicking the systemic action of PTH.

VITAMIN D

Structure and Biosynthesis

Although initially discovered as a fat-soluble vitamin, vitamin D is a classical steroid hormone having both dietary and endogenous precursors. Vitamin D_3, cholecalciferol, is formed by solar ultraviolet B radiation (wavelength, 290-315 nm) of precursor 7-dehydrocholesterol in skin, which is present in large amounts in keratinocytes of the basal or spinous epidermal layers (**Figure 3**). Adequate exposure to UV light is necessary, with more exposure being required for darker skinned races. Ergocalciferol, vitamin D_2 is the compound formed in plants from precursor ergosterol and differs from vitamin D_3 by the

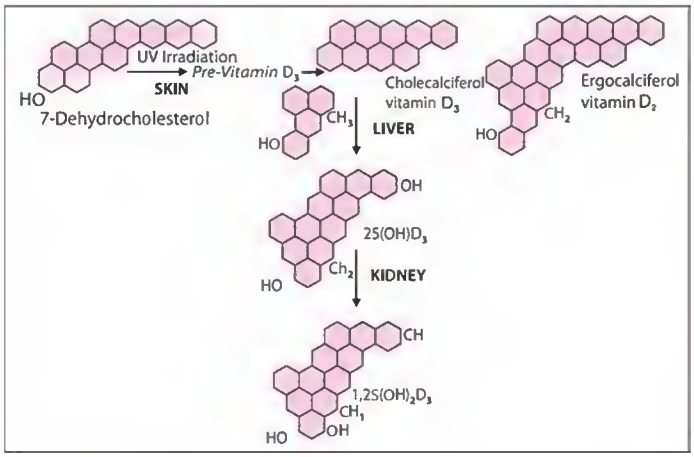


Figure 3: Biosynthesis of $1,25(OH)_2D$.

presence of a double bond between carbon 22 and 23 and a methyl group at carbon 24. Best dietary sources of vitamin D are fatty fish and its liver oils, although small amount is present in egg yolk and dairy products. Both vitamin D_2 and D_3 are prohormones and require subsequent modification to yield active hormone. As hormones derived from either vitamin D_2 or D_3 are equally active in man, the generic term vitamin D is generally used. In the liver, vitamin D is hydroxylated at C-25 by cytochrome P450 vitamin D 25-hydroxylases, resulting in the formation of 25-hydroxyvitamin D [25(OH)D]. In the proximal renal tubule, 25(OH)D is further hydroxylated, resulting in the hormonally active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), which is responsible for most of the biologic actions of vitamin D. In addition to $1,25(OH)_2D$, the kidney can also produce 24,25-dihydroxyvitamin D3 ($24,25(OH)_2D$), a relatively inactive metabolite. Human vitamin D binding protein (DBP) is a 52 kd α globulin synthesised in the liver. Approximately 88% 25-hydroxyvitamin D (25(OH)D) circulates bound to DBP, 0.03% is free and the rest circulates bound to albumin. In contrast, 85% of the circulating $1,25(OH)_2D_3$ binds to the vitamin D binding protein, 0.4% is free and the rest binds to albumin.

The most plentiful and stable metabolite of vitamin D is 25(OH)D and 25(OH)D level in the serum is the best indicator of vitamin D status in an individual. A 25(OH)D level of 30 ng/ml (75 nmol/L) or greater is considered indicating sufficient vitamin D for an individual. Vitamin D deficiency is defined as a 25(OH)D level less than 20 ng/ml (50 nmol/L), while a level between 20 ng/ml and 29 ng/ml is considered to indicate a relative insufficiency. Reports from across the world in last decade indicate that vitamin D deficiency and insufficiency is widespread and is re-emerging as a major health problem globally.

Regulation of $1,25(OH)_2D$ Formation

The renal 1α(OH)ase represents a key target of vitamin D regulation. Low dietary calcium and phosphate result in enhanced activity of 1α(OH)ase. Elevated PTH resulting from hypocalcemia is a primary signal stimulating the transcription of 1α(OH)ase. The 1α(OH)ase gene is negatively regulated by $1,25(OH)_2D$ and fibroblast growth factor 23 (FGF23), a phosphaturic factor.

Biological Effects

The active metabolite $1,25(OH)_2D$ enters the cell and binds to the vitamin D receptor. This complex forms a heterodimer with the retinoid receptor and binds to a vitamin D responsive element on responsive genes and followed by their transcription and translation. Recently, it has been demonstrated that other than these genomic actions, vitamin D may have certain nongenomic actions, and may work through a plasma membrane receptor and second messengers such as MAP kinase or cAMP. The intestine is the principal target for $1,25(OH)_2D$, where it enhances calcium and phosphate absorption as discussed above. Bone is the second major target for vitamin D. By increasing intestinal absorption of calcium and phosphate, vitamin D provides sufficient calcium and phosphate to initiate the crystallisation process at bone surfaces. $1,25(OH)_2D$ also directly affects bone cells to facilitate mineralisation even without measurable changes in the plasma concentrations of calcium and phosphate. Vitamin D deficiency is characterised by defective mineralisation of bone osteoid. Vitamin D receptor (VDR) are expressed on parathyroid cells and $1,25(OH)_2D$ inhibits the transcriptional activity of PTH gene and prevents proliferation of parathyroid gland. In recent years, there has been great interest in the role of vitamin D in non-classical actions like decreasing the risk of many chronic illnesses, including autoimmune diseases like multiple sclerosis and Type 1 diabetes, infectious diseases, cardiovascular disease and even common malignancies. Brain, prostate, breast and colon tissues, among others, as well as immune cells, have a vitamin D receptor. $1,25(OH)_2D$ has been found to have potent immunomodulator action, inhibits renin synthesis, increases insulin production and increases myocardial contractility. **Table 2** summarises the major biological actions of PTH and $1,25(OH)_2D$, in relation to calcium and phosphate homeostasis.

Table 2: Actions of PTH and $1,25(OH)_2D$ on Calcium/Phosphate Homeostasis

Hormone	Small intestine	Bone	Kidney	Parathyroid gland
PTH	No direct action	Promotes osteoblastic growth and survival	Stimulates 1α hydroxylase Stimulates Ca^{2+} reabsorption	No direct action
		Chronic high levels promotes bone resorption	Inhibits phosphate reabsorption	
$1,25(OH)_2D$	Increases Ca^{2+} and phosphate absorption	Sensitises osteoblasts to PTH	Increases phosphate reabsorption	Directly inhibits PTH gene expression
		Regulates osteoid production and calcification	Minimal effect on Ca^{2+} reabsorption	

CALCITONIN

Structure and Biosynthesis

Calcitonin is a 32-amino acid polypeptide, whose two major biological effects are to lower serum calcium and phosphate. It is synthesised by the parafollicular cells of the thyroid gland, also known as the clear or C cells, which originate from the neural crest. It has a circulatory half-life of about 10 minutes. Interestingly,

salmon calcitonin is 10 to 100 times more potent than mammalian hormone and is the one that is used therapeutically.

Regulation of Synthesis and Secretion

Synthesis and secretion of calcitonin is controlled by the concentration of ionised serum calcium. The stimulus for calcitonin synthesis is thus opposite to that for PTH secretion. Thus, its secretion is increased, when ionised serum calcium rises and vice versa. The calcium-sensing receptor cloned initially from parathyroid cells is also expressed in C cells and it contributes to the regulation of calcitonin secretion.

Biological Effects

Calcitonin reduces bone resorption by inhibiting osteoclast function, through its receptors on these cells. Thus it has a direct action on osteoclasts in contrast to PTH, whose effects are mediated through osteoblasts. In spite of the reproducible effects of calcitonin on bone and serum mineral content, the hormone does not appear to be a major physiological regulator. After removal of the thyroid-containing C cells and documented calcitonin deficiency or after development of medullary thyroid carcinoma, a neoplasm of C cell origin which results in markedly elevated calcitonin production, serum calcium and phosphate concentrations remain normal. In addition, it has a central analgesic effect, directly in cells of hypothalamus and related structures. Calcitonin is used in treatment of bone disorders associated with accelerated rate of bone turnover like Paget's disease and osteoporosis, and in the treatment of hypercalcaemia of malignancy. Calcitonin can serve as a tumour marker in medullary carcinoma of the thyroid as well as other tumours, including insulinomas, VIPomas and lung cancers, which can secrete calcitonin ectopically. In addition, high molecular weight forms of calcitonin may be elevated in acute pancreatitis, burns and infections.

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8.2 Investigations and Diagnosis of Bone Disorders

Sukumar Mukherjee

Bone is a highly dynamic tissue. About 70% of all bone mass contains inorganic material (calcium and phosphates) and 30% is of organic material (collagen and osteocalcin). Remodelling is a continuous process involving bone resorption and bone formation. The evaluation and diagnosis of metabolic bone disorders require the systematic elucidation of clinical history and thorough physical examination of musculo-skeletal system and other extra-skeletal features. The characteristics of bone pain, muscular weakness, anaemia, posture of the patient and deformities, linear-height, check-list of drug consumption and pre-existent risk factors need to be stressed; however, laboratory and radiological workup are usually necessary to clinch a diagnosis, even in early and asymptomatic stage of illness.

The laboratory aids for diagnosis and assessment are many but each one of them needs tailoring on the background of clinical information and risk factors assessment. These tests are:

I. Bone mineral profile
II. Calcitropic hormone profile
III. Imaging
IV. Bone biopsy and histomorphometry

BONE MINERAL PROFILE

The bone mass of women declines earlier than in men. Men have 30% to 50% more bone mass and are far less osteoporotic than woman. Preliminary workup consists of measurement of serum calcium, phosphorus, magnesium and alkaline phosphatase. The newer biochemical markers (bone markers) are classified depending upon their role on bone formation or bone resorption as in **Table 1**.

Table 1: Newer Biochemical Markers of Bone Formation and Bone Resorption

Bone Formation	Bone Resorption
Bone specific alkaline phosphatase	Urinary deoxypyridinoline (DPD)
Osteocalcin	Urinary N-telopeptide (NTX)
N - terminal propeptide of type 1 procollagen (PINP)	Serum C-terminal telopeptide (CTX) or β cross laps

These biochemical markers are sometimes useful in monitoring the response to treatment. They assess the risk for fracture in the stage of osteopaenia earlier than osteoporosis. The urinary NTX excretion, an indicator of bone resorption is to be determined on the second morning voiding, to predict early response to anti-resorptive therapy when compared to bone mineral density (BMD) follow-up every 1-2 years. The fall of NTX value by 35% from baseline is characteristic of effective anti-resorptive therapy. The resorption markers are also useful to identify patients with high risk of developing fractures. However, the limited availability of these newer markers are major hindrance towards their regular use in daily clinical practice.

Bone markers are reliable indicators of therapeutic success as early as three months after start of therapy. PINP (propeptide of type I procollagen) is the marker of osteoblastic activity for bone formation. The normal value is 26-110 microgram/L. Osteocalcin is a bone turnover marker and useful for therapy adherence and drug efficacy in bone diseases.

Serum Calcium

In circulation, the calcium is present in three forms namely ionised calcium (48% to 50%), protein-bound fraction (40%) and rest as complex calcium. The estimated normal value of calcium is around 9 to 10.6 mg/dL and because of diurnal variation, it reaches its peak value in mid-day and nadir in early morning. It is essential to correct serum calcium values to serum albumin levels as per formula.

Free Serum Calcium

Serum calcium (mg/dL) + [4 – serum albumin (gm%) × 0.8]. It is advisable to avoid tourniquet while drawing blood for serum calcium estimation irrespective of fasting or non-fasting state.

Ionised Calcium

It comprises 48% to 50% of total serum calcium, and is primarily responsible for physiological functions like muscle contraction, coagulation and bone mineralisation. The normal value of ionised calcium is around 4.5 to 5.2 mg/dL in fasting state (1.12 to 1.3 micromoles/L) with maximum at 10.00 hours and minimum at 18.00 to 20.00 hours. In heparinised samples, binding of calcium with heparin leads to low ionised calcium level. The significance of ionised calcium is of value in critical care patients with low albumin, altered acid-base balance and following massive blood transfusion.

The clinical disorders with hypercalcaemia and hypocalcaemia are mentioned as in **Tables 2 and 3**.

Table 2: Clinical Disorders with Hypercalcaemia

Hyperparathyroidism – Primary, tertiary
Prolonged immobilisation
Renal failure, Milk-alkali syndrome
Malignancies – Lung, Breast, Kidneys, Myeloma, Lymphoma
Endocrine – Thyrotoxicosis, Addison's disease, Pancreatic islet cell tumour
Granulomas – Tuberculosis, Sarcoidosis
Drugs – Vitamin D toxicity, Lithium, Thiazides, Foscarnet and Aluminium toxicity

Table 3: Clinical Disorders with Hypocalcaemia

Hypoparathyroidism, pseudohypoparathyroidism
Vitamin D deficiency – Nutritional, malabsorption, renal diseases
Drugs – Anti-convulsants (phenytoin and phenobarbitone), doxorubicin, bisphosphonates, cisplatin, calcitonin
Miscellaneous – Acute pancreatitis, tumour lysis syndrome, acute severe illness, toxic shock syndrome

Serum Phosphate

Out of total phosphorus in plasma, inorganic phosphate or phosphorus constitutes 1/3 fraction, the measurement of which is clinically useful for assessment of metabolic bone disorders. The normal range of inorganic phosphate is 2.5-4.5 mg/dL with higher values in elderly male and postmenopausal women. The inorganic phosphate is 20% protein bound and rest is free ionic form. The serum phosphorus level is higher in infants and children. Serum phosphorus level is measured by spectrophotometry from fasting plasma sample. The best index of phosphorus excretion is the maximal tubular reabsorption of phosphorus expressed as a function of GFR or TmP/GFR. This is decreased in primary hyperparathyroidism.

The clinical disorders associated with hyperphosphataemia and hypophosphataemia are listed below in **Tables 4 and 5**.

Table 4: Clinical Disorders Associated with Hyperphosphataemia

Disorders	Mechanism
Acute and chronic renal failure Hypoparathyroidism Pseudohypoparathyroidism Bisphosphonate therapy	Poor renal excretion
Hypothermia Acidosis Rhabdomyolysis Haemolysis	Intracellular to extracellular shift of phosphorus

Table 5: Clinical Disorders Associated with Hypophosphataemia

Disorders	Mechanism
Hyperparathyroidism Hypovitaminosis D Alcoholism Renal tubular acidosis	Increased renal excretion
Respiratory alkalosis Sepsis Recovery from diabetic ketoacidosis Salicylate toxicity	Extracellular to intracellular shift of phosphorus
Diuretics Steroids Calcitonin Beta agonists	Drug related adverse effect
Malabsorption Antacid abuse Vitamin D deficiency	Diminished intestinal absorption of phosphates

Serum Magnesium

Magnesium is present mostly in ionised form (55%), protein bound (30%) and rest in complex form. The normal value of serum magnesium is 1.7 to 2.6 mg/dL. The hypomagnesemia is observed in metabolic acidosis, prolonged diuretic therapy, prolonged nasogastric aspiration, hypoparathyroidism, acute pancreatitis, extensive bowel resection. Increase in serum magnesium level is seen in haemolysis. Severe and prolonged hypomagnesemia inhibits parathyroid hormone (PTH) release and induces resistance to PTH action on bones.

Serum Alkaline Phosphatase

The normal value in adults is 40-150 IU/L and in children 11-306 IU/L. The bone specific serum alkaline phosphatase (ALP) —a marker of osteoblastic activity is raised in Paget's disease of bones, metastatic bone disease, osteomalacia, osteoporosis. However, it is important to exclude hepatobiliary disease where ALP level is also high, especially in patients with cholestasis. The bone specific alkaline phosphatase fraction has better predictive value in evaluating bone disorders.

CALCITROPIC HORMONE PROFILE

Parathyroid Hormone (PTH)

The major 84-amino acid polypeptide hormone from parathyroid glands is metabolised in liver and present as intact PTH (iPTH) in circulation. PTH is measured by radioimmunoassay and the normal value ranges from 10-55 pg/mL (1-6.1 picomol/L). The sample for PTH assay is stored at –4°C and should be transported to laboratory in ice and centrifuged as early as possible and kept at –20°C or lower. The iPTH assay is indicated in: (a) to distinguish between PTH dependent versus PTH independent causes of hypercalcaemia; (b) to find out the cause of hypocalcaemia; (c) to evaluate Paget's disease and in hypophosphatemic rickets where iPTH level is normal.

Parathyroid Hormone-Related Protein (PTHrP)

The PTH-related peptide (PTHrP) is mainly significant in hypercalcaemia of malignancy. On the other hand, PTHrP levels are essentially normal in primary hyperparathyroidism and non-malignant causes of hypercalcaemia. This is measured by two-site isotopic immunoassay (IRMA) or by ELISA method.

Calcitonin

This 32-amino acid polypeptide is secreted by the parafollicular or C-cells of thyroid gland. It reduces bone resorption by inhibiting osteoclastic activity; and also reduces tubular resorption of both calcium and phosphorus and hence it has hypocalcaemic effect. Its estimation is useful in the diagnosis of hypercalcitoninaemia and medullary carcinoma of thyroid. The normal value is less than 0.08 microgram/L. The provocative tests for calcitonin estimation are done with calcium infusion and pentagastrin stimulation; calcitonin is the only hormone to actively lower serum calcium.

Vitamin D and Metabolites

Both vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are prohormones and are inert until activated in the liver and kidney through sequential hydroxylation. The major transport form of vitamin D is 25(OH)D (calcidiol) hydroxylated in liver and its circulating concentration reflects nutritional status of vitamin D. This is further hydroxylated in kidney to produce the active form of the hormone 1, 25 dihydroxy D (Calcitriol).

In clinical disorders with vitamin D deficiency or excess the best method for assessing vitamin D status is measurement of serum 25(OH)D level and its normal value is between 8 and 50 ng/mL by RIA. The levels of 25(OH)D reflect the body stores of vitamin D more accurately than $1,25(OH)_2D$. The level rises in summer and declines in winter and more so in elderly.

Estimation of 25(OH)D is indicated in vitamin D deficiency/toxicity and in some subsets of hypercalcaemia with low PTH level. The value is low in clinical osteomalacia and subclinical vitamin D deficiency states. The cut-off value for overt osteomalacia is less than 5 ng/mL whereas values less than 15 ng/mL is suggestive of subclinical deficiency. The estimated values also vary

periodically with the quality of diet and duration of sun exposure in an individual. In patients with vitamin D toxicity serum 25(OH)D level is high along with hypercalcaemia but low PTH level.

The measurement of most biologically active form serum $1,25(OH)_2D$ (normal value 20-60 pg/mL) is indicated in hypercalcaemic states with normal iPTH, PTHrP and 25(OH)D, e.g. sarcoidosis, lymphoma and William's syndrome.

IMAGING

Standard Radiographs in Metabolic Bone Disease

This remains a useful and simple modality for the diagnosis of metabolic bone diseasae. The regions of the skeleton meant for diagnostic radiology are skull (lateral view), thoraco-lumbar spine (lateral view), pelvis with both hips (AP view), hands (AP view) and long bones (AP and lateral). Mostly conventional radiology is indicated in Paget's disease, primary hyperparathyroidism, osteomalacia, osteoporosis, fluorosis and osteosclerosis. However, the standard x-rays are unable to pick up decreased bone mass until there is 40% to 50% reduction of bone mass. However, these X-rays are useful to pick up compression fractures and other minimal injury fractures. The characteristic features are summarised as in **Table 6** (**Figures 1 to 5**).

Table 6: Summary of Characteristic Radiological Features in Common Disorders

Disease	Radiological features	Anatomical areas
Paget's disease (**Figure 1**)	Cortical thickening, areas of sclerosis and lucencies, bowing of legs and kyphosis of spine	Femur, skull, tibia, pelvis and spine
Primary hyper-parathyroidism (**Figure 2**)	Subperiosteal resorption, osteitis fibrosa cystica pathological fractures, tufting of distal phalanges and salt and pepper skull	Radial border of middle phalanges long bones, femoral neck, distal clavicle, skull
Osteomalacia (**Figures 3 and 4**)	Symmetrical pseudo-fractures or Looser's zones demineralisation, deformities, radiological features	Pubic rami, ribs, scapula, femoral neck shafts of long bones
Osteoporosis	Demineralisation, thin cortex, prominent trabecular lines, spinal deformities and stress fractures	Thoraco-lumbar spine, pelvis with femoral neck and wrists
Fluorosis (**Figure 5**)	Diffuse osteosclerosis interosseous membrane calcification	Long bones, pelvis
Osteosclerosis (Renal osteody-strophy, bone metastasis and hyper-vitaminosis A and D)	Diffuse thickening of cortices with gradual obliteration of medulla	Spine, long bones



Figure 1: Paget's disease of skull.



Figure 2: Bone cyst left femur in primary hyperparathyroidism.

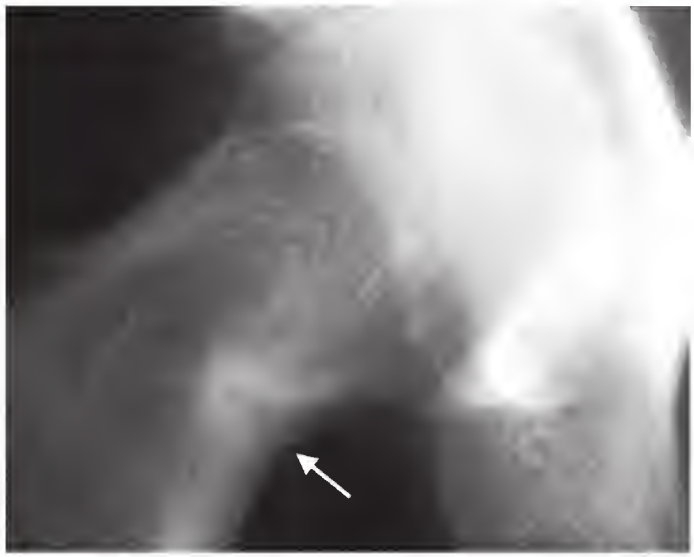


Figure 3: Pseudofracture or Looser's zone in osteomalacia.

Bone Scan or Scintigraphy

The principle behind metabolic bone scan is functional mapping of bone turnover and essentially it consists of accumulation of radioactive material in areas of bone depending upon blood flow and osteoblastic activity. The imaging is done with radioactive diphosphonates (DPN) labelled with technetium 99m. The bone scan is diagnostic in bone metastasis and vertebral fractures which are not always

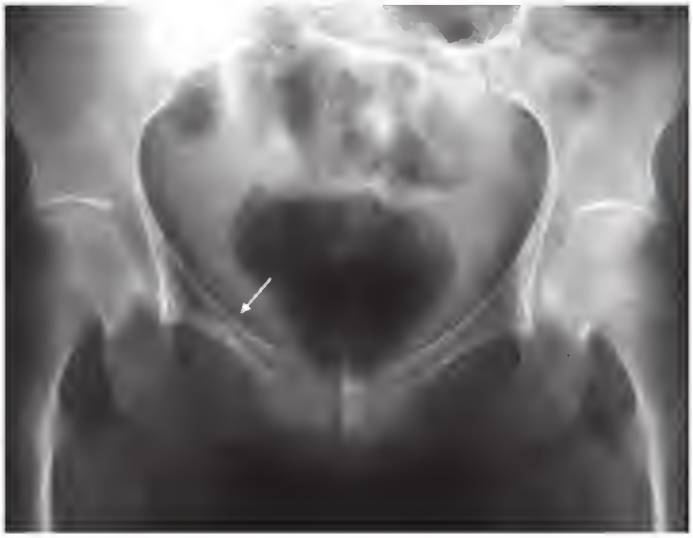


Figure 4: Pseudofracture in right pubic ramus in osteomalacia.



Figure 5: Fluorosis of spine

characteristic in conventional radiology (**Figure 6**). The 'hot spots' of vertebral fractures have time frame of two weeks to twelve months after the onset of fracture.

The metabolic 'superscan' with increased uptake in long bones, axial skeleton, skull, mandible is quite characteristic in primary hyperparathyroidism and renal osteodystrophy with secondary hyperparathyroidism. But this is negative in hypercalcaemia of malignancy. Bone scan is invaluable in Paget's disease for diagnosis and extent of disease; similarly it is useful to pick up Looser's zones in osteomalacia.

Bone Densitometry

The reduced bone mineral density (BMD) is the 'gold standard' for diagnosis with osteoporosis, yardstick of bone fragility and consequent risk of fracture. The correlation of BMD with risk of fracture is strong and sustained and comparable to hypertension and risk of stroke. It is estimated that 10% reduction of BMD doubles the risk of fracture.

There are number of methods to assess the BMD in a given individual which are mentioned in **Table 7**.

Table 7: Methodologies of BMD Measurement

Method	Common Anatomical Sites
Plain X-ray	Phalanges (hands) Thoracolumbar spine
Single energy X-ray absorptiometry (SXA)	Calcaneum, Radius/ulna
Dual energy X-ray absorptiometry (DEXA)	Lumbar spine Proximal femur Forearm
Quantitative computed tomography (QCT)	Lumbar spine
Broadband ultrasound attenuation (BUA)	Calcaneum, tibia

Out of all these modalities, DEXA is more accurate and consistent when compared with other methods.

The BMD measurement is recommended in several clinical states according to sex and age of the individuals as below in **Table 8**.

Table 8: Indications for BMD Measurement

1. Premenopausal women (Caucasian or Asian)
   (a) Long-term therapy with steroids, thyroxine, heparin
   (b) Primary or secondary amenorrhoea
   (c) Post-oophorectomy, organ transplantation
   (d) Malabsorption, chronic renal failure, hyperparathyroidism
2. Postmenopausal women
   (a) Patients not on oestrogen therapy
   (b) Vertebral or hip deformities or fractures plus premenopausal indications as above
3. Men
   (a) Hypogonadism
   (b) Unexplained fractures
   (c) Recurrent falls

Interpretation of BMD Measurement

The BMD reports express the standard deviation from the mean bone mass of normal 30-year-old young adults as the 'T' score and standard deviation from age and sex matched control as the 'Z' score.

WHO has established the following BMD-based diagnostic criteria for women:

- *Normal*—a BMD value within 1 (one) SD of the young adult mean.
- *Osteopaenia*—a BMD value more than 1 (one) SD but less than 2.5 SD below the young adult mean.
- *Osteoporosis*—a BMD value of 2.5 SD or more below the young adult mean.
- *Established or severe osteoporosis*—a BMD value 2.5 SD or more below the young adult mean with one or more fragility fractures.

Bone markers do not replace BMD, but are complimentary tools as they provide information about the rate of bone loss and not the patients' current bone mineral density.

Plain X-ray

It is insensitive to measure bone loss unless 30% to 50% of bone density has been lost. However, it is good to pick up fractures.



Figure 6: Bone metastasis in prostatic carcinoma in bone scintigraphy.

Single Energy X-ray or Photon Absorptiometry (SXA)

In this method the photon source is the digital X-ray system. The sites measured are the distal (90% cortical) and ultradistal (65% trabecular bone) radius of the forearm in prone position. However, it is inadequate to reflect the bone loss of BMD measurement.

Dual Energy X-ray Absorptiometry (DXA or DEXA) (Figure 7)

It is the gold standard for the diagnosis and monitoring treatment of patients with osteopaenia and osteoporosis. The sites commonly chosen are PA and lateral lumbar spine, hip, forearm and whole body. The positioning of femoral neck is critical to maintain good precision. The follow-up DXA after treatment is advisable after 1-2 years. Because of cost and non-availability of portable machines, its liberal use is somewhat limited.

Quantitative Ultrasound (QUS)

This method is portable, without any radiation risk which provides information both about bone quality and trabecular connectivity unlike DXA. The broadband ultrasonic attenuation (BUA) describes the increase in ultrasound attenuation and may be used for determination of bone density of calcaneum. The precision of this method is modest and the standardisation and quality control remains controversial. However, it can be utilised for community screening.

Quantitative Computed Tomography (QCT)

It takes the cross-sectional image of the vertebra and measures trabecular component in T_{12} to L_4 using regular CT scanner. Besides, volumetric QCT improves the spinal measurement.

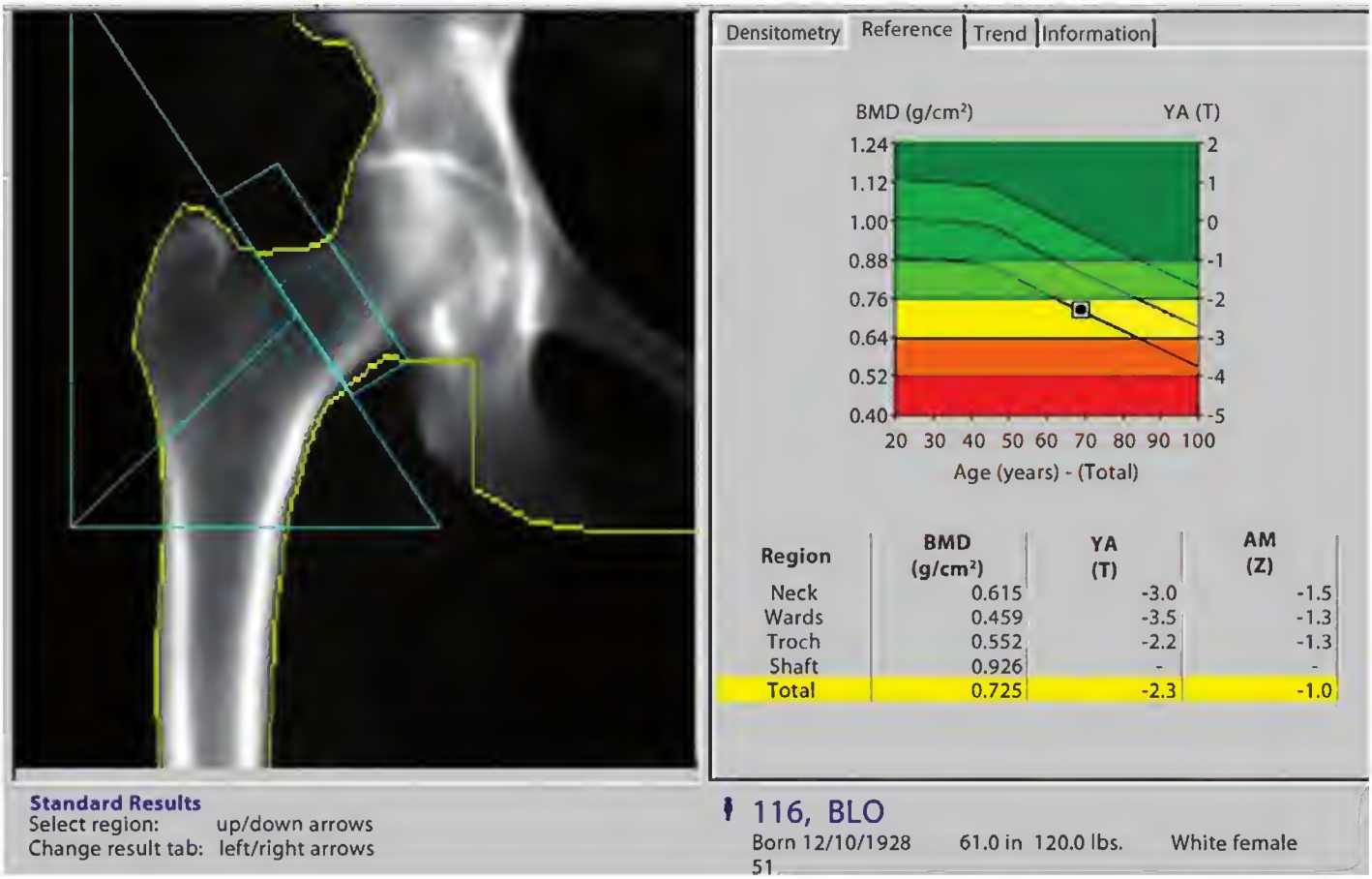


Figure 7: DEXA scan of right femur neck in osteoporosis.

The peripheral QCT gives higher spatial resolution which renders superior-modality when compared with other techniques.

Magnetic Resonance Imaging (MRI)

This is also valuable to recognise trabecular pattern more precisely but it is not cost effective for regular use.

BONE BIOPSY AND HISTOMORPHOMETRY

Bone biopsy is hardly indicated in metabolic bone disorders for diagnosis. In difficult situations of osteoporosis or osteomalacia of undetermined origin, it may be attempted to study the bone architecture under microscope with special histomorphometry. The biopsy is done through transilial approach on anterior superior iliac spine and processed in an undecalcified state prior to histologic evaluation. Rarely biopsy study is useful in follow-up of drug trial and other research purposes.

Lastly, in disease specific states with bone disorders additional tests may be carried out like serum protein electrophoresis, renal profile, serum thyroid hormones, cortisol, gonadal hormonal profile, genetic study on individual basis to settle the comprehensive diagnosis.

RECOMMENDED READINGS

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8.3 Rickets and Osteomalacia

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OSTEOMALACIA AND VITAMIN D DEFICIENCY IN INDIA

A large amount of literature is available indicating a widespread occurrence of vitamin D deficiency, osteopaenia and osteoporosis among Indians. Studies from India have reported a high prevalence (84% to 90%) of hypovitaminosis D among healthy Indians across all age groups including pregnant population. Genetic factors are also believed to play a role in causation of osteomalacia.

Osteomalacia and rickets are widely prevalent in India. Due to widespread occurrence of 25(OH)D deficiency, 25(OH)D levels may not be considered the hallmark for diagnosing osteomalacia in Indian population. Also, financial constraints and lack of laboratory support make it difficult to get the 25 hydroxy vitamin D and parathormone (PTH) levels in all patients. Instead, an integrated approach taking into consideration the socioeconomic background and history, serum biochemistry and 24-hour urinary calcium estimation can help in the diagnosis.

AETIOPATHOGENESIS

Vitamin D is the major steroid hormone involved in bone mineral homeostasis. The sources of calcium include milk and milk products like butter, ghee, curd and animal products like eggs and meat. Vegetable sources of calcium include pulses and gram. Some fruits like coconut, apricot, guava, banana and pumpkin are also rich in calcium. Though not regularly calculated, spices are also rich source of calcium with *dhaniya*, asafoetida, cloves, coriander and cumin seeds accounting for about 100 mg of daily calcium intake among Indians.

Sunlight is a good source of vitamin D. Vitamin D is naturally obtained in the animal products like cod liver oil and fish liver oil. Other sources are meat, fish, eggs and milk. Thus, there is a tendency for vitamin D deficiency in pure vegetarians. Activation of inactive vitamin D to its active vitamin D3 form occurs under the influence of ultraviolet light. This activation may be prevented by melanin in the skin which explains occurrence of vitamin D deficiency in dark skinned individuals. The first step in the activation of vitamin D is 25 hydroxylation in the liver followed by 1-alpha hydroxylation in the kidney. The active 1,25 dihydroxy vitamin D exerts its effects by binding to the vitamin D receptor, a member of steroid/thyroid hormone superfamily. The major actions of vitamin D include mineralisation of the bony matrix and growth plates. It is also known to have immunomodulatory and anti-proliferative effects. The absence of biologic effects of vitamin D could be due to a lack of dietary intake, deficient production of active form of vitamin D in the skin, impaired vitamin D activation or resistance to the biologic effects of 1,25 dihydroxy vitamin D.

For skeletal mineralisation, adequate calcium and phosphate must be present at mineralisation sites. Calcium levels in the blood are regulated by vitamin D mediated absorption from the gut and resorption of calcium from the bone that is regulated by PTH. 1,25 dihydroxy vitamin D enhances calcium and phosphorus absorption from the intestine. Reduction in the absorption of calcium in vitamin D deficiency and the resulting hypocalcaemia stimulates parathyroid glands to increase PTH secretion. PTH acts on osteoclasts to mediate resorption of the bone. At the renal level, PTH facilitates calcium reabsorption and phosphorus excretion through the tubules. PTH also stimulates the renal conversion of 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D which in turn stimulates more calcium and phosphorus absorption from the gut. Histopathology of osteomalacic bone shows an incompletely mineralised osteoid, an increase in the osteoid volume and thickness and a decrease in the calcification or mineralisation front.

Osteomalacia and rickets are disorders characterised by defective mineralisation of the bony matrix. Rickets occurs in the growing skeleton of children and both the long bones and the cartilaginous matrix of the growth plate are involved. Osteomalacia is defective matrix mineralisation of the bones in adults, in whom the epiphyseal bony fusion has occurred. The most common cause of these diseases in Indian population remains nutritional vitamin D deficiency. Inadequate sunlight due to *purdah* as practiced by Muslim women coupled with borderline vitamin D reserves could also result in osteomalacia. Other causes are enlisted in **Table 1**. Another common disorder in India is fluorosis. Excess fluoride mainly from water sources interferes with mineralisation of hydroxyapatite in bone.

Table 1: Aetiologic Profile of Osteomalacia

Vitamin D deficiency	Inadequate dietary intake Malabsorption Impaired cutaneous production
Impaired 25 hydroxylation	Liver disease Drugs like isoniazid ? Inherited mutation of 25 alpha hydroxylase
Impaired 1-alpha hydroxylation	Renal failure Renal tubular disorders, Fluorosis Vitamin D dependent rickets type 1 Oncogenic osteomalacia X-linked hypophosphatemic rickets
Accelerated vitamin D metabolism	Drugs, like phenobarbitone, primidone, phenytoin, rifampin, glutethimide
Vitamin D resistance	Vitamin D dependent rickets type II (receptor mutation)

Vitamin D dependent rickets type I (VDDR I) is a rare genetic disorder of mutation in the 1-alpha hydroxylase gene inherited in autosomal recessive fashion. Vitamin D dependent rickets type II (VDDR II), another inborn error of metabolism inherited in an autosomal recessive fashion, is due to mutations of the vitamin D receptor and is characterised by alopecia, vitamin D deficiency and lack of response to the conventional doses of vitamin D. Oncogenous osteomalacia is another rare cause of osteomalacia

where phosphaturic factor is secreted by tumours (usually of the mesenchymal origin) resulting in deficient mineralisation.

Calcipenic Rickets

Decrease in calcium intake or decrease in the intestinal calcium has also been associated with rickets. Such cases were reported from South Africa, also from India where children consumed no milk or dairy products and the intake of calcium was estimated to be less than 200 mg. Consumption of cereals and grain products high in phytate could lead to formation of intraluminal calcium phytate complexes and consequent calcium malabsorption. Other features and biochemistry is similar to vitamin D deficiency rickets except for 25 hydroxy vitamin D levels which are normal.

Clinical Features

Clinical signs may differ according to the age at presentation. Infants may present with hypotonia, feeding difficulties, irritability, or hypocalcaemic seizures. Clinical signs in infants include craniotabes (softened calvaria), widened fontanelle, frontal bossing, hypotonia, divarication of the recti and umbilical hernia. As the disorder progresses, the child finds increasing difficulty in walking and a progressive proximal muscle weakness. Pathological fractures may occur, growth is stunted. In children, the weight bearing joints may present with bowing deformities (genu valgum and varum) and wrist widening. Prominence of the costochondral junction (also known as rachitic rosary and indentation of the lower ribs (Harrison's groove) due to softening of skeleton may be present. Dentition is delayed and enamel hypoplasia may occur. Deformity of the back including kyphosis and lordosis along with limb bowing (**Figure 1**) can contribute to waddling gait. Patients with VDDR I and VDDR II usually present during infancy or childhood. Those with VDDR II also present with alopecia, multiple milia and epidermal cysts, milder defect could present during adolescence also.



Figure 1: Spinal, wrist and foot deformities in a child with rickets.

Adult patients with vitamin D deficiency may be asymptomatic or present with varying degrees of bony aches along with features of proximal muscle weakness. History of repeated fractures even on trivial trauma may be present. In severe cases, long bones may show bowing deformities (**Figure 2**). Seizures in adults due to hypocalcaemia caused by vitamin D deficiency are extremely rare. This is possibly due to PTH excess which prevents extreme decline in calcium levels and a relative metabolic alkalosis (PTH effect). Axial osteomalacia and resulting microfractures of the vertebrae may cause loss of the adult height. Rib involvement could result in a deformed chest. Enthesopathy and ligamentous calcification as occurs in X-linked hypophosphatemic osteomalacia or fluorosis could result in joint stiffness.



Figure 2: Photograph showing bowing of lower limbs.

Investigations

Routine investigations including haemogram, renal function tests, liver function tests and urine routine examination are important to rule out a systemic cause of metabolic bone disease. The basic investigation for a metabolic bone disease work-up includes calcium, phosphorus and alkaline phosphatase, 24-hour urinary calcium and fractional excretion of phosphorus as assessed by tubular reabsorption of phosphorus (TRP) and TmpGFR. Serum albumin is also needed to make appropriate corrections for the serum calcium level. A 24-hour urinary creatinine is also needed along with 24-hour urinary calcium to assess for adequacy of urine collection.

In osteomalacia, serum calcium levels are low to normal, phosphorus levels are low and alkaline phosphatase is high. In the initial stages, phosphorus levels may be low and normal calcium levels due to secondary hyperparathyroidism. A 24-hour urinary calcium level in patients with osteomalacia is low (normal calcium excretion is 2.5 to 4 mg/kg/day).This helps in distinguishing osteomalacia from other metabolic bone disorders like normocalcaemic hyperparathyroidism and renal tubular acidosis where the 24-hour urinary calcium levels are high. In osteomalacia, 25(OH)D levels are low and PTH levels are high. There is no utility of $1,25(OH)_2D$ in patients with nutritional osteomalacia since these levels are usually normal due to the enhanced 1-alpha hydroxylase activity, an action mediated by PTH. $1,25(OH)_2D$ levels are low in patients with osteomalacia due to renal causes, fluorosis or oncogenous osteomalacia. **Table 2** gives the differential biochemical parameters in patients with metabolic bone diseases due to different causes.

Table 2: Biochemical Parameters in Metabolic Bone Diseases

Calcium	Phosphorus	Alkaline Phosphatase	24-hour Urinary Calcium	Diagnosis
Normal	Decreased	Increased	Decreased	Osteomalacia
Decreased	Decreased	Increased	Decreased	Osteomalacia
Normal	Decreased	Normal	Decreased	Osteomalacia
Increased	Decreased	Increased	Increased	Hyperparathyroidism
Normal	Decreased	Increased	Increased	Normocalcaemic hyperparathyroidism, Renal tubular acidosis
Decreased	Increased	Normal	Decreased/normal	Hypoparathyroidism
Decreased	Increased	Increased	Decreased/normal	Renal failure, selective renal resistance to PTH action

Asymptomatic/Subclinical Osteomalacia

Some healthy Indian adults or some patients who report mild non-specific bony aches and pains have normal calcium, phosphorus and alkaline phosphatase vitamin D and PTH levels but low 25(OH)D levels. It is difficult to detect this subgroup since most of them have normal calcium, phosphorus and ALP levels. PTH levels are also within the normal range albeit high normal, a finding difficult to explain. A 24-hour urinary calcium in these patients is usually low.

A comprehensive evaluation of a patient with metabolic bone disease demands radiographs of the pelvis, skull, dorsolumbar spine (anteroposterior and lateral views), chest and bilateral forearms and hands. There is usually a generalised osteopaenia with coarsening of the trabeculae. Widening, fraying and cupping of the distal ends of the shaft and disappearance of the zone of provisional calcification is seen. Pseudofractures (thin cortical radiolucent lines at right angle to the shaft) may be present. The common sites of pseudofractures includes medial margins of the neck of femur, pubic rami (**Figures 3A and 3B**) borders of scapulae, ribs and rarely margins of forearm bones. Secondary hyper-parathyroidism manifests as diastasis of the pubic rami, though presence of cysts, pepper pot appearance of the skull, subperiosteal resorption and tufting of the phalanges points towards a diagnosis of primary hyperparathyroidism. Interosseous membrane calcification and calcification of the ligamentous joints is usually seen with fluorosis. Rarely, patients with fluorosis may masquerade as ankylosing spondylitis. **Figure 4** shows a female with florid osteomalacia and hypocalcaemic tetany in **Figure 5**.



Figure 3A: Radiograph of pelvis showing osteopaenia, pubic diastasis and pseudofractures of the pubic rami.

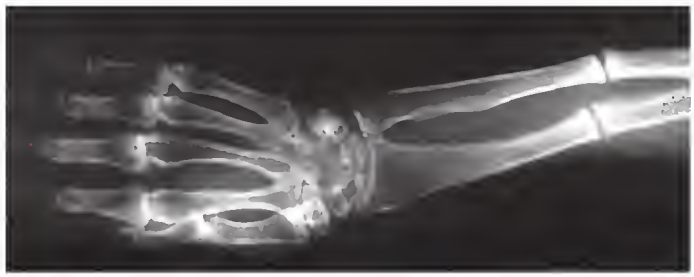


Figure 3B: Pseudofractures in forearm bones (looser zone).



Figure 4: Photograph shows a female with florid osteomalacia.

Management

Treatment of osteomalacia or rickets should be tailored to the underlying disorder. In almost all cases treatment with calcium 1 to 3 g daily is required. Patients with nutritional osteomalacia, where activation pathway is intact, could be supplemented with cholecalciferol instead of calcitriol which is more expensive. These patients could be given monthly cholecalciferol for 2 to 4 months. In more severe cases, where depleted vitamin D stores have to be replenished cholecalciferol 60,000 IU weekly for a month and then monthly for 3 to 6 months , sometimes per year are required. In patients with osteomalacia due to a renal cause or hypoparathyroidism or VDDR I where 1-alpha hydroxylation is defective, active metabolite, calcitriol in the dose of 0.25 to 0.5 mcg should be supplemented. In cases of malabsorption, vitamin D could be administered parenterally. In our practice, development of hypercalcaemia or nephrocalcinosis is extremely rare. This is possibly due to poor vitamin D stores which take a long time to normalise.



Figure 5: Photograph shows hypocalcaemic tetany.

In the initial stages of vitamin D therapy, bone pains may worsen and alkaline phosphatase levels may increase, thereby indicating active bone remodelling. There is a gradual increase in phosphorus levels as the PTH levels come down. The radiologic healing takes around 4 to 6 weeks. It is also important to reinforce the patients to ensure a healthy nutrition and a minimum exposure to sunlight (290-315 nm) for 30 minutes of unprotected skin per day.

It is advisable to check calcium, phosphorus and alkaline phosphatase levels of other unaffected family members, especially siblings. Similarly, dietary advice should be reinforced for the whole family.

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8.4 Osteoporosis

SNA Rizvi

INTRODUCTION

Osteoporosis is the second most common metabolic bone disease in India. The term describes a group of bone disorders in which the absolute bone mass is less than normal. There is deterioration of micro-architecture of the skeleton leading to increased bone fragility and risk. The mineral-to-matrix ratio is reduced. Histologically, it is characterised by a decrease in the number and size of the trabeculae, with normal width of the osteoid seams. It is a silent underlying condition which often remains asymptomatic until a fracture occurs. The actual prevalence of osteoporosis remains unknown because of its asymptomatic nature. In India it has been presumed that 35% of post-menopausal women are at the risk of developing osteoporosis. Osteoporotic bone fractures commonly occur at the spine, hip and wrist. On an average a post-menopausal woman has 40% to 50% chance of developing a fracture including 15% chance of hip fracture in her lifetime. More than 10% of hip fracture victims die within one year from various complications and nearly 50% of the survivors are incapacitated, some of them permanently.

Clinically, osteoporosis has been classified into two categories (**Table 1**).

Bone mass is the result of the amount of bone achieved during growth and at maturity, and the subsequent rate of bone loss. The remodelling of bone (its formation and resorption) is a continuous process throughout life. In normal individuals, for many years after closure of the epiphyses, skeletal mass remains constant and the rates of bone formation and resorption (bone remodelling) are approximately equal. In osteoporosis the rate of bone resorption exceeds that of bone formation.

AGE-RELATED OSTEOPOROSIS (POSTMENOPAUSAL AND SENILE)

Normally, bone mass is lost gradually in both sexes, but in women, the rate of bone loss is accelerated at the time of menopause. The suggested aetiopathogenesis of age-related (involutional) osteoporosis is shown in **Figure 1**.

The differentiating features between types I and II involutional osteoporosis are summarised in **Table 2**.

Table 2: Types of Involutional Osteoporosis

	Postmenopausal (Type I)	Age-related senile (Type II)
Age (years)	51-70	>70
Sex ratio (F : M)	5:2	2:1
Type of bone loss	Mainly trabecular	Cortical and trabecular
Rate of bone loss	Accelerated	Not accelerated
Fracture sites	Vertebrae (crush), distal radius	Vertebrae (multiple wedging), hip (extracapsular)
Parathyroid function	Decreased	Increased
Calcium absorption	Decreased	Decreased
Renal conversion of 25(OH)D to $1,25(OH)_2D$	Decreased secondary to decreased PTH secretion	Decreased due to decreased 25(OH)D α activity
Main cause	Factors related to menopause	Factors related to to aging

Table 1: Classification of Osteoporosis

A. Primary osteoporosis

I. *Postmenopausal (Type I)*
Senile (Type II)

B. Secondary osteoporosis

I. *Genetic (heritable disorders of connective tissue)*
Osteogenesis imperfecta
Homocystinuria
Marfan's syndrome

II. *Nutritional*
Calcium deficiency
Protein deficiency
Scurvy
Malabsorption
Malnutrition

III. *Endocrine*
Hypogonadism
Cushing's syndrome
Thyrotoxicosis
Hyperparathyroidism
Acromegaly
Diabetes mellitus

II. *Idiopathic*
Juvenile
In adults (premenopausal women, middle aged or young men)

IV. *Iatrogenic (prolonged drug administration)*
Steroids
Heparin
Anticonvulsants

V. *Disorders with associated osteoporosis*
Other metabolic bone diseases
Adult hypophosphatasia
Mast cell disease
Rheumatoid arthritis
Endemic skeletal fluorosis
Alcoholism

VI. *Regional osteoporosis*
Immobilisation
Post-traumatic (reflex sympathetic dystrophy)
Transient
Migratory

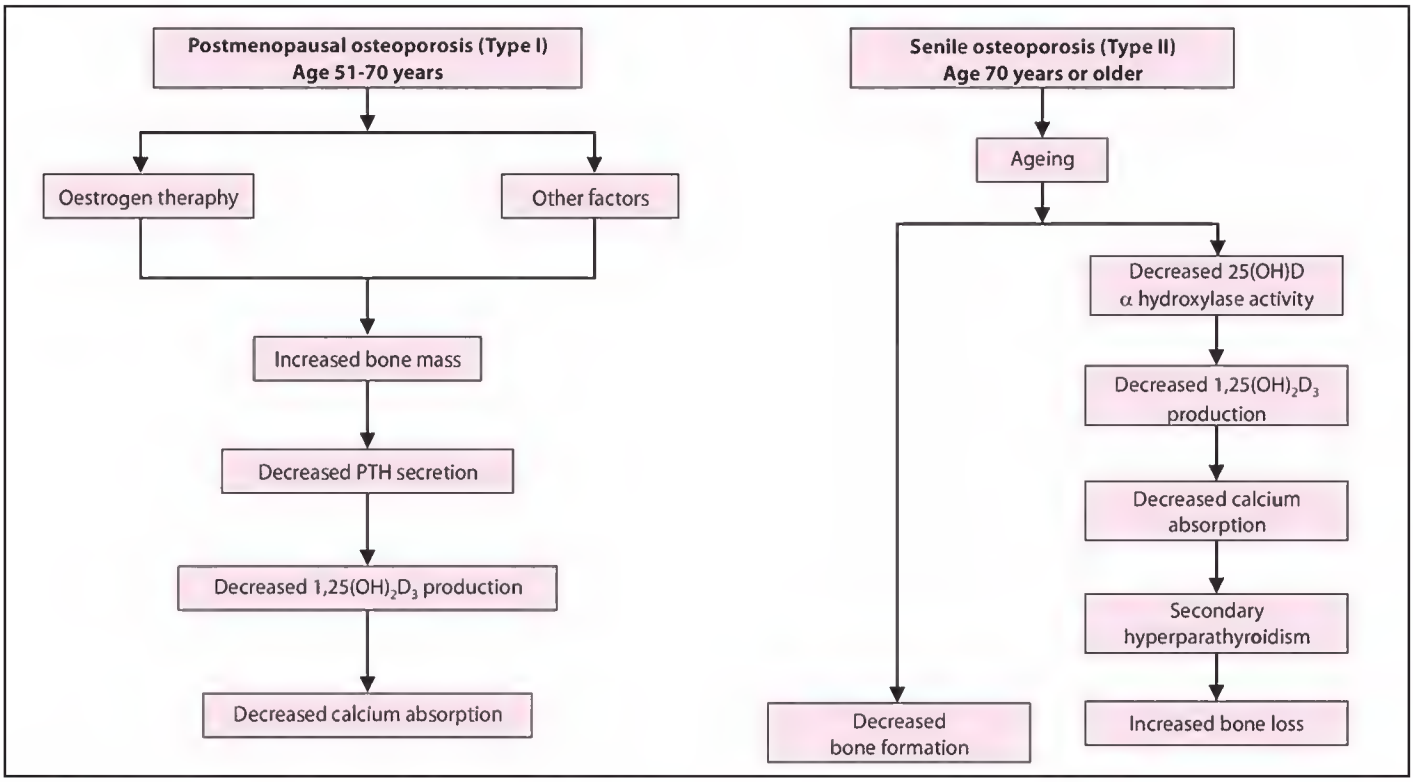


Figure 1: Mechanisms of bone loss in involutional osteoporosis.

CLINICAL FEATURES

Most patients are asymptomatic until they develop a complicating fracture which often occurs after minimal trauma. Fractures are most common in the hip, humerus, ribs and wrists. The most frequent symptoms are pain in the back, deformity of the spine (kyphosis) and loss of height. Pain usually results from collapse of the vertebral bodies, especially in the lower dorsal and upper lumbar regions; it is typically acute in onset. Generalised bone tenderness would suggest coexisting osteomalacia. Impaired movement of thoracic cage can produce cardiopulmonary embarrassment and exercise intolerance and disablility.

DIAGNOSIS

The calcium, phosphorus, and alkaline phosphatase levels in the blood are normal. In the past, osteoporosis used to be diagnosed after manifestation of fracture in old age but now can be achieved by *Bone Densitometry* which include dual energy X-ray absorptiometry (DEXA), quantitative computed tomography, quantitative ultrasound, radiographic absorptiometry and single energy X-ray absorptiometry. DEXA is being most preferred densitometry technique for diagnosis of osteoporosis. The results are interpreted in terms of T-Scores and Z-Scores. T-Scores represent the bone mass of the patient compared to the mean peak bone mass of the young adult reference population using standard deviations. Z-Scores compare the patients bone mineral density (BMD) with the mean BMD for the person of the same age. According to WHO osteoporosis is diagnosed using T-Scores as follows:

BMD within 1.0 SD	–	Normal
BMD between 1.0 and 2.5 SD	–	Osteopaenia
BMD below 2.5 SD or more	–	Osteoporosis
BMD beyond 2.5 SD with one or more fragility fractures	–	Severe osteoporosis

X-rays are the easiest but evident only after loss of 30% to 50% of bone mass. The radiological changes are more marked in the bones of the axial skeleton and consist of loss of bone density, reduction in the number and size of the trabeculae, and thinning of the cortex. The lumbar and thoracic vertebrae become biconcave, and later compression or collapse causes anterior wedging.

Some of the risk factors are shown in **Table 3**.

Table 3: Risk Factors for Osteoporosis

- Age (advanced : 50 years or more)
- Sex (female)
- Race (caucasian or oriental ethnic origin)
- Habitus (petite or thin)
- Menopause (premature, surgically induced)
- Positive family history for osteoporosis
- Reduced weight for height
- Diet
  - Calcium (low)
  - Caffeine (excess)
  - Alcohol (excess)
  - Protein (low)
  - Phosphate (low)
- Sedentary life-style
- Cigarette smoking
- Multiparity
- Other disorders affecting mineral metabolism
- Medications
  - Steroids
  - Anti-epileptics
  - Thyroid supplements
  - Anti-coagulants
- Hypogonadism

PREVENTION OF OSTEOPOROSIS

Prevention or early treatment of osteoporosis is still the most certain way to maintain a sound skeleton. The various elements for prevention are summarised in **Table 4**. It involves maintenance of normal oestrogen levels, high calcium intake, exercise, sensible weight and lifestyle modification (avoiding cigarette smoking, excess of alcohol and coffee).

Table 4: Elements of Osteoporosis Prevention

Calcium intake 1.0-1.5 g per day
Moderate phosphorus intake
Moderate vitamin D intake, 400-800 IU per day or calcitriol 0.25 µg/day
Appropriate exercise programme
Avoidance of alcohol and cigarette
Periodic assessment of skeletal status
Prophylactic agents when indicated, Alendronate 5 mg or Raloxifene 60 mg per day

Clinical deterioration due to further bone loss can generally be prevented by administration of oestrogens and anabolic steroids combined with calcium supplementation, small doses of vitamin D, and maintenance of physical activity. A typical programme consists of oral administration of 0.625 mg to 1.25 mg of conjugated oestrogen or the equivalent dosage of another natural oestrogen daily for the first 25 days of the month, with administration of medroxyprogesterone acetate 10 mg daily during the last 10 days of the month to complete shedding of the endometrium. The 19-nortestosterone derivatives (desogestrel, norgestinate) have negligible side-effects. Hormonal replacement therapy (HRT) slows down bone loss, helps to maintain bone mass and skeletal integrity and protects against osteoporosis.

Pelvic examination, vaginal smear for cytology and possibly endometrial biopsy, manual examination of breasts and mammography are indicated at frequent intervals for evidence of carcinoma. Any bleeding other than that associated with oestrogen withdrawal should be investigated. History of ischaemic heart disease or of venous thrombosis is a contraindication for hormone replacement therapy. Recently, a new agent Tibolone (2.5 mg) with oestrogenic and progestogenic activity has been launched as an alternative to traditional HRT.

TREATMENT OF ESTABLISHED OSTEOPOROSIS

The primary goals of treatment are:

1. Increasing bone mass
2. Reducing the incidence of osteoporotic fractures
3. Arresting and reversing bone loss by inhibiting bone resorption and stimulating bone formation
4. Symptom relief

Symptom relief from fracture pain is provided by analgesics. Calcitonin has an analgesic action mediated by endorphins. Salmon calcitonin, the most potent injectable form, is given in doses of 50 to 100 MRC unit daily two-three times a week. It is also available as nasal spray.

Various drugs used in the treatment of osteoporosis are outlined in **Table 5**.

Hormonal Replacement Therapy

Oestrogen alone or in combination of progesterone may be used. It inhibits osteoclasts and decreases the rate of bone resorption and promotes absorption of intestinal calcium and stimulates osteoblast function. Adverse affects of HRT include vaginal bleeding, breast tenderness and upper gastrointestinal symptoms. It also increases the risk of breast and endometrial malignancy. It is no longer first line of treatment for post-menopausal osteoporosis.

Table 5: Drug Treatment for Osteoporosis

Anti-resorptive agent
HRT/Oestrogen, progesterone
Bisphosphonates
Etidronate, alendronate, pamidronate, tiludronate, risedronate, zolendronate (transdermal formulation)
Calcitonin
Calcium
Tibolone
Stimulators of bone formation
Fluoride
Parathyroid hormone
Agents with unknown action
Vitamin-D and analogues
Anabolic steroids
Ipriflavone
Newer therapies
Selective oestrogen receptor modulators (SERMS)
raloxifene, idoxifene, tamoxifene, droloxifene.
Activator of non-genomic estrogen like signalling (ANGELS)
Growth factors (TGF-β , IGF-1 and 2)

Tibolone

It is a synthetic steroid with simultaneous weak oestrogenic, androgenic and progestational activity. It is given in the dose of 2.5 mg daily with its beneficial affect on the lumbar spine.

Bisphosphonates

They are synthetic analogues of pyrophosphate with potent anti-resorptive properties. First generation include etidronate and clodronate. Second generation agents are alendronate, pamidronate and tiludronate and third generation includes risedronate. It inhibits bone resorption by inhibiting osteoclasts. Alendronate is approved by US Food and Drug Administration (FDA). It reduces vertebral fracture rate by 50% at a daily dose of 10 mg. It is avoided in abnormalities of oesophagus such as stricture or achalasia, inability to stand or sit for at least 30 minutes and hypocalcaemia. An alternative to oral preparation is now available as transdermal formulation of zolendronate.

It has been shown that alendronate and risedronate have profound effects on reduction of vertebral fractures and non-vertebral fractures of hip.

Calcitonin

It is a peptide hormone which is an effective interesting antiresorptive agent with excellent safety profile. The principal side effects are nausea, nasal irritation, and dizziness. It is costly and should be reserved for treatment of osteoporosis when HRT or bisphosphonates are contraindicated or ineffective 50-100 MRC units daily to three times a week is used.

Calcium

Calcium supplementation has significant beneficial effect on bone mass irrespective of age. Dietary calcium derived mostly

from dairy products slows bone loss in post-menopausal women. Combining with oestrogen or calcitonin offers an even greater benefit. The recommended dose for calcium in post-menopausal women is 1500 mg/day and in men and women on HRT is 1000 mg/day.

Fluoride

It stimulates bone formation and substantially increases bone density. In view of potential toxicity and inconsistent anti-fracture effect, it is not approved for the treatment of osteoporosis even in USA.

Parathyroid Hormone (PTH)

It prevents bone loss upto 3.4% in lumbar spine with daily injection of 500 units of hPTH subcutaneously. The drug has to be administered parenterally and is costly too.

Teriparatide is given by subcutaneous injection. It acts on osteoblast cell and increases the bone density at spine and is given for 18 months and effect lasts another 18 months after stopping the therapy. It is given only in severe osteoporosis with spine fracture. It is contraindicated in hypercalcaemia, kidney disease, Paget's disease and radiation therapy.

Combination Therapy

PTH and bisphosphonate combination was tried but no substantial improvement in prevention of fractures and change in BMD was noted.

Strontium Ranelate

New modality for treatment of osteoporosis has dual action which increases bone formation and uncoupling of bone remodelling.

Vitamin D and its Analogues

It has been shown that vitamin D and its active metabolite calcitriol and its analogue alfacalcidol have beneficial effects on bone mass in osteoporosis. Calcitriol decreases rate of vertebral fracture and improves vitamin D deficiency which is not very uncommon in old age. Recommended dose for vitamin D supplementation is 400-800 IU / day or 0.25 μg calcitriol daily.

Phytoestrogens

These are plant derived molecules that have oestrogenic actions and obtained from dry soyabeans and all soya based products. Ipriflavone has been shown to increase bone mass in established osteoporosis, its safety is yet to be established.

Selective Oestrogen Receptor Modulators (SERMS)

Raloxifene, has recently been approved for the treatment of post-menopausal osteoporosis. It has mixed oestrogen agonist and antagonist activity. The usual dose is 60 mg orally once a day. Side effects are leg cramps and worsening of hot flushes. BMD of spine and hip increased by approximately 2% to 3%, but it does not increase the risk of breast cancer or endometrial cancer.

In recent years , a number of new agents have been devised with little effects on endometrium and breast. These include tamoxifen, droloxofen and idotoxifen. Their potential for treatment of osteoporosis remains to be assessed.

Clinical trials are on to see the potential application of GH and TGF-β and IGF-1 and 2 in the management of osteoporosis.

IDIOPATHIC OSTEOPOROSIS

This is the term used to describe the disorder in children, younger men or premenopausal women in whom no aetiological factor is detected. Juvenile osteoporosis is a rare disorder with onset usually between the ages of 8 and 14 years; it is characterised by abrupt appearance of bone pains and occurrence of fractures after minimal trauma. Investigations show malabsorption of calcium and/or a high urinary calcium loss. Bone resorption is generally high and vertebrae reveal regular biconcavity with large disc spaces. In many cases the disorder is self-limited. It differs from osteogenesis imperfecta which occurs since birth, lasts life-long and has associated connective tissue defects such as blue sclerae and abnormal teeth. It does not respond to treatment with vitamin D and calcium.

In idiopathic adult osteoporosis, present in a young man or a premenopausal woman, malabsorption of calcium is frequently present and symptomatic improvement often follows treatment with calcium and vitamin D.

STEROID-INDUCED OSTEOPOROSIS

Osteoporosis commonly accompanies Cushing's syndrome, both exogenous and endogenous, and in some instances is rapidly progressive, especially in children and women over the age of 50 years. Osteoporosis in conditions of glucocorticoid excess is accounted for by a combination of low rates of bone formation accompanied by high rates of bone resorption. This results partly from glucocorticoid-induced secondary hyperparathyroidism and alteration in the metabolism of vitamin D_3. Treatment consists of withdrawal of glucocorticoids or decrease in its dose, and treatment with vitamin D in doses of 1.25 mg three times a week with supplemental oral calcium 1 g per day. The use of vitamin D metabolites such as $25(OH)D_3$ or $1,25(OH)_2D_3$ may prove to be more effective. Alendronate can be prescribed in men with steroid induced osteoporosis. Testosterone may be given if testosterone level is low. Calcitonin can be prescribed if bisphosphonate is contraindicated.

OSTEOPOROSIS IN MEN

Primary osteoporosis is seen in 50% where no aetiological factor is detected (idiopathic) whereas secondary (50%) is commonly associated with glucocorticoid excess (15%), hypogonadism (10%), alcoholism (7%), hypercalciuria (2%), smoking, immobilisation and some gastrointestinal disorder.

Treatment in cases of secondary osteoporosis consists of treatment of the cause, androgen, limitation of corticosteroid therapy, alcohol or smoking and use of thiazides for hypercalciuria. Idiopathic osteoporosis is treated with most prescribed modalities, includes exercise and prevention of falls, calcium and vitamin-D supplements, PTH (teriparatide) and alendronate.

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8.5 Developmental Disorders of Bone

Rakesh K Sahay

A wide variety of inherited disorders affect the skeletal development. They affect the bone growth and remodelling and may also produce derangements in mineral homeostasis. From a practical clinical standpoint these disorders can be classified as sclerosing and non-sclerosing bone dysplasias (**Table 1**). An overview of some of the common clinically relevant developmental bone disorders has been provided.

Table 1: Developmental Disorders of Bone

Sclerosing bone dysplasias
- Osteopetrosis
- Carbonic anhydrase II deficiency
- Pycnodystosis
- Engelmann's disease
- Endosteal hyperostosis
- Osteopoikilosis
- Osteopathia striata
- Melorheostosis

Non-sclerosing bone dysplasias
- Osteogenesis imperfecta
- Fibrous dysplasia

Osteochondrodysplasias
- Multiple epiphyseal dysplasia
- Spondylo-epiphyseal dysplasia
- Handigodu disease
- Achondrodysplasia
- Metaphyseal chondrodysplasia
- Enchondromatosis
- Osteochondromatosis

Mucopolysaccharidosis
- Dysostosis multiplex
- Morquio's syndrome
- Hurler's syndrome

SCLEROSING BONE DYSPLASIAS

Osteopetrosis

Osteopetrosis (Marble bone disease, Albers-Schonberg disease): These disorders are caused by severe impairment of osteoclast-mediated bone resorption. Mostly two types of osteopetrosis include type I which is malignant (severe, infantile, autosomal recessive) and type II osteopetrosis, which is benign (adult, autosomal dominant). A rare autosomal recessive has a more benign prognosis. This is also known as intermediate form.

Clinical Presentation

Type I osteopetrosis presents in early childhood, and untreated is often fatal before age of five year. As bone and cartilage fail to undergo modelling, paralysis of one or more cranial nerves may occur due to narrowing of the cranial foramina and patient can at times present with resultant sensorineural deafness and blindness as initial complaints. Failure of skeletal modelling also results in inadequate marrow space, leading to extramedullary haematopoiesis with hypersplenism and pancytopaenia. Hypocalcaemia due to lack of osteoclastic bone resorption may occur in infants and young children.

Adult (benign) osteopetrosis type II is an autosomal dominant disease that is usually diagnosed by the discovery of typical skeletal changes in young adults who undergo radiologic evaluation of a fracture. The fractures may be accompanied by loss of vision, deafness, psychomotor delay, mandibular osteomyelitis, and other complications usually associated with the juvenile form. The milder form of the disease does not usually require treatment.

Radiography

Generalised symmetric increases in bone mass with thickening of both cortical and trabecular bone. The diaphyses and metaphyses are broadened (Erlenmeyer deformity), and alternating sclerotic and lucent bands may be seen in the iliac crests, at the ends of long bones, and in vertebral bodies. The cranium is usually thickened, particularly at the base of the skull, and the paranasal and mastoid sinuses are underpneumatised. The thickened cranium along with the vertebral end plate sclerosis gives the appearance of Rugger-Jersey spine.

Laboratory Findings

Elevated serum levels of osteoclast-derived tartarate-resistant acid phosphatase (TRAP) and the brain isoenzyme of creatine kinase are characteristic. Serum calcium may be low in severe disease, and parathyroid hormone and 1,25-dihydroxy vitamin D levels may be elevated in response to hypocalcaemia.

Treatment

Allogenic HLA-identical bone marrow transplantation has been successful in some children. Following transplantation, the marrow contains progenitor cells and normally functioning osteoclasts. A cure is most likely when children are transplanted before age of four years. Marrow transplantation from non-identical HLA-matched donors has a much higher failure rate. Limited studies in small numbers of patients have suggested variable benefits following treatment with interferon gamma-1b, 1,25-dihydroxy vitamin D (which stimulates osteoclasts directly), methylprednisolone, and a low calcium/high-phosphate diet. Decompression of the optic or auditory nerve compression may be needed. Orthopaedic management is required for the surgical treatment of fractures and their complications including malunion and post-fracture deformity.

NON-SCLEROSING BONE DYSPLASIAS

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI), characterised by generalised osteopenia and brittle bones (hence called brittle bone disease) is the most common genetic bone disorder and its prevalence is estimated around 1 in 10,000-20,000 births. The disorder is frequently associated with blue sclerae, dental abnormalities (dentinogenesis imperfecta), progressive hearing loss, and a positive family history. The clinical manifestations based on the mode of inheritance of OI are summarised in **Table 2**.

Table 2: Clinical Features of Osteogenesis Imperfecta Based on Mode of Inheritance

OI Type	Major clinical features	Inheritance
I	Normal stature, blue sclerae, hearing loss in about 50% of patients	AD
II	Lethal in perinatal period, minimal calvarial mineralisation, long bone deformities, platyspondyly	AD (new mutation) AR (rare)
III	Short stature, bone deformities, variable hue in sclerae, Dentigerous imperfecta (DI) and hearing loss common	AD or AR
IV	Normal sclerae, bone deformity, DI common, short stature and hearing loss variable	AD

AD = Autosomal dominant; AR = Autosomal recessive.

Skeletal Changes

Radiographs of the skull in patients with mild disease may show a mottled appearance because of small islands of irregular ossification. In type II OI, bones and other connective tissues are so fragile that massive injuries can occur in utero or during delivery. Ossification of many bones is frequently incomplete. Continuously beaded or broken ribs and crumpled long bones (accordina femora) may be present. In types III and IV, multiple fractures from minor physical stress can produce severe deformities. Kyphoscoliosis can impair respiration, cause cor pulmonale, and predispose to pulmonary infections. On radiographs the appearance of "popcorn-like" deposits of mineral on the ends of long bones is an ominous sign. In all forms of OI, bone mineral density in unfractured bone is decreased. However, the degree of osteopenia may be difficult to evaluate because recurrent fractures limit exercise and thereby worsen already reduced bone mass. Surprisingly, fractures appear to heal normally.

Ocular Changes

The sclerae can be normal, slightly bluish, or bright blue. Thinning of the collagen layers of the sclerae allows the choroid layers to be seen. Blue sclerae may also be seen in other conditions.

Dentinogenesis Imperfecta

Improper deposition or deficiency of dentine leads to yellowish brown or translucent bluish grey colour of teeth. The enamel generally appears normal. The deciduous teeth are usually smaller than normal, whereas permanent teeth are frequently bell-shaped and restricted at the base. These discoloured teeth may also fracture and need to be extracted.

Hearing Loss

The middle ear usually exhibits maldevelopment, deficient ossification, persistence of cartilage in areas that are normally ossified, and abnormal calcium deposits. This usually presents as hearing loss beginning during the second decade of life and occurs in more than 50% of individuals over age 30. The loss can be conductive, sensorineural or mixed and varies in severity.

Associated Features

Thinning of skin that scars extensively, joint laxity, cardiovascular manifestations such as aortic regurgitation, floppy mitral valves, mitral incompetence, and fragility of large blood vessels can also be seen. Short stature is the most prevalent secondary feature of OI.

Cardiopulmonary complications of osteogenesis imperfecta are the major cause of mortality directly related to the disorder. There is a high frequency of basilar invagination (BI) in patients with severe osteogenesis imperfecta, which is an upward displacement of vertebral elements into the foramen magnum. It may lead to static or dynamic stenosis of the foramen magnum, and compression of the medulla oblongata. Children should be screened by CT every 2-3 years, and followed annually by MRI if radiographic signs of BI develop.

Pathogenesis

OI results from a qualitative or quantitative defect in the type 1 collagen, which is the most abundant protein in bone. This is generally caused by mutations in the genes encoding for type 1 procollagen.

Diagnosis

Diagnosis is usually made on the basis of clinical criteria. The presence of fractures together with blue sclerae, dentinogenesis imperfecta, or family history of the disease is usually sufficient to make the diagnosis. The characteristic radiological features are decreased bone density, modelling defects of long bones and deformities caused by recurrent fractures. Osteogenesis imperfecta is frequently associated with either relative or absolute macrocephaly. Individuals with OI frequently have relatively long arm span for length and a shortened lower segment (pubis to floor). Elevated serum alkaline phosphatase, hypercalciuria and increased urinary excretion of hydroxyproline have also been noted. The mutation in type I procollagen gene can also be identified and if done in an individual patient, a simple test based on the polymerase chain reaction (PCR) can be used to screen family members at risk and for prenatal diagnosis. A lateral view of the skull should also be obtained to detect wormian bones.

Treatment

The recurrent fractures require orthopaedic care including surgical management, and in some instances, physical and rehabilitative therapy.

Treatment with bisphosphonates to decrease bone loss has been found to be helpful although long-term effects are not completely understood. Systemic infusion of stromal cells from bone marrow that can differentiate into osteoblasts and bone marrow transplantation from a HLA compatible donor have been tried. Growth hormone therapy has been found to increase growth in a small number of children with OI. Management of pneumonia and cor pulmonale is done as in any other patient but more aggressively. For severe hearing loss with stapedectomy or replacement of the stapes with a prosthesis may be required.

Prenatal Diagnosis

It can be diagnosed by ultrasonography at 18 to 24 weeks' gestation. DNA sequencing on chorionic villus sample (CVS) biopsies is possible. Cultured CVS cells can be used for DNA or RNA extraction and detection by either PCR and restriction enzyme digestion or sequencing. Appropriate genetic counselling is then required.

Fibrous Dysplasia

It is discussed in Chapter on 'Miscellaneous Bone Disorders'.

Achondroplasia

Achondroplasia is the commonest form of short-limb dwarfism. It is characterised by the presence of short limbs (particularly the proximal portions), normal trunk, large head, frontal and parietal bossing and flattening of the occiput, saddle nose, and an exaggerated lumbar lordosis. The tip of the nose is fleshy, with upturned nostrils. All the bones are affected but abnormal configuration of the skull, lumbar spine and pelvis are hallmarks of the disease. Radial heads may be dislocated and posterior scalloping of the vertebral bodies and dorsolumbar kyphosis is seen. Severe spinal deformity may lead to cord compression.

The disease is caused by a mutation of the fibroblast growth factor receptor 3 (FGFR3) gene that results in a gain-of-function state. The primary defect is abnormal chondrocyte proliferation at the growth plate that causes development of short but proportionately thick long bones. Other regions of the long bones may be relatively unaffected. This disorder has an autosomal dominant inheritance, but sporadic mutations also may be seen. Pseudo-achondroplasia clinically resembles achondroplasia but has no skull abnormalities.

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8.6 Miscellaneous Bone Disorders

CV Harinarayan

PAGET'S DISEASE (OSTEITIS DEFORMANS)

Paget's disease of bone is a chronic skeletal disorder which may result in enlarged and/or deformed bones in one or more regions of the skeleton. The disease is characterised by abnormal bone turnover, structure and architecture. It was first described by James Paget in 1877. This disorder is quite common in Europe, North America, Australia and New Zealand. There are occasional cases reported from India.

Definition

It is a focal disorder of accelerated (anarchic) skeletal remodelling due to increase in osteoclastic activity and bone resorption followed by excessive bone formation resulting in an abnormal highly vascularised bone that is structurally disorganised, with an excess of fibrous connective tissue. It is the second most common disease after osteoporosis in Western population. Raised alkaline phosphatase in the presence of classical radiological picture is diagnostic of Paget's disease and is further substantiated by bone scan and/or bone histology.

Aetiology

Genetic and environmental factors are implicated in the pathogenesis. Environmental factors may be due to viral pathogen belonging to paramyxovirus group, such as measles virus. This disease has a strong genetic predisposition and several genetic loci have been linked to familial Paget's disease. It has autosomal dominant transmission. Different predisposition loci have been identified on chromosome 18 and on chromosome 6. Recently, many susceptible loci (2q36, 5q31, 5q35, 10p13) have been described.

Pathogenesis

Little is known about its pathogenesis. Characteristic feature is increased resorption of bone accompanied by increased formation. In early phase, bone resorption predominates and bones are very vascular. Excessive bone resorption is followed closely by formation of new pagetic bone. With decline in disease activity, there is decrease in bone resorption relative to formation leading to development of hard, dense, less vascular bone.

Clinical Features

The disease affects both sexes with male predominance. Age at presentation is fourth and fifth decades of life. The clinical features include bone pains, joint pains, skeletal deformities, low backache, fractures, painless swellings, skull enlargement, headache, deafness, visual impairment, loss of facial sensation, difficulty in biting, ataxic gait, neurogenic claudications and renal stones. Paget bones are fragile and susceptible to fractures with trivial trauma. In patients with skull involvement increase in size of head as reflected by increase in hat size, increased sweating and warmth over skull due to increased vascularity are seen. Paget's disease can lead to wide pulmonary artery pressure and high output failure.

Biochemical Features

Calcium and phosphorus levels are within normal range with raised alkaline phosphatase levels. Markers of bone turnover such as urinary N-telopeptide, urinary hydroxyproline/creatinine and urinary and serum deoxypyridinoline, C-telopeptide are increased. Hyperuricaemia may be present.

Radiological Features

The most commonly affected bones are the pelvis, lumbar vertebrae, skull, femur and tibia. Small bones in the hands and feet are seldom affected. The disease may be uni- or multi-focal (mono-ostotic or poly-ostotic) in distribution. Radiologically, Paget's bone consists of focal area of osteolysis which has blade of grass or candle-flame appearance. Unique radiological features differentiate Paget's disease from other bone diseases. The radiological features follow the histological findings on light microscopy. The correlation of the different phases with the clinical, radiological and pathological features of Paget's disease allows accurate diagnosis and treatment. These features can be divided into three phases: initial phase, mid phase, and late phase.

In the initial or active phase (osteolytic), skull shows osteoporosis circumscripta, especially of the frontal and occipital bones. In the long bones, there is a well-defined, advancing radiolucency with a V-shaped margin which begins subarticularly. In the mid phase, there are osteolytic and sclerotic lesions of the skull, pelvis and long bones. In the late or inactive (osteosclerotic) phase, there are 'cotton wool' areas of sclerotic bone. The spine shows enlargement of the vertebrae. Cortical thickening produces the 'picture frame' vertebral body or the 'Ivory vertebra'. Affected vertebral bodies have an almost 'bone within bone' appearance. Pelvis shows widening and coarsened trabeculation of pelvic ring with splitting of iliopectineal line. In late phase, the long bones show sclerosis with coarse and thickened trabeculae. Cortical thickening gradually encroaches the medullary canal and the epiphysis is nearly always involved.

The unusual radiological presentations of Paget's disease include unusual disease progression, massive post-immobilisation lysis, metastatic spread to Pagetic bone, and vertebral end-plate destruction that mimics infection. The radiological picture of Paget's disease before and after treatment is shown in **Figure 1**. The bone involvement as seen in Indian population is given in **Table 1**.

Bone Scan Features Tc-99m (MDP)

The scintigraphic uptake pattern ranges from diffuse uptake in a relatively early mixed phase to a mottled uptake pattern of the late sclerotic phase (**Figure 2**). Bone lesions begin at metaphyseal region and extend into diaphysis towards the

other end. Intense uptake in long bones involving one end to mid-shaft or further suggests Paget's disease. The 'butterfly' pattern of vertebral involvement suggests Paget's disease, which affects the entire vertebral body rather than metastatic disease, which has predilection for the pedicles.

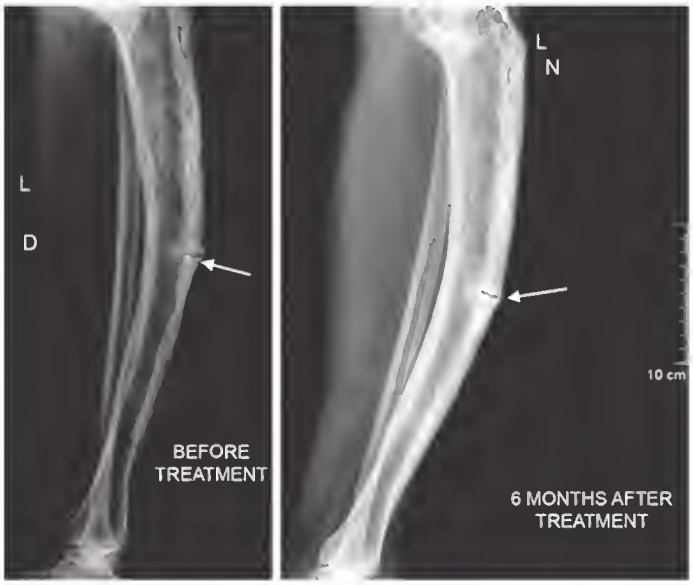


Figure 1: Radiological appearance in Paget's—pre- and post-therapy.

Table 1: Skeletal Site Involvement in Patients with Paget's Disease

Site of bone involvement	Cases (Percentage)
Skull	60
Spine	60
Pelvis	40
Femur	35
Tibia	18
Fibula	8-10
Ulna	9
Radius	10
Scapula	10
Sacrum	10
Clavicle	6

Complications

Hyperuricaemic gout and deafness are relatively common. An enlarged skull can lead to headaches or hearing loss. If the spine is involved, enlarged vertebrae may cause compression of the spinal cord or nerve roots. Secondary osteoarthritis, radiculopathy and renal stones are also seen. Bones can soften and lead on to bowed bones, basilar invagination and protrusio acetabuli. Transverse fractures with a predilection for the convex aspect of the bone, osteomyelitis and extra-medullary haematopoiesis are seen. Osteosarcomas or other types of sarcomas occur in less than 1% of patients with Paget's disease and carries a poor prognosis. High output cardiac failure can occur.

Treatment

Since the major defect is exaggerated bone remodelling, the treatment is based on the use of bisphosphonates. Bisphosphonates suppress or reduce bone resorption by osteoclasts. These include pamidronate given intravenously or

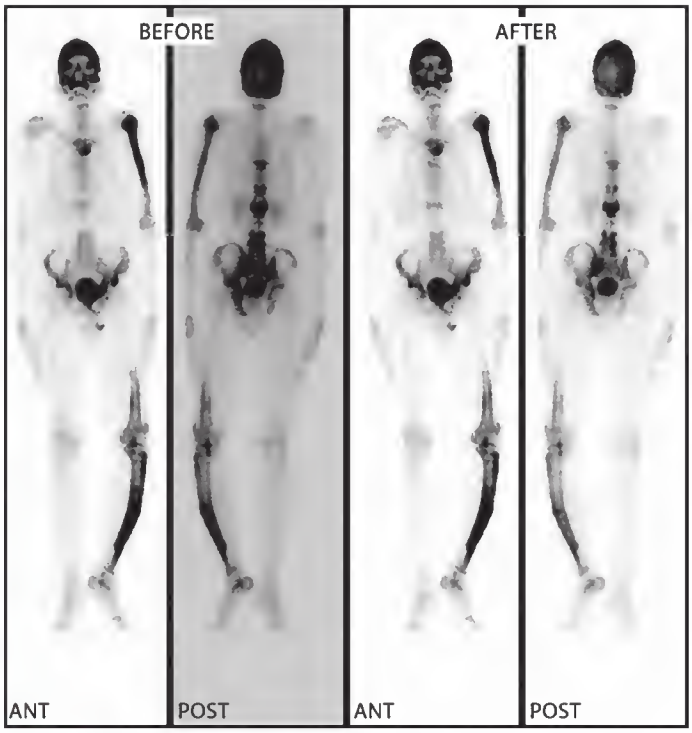


Figure 2: Nuclear scan of patient with Paget's disease before and 6 months after the treatment.

etidronate, tiludronate, alendronate and risedronate given orally. Zolendronic acid is said to produce more rapid, more complete and more sustained response. Calcitonin is now infrequently used. Non-pharmacological measures for pain management and surgery are used when indicated.

Prognosis

The disease is slowly progressive and the course can vary from stable to rapid progression. The outlook is good if the treatment is given early before major complications set in. The treatment can control the symptoms but not cure the disease and duration of the disease.

McCUNE-ALBRIGHT SYNDROME (FIBROUS DYSPLASIA)

McCune-Albright syndrome (MAS) is a triad of poly-ostotic fibrous dysplasia (FD), *Café-au-lait* skin pigmentation and endocrine disorder. The disease may present as mono-osototic, poly-ostotic or MAS and its variants or even panosteotic (entire skeleton). Mono-osototic form is the commonest.

Pathophysiology

It is mediated by activating mutation in the receptor associated heterotrimeric G protein $G_s\alpha$. The effect of $G_s\alpha$ results in hyperphosphaturic hypophosphataemia leading on to rickets and osteomalacia. The pathological effects of $G_s\alpha$ mutation in osteogenic cells are most pronounced during the rapid phase of growth. Thus, the disease is commonly present in childhood or adolescence.

The multiple endocrine hyperfunction and possibly fibrous dysplasia is due to defect in the G protein-cyclic AMP-protein kinase A-dependent pathway. Activating mutation in the G protein stimulates adenyl cyclase $G_s\alpha$. This signal transduction induces end-organ hyperfunction. It is of interest to note that the defect in Albright's hereditary osteodystrophy (pseudo-hypoparathyroidism) is converse to that found in MAS.

In Albright's hereditary osteodystrophy, the mutation in $G_s\alpha$ proteins results in deficient activity and decreases responsiveness to hormones mediated through cAMP-mediated signal transduction.

Clinical Picture

Clinical course is variable and depends on the skeleton involved. The disease is detected because of localised pain, deformities or fractures. The base of the skull and the proximal metaphysis of the femur are the sites commonly involved. Symptoms related to bone involvement include headache, seizures, hearing loss, narrowing of the external ear canal or even spontaneous scalp haemorrhages. Cutaneous pigmentation consisting of isolated dark-brown to light-brown macules on one side of the midline is seen. The borders are irregular or jagged (coast of Maine) in contrast to smooth borders of macules in neurofibromatosis (coast of California). The macules range from 1 cm to large areas, particularly the back, buttock or sacral region. When present in the scalp, the overlying hair may be more deeply pigmented than the remaining areas of the scalp.

Sexual precocity is common in females. Premature vaginal bleeding and development of breast, axillary and pubic hair are the main features. Hyperthyroidism is a common associated endocrine abnormality. Sexual precocity and adrenal and thyroid hyperfunctions associated with fibrous dysplasia are due to autonomous end-organ activity and not due to pituitary or hypothalamic dysfunction. Some subjects can have features of high cardiac output similar to Paget's disease.

Radiology

Radiographically, the lesion is limited to metaphysis or extends along the diaphysis for variable length. In children and adolescents, the picture consists of expansile, deforming medullary lesion with cortical thinning and an overall 'ground-glass' density. Femoral disease can present with fracture and deformity ranging from coxa vara to the classical 'Shepherd's crook deformity' of the femur, bowing of tibia, Harrison's grooves and protrusio acetabuli. Advanced skeletal age is correlated with skeletal precocity. Before puberty the lesion spares the epiphyseal region but involves the epiphysis in older individuals. Sclerosis in the lesion suggests less active disease. Involvement of facial bones usually with increased radiodensity may create leonine appearance (leontiasis ossea). The presentation in childhood may be with facial asymmetry or a 'bump' that persists, but symmetrical expansion of the malar prominences and/or frontal bosses may also be seen. Abnormal growth and deformity of the craniofacial bones may result in encroachment of cranial nerves. Involvement of temporal bones can cause progressive loss of hearing. Malignancy is very rare. Fibrous dysplasia and Paget's disease of the bone are two disorders that can cause a bone to become larger than normal.

Diagnosis and Management

Diagnosis is based on expert assessment of clinical, radiological and histopathological features. The extent of the disease must be assessed to predict the functional outcome. The metabolic derangements especially hypophosphataemia and growth hormone excess worsen the clinical outcome and should be assessed. Calcitonin may be effective in treatment of widespread disease associated with bone pain and high serum alkaline phosphatase.

OSTEONECROSIS OF THE JAW

Osteonecrosis of the jaw is an extremely painful condition, characterised by bone erosions and exposure of the bone which affects the mandible or maxillary bones. Inhibition of osteoclasts by bisphosphonates is hypothesised to disrupt the critical balance between the osteoclast and the osteoblast. In situations where healing of the bone is necessary, after chronic inflammation and infection associated with gum disease, disruption of the dynamic process of bone resorption and formation could contribute to the development of osteonecrosis of the jaw. In addition to chronic bisphosphonates therapy, it is associated with oral fungal infections, trauma, herpes zoster and radiation therapy.

BONE LOSS WITH CANCER THERAPIES

Chemotherapy, hormonal therapy and radiation have improved the survival rates in patients suffering from malignancies but they carry significant side effects.

Oestrogens play a key regulatory role in bone remodelling through oestrogen receptors (ER). Current breast cancer therapies decrease the circulating oestrogen levels by blocking or downregulating the receptor itself. Some agents do disrupt the oestrogen-skeleton axis leading to decreased bone mineral density, and increased risk of osteoporosis and fracture. There are two major classes of aromatase inhibitors; the non-steroidal reversible inhibitors, anastrozole and letrozole; and steroid irreversible inhibitors, exemestane. Both classes of aromatase inhibitors result in bone loss to some extent.

Prostate cancer patients with metastasis often receive palliative therapy in the form of androgen deprivation therapy (ADT) which includes surgical castration, pharmacological castration with LHRH agonists and antiandrogen therapy with agents like flutamide, nilutamide, bicalutamide or cyproterone. One of the potential complications with castration or LHRH agonist therapy is the decrease in bone mineral density.

Radiotherapy is also known to induce fractures. Rib-fracture after X-ray exposure is a potential complication of radiotherapy used for breast cancer. Brachytherapy (radiotherapy) for non-metastatic carcinoma prostate patients can lead to pelvic fracture.

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Section 9

Diabetes Mellitus

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9.1 Epidemiology and Basic Considerations of Diabetes

A Ramachandran, C Snehalatha

DEFINITION OF DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The long-term effects of diabetes include damage, dysfunction, and failure of various organs. The long-term effects include progressive development of retinopathy with potential blindness, nephropathy that may lead to renal failure, neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular, and cerebrovascular diseases.

DIAGNOSIS OF DIABETES

Clinical diagnosis of diabetes is made if a person has the symptoms, viz. polyuria, polydipsia, polyphagia, recurrent infections, unexplained weight loss and in severe cases drowsiness, coma and a casual plasma glucose concentration of ≥ 200 mg/dL or a fasting plasma glucose (FPG) of ≥ 126 mg/dL or a two hours post-glucose (2hPG) (75g load) of ≥ 200 mg/dL during an oral glucose tolerance test (OGTT). For clinical purposes, the diagnosis should always be confirmed by a repeat blood test on another day, unless there is unequivocal hyperglycaemia with acute decompensation or obvious symptoms.

Table 1 shows the diagnostic criteria for diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) using capillary or venous plasma or whole blood. The diagnostic criteria are the same for adults or children. For children, a glucose load of 1.75 g per kg is used. For epidemiological studies, a single plasma glucose value measured after an overnight fast and/or 2hours after a glucose load can be used. In some populations, such as the Asians, the diagnostic sensitivity of the FPG is lower than that of the 2 hours PG. Pregnant women, who meet the WHO criteria for diabetes or IGT are classified as having gestational diabetes mellitus (GDM). After the pregnancy ends, the women should be tested with an OGTT, six weeks or more after delivery to reclassify the glucose tolerance.

CLASSIFICATION OF DIABETES MELLITUS

Type 1 Diabetes

Type 1 diabetes, formerly called juvenile diabetes, is usually diagnosed in children, teenagers, and young adults. Type 1 diabetes may develop in adults also. This is an autoimmune disease causing specific destruction of β-cells of pancreas which results in an absolute insulinopaenia.

Type 2 Diabetes

Type 2 diabetes, formerly called adult onset diabetes, is the most common form and has an insidious onset. It remains asymptomatic for many years. It is commonly seen in adults, but can occur even in childhood. Weight loss is uncommon unless hyperglycaemia is severe while ketosis is rare. Familial inheritance is very common. This form of diabetes usually begins with insulin resistance and initially there is a counter regulatory hyperinsulinaemia. With time, the pancreas loses its ability to secrete enough insulin in response to meals and clinical diabetes develops.

Table 1: Values for Diagnosis of Diabetes – (WHO 1999)

	Venous Plasma	Whole Blood Venous	Whole Blood Capillary
	Glucose Concentration in mg/dL		
Diabetes Mellitus:			
Fasting	≥126	≥110	≥110
2-hour PG	≥200	≥180	≥200
Impaired glucose tolerance (IGT):			
Fasting (if measured)	<126	<110	<110
2-hour PG	≥140 to <200	≥120 to <180	≥140 to <200
Impaired fasting glucose (IFG):			
Fasting	≥110 to <126	≥100 to <110	100 to <110
2-hour PG (if measured)	<140	<120	<140

To convert mg/dL to mmol/L, divide mg/dL by 18.

Gestational Diabetes

Gestational diabetes is carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has not been previously recognised.

Other Types of Diabetes

A number of other types of diabetes exist which develop due to:

- Genetic defects of the β-cell,
- Genetic defects in insulin action,
- Diseases of the pancreas,
- Excess amounts of counter regulatory hormones,
- Infections,
- Rare autoimmune disorders, and
- Genetic syndromes associated with diabetes.

AETIOLOGY AND RISK FACTORS

Diabetes, either type 1 or type 2, has equally strong genetic and environmental risk factors, an interaction of which leads to the clinical expression of the disease. The genetic susceptibility for type 1 is associated with certain human leucocyte antigen (HLA) combinations (DR3+DR4) and the environmental insults are rather ill defined. Possibility of some aspects of diet and viral infections triggering an autoimmune exposure causing specific destruction of the β-cells of pancreas has been proposed.

Type 2 diabetes has a more complex aetiopathology. Though it has a strong genetic basis, as shown by its hereditary nature,

the major susceptibility genes have not yet been identified. Racial predisposition as seen in Asian populations, also is common. The environmental factors showing strong association with diabetes are increasing age, family history of diabetes, obesity, unhealthy diet, physical inactivity, insulin resistance, adverse intrauterine environment, and stress factors.

The pathophysiology of type 2 diabetes includes, impaired insulin secretion, impaired insulin action, insulin resistance and impaired incretin effect on the β-cell function and non-suppression of the action of α-cells, with rising blood glucose levels.

EPIDEMIOLOGY

Type 1 Diabetes

Type 1 diabetes is one of the most common metabolic disorders which occurs due to an absolute insulin deficiency. The disease shows an acute onset, with severe symptoms including weight loss. Positive family history of diabetes is rare and ketonuria is common. The patients are dependent on exogenous insulin for metabolic control and survival. The Diabetes Mondiale Study (DIAMOND) and the Europe and Diabetes Study have established population based national registries using standardised methods. There are wide geographic differences in the prevalence and incidence of type 1 diabetes. Finland has the highest number of patients with type 1 diabetes. The estimated global number of children (0 to 14 years) with type 1 diabetes is 4,80,000 and annually approximately 76,000 children develop the disease. Data from developing countries is sparse.

Type 2 Diabetes

The global burden due to diabetes is mostly contributed by type 2 diabetes which constitutes 80% to 95% of the total diabetic population. Diabetes mellitus is the most common metabolic disease which is prevalent in every part of the world and is a major public health challenge of the twenty-first century. The explosive increase in the prevalence of diabetes seen in the last three decades poses huge clinical and economic burden in many countries. The estimates by the International Diabetes Federation (IDF) show that 285 million adults (20 to 79 years) are affected by the disorder in 2010. Epidemiological trends indicate that without proper control and prevention, its prevalence will increase further to 438 million in 2030. This accounts for a global increase by 54%, i.e. a rise from a prevalence of 6.6% to 7.8% in 20 years. Nearly 70% of the people with diabetes live in developing countries; the largest numbers are in the Indian subcontinent and China. Nauru has the highest prevalence of diabetes (30.9%) and will continue to be so in 2030 (33.4%). Many Arab countries, Tonga, and Malaysia are among the top ten countries having high percentages of people with diabetes. There is little gender difference in the distribution in the number affected with diabetes. The largest numbers with diabetes are in the 40 to 59 age groups (132 million, in 2010) which is expected to rise further. By 2030, there will be more diabetic people in the 60 to 79 age groups (196 millions).

Children with Type 2 Diabetes

Type 2 diabetes in children is becoming common in many countries, especially so among Asian populations. There is little data about the onset and progress of complications in these children. Occurrence of cardiovascular diseases (CVD) is dependent on the duration and hence, there are no data available in children. Data from Japanese and Pima Indian children indicate presence of microvascular diabetic complications even at the time of diagnosis and with a short period of follow-up.

Gestational Diabetes

Gestational diabetes mellitus (GDM) is common in many populations, including Asian Indians. Pregnant women should be tested for GDM, in 24 to 28 weeks of gestation. GDM is a pre-diabetic state with an increased risk of development of the disorder in the subsequent pregnancies, in 60% to 90%. It is also known that women with GDM have a high-risk (up to 30%) of developing diabetes within 7 to 10 years after the index pregnancy.

Asian Scenario

The rising trend in prevalence of diabetes is evident globally. The changes are marked in developing countries, particularly in the Asian continent. Increasing levels of urbanisation, industrialisation and economic advancements adversely affect the biological, and environmental risk factors for diabetes and other non-communicable diseases. Unhealthy diet, physical inactivity and stress factors cause overweight/obesity and insulin resistance. Asian populations, particularly people of the Indian subcontinent have a strong genetic predisposition for diabetes. They also have high levels of insulin resistance and also have a low threshold for risk factors such as age, body mass index, and upper body adiposity. Both thrifty genotype and thrifty phenotype appear to operate in them. Clustering of cardiovascular risk factors, the metabolic syndrome is common in these populations, at a young age itself.

PREVALENCE OF DIABETES IN INDIA

The prevalence of diabetes in India in 1970's was 2.3% in urban and 1.5% in rural areas, as shown by the multi-centric study by the Indian Council of Medical Research (ICMR). In 2000s, the prevalence has risen to 12% to 19% in urban areas and to 4% to 9% in rural areas. A study from rural Andhra Pradesh reported a prevalence of 13.2%. Though, the studies are not strictly comparable due to methodological differences (**Table 2**) the rising trend in prevalence of diabetes in urban and rural areas in India, is evident. The narrowing of urban, rural divide in the prevalence is due to the rapid urbanisation and socio-economic transitions occurring in rural areas also.

India which has a large pool of pre-diabetic subjects (IGT and IFG) shows a rapid conversion of these high-risk subjects to diabetes. The Indian Diabetes Prevention Programme-1 (IDPP-1) has shown an annual incidence of approximately 18% among subjects with IGT.

National studies or population based studies on diabetic complications are sparse in India. A few population based studies indicate the prevalence of retinopathy to be 18% to 27.0% and overt nephropathy to be about 2.2% with a large percentage (27%) having microalbuminuria. Peripheral vascular disease is prevalent in 6.3%, peripheral neuropathy in 26%, and coronary artery disease (CAD) is detected in 21%.

The major contributory factors for the high prevalence of the complications are; delayed diagnosis of diabetes, inadequate control of glycaemia, hypertension, and lack of awareness about the disease among majority of the public.

Table 2: Prevalence of Diabetes in Rural and Urban India Since 2000

Reference (Year)	Diabetes Prevalence (%)	
	Urban	Rural
National		
Ramachandran *et al* (2000)	12.1	—
Reddy *et al* (2003)	8.4	—
Sadikot *et al* (2004)	5.9	2.7
Northern India		
Delhi (2000)	11.6	—
Delhi (2001)	10.3	—
Delhi (2005)	15*	—
Kashmir (2000)	—	4.0
Jaipur (2003)	8.6	—
Rajasthan (2004)	—	1.8
Maharashtra (2006)	—	9.3
Southern India		
Chennai (2000)	13.9	—
Kerala (2000)	12.4	2.5
Chennai (2003)	—	6.4
Chennai (2004)	14.3	—
Kerala (2005)	19.5	—
Mysore (2005)	—	3.8
Andhra Pradesh (2006)	—	13.2
Chennai (2006)	18.6	9.2

** Study in industrial workers (men only)*

ECONOMIC BURDEN DUE TO DIABETES

The cost of diabetes care is high and is escalating world wide. It is estimated by the WHO that the global expenditure for diabetes care would increase from 234 billions in 2007 to 411 billions in the next 20 years. The WHO estimate is based on lost productivity due to diabetes, heart diseases, and stroke together show that over the next 10 years, lost national income in billions of USD will amount to 555.7 in China, 303.2 in Russian Federation, 336.6 in India, 49.2 in Brazil, and 2.5 in Tanzania.

A study by us in India showed that the median expenditure had risen from INR 4,200 (USD 95) to INR 9,000 (USD 203) between 1998 to 2005. The indirect cost is more difficult to assess and is much higher than the direct cost. The proportion of annual income spent on health care is about 25% to 30% by the poor people. The cost increases many fold when diabetic complications are present.

PRE-DIABETES

Type 2 diabetes is a lifestyle disorder and an interaction of genetic and environmental factors precipitates the metabolic abnormalities existing in pre-diabetic subjects to the clinical stage of diabetes. There is a long asymptomatic pre-diabetic stage(s) before the development of diabetes. These stages are easily identifiable by OGTT. For the development of diabetes, both the basic pathophysiological defects, i.e. insulin resistance and β-cell secretory defect have to co-exist.

The definition of IGT has been stable. The American Diabetes Association (ADA) recommends that the normal cut-off for FPG of < 100 mg/dL. Both IGT and IFG have heterogeneous pathogenesis and hence may have different rates of progression to diabetes. People with combined IFG and IGT have approximately double the rate of conversion to diabetes than those with any one of the abnormalities. Both the states are associated with insulin resistance and other cardiovascular risk factors such as dyslipidaemia and hypertension. IGT is shown to be a stronger risk predictor than IFG.

PREVENTION OF DIABETES

Several systematic long-term prospective studies from different parts of the world have shown that type 2 diabetes is largely preventable. Although the genetic factors cannot be modified, its interaction with the diabetogenic environmental factors can be prevented by modifying obesity, diet, and physical activity. Indian Diabetes Prevention Programmes (IDPP-1 and IDPP-2) have shown that by improving physical activity and by using healthy diet, incidence of diabetes can be significantly reduced with a relative risk reduction of ~ 30%, in persons with IGT. Metformin in small doses was also found to be effective in primary prevention of diabetes.

Lifestyle changes due to urbanisation and modernisation have caused unhealthy diet habits, lack of physical activity, and increased stress leading to overweight or obesity with higher levels of insulin resistance. India and many other developing countries are going through this scenario and as a result, we notice more of chronic metabolic disorders than communicable diseases posing increasing challenge to the national health.

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9.2 Pathogenesis of Type 1 Diabetes Mellitus

V Mohan, Rakesh Parikh

Understanding the pathogenesis of type 1 diabetes mellitus (type 1 DM) is crucial for developing preventive strategies. However, despite much research, it still remains largely unclear. As per current understanding, type 1 DM develops in people who are genetically predisposed. In addition, certain environmental triggers start the process of autoimmune destruction leading to complete β cell destruction and insulinopaenia that is characteristic of type 1 DM.

It is estimated that 50% to 90% of type 1 DM patients have evidence of auto-antibodies and they are labelled as type 1A DM or autoimmune type 1 DM while the remaining are called type 1B DM or idiopathic type 1 DM. The prevalence of type 1B DM is reported to be 5% to 10% in Caucasian populations. Though limited data is available on type 1 DM from India, in one study as much as 45% of recently diagnosed subjects were found to have idiopathic or type 1B DM. Though the exact pathophysiology is unknown for this subtype, various factors like viral infection, toxins, subclinical pancreatitis or some unidentified genetic defects might be responsible.

The pathogenesis of type 1 DM will be discussed here under the subheadings of genetic factors, environmental triggers and autoimmune destruction. As per the current understanding most of the type 1 diabetic subjects have some or the other genetic predisposition, though alone it is not sufficient to cause type 1 DM. In such genetically predisposed subjects, one or the other environmental trigger sets the process of insulitis. Its only after the β-cells are destroyed critically enough to cause insulinopaenia, that the subject might present with classical symptoms of type 1 DM. As the environmental triggers are highly unpredictable, routine screening in genetically predisposed subjects (first degree relatives of type 1 DM patients) have not been shown to be cost effective.

GENETIC FACTORS

Several studies have shown familial clustering of type 1 DM with siblings of type 1 diabetic subjects having a risk of 5% to 6%, while the risk of transmission of type 1 DM from parents is about 10%. The greatest risk is provided by an identical (monozygotic) twin with type 1 DM. The concordance rate even for monozygotic twins is only in the range of 25% to 50% while that of dizygotic twins is much lower. This suggests that in addition to genetic factors, there is a strong role for environmental factors in the development of type 1 DM.

The inheritance pattern of type 1 DM is complex and polygenic. Ongoing research over the last few decades has identified at least 20 candidate genes associated with type 1 DM. Different candidate loci are named with a prefix of IDDM, viz. IDDM 1, IDDM 2 and so on (**Table 1**). Among these, two chromosomal regions have emerged consistently across multiple studies. These are the human leucocyte antigen (HLA) region located on chromosome 6p21.3, and the Insulin gene region on chromosome 11p15 and these are labelled as IDDM 1 and IDDM 2, respectively.

Table 1: Genetic Loci Associated with Type 1 Diabetes Mellitus

Locus	Chromosome	Candidate Genes	Markers
IDDM1	6p21.3	*HLA* DR/DQ	TNFA
IDDM2	11p15.5	Insulin VNTR	D11S922
IDDM3	15q26	D15S107	D15S107
IDDM4	11q3.3	MDU1, ZFM1, RT6, IC, LRP5, FADD, CD3	FGF3, D11S1917
IDDM5	6q25	*SUMO4*, MnSOD	ESR, a046xa9
IDDM6	18q21-21	JK (Kidd), ZNF236	D18S487, D18S64
IDDM7	2q31-33	NEUROD	D2S152, D251391
IDDM8	6q25-27	—	D6S-281,-264, -446
IDDM9	3q21.25	—	D3S1303, D10S193
IDDM10	10p11.q11	—	D10S565
IDDM11	14q24.3.q31	ENSA, SEL-1L	D14S67
IDDM12	2q33	*CTLA4*	(AT)n 3'UTR, A/G, Exon1
IDDM13	2q34	IGFBP2, IGFBP5, NEUROD, HOXD8	D2S137, D2S164, D2S1471
IDDM15	6q21	—	D6S-283, -434, -1580
IDDM16	14q32	IGH	—
IDDM17	10q25.1	—	D10S1750, D10S1773
IDDM18	5q31.1.33.1	IL-12B	IL-12B
IDDM19	2q24.3	IFIH1	—
	1q42	—	D1S1617
	16p12-q11.1	—	D16S3131
	16q22-q24	—	D16S504
	17q25	—	—
	19q11	—	—
	3p13-p14	—	D3S1261
	9q33-q34	—	D9S260
	12q14-q12	—	D12S375
	19p13.3-p.13.2	—	INSR
PTPN22	1p13	*PTPN22*(LYP)	SNP = R620W
CLEC16A	16p13	—	rs2903692

IDDM = Insulin-dependent diabetes mellitus; HLA = Human leucocyte antigen; TNFA = Tumour necrosis factor; VNTR = Variable number tandem repeat.

HLA MOLECULE AND IDDM1 GENE

IDDM 1 (genes encoded within HLA region) remains the most powerful determinant of type 1 DM accounting for approximately 40% of familial inheritance of the disorder.

HLA Molecules

HLA are glycoproteins found on the surface of cells. They are comprised of class I and class II, both being encoded by different genes within the HLA region of chromosome 6. Class I molecules are found on surface of all nucleated cells and are involved in the 'restriction' of cytotoxic T lymphocyte activity. The antigen

peptides are recognised by CD8+ T lymphocytes only when they are presented along with HLA molecule. Class II molecules are normally confined to antigen presenting cells such as macrophages, B lymphocytes and activated T lymphocytes. Class II molecules are comprised of α and β chains which bind to foreign and self antigens in a cleft on the surface of molecule to be presented to CD4+ helper T lymphocytes.

Owing to the crucial role played by HLA molecules in immune response, any alterations in their structure might influence the predisposition to autoimmune disorders. The genes for class I HLA are encoded in HLA, A, B and C loci while that for class II are located on HLA, DP, DQ and DR regions.

The first evidence of allelic association between the HLA complex and type 1 DM was reported for the HLA-B15 allele and was based on serology. In subsequent studies, a positive association of type 1 DM with HLA-B8 and a negative association with HLA-B7 were established. Higher risks were shown to be associated with HLA class II specificities, namely DR3 and DR4, whereas DR2 (now renamed DR15) was shown to be protective. More than 90% of white Caucasian patients with type 1 DM have DR3 and/or DR4 as compared with 40% to 50% of controls. The greatest risk of type 1 DM is conferred by the simultaneous presence of DR3 and DR4, which are found together in 30% to 50% of patients but in only 1% to 6% of controls.

Recent molecular studies indicated that the primary susceptibility genes are situated in the HLA-DQ rather than the DR region. In white Caucasians, the DQA1*0301, DQB1*0302 (DQ8) allele (associated with DR4) and DQA1*0501-DQB1*0201 (DQ2) allele (associated with DR3) have the strongest association with type 1 DM. In contrast, DR2 and DQ6 (DQA1*0102-DQB1*0602) provide protection against the development of type 1 DM.

North Indian data suggests the strongest association is with DR3 unlike in south Indians where both DR3 and DR4 are associated with type 1 DM. Data from Orissa shows that DRB1*03 and DQ2 (DQA1*501, DQB1*0201), but not DR4 and DQ8, was significantly increased in patients with type 1 DM.

IDDM2

IDDM2 has been mapped to 5' end of insulin gene with variable number of tandem repeats (VNTR). IDDM2 contributes to 10% of familial inheritance. The class I allele of IDDM2 is associated with development of type 1 DM while class III is protective.

As shown in **Table 1**, there are several other genes associated with type 1 DM but these play a relatively minor role.

ENVIRONMENTAL FACTORS

Identification of the exact environmental trigger in any given case of type 1 DM is difficult owing to the larger number of environmental triggers. Epidemiological studies have suggested differences in incidence rates even among countries with similar genetic make-up, like Finland and Estonia or Norway and Iceland. Pointing to the role of environmental factors, it is of interest that children of Asian origin who moved to UK (traditionally having a low risk of type 1 DM) now have incidence rates approaching that of local white population strongly suggesting that environmental factors modulate the risk of developing type 1 DM. The incidence of type 1 DM is increasing in many countries, e.g. in Europe there has been an overall increase of 3.4% per year and even higher increase (6.3% per year) in children below 5 years of age. This sharp rise in incidence rates over a short period of time suggests the role of changing environmental factors operating in early life. Finally, seasonal variations in occurrence of new onset type 1 DM also suggest the role of environmental triggers for type 1 DM. Among the various environmental factors studied viruses and dietary factors have been reported and these are discussed below.

Viruses

Recently diagnosed type 1 DM patients may show serological or other evidence of viral infection. There are a few case reports of type 1 DM being diagnosed during or soon after viral infection. Viruses can damage β-cells either directly by cytolytic effects or indirectly by an autoimmune response that is initiated or enhanced by a viral infection. In certain patients in whom β-cell destruction is going on, viral infection can act as a terminal insult destroying a critical number of residual β-cells. A few of the viruses implicated in development of type 1 DM are described below.

Mumps virus

This was one of the first viruses implicated in the development of type 1 DM. Some children with mumps parotitis develop islet cell antibodies suggesting an autoimmune basis.

Coxsackievirus B

Coxsackievirus B is the virus implicated more often. It has been shown to have cytolytic activity on β-cells in animal experiments. Autoimmune mechanisms have also been suggested through cross reactivity of the virus with specific β-cell antigens. An alternative hypothesis of the virus acting as a 'bystander' activating autoreactive T cells against islet antigens has also been suggested.

Other viruses, like rubella, cytomegalovirus, retroviruses, Epstein-Barr virus, echoviruses, hepatitis A virus, varicella zoster, measles, polio, influenza and rotavirus have also been suggested to be associated with type 1 DM based on circumstantial evidence. Some viruses, such as lymphocytic choriomeningitis virus (LCMV) and mouse hepatitis virus also have been shown to be protective against type 1 DM in animal experiments.

Overall, the role of viruses causing type 1 DM is less recognised nowadays.

Dietary Factors

Nitrites and nitrates are common components in food and can react with amines and amides to produce nitrosamines and nitrosamides. The high incidence of type 1 DM in Sicily and Finland has been reported to be due to these compounds in drinking water. An increased incidence of type 1 DM in Icelandic boys was observed and linked to the consumption of smoked and cured mutton.

Exposure to cow milk early in life has been linked to the development of type 1 DM in humans particularly in Scandinavia. Some studies have suggested milk powder based diets to be diabetogenic.

Five to ten per cent patients with type 1 DM have coeliac disease. Wheat gluten has been found to be diabetogenic in BB rats.

In a Finnish study dietary supplementation of children with vitamin D was found to be protective against type 1 DM. Cod liver oil which is a good source of vitamin D, when taken during pregnancy has also been shown to be beneficial.

Other Factors

Bafilomycin A1 produced by *Streptomyces* (which are ubiquitous bacteria found in soil and tubers) could be a source of β-cell toxins. Other bacteria may also act as adjuvant to food antigens. It has been observed that heat killed bacteria or microbial products can act as an adjuvant.

AUTOIMMUNE DESTRUCTION

The strongest evidence to support autoimmunity as the ultimate pathogenesis comes from the presence of insulitis (presence of inflammatory cells consisting of T lymphocytes, B lymphocytes, and macrophages) around the islets in recently diagnosed patients of type 1 DM. Fifty per cent to ninety per cent of type 1 DM patients have presence of antibodies against, islet cells (ICA), glutamic acid decarboxylase (GAD) 65, and IA2. Moreover type 1 DM has a strong association with other autoimmune disorders, like Hashimoto's thyroiditis, Grave's disease, pernicious anaemia, coeliac disease, etc. Subjects with genetic predisposition to type 1 DM, if exposed to certain environmental trigger, autoimmune destruction of β-cells starts. If the β-cells are destroyed to such an extent that the patient becomes insulinopaenic, he or she would develop hyperglycaemia and present with classical features of type 1 DM.

Cellular Immune Response

Type 1 DM is a T cell mediated disease. β-cells can become the target of CD8 T cells due to their close resemblance with other foreign antigens (e.g. virus), the immune response being directed towards the foreign antigen. Alternatively some virus may infect β cells and the viral proteins may get expressed over the β cells. In this case, the CD8 T cells directed against the virus, would attack the β-cells.

Humoral Response

Humoral response does not cause type 1 DM *per se* but is considered to be the result of insulitis. In the process of insulitis, islet cell antigens leak out of the damaged β-cells and initiate a humoral immune response. Islet cell antibodies (ICA), GAD 65 antibodies, IA-2 antibodies, and insulin autoantibodies (IAA) are produced. These antibodies can be detected in the subject long before development of type 1 DM as insulitis is slowly progressive disease. However, all subjects with ICA or GAD – Ab do not necessarily develop type 1 DM. Insulin antibodies carry a very small risk of type 1 DM, but its presence along with ICA increases the 5-year risk of type 1 DM to 50% to 70% particularly in childhood type 1 DM below 5 years of age. Presence of two or more antibodies suggests a greater risk of type 1 DM. Approximately 80% of patients with type 1 DM express two or more autoantibodies. Although around 3% of normal subjects might express one or more antibodies, the chances of having two or more antibodies being present in a normal subject, is less than 0.3%. Indians have a high prevalence of type 1B DM and hence absence of these antibodies does not rule out type 1 DM.

CONCLUSION

In subjects who are genetically predisposed to type 1 DM, certain, as yet, poorly defined environmental triggers initiate T-cell mediated immune response. With the development of insulitis, autoantibodies are produced, which can be detected long before the development of clinical type 1 DM. Insulitis is a slowly progressive disease and over a period of months or years, may cause complete destruction of β-cells (insulinopaenia) leading to clinical manifestation of type 1 DM (**Figure 1**).

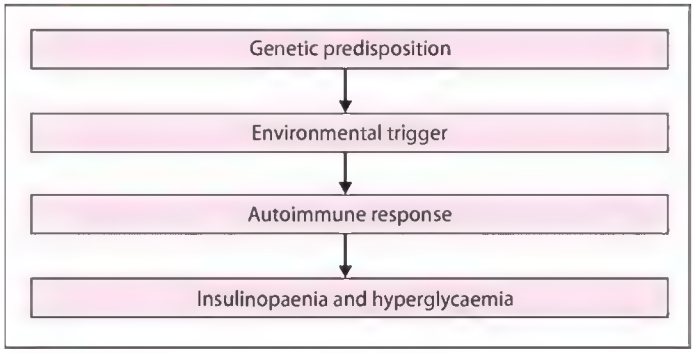


Figure 1: Pathogenesis of type 1 diabetes mellitus.

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9.3 Pathogenesis of Type 2 Diabetes Mellitus

Hemraj B Chandalia

INTRODUCTION

Simply stated, type 2 diabetes is caused by the interaction of certain genetic abnormalities with adverse environmental factors. To further identify the genetic and environmental factors and unravel the pathogenetic mechanisms is a daunting task. A clear picture is emerging in certain areas, while it is blurred in others. However, elucidation of these mechanisms holds the key to vast opportunities for therapeutic interventions.

GENETIC FACTORS

Type 2 diabetes is a polygenic disorder, caused by a cluster of susceptibility genes. It is very difficult to pinpoint these genes, as they may be present without the phenotypic manifestations or the disease may be seen at times in the absence of these genes. It is also possible that these genes vary in various ethnic groups. The classic method of candidate gene identification has been unsuccessful in unravelling these genes. The problem has also been approached by studying the functional candidate genes, tracing back the functional or biochemical abnormality to the genetic abnormality. Further, linkage analysis and micro satellite genotyping technique followed by positional cloning has been tried with limited success.

The genetic aetiology is clear in a group of monogenic type 2 diabetes (**Table 1**). Here the gene is clearly identifiable and the phenotypic presentation and treatment approaches well elucidated. Some of these genes operate by producing insulin resistance while others do so by producing a β-cell secretory defect. These forms of diabetes show an autosomal dominant inheritance, identified by a vertical transmission. Mitochondrial diabetes is maternally transmitted diabetes, caused by an A to G transition in the mitochondrial tRNA Leu (UUR) gene at base pair 3,243. The disease is associated with sensorineural hearing loss. The same genetic anomaly at times produces a syndrome of Mitochondrial myopathy, encephalopathy, lactic acidosis and strokes (MELAS), the different phenotypic expression of the same genetic anomaly is not yet well understood. Although the prevalence of these varieties of diabetes would vary in various ethnic groups, it is estimated that they do not make more than about 5% to 10% of young-age diabetes. Some rare genetic abnormalities described are insulin gene abnormality which produces an abnormal insulin or a convertase deficiency which impairs the conversion of proinsulin to insulin.

Abnormalities of insulin receptor are rare. They produce syndromes of extreme insulin resistance (type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome; **Table 1**). If all these anomalies are put together, they may not make more than 1% of all type 2 diabetes.

The search for genetic abnormalities in the common form of type 2 diabetes has been very intense but not very fruitful. Most susceptibility genes described increased the hazard ratio in diabetics versus the normal population only marginally.

Of a variety of candidate genes, calpain-10, Kir 6.2, peroxisome proliferator activated receptor-γ, hepatocyte nuclear factor-4α gene and transcription factor 7-like 2 gene are important. Many of these genes predispose to obesity, thus leading to diabetes. However, an interesting gene, ENPP-1 K121Q causes insulin resistance in the non-obese Asian Indians and is one of the susceptibility genes in this population.

Table 1: Monogenic Forms of Type 2 Diabetes

Phenotype characterised by defective insulin secretion
Maturity-onset diabetes of the young (MODY)
MODY 1: Mutation in hepatic nuclear factor 4α (HNF-4α) gene
MODY 2: Mutation in glucokinase gene
MODY 3: Mutation in hepatic nuclear factor 1α (HNF-1α) gene
MODY 4: Mutation in insulin promoter factor 1 (IPF-1) gene
MODY 5: Mutation in hepatic nuclear factor 1β (HNF-1β) gene
MODY 6: Mutation in neurogenic differentiation-1 transcription factor (Neuro D1/β-2)
Mutations in the insulin or proinsulin genes
Mitochondrial gene mutations
Phenotype characterised by insulin resistance
Mutations in the insulin receptor gene
Type A insulin resistance
Leprechaunism
Rabson-Mendenhall syndrome
Lipoatrophic diabetes
Mutations in the PPAR-γ gene

ENVIRONMENTAL FACTORS

Physical inactivity and excessive caloric intake are well recognised environmental factors producing type 2 diabetes. These factors can produce the disease independently in a genetically susceptible person, but usually work via production of obesity.

Obesity and type 2 diabetes are inextricably interrelated. They further coexist in the form of metabolic syndrome, together with other anomalies like hypertension, high triglycerides, and low HDL-cholesterol. It is estimated that 25% to 30% of the population in India and elsewhere suffers from the metabolic syndrome. In the shadow of a global spurt of obesity, type 2 diabetes is emerging as an epidemic.

Obesity results from the interaction of multiple susceptibility genes with environmental factors. By various estimates, aetiologically hereditary factors account for 50% to 70% of the obesity. Obesity is characterised by insulin resistance, an important feature of type 2 diabetes.

GENE-ENVIRONMENT INTERACTIONS

The mechanism of interaction of gene and environment is a very complex issue. The environmental factors interact by altering the expression of genes. There is also a gene-gene

interaction. Intrauterine environment also may influence the subsequent development of many non-communicable diseases like diabetes, obesity, and hypertension. Low birth weight, presumably due to poor maternal nutrition leads to development of insulin resistance in childhood and adult life. This is further exacerbated by over-nutrition in the post-natal period.

Epigenetic phenomenon, where unchanged DNA sequence can lead to altered phenotype, probably due to enhanced or suppressed expression of certain genes that may be responsible for obesity and diabetes Environmental factors may operate through epigenesis.

BIOCHEMICAL PERTURBATIONS

The biochemical perturbations in type 2 diabetes were described earlier than the genetic factors. Of these, the most well known abnormalities are of peripheral and hepatic insulin resistance, and impaired β-cell function.

Peripheral and Hepatic Insulin Resistance

With the advent of radioimmunoassay, massive data on serum insulin levels in obesity and diabetes became available. Hyperinsulinaemia was described first in obesity and later in type 2 diabetes, including type 2 normal weight diabetic. Thus, the concept of insulin resistance emerged. In spite of high insulin levels, there is poor glucose utilisation and insulin inaction in the muscle, adipose tissue, and liver.

In type 2 diabetes, adipose tissue in general and visceral fat in particular, exhibits a decreased inhibition of lipolysis and increased lipoprotein lipase activity, both resulting in a heightened flux of fatty acids in the liver and other tissues. High fatty acids levels are known to inhibit glucose utilisation, as demonstrated by Randle (glucose-fatty acid cycle). In type 2 diabetes and obesity, the adipose tissue also expresses increased amounts of 11β-hydroxysteroid dehydrogenase type 1 (11 β HSD-1), leading to increased cortisol levels and increased lipolysis locally. Adipose tissue is known to cause insulin resistance by secreting TNF-α and interleukins. Of the multiple adipose tissue hormones, resistin is responsible for insulin resistance, while adiponectin and leptin ameliorate insulin resistance. Although leptin levels are high in type 2 diabetes, there is also a state of leptin resistance. These biochemical abnormalities are accentuated in the abdominal adipose tissue, which is known to be abundant in type 2 diabetes. Interestingly, Asian Indians have increased adiposity even at a relatively low BMI, which may be one of the reasons for the increased type 2 diabetes. For this reason, the BMI above 23 kg/m^2 is also considered overweight in the Asian Indians, unlike the cut-off point of 25 kg/m^2 in the Caucasians.

The skeletal muscle glucose utilisation is impaired to a greater degree than adipose tissue in type 2 diabetes (**Figure 1**). In the post-prandial state, the glucose is primarily deposited as glycogen in the muscle. Hyperinsulinaemic-euglycaemic clamp studies have shown that the non-oxidative glucose disposal, like that in hexose monophosphate (HMP) shunt is severely impaired in type 2 diabetes and other insulin resistant states. The cause of this resistance is a high free fatty acid (FFA) concentration in the myocytes, as demonstrated in several studies by using a nuclear-magnetic resonance imaging. This would limit the glycogen synthesis through the HMP shunt. Recently, a defect in glucose transport has been described in the milieu of high fatty acids. In insulin resistant state, fatty acid oxidation or re-esterification leading to triglyceride synthesis is also impaired, thus leading to high levels of intra-myocellular FFA. On exercise, many of the abnormalities, including the diminished amount of glycogen synthase gets corrected, thus improving insulin sensitivity. Exercise increases glucose transporter activity, improves capillary density, increases mitochondrial mass, and increases type 2 A muscle fibres which are involved in the glycolytic process.

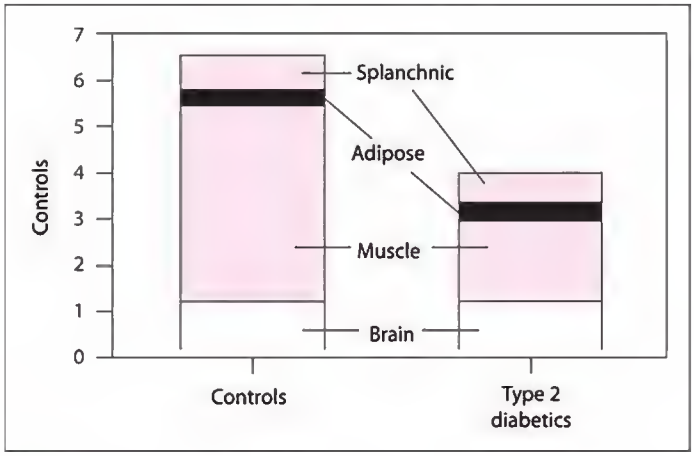


Figure 1: Diminished glucose utilisation in type 2 diabetics, primarily in the skeletal muscle.
Courtesy: DeFronzo RA. Lilly Lecture 1987: The triumvirate: beta cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988; 37: 667-87.

The hepatic insulin resistance leads to enhanced gluconeogenesis and glycogenolysis. Thus, increased hepatic glucose production is a hallmark of uncontrolled diabetes. Type 2 diabetes is often associated with a fatty liver, with or without elevated liver enzymes and evidence of hepatic necrosis. It is also a manifestation of hepatic insulin resistance and is often reversed by weight loss and the use of insulin sensitisers.

The molecular mechanism of insulin resistance has been a subject of intensive studies (**Figure 2**). The resistance is very rarely due to an abnormal insulin or insulin receptor. Sustained hyperglycaemia produces glucotoxicity, probably by a failure to enhance hexosamine pathway, leading to increased glucosamine levels. Increased glucosamine levels can produce insulin resistance in adipose tissue and skeletal muscle. Sustained hyperinsulinaemia also down-regulates the insulin receptor and further aggravates insulin resistance. The main locus of the resistance appears to reside at the post-receptor level. Insulin signalling is initiated by the binding of insulin to alpha subunits of the receptors. This initiates a cascade of auto-phosphorylation and dephosphorylation through the intra-cellular tyrosine kinase, insulin receptor substrates (IRS-1, 2, 3, 4) and other signal regulatory protein family (Gab-1, Cb-1, CAP, APS).

The β subunit of insulin receptor has been shown to undergo besides tyrosine auto-phosphorylation, a serine-threonine phosphorylation. The latter type of phosphorylation increases insulin resistance and impairs insulin signal transduction. The insulin signal is terminated by dephosphorylation of the β subunit of receptor by tyrosine phosphatases, the activities of which is increased in insulin resistant states.

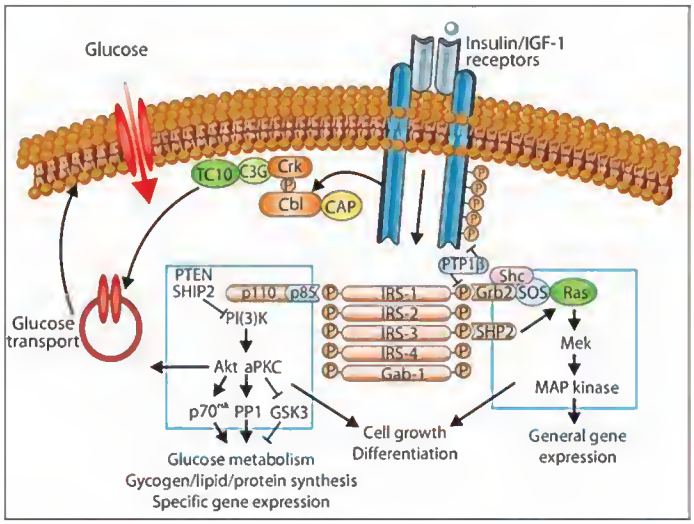


Figure 2: Molecular mechanisms of insulin resistance. Altered post-receptor events, tyrosine kinase phosphorylation, IRS and other signal regulatory proteins are responsible for the resistance.

Source: Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001; 414: 799-806.

aPKC = Atypical protein kinase C; GSK3 = Glycogen synthase kinase 3; IGF= Insulin-like growth factor; MAP = Mitogen activated protein; PI (3)K = Phosphatidyl inositol 3 kinase; PPI = Protein phosphatase 1; PTEN = Phosphatase and tensin homologue deleted on chromosome 10; SH1P2 = SH2-domain-containing inositol-5-phosphatase

Following the insulin receptor phosphorylation a number of down stream events, including an increase in phosphatidyl inositol-3 kinase (PI-3 kinase) leads to the translocation of GLUT-4. In insulin resistant state, the GLUT-4 is not depleted, but its translocation is hampered. The glucocorticoid-induced insulin resistance is also associated with a reduced insulin stimulated IRS-1 associated PI-3 kinase.

Insulin Secretory Defects in Type 2 Diabetes

In a non-diabetic individual, besides the meal-related insulin secretion, there are rapid oscillations in insulin secretion every 8 to 15 min, without any glycaemic stimulus. There is also a circadian rhythm occurring every 80 to 150 min. Overall, about 18 to 32 units of insulin are secreted daily and about 50% is extracted by the liver for local action during its first passage.

In type 2 diabetes, the rapid meal-related insulin secretion, which primarily occurs in about 30 min post-meal and mostly represents the preformed insulin, is attenuated. The post-meal response for the 2-hour period post-meal appears to be exaggerated but in relation to the high glycaemic levels is indeed also impaired. In obesity and impaired glucose tolerance group, absolute amounts of insulin secreted may be excessive. The molecular mechanism of this phenomenon is probably an overexpression of hexokinase gene as compared to the glucokinase gene. As the former has a low Michaelis constant (K_m) for glucose, hypersecretion is produced. The circadian rhythm of both types of non-meal related insulin responses is also altered or attenuated.

The β-cell mass appears to be slightly reduced at the time of diagnosis of diabetes; however, the functional capacity is impaired out of proportion to its mass and hence in many studies, a 50 % reduced insulin response has been described at the onset of type 2 diabetes. Subsequently, the β cell mass declines further in a relentless fashion with increasing insulinopaenia. This is at time correlated to fibrillary amylin deposition in the β-cells.

The genetic factors that determine β cell differentiation, growth and apoptosis are being intensively studied at present. The growth factors and their biology is yet to be elucidated. It obviously holds the key to a fruitful avenue for intervention. However, it is characterised by an early apoptosis of β cells. The insulin resistance and β cell failure exist and progress pari passu. In early phases there is predominately a resistant state. Subsequently, β cell failure dominates the scene. The β-cell is able to compensate by increased insulin secretion in the face of rising blood glucose, but at about 140 mg/dL of blood glucose the insulin secretion levels off and a further rise in blood glucose results in diminishing insulin secretion (**Figure 3**).

In about 10% of type 1 diabetics, the β cell failure may be due to auto immunity. This is called latent autoimmune diabetes of adults (LADA) and aetiologically represents a forme fruste of type 1 diabetes.

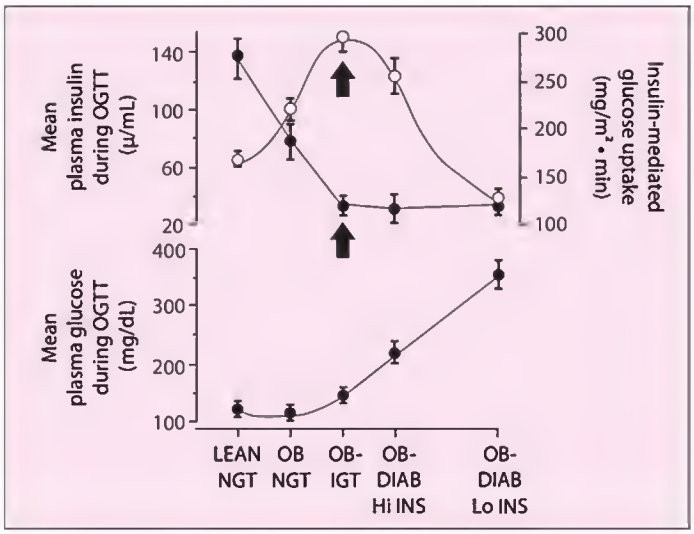


Figure 3: Natural history of type 2 diabetes. The plasma insulin response depicts the classic Starling's curve of the pancreas. Upper panel, ●: insulin-mediated glucose uptake, ○: plasma insulin response.

(DeFronzo, RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes. Diabetes 2009; 58: 773-95).

OTHER PATHOGENETIC MECHANISMS

Besides the role of β cell, skeletal muscle, adipose tissue, and liver in the genesis of type 2 diabetes, a few other important pathogenetic mechanisms have been described. The gastro-intestinal tract secretes a group of important hormones, collectively labelled as incretins. This includes two extremely well-known members: glucagon like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP). The former is secreted from the L-cells of the ileum and the latter from the K-cells located in the proximal small intestine. These hormones account for the enhanced insulin secretory response upon ingestion of glucose orally, as compared to that obtained by intravenous glucose administration. This has been termed the incretin effect. In type 2 diabetes, the incretin effect is blunted, which can be corrected by injecting GLP-1 or its longer acting analogue, like exenatide or liraglutide. GLP-1 is normally destroyed by a group of enzymes called dipeptyl peptidases, of which dipeptyl peptidase-IV (DPP-IV) is the predominant one. Compounds inhibiting DPP-IV inhibitors prolong the effect of endogenous GLP-1 and are being used therapeutically at present.

Although non-suppressibility of glucagon following a meal was described in type 2 diabetes almost 4 to 5 decades ago, it gained further relevance recently, with the availability of therapeutic tools to correct this anomaly. GLP-1 analogues and DPP-IV inhibitors described above correct this defect by suppressing glucagon levels post-prandially. Tachy-alimentation has also been described to aggravate diabetes by exposing the body to sudden surge of nutrients. GLP-1 analogues and DPP-IV inhibitors are known to retard gastric emptying, thus offering an additional mechanism of action.

The hypothalamic neurons and neurotransmitters have been considered in the pathogenesis of type 2 diabetes. There are numerous changes described in the neurotransmitter secretion in obesity and type 2 diabetes. The rapid first phase insulin response is mediated through these pathways. It has been demonstrated that the hypothalamic nuclei regulating appetite are also insulin resistant. After the ingestion of glucose, the elevated plasma insulin levels are unable to exert the inhibitory response in these nuclei in obese, insulin resistant individuals. Hence, pharmacological manipulation of these neurons by promoting satiety can be utilised in type 2 diabetes. More recently, dopamine agonists, like bromocriptine have been shown to improve hyperglycaemia in type 2 diabetes.

Another new pathogenetic mechanism described shows involvement of kidney in the pathogenesis of type 2 diabetes. Normally about 160 g of glucose is filtered in the glomerular filtrate; 90% of it is absorbed in the proximal convoluted tubule by a high capacity glucose transporter called SGLT2. Remaining 10% of the filtered glucose is absorbed in the straight descending part of the proximal tubule by another glucose transporter SGLT-1. It has been demonstrated that in type 1 diabetes the tubular maximum for the glucose absorption is increased. Although it is not clear whether the same holds true of type 2 diabetes, the levels of SGLT-2 mRNA is four-fold increased in the proximal tubular renal cells. This may account for increased glucose resorption and hence, hyperglycaemia. Inhibition of SGLT has provided another avenue to treat type 2 diabetes.

In summary, type 2 diabetes originates from a complex interaction of genetic and environmental factors, which express themselves in the form of myriad biochemical abnormalities.

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9.4 Clinical Features and Diagnosis of Diabetes Mellitus

D Maji

Diabetes mellitus is a group of metabolic disorder involving carbohydrate, lipid and protein metabolism, characterised by chronic hyperglycaemia, as a result of defects in insulin secretion from the β-cells of pancreas or peripheral action of insulin (insulin resistance) or both. During the course of the disease the diabetic subjects are at risk of development of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery, cerebrovascular and peripheral vascular disease) complications later in the course of the disease. The features of long term complications then become a part of the diabetic phenotype.

CLINICAL FEATURES

Clinical features of diabetes mellitus are variable and depend upon the type of diabetes and the stages of the natural history of diabetes at which it is seen (**Figure 1**).

In the earlier part of development of diabetes, the patient may remain asymptomatic for a long period of time; on the other hand in the later part of the disease the features of long-term complications of diabetes may manifest and become part of the diabetic syndrome. There are four major types of diabetes—type 1 diabetes, type 2 diabetes, other specific types of diabetes and gestational diabetes (**Figure 2**).

As the clinical manifestations of these types of diabetes may be different, they will be considered separately.

TYPE 1 DIABETES

Type 1 diabetes constitutes less than 2% of total diabetic population in India. In majority of type 1 diabetes patients; there is rapid destruction of β-cells of pancreas; in a susceptible subject due to viral mediated autoimmune process. A typical type 1 diabetes patient is below 30 years, is underweight and present with frank symptoms, e.g. polyuria, polydipsia, polyphagia, weakness, weight loss, restlessness and if continued for some period, may lead to diabetic ketoacidosis with altered sensorium and severe dehydration. Occasionally a child with similar clinical presentation in a remote area may die before the diagnosis is made. Any comatose child presenting with severe dehydration without diarrhoea; a diagnosis of type 1 diabetes should be in the list of diagnostic consideration. In some type 1 diabetic subjects; β-cell destruction is slower and may mimic a type 2 diabetes in clinical presentation (latent autoimmune diabetes in adult; (LADA). After initial treatment with insulin, a type 1 diabetic may recover some residual β-cell function (the so-called 'honeymoon phase') when they can be maintained with a small daily dose of insulin; rarely, they do not even need insulin for some period of time. However, this phase of recovery of residual β-cell function is temporary and the autoimmune process ultimately destroys the remaining β-cells and the subject becomes completely insulin deficient and require insulin for survival.

TYPE 2 DIABETES

Type 2 diabetes constitutes almost 98% of diabetic population in India. Age, obesity, lack of physical activity, and family history of diabetes are the predisposing factors for type 2 diabetes. Other risk factors are – hypertension, dyslipidaemia, and past history of gestational diabetes mellitus (GDM). Some may

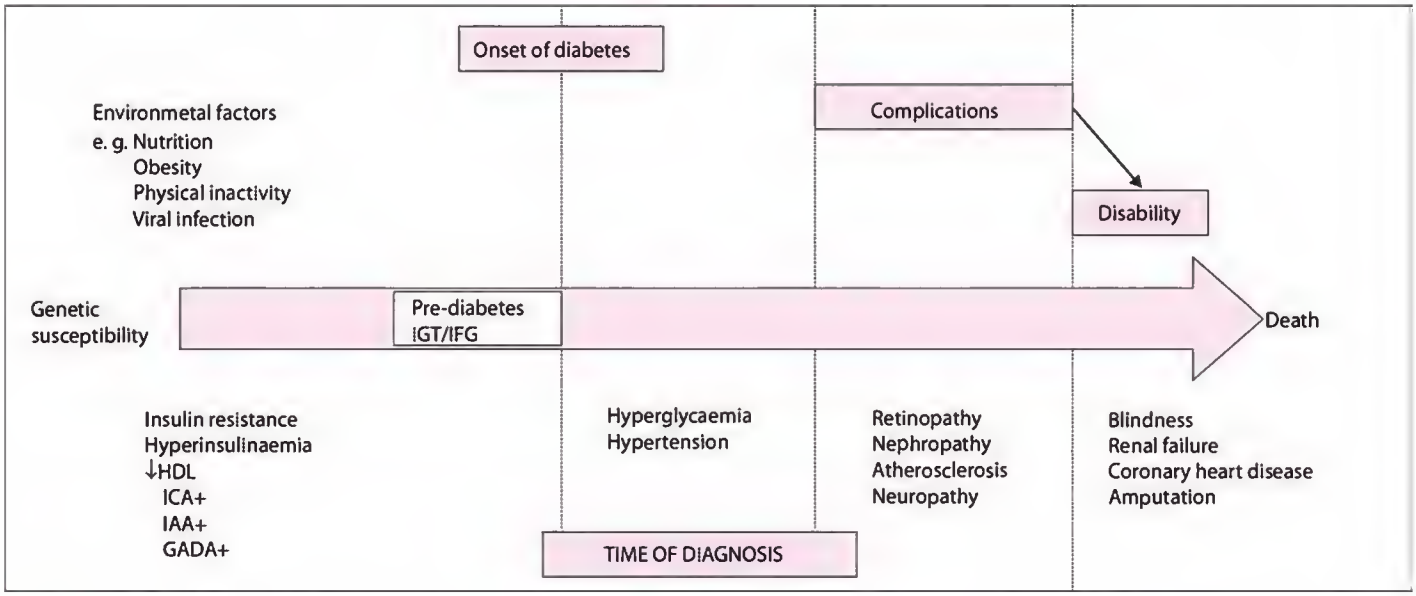


Figure 1: The natural history of diabetes mellitus.

IGT = Impaired glucose tolerance; IFG = Impaired fasting glucose; HDL = High density lipoprotein; ICA = Islet cell antibody; IAA = Insulin autoantibody; GADA = Glutamic acid decarboxylase antibody

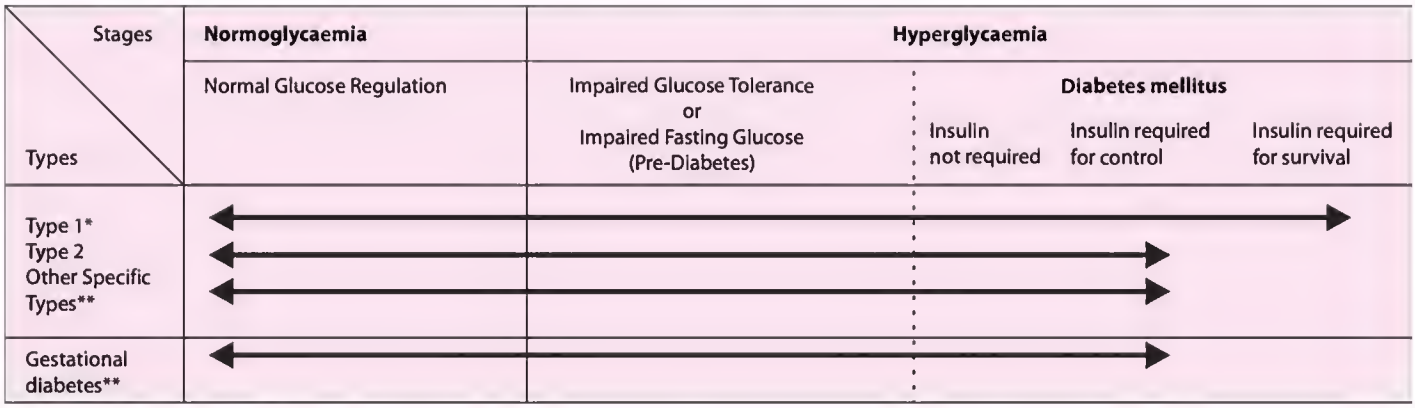


Figure 2: Four major types of diabetes.

Disorders of glycaemia: aetiologic types and stages.
** Even after presenting in ketoacidosis, these patients can briefly return to normoglycaemia without requiring continuous therapy (i.e.'honeymoon remission').*
*** In rare instances patients in these categories (e.g. Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival.*

present with the characteristic symptoms of polyuria, polydipsia and polyphagia with weakness and weight loss, many type 2 diabetics are asymptomatic and remain silent for many years and at diagnosis may have features of long-term complications like neuropathy (tingling, numbness, paraesthesia of lower limbs), retinopathy or even nephropathy. A middle-aged female often consult gynaecologist for pruritus vulva, a male subject may consult physician for balanitis; because chronic hyperglycaemia makes a subject prone to several type of bacterial or fungal infections. Asymptomatic patients are diagnosed during routine health check-up for LIC policy, or job recruitment or before surgery. In spite of this, about half of the type 2 diabetic population in India remain undiagnosed.

LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA)

LADA includes a heterogeneous group of conditions that are phenotypically similar to type 2 diabetes, but patients have autoantibodies that are common to type 1 diabetes (**Table 1**).

Table 1: Characteristic of Special Tests for the Diagnosis of Diabetes Mellitus

	Type of Diabetes		
Test	**Type 1**	**Type 2**	**LADA**
C-peptide	<1.51 ng per mL (0.5 nmol per L): PPV of 96% for diagnosis in adults and children	<1.51 ng per mL: NPV for diagnosis in adults and children	
GADA	60% prevalence in adults and children	7% to 43% prevalence in adults and children	Presence: PPV of 92% for requiring insulin at 3 years
	73% prevalence in children	NPV of 94% for requiring insulin at 6 yrs in adults	Absence: NPV of 49% for requiring insulin at 3 years
IA-2α and IA-2β	40% prevalence in adults and children	2.2% prevalence in adults	PPV of 75% for requiring insulin at 3 years in persons 15 to 34 years of age
ICA	75% to 85% prevalence in adults and children	4% to 21% prevalence in adults	PPV of 86% for requiring insulin at 3% in persons 15 to 34 years of age

GADA = Glutamic acid decarboxylase antibody; ICA = Islet cell antibody; LADA = Latent autoimmune diabetes in adults; NPV = Negative predictive value; PPV = Positive predictive value

Diagnostic criteria includes age of 30 years or older, no insulin treatment required for six months after diagnosis and the presence of antibodies to glutamic acid decarboxylase (GAD), islet cells (ICA), tyrosine phosphate (IA 2α and IA 2β), or insulin (IAA).

OTHER SPECIFIC TYPES

These group of diabetes refers to glucose intolerance that develops in association with other disorders other than those currently defined as type 1 or type 2 diabetes.

Genetic Defect of the β-Cell

Several forms of diabetes are associated with monogenic defects in β-cell. They are characterised by early onset in young age before 25, inheritance is autosomal dominant and they have impaired insulin secretion from β-cell with minimal insulin resistance, they are called maturity onset of diabetes in young, (MODY). Six different chromosomal locations have been identified (**Table 2**).

Table 2: Classification of Currently Recognised Genetic Defects of β-cell Function: Maturity-Onset Diabetes of the Young (MODY)

MODY Type	Chromosome	Defective Gene Product	Molecular Defect	Most Common Therapy
1	20q	HNF-4α	β-cell mass, insulin secretion	Oral hypoglycaemic agent, Insulin
2	7p	Glucokinase	Glucose phosphorylation	Diet and exercise
3	12q	HNF-1α	β-cell mass, insulin secretion	Oral hypoglycaemic agent, Insulin
4	13q	IPF-1 (PDX-1)	β-cell development and function	Oral hypoglycaemic agent, Insulin
5	17 cen-q	HNF-β	β-cell mass, insulin secretion	Insulin
6	2q	Neuro D1/ β-2	β-cell development and function	Insulin

Endocrinopathy

Hormone like growth hormone, cortisol, glucagon and epinephrine are diabetogenic. Syndromes associated with the excess of these hormones are associated with hyperglycaemia leading to secondary diabetes, e.g. Cushing, syndrome,

acromegaly glucagonoma, phaeochromocytoma. Apart from symptoms of hyperglycaemia, they will have clinical features related to respective endocrine disorder.

Drugs

Some drugs affect β-cell functions, e.g. Vacor (a rat poison), pentamidine, glucocorticoids (quite often used in pharmacologic doses), can cause or precipitate diabetes. Some of the anti-psychotic drugs also have diabetogenic effect, e.g. clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole.

Other syndromes

Many genetic syndromes, are associated with increased incidence of hyperglycaemia; chromosomal disorders like Klinefelter's syndrome, Turner's syndrome, and Down's syndrome. Wolfram's syndrome, an autosomal recessive disorder, is associated with insulin deficient diabetes and absence of β-cells seen at autopsy.

Chronic Pancreatic Disease

Chronic calcific pancreatitis develop hyperglycaemia, along with defects of exocrine function of pancreas. Fibrocalcific pancreatic disease (FCPD) which was earlier considered as a separate type, are now put in this category of secondary diabetes.

Haemochromatosis

Abnormal glucose intolerance occurs in 75% to 80% of haemochromatosis patients where iron deposition is found in different tissues of the body including liver and pancreas. The severity of cirrhosis and iron load is correlated with the degree of glucose intolerance. Characteristic bronze colour skin and hepatospl-enomegally are prominent clinical features in this condition.

DIAGNOSIS

Diagnosis of diabetes should be made in the early stage of development of the hyperglycaemic state, as several reports including that of Diabetes Control and Complication Trial (DCCT), United Kingdom Prospective Diabetes Study (UKPDS) and Steno 2 trial, clearly suggest that long-term complications of diabetes can be prevented or delayed if treatment is started early. In clinical practice, however, diabetes is diagnosed late.

A plethora of diagnostic criteria existed before the publication of National Diabetes Data Group (NDDG) in 1979 and WHO Expert Committee Report, 1980. WHO has published several technical reports relating to diabetes in 1965, 1980, 1985, 1994, and 1999. The diagnostic criteria used over this period are not accepted any more. Today there is wide acceptance of the fact that there is a continuous spectrum of glucose levels between those considered normal and those to be considered as diabetic.

ORAL GLUCOSE TOLERANCE TEST

Oral glucose tolerance test (OGTT) should be done in the morning after fasting for 10 to 16 hours before the test; having unrestricted carbohydrate diet for 72 hours. No smoking should be done during the test. Any concomitant medication or illness should be noted. The test should be performed with 75 g of anhydrous glucose in 150 to 300 mL of water taken over 5 minutes time. Children to be given 1.75 gm/kg body weight, up to total of 75 gm of glucose. It is recommended in asymptomatic individuals to reconfirm the results on another occasion. Interpretation of OGTT is described in **Table 3**.

Table 3: WHO Diabetes Criteria-Interpretation of OGTT

Glucose levels	Normal		Impaired fasting glycaemia (IFG)		Impaired glucose tolerance (IGT)		Diabetes Mellitus	
Venous Plasma	Fasting	2 hrs	Fasting	2 hrs	Fastin;g	2 hrs	Fasting	2 hrs
(mmol/L)	<6.1	<7.8	≥6.1 & <7.8	<7.8	<7.0	≥7.8	≥7.0	≥11.1
(mg/dL)	<110	<140	≥110 & <126	<140	<126	≥140	≥126	≥200

To convert mmol/L to mg multiply by 18

HbA1c AND DIAGNOSIS OF DIABETES MELLITUS

HbA1c is an index of mean blood glucose in fasting and post-prandial state and is well established, and widely used as a clinical measure of chronic glycaemia, in the follow-up monitoring of diabetes. Several studies indicate that HbA1c may show a glycaemic threshold with microvascular complications, suggesting it may additionally be useful as a diagnostic test for diabetes (**Table 4**). The main factors in support of using HbA1c as a screening and diagnostic test include: (1) HbA1c does not require patient to remain fasting, (2) HbA1c reflects longer-term glycaemia than does plasma glucose, (3) HbA1c laboratory methods are now well standardised and reliable, and (4) errors caused by non-glycaemic factors affecting HbA1c such as haemoglibinopathies are not frequent and can be minimised by confirming the diagnosis of diabetes with a plasma glucose specific test.

Table 4: Interpretation of HbA1c Test in Hyperglycaemic States as Proposed by Experts

Normal	<5.7%
Pre-diabetes	5.7% to 6.4%
Diabetes	6.5% or more

Gestational Diabetes Mellitus (GDM)

When hyperglycaemia is just recognised during pregnancy, it is defined as gestational diabetes. Majority of GDM are asymptomatic and diagnosed on routine check-up in the obstetric clinic. In general glucose intolerance resolves after the pregnancy is over, but in those who continue to have hyperglycaemia after delivery might have had unrecognised diabetes before pregnancy.

Table 5: Interpretation of OGTT for GDM Plasma Sugar Value Given Below in mg/dL

	100 gm 3 hours OGTT	100 gm 3 hours OGTT	100 gm 3 hours OGTT	75 gm 2 hours OGTT	75 gm 2 hours OGTT
	O'Sullivan and Mahan 1973	NDDG 1979	Carpenter and Couston' 82 ADA 1997	ADA 1998	WHO 1999
Fasting	90	105	95	95	126
1 hours	165	190	180	180	—
2 hours	145	165	155	155	140
3 hours	125	145	140	—	—
	Any two	Any two	Any two	Any two	

DIAGNOSIS OF GESTATIONAL DIABETES

Diversity of opinion exists for the diagnosis of gestational diabetes. O'Sullivan was the first to use the term Gestational Diabetes in 1961. In 1964 O'Sullivan and Mahan suggested the 100 gm 3 hours OGTT in the 2nd and 3rd trimester of pregnancy to diagnose GDM.

In 1979, the NDDG recommended a 15% upward adjustment of the diagnostic threshold using the venous plasma glucose in place of whole blood glucose. In 1982, Carpenter and Loustan modified the O'Sullivan and Mahan criteria using new enzymatic glucose oxidase method. The present American Diabetes Association (ADA) criteria recommends both 100 gm and 75 gm OGTT done between 24 and 28 weeks of gestation.

The WHO criteria is based on the 75 gm OGTT. The International Association of Diabetes and Pregnancy Study Group also recommends that all women with no prior history of diabetes undergo a 75 gm 2 hours OGTT between 24 and 28 weeks.

SCREENING FOR DIABETES

Diabetes is a common disease and associated with significant morbidity and mortality. It has an asymptomatic phase that may be up to 7 to 10 years before the diagnosis is made. If treated early, the long-term complications may be preventable, so testing is rationale for screening diabetes. Both fasting plasma glucose (FPG) and 2 hours post-glucose values (after 75 gm glucose) are now used widely in clinical practice as well as in epidemiological studies. Though a casual plasma glucose more commonly called random plasma glucose (RPG) 200 mg/dL or greater with symptoms is an established diagnostic criteria for diabetes; but as a screening test for diabetes it is insensitive specially when the value is on the lower side (**Tables 6 and 7**).

Table 6: Sensitivity and Specificity of Achieved in Screening for Diabetes Based on Random Plasma Glucose of Various Levels

Random Plasma Glucose (mg/dL)	Sensitivity (%)	Specificity (%)
≥110	84	65
≥120	76	77
≥130	63	87
≥140	55	92
≥150	50	95
≥160	44	96
≥170	42	97
≥180	39	98

The following ADA guidelines are widely accepted for screening of diabetes.

Additional Risk Factors for Diabetes

- Physical inactivity
- Hypertension
- HDL cholesterol <35 mg/dL
- Triglyceride >250 mg/dL
- History of cardiovascular disease
- Previous IFG or IGT
- First degree relative is diabetic
- History of GDM
- Member of high-risk ethnic group
- Delivery of baby >9 lb
- History of PCOD

Table 7: Criteria for Screening and Diagnosis of Diabetes at a Glance

Screening	Diagnosis
FPG ≥100 mg/dL	FPG ≥126 mg/dL
A1c >6.0%	A1c ≥6.5%
RPG ≥130 mg/dL	RPG ≥200 mg/dL
If screening result is negative, screen again in 3 years	2-hour OGTT ≥200 mg/dL
If screening result is positive but below the diagnostic threshold, do another test for diagnosis, using a different method	Diagnosis requires confirmation unless unequivocal symptoms of hyperglycaemia are present
If screening result is above the diagnostic threshold but a second test does not reach the threshold, test again in 1 year	Diagnosis based on HbA1c requires confirmation using a glucose dependent test (FPG or OGTT) or, if first HbA1c is ≥7.0%, by a second HbA1c ≥6.5%
	In asymptomatic persons with Hba1c ≥6.5%, if FPG ≥126 mg/dL or RPG ≥200 mg/dl, diagnosis is confirmed
	If screening is positive but less than the diagnostic threshold, two tests are required to reach the diagnostic threshold

Testing to detect type 2 diabetes should be considered in asymptomatic adults with BMI of 25 or greater and one or more additional risk factors for diabetes.

Screening for Gestational Diabetes (GDM)

Risk assessment at the 1st prenatal visit: High-risk GDM

- Marked obesity
- Previous GDM
- F/H/O diabetes
- Glycosuria

If testing is negative, re-testing should be done at 24 to 28 weeks of gestation.

Women with GDM should be screened for diabetes 6 to 12 weeks post-partum and subsequent screening for the development of diabetes.

CONCLUSIONS

In summary, diabetes is a heterogeneous metabolic disorder with varied manifestation. Prevention, timely diagnosis, and early initiation of treatment are important in patients with diabetes mellitus. Many of the complications associated with diabetes such as nephropathy, retinopathy, neuropathy, cardiovascular disease, stroke, and death can be delayed or prevented with early and appropriate treatment of elevated blood sugar, blood pressure, and blood lipids. Based on aetiology, diabetes is presently classified as type 1 diabetes, type 2 diabetes, diabetes due to other illness and gestational diabetes. At present there has been wide acceptance of the WHO criteria (1997) for the diagnosis of diabetes on the basis of fasting plasma glucose and modified oral glucose tolerance test. Of late; estimation of HbA1c has been proposed by experts to diagnose and screen diabetes. The lack of availability of HbA1c testing in more remote or underserved areas, the cost of the test and lack of standardisation of the test are of legitimate concern. There is uniform agreement that earlier the diabetes is diagnosed and measures taken, the greater is the benefit of the patient.

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9.5 Lifestyle Modifications in Management of Diabetes

BK Sahay

INTRODUCTION

Lifestyle measures which combines increased physical activity and dietary modifications are an important component in the management of both type 1 and type 2 diabetes mellitus (DM). The role of exercise in the control of DM has been known since ages. Our ancient ayurvedic physicians Sushruta and Charaka stressed on the role of exercise in the treatment of DM. Even after the advent of insulin, Joslin emphasised the importance of exercise as one of the basic principles of management of diabetic patients. All major guidelines for diabetes management recommend lifestyle changes as part of the standard treatment in all patients of DM.

DIETARY THERAPY

The goal of dietary therapy is to provide a nutritionally balanced diet to maintain the ideal body weight (IBW) of the patient to achieve good glycaemic control along with correction of the dyslipidaemia. The dietary planning is based on the type of diabetes, weight of the patient, activity profile, and presence of co-morbid conditions.

Dietary macronutrient composition is one of the important consideration for the dietary therapy in diabetes. Studies have shown that higher intakes of saturated and trans-fats are associated with an increased risk of diabetes, whereas higher intake of mono-unsaturated and poly-unsaturated fats is associated with decreased risk of diabetes. The importance of consuming minimally processed foods with low glycaemic index and glycaemic load is recommended in the management of diabetes. Whole grain products such as whole wheat breads, brown unpolished rice, oats, and barley tend to produce lower glycaemic and insulinaemic responses than highly processed refined grains. Such unprocessed whole grains are also rich in fibre, antioxidants, vitamins, and phytochemicals.

The calorie requirements are calculated for each individual (**Table 1**) based on his weight and physical activity. These are distributed into three principal meals and two snacks. The calories are derived mainly from carbohydrates 50% to 60%, 20% from proteins and 20% from fats. The carbohydrates should be of low glycaemic index and should be rich in fibre, the source of fat should be 7% each of saturated mono- and poly-unsaturated fats. Three percent of total energy should be derived from essential fatty acids. Cholesterol intake should be less than 300 mg per day. With regard to fat in the diet, one should take into account the invisible fat in the diet derived from cereals and legumes and milk products which nearly contributes to 50% of the required fat. As per the choice of oils in the diet, none of the available oils are ideal, however the choice of cooking oil should be as follows: (a) use an oil which has moderate quantity of linoleic acid like groundnut oil, rice bran or sesame, (b) use an oil which has high amounts of linoleic acid like safflower oil, sunflower oil, cotton seed or corn oil along with an oil which has relatively low levels of linoleic acid like palm oil (mix equal quantities or use equal quantities separately), (c) use any of the above oils with alpha-linoleic acid containing oil like mustard oil or soyabean oil. Roughly the oil intake should be half a litre per person per month. The salt intake should be between 5 to 6 g per day. Dietary guidelines are summarised in **Table 2**.

Table 1: Calorie Requirements Based on Activity and Ideal Body Weight (IBW)

Category	Sedentary	Moderately Active	Strenuous Physical Activity
Overweight/Obese	20	25	30
Ideal weight	25	30	35
Underweight	30	35	40

IBW is calculated as (Height in cm -100) x 0.9
Grid for calculating the recommended caloric intake (Kcal/kg/day) based on physical activity and weight of the individual

Table 2: General Guidelines for Diet in Diabetes Mellitus

Energy (Calories)	25 to 30 calories/kg IBW, reduce calories in obese and increase in underweight individuals
Protein	0.8 g/kg body weight, supplement provided for pregnancy, lactation and growth. A small quota of animal proteins—fish, chicken, milk and yoghurt and appropriate food intake recommended, avoid cattle meat and eggs
Fats	20% to 25% of total calories
Saturated	6% to 7% of total calories
PUFA total	6% to 7% of total calories
N6/N3 ratio	1:1 to 4:1
MUFA	6% to 7% of total calories
Cooking oil	0.5 kg/month/person Total fat intake, with cholesterol 300 mg per day
Carbohydrates	55% to 60% of total calories To encourage complex carbohydrates, i.e. mainly whole grain cereals, pulses, beans, vegetables, and salads. Avoid simple and refined carbohydrates like bakery products or deep fried items
Fruits	Fresh fruits up to 400 g per day. Avoid juices
Dietary fibre	30 to 40 g per day preferably from natural sources; avoid loss from refining and processing. Indian diet is rich in fibre and generally does not require addition of fibre supplements
Common salt	Up to 5 to 6 g per day. Reduced intake to 4 g per day in the presence of hypertension, renal failure and hearing problems
Condiments and spices	Provides anti-oxidants, trace elements, minerals, and n-3 fatty acids
Artificial sweetners	Use of saccharin and aspartame in limited quantity is acceptable. Avoid in pregnancy and lactation
Alcohol	Avoid if possible. If not, drastically restrict. It is utilised as fats. 1 g = 7 calories (2 small drinks/one glass of wine/ pint of beer (preferably avoided)
Tobacco	Avoid smoking or its use in any form

Fresh fruits up to 400 grams per day are advisable. Consuming the whole fruit is better than the fruit juice which needs to be avoided. Ideal fruits are citrus fruits, orange sweat lime, guava, apple, papaya and pomegranate. They provide vitamins and fibre. Each one portion contains 40 to 50 calories.

Indian diets traditionally are high in carbohydrate content. There have been concerns expressed regarding difficulty in achieving glycaemic control and an increase in the risk of development of complications with such diets. However, studies from India and Japan have shown that even with diet high in carbohydrate content, good glycaemic control can be achieved without increasing the risk for complications.

EXERCISE THERAPY

Adequate physical activity helps in correcting obesity which is a major modifiable risk factor in type 2 DM. In addition, physical activity may independently enhance insulin sensitivity and glucose tolerance. Exercise increases the skeletal glucose transporter protein GLUT4 which is responsible for insulin independent glucose transport into the skeletal muscle.

Regular physical exercise is associated with changes in body composition with a reduction in body fat and increase in muscle mass, a reduction in triglycerides, increase of high density lipoprotein 2 fraction. Exercise causes a reduction in blood pressure, corrects the endothelial dysfunction and brings about improvement in the fibrinolytic activity. Exercise also induces weight loss and subsequently helps in maintenance of the weight.

To be effective, exercise should be performed regularly. An exercise schedule that is enjoyable and suits the needs of an individual should be chosen. Daily exercise of 30 to 45 minutes is preferable. It should be done on an empty stomach either in the morning or evening. An exercise session should have a warning up and cooling down. Following a session of exercise, there is an increase in insulin sensitivity which returns to baseline after 72 hours of cessation of exercise. This underlies the importance of persistent and regular exercise. Apart from the aerobic exercises (isotonic exercises), resistance training exercises (isometric exercises) are also useful since they increase the muscle mass, particularly in the elderly patients.

Before an exercise programme is initiated a thorough clinical evaluation of the patient should be made particularly in regard to cardiovascular disease, neuropathy, autonomic neuropathy, nephropathy and retinopathy. If any of these is present, suitable precautions and modification should be made in the exercise schedule. Treadmill exercise test should also be performed in all cases in order to detect myocardial ischaemia. A fair degree of glycaemic control has also to be achieved before initiating the exercise programme particularly in patients with type 1 diabetes, wherein exercise done in the background of a poor glycaemic control can precipitate diabetic ketoacidosis (**Table 3**).

Presence of autonomic neuropathy may limit an individual's exercise capacity and increase the risk of adverse cardiovascular events. Hypotension and hypertension are more likely to develop in patients with autonomic neuropathy. These patients have difficulties in thermoregulation and should be advised to avoid exercises in extremely hot or cold environments and to be careful about their hydration.

Hitherto it was thought that exercise should not be recommended for type 1 DM, currently there is enough evidence that regular physical exercise helps in improving the insulin sensitivity as well as cardiovascular risk factors.

Table 3: Summary of Exercise Recommendations for Patients with Type 2 Diabetes Mellitus

Screening	Search for vascular and neurological complications including silent ischaemic heart disease Stress electrocardiogram in patients >35 years of age or >10 years of diabetes
Exercise programme and type	Aerobic Resistance Yogic practices
Intensity	50% to 70% of maximum aerobic capacity
Duration	20 to 60 minutes with warm up and cool down
Frequency	Ideally daily or at least 5 times a week
Avoid complications	Careful selection of exercise type and intensity Patient education Monitoring of blood glucose by patient and overall programme by medical personnel
Compliance	Make exercise enjoyable Convenient location

Many of the elderly patients tend to avoid physical exercise. However, with increasing age there is a progressive decline in insulin sensitivity, muscle mass and strength and loss of mineral from bones. Regular physical exercise can prevent and reverse these changes. Exercise also improves the quality of life in the elderly diabetics.

Upper body exercises should be routinely recommended for diabetic subjects with arthritis. Pregnant women with diabetes should also be advised walking and if this is not possible they should be advised upper body exercises.

For cardiovascular conditioning, the exercise intensity in healthy adults should be such that 75% to 90% of the target heart rate (THR) is achieved for at least 15 minutes (THR = 220-Age). However, for the diabetic subjects, the intensity of the exercise should achieve 50% to 70% of THR.

Missing exercise for more than 72 hours may increase the blood glucose by 80 to 100 mg in subjects on oral hypoglycaemic agents (**Table 4**).

Table 4: Caloric Expenditure in a 60 kg Individual Performing Various Forms of Exercise for 60 Minutes

Type of Exercise	Caloric Expenditure
Aerobics	450+
Cycling, moderate	450+
Jogging (5 m per hour)	500
Gardening, digging	500
Skipping with rope	700+
Running	700+
Swimming, active	500+
Walking (3 m per hour)	280
Table Tennis	290
Gardening	350
Tennis	350+

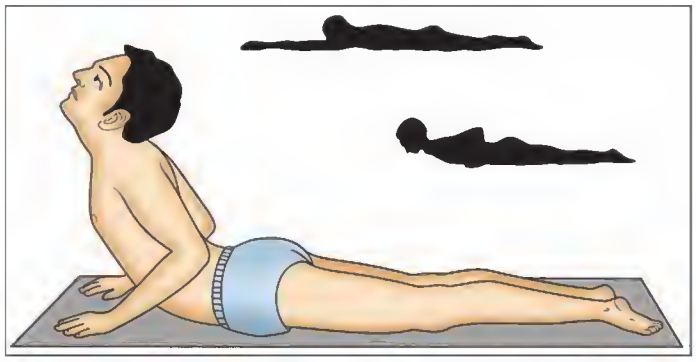


Figure 1: *Bhujangasana.*

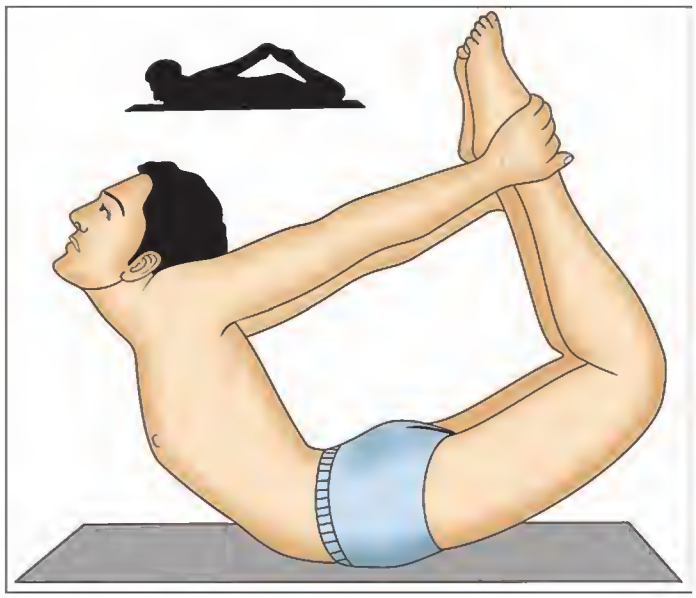


Figure 2: *Dhanurasana.*

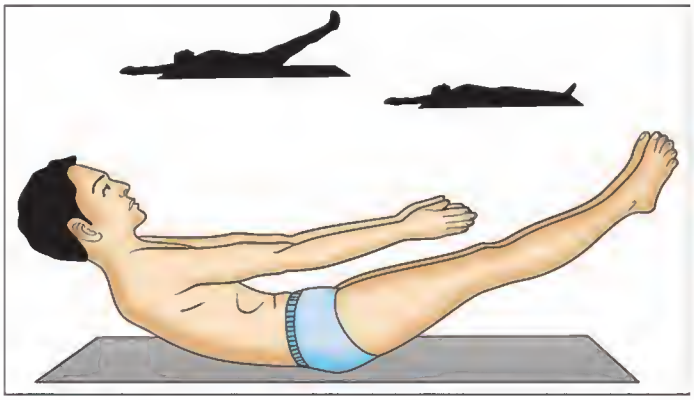


Figure 3: *Naukasana.*

ROLE OF YOGIC PRACTICES

Several recent studies have documented the beneficial effect of yogic practices in both type 2 and type 1 DM yogic practices improve glycaemic control, reduce blood pressure, correct dyslipidaemia, reduce insulin resistance and eliminate stress leading to effective control of diabetes and prevention of its long-term complications. Some of the common yogic exercises are shown in (**Figures 1 to 6**).



Figure 4: *Ardha Matsyendrasana.*

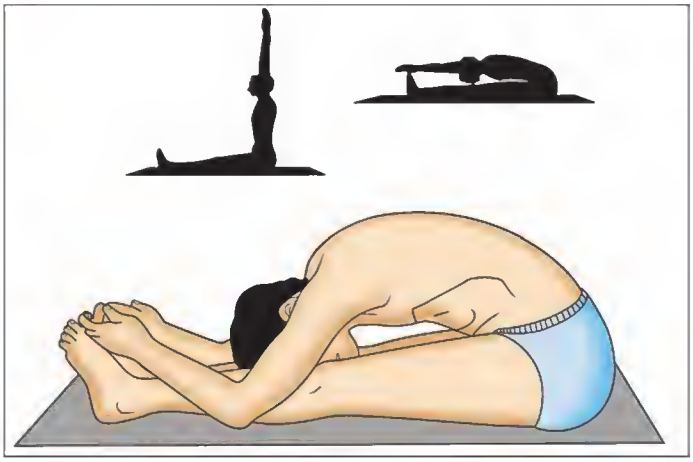


Figure 5: *Paschimotasana.*

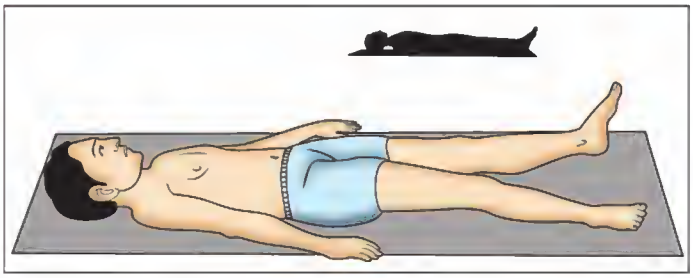


Figure 6: *Shavasana.*

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1. Lifestyle Changes in Management of Diabetes Mellitus in the Indian Diabetes Guidelines. *J Assoc Physicians of India* 2002; 50.
2. Management of diabetes mellitus: exercise and yoga. In: Ahuja MMS, Tripathi BB, Moses SGP *et al*, editors. *RSSDI Textbook of Diabetes Mellitus*. Research Society for Study of Diabetes in India 2002; 369-78.

9.6 Oral Anti-Diabetic Drugs

Anil Bhansali, Viral Shah

INTRODUCTION

Oral anti-diabetic drugs (OADs) have been used for more than five decades in the management of type 2 diabetes mellitus (T2DM). T2DM is characterised by insulin resistance and insulin deficiency. Therefore, there are two main classes of drugs, one which decreases insulin resistance and the other which increase insulin secretion. The basic mechanism and target organs have been illustrated in **Figure 1**. This chapter gives an overview of different OADs and their brief details.

HISTORICAL PERSPECTIVE

The quest for oral anti-diabetic agent began in the backdrop of the discovery of insulin. Lacklustre introduced guanidine derivative, synthalin A, in 1926 that marked the journey of OADs. It was serendipity when chemist Marcel Janbon and co-workers, who were studying sulphonamide antibiotics, discovered that the compound sulphonylurea can induce hypoglycaemia in animals. Sulphonylurea was first discovered by Frank and Fuchs but later on withdrawn from market due to bone marrow suppression. Subsequently, number of drugs came in the market. First synthesis of dimethylbiguanide (metformin) is attributed to Werner and Bell in 1922 and it was Sterne's work that studied mechanism of metformin in great detail and popularised it. Thiazolidinediones were discovered in late 1970s when lipid lowering drug ciglitazone was found to possess hypoglycaemic effects. Acarbose was isolated in 1975 from the strains of actinoplanes species and synthesised in laboratory in 1988 and found to be the inhibitor of alpha-glucosidase.

CLASSIFICATION OF ORAL ANTI-DIABETIC DRUGS

1. Agents stimulating insulin release (secretagogues)
   - A. Sulphonylureas
     - (a) First generation: chlorpropamide and tolbutamide
     - (b) Second generation: glibenclamide, glipizide and gliclazide
     - (c) Third generation: glimepiride
   - B. Non-sulphonylureas
     - Meglitinides: repaglinide and nateglinide
   - C. GLP-1 analogues
     - Exenatide and liraglutide
   - D. DPP-IV inhibitors
     - Sitagliptin, vildagliptin and saxagliptin
2. Agents lowering insulin resistance (sensitisers)
   - A. Biguanides: phenformin and metformin
   - B. Thiazolidinediones: pioglitazone and rosiglitazone
3. Agents reducing carbohydrate absorption
   - A. Alpha-glucosidase inhibitors: acarbose, voglibose and miglitol
4. Agents decreasing renal reabsorption of glucose
   SGLT-2 inhibitors

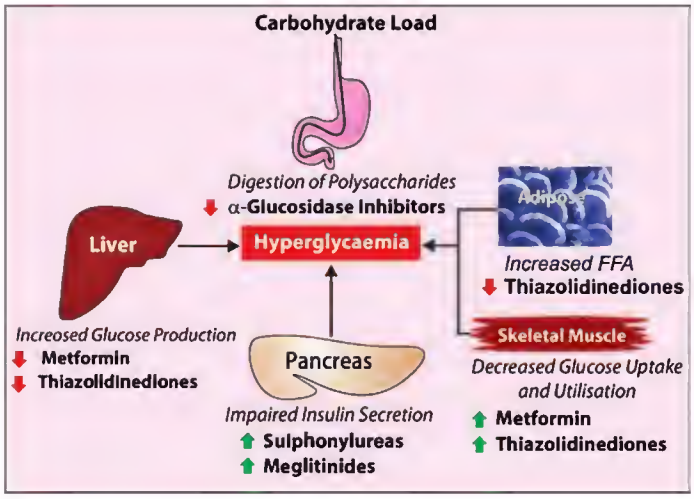


Figure 1: Site of action of different OADs.

SULPHONYLUREA

Structure

Basically sulphonylureas have a benzene ring plus sulphonyl group plus urea. Differences in the para position of the benzene ring and in addition of a group to the urea results in different sulphonylurea compounds.

Mechanism of Action

Insulin secretion is regulated by an ATP dependent K^+ channel located in the plasma membrane of the β cell. Under fasting conditions, most of the channels are open, and K^+ is actively extruded from the β-cell. When the plasma glucose rises, glucose is transported into the β-cell through GLUT receptor and phosphorylated by glucokinase enzyme. This results in the formation of ATP from ADP. Increase ATP/ADP ratio cause ATP dependent K^+ to close resulting into depolarisation of cell. Voltage dependent Ca^{2+} channel opens and calcium moves from extracellular space to β-cell cytosome causes the insulin granule to migrate to cell surface whereas its contents are released by exocytosis. ATP dependent K^+ channel consists of two subunits named SUR which is the binding site for various sulphonylurea drugs, other is KIR channel. The potency of sulphonylurea is a function of its binding affinity to the SUR receptor (**Figure 2**).

Indications

Sulphonylureas are drugs of choice after lifestyle modification and metformin fails to achieve glycaemic target. However, when A1c is more than 9%, sulphonylureas are usually to be started in combination with metformin. Good responders to sulphonylureas include: (a) short duration of diabetes, (b) normal weight subjects, (c) fasting plasma glucose less than 200 mg/dL, and (d) preserved β-cell mass.

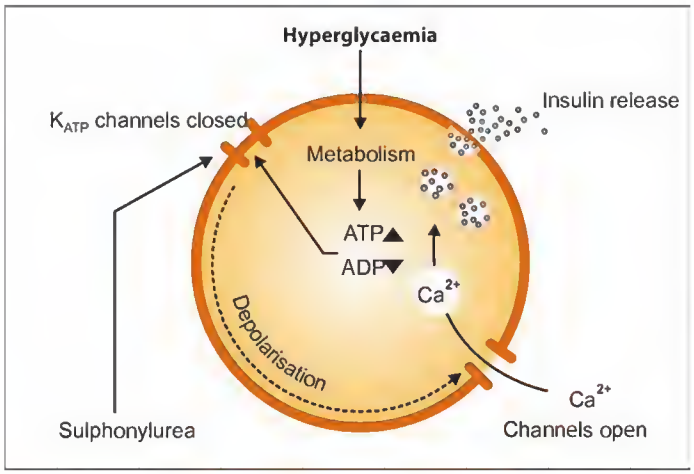


Figure 2: Mechanism of action of sulphonylureas.

secondary failure are dietary indiscretion, lack of physical activity, intercurrent illness and declining β-cell function.

NON-SULPHONYLUREA SECRETAGOGUES

Structure

The meglitinide analogues are non-sulphonylurea compounds derived from the benzimido non-sulphonylurea portion of glibenclamide. **Table 2** shows the differences between sulphonylureas and non-sulphonylureas.

Mechanism of Action

Mechanism of these agents are similar to that of sulfonylureas but they bind to a site on the SUR 1 sub unit of the β-cell ATP dependent K^+ channel that is different from the binding site for sulfonylureas.

Characteristic of Each Agent

Repaglinide is a carbamoylmethyl benzoic acid derivative, which can be safely used in patients with renal failure. Nateglinide is a derivative of phenylalanine and very rapid acting insulin secretagogue. Its rate of association and dissociation are much more rapid. It has very low binding affinity for cardiovascular ATP dependent K^+ channels.

These agents are generally indicated for the control of post-prandial hyperglycaemia alone or as an adjuvant treatment with other anti-diabetic agents. Their use is contraindicated in hepatic insufficiency and pregnancy.

Table 1: Characteristics of Different Oral Anti-Diabetic Agents

Drug	Dose Range (mg)	Peak Level (hours)	Half-life (hours)	Duration of Action (hours)	Route of Excretion	Reduction in A1c
Sulphonylureas						
Tolbutamide	500 to 3,000	3 to 4	4.5 to 6.5	6 to 12	Kidney	1% to 2% with almost all agents
Chlorpropamide	100 to 500	2 to 4	36	Up to 60	Kidney	
Tolazamide	100 to 1,000	3 to 4	7	10 to 14	Kidney	
Glipizide	2.5 to 40	1 to 3	2 to 4	8 to 10	Kidney 80%, faeces 20%	
Glyburide (Glibenclamide)	1.25 to 20	~4	10	10 to 24	Kidney 50%, faeces 50%	
Gliclazide	40 to 240	3 to 4	6 to 15	Up to 20	Kidney 70%, bile 30%	
Glimepiride	1 to 8	2 to 3	9	12 to 24	Kidney 60%, faeces 40%	
Non-sulphonylurea secretagogues						
Repaglinide	0.5 to 4	1	1 to 2	3 to 4	Faeces	0.5% to 1%
Nateglinide	60 to 120	1.8	1 to 2	3 to 4	Kidney 80%, faeces 50%	
Biguanide						
Metformin	500 to 2,500	—	1.5 to 2.8	6 to 8	Kidney	1% to 2%
Thiazolidinediones						
Pioglitazone	15 to 45	—	3 to 7	24	Kidney 35%, faeces 30%	0.5% to 2%
Rosiglitazone	2 to 8	—	3 to 4	12 to 14	Kidney 70%	
Alpha-glucosidase inhibitors						
Acarbose	50 to 300	—	—	—	GIT	0.5% to 1%

Pharmacokinetic properties of different OADs are given in **Table 1**. Adverse effects, contraindications and drug interactions of different OADs are listed in **Table 3**. Commonly used drugs which can enhance the effect of OADs are listed in **Table 4**.

Primary Sulphonylurea Failure

For unknown reasons, not all T2DM patients respond to the anti-diabetic action of sulphonylureas and this is known as primary sulphonylurea failure.

Secondary Sulphonylurea Failure

Most patients of T2DM who respond very well initially may have a loss of effective anti-diabetic response after several years of treatment and this is known as secondary sulphonylurea failure. In the United Kingdom Prospective Diabetes Study (UKPDS), treatment with sulphonylureas achieved an A1c less than 7% in 50% of patients at three years, 34% at six years and 24% at nine years. Six and nine year data from the UKPDS showed that this secondary failure is a characteristic of all anti-diabetic treatments and not just sulphonylureas. Still, the term secondary sulphonylurea failure remains in clinical practice. Secondary failure is usually considered as a good initial response to the oral glycaemic agents for at least 1 month. The causes of this

Table 2: How Non-Sulphonylureas Differ from Sulphonylureas?

Sulphonylureas	Non-Sulphonylureas
Act on SUR1 K^+ channel	Act on different channel
Intermediate or long acting	Short acting
To be taken before meal	Taken along with meal
Major effect to decrease FPG and modestly PPG	Mainly reduce PPG
Hypoglycaemia is common	Hypoglycaemia is rare
A1c reduction is good (1% to 2%)	Modest A1c reduction (0.5% to 1%)
Weight gain is a problem	Less weight gain

Table 3: Contraindication, Adverse-events and Drug Interactions of Different OADs

Drug	Contraindications	Adverse Effects	Drug Interactions
Sulphonylureas	(a) T1DM Pregnancy Major surgery Severe infections	Hypoglycaemia Weight gain Hypersensitivity reaction (rare) ? Concern about cardiovascular ill-effects	Drugs increase hypoglycaemic response: aspirin, fibrates, alcohol, H2 blockers, allopurinol, probenecid Drugs decrease hypoglycaemic effects: barbiturate, rifampicin, steroid, oestrogen, phenytoin, β-blockers
	(b) Hypersensitivity to sulpha compounds Significant liver or kidney disease	Chlorpropamide causes hyponatraemia	—
Non-sulphonylurea secretagogues	Renal and liver disease	Hypoglycaemia and weight gain less common than sulphonylureas	Drugs increase repaglinide metabolism: rifampicin, barbiturate, carbamazepine Drugs decrease metabolism: antifungal, erythromycin NSAIDs, and sulphonamides may increase its action
Biguanide	Serum creatinine >1.5 mg/dL in males and >1.4 mg/dL in females. Hepatic dysfunction Congestive heart failure (CHF) class- III, IV Alcohol abuse/binge drinking. Acute or chronic metabolic acidosis Relative contraindications are acute myocardial infarction, pregnancy, and severe infections. It should be withheld 24 hours prior to radiological procedure requiring contrast agent and surgery	Nausea, vomiting, dysgeusia, occasional diarrhoea, lactic acidosis and B12 deficiency are rare	Cimetidine increases the metformin level Nifedipine enhances absorption
Thiazolidinediones	Liver disease (AST >3 times), CHF requiring treatment (class III and IV)	Weight gain, oedema, precipitation of CHF, hepatotoxicity (rare), anaemia decrease bone mineral density	Rosiglitazone metabolised by CYP2C8 and pioglitazone by CYP3A4, hence, drugs metabolised by this pathway may interfere with its level
Alpha-glucosidase inhibitors	Inflammatory bowel disease, gastroparesis, serum creatinine >2 mg/dL	Flatulence, diarrhoea, abdominal discomfort, and distension	May increase level of sulphonylureas Resin and antacid decrease the effect

Table 4: Drugs which Enhance the Effect of OADs Causing Hypoglycaemia

Drugs with Moderate-Quality Evidence	Drugs with Low-Quality Evidence
Gatifloxacin	Artesunate/artemisinin/artemether
Glucagon	Chloroquine, oxaline, sulphonamide
Indomethacin	IGF-I
Pentamidine	Lithium
Quinine	Propoxyphene and dextropropoxyphene

BIGUANIDES

Structure

Metformin is chemically 1,1-dimethylbiguanide, derived from herb *Galega officinalis*.

Mechanism of Action

Metformin decreases hepatic glucose production, principally due to reduced gluconeogenesis and also through reduced glycogenolysis, and thus, its main effect is reduction in fasting plasma glucose. At therapeutic concentrations, metformin suppresses hepatic gluconeogenesis by potentiating the effect of insulin and increasing the activity of activated protein kinase (AMP). It can also reduce hepatic extraction of lactate. The rate of glycogenolysis is decreased by reducing the effect of glucagon and impeding the activity of hepatic glucose 6-phosphatase. Insulin-mediated glucose uptake is also enhanced by metformin. Metformin increases the translocation of insulin sensitive GLUT4 into the cell membrane. It also suppresses fatty acid oxidation and reduces triglycerides. It also increases glucose turnover particularly in the splanchnic bed which may benefit both glucose lowering and weight stabilising effect.

Indication of metformin as per American Diabetes Association (ADA) guideline is 'it is to be given in all T2DM patients in absence of contraindications'.

THIAZOLIDINEDIONES

Mechanism of Action

The thiazolidinediones were found to be ligands for an orphan receptor known as peroxisome proliferator-activated receptor

gamma (PPAR-γ). This receptor is a member of the nuclear receptor superfamily of ligand-activated transcription factors. The specific genes that are PPAR-γ responsive are lipoprotein lipase, fatty acid-binding proteins and, PEPCK which regulates lipid metabolism, insulin action, and adipose tissue differentiation. The major pharmacological action includes; increased insulin mediated glucose uptake in muscle and to increase adipogenesis. The beauty of this class of drugs is that it increases subcutaneous fat and not the visceral, and hence, despite increase in adipogenesis it increase insulin sensitivity. It converts the larger adipocyte into smaller one. These convert small dense LDL into large LDL, increases HDL, decreases TG, decrease plasma free fatty acids. Their vascular actions include; improve endothelial dysfunction, reduce peripheral resistance, decrease plasma fibrinogen and PAI-1, and thus, improve procoagulant state, decrease carotid intima media thickness. These are also shown to have inhibitory effect on neo-intimal proliferation after coronary stent. These also have shown to reduce β-cell loss.

Rosiglitazone is surrounded with recent controversies. This drug is found to increase cardiovascular mortality and also increase in incidence of atypical bone fracture due to decrease in bone mineral content.

Indication

These can be used as mono-therapy or in combination with other drugs in type 2 DM patients. These are more useful in patients with insulin resistance.

ALPHA-GLUCOSIDASE INHIBITORS

Mechanism of Action

Alpha-glucosidase inhibitors are competitive suppressants of small intestine brush border α-glucosidases, which are essential to hydrolyse disaccharides, oligosaccharides, and polysaccharides to monosaccharides. Therefore, carbohydrate absorption and digestion is delayed and prolonged resulting in lowering of postprandial hyperglycaemia. These agents do not interfere in absorption of lactose as they require β-glucosidase (lactase) for their digestion. Furthermore, these increase the secretion of GLP-1 and decrease secretion of GIP, significance of which still remains elusive.

Indication

These can be used in both type 1 DM and type 2 DM. However, their main use is to treat postprandial hyperglycaemia. It can delay the progression of IGT to diabetes, and hence, can be used to treat IGT. These can be used in combination with other drugs to achieve glycaemic control.

ADVERSE EVENTS

The side effects, contraindications and drug interactions are summarised in **Table 3. Table 4** gives a list of drugs which potentiates effect of OAD and induce hypoglycaemia.

Cardiovascular Safety of OADs

Cardiovascular safety has become hot issue after a meta-analysis by Nissen in May 2007. He showed increased risk of myocardial infarction with rosiglitazone. Since then FDA warned that it is mandatory for all anti-diabetic drugs to establish their cardiovascular safety. Among thiazolidinediones, rosiglitazone but not the pioglitazone is associated with high cardiovascular risk. The large, pro active study clearly demonstrated the cardiovascular safety of pioglitazone. Older studies, beginning in the 1970s with the University Group Diabetes Programme trial have suggested that diabetic patients receiving sulphonylureas were at increased cardiovascular risk compared with diabetic patients who did not receive such medications. Therefore, it was believed that sulphonylureas particularly glibenclamide through SUR1 receptor on cardiac myocyte can adversely affect the ischaemic preconditioning. However, in the United Kingdom Prospective Diabetes Study (UKPDS), treatment with sulphonylureas was not associated with increased risk of cardiovascular morbidity and mortality. Furthermore, a number of studies did not show any adverse cardiovascular effect of newer sulphonylureas. Metformin is the only drug shown to reduce cardiovascular morbidity and mortality. A meta-analysis of eight different trials showed no increase in cardiovascular mortality with the use of acarbose.

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9.7 Insulin Therapy

Rama Walia

Insulin is one of the oldest, best studied and most effective treatment for diabetes. Insulin therapy is a must and life saving for patients with type 1 diabetes while many patients with advanced duration of type 2 diabetes also require insulin therapy for optimal glycaemic control. Insulin was discovered by an orthopaedic surgeon, Frederick G. Banting (**Figure 1**) who was assisted by a medical student Charles H. Best (**Figure 2**). The first clinical trial took place on January 1922 on a patient, Leonard Thompson. The rest is history of success of insulin.

PHYSIOLOGY OF INSULIN SECRETION

Insulin is a two chain polypeptide having 51 amino acids (**Figure 3**). A-chain has 21 amino acids while B-chain has 30 amino acids. Insulin is secreted in a pulsatile manner. There are rapid oscillations occurring every 8 to 15 minutes that are superimposed on slower oscillations occurring at a rate of once per 80 to 150 minutes. Fifty per cent of total insulin secreted by pancreas is secreted under basal conditions and the remainder is secreted in response to meals as postprandial bursts.

Under basal conditions insulin secretion rate is 0.5 to 1 U/h. After food intake insulin is released in two phases. First phase is transient (2 to 5 minutes) followed by a second phase in which there is progressive increase in insulin secretion for 5 to 52 minutes.

INSULIN PREPARATIONS

Initially commercial preparations of insulin were derived from beef and pork pancreas. In 1980s, human insulins were produced by recombinant deoxyribonucleic acid (DNA) technology in *Escherichia coli* and yeast. In 1990s, insulin was genetically engineered to produce various insulin analogues.

Conventional Insulin

Regular insulin is short-acting soluble crystalline zinc insulin. Regular insulin been modified by adding zinc with or without protamine to retard its absorption and prolong the duration of action, e.g. neutral protamine Hagedorn (NPH) or isophane insulin which is an intermediate acting insulin.

Insulin Analogues

The self association of insulin molecules in a hexamer leads to slow absorption with a lag period of 30 to 60 minutes. With recombinant DNA technology, rapid acting insulin analogues have been synthesised which remain in monomeric form and are, therefore, rapidly absorbed, e.g. insulin lispro, insulin aspart, and insulin glulisine. The action profile and structural change of various insulin preparations are shown in **Table 1**. The use of rapid acting insulin analogues allows more flexibility and convenience as these are to be injected only 5 to 15 minutes prior to meals, although overall glycaemic control may not improve as assessed by HbA1c. Because of the shorter duration of action than regular insulin (**Table 1**), the incidence of post-absorptive hypoglycaemia is decreased by almost 25% thereby reducing the requirement for inter-prandial snacking.

Currently available long-acting insulin analogues include insulin glargine and insulin detemir (**Table 1**). Insulin glargine has a pH of 4 and it makes microprecipitates in subcutaneous tissue from which insulin is slowly released. Insulin detemir is designed to bind albumin in plasma after absorption (**Table 1**). These alterations result in prolonged duration of action with little peak activity thereby reducing the incidence of hypoglycaemia. Additionally, weight gain associated with insulin therapy may be avoided particularly with insulin detemir. This probably



Figure 1: Dr. Frederirk G. Banting.



Figure 2: Dr. Charles H. Best.

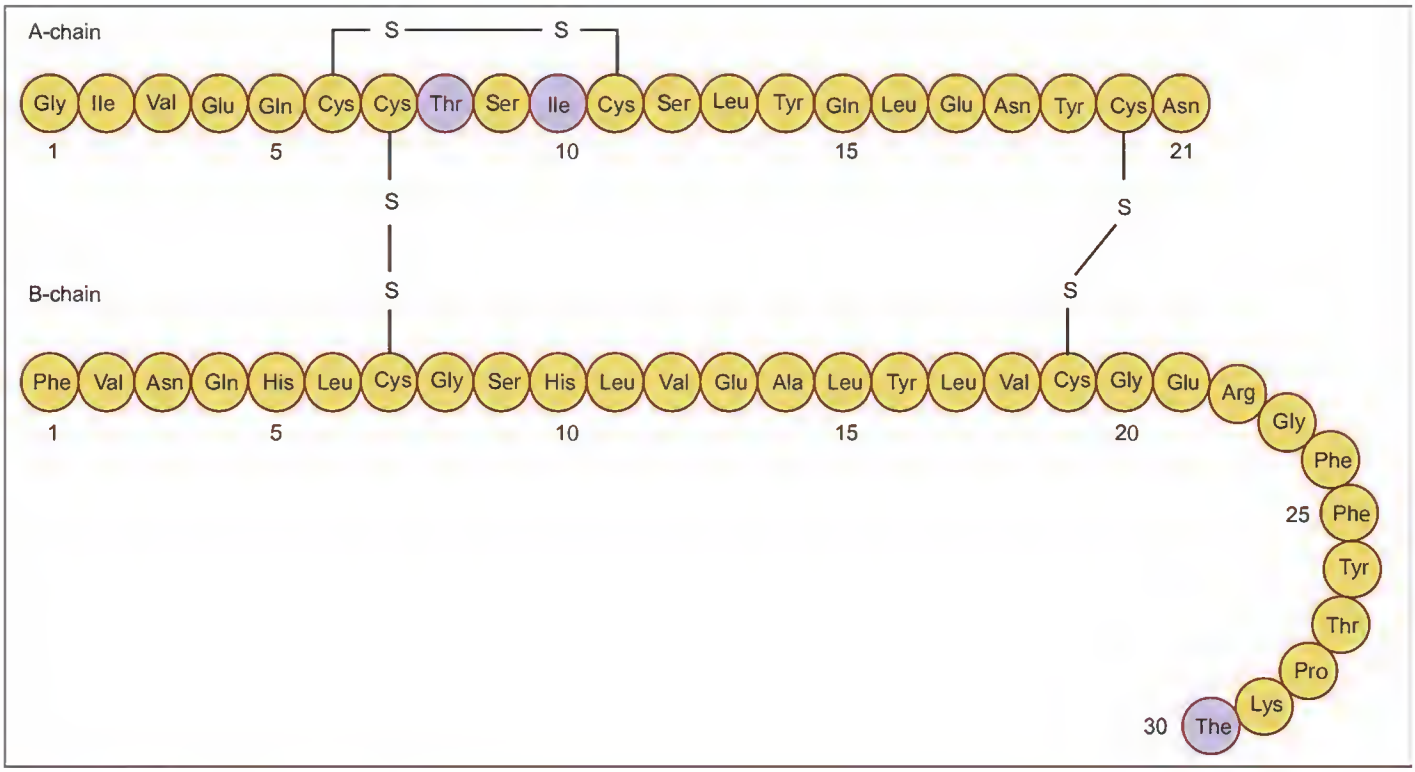


Figure 3: Amino acid sequence of human insulin.

Table 1: Action Profile of Various Insulin Preparations

Insulin Preparations	Structural Change	pH	Onset (h)	Peak (h)	Duration (h)
	Conventional insulin				
Short-acting insulin					
Regular insulin(human)	—	N	0.5 to 1	2 to 3	6 to 8
Intermediate-acting insulin					
Neutral protamine Hagedorn, NPH (human)	Addition of protamine	N	1.5	4 to 10	16 to 24
	Insulin analogues				
Rapid-acting insulin					
Lispro	Lysine-proline conversion in B-chain	N	0.2 to 0.5	0.5 to 2	3 to 4
Aspart	Aspartic acid for proline substitution in B-chain	N	0.2 to 0.5	0.5 to 2	3 to 5
Glulisine	Lysine for asparagine substitution in B-chain	N	0.2 to 0.5	1	4
Long-acting insulin					
Glargine	Glycine for asparagine substitution in A-chain and a prolonged B-chain	4	2 to 4	none	20 to 30
Detemir	Acylation of lysine in B-chain with saturated fatty acid	N	1 to 2	none	20

N= Neutral

happens due to less snacking as hypoglycaemias are reduced and secondarily due to a selective appetite modulating effect of insulin detemir.

Insulin lispro and insulin aspart are approved for use during pregnancy and marginally reduce glycosylated haemoglobin (HbA1c) as well as incidence of hypoglycaemia with no differences in gestational outcome when compared with human regular insulin. Insulin detemir and insulin glargine are still not approved for their use during pregnancy. Patients having significant hyperglycaemia require higher proportion of short/ rapid acting insulin.

Indications for Insulin Therapy

Insulin therapy is a must and life saving in patients with type 1 diabetes. Therefore, omission of insulin in these patient is suicidal. Insulin therapy is also treatment of choice for gestational diabetes mellitus. Indications for insulin therapy in patients with type 2 diabetes at diagnosis include fasting plasma glucose >250 mg/dL, HbA1C >10%, patients having severe osmotic symptoms, and weight loss and/or ketosis. During follow-up, insulin is to be initiated if patient has inadequate glycaemic control (HbA1c >7%) on maximal doses of two or more oral anti-diabetic drugs. Insulin also

needs to be started during inter-current illness and patients undergoing surgery.

TIMINGS AND DOSAGES OF INSULIN THERAPY

Short-acting regular human insulin needs to be injected 30 to 60 minutes prior to meals while rapid acting insulin analogues can be injected 5 to 15 minutes prior to meals. However, if pre-prandial plasma glucose is higher, then short-acting analogues are to be injected 30 minutes prior to meal to achieve adequate glycaemic control. If required, in case of children and in patients with gastroparesis these can be injected even after meals.

Insulin NPH is to be injected once or twice a day usually with regular insulin 30 minutes prior to meals. In basal bolus regimen, it can be drawn in the same syringe containing regular insulin with out change in efficacy or pharmacokinetics reducing the number of injection. In this way, peak action of NPH insulin takes care of post-lunch hyperglycaemia. Similarly, the night dose of NPH insulin can be injected before dinner along with regular insulin. However, if the total dose of insulin being injected at one time exceeds 30 units, then regular and NPH insulins need to be injected at separate sites. If a patient develops nocturnal hypoglycaemia, then along with reducing the night dose of insulin, the timing of the NPH insulin can also be shifted to 10 p.m. so that the peak activity of the NPH insulin overlaps with the early morning surge of counter-regulatory hormones thereby avoiding hypoglycaemia.

Insulin glargine can be given once a day at fixed time, usually at 8 pm or 8 am Insulin detemir needs to be injected twice a day at fixed timings, e.g. 8 am and 8 pm, as its duration of action is around 20 hours. Long-acting analogues cannot be mixed with rapid/short-acting insulins.

In patient having mainly fasting hyperglycaemia, intermediate or long-acting insulin can be injected at 10 pm It is convenient and improves glycaemic control with lesser weight gain. The dose can be modified according to fasting plasma glucose (FPG) every third day. If post-prandial glycaemic control remains inadequate, short/rapid acting insulin is to be added either in form of pre-mixed preparation insulin or as basal bolus regimen. At this time insulin secretagogues should be stopped. Patients with FPG less than 200 mg/dL can be managed with pre-mixed insulin injected twice a day before meals. The usual preparation used is 30:70 or 25:75 ratio of short/rapid acting insulin to intermediate acting insulin. Higher percentage of short/rapid acting insulin (50%) is sometimes required to control post-prandial hyperglycaemia. Usually 50% to 70% of the required daily dose is injected before breakfast and 30% to 50% is injected before dinner. If required short/rapid acting insulin can be injected prior to lunch to control post-lunch hyperglycaemia. If FPG is more than 200 mg/dL, then the patient needs to be started on basal bolus regimen which means short/rapid acting insulin being injected prior to meals while intermediate/long-acting insulin injected separately at timings as described before. In this each component of insulin therapy can be manipulated separately according to individual requirement but at the cost of increased number of insulin injections. Insulin dose can be modified according to the rough 1,500 rule. 1,500/total insulin dose per day is equal to the effect of 1 unit of insulin on blood glucose in mg/dL. Insulin dosage needs to be individualised in each patient to achieve satisfactory glycaemic control. The reader is referred to chapter 7 Insulin Therapy in management diabetic ketoacidosis.

Site and Technique of Injection

Conventionally, insulin is injected with syringe subcutaneously in anterior abdominal wall. Other sites like arms and thighs are not preferred because of erratic absorption, especially if patient undertakes any physical activity leading to increased blood flow to the limb and hence rapid absorption of the insulin. After raising a skin fold the injection must be given perpendicular to the skin in obese individuals and at 45 degrees in thin patients. The site of injection must be rotated to avoid lipodystrophy.

Insulin vials are available in two strengths, namely 40 and 100 units per mL. One should be careful that the 'number' of units/mL on insulin vial must match the 'number' of units/mL on insulin syringe. Insulin pen devices are certainly user-friendly and convenient to carry. Insulin needs to be stored in refrigerator at 2 to 8 degree Celsius.

GLYCAEMIC TARGETS

The targets for fasting and post-prandial plasma glucose are 70 to 130 mg/dL and <180 mg/dL, respectively for adult population according to American Diabetes Association (ADA). The HbA1c needs to be targeted <6.5% to 7%. Glycaemic targets for children are described in **Table 2**. The goals need to be individualised, depending on the age of the patient, associated co-morbidities, and the risk of hypoglycaemia.

Table 2: Glycaemic Targets in Paediatric Age Group

Age (year)	Plasma Glucose (mg/dL)		HbA1c
	Before Meals	Bedtime	
<6	100 to 180	110 to 200	<8.5% but >7.5%
6 to 12	90 to 180	100 to180	<8%
13 to 19	90 to 130	90 to 150	<7.5%

Self Monitoring of Blood Glucose on Insulin Therapy

Patients on insulin therapy need to monitor blood glucose three or more times daily as recommended by ADA. The blood glucose is monitored pre-prandially to adjust insulin dosage. If HbA1c still remains high then post-prandial blood glucose needs to be targeted to achieve desired HbA1c.

INSULIN DELIVERY DEVICES

Conventionally, insulin is injected subcutaneously with the help of syringe. Pen devices have the advantage of hidden needles and convenience. Continuous subcutaneous insulin infusion (CSII) with insulin pump is another option. In this, rapid-acting insulin provides basal as well as prandial cover. This improves glycaemic control with decreased incidence of hypoglycaemia while reducing the number of pricks. Non-invasive insulin delivery includes use of inhaled insulin, buccal spray, and in form of tablets. The absorption of inhaled insulin starts immediately as that of rapid-acting insulin analogues but its duration of action is similar to regular insulin. In smokers, the bronchial tumour rate under inhaled insulin seems to be increased. With buccal spray device, insulin

particles get deposited in buccal cavity while oral insulin is in tablet form and delivers insulin to gastro-intestinal tract. The bioavailability of these preparations is approximately 10% and these mimic rapid-acting insulin in onset and duration of action. Other investigational routes of delivery include transdermal iontophoretic transport, powdered insulin delivery though skin using helium gas, liposome based formulation for insulin delivery, etc.

Adverse Effects of Insulin Therapy

The commonest problem with insulin therapy is hypoglycaemia (blood glucose <70 mg/dL) and weight gain. Risk factors for hypoglycaemia include-mismatched insulin syringe, mismatched meal timings, unusually vigorous exercise, impaired ability to defend against hypoglycaemia and hypoglycaemia unawareness in patients with autonomic neuropathy. Weight gain happens partly due to improved glycaemic control and partly due to inter-prandial snacking to avoid hypoglycaemia. These can be reduced by carefully titrating insulin therapy and educating the patient about it. Lipoatrophy, lipohypertrophy, and insulin allergy is rare now-a-days because of the availability of purified insulins.

Although there were some reports of association of increased risk of malignancies with insulin glargine but other studies have refuted it. This can be due to its higher affinity to IGF-1 receptor which determines the mitogenicity of insulin. However, insulin glargine is still not approved for pregnant patients and children less than six years of age.

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9.8 Newer Modalities of Treatment in Type 2 Diabetes Mellitus

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INTRODUCTION

Type 2 diabetes mellitus is characterised by multiple metabolic abnormalities that result in hyperglycaemia. These include obesity, insulin resistance in skeletal muscle, adipose tissue and liver, increased hepatic production of glucose, and dysfunction of the islet cells of the pancreas. Islet cell abnormalities include qualitative and quantitative defects of insulin secretion from β-cells and dysregulated glucagon secretion from α-cells. It has also been shown that patients with type 2 diabetes have an impaired incretin effect. These multiple metabolic abnormalities lead to persistent hyperglycaemia unless intervened, results in the long-term complications of type 2 diabetes including micro- and macrovascular diseases. These long-term complications, in turn, cause considerable morbidity, and are associated with reduced life expectancy and increased health care costs.

Current treatment options have different mechanisms of action and are variably effective at lowering blood glucose levels. This includes biguanides, insulin secretagogues, thiazolidinediones, alpha-glucosidase inhibitors, and insulin.

Challenges in Achieving Good Glycaemic Control in Type 2 Diabetes

Clinical and observational studies clearly link glycaemic control to diabetes complications. However, while the beneficial effects of glucose-lowering interventions are established for microvascular disease, the data for macrovascular disease are less convincing, with recent trials suggesting that very intensive glucose-lowering may even result in an increase in cardiovascular events if implemented late in the course of the disease. However, the long-term follow-up of UK Prospective Diabetes Study Group (UKPDS) patients suggests persistent effects of good control if implemented early. The main limitations and unwelcome effects of most commonly used drug therapies are hypoglycaemia, fluid retention and weight gain, all of which may theoretically increase the risk of cardiac events (**Table 1**).

NEWLY AVAILABLE THERAPIES

New therapies are emerging, some of them address the unwanted side-effects and limitations of older therapies (**Table 2**).

INCRETIN-BASED THERAPIES

Incretins are intestinal hormones that increase insulin release from the pancreas and inhibit glucagon release. They are released after the ingestion of food from the L and K cells of the gastrointestinal tract. The main incretin that has found therapeutic use is glucagon-like peptide-1 (GLP-1). GLP-1 improves β-cell responsiveness to glucose and, unlike GIP, inhibits gastric emptying and has a central nervous system effect, resulting in reduced food intake and a decrease in body weight. Endogenous incretin peptides are short-lived due to their degradation by the enzyme dipeptidyl-peptidase-4 (DPP-4). The discovery of the incretin-DPP-4 pathways led to the development of GLP-1 analogues, which are resistant to the actions of DPP-4 and DPP-4 inhibitors, which protect the natural incretin hormones from deactivation.

Table 1: Adverse Effects of Commonly Used Oral Hypoglycaemic Agents

Type	Prototype	Hypoglycaemia	Fluid Retention	Weight Homeostasis	Typical Problems
Biguanide	Metformin, Metformin SR	No	No	Weight neutral or modest weight loss	Lactic acidosis; thus C.I in renal failure. Do not use in CKD 4, caution in CKD 3, liver and heart failure, GI intolerance
Sulphonylureas + other insulin secretagogues	Gliclazide, Glimeperide, Glipizide Glibenclamide, Repaglinide	Particularly in the elderly	No	Weight gain	No β- cell preservation
Thiazolidenediones/ Glitazones	Rosiglitazone, Pioglitazone	Uncommon	Frequent, especially in combination with insulin	Weight gain	CI in heart failure; avoid rosiglitazone in IHD, increased fracture risk in women
Insulin	Soluble, basal and biphasic insulin preparations	Frequent	Occasional	Weight gain	Other drawbacks: injection. First inhaled insulin withdrawn for economic reasons; also concerns regarding lung function and cancer risk
	Detemir			Weight neutral	

Table 2: Summary of Newer Glucose Lowering Therapies

Drug	Examples	Mechanism of Action	Dose Range	HbA1c Reduction	Advantages	Adverse Effects/ Disadvantages
Incretin mimetics	Exenatide Liraglutide	↑ Insulin, ↓ Glucagon, slow gastric emptying	5 or 10 µg BD 1.2 or 1.8 mg OD	0.5% to 1.0%	Weight loss	Injection—nausea, pancreatitis
Incretin enhancers	Sitagliptin Vildagliptin	Prolong endogenous GLP-1 action	100 mg OD 50 mg BD	0.4% to 0.9%	Weight neutral, no hypoglycaemia	Nausea, pancreatitis, dose reduction in renal failure
	Saxagliptin	Care while using in renal failure	5 mg OD			
SGLT-2 inhibitors	Dapagliflozin	Inhibits glucose re-absorption	5 to 10 mg OD	0.5% to 0.9%	Weight loss	Polyuria, genital infections
Amylin agonist	Pramlintide	Slow gastric emptying, ↓ glucagon	60 to 120 µg TDS	0.3% to 0.5%	Reduce postprandial glycaemia, weight loss	Injection, nausea Hypoglycaemia with insulin use

BD = Twice daily; OD = Once daily; TDS = Thrice daily; SGLT-2 = Sodium glucose transporters-2

INCRETIN MIMETICS

Exenatide

It is the synthetic version of exendin-4, a specific agonist of the GLP-1 receptor originally isolated from the salivary secretions of the lizard *Heloderma suspectum*, otherwise known as the gila monster. Its duration of action is longer compared with GLP-1, largely due to its resistance to degradation by DPP-4. It is a DPP-4 resistant peptide with a half-life of more than 2 hours, giving a therapeutic effect for 4 to 6 hours, it is administered twice daily by subcutaneous injection (5 or 10 µg) before main meals. It typically decreases HbA1c by 0.8% to 1.0% over 6 to 12 months, with substantially decreased postprandial glycaemic excursion, modestly decreased basal glycaemia and weight loss of 2 to 5 kg.

The improvement in glycaemic control is due to enhanced glucose-dependent insulin secretion, the suppression of postprandial glucagon secretion and slower gastric emptying. In addition, GLP-1 analogues reduce food intake, with subsequent weight reduction, and therefore, higher insulin sensitivity. Because their effect on insulin secretion is dependent on the prevailing glucose concentration, incretin analogues have a low risk of hypoglycaemia when used alone or in combination with metformin or thiazolidinediones but can increase the risk of hypoglycaemia when used with sulphonylureas.

Nausea is the most commonly reported side-effect, affecting up to 44% of patients in clinical trials. This, however, tends to reduce with time, and only 4% of patients in clinical trials withdrew from treatment as a result of nausea. There are case reports of acute pancreatitis in association with exenatide use, but it is currently unclear whether this is a true side-effect or a chance association. Meanwhile, it seems wise to avoid the use of this drug in patients with a history of pancreatitis or those at high risk (e.g. with severe hypertriglyceridemia).

Liraglutide

Liraglutide is another GLP-1 agonist which is now available. It is nearly identical to human GLP-1; consequently, the rate of antibody formation is low. Liraglutide has a significantly longer half-life (12 to 14 hours) than exenatide and can be dosed once daily. Like exenatide, liraglutide appears to reduce HbA1c levels (0.7 to 1.2) in patients poorly controlled on oral anti-diabetic medications, reduces fasting and postprandial plasma glucose levels, and results in progressive weight loss (4 to 6 kg). Improvements in glycaemic control appear to be better with liraglutide than with exenatide, probably because the former has a better effect on fasting plasma glucose levels. Risk of hypoglycaemia is low.

Incretin Enhancers

Gliptins acts as inhibitors of the enzyme DPP-4, which is responsible for the very rapid inactivation of the circulating incretin GLP-1 and GIP. Thus, DPP-4 inhibitors have been developed to prolong the circulating half-life of incretins, and thus, enhance the biological effects of endogenous incretins particularly GLP-1. Currently available gliptins include sitagliptin, vildagliptin and saxagliptin, which almost completely inhibit DPP-4 activity for about 12 to 18 hours causing increased endogenous incretin concentration to two-to-three-folds.

Sitagliptin

The usual recommended dose of sitagliptin is 100 mg per day, but 25 mg and 50 mg tablets are available for dosing in patients with moderate-to-severe renal impairment. The recommended doses for patients with renal impairment are 50 mg per day if the creatinine clearance is between 30 and 50 mL/min, and 25 mg per day if the creatinine clearance is <30 mL/min. Sitagliptin can be taken with or without food. It has been shown to be safe and efficacious in clinical trials, producing A1c reductions of 0.65% to 0.94%, with patients who had higher A1c levels (>9.0%) receiving the most benefit. No severe hypoglycaemia was reported with its use.

Vildagliptin

Clinical trials show that vildagliptin is similar to sitagliptin for dosing, efficacy, and safety profiles. A recent Cochrane review 19 compared the efficacy and safety of vildagliptin and sitagliptin in multiple studies, and concluded the following: 'Compared with placebo, A1c reductions of ~0.7% (sitagliptin) and 0.6% (vildagliptin) were noted; there were improvements in metabolic control when compared with other hypoglycaemic agents; neither medication produced weight gain, both were well tolerated, and there was no severe hypoglycaemia; and no definite conclusion could be drawn from published data about their effects on β-cell function'.

Saxagliptin

This drug is also available. Dose is 5.0 mg OD. It has similar action profile and effectiveness in glucose reduction. Other important

side-effects are pertaining to gastrointestinal tract like nausea, flatulence and diarrhoea.

Pramlintide

Pramlintide is an analogue of amylin, a small peptide hormone that is released into the blood stream by the β-cells of the pancreas along with insulin, after a meal. Like insulin, amylin is deficient in individuals with diabetes. By augmenting endogenous amylin, pramlintide aids in the absorption of glucose by slowing gastric emptying, promoting satiety via hypothalamic receptors (different receptors than for GLP-1), and inhibiting inappropriate secretion of glucagon, a catabolic hormone that opposes the effects of insulin and amylin.

It is used as an adjunct to insulin therapy for type 1 and type 2 diabetes. Although it has received only minor use, possibly due to the need for multiple daily subcutaneous injections separately from insulin, it has been shown to benefit glycaemic control while enabling a reduced insulin dose and a decrease in body weight.

SGLT-2 Inhibitor

The sodium glucose co-transporter-2 is located predominantly in the first segment of the proximal tubules of the kidney, where it acts as the conduit to re-absorb most of the filtered glucose. Dapagliflozin is a potent and highly selective SGLT-2 inhibitor. It causes urinary energy loss of up to 200 to 300 Kcal per day and can lower HbA1c up to 0.5% to 0.9% over 3 months with weight loss of 2.5 to 3 kg. Potential side-effects include polyuria and an increased risk of urinary and genital fungal infections. Other drugs in this group are sergliflozin and remogliflozin.

Glucokinase Activators

Glucokinase is the main 'glucose sensor' in the pancreas and liver. Defects in the glucokinase gene cause one form of maturity onset diabetes of the young, MODY 2. Glucokinase activators increase the sensitivity of glucokinase to high levels of glucose, leading to increased insulin secretion, increased liver glycogen synthesis and a decrease in liver glucose output. Potential concerns include hypoglycaemia due to increased insulin secretion. However, 'liver-selective' glucokinase activators with lower potential for hypoglycaemia have also been developed and tested in pre-clinical models.

Glucagon-Receptor Antagonists

The abnormal increase of liver-derived gluconeogenesis in type 2 diabetes mellitus is targeted by glucagon-receptor antagonists, which are currently being tested in humans.

Sirtuins

Sirtuin deacetylases have been discovered with the study of calorie restriction and resulting prolonged lifespan. SIRT1-activators do not only increase mitochondrial activity but also improve insulin secretion and glycaemia. Human studies in diabetic patients are in progress.

Other agents are expected to emerge from targeting gut hormones and appetite regulators, e.g. PYY3-36, ghrelin-antagonists, melanocortin-4 (MC4)-antagonists and MTP-antagonist (which limit gut absorption of fat) and various combinations of the above.

Insulin Pumps

Rather than receiving multiple daily subcutaneous injections of short- and either long- or intermediate-acting insulin, patients using an insulin pump receive a continuous subcutaneous infusion of short-acting insulin. These devices hold insulin reservoir and supply insulin via a plastic tube into subcutaneous tissue. Pumps are able to more precisely dose insulin compared to insulin syringes or pens. Pumps are also programmable to provide different doses of basal insulin throughout the day. This feature allows patients to increase their basal insulin, for example, to counteract the 'dawn phenomenon' or to decrease their basal rate to compensate for increased physical activity.

Insulin pumps in some, but not all, studies have been associated with improved metabolic control and lower risk of mild and severe hypoglycaemia in patients with type 1 diabetes. Most studies also show that the A1C improvement is modest, usually less than one percentage point. Some of the newest insulin pumps are also available with integrated continuous glucose monitoring devices mimicking pancreas.

CONCLUSIONS

Control of blood glucose in type 2 diabetes mellitus is important to improve outcomes, but achieving long-term control is challenging and all existing agents have limitations, particularly as most of the older agents and insulin cause an increase in body weight and hypoglycaemia. Newer agents, especially those that target body weight, have significant potential, but their place in the therapeutic algorithm is not yet determined possibly because of lack of data on cardiovascular safety profile.

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9.9 In-Hospital Management of Diabetes Mellitus

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INTRODUCTION

A study has shown that India has spent a mind-boggling Rs.1.5 trillions on diabetes care in 2010. A significant proportion of inpatients with hyperglycaemia have undiagnosed diabetes and stress hyperglycaemia. Hospitalisation should be resorted to in diabetes patients only when absolutely necessary to cut down on costs.

EVIDENCE OF HARM FROM IN-HOSPITAL HYPERGLYCAEMIA AND BENEFITS OF GLUCOSE LOWERING

There is compelling evidence that poorly-controlled glucose levels are associated with a higher in-hospital morbidity and mortality, prolonged length of stay, unfavourable post-discharge outcomes and significant increase in healthcare costs. We have tried to stratify the impact of inpatient diabetes management, relying on evidence-based norms.

Which Patient Requires Hospitalisation?

Hospitalisation for a patient for reasons related to diabetes may be indicated in specific situations.

1. Acute metabolic complications like diabetic ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia with neuroglycopaenia.
2. Newly diagnosed diabetes in children and adolescents when unstable or brittle, for the purpose of dose adjustment or monitoring (when not possible on outpatient basis).
3. Chronic poor metabolic control that necessitates close monitoring to determine the aetiology and modify therapy as in hypoglycaemia unawareness.
4. Severe chronic complications requiring intensive treatment or other conditions unrelated to diabetes that significantly affect its control, particularly wherein ambulation may be a problem.
5. Uncontrolled insulin-requiring diabetes during pregnancy for rapid control.
6. The institution of insulin pump therapy or other intensive insulin regimens.

Diabetes In-Hospital Team

The patient

The patient forms the core of the team and is encouraged to participate in the formulation and conduct of their own care plan while admitted in the hospital.

Consultant physician/diabetologist/endocrinologist

The primary role of the consultant is as a leader of the multi-disciplinary team. They work closely to provide clinical support to diabetes specialist nurses and diabetes educators. The practical knowledge of 'on the spur of the moment' innovation is vital towards patient care, and over-rides theoretical knowledge.

Diabetes educator or diabetes specialist nurses

They play a key role in patient and staff education and implementation of glycaemic control strategies and are able to facilitate a smooth patient pathway from hospital to home. The diabetes educator could also be the leader of the team.

Diabetes specialist dietician

They play a pivotal role in those with complex nutritional needs —those unable to swallow, those with renal failure, pregnancy, cystic fibrosis, and the elderly.

Targets to be Achieved

1. Initiate glucose monitoring in any patient not known to have diabetes, but who receives therapy associated with high-risk for hyperglycaemia, including high-dose glucocorticoid therapy and initiation of enteral or parenteral nutrition. If hyperglycaemia is documented and persistent, treatment is necessary. Such patients should be treated to the same glycaemic goals as patients with known diabetes.
2. A plan for treating hypoglycaemia should be established for each patient. Episodes of hypoglycaemia in the hospital should be tracked.
3. All patients with diabetes admitted to the hospital should have their glycosylated haemoglobin (HbA1c) obtained if the result of testing in the previous 3 months is unavailable.
4. Patients with hyperglycaemia in the hospital should have appropriate plans for follow-up testing and care documented at discharge.

GOALS FOR BLOOD GLUCOSE LEVELS

Critically-Ill Patients

Insulin therapy should be initiated for treatment of persistent hyperglycaemia starting at a threshold of 180 mg/dL (10 mmol/L). Once insulin therapy is initiated, a glucose range of 140 to 180 mg/dL (7.8 to 10 mmol/L) is recommended for the majority of critically-ill patients.

Non-Critically-Ill Patients

There is no clear evidence for specific blood glucose goals. If treated with insulin, the pre-meal blood glucose target should generally be less than 140 mg/dL (7.8 mmol/L) and random blood glucose less than 180 mg/dL (10.0 mmol/L), provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycaemic control and less stringent targets in those with severe co-morbidities.

Hospital Barriers to Glucose Control

This may seem to be a paradox. However, hospitalisation may in fact hamper the efforts to achieve glycaemic control in some situations. Indeed, it may be more prudent to have good educational facilities on an out-patient basis to enable patient self-emancipation.

1. Majority of diabetes patients are hospitalised for reasons other than diabetes, e.g. vascular complications. The care of diabetes *per se* becomes subordinate to care for the primary diagnosis.
2. Infection, fever, glucocorticoid therapy, surgical trauma and general medical stress exacerbate hyperglycaemia due to release of counter regulatory hormones.
3. Decreased physical activity (in previously active patients) also exacerbates hyperglycaemia.
4. Strict diet and supervised compliance with drugs may result in hypoglycaemia in patients who were not compliant earlier.

COMMON ERRORS IN MANAGEMENT

Admission Orders and Lack of Therapeutic Adjustment

The out-patient treatment regimen is often continued unchanged or withdrawn entirely upon admission. Although either of these choices may occasionally be indicated, patients more commonly will require some modification of their out-patient regimen. A patient may be treated with regular insulin alone during the entire hospital stay, which will deprive the treating physician of an opportunity to observe the patient's response to regimens that can be transferred home.

High glycaemic targets

Blood glucose levels are commonly allowed to be more than 200 mg/dL. In-patient care is sometimes taken for granted to be superior; however, infrastructural limitations and nursing staff inadequately trained in diabetes could work contrary.

Overutilisation of 'sliding scales'

There are opinions that sliding scales are illogical, as they are designed to correct the therapeutic inadequacies of the previous 4- to 6-hour period rather than anticipating future requirements. Sliding scale is used frequently as the only means of insulin dosage, rather than concurrently with intermediate-acting insulins, which may lead to fluctuations of insulin supply and erratic glucose control. Sliding scale may be used in certain situations outlined in **Table 1**.

Table 1: Situations in which Sliding Scales may be Useful

To adjust pre-prandial insulin based on the pre-meal capillary glucose level and the anticipated carbohydrate consumption
With basal insulin analogues, such as insulin glargine
To evaluate patient's initial response to insulin
In patients receiving parenteral nutrition, in whom each 6-hour period is similar to the last

Underutilisation of insulin infusions

Intravenous insulin is recommended for patients with hyperglycaemic emergencies and also in the peri-operative setting or when glucose control has deteriorated with conventional subcutaneous insulin. The intravenous route provides predictable insulin delivery and enables quick control of glucose levels. Adequate nurse training, staffing and supervision is required for their safe implementation.

Blood Glucose Monitoring

In patients on enteral or parenteral nutrition, glucose monitoring is optimally performed every 4 to 6 hours. Glucose testing should be performed every 1 to 2 hours in patients on intravenous insulin infusions. In patients eating usual meals, glucose levels should be monitored as fasting and 2 hours post-prandial after three major meals. The common error in SMBC monitoring have to be kept in mind and taken care (**Table 2**).

Table 2: Sources of Errors in Bedside Blood Glucose Results

Sources of analytical error	Sources of use error
False high	Inadequate metre calibration
Low haematocrit	Inadequate quality-control
Hyperbilirubinaemia	Poor technique in finger prick
Severe lipaemia	Poor technique of applying blood drop on test strip
False low	Test strip with unmatched meter code or that has passed the expiration date
High haematocrit	
Either false high or false low	
Hypoxia	
Shock and dehydration	
Drugs: acetaminophen overdose, dopamine, mannitol, salicylate	

GLUCOSE CONTROL

General Recommendations

A key component of providing effective insulin therapy in the hospital setting is to determine whether a patient has the ability to produce endogenous insulin or not (**Table 3**).

Table 3: Characteristics of Patients with Insulin Deficiency

Known type 1 diabetes
History of pancreatectomy or pancreatic dysfunction
History of wide fluctuations in blood glucose levels
History of diabetic ketoacidosis
History of insulin use for >5 years and/or diabetes for >10 years

Patients with type 1 diabetes will require some insulin at all times to prevent ketosis, even when not eating. The insulin regimen should be revised frequently based on the values of glucose monitoring. Intermediate-acting insulin added once or twice daily, even at small doses, will stabilise the control. Glucose levels should be maintained as close to the normal range as possible in the post-operative, post-myocardial infarction, and intensive care settings. Conservative targets should be set in patients prone to hypoglycaemia (e.g. brittle diabetes, hypoglycaemia unawareness), in very elderly or in those with short life expectancy due to co-morbid conditions and with inadequate nursing or monitoring support.

Patient Specific Recommendations

Patient on oral agents and not consuming food

In patients on sulphonylurea or other secretagogues, the drugs should be withheld and a short-acting insulin sliding scale should be used temporarily. Addition of intermediate-acting insulin should be considered, if insulin is needed for more than 24 hours. Metformin may be withheld owing to concerns about altered renal function in the acutely ill. Avoid α-glucosidase inhibitors as these are effective only when taken with food. Thiazolidinediones are discontinued in patients with abnormal hepatic or cardiac function.

Patient on oral agents and consuming food

In patients on oral agents with controlled sugars, continue the medication but consider a dosage adjustment of 25% to 50%, due to the likelihood of better dietary adherence. Metformin should

be withheld in peri-operative patients (general anaesthesia), in those with standard contraindications, or when dehydration is suspected or anticipated and if radio-contrast studies are planned. α-glucosidase inhibitors and thiazolidinediones may be continued. Insulin should be started if sugars are uncontrolled.

Patient on insulin and not consuming food

Intravenous insulin infusion should be strongly considered in type 1 diabetes patients. Alternatively, half to two-thirds of the patient's usual dose of intermediate-acting insulin may be given along with a short-acting insulin sliding scale.

Some patients with type 2 diabetes on insulin may have improved control with diet restriction and require only short-acting insulin. A 5% dextrose solution intravenously at 75 to 125 mL per hour should be provided.

Patient on insulin and consuming food

Continue insulin, although consider dosage reduction (10% to 50%) in well-controlled patients because of the likelihood of more rigid dietary adherence.

Patient Scheduled for Surgery

Peri-operative instructions

In general, patient's treatment programme is least affected if surgeries are scheduled for early morning. Blood glucose levels should be monitored every 1 to 2 hours before, during and after the procedure.

Type 1 diabetes

Insulin infusion should be given at a maintenance rate (1 to 2 units per hour) with a 5% dextrose solution at 75 to 125 mL per hour, adjusted to maintain glucose levels between 100 and 150 mg/dL. Alternatively, give one-half to two-thirds of the usual dose of intermediate-acting insulin on the morning of procedure.

Type 2 diabetes

If the patient is taking an oral anti-diabetic agent, hold the medication on the day of procedure and resume when tolerating a normal diet.

If the patient is treated with insulin, give one-half of intermediate-acting insulin on the morning of procedure. Do not give short-acting insulin unless the blood glucose level is >200 mg/dL. Alternatively, an insulin infusion can be used.

SPECIFIC CLINICAL SITUATIONS

Insulin Pumps

Patients who use continuous subcutaneous insulin infusion (CSII) therapy in an out-patient setting can continue using it in the hospital, provided they are mentally and physically fit to do so. The availability of hospital personnel with expertise and experience in CSII therapy is essential.

Enteral Nutrition

For intermittent enteral feedings, intermediate-acting insulin with a small dose of regular insulin is adequate. For continuous feeding, once or twice daily insulin glargine (or NPH) can be used. Start with a small basal dose and use correction-dose insulin as needed while the glargine dose is being increased.

Parenteral Nutrition

The high glucose loads in standard parenteral nutrition frequently results in hyperglycaemia. Insulin therapy is recommended with glucose targets according to severity of illness.

Glucocorticoid Therapy

The best predictors of glucocorticoid-induced diabetes are family history of diabetes, increasing age and glucocorticoid dose and duration. For patients receiving high-dose intravenous glucocorticoids, an intravenous insulin infusion may be appropriate. During steroid tapers, insulin dosing should be proactively adjusted to avoid hypoglycaemia.

Switching from Intravenous to Subcutaneous Insulin

It is important to administer short-acting insulin subcutaneously 1 to 2 hours before discontinuation of the intravenous insulin infusion. Intermediate or long-acting insulin must be injected 2 to 3 hours before discontinuing the insulin infusion.

Prevention of Hypoglycaemia

Hypoglycaemia is the most important limiting factor in the management of diabetes, more so in patients on insulin. Institutions are more likely to have protocols for the treatment of hypoglycaemia than for its prevention. Tracking such episodes and analysing their causes are important quality improvement activities (**Table 4**).

Table 4: Causes of Hypoglycaemia in Patients on Insulin

Sudden reduction in oral intake or nil per oral status
Discontinuation of enteral feeding/TPN/IV dextrose
Pre-meal insulin given and meal not ingested
Unexpected transport from nursing unit after rapid acting insulin given
Reduction/omission of corticosteroid dose

Medical Nutrition Therapy in the Hospital

Current nutrition recommendations advise individualisation based on treatment goals, physiologic parameters, medication usage and other co-morbid conditions, such as obesity, dyslipidaemia, hypertension and renal failure. A registered dietician, skilled in diabetic MNT, should serve as an in-patient team member.

DISCHARGE PLANNING

Patients (and their families) should be familiar with their glucose targets and drug regimens after discharge from hospital and should understand any changes made in their treatment (**Table 5**).

Table 5: Issues to be Addressed Prior to Hospital Discharge

Level of understanding related to the diagnosis of diabetes
Self monitoring of blood glucose and explanation of home blood glucose goals
Recognition, treatment and prevention of hyperglycaemia and hypoglycaemia
Identification of health care provider who will provide diabetes care after discharge
Information on consistent eating patterns
When and how to take oral medications and insulin administration
Sick-day management
Proper use and disposal of needles/lancets/syringes

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9.10 Hypoglycaemia

Siddharth N Shah

INTRODUCTION

Hypoglycaemia occurring several hours after meals was described for the first time in 1922. In 1927, hyperinsulinism as a cause was recognised in a patient with malignant pancreatic islet cell tumour who had episodes of severe hypoglycaemia. Hypoglycaemia is the major hazard of insulin treatment and to a lesser extent with OAD, while trying to achieve tight control. The patient may experience symptoms of hypoglycaemia when the blood glucose concentration is less than 50 mg/dL but individual susceptibility varies considerably. At its mildest it is no more than a slight inconvenience, but at its severest unconsciousness, it is both a hazard and an embarrassment. Hypoglycaemia occurs commonly in patients on sulphonylureas especially elderly patients on long-acting drugs like chlorpropamide and glibenclamide. Neonatal hypoglycaemia of infants born to diabetic mothers is well known.

DEFINITION

Hypoglycaemia or low blood glucose is a clinical state associated with low (less than 50 mg/dL) or relatively low plasma glucose concentration usually associated with signs and symptoms of autonomic hyperactivity and neuroglycopaenia. The Diabetes Control and Complications Trial (DCCT) has defined hypoglycaemia as an event resulting in seizure, coma, confusion, irrational or other prodromal symptoms consistent with hypoglycaemia (e.g. sweating, palpitations, hunger or blurred vision) in conjunction with a laboratory-determined or finger stick blood glucose less than 50 mg% and amelioration by treatment that raises blood glucose. Prodromal symptoms of hypoglycaemia remembered by the subject as occurring shortly before the event. Severe hypoglycaemic coma or seizure requires hospitalisation or intravenous glucose or glucagon.

AETIOLOGY

The most common cause of hypoglycaemia is iatrogenic, i.e. drug-induced oral hypoglycaemic agents or insulin. Hypoglycaemia secondary to alcohol, insulinoma, kidney and liver disease and that associated with endocrine dysfunction and neonatal hypoglycaemia are among the other causes of hypoglycaemia.

PHYSIOLOGY OF GLUCOSE COUNTER-REGULATION

Energy requirements are made from the substrate derived from food and excess substrates stored as fat, protein and glycogen. Insulin is the primary hormone mediating the anabolic phase of metabolism when the counter-regulatory hormone levels are suppressed. The metabolic adjustment during the catabolic phase includes the activation of liver for glycogenolysis and gluconeogenesis and use of free fatty acid from triglycerides stored in adipose tissue.

HYPOGLYCAEMIA AND THE BRAIN

Glucose is an obligate oxidative fuel for the brain under physiological conditions. The brain accounts for > 50% of whole-body glucose utilisation. The brain can oxidize alternative fuels, such as ketones, if their circulating levels are high enough to enter the brain in a substantial quantity, but that is seldom the case. Because it cannot synthesise glucose, it utilises physiological levels of circulating non-glucose fuels effectively, or store more than a few minutes supply of glucose as glycogen. The brain requires virtually continuous supply of glucose from the arterial plasma glucose concentration. This supply is required for maintenance of neural function and integrity. At some level of hypo-glycaemia (perhaps 50 to 55 mg/dL) (2.8 to 3.1 mmol/L) since symptoms normally occur at that level, blood-to-brain glucose transport becomes limited to brain glucose metabolism and therefore, function is impaired.

Maintenance of Systemic Glucose Balance

Falling plasma glucose concentrations elicit a sequence of responses that normally prevent or rapidly correct hypoglycaemia. Because obligatory glucose utilisation by the brain is fixed and exogenous glucose delivery from food is intermittent, systemic glucose balance is maintained and hypoglycaemia (as well as hyperglycaemia) is prevented by dynamic regulation of endogenous glucose production by the liver (and the kidneys) and of glucose utilisation by non-neural tissues such as muscle.

The physiological defence against declining plasma glucose concentrations include: (1) a decrease in insulin secretion; (2) an increase in glucagon secretion, in absence of the latter, an increase in epinephrine secretion. The behavioural defence is the ingestion of carbohydrates prompted by awareness of hypoglycaemia. The first physiological defence against hypoglycaemia is a decrease in pancreatic islet β-cell insulin secretion. That occurs as plasma glucose concentration decline and within the physiological range and increase hepatic (and renal) glucose production with virtual cessation of glucose utilisation by insulin-sensitive non-neural tissues. The second physiological defence is an increase in pancreatic islet α-cell glucagon secretion that occurs as plasma glucose concentrations fall just below the physiological range and increases hepatic glucose production (largely by stimulating glycogenolysis). Increased glucagon secretion is signalled by a decrease in intra-islet insulin, perhaps among other β-cell secretory products, in the setting of low plasma glucose concentration. The third physiological defence, which becomes critical when glucagon secretion is deficient, is an increase in adrenomedullary epinephrine secretion that too occurs as plasma glucose concentration through an array of mechanisms which include direct stimulation of hepatic (and renal) glucose production, limitation of glucose clearance by insulin-sensitive tissues, mobilisation of gluconeogenic substrates such as lactate

and amino acids from muscle and glycerol from fat, and limitation of insulin secretion. Unlike insulin and glucagon secretion, which are regulated primarily by changes in glucose concentrations within the pancreatic islets and only secondarily by central nervous system-mediate autonomic inputs, sympathoadrenal activity, including epinephrine secretion, is regulated with the central nervous system.

Hypoglycaemia-Associated Autonomic Failure in Diabetes

The concept of hypoglycaemia-associated autonomic failure (HAAF) in diabetes (**Table 1**) postulates that recent antecedent hypoglycaemia as well as prior exercise or sleep, causes both defective glucose counter-regulation (by reducing increments in epinephrine in the setting of absent decrements in insulin and absent increments in glucagon during subsequent hypoglycaemia) and hypoglycaemia unawareness (by reducing sympathoadrenal and the resulting neurogenic symptom response during subsequent hypoglycaemia) and, therefore, a vicious cycle of recurrent iatrogenic hypoglycaemia. Perhaps the most compelling support for the concept of HAAF is the finding, in three independent laboratories, that as little as 2 to 3 weeks of scrupulous avoidance of hypoglycaemia reverses hypoglycaemia unawareness and improves the attenuated epinephrine component of defective glucose counter-regulation in most affected patients. While HAAF is largely a functional, dynamic disorder that can induce and reverse, there may also be a structural (neuropathic) contribution to the attenuated sympathoadrenal response.

Table 1: HAAF (Hypoglycaemia-Associated Autonomic Failure)

Absolute endogenous insulin deficiency
A history of severe hypoglycaemia, hypoglycaemia unawareness, or both as well as recent antecedent hypoglycaemia, prior exercise, and sleep
Aggressive glycaemic therapy *per se* (lower AIC levels, lower glycaemic goals)

The first defence against falling plasma glucose concentration is decreased insulin secretion and the glucose counter regulatory hormones are activated. Glucagon plays a primary role in the glucose counter-regulatory process. Epinephrine becomes important when glucagon is deficient. Other factors such as cortisol and growth hormone are involved in prolonged hypoglycaemia; other hormonal neuro-transmitters and normal physiological response to falling blood glucose concentration is the decline in insulin secretion and it occurs at a glycaemic threshold of 83 mg/dL. The symptoms of hypoglycaemia are felt at blood glucose of 54 mg/dL and those of cognitive dysfunction at 49 mg/dL.

PATHOGENESIS

Hypoglycaemia is most commonly encountered due to over dosage with insulin or oral hypoglycaemic drugs. This may be due to any one or a combination of the following; if more than the required dose of insulin or oral drug is taken; if a meal is skipped, is inadequate or is unduly delayed after insulin injection or oral antidiabetic drugs and; unusual heavy physical exertion, after taking insulin.

In early diabetes with partial decompensation there is islet inertia and insulin is not released till blood glucose level reaches 200 mg/dL. Blood sugar then falls rapidly due to sudden release of insulin, leading to hypoglycaemia (reactive hypoglycaemia). Rapid gastric emptying in post-gastrectomy patients with brisk absorption of glucose results in excessive insulin release, leading to rapid fall of glucose concentration and hypoglycaemia symptoms.

When the liver function is severely impaired, hypoglycaemia occurs because glycogen stores in liver are poor and perhaps insulin destroying complex (insulinase) is deficient in hepatic disease. Recurrent hypoglycaemia can occur in patient with deteriorating renal function. Accumulation of serum insulin leads to fasting hypoglycaemia, (**Table 2**), diabetic type of glucose tolerance test due to inability of the liver to store glucose as glycogen, and poor glucose response to administration of glucagon or epinephrine. Alcohol induces slowing of the Krebs cycle with impairment of gluconeogenesis, giving rise to reduced glucose output and hypoglycaemia. There is no rise of serum insulin during fed state hypoglycaemia (**Table 3**).

Table 2: Causes of Fasting Hypoglycaemia

Underproduction	Overutilisation
Hormone deficiencies	Hyperinsulinism
Hypopituitarism	Insulinoma
Adrenal insufficiency	Exogenous insulin overdose
Catecholamine deficiency	Sulphonylurea overdose
Glucagon deficiency	Insulin autoimmunity
Enzyme defects	Inappropriate insulin level
Glucose-6-phosphatase	Extrapancreatic tumours
Liver phosphorylases	Carnitine deficiency
Pyruvate carboxylase	Cachexia with fat depletion, e.g. advanced cancer
Substrate deficiency	
Ketotic hypoglycaemia of infancy	
Severe malnutrition, muscle wasting (?)	
Late pregnancy	
Acquired liver disease	
Hepatic congestion	
Cirrhosis	
Severe hepatitis	
Drugs	
Alcohol	
Propranolol	
Salicylates	

Table 3: Fed State (Reactive) Hypoglycaemia

Underproduction	Overutilisation
Early (alimentary) within 2 to 3 hours after meals	Late (occult) diabetic 3 to 5 hours after meals
Alimentary hyperinsulinism	Delayed insulin release due to β-cell dysfunction
Post-gastrectomy (dumping syndrome)	Counter-regulatory deficiency of growth hormone, glucagon, cortisone, epinephrine
Hereditary fructose intolerance	
Galactosaemia	
Leucine sensitivity	

Non-specific reactive functional hypoglycaemia is the most frequent cause of hypoglycaemia in the normal population and is associated with anxiety. These patients tolerate physical exercise and prolonged fasting very well. In early diabetes, hypoglycaemia is seen to occur 3 to 5 hours after a carbohydrate-rich meal. Specially in patients with a strong

family history of diabetes. Fasting blood sugar is normal or elevated and prolonged fast is well tolerated. In reactive hypoglycaemia due to leucine sensitivity which releases insulin from the β-cells, hypoglycaemic convulsions occur after an injection of leucine in infants and small children. There is a fall in blood glucose within 20 minutes and marked rise of serum insulin levels. It is a self-limiting disease occurring in infants up to 5 months of age and is rarely seen in adults.

Pseudohypoglycaemia

Pseudohypoglycaemia occurs in certain chronic leukaemias when the leucocyte counts are markedly elevated. This artefactual hypoglycaemia reflects utilisation of glucose by leucocytes after the blood sample has been drawn. Such a hypoglycaemic condition, therefore, is not associated with symptoms. Other artefactual hypoglycaemias may be seen with improper sample collection or storage, errors in analytic methodology.

CLINICAL FEATURES

The signs and symptoms of hypoglycaemia can be divided into those due to autonomic hyperactivity and those resulting from neuroglycopaenia, as shown in **Table 4**. The manifestations are varied and will depend mainly on the rate of fall of blood glucose level and the ability of the patient's endocrine system to counteract. For example, a patient on insulin may complain of few symptoms despite very low glucose levels whereas a patient with Sheehan's syndrome may feel very uncomfortable even with moderately low blood glucose level.

Table 4: Signs and Symptoms of Hypoglycaemia

Autonomic Hyperactivity	Neuroglycopaenia
Adrenergic	Headache
Palpitation	Fatigue
Sweating	Mental dullness
Anxiety	Dizziness
Tremors	Blurring/clouding of vision
Parasympathetic	Confusion
Hyperactivity	Amnesia
Nausea	Seizure
Hunger	Unconsciousness

Patient may present with weakness, palpitation, nervousness, sweating and mental confusion, progressing to unconsciousness. History of insulin being administered or history of having consumed oral hypoglycaemic may be available. Short acting insulin may produce hypoglycaemia up to 4 to 6 hours after injection whereas intermediate acting insulin may produce hypoglycaemia in the evening or at midnight. It is rare to find prolonged hypoglycaemia with short-acting oral drugs like tolbutamide and glipizide whereas prolonged hypoglycaemia leading to coma is more commonly encountered in elderly diabetics who are on chlorpropamide or glibenclamide. Whipple's triad consisting of symptoms of hypoglycaemia, low blood glucose values during this period and immediate relief of symptoms and signs after ingestion of glucose is characteristic of β-cell tumours. Occasionally the tumour is associated with severe diarrhoea, muscle wasting or carcinoid syndrome. These patients get tired easily and do not tolerate prolonged exercise. It may also present as a part of multiple adenomatosis or neurofibromatosis. Even gastrin producing Zollinger-Ellison syndrome may be associated. After a severe bout of alcohol, hypoglycaemia can occur especially if the patient takes very little food. Hypoglycaemia is intermittent and cannot be reproduced by fasting. Patients who have undergone gastrectomy complain of nausea, abdominal discomfort, diarrhoea, sweating, palpitation and giddiness (dumping syndrome).

After ingestion of sugar or a fruit, severe vomiting and hypoglycaemia occur in hereditary fructose intolerance. Liver enlargement, jaundice, cirrhosis, albuminuria, aminoaciduria, and mental retardation due to chronic hypoglycaemia have been observed in children. Older children show strong dislike for sugar and fruits.

INVESTIGATIONS

Diagnosis of post-prandial hypoglycaemia, the only unequivocal diagnostic test is the demonstration of low plasma glucose concentration (less than 50 mg/100 mL) during spontaneously developed symptoms. A 5-hour oral glucose tolerance examination showing a plasma glucose value of 50 mg/mL or less is suggestive.

Diagnosis of β-cell adenomas (insulinoma) is based on serum insulin level of 20 µg/mL or more in the presence of blood glucose values below 40 mg/mL. Elevated circulating proinsulin level, differentiates between insulinoma and factitious hyperinsulinism. The ratio of insulin to glucose and absence of suppression of C-peptides during hypoglycaemia induced by 0.1 unit of insulin per kg body weight per hour are diagnostic. A normal person would suppress the peptide level to 50% or more during hypoglycaemia. Glucose tolerance test is not helpful. CT scan may not pick-up the tumour and pancreatic arteriography may be required to locate the tumour preoperatively.

In normal persons, the insulin/glucose ratio is always less than 0.4. In insulinomas, the ratio is greater than 0.4 and often above 1.0. Multiple sampling is required because patients with insulinoma may secrete insulin episodically. In islet cell tumours, provocative tests with tolbutamide, glycogen or leucine may be of help but the overlap between normal and insulinoma patients is so great as to render the tests of little value.

In factitious hypoglycaemia, the triad of low blood sugar, high immunoreactive insulin and low C-peptide level are pathognomonic of exogenous insulin administration. When sulphonylureas are suspected as being responsible, a chemical test of the plasma to detect the drugs may be required.

DIFFERENTIAL DIAGNOSIS

Hypoglycaemia may be misdiagnosed as hyperglycaemia and if not treated promptly may lead to death. Chronic hypoglycaemia may lead to loss of memory, clouding of vision, blunted mental activity, confusion, abnormal behaviour, convulsions and coma.

Hypoglycaemia should be differentiated mainly from hyperglycaemia especially when a patient is in coma. **Table 5** shows differential diagnostic features of hyperglycaemia and hypoglycaemia. Hypoglycaemia may also present as transient ischaemic attacks, giddiness, mental confusion, convulsion or

Table 5: Differential Diagnosis of Hypoglycaemic and Hyperglycaemic Coma

Symptoms, Signs and Laboratory Findings	Hypoglycaemic Coma	Hyperglycaemic Coma
Physical findings		
Pulse rate	Increased	Increased
Pulse volume	Full	Weak
Temperature	May be decreased	May be decreased
Respiration	Shallow or normal	Rapid and deep (air hunger)
Blood pressure	Normal, may be increased	Decreased
Skin	Clammy, sweating	Dry
Tongue	Moist	Dry
Tissue turgor	Normal	Reduced
Eyeball tension	Normal	Reduced
Breath	No acetone	Acetone may be present
Reflexes	Brisk reflexes	Diminished reflexes
Laboratory tests		
Urine glucose	Negative to positive depending on time of last voiding	Positive
Plasma glucose	Negative* to positive**	Positive** >200 mg/dL
Plasma acetone	Negative	Usually present
Plasma bicarbonate	Normal	Low <20 mg/L
Plasma CO_2	Normal	Diminished***
Blood pH	Normal	<7.35

** In case of diabetic ketoacidosis with very severe complicating lactic acidosis, urine and plasma acetone may be negative. Rarely, uraemic patients with diabetic ketoacidosis have positive plasma acetone but negative urine acetone.*
*** Sometimes urine is negative for sugar but positive for acetone in patients with hypoglycaemic coma. This is due to starvation ketosis.*
**** In patients with severe acute or chronic respiratory failure, plasma bicarbonate may be normal or increased despite concomitant presence of metabolic acidosis or diabetic ketoacidosis.*

coma and may be mistaken for a neurological illness. Although food, especially free carbohydrates, will relieve symptoms regardless of the cause, persons without a hypoglycaemic disorder may feel better after eating. A suspected patient has to undergo a 5-hour oral glucose tolerance test with plasma sampling every half hour and at the time the symptoms occur. A good history will clinch the diagnosis of iatrogenic hypoglycaemia.

COURSE AND PROGNOSIS

If detected early, hypoglycaemia is reversible and can be prevented. Surgical removal of β-cell tumour alleviates all symptoms. If hypoglycaemia occurs only at night and is not detected, it might lead to loss of memory and mental dullness.

SOMOGYI EFFECT

Insulin treated diabetic patients may show a rapid swing to hyperglycaemia after episodes of hypoglycaemia , the rebound hyperglycaemia or Somogyi effect is thought to be caused by actions of hormonal antagonists of insulin secreted in response to hypoglycaemia.

HYPOGLYCAEMIA UNAWARENESS

Some elderly long standing diabetics on sulphonylurea do not get adrenergic symptoms and present with severe neuroglycopaenic symptoms such as convulsions or coma during the hypoglycaemic episodes. About a decade back, when patients taking porcine insulin were shifted on human insulin in UK, some insulin-dependent diabetic patients also developed hypoglycaemia unawareness. It is characterised by low sympathetic response with insignificant increase in circulating epinephrine and glucagon. Since the hypoglycaemia-induced glucagon response is invariably reduced in patients with diabetes after 5 years, the main factor responsible for unawareness of hypoglycaemia is inadequate response of epinephrine. Autonomic neuropathy was initially thought to be the main factor responsible for inadequate counter-regulation. However, many with inadequate response have no evidence of autonomic neuropathy. It is postulated that the hypothalamus has a specialised area which detects hypoglycaemia and triggers autonomic response. Exposure of this area to hypoglycaemia would reset the trigger threshold at a lower level resulting in diminished counter-regulation.

TREATMENT

Hypoglycaemia associated with unconsciousness or stupor should be treated as an emergency. The treatment of choice is to give 25 to 50 mL of 50% glucose solution over a period of 2 to 3 minutes. One mg of glucagon injected IV is preferable in an emergency where peripheral veins are collapsed, the patient regaining consciousness within 15 min to permit ingestion of sugar. History of the precipitating cause of hypoglycaemia must be ascertained and the future course of action chalked out to prevent further episodes.

The treatment of reactive hypoglycaemia of fed state is alteration in dietary habits. Frequent small feeds are advised in non-specific reactive hypoglycaemia; the diet should contain some slowly absorbable carbohydrates and more protein. Anticholinergic drugs such as probanthine, 15 mg 3 times a day, may be useful in reducing rapid gastric emptying. Tolbutamide in small doses may be given twice daily before meals in patients with early diabetes. Reactive hypoglycaemia in leucine sensitivity can be treated by avoiding leucine containing protein

such as milk. Diazoxide has also been tried. Propranolol in small doses may be useful in both situations. Alcohol induced hypoglycaemia is prevented by reducing the intake of alcohol and increasing the ingestion of food. Hereditary fructose intolerance requires avoiding foods containing sugar or fructose. Other carbohydrates and milk can be taken without fear.

β-CELL TUMOURS

Surgical removal, chemotherapy and irradiation help in eradication of the tumour. If hypoglycaemia occurs it is treated symptomatically, e.g. carbohydrate feeding every 2 to 3 hours is usually effective in preventing hypoglycaemia. Glucagon should be available for emergency use. Diazoxide 300 to 600 mg daily orally has been useful along with a thiazide diuretic. Octreotide, somatostatin analogues have been used in metastatic tumours.

NON-β-CELL TUMOUR HYPOGLYCAEMIA

Mesenchymal tumours—45% to 64% of reported cases of non-β-cell tumour cause hypoglycaemia. Histological types – fibrosarcoma, lymphosarcoma, liposarcoma, rhabdom-yosarcoma, haemangiopericytomas, leiomyosarcoma, mesotheliomas. In both sexes; 5th to 7th decade; 1/3 in chest, 2/3 in abdomen; large and easily detectable, hepatomas, large adrenal tumours and carcinoma lung. These large tumours metabolise large amount of glucose. They may secrete insulin like material.

NEONATAL HYPOGLYCAEMIA

Hypoglycaemia in the immediate postpartum period needs recognition, as this phenomenon is transient. Associated with hypoglycaemia there are other parameters like hypocalcaemia, hyperbilirubinaemia, polycythaemia and hyperviscosity, respiratory distress syndrome and necrotising enterocolitis which must be recognised and treated. Every newborn of diabetic mothers must be given a 5% glucose infusion for the first six hours and subsequently blood glucose monitored to prevent fatal hypoglycaemia and hypoglycaemic convulsions.

AUTOIMMUNE HYPOGLYCAEMIA

This may be associated with insulin antibodies or insulin receptor antibodies. The age of onset varies from a few days to the elderly. Hypoglycaemia occurs at any time and is often limited. Insulin receptor antibodies are observed in diabetic patients with type B insulin resistance associated with acanthosis nigricans. Most of these patients have pre-existing insulin resistant diabetes and evidence of autoimmune disease before the development of hypoglycaemia.

Hypoglycaemia risk factor reduction. It is, of course, preferable to prevent rather than treat iatrogenic hypoglycaemia. The prevention of hypoglycaemia requires the practice of hypoglycaemia risk factor reduction (**Table 6**).

Table 6: Risk Factors for Hypoglycaemia in Diabetes

Absolute or relative therapeutic insulin excess

1. Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type
2. Exogenous glucose delivery is decreased (e.g. following missed meals and during the overnight fast)
3. Glucose utilisation is increased (e.g. during and shortly after exercise)
4. Endogenous glucose production is decreased (e.g. following alcohol ingestion)
5. Sensitivity to insulin is decreased (e.g. in the middle of the night and following weight loss, improved fitness or improved glycaemic control)
6. Insulin clearance is decreased (e.g. with renal failure)

PROPHYLACTIC MEASURES

Minimising the risk of hypoglycaemia while maintaining meaningful glycaemic control is a challenge for people with diabetes and their caregivers, adequate education of diabetic patients and their relatives is necessary so that hypoglycaemia can be avoided or treated effectively at an early stage. Patients should carry a card stating that they have diabetes and are treated with insulin or oral hypoglycaemic agents. Relatives, friends or colleagues at work or at school should be familiar with the signs of hypoglycaemia and its emergency treatment. The importance of regular meals and snacks must be emphasised, and treatment should be adjusted appropriately for sporting activities or for special situations such as fasting before radiological procedures or minor surgery. If Beta-blocking drugs are needed, cardioselective agents should be used. The widespread use of highly purified human insulins should reduce the problem of hypoglycaemia associated with high titres of insulin antibodies. The therapeutic goal has to be modified in diabetic patients with autonomic neuropathy, hypoglycaemia unawareness of severe diabetic complications. Very strict glycaemic control should be avoided where the risks of hypoglycaemia outweighs any potential benefit, such as in long-standing, type 1 patients who have impaired glucose counter-regulation, or in elderly or mentally subnormal patients. Intensive insulin therapy may also be impractical in treating infants or very young children. Moderate hyperglycaemia may have to be accepted in these individuals to avoid the greater risks of low blood glucose concentrations. Although there is no evidence in humans that hypoglycaemia causes foetal damage in early pregnancy, very tight glycaemic control reduces the ability to perceive hypoglycaemic symptoms and increases the risk of coma and convulsions, which are clearly undesirable for foetal development. Rapid tightening of glycaemic control is now considered to have an initial potentially adverse effect on established microangiopathy and also increase vulnerability to hypoglycaemia. Because of the potential risk of hypoglycaemia, type 1 individuals are usually advised not to participate in high-risk sporting activities such as hand-gliding, parachute jumping or scuba-diving. They may also be excluded from certain types of employment. They are usually debarred from driving public-service vehicles, fly aeroplanes and may not be permitted to operate some forms of machinery.

9.11 Diabetic Ketoacidosis, Hyperosmolar Hyperglycaemic State and Lactic Acidosis

Rajesh Rajput

INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are potentially life-threatening complications in patients with diabetes mellitus representing two extremes in the spectrum of uncontrolled diabetic state. DKA happens predominantly in those with type 1 diabetes, while HHS is seen in patients with type 2 diabetes under certain circumstances. HHS differs from DKA in the magnitude of dehydration, ketosis, and acidosis. In as many as one-third of cases, the clinical features of HHS and DKA overlap and are observed simultaneously (overlap cases).

PATHOPHYSIOLOGY

In both DKA and HHS, the underlying metabolic abnormality results from combination of absolute or relative insulin deficiency and increased amount of counter-regulatory hormones (**Figure 1**). In DKA, the lack of insulin and corresponding excess of glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver. The combination of insulin deficiency and hyperglycaemia reduces hepatic levels of fructose 2,6-biphosphate, which alters the activity of phosphofructokinase and fructose 1,6-bisphosphate. Glucagon excess decreases the activity of pyruvate kinase, whereas insulin deficiency increases the activity of phosphoenolpyruvate carboxykinase and, thus, promoting gluconeogenesis. Ketosis results from marked increase in free fatty acid release from adipocytes secondary to insulin deficiency and increases ketone body (acetoacetate and β-hydroxybutyrate) formation in the liver through activation of carnitine palmitoyl-transferase I secondary to hyper-glucagonaemia. This enzyme is crucial for regulating fatty acid transport into the mitochondria, where β-oxidation and conversion to ketone body occurs. The ketone bodies, however, have a low pH and cause metabolic acidosis. The absence of ketosis in HHS is not completely understood. Contributing factors include availability of insulin in amounts sufficient to inhibit ketogenesis but not sufficient to prevent hyperglycaemia. Additionally, hyperosmolarity itself may decrease lipolysis, limiting the amount of free fatty acids available for ketogenesis. Also, lower levels of counter-regulatory hormones have been found in patients with HHS compared with those with DKA.

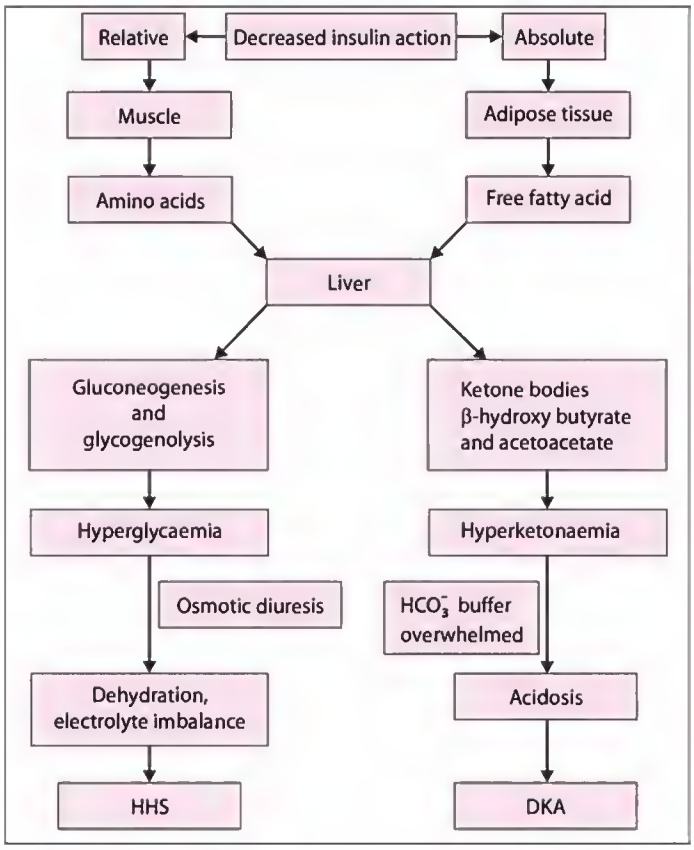


Figure 1: Pathophysiology of DKA and HHS.

CAUSES

Infections, especially pneumonia and urinary tract infection, remain the most common precipitating factor in the development of DKA and HHS. DKA may also be the first presentation in patients with type 1 diabetes. Young patients with recurrent episodes of DKA may have an underlying eating disorder, or may be using insufficient insulin for fear that it will cause weight gain. In around 5% of cases, no cause for the DKA is found. Any illness that predisposes to dehydration may lead to HHS. Various other precipitating factors for HHS are silent myocardial infarction, cerebrovascular accident, mesenteric ischaemia, acute pancreatitis and use of various medications, such as steroids, thiazides, diuretics, calcium channel blockers, propranolol, and phenytoin.

CLINICAL FEATURES

DKA usually develops in younger, lean type 1 diabetes patients and develops within a day or so while HHS is usually occurs in older and obese type 2 diabetic patient and develop over days or weeks and is often preceded by illness, e.g. vomiting or chronic co-morbidity, e.g. dementia, immobility that results in several days of increasing dehydration. Predominant symptoms in DKA are nausea and vomiting, pronounced thirst, excessive urine production, and abdominal pain that may be severe. In severe DKA, breathing becomes laboured and of a deep, gasping character known as 'Kussmaul respiration'. The abdomen may be tender to the point that an acute abdomen may be suspected, such as acute pancreatitis, appendicitis or gastrointestinal perforation.

On physical examination there is usually clinical evidence of dehydration, such as a dry mouth and decreased skin turgor. If the dehydration is profound enough to cause a decrease in the circulating blood volume, tachycardia and low blood pressure may be observed. In DKA a 'ketotic' odour is present, which is

often described as 'fruity'. If Kussmaul respiration is present, this is reflected in an increased respiratory rate. The patient of HHS may present with focal or global neurologic changes like drowsiness, lethargy, delirium, coma, focal or generalised seizures, hemiparesis, and sensory deficits.

DIAGNOSIS AND LABORATORY INVESTIGATIONS

Laboratory features differentiating between DKA and HHS are summarised in **Table 1**. DKA is characterised by hyperglycaemia, ketosis and increased anion gap metabolic acidosis. American Diabetes Association categorises DKA into one of the three stages of severity:

Mild: Blood pH mildly decreased to between 7.25 and 7.30 (normal 7.35 to 7.45); serum bicarbonate decreased to 15 to 18 mmol/L (normal above 20); the patient is alert

Moderate: pH 7.00 to 7.25, bicarbonate 10 to 15, mild drowsiness may be present

Severe: pH below 7.00, bicarbonate below 10, stupor or coma may occur.

Table 1: Differences Between DKA and HHS

	DKA	HHS
Plasma glucose (mg/dL)	>250	>600
Arterial pH	<7.3	>7.3
Sodium bicarbonate (mEq/L)	<15	>15
Serum and/or urinary ketones	Positive (>1:2 dilution)	Negative
Effective serum osmolality (mOsm/kg)*	Variable	>320
Anion gap**	>12	<12
Mental status	Variable (depends on severity)	Usually stupor or coma
Total water deficit (mL/kg)	100	100 to 200
Sodium (mEq/kg)	7 to 10	5 to 13
Chloride (mEq/kg)	3 to 5	5 to 15
Potassium (mEq/kg)	3 to 5	4 to 6

**Total and effective serum osmolality:*
Total serum osmolality (mOsm/kg): 2[measured serum sodium (mEq/L) + glucose (mg/dL)/18] + BUN (mg/dL)/2.8] (normal 290 ± 5)
Effective serum osmolality (mOsm/kg): 2[measured serum sodium (mEq/L) + glucose (mg/dL)/18] (normal 285 ± 5)
*** Anion gap: Na^+-Cl^- + HCO_3^- (normal 12 ± 2)*

While diagnostic features of HHS include plasma glucose level of 600 mg/dL or greater, total serum osmolality of 330 mOsm/kg or greater and absence of severe ketoacidosis. Since pH on a venous blood gas level is 0.03 lower than pH on an arterial blood gas (ABG) analysis, venous pH may be used for repeat pH measurements. Because this difference is relatively reliable and not of clinical significance, there is almost no reason to perform the more painful ABG. The Acetest and Ketostix products measure blood and urine acetone and acetoacetic acid. They do not measure the more common ketone body, β-hydroxybutyrate, so the patient may have paradoxical worsening of ketosis as the latter is converted into the former during the treatment. However, this should not be a matter of concern when patient is improving as suggested by change in pH and bicarbonate levels. Serum or capillary β-hydroxybutyrate can be used to follow response to treatment. Levels greater than 0.5 mmol/L are considered abnormal, and levels of 3 mmol/L correlate with the need for DKA treatment. Patients with DKA who are in a coma typically have effective osmolalities >320 mOsm/kg H_2O. If the osmolality is less than this in a patient who is comatose, search for another cause of obtundation such as cerebrovascular accident, head injury, hyponatremia, meningitis and or rhinocerebral mucormycosis. Hyperamylasemia may be seen, even in the absence of pancreatitis. BUN level is increased due to dehydration. Other relevant investigations include measurement of serum potassium, blood culture, urinalysis and urine culture, chest radiography and electrocardiography.

DIFFERENTIAL DIAGNOSIS

Ketoacidosis is not always the result of diabetes. It may also result from alcohol excess and from starvation; in both states the glucose level is normal or low. Metabolic acidosis may occur in diabetics for other reasons, such as chronic renal failure, shock due to any cause and poisoning with ethylene glycol or paraldehyde (**Tables 2 and 3**).

MANAGEMENT

Volume contraction is hallmark of DKA and HHS. It contributes to hyperglycaemia by decreasing renal clearance of glucose, causes insulin resistance by decreasing insulin delivery to the site of insulin-mediated glucose disposal and through stimulation of catecholamine and glucocorticoids. If severe enough to cause hypotension, it contributes to

Table 2: Differential Diagnosis of Acidosis and Coma

	Diabetic Ketoacidosis	Lactic Acidosis	Uraemic Acidosis	Alcoholic Ketosis	Starvation Ketosis	Methanol or Ethylene Glycol Toxicity	Rhabdomyolysis
Plasma glucose	↑	N	N	↓	N or ↓	N	N
Glucosuria	++	–	–	–	–	–	–
Plasma ketones	↑↑	N	N	↑	↑	N	N
pH	↓	↓	↓	N or ↓	N	↓↑	↑
Anion gap	↑	↑	↑	↑	↑	↑	↑
Osmolality	↑	N	↑	N	N	↑↑	N or ↑
Others		Serum lactate >5 mmol/L	↑ Urea and creatinine			Serum levels positive	Myoglobinuria Haemoglobinuria

acidosis through lactic acid production as well as decreased renal clearance of organic as well as inorganic acids. Therefore, fluid resuscitation is a critical part of treating DKA and HHS and it should be started even before insulin therapy. Intravenous solutions replace extravascular and intravascular fluids and electrolyte losses. They also dilute both the glucose levels and the levels of circulating counter-regulatory hormones.

Administer high volumes of isotonic saline (1 to 3 L) in 2 hours. Further isotonic saline should be administered at a rate appropriate to maintain adequate blood pressure and pulse, urinary output, and mental status. After initial stabilisation with isotonic saline, switch to half-normal saline at 200 to 500 mL per hour (half-normal saline matches losses due to osmotic diuresis).

Table 3: Clinical Pearls in Diagnosis and Management

Pseudohyponatraemia: Osmotic effect of hyperglycaemia moves intravascular water to the extravascular space and causes pseudohyponatraemia. Correct serum sodium by approximately 1.6 mEq/L for 100 mg/dL of glucose over 100 mg/dL.

Potassium: May be normal despite depletion of body stores due to metabolic acidosis.

Serum creatinine: May be falsely elevated due to elevated acetoacetate (ketone body).

Captopril (ACE-Inhibitor): May cause false positive reaction for ketone by nitroprusside test/ketostix.

Total leucocytes: Raised with DKA *per se* and does not suggest presence of infection until more than 15×10^9/L or marked left shift is present.

Body temperature cannot be used as a guide to the presence of infection: vasodilation causes warm feeling while core body temperature is reduced.

Hyperamylasaemia: Seen in DKA and is of salivary origin. Cannot be used as a marker for the diagnosis of pancreatitis.

Hypertriglycridaemia: Seen in DKA due to enhanced lipolysis and decreased uptake by liver. It can cause pseudohyponatraemia and when marked, precipitates pancreatitis.

Ketosis may worsen paradoxically with treatment due to conversion of β-hydroxybutyrate to acetoacetate.

Bicarbonate should be given only if pH is less than 6.9 or if pH is less than 7.1 along with hypotension or if hyperkalaemia is present.

Euglycaemic DKA: Plasma glucose may be normal in patient with decreased oral intake and in pregnancy.

Insulin is needed to help switch from a catabolic state to an anabolic state, with uptake of glucose in tissues and the reduction of gluconeogenesis as well as free fatty acid and ketone production. It should be started about an hour after intravenous fluid replacement. It is stared at a dose of 0.2 U/kg, intravenous, bolus followed by 0.1 U/kg per hour as continuous infusion. The rationale to give bolus dose is to saturate insulin receptors fully before beginning insulin infusion and to avoid lag time necessary to achieve steady-state insulin levels. There is no need to add albumin to prevent insulin absorption to the infusion set. However, intravenous tubing should be flushed with insulin infusate before use. In case glucose does not decrease by at least 10% or 50 mg/dL in an hour, insulin infusion rate should be doubled and a second bolus of insulin should be administered. When glucose levels have dropped to 250 mg/dL in DKA and 300 mg/dL in HHS, intravenous fluids should be switched to D5/1/2 NS to prevent hypoglycaemia, recognising that insulin is still needed to treat ketonaemia and rate of insulin infusion should be reduced to 1 to 2 U per hour. The glucose should be checked every 2 hours initially and at least every 4 hours subsequently until a stable insulin regimen is determined. After resolution of DKA (i.e. HCO_3^- >18, anion gap ≤12, and pH >7.3) or HHS (i.e. serum osmolality < 315 mOsm/kg and patient is alert) patient should be switched to subcutaneous insulin. In DKA insulin drip should be discontinued 30 minutes after giving subcutaneous insulin. In newly diagnosed diabetic patients, the initial dose of insulin should be 0.6 U/kg per day divided into a mixed regimen including both short- and long-acting insulin, until an optimal dose is established.

Potassium Replacement

Potassium replacement should be started with initial fluid replacement if potassium levels are normal or low. Add 20 to 40 mEq/L of potassium chloride (KCl) to each litre of fluid once K^+ is under 5.5 mEq/L. Potassium should ideally be given as two-thirds as KCl, one-third as potassium phosphate. If patient is oliguric do not administer potassium unless serum concentration is less than 4 mEq/L or there are ECG changes of hypokalaemia (U waves).

Bicarbonate typically is not replaced in DKA since acidosis will improve with the above treatments alone. Administration of bicarbonate has been correlated with cerebral oedema in children. Bicarbonate should be given only if pH is less than 6.9 or if pH is less than 7.1 along with hypotension or if hyperkalaemia is present. When indicated it should be given at the rate of 1 mEq/kg of bicarbonate as rapid infusion over 10 to 15 minutes with further therapy based on repeated ABG measurement done every 30 to 120 minutes. Additional potassium should be given with bicarbonate therapy as transient hypokalaemia is not uncommon during alkali administration.

Phosphate and magnesium replacements are not typically needed, since levels correct when the patient resumes eating.

COMPLICATIONS

Most patients with DKA recover when treated properly and majority of deaths result from late complications rather than from DKA itself (**Table 4**). Patients with HHS are predisposed to develop thromboembolic complications including cerebrovascular accident, myocardial infarction, mesenteric thrombosis, pulmonary embolism and disseminated intravascular coagulation. Various other complications seen in patients with HHS are cerebral oedema, adult respiratory distress syndrome and rhabdomyolysis.

PROGNOSIS

DKA accounts for 14% of all hospital admissions among diabetics and 16% of all diabetes-related fatalities. In children younger than 10 years, DKA causes 70% of diabetes-related fatalities. When managed appropriately the overall mortality is less than 5%. The overall mortality rate in HHS is between 10% and 20% and is dependent on co-existing conditions and complications.

Table 4: Complications in DKA

Complication	Clues	Treatment
Hypoglycaemia	Rebound ketosis, adrenergic or neurologic sign	Shift to DNS once plasma glucose falls to < 250 mg/dL and reduce insulin infusion to 2 to 3 U per hour
Hypokalaemia	Cardiac arrhythmia	Potassium replacement
Infection	Fever, WBC >15 × 10^9/L or marked left shift	Appropriate antibiotics
Myocardial infarction	Chest pain, new onset heart failure, hypotension despite adequate fluid therapy, ECG	Thrombolysis and other adjunctive measures
Cerebral oedema	Drowsiness, coma with or without neurological signs, especially if occurring after initial improvement	Intravenous mannitol 1 mg/kg, forced hyperventilation with aim to keep PCO_2 around 28 mm Hg
Acute gastric dilatation or erosive gastritis	Vomiting of blood or coffee ground material	Proton pump inhibitors
Mucormycosis	Facial pain, bloody nasal discharge, blackened nasal turbinates, blurred vision, proptosis	Intravenous amphotericin
Respiratory distress syndrome	Hypoxemia in the absence of pneumonia, chronic pulmonary disease or heart failure	Ventilatory support
Acute pulmonary oedema	Bilateral basal crepts with raised pulmonary capillary wedge pressure	Judicious fluid replacement, especially in those with co-morbidities such as renal failure or congestive heart failure. Diuretics, if needed
Vascular thrombosis	Stroke like picture or signs of ischaemia in non-nervous tissue	Anti-fibrinolytic and anti-coagulant therapy

PATIENT EDUCATION AND SICK DAY GUIDELINES

All patients with diabetes should be educated about the importance of monitoring plasma glucose levels during infection, trauma, and other periods of stress and not to stop insulin therapy in presence of any intercurrent illness (**Table 5**).

Table 5: Sick Day Guidelines

Never stop insulin and check for ketones
Measure plasma glucose four times a day
If RBG <200 mg/dL continue normal insulin
If RBG 200 to 250 mg/dL add extra 4 U with meals
If RBG >250 mg/dL add extra 6 U with meals, drink milk, fruit juice, plenty of fluids
If nausea, vomiting and RBG >250 mg/dL, consult your physician immediately

LACTIC ACIDOSIS

Definition and Epidemiology

Lactic acidosis is a condition of increased anion gap metabolic acidosis characterised by an excess of serum lactate due to lactate production that exceeds its systemic consumption. The normal blood lactate concentration in unstressed patients is 0.5 to 1 mmol/L. Patients with critical illness can be considered to have normal lactate concentrations of less than 2 mmol/L. Hyperlactataemia is defined as a mild-to-moderate persistent increase in blood lactate concentration (2 to 5 mmol/L) without metabolic acidosis, whereas lactic acidosis is characterised by persistently increased blood lactate levels, i.e. >5 mmol/L in association with metabolic acidosis. The overall incidence of lactic acidosis in critically-ill patients is unknown; however, increasing acid-base evaluations of critically-ill patients indicate that its presence is associated with increased morbidity and mortality.

Pathophysiology and Aetiology

Lactate is a product of anaerobic glycolysis and is generated from pyruvate with lactate dehydrogenase as a catalyst. Pyruvate is normally aerobically metabolised to CO_2 and H_2O in the mitochondrion in the process of gluconeogenesis. In the setting of decreased tissue oxygenation, lactic acid is produced as the anaerobic cycle is utilised for energy production. Lactate is cleared from blood, primarily by the liver (80% to 90%) and kidneys (10% to 20%). The lactate exits the cells and is transported to the liver where it is oxidised back to glucose. With a persistent oxygen debt and overwhelming of the body's buffering abilities (whether from chronic dysfunction or excessive production), lactic acidosis ensues. Lactic acidosis was described and classified into 2 types:

1. ***Type A lactic acidosis***

Occurs with decreased tissue ATP production due to poor tissue perfusion or oxygenation. It can further be sub-classified into two types:

(a) *Overproduction:* Circulatory, pulmonary, or haemoglobin transfer disorders are commonly responsible.

(b) *Underutilisation:* Liver disease, gluconeogenesis inhibition, thiamine deficiency, and uncoupled oxidative phosphorylation.

2. ***Type B lactic acidosis***

Occurs when evidence of poor tissue perfusion or oxygenation is absent. It is further divided into 3 subtypes based on underlying aetiology.

(a) *Type B1:* Seen in association with systemic disease, as such diabetes mellitus, bowel ischaemia, severe iron-deficiency anaemia, liver disease, alcoholic ketoacidosis, pancreatitis, malignancy (leukaemia, lymphoma, lung cancer), infection, renal failure, seizures, heat stroke, pheochromocytoma, thiamine deficiency, short gut syndrome, and other carbohydrate malabsorption syndromes.

(b) *Type B2:* Several classes of drugs and toxins are implicated including biguanides (phenformin, metformin), acetaminophen, alcohols, iron, isoniazid, nucleoside analogues (zidovudine, didanosine, lamivudine), β-adrenergic agents

(epinephrine, ritodrine, terbutaline), sodium nitroprusside, 5-flourouracil, sugars and sugar alcohols (fructose, sorbitol and xylitol), salicylates, sulphasalazine, strychnine and valproic acid.

(c) *Type B3:* Is due to inborn errors of metabolism. These include glucose-6-phosphatase deficiency (von Gierke disease), fructose-1,6-diphosphatase deficiency, pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, oxidative phosphorylation deficiency, and methylmalonic aciduria.

Clinical Features

No single clinical feature itself is indicative of the presence of lactic acidosis, as symptoms are dependent on the underlying aetiology. Nevertheless, a careful history is vital to determine the underlying pathology. The onset of acidosis may be rapid (i.e. within minutes to hours) or progressive (i.e. over a period of several days). The physical examination also depends on the underlying cause of lactic acidosis. Signs of cardiovascular compromise frequently include cyanosis, cold extremities, tachycardia, hypotension, dry mucous membranes, dyspnoea, confusion, lethargy, stupor, or coma. Hyperventilation is common as a compensatory mechanism causing respiratory alkalosis.

Laboratory Work-Up

No significant differences in serum lactate levels are noted in arterial and venous blood samples. The concentration of serum lactate must be measured as quickly as possible (within 4 hours of collection) in a sample transported on ice. The normal serum lactate level is approximately 1 mmol/L with a range up to 2 mmol/L. Values above 5 mmol/L in the setting of acidaemia are indicative of lactic acidosis. Additional laboratory tests may be selected on the basis of the suspected underlying aetiology of lactic acidosis.

Treatment

Treatment of lactic acidosis requires identification of the primary illness and appropriately directed therapy. Restoration of tissue oxygen delivery, thereby causing cessation of acid production, remains the primary therapeutic focus. Early goal-directed therapy for sepsis is well described and is associated with improved outcomes. Appropriate measures include treatment of shock, restoration of circulating fluid volume, improved cardiac function, identification of sepsis source and appropriate therapy, and resection of any potential ischaemic regions. Vital signs and cardiac rhythms must be monitored closely because acidosis predisposes to arrhythmias including tachyarrhythmias and fibrillation. Specific medications for the treatment of lactic acidosis include sodium bicarbonate, tris-(hydroxymethyl) aminomethane, carbicarb, and dichloroacetate. Toxic aetiologies of lactic acidosis such as methanol, ethylene glycol, and cyanide poisoning are unique circumstances that require bicarbonate therapy to facilitate the detoxification processes.

Prognosis

The duration and degree of increased serum lactic acid appear to predict morbidity and mortality. Normalisation of serum lactate concentration (<2 mmol/L) within the first 24 hours is associated with 100% survival, 78% survival if normalisation occurred in 24 to 48 hours, and only 14% survival if after 48 hours. The lactate level should be used only as a single tool in combination with clinical findings and other measures of circulatory failure rather than as a decisive indicator of disease severity.

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9.12 Infections in Diabetes Mellitus

Samar Banerjee

INTRODUCTION

Infection in diabetes mellitus (DM) is very common and important complication. DM predisposes to infection and infection in turn overwhelms the metabolic control. Effective control of each affects the control of the other condition. Diabetes is considered as a secondary immune deficiency disorder by World Health Organization (WHO).

Chronic hyperglycaemia impairs host defence. Some infections occur more in diabetics, whereas some other infections occurs both in diabetics and non-diabetics. The different types of immune alterations that occur in diabetes are described below.

IMMUNE ALTERATIONS IN DIABETES

1. Diminished chemotaxis, phagocytosis, and killing activity, of lymphocyte function (especially CD4 cells)
2. Lower levels of immunoglobulins and complement level (C4, C4A, C1q and C3)

Beyond these immune factors, local factors also predispose to infections as follows:

(a) Hyperglycaemia alters the endothelial function and increase the oxidative stress

(b) Angiopathy both micro and macro, produces anoxia and results in microbial proliferation, impairment of oxygen dependent polymorphonuclear function, and perfusion of antibiotics, etc.

(c) Sensory motor neuropathy produces pressure sores, ulcers, abnormal pressure points in the foot due to small joint arthropathy and small muscle myopathy of foot and microangiopathy predisposing to diabetic foot.

(d) Autonomic neuropathy is a predisposing cause of chronic urinary tract infection because of retention of urine in bladder. It also impairs the microvascular circulation. Microvascular impairment also leads to reduced renal blood flow and frequent renal infection and papillary necrosis is the consequence.

OTHER CONTRIBUTORY FACTORS

As part of disease management and the disease process, factors which make a diabetic more vulnerable to infection are as follows:

- Frequent hospitalisations
- Diabetic ketoacidosis
- Administrations of drug/fluid/blood intramuscularly or intravenously
- Inappropriate antibiotic usage
- Peripheral vascular diseases
- Neuropathy
- Gastroparesis, reflux and pulmonary aspiration
- Indwelling catheterisation
- Frequent minor/major surgery
- Chronic renal failure requiring dialysis and blood transfusion.

Infections commonly seen in diabetics are presented in **Table 1**. Out of all these chronic infections, which are most important are diabetic foot, cholecystitis, pyelonephritis, candidiasis, rhinocerebral mucormycosis, Hepatitis C and HIV, etc.

Table 1: Common Infections in Diabetes

Bacterial
Tuberculosis, bacterial pneumonia
Malignant otitis externa
Pyelonephritis
Necrotising fasciitis
Staphylococcal infections
Erythrasma
Perinephric abscess
Non-clostridial gas gangrene
Cholecystitis
Periodontal infection
Fungal
Candidiasis
Mucormycosis
Viral
Viral hepatitis, particularly C
HIV infections

HEPATITIS C AND DIABETES

Hepatitis C virus (HCV) infection and diabetes both are slowly and silently developing, diagnosed very late and often with complications at diagnosis. Patients with chronic HCV infection can lead to the development of type 2 diabetes. Allison *et al*, in 1994 reported in a study of 100 patients, with cirrhosis, 50% of cases related to hepatitis had diabetes whereas hepatitis C negative cirrhosis group had diabetes in 9% of cases. Similarly, higher incidence of HCV infection is noted amongst diabetics than non-diabetics.

Amarapurkar *et al*, in 2002, from India compared the aetiology of chronic liver diseases with and without DM, and found higher evidence of HCV than hepatitis B virus (HBV) in diabetics than non-diabetics.

DM may also be significantly associated with hepato-carcinogenesis in chronic HCV patients. Incidence of DM amongst HCV chronic infection are much higher than those with chronic HBV infection, alcoholic liver disease, and biliary cirrhosis. Older age, obesity, severe liver fibrosis and family history of DM are related to potential risk or developing DM in HCV infected patients. In patients with cirrhosis planned for hepatic transplantation, development of type 2 DM is 5 times higher than of HCV origin.

Though finger prick for blood sugar examination and insulin injection is a mode of transmission, different studies have ruled out the possibility.

Pathogenesis of Diabetes in HCV Infection

Multiple patho-mechanisms have been suggested but none is definitely confirmed. These are presented in **Table 2**. HCV infection is reported to induce insulin resistance due to liberation of different cytokines like TNFα, which inhibits tyrosine kinase phosphorylase pathway.

Table 2: Pathogenesis of Diabetes Mellitus in Hepatitis C Virus Infection

Hyperinsulinaemia, insulin resistance
Insulin deficiency or poor insulin secretion
Pancreatic infection by hepatitis C virus
Autoimmune β-cell damage
Non-alcoholic fatty liver disease
Increased iron stores

Effect of DM on HCV Positive Chronic Liver Disease

The three way interaction between the stages of chronic liver disease, diabetes and enzymatic cholestasis suggests that diabetes is a risk factor for the progression of viral liver disease at least in part by induction of cholestasis. High blood glucose in HCV infected persons leads to advanced and higher fibrosis.

DIABETES MELLITUS AND TUBERCULOSIS

Tuberculosis (TB) in diabetes is 2 to 5 times higher, diagnosed late, asymptomatic, and is usually due to reactivation of an old focus than fresh infection. In a large cohort of 8793 patients from India, Patel reported TB to be the most common associated illness (5.9%) with DM in India. Swai *et al*, in a prospective 7-year follow-up of 1250 diabetes patients, found that 5.4% cases developed pulmonary TB and 0.2% spinal TB. In 25.7% cases, TB was detected before DM, in 45.7% after DM and in 20.6% simultaneously. Though chances of TB are higher in diabetics, infection rate by *Mycobacterium tuberculosis* and tuberculin sensitivity are not higher compared to non-diabetics. Higher sputum positivity, more incidences of lung involvement particularly cavitations than other lung changes are noted. Though lower lobe involvement was claimed to be more in diabetes in earlier reports, recent observations are in consensus that distribution of lung affection are same as in non-diabetics (involving upper zone predominantly). Anorexia, weakness, sweating, and weight loss are common both to TB and DM. So appearance of any one illness over the other is detected very late.

Additional causes of increased susceptibility to TB in diabetes are: (a) thickened alveolar epithelium and pulmonary basal lamina leading to reduction of lung diffusion capacity, lung capacity and elastic recoil; and (b) reduced bronchial reactivity and dilation due to diabetic autonomic neuropathy.

Bacteriological conversion, relapse rate are same with diabetics and non-diabetics. But relapse in diabetes are mostly with resistant strain and with poor prognosis.

Probable causes of higher prevalence of DM in TB are shown in **Table 3**. Diabetic state usually improves with anti-TB drugs. But rifampicin can produce alimentary glycosuria and early phase hyperglycaemia.

Table 3: Various Causes of Higher Prevalence of Diabetes Mellitus (DM) and Tuberculosis (TB)

Reciprocal worsening by one of the other
Malnutrition and low body mass index
Pancreatic tuberculosis in rare cases
Stress induced DM due to TB
Pituitary and adrenocortical hyper-reactivity
Vitamin D deficiency

DM does not alter the symptomatology, drug response, resistance or localisation of the lung lesion. But in persons above 40 years and in females genders, lower lung field involvement is significantly high. Smear positive cases and radiologically reticulo-nodular appearance were less in TB with DM than opacity, cavitation, and pleural involvement. Cavitary lesions were higher in type 1 DM than type 2 DM.

Cavitary lesions though maintain high bacterial population, less smear positivity are noted in diabetes because this may be related to muscle weakness due to uncontrolled glycaemia and less effective expectoration. Higher frequency of lower lobe disease in elderly may be due to immunological alteration or higher frequency of primary TB, increased alveolar oxygen pressure in lower lobes.

Management strategy in TB and DM requires some special attention.

1. Requirement of high calorie and high protein diet (2,000-2,400 cal per day)
2. Problems with anti-tuberculosis drugs in DM
   (a) Rifampicin
   Accentuates destruction of sulphonylurea by drug interaction through P450 cytochrome oxidase enzyme
   Augments intestinal glucose absorption
   (b) Isoniazid
   Antagonises sulphonylurea action
   Rarely causes pancreatitis
   (c) Biguanides
   Loss of appetite and weight
   Malabsorption of glucose

Choice of anti-diabetic agents: sulphonylurea and biguanides have its real problems in TB. Moreover to combat higher calorie intake and rare cases of pancreatic TB, pancreatic stimulant oral hypoglycaemic should be avoided. Insulin is the only mode of treatment for lowering any degree of blood sugar within minimum time as few days of hyperglycaemia may affect the anti-TB drug response. Insulin also helps in inflammatory response and healing process.

Peculiarities of TB in DM

In DM, TB has got the following characteristics:

1. Relative paucity of physical signs and diagnosis made at far advanced stage.
2. Extensive caseation of lung tissue and cavitary lesions (bilateral or unilateral) are more in number.
3. Little pleural involvement.
4. Greater tendency of haemoptysis.

5. Less chance of extra-pulmonary involvement and endobronchial TB.
6. More cases of sputum positive disease

The intensity of TB depends upon the duration of DM in uncontrolled stage and if controlled judiciously, response of TB is same as in non-diabetic groups.

Preventive management

1. Persons who were Monteaux test negative and have recent conversion to tuberculin test should have isoniazid prophylaxis, if they are in close contact with an infective person.
2. All diabetics at the initial diagnosis and every year must have a chest radiograph done.
3. All diabetics with abnormal weight loss, unexplained cough or sudden increase of insulin requirement should have sputum examination and chest radiograph.

PERIODONTAL DISEASE AND DIABETES MELLITUS

Periodontitis or infection of the anchoring tissues surrounding the teeth due to anaerobic Gram-negative organisms has been claimed as sixth complication of DM. Poorly controlled diabetics are likely to develop this chronic infection as periodontal disease (PD) and in turn, this has the potential to alter blood sugar control also.

It has been postulated that sub-gingival bacterial content are higher in DM, leading to more severe disease. This is equally for type 1 and type 2 diseases but is dependent upon glycaemic control. Severe degree PD is also considered to be associated with higher risk of diabetic complications like proteinuria, stroke, angina, myocardial infarction, and heart failure than in diabetic patients with mild PD.

Treatment of PD shows significant reduction of HbA_1c. Finally these can be accepted that, periodontopathic bacteria increase cytokine release, which may amplify advance glycation end products (AGE) mediated cytokine response and *vice versa*. Thus, PD either precipitates or aggravates the diabetic process and its complications, and PD and DM enjoy a two-way relation. Proper dental health is another avenue to diabetes control.

HIV INFECTION AND DIABETES

The prevalence of frank DM in people with HIV is low with study reports from 0.5% to 15%. But IGT is much higher as estimated to be 15% to 25%. Some degree of insulin resistance is also noted up to 50% cases on protease inhibitor therapy. Co-infection with HCV is found in 40% cases of HIV positive persons and is more likely to develop DM or insulin resistance. If HCV infection occurs in HIV positive cases, the risk of developing hyperglycaemia becomes five times. Elevated levels of ALT liver enzyme is an indicator for liver inflammations and predicts insulin resistance in HIV cases with lipodystrophy in the presence or absence of hepatitis B and C. HIV-related hyperglycaemia, whether will have the negative health sequences like complications of DM are not yet settled but probably will have the same fate as in HIV negative cases with hyperglycaemia.

Common causes of insulin resistance in HIV infection are shown in **Table 4**.

Table 4: Common Causes of Insulin Resistance in HIV Infection

Protease inhibitor therapy
Lipodystrophy
Increased local or systemic inflammatory mediators
Hepatic lipid accumulation
Muscle lipid accumulation
Hepatitis C infection
Reduced systemic adiponectin, leptin and increased resistin
Low testosterone

Protease Inhibitor Therapy

Protease inhibitor therapy directly affects blood glucose metabolism than due to alteration of body fat gain or loss.

Among the protease inhibitors (PIs), indinavir is strongly related to glucose intolerance and insulin resistance has been detected within 2 to 8 weeks of treatment even in HIV-negative persons. Regarding other proteases inhibitor, atazanavir has lowest effect and amprenavir (after 48 weeks of therapy) and saquinavir have got moderate effect on insulin glucose axis.

Diagnosis and Monitoring of DM in HIV Positive Cases

International acquired immunodeficiency syndrome (AIDS) Society recommends (2002 guidelines) fasting blood glucose before HAART, 3 to 6 months after drugs and at least annually or protease inhibitor therapy. For person's high-risk for insulin resistance, OGTT may be performed. Substitution of protease inhibitor by other antiretroviral drugs if possible (e.g. nevirapine or efavirenz or abacavir) may be practiced.

Diabetic patients are at higher risk for acquiring HIV infection because of multiple needle pricks. Diabetics can also contract HIV from multiple surgical interventions or dialysis and blood transfusion when chronic renal failure develops.

Whether HIV infections alone like HCV infection can produce DM or IGT is not yet clear but it is proved beyond doubt that HAART regimen particularly indinavir is definitely correlated. The risk of acquiring DM in HIV positive cases are more with concomitant HCV infections, obesity, genetic background, etc. Screening for DM should be done with protease inhibitor therapy and more frequently in high-risk cases. Lifestyle modification is of choice, metformin or glitazones can be added subsequently.

RHINOCEREBRAL MUCORMYCOSIS

50% cases of these occurs in a diabetic person and is a life-threatening flare in a person chronically infected with the organism, *Rhizopus oryzae*. During diabetic ketoacidosis the inhibitory effect of serum passes away and the disease flares. But this inhibitory effect is restored after correcting acidosis. Early manifestations are facial, ocular or nasal pain with nasal stuffiness and discharge. Subsequent manifestations are proptosis, chemosis, necrotic black lesions on palate or nasal mucosa, fever, headache, ophthalmoplegia, and visual loss from cavernous sinus thrombosis. Haemiparesis may be seen due to thrombosis of carotid artery or jugular vein.

Diagnosis is confirmed by demonstration of non-septate, haphazardly branching hyphae from biopsy of necrotic tissue. Magnetic resonance imaging is essential to identify the extent of involvement. Surgical debridement of infected tissue,

drainage of the sinuses with amphotericin B injection is the treatment of choice.

CHOLECYSTITIS

Chronic cholecystitis with or without cholelithiasis is very common in diabetes, probably because of supersaturation of bile, chronic infection, impaired gall bladder motility, decreased cholecystokinin release and hepatic impairment. Emphysematous cholecystitis, an uncommon gas producing virulent infection is similar to acute cholecystitis, but more frequent in males, with higher mortality due to gangrene or perforation. 35% of cases occur in diabetes and 50% contain gallstone. Crepitus on abdominal palpation, demonstration of gas in radiograph or computed tomography (CT) helps in diagnosis. Prompt cholecystectomy with broad-spectrum antibiotics like ampicillin-sulbactam 3g intravenously every 6 hours are the choice of treatment. Autonomic nervous dysfunction, BMI, LDL cholesterol, and advancing eye have been shown to have adverse impact on function of gall bladder.

CHRONIC PYELONEPHRITIS AND CYSTITIS

Chronic urinary tract infection is 2 to 4 times common in diabetics, particularly in women and in the presence of autonomic neuropathy and retained bladder. Bilateral infection is also more frequently seen with diabetes. Acute manifestations as emphysematous pyelonephritis presenting with fever, loin pain, haematuria, pneumaturia, is a life-threatening situation and in 90% cases occurs in diabetes only. It is produced by gas forming organisms, *Escherichia coli* in 50% to 70% cases and is complicated by papillary necrosis in 21% of cases.

Failure of remission of fever with therapy for urinary tract infection after 3 to 4 days in diabetics, possibility of emphysematous pyelonephritis and perinephric abscess should be thought of. Abdominal CT is better than other radiological methods for the diagnosis. Vigorous hydration and intravenous antibiotics with percutaneous CT guided drainage or nephrectomy are the modalities of treatment. Chronic fungal urinary tract infection particularly due to candidiasis is also common in diabetes. It can involve both upper and lower urinary tracts. Affection localised to the bladder may be also due to colonisation than infection but pyuria supports the later. Indwelling catheter if any should be removed. Bladder irrigation with amphotericin B, single dose of amphotericin B or oral fluconazole for 4 days is the treatment of choice.

CHRONIC INFECTIONS IN DIABETIC FOOT

This is a frequent complication and most neglected issue by both the patient and the treating physician. This is discussed in a separate chapter (Chapter 19 of this section).

FUNGAL INFECTIONS IN DIABETES

These are very common but most neglected situation presenting as oropharyngeal candidiasis, candidial vulvovaginitis a common mode of presentation in type 2 DM, inter-triginous candidiasis leading to gangrene of foot and paronychia.

Prevention of infections in diabetes can be adopted as follows:

Maintenance of good hygiene
Standard immunisation
Frequent check-ups
Foot care
Antibiotics usage
Catheterisation, IV lines with proper care

CONCLUSIONS

DM produces immune alterations of both cellular and humoral immunity and often complicated by acute or chronic infections. Common infections in DM are TB, pyelonephritis, *Staphylococcal* infections, cholecystitis, candidiasis, viral hepatitis, etc. Hepatitis C may be an aetiological agent for DM. TB in DM is 2 to 5 times higher. Chances of recurrence with multidrug resistant bacteria are common. More cavitary lesions, less sputum positivity and with relative paucity of symptoms and signs are the features. Treatment for DM should be done with insulin. Periodontitis is a complication of DM and DM may worsen from periodontitis also. Proper dental care should be a part of diabetic control. Protease inhibitor therapy in HIV infection can lead to development of insulin resistance. But whether HIV produces β-cell damage is not known. HIV and DM may be complicated by HCV infections. Rhinocerebral mucormycosis, cholecystitis, chronic urinary tract infection, and candidiasis are other common chronic infections in DM.

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9.13 Macrovascular Complications of Diabetes

Murlidhar S Rao

Diabetes mellitus (DM) directly and indirectly affects on human vascular tree and these constitute major source of morbidity and mortality in both type 1 and type 2 diabetes. Generally, injurious effects of hyperglycaemia are divided into: (a) macrovascular complications, viz. coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular stroke; and (b) microvascular complications, viz. diabetic nephropathy, neuropathy, and retinopathy.

MACROVASCULAR DISEASE IN DIABETES

Unlike the microvascular disease which gets clicked with the onset of diabetes, the macrovascular disease antedates the development of diabetes by several years. Around 75% to 80% of all diabetic patients will die, many prematurely of cardiovascular (macrovascular) disease (CVD), particularly coronary heart disease (CHD). Diabetic foot problems (gangrene, large non-healing infected ulcers) are the commonest cause of non-traumatic lower limb amputation. In one Indian study done at Chennai, the prevalence of CHD was 21.4% among diabetic patients, 14.9% among IGT subjects and 11% among non-diabetic patients. The prevalence of PAD in the same population was 6.3%. There is a close relationship existing between pre-diabetes, diabetes and macrovascular (cardiovascular) disease throughout life; and the substantial body of evidence supports the concept that increased risk of morbidity and mortality due to CVD is associated with abnormalities in glucose metabolism across the entire continuum of glucose tolerance ranging from normal to clinical diabetes.

Aetiopathogenesis

The central mechanism in macrovascular disease is the process of atherosclerosis which leads to narrowing of the arteries throughout the body. Atherosclerosis is a progressive disease of the arterial wall involving the components of inflammation, vascular lipid deposition and remodelling, fibrosis, and thrombosis. Diabetes is a major independent risk factor for CHD resulting from accelerated atherosclerosis of the coronary arteries occurring at a much earlier age and advancing more rapidly to clinical cardiovascular events in persons with diabetes than in those without it. This was shown in the very early studies like 'Framingham study' and more recent studies have shown that the risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in non-diabetic patients with a history of previous MI. American Diabetes Association (ADA) and American Heart Association (AHA) have declared that diabetes is a coronary artery disease equivalent rather than a risk factor. Multivariate analyses of a number of large prospective studies with a follow-up of 12 to 20 years have shown that diabetes is associated with 2- to 5-fold increase in CHD and premature cardiovascular-related deaths in both type 1 and type 2 diabetes.

Atherosclerosis in diabetes is typically more diffuse, heterogeneous and extensive, occurring earlier and faster and more often associated with high-risk, unstable and vulnerable plaque with a large lipid core covered by thin fibrous cap which can easily rupture and result in acute coronary syndrome and death than in those without the diabetes. Diabetes, therefore, has definite accelerating impact on the pathogenesis of atherosclerosis which, in fact, is not qualitatively different from that occurring in non-diabetic individuals.

EFFECTS OF DIABETES ON PATHOGENESIS OF ATHEROSCLEROSIS

1. Endothelial Dysfunction

Endothelium which is the innermost layer of the blood vessels and in fact the largest organ of the body is the initial and common target of all cardiovascular risk factors. The functional impairment of the vascular endothelium in response to injury occurs long before the development of visible atherosclerosis. The endothelial cell behaves as a receptor-effective structure which senses different physical or chemical stimuli that occur inside the vessel and, therefore, modifies the vessel shape or releases the necessary products to counteract the effect of the stimulus and maintain homeostasis. The endothelium is capable of producing a large variety of different molecules including the vasodilators (nitric oxide [NO] and prostacyclin) and vasoconstrictors (endothelin-1 and angiotensin II) and nicely balancing their effects. When this delicate balance is lost, the conditions are given for the endothelium to be invaded by lipids and leucocytes (monocytes and T-lymphocytes). The inflammatory response is incited and fatty streaks appear – the first step in the formation of the atheromatous plaque which may later rupture and set the conditions for thrombogenesis and vascular occlusion. Therefore, endothelial dysfunction which is universal in diabetes is the starter in the process of atherosclerosis and many other factors are the chasers. As a result of this, vascular NO synthesis and stability are reduced and there is an impairment of endothelium-dependent NO-mediated vasodilatation in diabetes. In the presence of endothelial dysfunction the powerful vasoconstrictors like endothelin-I and angiotensin-II replace the vasodilators, NO and prostacyclin.

2. Oxidative Stress

Oxidative products are produced as a consequence of normal aerobic metabolism. These molecules are highly reactive with other biological molecules and are referred to as reactive oxygen species (ROS). Under normal physiological conditions, ROS production is balanced by an efficient system of antioxidants, molecules that are capable of neutralising them and, thereby, preventing oxidant damage. In pathological states, ROS may be present in relative excess. This shift of balance in favour of oxidation termed 'oxidative stress' may have detrimental effects on

cellular and tissue function and the cardiovascular risk factors generate oxidative stress.

Both type 1 and type 2 diabetic patients are under enhanced oxidative stress. Hyperglycaemia causes non-enzymatic glycosylation of proteins and phospholipids, thus increasing the intracellular oxidative stress. Therefore, advanced glycosylation end products (AGEs) formed later in this process are stable and virtually irreversible and generate ROS with consequent increased vessel oxidative damage and atherogenesis.

3. **Activation**

Activation of polyol pathway and diacylglycerol (DAG), protein kinase C (PKC) cascade are the other consequences of persistent hyperglycaemia (uncontrolled diabetes). Excess of intracellular glucose is metabolised by sorbitol pathway; and there is also rise in DAG, PKC levels intracellularly consequent to persistent hyperglycaemia. This occurs in many tissues including heart, aorta, glomeruli and retina.

4. **Other Factors**

There are many cardiovascular risk factors in diabetes and insulin resistance (IR). These are metabolic and lipid-related factors, coagulation and inflammatory factors and vascular-related factors (**Table 1**). Some of them are primarily related to diabetes while others may be found in diabetic as well as non-diabetic individuals.

Type 2 diabetes and IR typically occur in the setting of metabolic syndrome which also includes visceral (abdominal) obesity, hypertension, dyslipidaemia, and increased coagulability all of which lead to atherosclerosis (**Figure 1**). Even in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of ischaemic heart disease (IHD), stroke, and death. Among people with type 2 diabetes women may be at a higher risk for CHD than men. The prevalence of microvascular disease in itself is also a predictor of CHD.

Diabetes is a strong independent predictor of risk for stroke and cerebrovascular disease. Patients with type 2 diabetes have a much higher risk of stroke nearing 150% to 400%. Stroke-related dementia, cognitive disturbances, recurrence as well as stroke-related mortality are elevated in patients with diabetes. The impressive correlation between CAD and alteration in glucose metabolism has raised the hypothesis that atherosclerosis and diabetes may share common antecedents. Large vessel atherosclerosis can precede the development of diabetes suggesting that rather than atherosclerosis being a complication of diabetes both conditions may share common genetic and environmental antecedents, a 'common soil'.

Important steps in the initiation and growth of atherosclerotic plaque are:

1. Endothelial dysfunction and injury
2. Sub-endothelial monocyte/macrophage accumulation
3. Lipoprotein infiltration
4. Smooth muscle cell proliferation
5. Influence of T lymphocytes and other inflammatory cells and protein lipid accumulation in foam cells finally leading to plaque formation and adhesion thrombosis.

Table 1: Cardiovascular Risk Factors Associated with Diabetes and IR

Metabolic Factors
- Hyperglycaemia
- Insulin resistance
- Visceral obesity
- Hyperinsulinaemia
- Hypertriglycerdaemia
- Reduced HDL cholesterol
- Small dense LDL
- Hyperhomocysteinaemia
- Increased lipoprotein (a)
- Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

Coagulation and Inflammatory Factors
- Increased PAI-1 (plasminogen activator inhibitor-1)
- Increased platelet activation
- Increased fibrinogen
- Increased adhesion molecules (VCAM1 and ICAM1)
- Increased tissue factor and factor 7
- Decreased NO bioavailability
- Increased C-reactive protein
- Infections: Cytomegalovirus, *Chlamydia pneumoniae*, *Helicobacter pylori*, *Bacteroides gingivalis*

Vascular-Related Factors
- Hypertension
- Impaired endothelium-dependent vasorelaxation
- Chronic smoking
- Microalbuminuria
- Increased arterial calcification
- Decreased arterial compliance

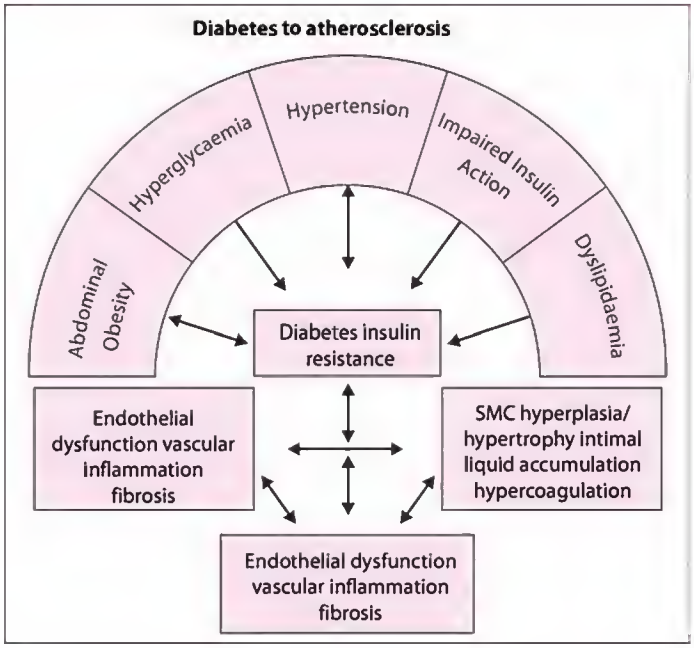


Figure 1: Diabetes to atherosclerosis

SMC = Smooth muscle cell

CLINICAL MANIFESTATIONS OF MACROVASCULAR DISEASE

Cardiovascular Disease

Cardiovascular syndromes in patients with diabetes present in similar ways to those in non-diabetic population, although many patients are younger, outcomes are worse, and ischaemic

events are more likely to be 'painless' (or rather silent) due to associated cardiac autonomic neuropathy. A cluster of cardiovascular risk factors clinically relevant are associated with diabetes, pre-diabetes, and IR and have to be looked into while evaluating the diabetic patients. These are:

1. Abdominal obesity with increased waist circumference (> 90 cm in men and >80 cm in women) *acanthosis nigricans*, 'hump'-like fatty bulge nape of the neck
2. Hypertension (>140/90 mmHg)
3. Dyslipidaemia
   - Increased triglycerides
   - Decreased HDL cholesterol
   - Small dense atherogenic LDL particles
   - Post-prandial lipaemia
4. Microalbuminuria
5. Increased levels of PAI-1 activity and fibrinogen

The clinical syndromes of myocardial ischaemia due to occlusive CAD are:

1. Angina

Angina may be relatively painless and can present atypically in long-standing type 2 diabetic patients, particularly the older ones with autonomic (sensory) neuropathy. Diabetic patients are more likely to remain asymptomatic while showing the ECG changes during exercise testing or ambulatory (Holter) ECG monitoring. Such diabetic patients of angina show reversible ischaemia on myocardial isotope perfusion scanning in the absence of obvious angina. Silent myocardial ischaemia carries a more ominous prognosis in diabetic patients than in the non-diabetic people.

2. Acute coronary syndromes

Unstable angina, non-ST elevation MI, and ST elevation MI represent a major cause of death in the diabetic population. These may also be painless or present with other symptoms like acute dyspnoea (left ventricular failure, LVF), a variety of cardiac arrhythmias often lethal, cardiogenic shock, or sudden death. Malaise, nausea and vomiting, profuse sweating or collapse are the accompanying features. Because of loss of normal circadian pattern of autonomic cardiovascular regulation, most acute ischaemic events occur during the evening and at night among diabetic patients. Diabetic patients who suffer an MI have a higher mortality than non-diabetic patients both in acute phase and on long-term follow-up. Infarct expansion or/and extension and recurrence of infarction, acute LVF, and congestive heart failure (CHF) all occur more commonly in the diabetic population than the non-diabetic population.

Serial determinations of CK-MB and quantitative estimation of troponins are more useful in assessing the infarct size and recurrence. All modes of echocardiography (2-D, Doppler and myocardial contrast echo) are extremely useful in assessing the LV size and function, myocardial viability, presence of any thrombus in the LV or its walls and other mechanical complications like mitral regurgitation, ventricular septal rupture or ventricular aneurysm. A major cause of adverse outcomes is the five-fold higher frequency of cardiac failure.

3. Heart failure

Heart failure (HF) is 2 to 5 times more common in diabetic population than in non-diabetic population. HF can occur even in the absence of obvious CAD. Aetiology of HF in diabetes is complex; factors include the systolic and diastolic performance of the LV affected by diabetic cardiomyopathy (diabetic heart muscle disease), the superimposed deleterious consequences of hypertension and further loss of functioning myocardium following acute coronary artery occlusion. The contractility of the non-infarcted myocardium in diabetes is much reduced which adds further to HF.

4. Cardiac dysrhythmias

They are related to ischaemia, left ventricular hypertrophy or CAN and frequently occur in diabetic subjects following MI and may result in sudden death. Decreased heart rate variability and subtle changes in CV reflexes due to CAN in the diabetic patients result in lethal cardiac dysrhythmias.

5. Diagnosis of ischaemic heart disease

ECG, stress testing either treadmill (TMT) or pharmacologic (Dobutamine), ambulatory ECG (Holter) monitoring, echocardiography and ultimately coronary angiography should be done at appropriate times in the diabetic patients with IHD with or without symptoms. Coronary revascularisation can be very beneficial in the diabetic patients with CAD.

Cerebrovascular Disease

Transient ischaemic attack and stroke are more frequent among diabetic patients, than in the non-diabetic patients particularly those who had acute coronary ischaemic event earlier. Lacunar infarcts, large infarcts and multi-infarct disease occur more often among the diabetic population than in the non-diabetic population. Haemorrhagic strokes occur less commonly. The prognosis of stroke is also worse in the diabetic patients. Hypertension often coexists and worsens the situation. Coma, convulsions and dense hemiplegias are often present. Carotid artery Doppler and B-Mode ultrasound imaging to measure the carotid intima-media thickness (IMT, abnormal if more than 1.1 mm) is an extremely simple and yet accurate indication of the diffuse atherosclerosis occurring in coronary and other arteries. The obstructive athero-plaques may be found in the carotid arteries by ultrasound and colour Doppler. CT or MRI brain and MR angiography of the brain are extremely useful in diagnosis as well as in prognosticating the stroke. Stroke-related dementia and recurrence of stroke are more frequent in diabetic patients. Cerebrovascular mortality rate is higher in both type 1 and type 2 diabetic patients.

Peripheral Arterial Disease

PAD is 2 to 3 times more frequent in diabetic males and 5 to 6 times more common in diabetic females. Diabetes is the commonest cause of non-traumatic limb amputation. Smoking, hypertension and dyslipidaemia and associated peripheral neuropathy contribute to the increased prevalence of PAD in diabetic patients. Clinical presentation of ischaemic limb disease extends over a wide spectrum of intermittent claudication, critical limb ischaemia, and gangrene resulting from total peripheral artery occlusion. Limb pain either at rest or on walking is suggestive of occlusive PAD. Acute limb ischaemia

characterised by pain, paraesthesia, pallor, pulselessness and perishingly cold limb may also occasionally occur. Chronic lower limb ischaemia involving popliteal and tibial arteries results from atherosclerosis in the diabetic individuals. The combination of ischaemic PAD, peripheral neuropathy, injury and infection results in diabetic foot disease.

MANAGEMENT OF CARDIOVASCULAR DISEASE IN DIABETES

The principles of management are the same as in normal population and are dealt with in detail in respective chapters. The difference is that diabetic patients require high degree of suspicion and aggressive treatment plan because of their poor prognosis as compared to non-diabetic patients.

HEART FAILURE AND DIABETIC CARDIOMYOPATHY

Please see chapter on Heart Failure and Cardiomyopathy in Cardiology Section 12, Chapter 10.

MANAGEMENT OF CEREBROVASCULAR DISEASE AND PERIPHERAL ARTERIAL DISEASE IN DIABETES

This is broadly similar for diabetic and non-diabetic patients although additional impact of neuropathy and microvascular disease presents special problems in treating ischaemia in the diabetic leg and foot. The outcomes tend to be worse and mortality rates higher. Cilostazol 100 to 200 mg/day and anti-platelet drugs along with exercise programme are useful in improving limb ischaemia. Percutaneous transluminal angioplasty with stenting is performed for claudication. The role of bypass grafts for longer arterial occlusions remains poorly defined. Acute limb ischaemia should be treated with thrombolysis.

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9.14 Microvascular Diseases—Pathogenesis of Chronic Complications

Suman Kirti

INTRODUCTION

Chronic microvascular complications of diabetes mellitus are retinopathy, sensory motor, and autonomic neuropathy and nephropathy. Three-fourth of diabetics develops retinopathy after more than 15 years of diabetes, half of the diabetics have neuropathy, and one-third have nephropathy in large population studies in the US. The prevalence rates of retinopathy and overt nephropathy are reportedly lower while that of microalbuminuria is comparable with that reported in other ethnic groups in a study from South India. Risk factors for overt nephropathy in this study were poor glycaemic control, long duration of diabetes and systolic blood pressure, while for microalbuminuria smoking, and diastolic blood pressure were additional risk factors.

Risk of chronic complications in type-1 and type-2 diabetes result from chronic hyperglycaemia. Large randomised clinical trials of individuals with type-1 or type-2 diabetes have conclusively demonstrated that a reduction in chronic hyperglycaemia prevents or delays retinopathy, neuropathy, and nephropathy. Other incompletely defined factors may moderate development of complications. For example, despite longstanding diabetes, some individuals never develop nephropathy or retinopathy though they may have similar glycaemic control to patients with microvascular complications suggesting genetic susceptibility for developing particular complications.

MECHANISM

Though hyperglycaemia is an important factor, the mechanism of such diverse cellular and organ dysfunction is unknown. Four prominent theories have been proposed.

AGEs Theory

Increased intra-cellular glucose causes nonenzymatic glycosylation of intra- and extra-cellular proteins by interaction of glucose with amino acid groups on proteins, resulting in formation of advanced glycosylation end products (AGEs). Early non-enzymatic glycation products are reversible. As hyperglycaemia continues, intermediate poorly reversible products are formed and later irreversible AGEs are formed. Serum levels of AGEs correlates with the level of glycaemia and these products accumulate as glomerular filtration rate declines. AGEs have been shown to crosslink proteins (e.g. collagen, extracellular matrix protein), accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide (NO) synthesis, induce endothelial dysfunction, and alter extra-cellular matrix composition and structure. AGEs bind to specific receptors in endothelial cells, macrophages, and cultured mesangial cells. Interaction of AGEs with the receptors in mesangial cells leads to increased transforming growth factor-β (TGF-β) expression and extra-cellular matrix synthesis. Aminoguanidine, a compound that inhibits AGEs, was useful in experimental studies but resulted in occurrence of ANCA positive vasculitis and is not approved for clinical use.

Sorbitol Pathway (Polyol Pathway)

Intra-cellular glucose is pre-dominantly metabolised by phosphorylation and subsequent glycolysis, but when increased some glucose is converted to sorbitol by the enzyme aldose reductase. Increased sorbitol concentration alters redox potential, increases cellular osmolality, generates reactive oxygen species and increases AGEs formation, and likely leads to other types of cellular dysfunction. Cataract formation and neuropathy and retinopathy to some extent have been linked to this pathway. However, testing this theory in humans, using aldose reductase inhibitors, has not demonstrated significant benefit on clinical endpoints of retinopathy or nephropathy, and marginal benefits in neuropathy. Newer aldose reductase inhibitors like fidarestat are undergoing clinical trials; epelrestat has been approved for use.

Protein Kinase C Pathway

Hyperglycaemia increases formation of diacylglycerol, leading to activation of protein kinase C (PKC). PKC is a family of serine-threonine kinases that alter the transcription of genes for fibronectin, type IV collagen, contractile proteins and extracellular matrix protein in endothelial cells and neurons. Thereby PKCs regulates diverse vascular functions like contractility, blood flow, cellular proliferation, and vascular permeability. PKC mediates TGF-β1, angiotensin-II and vascular endothelial growth factor (VEGF) and modulates mitogen activated protein kinase (MAPK), which mediates sclerosis. Inhibitors of PKC-b like ruboxistaurin mesylate that reduce the direct cellular actions of AGEs, VEGF, Endothelin-1, reduce oxidised lipids and oxidant production, are being studied in clinical trials in diabetes mellitus (DM) for retinopathy and neuropathy.

Hexosamine Pathway

Hyperglycaemia increases flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production. Hexosamine pathway may alter function by glycosylation of proteins, such as endothelial nitric oxide synthase, or by changes in gene expression of transforming growth factor β (TGF-β) or plasminogen activator inhibitor-1 (PAI-1).

Growth Factors

Growth factors appear to play an important role in DM related complications and their production is increased by most of these proposed pathways. VEGF-A is increased locally in diabetic proliferative retinopathy and decreases after laser photocoagulation. Inhibition of angiotensin-II also reduces VEGF, which could explain one of the beneficial effects of angiotensin-II receptor blockers on microangiopathic diseases. Monoclonal antibodies to VEGF like ranibizumab in experimental studies have

shown improvement in proliferative diabetic retinopathy. TGF-β is increased in diabetic nephropathy and stimulates basement membrane production of collagen and fibronectin by mesangial cells. Other growth factors, such as platelet derived growth factor, epidermal growth factor, insulin like growth factor, growth hormone, basic fibroblast growth factor, connective tissue growth factor and even insulin, have been suggested to play a role in DM related complications. Figure 1 shows the pathways and their interaction in the pathogenesis of microvascular disease.

Angiotensin-II

The renin-angiotensin system (RAS) in the kidney is abnormally activated in diabetes. Angiotensin-II directly binds to receptors in renal cells and induces matrix deposition in mesangial and tubular cells through TGF-β1. Angiotensin-II stimulates VEGF production in mesangial cells and impairs glomerular structure and function. Similar effects are observed in the retina.

Glycaemic Control and Complications

The diabetes control and complications trial (DCCT) provided definitive proof that reduction in chronic hyperglycaemia can prevent many early complications of type 1 DM. This large multicentre clinical trial randomised 1,400 type 1 diabetics to either intensive or conventional diabetes management and prospectively evaluated the development of retinopathy, nephropathy, and neuropathy. The intensive group achieved a substantially lower HbA1c (7.3%) than the conventionally managed group (9.1%).

DCCT showed that improvement of glycaemic control reduced non-proliferative and proliferative retinopathy by 47%, microalbuminuria by 39%, and clinical nephropathy by 54% and neuropathy by 60%. Improved glycaemic control also slowed the progression of early diabetic complications. A non-significant trend in reduction of macrovascular events was observed during the trial (most individuals were young, with a low risk of cardiovascular disease). Results of DCCT predicted that type-1 diabetics with intensive management gain 7.7 additional years of vision, 5.8 additional years free from ESRD and 5.6 additional years free from lower limb amputations. If all the complications were combined, intensively managed group would experience 15.3 more years of life without significant

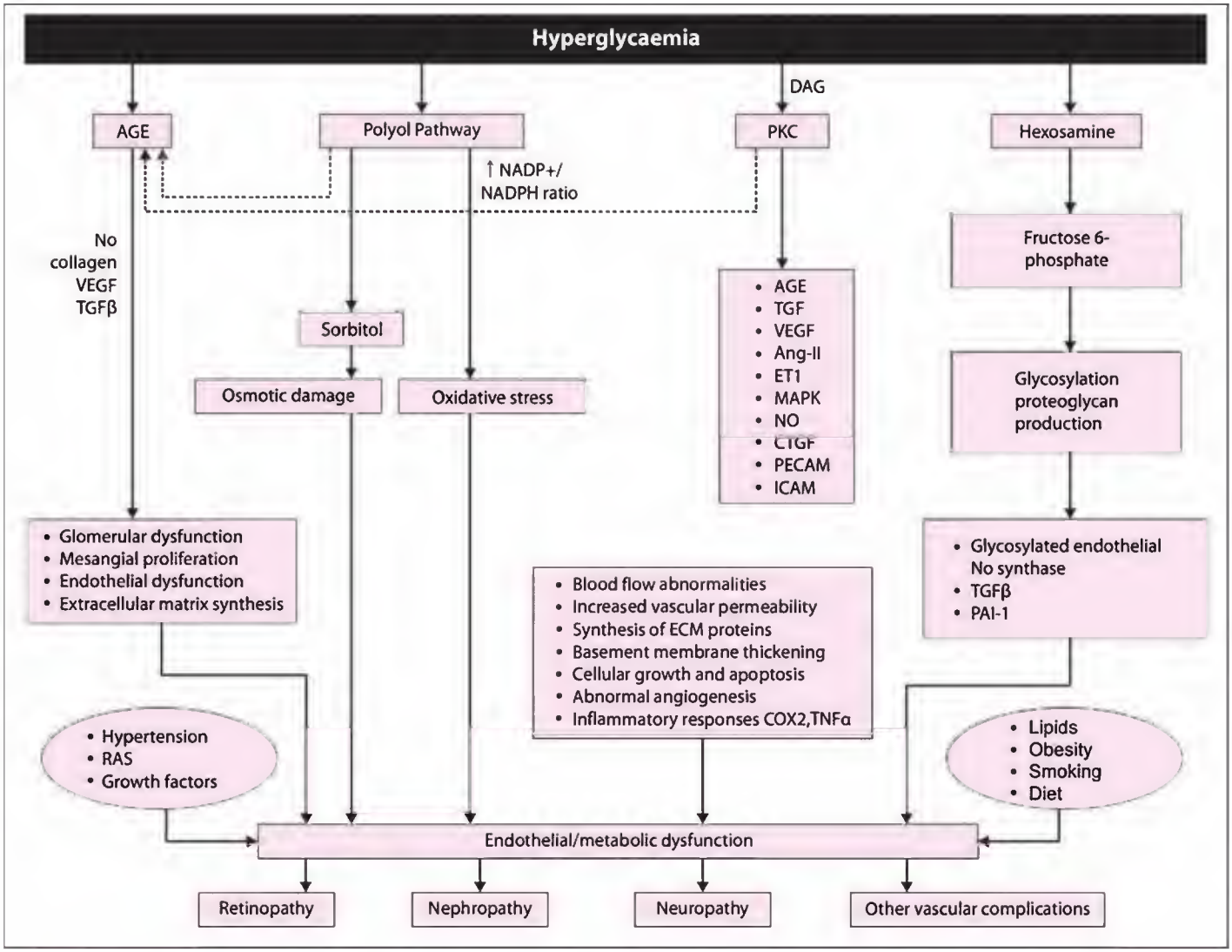


Figure 1: Pathways leading to microvascular diseases in diabetes mellitus.

AGE = Advanced glycation end products; PKC = Protein kinase C; NO = Nitric oxide; DAG = Diacylglycerol; TGF = Transforming growth factor; VEGF = Vascular endothelial derived growth factor, Ang-II-Angiotensin-II, ET1, endothelin1; MAPK = Mitogen activated protein kinase; CTGF = Connective tissue growth factor; PECAM = Platelet/endothelial cell adhesion molecules; ICAM = Inter-cellular cell adhesion molecules; PAI-1 = Plasminogen activator inhibitor; COX = Cycloxygenase; TNF = Tumour necrosis factor; RAS = Renin-angiotensin system; NADPH = Nicotinamide adenine dinucleotide phosphate

microvascular or neurological complications of diabetes as compared to diabetics receiving standard therapy. This translates into an additional 5.1 years of life expectancy for the intensively treated diabetic. Intensive control for a mean of 6.5 years resulted in 42% to 57% reduction in cardiovascular events (nonfatal myocardial infarction, stroke or death from cardiovascular event) when followed-up for a mean of 17 years even though their subsequent control was same as the conventionally treated group. Thus, the benefit of improved glycaemic control during the DCCT persisted even after the study concluded and the glycaemic control worsened. There is a benefit of improved glycaemia over an entire range of HbA1c values. The goal of therapy is to achieve HbA1c levels as close to normal as possible without excessive risk of hypoglycaemia.

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of more than 5,000 newly diagnosed type-2 diabetics randomised to: intensive management using various combinations of insulin, a sulphonylurea or metformin or; conventional therapy using dietary modification and pharmacotherapy with goal of symptom prevention. Individuals were also randomly assigned to different antihypertensive regimens. Intensively managed group achieved an HbA1c of 7.0% compared to HbA1c of 7.9% in the standard treatment group. UKPDS demonstrated that each percent point reduction in HbA1c was associated with 35% reduction in microvascular complications. As in the DCCT, there is a continuous relationship between glycaemic control and development of complications. Improved glycaemic control was associated with improvement in lipoprotein risk profiles such as reduced triglycerides and increased HDL, though conclusive evidence of any change in cardiovascular risk was not seen. An important finding of the UKPDS was that strict blood pressure control significantly reduced both microvascular and macrovascular complications, and the beneficial effects of blood pressure control were greater than those of glycaemic control. Lowering the blood pressure to moderate goals (144/82 mm Hg) reduced the risk of death, stroke, microvascular endpoints, retinopathy, and heart failure (risk reduction between 32% and 56%). Deterioration in maculopathy and visual acuity was also reduced. Post-trial follow-up of 10 years of these patients showed that the beneficial effect of BP control during the trial did not persist as did the glycaemic control effects and the outcomes depended on the subsequent control of blood pressure.

Action to control cardiovascular risk in diabetes eye subgroup (ACCORD-Eye) trial on 4065 type 2 diabetics from 77 centres over US and Canada also showed 40% reduction in retinopathy with intensive glycaemic control, and lipid control especially with fenofibrate within a short period of 4 years.

The Action in Diabetes and Vascular Disease

Preterax and diamicron modified release-controlled evaluation (ADVANCE) randomised-controlled trial at 215 centres in 20 countries in Asia, Australia, Europe, and US involving 11140 type 2 diabetics, studied over 5 years showed 21% reduction in development of new or worsening nephropathy and reduction in new onset microalbuminuria with intensive glycaemic control (HbA1c 6.5%) versus standard glycaemic control (HbA1c 7.3%). These two large trials also confirm the importance of glycaemic control in prevention of microvascular disease.

Other Risk Factors

Hypertension is a major determinant of microangiopathy and macroangiopathy in diabetes. It causes endothelial dysfunction, impaired NO availability, renal vasoconstriction and decreased glomerular filtration, impaired tubuloglomerular feedback, decreased medullary flow and impaired pressure natriuresis, and progressive proteinuria. Intraglomerular pressure rise and stretch set off series of matrix changes. Strict blood pressure lowering with ACE-inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) that reduce intraglomerular pressure and block the RAS, along with glycaemic control has been shown to reduce nephropathy. Large trials like microalbuminuria, cardiovascular and renal outcomes-heart outcomes prevention evaluation (MICRO-HOPE), showed that adding ramipril, an ACE-I, slowed the progress and reduced the occurrence of nephropathy in diabetics by 24%. ARBs are more effective blockers of the RAS and also target the angiotensin-II, VEGF and endothelial dysfunction, as well as acting favourably through the peroxisome proliferator-activated receptor (PPAR) in case of newer ARBs.

Dyslipidaemia has been implicated in increase in urinary albumin excretion in diabetics and causes endothelial damage by oxidative stress. Treatment of dyslipidemia with fenofibrate [fenofibrate intervention in event lowering in diabetes (FIELD)] and atorvastatin [collaborative atorvastatin diabetes study (CARDS)] in large multicentric trials has shown improvement in retinopathy and maculopathy. Fibrates acting through PPAR suppress endothelial proliferation and inhibit VEGF production.

Obesity contributes to microangiopathy by multiple factors including mediators, directly secreted by adipocytes, such as non-esterified fatty acids (NEFAs), tumour necrosis factor-α (TNF-α), leptin and adiponectin, which modulate microvascular changes, endothelial function, NO production and inflammation. Smoking aggravates microangiopathy by inducing endothelial damage, oxidative stress, and vasoconstriction. Diets containing excess of saturated and trans fats result in oxidative stress. Definitive benefit is demonstrated in clinical studies by targeting hyperglycaemia, hypertension, obesity, smoking, dyslipidemia and modifying diet and lifestyle in microangiopathic disease.

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9.15 Diabetes and Kidney Disease

Jamal Ahmad

DEFINITION AND EPIDEMIOLOGY

Diabetic kidney disease (DKD) is characterised by excessive urinary albumin excretion (UAE) followed by loss of kidney function. Proteinuria is a hallmark of diabetic kidney disease (DKD). DKD has been classically defined by the presence of proteinuria ≥0.5 gm/24 hours or persistent albuminuria (≥ 300 mg/24 hours or ≥200 µg/min) if one of the following additional criteria are fulfilled: presence of diabetic retinopathy and the absence of clinical or laboratory evidence of the other kidney and renal tract disease. Persistent albuminuria in the range of 30 to 299 mg/24 hours (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy (DN) in type 1 diabetes and marker for development of nephropathy as well as cardio vascular disease (CVD) risk in type 2 diabetes.

STAGES OF DIABETIC NEPHROPATHY

According to UAE values, DKD has been didactically categorised into stages. The cut-off values used to characterise these stages are described in **Table 1**. Recent studies suggest that only 30 to 45% of microalbuminuria patients will progress to proteinuria over 10 years of follow-up and some might regress to normoalbuminuria.

Table 1: Diabetic Nephropathy Stages Based on Urinary Albumin Excretion

Stages	Urine with Marked Time (µg/min)*	24 hours Urine (mg/24 h)*	Random Urine Sample	
			Albumin Concentr-ation (mg/Lit)**	Albumin Concentr-ation Ratio (mg/g)*
Normoalbuminuria	<20	<30	<17	<30
Microalbuminuria	20 to 199	30 to 299	17 to 173	30 to 299
Macroalbuminuria	≥200	≥300	≥174	≥300

** Values according to the American Diabetic Association.*

*** Gross et al, Diabetes Care 2005.*

AETIOPATHOGENESIS

The important mechanism of proteinuria cited for excessive protein excretion in general are increased filtration, inadequate tubular absorption, overflow, and increased glomerular filtration, inadequate tubular absorption, and increased tubular secretion with the dominant mechanism being glomerular. Angiotensin exerts complex haemodynamic and non-haemodynamic actions that includes induction of systemic vasoconstriction, increased glomerular arteriolar resistance, glomerular capillary pressure and glomerular capillary permeability, reduction in the filtration surface area, stimulation of extracellular matrix proteins, and stimulation of renal proliferation and fibrogenic chemokinase.

SCREENING AND DIAGNOSIS

Screenings for microalbuminuria (MA) can be performed by measurement of the albumin-to-creatinine ratio in a random spot collection (preferred method), as 24 hours or timed collections are more burdensome and add little to prediction or accuracy. Because of variability in UAE , two of the three specimens collected within a 3 to 6 months period should be abnormal. Exercise within 24 hours, infection, fever, congestive heart failure (CHF), marked hyperglycaemia, and marked hypertension may elevate UAE over baseline values. Serum creatinine should be measured at least annually in all adults with diabetes, regardless of the degree of UAE. Estimated GFR (eGFR) is commonly co-reported by laboratories or can be estimated using formulae such as the modifications of diet in renal disease (MDRD) study equation. Based on GFR the chronic kidney disease may be graded into five grades (**Table 2**). These have prognostic importance. DM screening must be performed at diagnosis in patients with T2DM and fifth year onwards in T1DM patients.

Table 2: Chronic Kidney Disease Stages

Stages	Description	GFR (mL/min/1.73 m²)
1	Renal damage with GFR* normal increased	≥90
2	Renal damage with GFR* slightly decreased	60 to 89
3	GFR moderately decreased	30 to 59
4	GFR severely decreased	15 to 29
5	End-stage chronic renal failure	<15 or dialysis

** Renal damage is defined by abnormalities in urine and below tests, imaging exams or in pathology, GFR= glomerular filtration rate.*

MANAGEMENT OF DIABETIC KIDNEY DISEASE

The best treatment for DKD is multiple risk factor interventional approach. The goal to be pursued is retarding the development or progression of DKD and to decrease cardiovascular risk and mortality.

Hyperglycaemia

Hyperglycaemia is a significant risk factor for the development of microalbuminuria; both in type 1 and in type 2 DM. A reduction of 1% in haemoglobin A1c is associated with a 37% decrease in microvascular endpoints.

Clinical trials have demonstrated that intensive treatment of hyperglycaemia is associated with a decreased risk for the development of DKD in type 1 and type 2 diabetic patients. In the Intensive Blood Glucose Control and Vascular Outcomes in patients with type 2 Diabetes (ADVANCE) trial, the group in the intensive arm for an average of 5 years showed a small reduction in the number of cases with new onset microalbuminuria compared to the standard therapy group.

Arterial Hypertension

Arterial hypertension is a main risk factor for the development of DKD and probably the best known relevant factor related to its progression. Analysis of UK prospective diabetes study (UKPDS)

showed that every 10 mm Hg reduction in systolic BP is associated with a 13% reduction in the risk of microvascular complications, with the smallest risk among those patients with systolic BP <120 mm Hg. In order to reach the BP goal of 130/80 mm Hg diabetic patients in general or 125/75 mm Hg in patients with proteinuria >1.0 g/24 hours, three to four antihypertensive agents are usually necessary. Due to the known renoprotective effect of ACE-inhibitors and ARB, these agents should be used initially along with a diuretic.

Renin-Angiotensin System Blockade

Angiotensin-converting enzyme (ACE) inhibitors could be used in normotensive subjects to prevent or postpone the development of microalbuminuria. The aim of ACE inhibitors and ARBs use is not only to diminish the risk for the development of microalbuminuria and macro-albuminuria but also to decrease the occurrence of cardiovascular events.

An acute increase in serum creatinine up to 30% to 35% that stabilises within 2 months is expected. Increase in serum creatinine above these values should raise the possibility of renal artery stenosis. Acute hyperkalaemia (>5.5 mEq/L) is an indication to stop these medications. Therefore, albuminuria, serum creatinine and potassium should be checked monthly in the first 2 to 3 months after starting treatment with ACE inhibitors or ARB.

Dual RAS blockade has been suggested to have an additive effect on renoprotection. A recent large trial (ONTARGET) in diabetic and non-diabetic subjects showed that the association of the two classes of drugs had a major effect on decreasing proteinuria but not on GFR decline or mortality. More recently, the dual blockage of the renin-angiotensin-aldosterone system with Aliskiren, a direct renin inhibitor, and losartan at maximal recommended dose (100 mg daily) showed a greater reduction in proteinuria (20%) compared to Losartan and placebo.

Dietary Intervention

There are several modalities for a dietary intervention in DKD, whether changing protein content or through the manipulation of lipid content. In patients with type 1 DM, in different stages of renal disease, protein restriction in the diet has shown to reduce the decline of renal function and albuminuria.

Dyslipidaemia

The desired target of low density lipoprotein (LDL) is <100 mg/dL for patients with DM in general, and <70 mg/dL when cardiovascular disease is present. No data based on a large clinical trial is available showing that the treatment of dyslipidaemia is able to prevent the development or progression of DKD. In the Heart Protection Study (HPS), simvastatin, 40 mg, reduced vascular event rates and GFR decline in patients with DM by 25%, independent of baseline cholesterol levels. Collaborative atorvastatin diabetes study (CARDS) showed a modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria.

Renal Replacement Therapy

Diabetic patients with advance renal disease may require renal replacement therapy to restore their body homeostasis and reduce symptoms of renal failure. Renal replacement can be provided by continuous ambulatory peritoneal dialysis (CAPD, or haemodialysis). In some patients, where a kidney is available, renal transplant may be considered. The indications and contraindications are the same as for any other patient requiring RRT. It is advisable to start therapy early rather than delaying it for terminal stages. These modalities are discussed in details in section 19, chapter 11 and 12.

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9.16 Diabetic Retinopathy

Amod Gupta, Reema Bansal

DEFINITION AND EPIDEMIOLOGY

Diabetic retinopathy (DR) is a retinal microvasculopathy resulting from prolonged hyperglycaemia. The prevalence of DR increases with the duration of diabetes and nearly all with type 1 and 60% with type 2 diabetes mellitus (DM) may develop some retinopathy after 20 years. The major risk factors for the onset and progression of DR are duration of diabetes, degree of glycaemic control, hypertension, and hyperlipidaemia.

Prevalence rate of DR in the Indian subcontinent is reported from 12% to 37% in type 2 DM.

AETIOPATHOGENESIS

Diabetic retinopathy (DR) starts from hyperglycaemia-induced vascular injury. The earliest histological lesion is loss of pericytes and thickening of the basement membrane of the retinal capillaries. These changes result from various biochemical, haemodynamic and endocrine factors, and eventually lead to closure/incompetence of the capillaries.

SPECTRUM OF DIABETIC RETINOPATHY

Non-Proliferative Diabetic Retinopathy

Mild

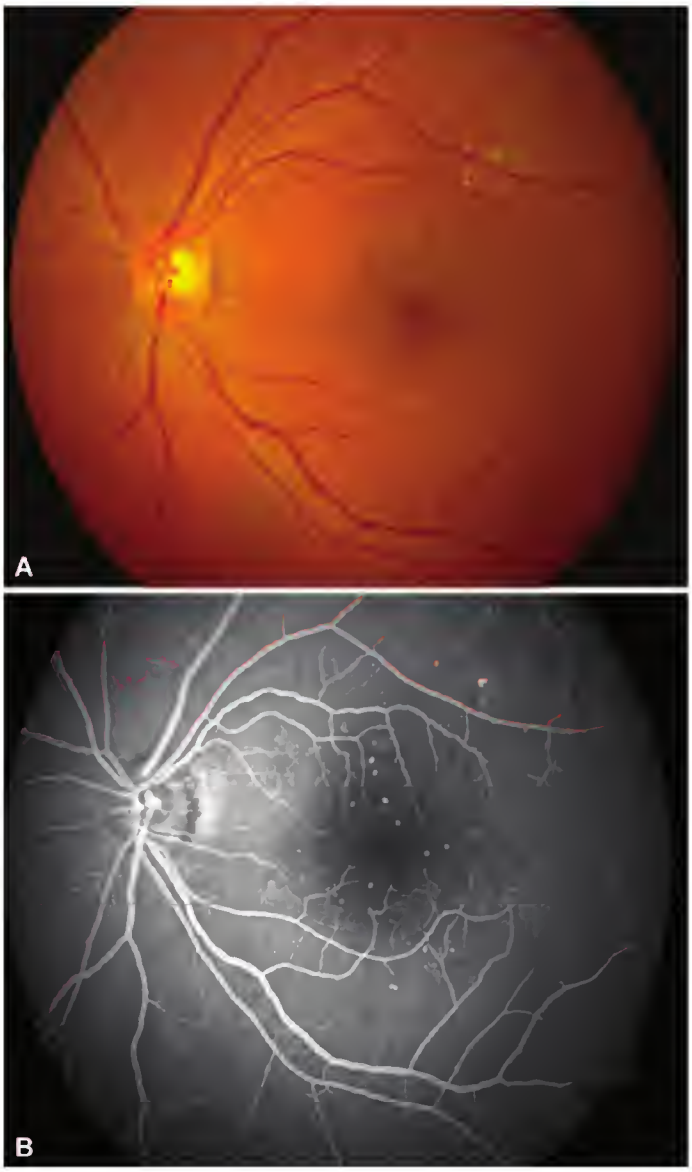
Microaneurysms are out pouching of the retinal capillary walls and are the first clinically detectable lesions on ophthalmoscopy. The microaneurysms tend to cluster around small areas of capillary non-perfusion (**Figure 1**). Hard exudates, located in the outer plexiform layer of the retina, are extracellular accumulation of lipids derived from leakage of serum from microaneurysms. These are small white or yellowish white deposits with sharp margins and glistening appearance (**Figure 2**). Dot and blot-retinal haemorrhages are also seen.

Moderate

Soft exudates or cotton wool spots reflect an increasing sign of ischaemia secondary to pre-capillary arteriolar occlusion. In the area of retinal ischaemia the axoplasmic flow is impaired resulting in accumulation of the axonal intracellular fluid or organelles which is clinically seen as swelling of the retinal nerve fiber layer or cotton wool spots (**Figure 3**).

Severe

Venous beading and loops, intra-retinal microvascular abnormalities (IRMA), and widespread areas of capillary non-perfusion develop as parts of the retina are deprived of blood and nourishment. Venous loops are hairpin or semi-circular deviations of the vein from its normal course. The IRMAs are narrow, tortuous, intra-retinal vascular segment representing either dilated retinal capillaries and/or intra-retinal new vessels (**Figure 4**). These may represent intra-retinal neovascularisation. These serve as warning signs of future proliferative DR (PDR).



Figures 1A and B: Fundus photograph of (A) the left eye with non-proliferative diabetic retinopathy showing dot and blot haemorrhages with hard exudates, and (B) leaking microaneurysms on fundus fluorescein angiography.

Proliferative Diabetic Retinopathy

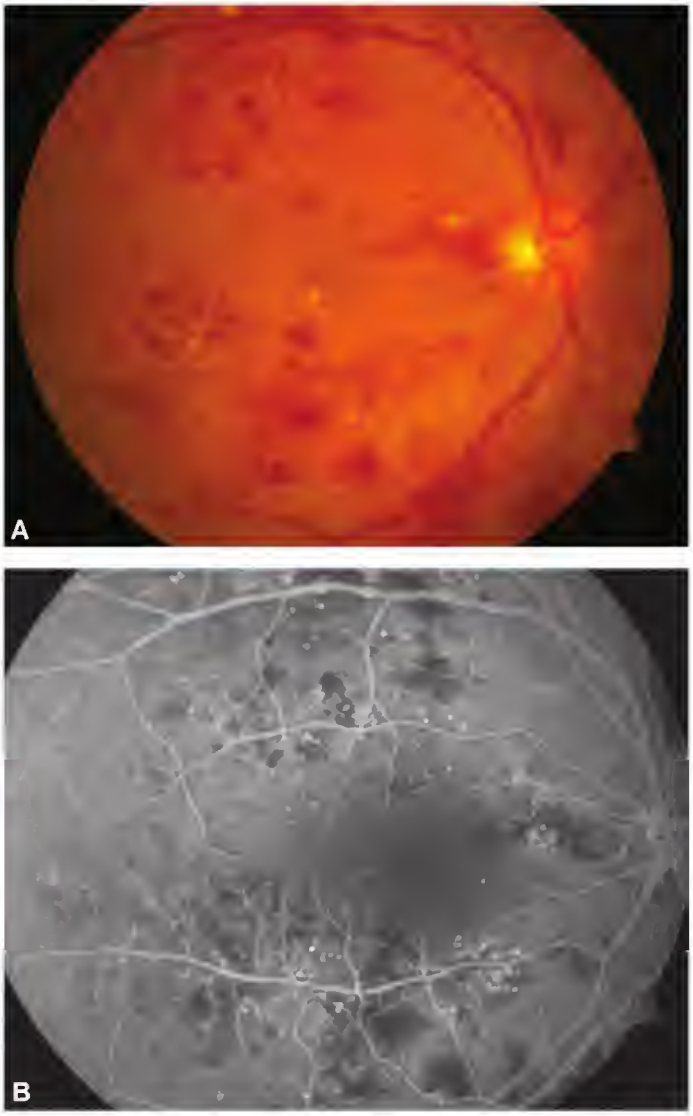
It is defined as the presence of newly formed blood vessels and/or fibrous tissue arising from the retina or optic disc, extending along the posterior hyaloid surface. Ischaemia of the inner retinal layers stimulates the production of angiogenic factors, namely vascular endothelial growth factor (VEGF) which act locally, diffuse through the vitreous to other areas of the retina, to the optic disc and also into the anterior chamber. The new vessels may be found on the optic disc (neovascularisation on the disc or NVD) or elsewhere (neovascularisation elsewhere or NVE) on the retina (**Figures 5 and 6**).



Figure 2: Fundus photograph of the left eye showing hard exudates.



Figure 3: Fundus photograph of the left eye showing soft exudates as cotton wool spots.



Figures 4A and B: Fundus photograph of the right eye with severe non-proliferative diabetic retinopathy showing superficial haemorrhages in all quadrants of retina (A) with venous beading and intra-retinal microvascular abnormalities on fundus fluorescein angiography (B).

Advanced Disease

Complications of PDR include vitreous haemorrhage (**Figure 7**) or subhyaloid haemorrhage (**Figure 8**), tractional/combined retinal detachment (**Figure 9**), and neovascular glaucoma that lead to severe visual loss and blindness if left untreated.

Role of Statins

In case of high basal serum cholesterol levels, it has been established that statins enhance the efficacy of macular gril in exudative maclupathy but definitive evidence is lacking that statins benefit patient's exudative maculopathy.

CLINICAL COURSE OF DIABETIC RETINOPATHY

In the initial stages, DR is asymptomatic, and hence, it is recommended that patients with type 1 DM undergo annual dilated fundus examination till they develop signs of retinopathy. Since in patients with type 2 DM, the onset and duration of the disease is unknown, they should undergo fundus examination at the time of diagnosis of DM. Frequency of the fundus examination thereafter will depend on the severity of the DR.

Diabetic macular oedema (DME) develops insidiously and is the most common cause of moderate visual loss in patients with DR. It is caused primarily by a breakdown of the inner blood retinal barrier resulting in leakage of fluid and plasma constituents from abnormally permeable microaneurysms, IRMAs and dilated retinal capillaries. It may be focal or diffuse.

The early treatment of diabetic retinopathy study **Table 1** (ETDRS) defined clinically significant macular oedema (CSME) as follows (**Figure 10**):

1. Retinal thickening at or within 500 µm of the centre of the macula, and/or
2. Hard exudates at or within 500 µm of the centre of the macula, if associated with thickening of the adjacent retina, and/or
3. Zone(s) of retinal thickening at least one disc area in size part of which is within one disc diameter of the centre.

Patients may present with acute onset cobwebs/floaters or complete obscuration of vision caused by vitreous



Figure 5: Fundus photograph of the right eye showing neovascularisation on the optic disc.

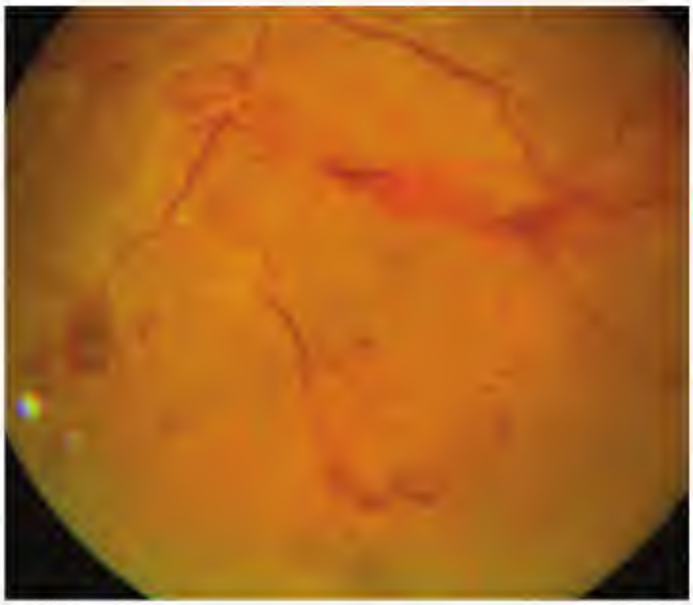


Figure 6: Fundus photograph of the left eye showing neovascularisation elsewhere on the retina.

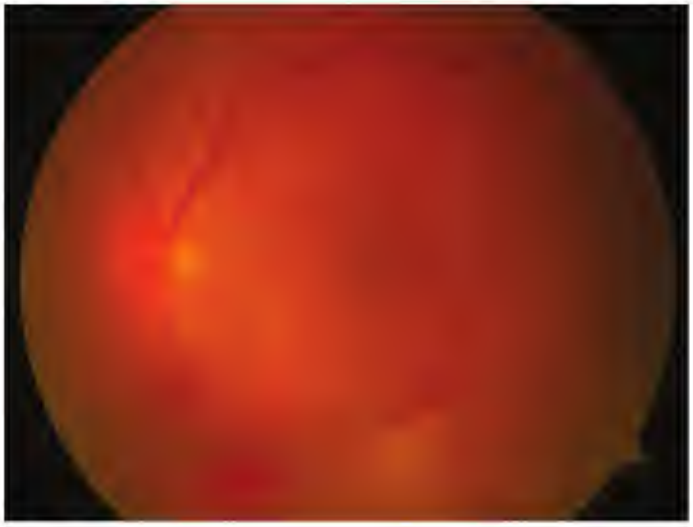


Figure 7: Fundus photograph of the left eye showing vitreous haemorrhage.

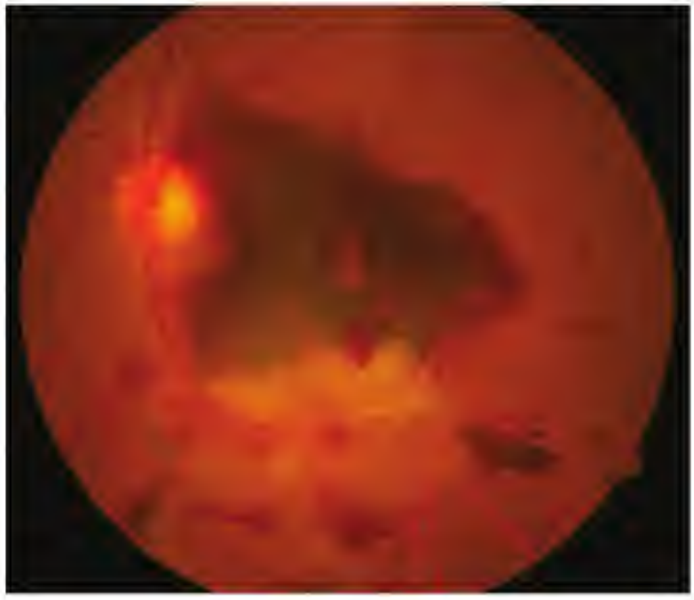


Figure 8: Fundus photograph of the left eye showing extensive subhyaloid haemorrhage over the macula.

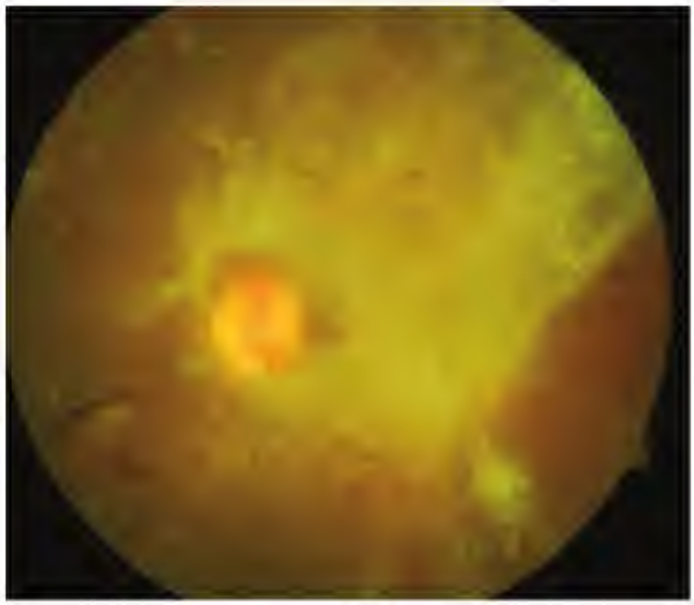


Figure 9: Fundus photograph of the left eye showing extensive fibrovascular proliferation around the optic disc causing tractional retinal detachment.



Figure 10: Fundus photograph of the right eye showing clinically significant macular oedema.

haemorrhage from new vessels growing on the retina or optic disc. The vitreous haemorrhage may absorb spontaneously over the next few days/weeks but is often complicated by recurrent attacks of fresh haemorrhage. The accompanying scar tissue may contract leading to tractional retinal detachment. In severe cases constant traction on retina may lead to retinal tearing resulting in combined rhegmatogenous retinal detachment. Patients with extensive retinal ischaemia tend to develop neovascularisation of the iris and angle of the anterior chamber leading to intractable neovascular glaucoma.

Correlation Between Pathogenesis of Retinopathy and HbA1c

It is well established that good control of diabetes leads to reduction in the microvascular complications including DR by as much as 37% by 1% reduction in HbA1c (UKPDS) other studies also prove this point.

DIAGNOSIS AND MANAGEMENT (TABLE 1)

The diagnosis of DR is essentially clinical by using a direct ophthalmoscope. The ophthalmologists may, however, use stereoscopic biomicroscopic fundus examination besides several ancillary investigations such as fundus fluorescein angiography, and optical coherence tomography to plan treatment and monitor the response to treatment. In patients with obscure media, ultrasonography is helpful in surgical planning.

Table 1: Early Treatment Diabetic Retinopathy Study (ETDRS) Levels of Diabetic Retinopathy, Non-Proliferative Diabetic Retinopathy (NPDR)

Non-Proliferative Diabetic Retinopathy (NDPR)
Mild NPDR
At least one microaneurysm
Moderate NPDR
Haemorrhages or microaneurysms (H/Ma)
Soft exudates, venous beading (VB), and intraretinal microvascular abnormalities (IRMAs) definitely present
Severe NPDR
H/Ma in all 4 quadrants
VB in 2 or more quardrants
Intra-retinal microvascular abnormalities (IRMA) in at least 1 quadrant
Very Severe NPDR
Any two or more of severe NPDR levels
Proliferative Diabetic Retinopathy (PDR)
Early PDR
New vessels on the retina
Definition not met for high-risk PDR
High-Risk PDR
New vessels on the disc of 1/4 to 1/3 or more of the disc area or
Any new vessel and vitreous or preretinal or vitreous haemorrhage
Clinically Significant Macular Oedema (any one of the following):
Thickening of the retina located 500 µm or less from the centre of the macula
Hard exudates at 500 µm or less from the centre of the macula with thickening of the adjacent retina
A zone of retinal thickening, one disc area or larger in size, any portion of which is one disc diameter or less from the centre of the macula

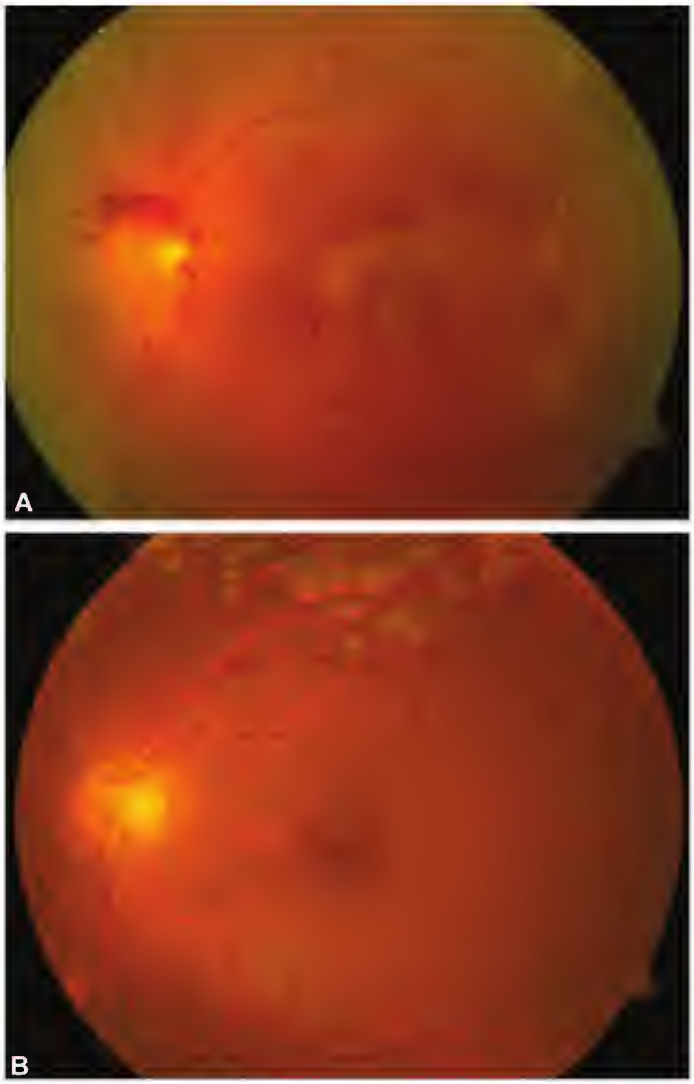
TREATMENT

Since DM has multifactorial origin, an optimal metabolic control of hyperglycaemia, HbA1c levels, hypertension, dyslipidaemia, anaemia and nephropathy should be an important treatment goal. Medical management of diabetic macular oedema (DME) includes systemic control of risk factors combined with local treatment that includes laser photocoagulation.

Laser Photocoagulation

Laser photocoagulation for CSME is currently the standard of care. The goal of macular laser photocoagulation for diabetic macular oedema is to limit vascular leakage through focal laser burns of leaking microaneurysms or grid laser burns in areas of diffuse breakdown of the blood-retinal barrier. The green wavelength (Argon green, Frequency doubled Nd:YAG) is better absorbed by the haemoglobin and hence ideal for laser photocoagulation.

In recalcitrant cases pharmacological agents including intravitreal corticosteroids and anti-VEGF agents are being



Figures 11A and B: Fundus photograph of the left eye showing (A) vitreous haemorrhage with fibrovascular proliferation, and (B) same eye following pars plana vitreous surgery.

increasingly used as adjuvant to the standard laser photocoagulation therapy.

Pan retinal photocoagulation (also called scatter laser photocoagulation) is indicated in patients with severe NPDR and PDR. This involves applying 1,500 to 2,000 spots of 500 μ size laser burns of moderate intensity to ablate the peripheral ischaemic retina. This leads to significant reduction in the release of VEGF from the hypoxic retinal tissues. Full scatter treatment for PDR results in partial or complete regression of retinal and optic disc neovascularisation.

Pars Plana Vitreous Surgery

The major indications are non-clearing vitreous haemorrhage, macula-threatening traction retinal detachment and combined traction-rhegmatogenous detachment. The surgical objective includes clearing the media, relieving all anterior-posterior and tangential traction using delamination, segmentation or en-bloc techniques and performing adequate platelet-rich plasma (PRP) to prevent development of subsequent immune reconstitution inflamm-atory syndrome (IRIS) neovascularisation (**Figures 11 A and B**).

PROGNOSIS AND PREVENTION

All people with DM (type 1 as well as type 2) are at risk. The longer a person has diabetes, the higher the risk of developing DR. Early detection, education, and research are the key to prevent visual impairment/blindness from DR. Ophthalmoscopy is the most commonly used technique to screen for DR. It is critical to identify patients who are in immediate need of treatment with laser photocoagulation.

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9.17 Diabetic Neuropathy

Manish Modi

DEFINITION AND EPIDEMIOLOGY

Diabetic neuropathy (DN) is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. The importance of excluding nondiabetic causes was emphasised in the Rochester diabetic neuropathy study, in which up to 10% of peripheral neuropathy in diabetic patients was deemed to be of nondiabetic causes.

There is a higher prevalence of DM in India (4.3%) compared with the West (1% to 2%). Probably Asian Indians are more prone for insulin resistance and cardiovascular mortality. The prevalence of neuropathy increases with the duration of diabetes mellitus. The incidence of DN in India is not well known but in a study from South India 19.1% type 2 diabetic patients had peripheral neuropathy. According to an estimate, two-thirds of the diabetic patients have clinical or subclinical neuropathy.

AETIOPATHOGENESIS

The most important aetiological factors that have been associated with DN are poor glycaemic control, diabetes duration, visceral obesity and height, with possible roles for hypertension, age, smoking, alcohol consumption, hypoinsulinaemia, and dyslipidaemia. The pathogenesis of diabetic neuropathy involves an interaction between metabolic and microvascular injury to nerve.

1. Vascular Injury

Endoneural ischaemia occurs by several mechanisms. Vasodilatory signalling pathways including prostacyclins are inhibited and there is occlusion of vessels due to thickening of endothelial basal lamina and fibrin and platelet deposition.

2. Direct Metabolic Injury

Increased polyol production by overexpression of aldose reductase induces neuropathy in animal models. Advanced glycation endproducts (AGEs) are directly neurotoxic by promoting inappropriate crosslinks among proteins, which is further accelerated in response to hyperglycaemia and greater polyol pathway flux.

Reactive oxygen species (ROS) are induced by AGEs, hyperglycaemia and ischaemia. Reactive oxygen species damage proteins, and inhibit mitochondrial electron transport. Mitochondrial dysfunction may serve as a final common pathway for neuronal damage mediated by polyol, AGEs, and ROS. Mitochondrial dysfunction might account for persistent injury that occurs during periods of relative normoglycaemia and contributes to genetic differences in susceptibility to hyperglycaemic complications.

CLINICAL FEATURES

Table 1 gives the classification of DN which are discussed in the following paragraphs.

Table 1: Classification of Diabetic Neuropathies

Symmetrical Polyneuropathies
Distal sensory or sensorimotor polyneuropathy
Large-fibre neuropathy
Small-fibre neuropathy
Autonomic neuropathy
Asymmetrical Neuropathies
Cranial neuropathy (single or multiple)
Truncal neuropathy (thoracic radiculopathy)
Lumbosacral radiculopathy (asymmetrical proximal motor neuropathy)
Limb mononeuropathy (single or multiple)
Entrapment neuropathy
Combinations
Polyradiculoneuropathy
Diabetic neuropathic cachexia
Symmetrical polyneuropathies

Distal Symmetrical Polyneuropathy

Distal symmetrical polyneuropathy DSPN is the commonest type of DN and probably accounts for 75% of the DNs. It may be sensory and/or motor and may involve small or large fibres, or both. Sensory impairment occurs in glove and stocking distribution and motor signs are not prominent. Large fibre involvement causes painless paraesthesias with impairment of vibration, joint position, touch and pressure sensations, and loss of ankle reflex. In advanced stage, sensory ataxia may occur. Small fibre neuropathy on the other hand is associated with pain, burning, and paraesthesias.

Diabetic Autonomic Neuropathy

Diabetic autonomic neuropathy affects various organs of the body resulting in cardiovascular, gastrointestinal, urinary, sweating, pupils, and metabolic disturbances. It ranges from subclinical functional impairment of cardiovascular reflexes and sudomotor functions to severe cardiovascular, gastrointestinal, or genitourinary dysfunction. Orthostatic hypotension, resting tachycardia, and heart rate unresponsiveness to respiration are a hallmark of diabetic autonomic neuropathy.

Asymmetric Neuropathies

Cranial neuropathy

Cranial neuropathy in diabetic patients most commonly involves the oculomotor nerve, followed by trochlear and facial nerve in order of frequency. Third nerve palsy with pupillary sparing is the hallmark of diabetic oculomotor palsy and is attributed to nerve infarction. The pupillary fibres are peripherally located and, therefore, escape in diabetic oculomotor palsy.

Truncal neuropathy

Diabetic truncal neuropathy is associated with pain and paraesthesias in T4-T12 distribution in chest or abdominal

distribution. Bulging of abdominal wall may occur because of muscle weakness. It usually occurs in older patients with NIDDM. The onset may be abrupt or gradual and the patient may be confused with an intra-abdominal/thoracic disease, or herpes zoster.

Asymmetrical Proximal Diabetic Neuropathy

It is also referred to as diabetic amyotrophy. The patients complain of pain in the lower back, hip, anterior thigh, typically unilateral but may be bilateral. Within days or weeks, the weakness and wasting of thigh and leg muscles follows. Knee reflex is reduced or absent. Numbness or paraesthesias are a minor phenomena. Nerve biopsy shows multifocal nerve fibre loss suggesting ischaemic injury, and perivascular infiltrates suggesting an immune mechanism. This has prompted intravenous immunoglobulins (IVIg) and cyclophosphamide therapy, which have resulted in rapid recovery.

Limb Neuropathies

There are two major mechanisms of limb neuropathies in diabetics, viz. nerve infarction and entrapment. *Nerve infarctions* are associated with abrupt onset pain followed by variable weakness and atrophy. The recovery is slow over a period of months, as the primary pathology is axonal degeneration. Median, ulnar, and peroneal nerves are most commonly affected. In diabetic patients, *nerve entrapment* is commoner than nerve infarction. The entrapment neuropathies have insidious onset, have characteristic electrodiagnostic features such as conduction block or segmental nerve conduction slowing in the entrapped segment of the nerve. Carpal tunnel syndrome is three times more common in diabetic patients than the normal population. The other entrapment neuropathies in diabetic patients are ulnar, radial, lateral femoral cutaneous nerve of thigh, peroneal, and medial and lateral planter nerves.

DIAGNOSIS

The American Academy of Neurology recommends that DN is diagnosed in the presence of somatic or autonomic neuropathy when other causes of neuropathy have been excluded. At least two of the five criteria are needed: Symptoms, signs, electrodiagnostic test, quantitative sensory and autonomic testing.

For diagnosis of DN, bedside examination should include assessment of muscle pain; sensation of pin prick, joint position, touch, vibration and temperature in the hands and feet; and tendon reflexes. Electrodiagnostic tests like nerve conduction studies typically show low amplitude sensory response with prolonged distal latency. Compound muscle action potential (CMAP) amplitudes are initially normal, but decline with disease progression.

Nerve biopsy is useful only in situations, when other causes of neuropathy need to be ruled out. Skin biopsy has been used in diagnosis of small fibre neuropathy. Recently, confocal corneal microscopy in the assessment of diabetic polyneuropathy has been reported. In confocal microscopy, the cornea is scanned and images of Bowman's layer, which contains a rich nerve plexus, are examined for nerve fibre density, length and branch density, which is significantly reduced in DN and correlates with the severity of neuropathy.

TREATMENT

Currently, no medication has been shown to reverse neuropathy. The treatment is aimed at preventing the progression of neuropathy and providing symptomatic relief. Aggressive control of blood glucose is central to the treatment of diabetes and remains the only treatment shown to delay the onset and slow progression of neuropathy.

Agents that have been shown to slow and reverse nerve injury in animal models include aldose reductase inhibitors (ARIs) that reduce shunting of glucose into polyol pathway; drugs that decrease ROS (alpha lipoic acid, glutathione, dimethylthiourea and vitamin E), lipid lowering agents, and transition metal chelators (desferrioxamine and α lipoic acid). Although ARI have been shown to improve nerve conduction velocity and the density of small fibres on sural nerve biopsy and α lipoic acid showed improvement in pain following intravenous therapy, no agent has resulted in clinically meaningful improvement in human trials.

Immunosuppressing therapies have been used in diabetic lumbosacral radiculoneuropathy, based on the evidence that it may have an autoimmune basis. Therapies tried include corticosteroids, immunoglobulins and plasma exchange.

Symptomatic Treatment

Neuropathic pain relief is one of the most challenging issues in DN. The mainstays of therapy are anticonvulsant agents, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and opiates (**Table 2**). Each of these classes of medication has

Table 2: Therapeutic Agents for Neuropathic Pain

Class of Drugs	Compounds	Mechanism of Action	Dose Per Day	Adverse Effects
Tricyclic Antidepressants	Amitriptyline	Na-channel inhibition, 5-HT/noradrenaline inhibition	10 to 150 mg	Sedation, dry mouth, blurred vision, weight gain, urinary retention, cardiac effects
	Imipramine		25 to 150 mg	
	Nortriptyline		25 to 150 mg	
Serotonin/ reuptake inhibitor	Venlafaxine	5-HT/Noradrenaline reuptake inhibition	75 to 225 mg	Nausea, sedation, hypertension
	Duloxetine		20 to 120 mg	
Anticonvulsants	Carbamazepine	Sodium channel blocking	200 to 800 mg	Hyponatraemia, ataxia, hepatic dysfunction
	Oxcarbamazepine	Sodium channel blocking	600 to 2400 mg	Hyponatraemia, sedation
	Gabapentin	Calcium channel agonist	900 to 3600 mg	Sedation, dizziness
	Pregabalin	Calcium channel agonist	150 to 600 mg	Sedation, peripheral oedema
Ion channel blockers	Mexiletine	Sodium channel blocking	300 to 750 mg	Arrhythmia
Opioids	Tramadol	Opioid receptor agonist	50 to 400 mg	Nausea, vomiting, constipation, orthostatic hypotension, dizziness somnolence
	Oxycodone		Add on	

drug interaction and side-effects that may be more profound in the elderly. Transcutaneous nerve stimulation (TNS), magnetic field therapy, infrared high therapy and spinal cord stimulation has also been tried in a small number of patients with painful DN.

COMPLICATIONS

Foot Ulcers

The late sequelae of diabetic neuropathy are recognised to be foot ulceration, which may occasionally result in amputation and Charcot (neuropathic) arthropathy. Foot ulcers occur in 15% of the diabetic patients and are responsible for 20% of the hospitalisation among diabetic patients. Peripheral neuropathy causes loss of protective sensation. The intrinsic foot weakness and atrophy associated with moderate and advanced neuropathy alter the anatomy of the foot and potentiate friction injury. Autonomic neuropathy reduces foot sweating and increases foot oedema. On top of this, small and large vessel stenosis and loss of vasodilatory regulation result in distal limb ischaemia promoting tissue fragility and impaired wound healing.

PROGNOSIS

There is accumulating evidence suggesting that not only surrogate markers of microangiopathy such as albuminuria, but also those used for polyneuropathy, such as nerve conduction velocity and vibration perception threshold, may predict mortality in diabetic patients. Autonomic neuropathy may be associated with early mortality from cardiac involvement.

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9.18 Sexual Dysfunction in Diabetes

Shashank R Joshi

BACKGROUND AND INTRODUCTION

Sexual and urologic complications of diabetes frequently occur in diabetes but are often under reported. Men may have difficulty with erections or ejaculation. Women may have problems with sexual response and vaginal lubrication. Urinary tract infections and bladder problems occur more often in people with diabetes. Diabetes mellitus (DM) may lead to abnormalities of normal sexual function in both men and women via diabetic induced vascular and neuropathic damage. Also, poorly-controlled diabetes may increase the morbidity associated with the treatment of erectile dysfunction (ED) in men. Erectile dysfunction is a common clinical problem and it seriously hampers quality of life for men and their spouse. It is well known that the incidence of ED increases with age and usually is often associated with co-morbid conditions like smoking, cardio vascular disease, hypertension, dyslipidemia and diabetes. The incidence of ED in men with diabetes is approximately 3 to 7 folds higher than in the general population. ED may also be the presenting symptom for DM and can predict both vascular or neurologic sequelae, which may occur later. Often ED is a marker of endothelial dysfunction. Fifty per cent of the Indian diabetic men in their lifetime will have the risk of developing ED if glycaemic control is not well controlled. As 50% of the diabetic men suffer from erectile dysfunction, the onset of ED in diabetics is associated with increasing age, duration of the diabetes, development of microangiopathy, neuropathy, alcohol intake and anti-hypertensive medication.

MECHANISMS OF ERECTILE DYSFUNCTION IN DIABETES

The pathophysiology of ED in diabetes is multifactorial with endothelial, vascular, autonomic, endocrine and neurologic factors either in isolation or in harmony. The neurogenic factors involve loss of unmyelinated C fibres in the early stage and large myelinated fibres in the late stage. The vascular factors implicated are atherosclerosis and microangiopathy, stenosis of internal pudendal artery, small penile vessels show changes like endothelial proliferation, subintimal fibrosis, endarteritis obliterans. Diabetes mellitus associated with hypercholesterolaemia and hypercoagulability which also additionally impair vascular function. There is impaired relaxation of the corpus cavernosal smooth muscle in diabetics in response to neuronal- and endothelial-derived nitric oxide, which may be due to the advanced glycosylation and its end products. It is now well known that adult male hypogonadism is seen with at least 10% of men who have ED with diabetes. Usually, the hypogonadism is central, viz. hypothal-amopituitary in origin. It is well known that the low levels of testosterone, lead to a decline in sexual desire as well as erectile dysfunction. Psychogenic factors are supplementary to the organic component and contribute to 30% of the ED in diabetes.

MANAGEMENT

Investigations

The patients with ED are often evaluated with the erectile function (EF) domain of the 15 item international index of erectile function (IIEF), two diary questions regarding the patient's ability to penetrate (SEP2) and have successful intercourse (SEP3), and a global assessment question (GAQ). The work-up includes fasting and prandial glucose, HbA1c, lipids profile, kidney function and prostate specific antigen (PSA). It also includes sometimes gonadal evaluation of testosterone, follicle-stimulating hormone (FSH), luteinising hormone (LH), prolactin and thyroid-stimulating hormone (TSH). It is useful to do an ultrasound of abdomen and pelvis for gonadal as well as bladder function/residual urine estimation. In few cases, semen and scrotal sonography and Doppler may also be done.

TREATMENT

Role of Phosphodiesterase Type-5 (PDE5) Inhibitors

The treatment of ED, in general, was revolutionised by the availability of sildenafil, followed by tadalafil and vardenafil. All the three medications work by inhibiting the enzyme PDE5 in the penile tissue. Sexual stimulation provokes the release of nitric oxide (NO), leading to increased cellular concentrations of cyclic guanosine monophosphate (cGMP) and subsequent penile smooth muscle relaxation. This process is reversed by the conversion of cGMP to guanosine monophosphate, which is mediated by phosphodiesterase type-5 (PDE5), the predominant functional PDE type found in the penis. Phosphodiesterase type-5 inhibitors (PDE5i) act at this step to maintain elevated levels of cGMP and continued smooth muscle relaxation. Since the release of NO is a neurologically-mediated event, neuropathy (as may occur with diabetes) may blunt the efficacy of PDE5i. This is indeed borne out clinically, as diabetics have a poorer response overall to PDE5i than men with ED of other causes. Therefore, diabetics need a higher dose as well as have a non-responder group.

Other Therapy Options

The other therapy options are intracavernosal alprostadil injection, vacuum erection devices (VED) penile prosthesis. Intracavernosal injections and penile prosthesis are useful in diabetics while VED are not very useful in diabetics.

Unlike the other modalities, prosthesis surgery is irreversible. In that the corporal tissue is permanently altered such that physiologic erections are no longer possible. If the prosthesis has to be removed, there will be complete erectile failure.

Treatment of Hypogonadism

There are now few studies of sexual function in hypogonadal, diabetic men treated with testosterone. It is now well known that testosterone improves sexual function (particularly sexual desire

and response to PDE5i in cases of initial failure to respond) in some selected patients. Additional testosterone replacement therapy also has beneficial effects on lean body mass and insulin sensitivity in diabetic men with hypogonadism. A number of different testosterone formulations are available which are discussed elsewhere (see Section 10 Chapter 11 Disorders of Gonads).

EJACULATORY DYSFUNCTION

Most men with diabetes may have sexual disorders other than erectile dysfunction like diminished sexual desire, lack of ejaculation with sexual climax (an ejaculation or retrograde ejaculation) and premature ejaculation. Successful antegrade ejaculation depends on the co-ordination of three neurologic events: seminal emission, bladder neck closure and contraction of the muscles of the pelvic floor (e.g. bulbocavernosus, ischiocavernous, etc.). In diabetes, neuropathy disrupts the ischiocavernosus nerve signals which control the closure of the connection between the bladder and urethra which, in turn, causes abnormal ejaculation. In this situation ejaculate is deposited in the innermost portion of the urethra but the connection between the bladder and urethra does not close. Since the bladder neck is open, some or all of the ejaculate may leak backwards into the bladder during the muscle contractions that normally expel the semen from the penis. In the most severe cases there may be total lack of seminal emission. Either of these conditions will impact fertility. It may also be a source of psychological disturbance to the man; indeed, some men report that they are not able to fully enjoy orgasm in the absence of ejaculation. From a fertility standpoint, sperm may be retrieved from post-ejaculate urine and then used for artificial insemination. Alternative strategies to overcome retrograde ejaculation generally focus on attempts to help the bladder neck close. A variety of pharmacologic agents have also been used including anticholinergics, antihistamines and alpha-adrenergics.

FEMALE SEXUAL DYSFUNCTION IN DIABETICS

This is a poorly understood and studied subject in diabetics. The best studied class of female sexual dysfunctions is arousal disorder; physiologically, this is accompanied by vasodilatation and engorgement of the female external genitalia. Given that the processes involved in female genital engorgement are governed by many of the same molecular processes that occur during male genital engorgement. Caruso *et al*, undertook a randomised controlled double-blinded (RCDB) trial of 100 mg sildenafil in type 1 diabetic women with sexual dysfunction. Of the 28 women, who have completed the trial, significant improvement was seen in both subjective and objective parameters. Subjectively, arousal, orgasm and dyspareunia were all improved in those taking sildenafil in comparison to baseline and those taking placebo. Colour Doppler ultrasonography was performed on the clitoral arteries, revealing an increase in blood flow in these women. However, it should be noted that the use of ultrasonography in the evaluation of women with sexual dysfunction is not routine and these results should be interpreted with caution. Usually, a gynaecological and urological test should be done.

THE IMPORTANCE OF MANAGING LIFESTYLE FACTORS IN TREATING SEXUAL PROBLEMS IN DIABETES

As with most aspects of diabetes care, routine exercise, careful monitoring of glucose levels and usage of appropriate therapies to prevent hyperglycaemia are the keys to prevent progression of diabetes-induced sexual problems. Weight management and dietary prudence are also critical in the management of diabetes. There is an evidence to suggest the weight loss may reverse erectile dysfunction in some men. In a study of 65 obese men with ED and the metabolic syndrome (MetS, obesity with associated abnormalities of blood pressure, abnormal glucose level/diabetes and abnormal cholesterol levels), eating a 'Mediterranean diet' (emphasising fresh fruit and vegetables) for 2 years led to normalisation of erectile function (as determined by an International Index of erectile function score greater than 22) in men as compared to men in the group that did not have dietary manipulation. A similar study in women with sexual dysfunction and metabolic syndrome showed a significant improvement in mean sexual function (mean increase on the female sexual function index from 19.7 to 26.1 in the treatment group versus no change from baseline in the control group). Also noted in both these studies were was improvements in serum insulin and glucose level in men and women who ate the Mediterranean diet. So, lifestyle plays a key role in sexual health in both sexes in a diabetic.

CONCLUSION

Sexual dysfunctions are common in people with diabetes but neglected and may arise from a variety of vascular, neurologic and hormonal causes. While PDE5i do not work as well in diabetics as in other populations, they still represent a good first-line treatment. If their use is unsatisfactory, intracorporal injections and implantable prosthesis are excellent alternatives. Vacuum devices represent another viable alternative, although satisfaction is generally not as high. Beyond erectile difficulties, men may complain of ejaculatory symptoms which arise from neuropathy of sympathetic nerves. Female sexual dysfunctions is mostly under reported in diabetics but further clinical advances may lead to increased hope and more efficacious treatments for these disorders.

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9.19 The Diabetic Foot

Pendsey Sharad Purushottam

INTRODUCTION

Diabetic foot is one of the commonest chronic complications of diabetes. It is the leading indication for hospital admissions and prolonged stay.

A classical triad of neuropathy, ischaemia and infection characterises the diabetic foot.

The presence of infection rapidly worsens the clinical picture often requiring limb amputation. Diabetic foot ulcers are common and estimated to affect 15% of all diabetics. In India, it is estimated that approximately 40,000 legs are being amputated every year, of which 75% are neuropathic feet which are potentially preventable.

CLASSIFICATION

Diabetic foot is mainly classified into two types: neuropathic foot, in which neuropathy dominates; and neuroischaemic foot, in which occlusive vascular disease dominates although neuropathy is present. Neuropathy leads to fissures, dry skin, deformities, callus formation at plantar pressure points and plantar ulcerations (**Figure 1**), bullae and neuropathic (Charcot) joint. Ischaemia leads to pain at rest, ulceration on foot margins (**Figure 2**), digital necrosis and gangrene. Differentiating between these entities is essential because their complications are different and require different therapeutic strategies.

Wagner's (**Table 1**) and University of Texas wound classification (**Table 2**) are the most acceptable classifications. Wagner classification accounts only for wound depth and does not consider presence of ischaemia or infection. In Texas system, one needs to mention both the grade and the stage of the wound.



Figure 1: Neuropathic plantar ulcer.



Figure 2: Neuroischaemic foot.

Table 1: Wagner's Classification

Grade 0	No ulceration in a high-risk foot
Grade 1	Superficial ulceration
Grade 2	Deep ulceration that penetrates up to tendon, bone or joint
Grade 3	Osteomyelitis or deep abscess
Grade 4	Localised gangrene
Grade 5	Extensive gangrene requiring amputation

Table 2: The University of Texas Wound Classification System

Stages	**Description**
Stage A	No infection or ischaemia
Stage B	Infection present
Stage C	Ischaemia present
Stage D	Infection and ischaemia present
Grading	**Description**
Grade 0	Epithelialised wound
Grade 1	Superficial wound
Grade 2	Wound penetrates to tendon or capsule
Grade 3	Wound penetrates to bone or joint

AETIOPATHOGENESIS

Neuropathic Foot

Chronic symmetrical progressive sensorimotor neuropathy leads to loss of protective sensation. The majority of foot ulcers are a consequence of mechanical trauma unnoticed by the patient. Commonest sites of ulcerations are in the forefoot. Ulcers occur at sites of high pressure on either plantar or dorsal surfaces and are caused by bony prominences, ill-fitting footwear and toe deformities. Chronic hyperglycaemia leads non-enzymatic glycosylation of proteins causing limited joint mobility. Foot deformities occur as a result of atrophy of intrinsic muscles of the foot which alter the architecture of the foot. The combination

of these risk factors increase the plantar pressures significantly in the forefoot and the risk of foot ulceration (**Table 3**).

Table 3: Factors Contributing to Foot Ulceration

Extrinsic Factors	Intrinsic Factors
Inappropriate footwear	Bony prominences
Walking barefoot	Limited joint mobility
Falls and accidents	Joint deformity
Objects inside shoes	Callus
Sharp injuries	Fissures
Thermal trauma	Previous foot surgery
Activity level	Neuro-osteoarthropathic joint

Charcot Foot

A Charcot joint or neuroarthropathy is defined as a relatively painless progressive arthropathy of single or multiple joints. The most frequent location of the neuropathic joint is the tarsal-metatarsal region, followed by the metatarsophalangeal joints, and then the ankle and subtalar joints. The initial presentation is often a hot swollen foot (acute stage), the precipitating event usually being a minor trauma.

The process of destruction takes place over a few months (chronic stage, **Figure 3**) and leads to classic rocker bottom deformity. Multiple factors appear to contribute to the development of the Charcot foot. A peripheral neuropathy with loss of protective sensations, an autonomic neuropathy with increased blood flow to the bone, and mechanical trauma, have emerged as the most important determinants. Diagnosis is usually made on clinical grounds and typical radiological features such as fragmentation of bones, fractures, subluxation and dislocation of the joints. Osteolysis of bones leads to 'sucked candy' appearance of metatarsals or 'pencil-like' appearance of phalanges.



Figure 3: Radiograph showing Charcot Foot destruction of tarsal bones.

Goal of management is to convert destructive stage into phase of stabilisation. Strict rest, off loading by total contact cast and, finally, rehabilitation by using custom-made indepth shoes. Those with extensive destruction of ankle joint, may require surgical fixation.

Foot Infection

Infection in diabetic foot is a limb threatening condition because the consequences of deep infection in a diabetic foot are more disastrous than elsewhere mainly because of certain anatomical peculiarities. Foot has several compartments which are inter-communicating and the infection can spread from one into another, lack of pain allows the patient to continue ambulation further facilitating the spread. The foot also has soft tissues, which cannot resist infection, like plantar aponeurosis, tendons, muscle sheaths and fascia.

Osteomyelitis generally results from contiguous spread of deep soft tissue infection through the cortex to the bone marrow. Majority of the deep longstanding foot infections are associated with osteomyelitis (**Figure 4**).



Figure 4: Radiograph showing osteomyelitis of great toe phalanges.

The diagnosis of osteomyelitis can be made by plain radiography which usually shows focal osteopaenia, cortical erosions or periosteal reaction in early stage and sequestration in the late stage. A simple clinical test is probing to bone. A sterile metal probe is inserted into the ulcer, if it penetrates to the bone it almost confirms the diagnosis of osteomyelitis. Chronic discharging sinus and sausage-like appearance of the toe are the clinical markers of osteomyelitis. Definitive diagnosis requires obtaining bone biopsy for histopathology.

Newer imaging techniques are like nuclear bone scan, computerised tomography scan (CT), positron emission tomography (PET), magnetic resonance imaging (MRI). Of these, MRI is more sensitive and specific.

EXAMINATION AND DIAGNOSIS

Examination of feet is an integral part of physical examination of every patient, more so a diabetic patient. Look for changes like dry skin, fissures, interdigital mycoses, deformities, callus, abnormal shape of foot, ulceration, prominent veins and nail lesions.

Feel peripheral pulsations. Chronic sensorimotor neuropathy can be assessed by detecting sensation to pinprick and cotton wool and vibration using 128 Hz tuning fork. Hand-held biothesiometer can assess vibration perception threshold. 10 gm monofilament can detect the loss of protective pain sensation. The filament is applied perpendicular to the foot over metatarsal heads till it buckles. Buckling of the filament occurs at 10 g equivalent of linear pressure. Measuring ankle/brachial pressure index (ABI) using hand-held Doppler helps in assessment of vascular supply. Normal ABI is >0.9, in ischaemia it is <0.9.

MANAGEMENT

Diabetic foot should be managed using a multidisciplinary team approach. Off-loading and debridement are considered vital to the healing process for diabetic foot wounds. The goal of off-loading is to redistribute force from ulcers sites and pressure points at risk to a wider area of contact. There are multiple methods of pressure relief, including total contact casting, half shoes, removable cast walkers, wheelchairs and crutches. The open diabetic foot ulcer may require debridement if necrotic or unhealthy tissue is present. The debridement of the wound will include the removal of surrounding callus and aid in decreasing pressure points at callused sites on the foot. Additionally, the removal of unhealthy tissue can aid in removing colonising bacteria in the wound. It will also facilitate the collection of appropriate specimens for culture and permit examination for the involvement of deep tissues.

Infection in a diabetic foot is limb-threatening and at times life-threatening and must be treated aggressively. Superficial infections should be treated with debridement, oral antibiotics. All patients with deep infections should be hospitalised and started on broad-spectrum antibiotics. The choice of antibiotics initially should be empirical but once the culture reports are known, it should be specific. Surgical debridement should be carried out which should include all the devitalised tissues, sloughed tendons and infected bones.

Dressing Material

The selection of wound dressings is also an important component of diabetic wound care management. Saline-soaked gauze dressings are inexpensive, variety of new dressing materials have been developed, such as film and foam dressings, hydrogels, hydrocolloids and alginates.

Vaccum assisted closure (VAC), sterile maggots therapy have been shown to promote wound healing in diabetic ulcers. A recombinant platelet-derived growth factor (PDGF) is also currently in use and has been shown to stimulate wound healing in non-infected neuropathic ulcers.

Empiric Antibiotic Management of Patients

Antibiotic therapy is necessary for all infected wounds; all Grade 2 and Grade 3 ulcers; superficial ischaemic ulcers that are deteriorating, as ischaemia can mask signs of infection.

- Antibiotic therapy is insufficient without appropriate wound care. Proper wound cleansing, debridement of any callus and necrotic tissue and, especially, off-loading of pressure has to be done completely and early.
- Take into consideration any recent antibiotic therapy and, if concerns about resistant organisms exist (e.g. MRSA), treatment has to be modified accordingly.
- Treatment can be modified based on the clinical response, as determined by the diabetes specialist, podiatrist's clinical assessment. Microbiology results (cultures and sensitivities) can then be used to modify antibiotic usage, depending on clinical response.
- Continue antibiotic therapy until there is an evidence that the infection has resolved, but not necessarily until a wound has healed.

PREVENTION

Early detection and surveillance of potential risk factors for ulceration can decrease the frequency of wound development (**Table 4**). Patients should be educated regarding the importance of maintaining good glycaemic control, wearing appropriate footwear, avoiding trauma and performing frequent self-examinations.

Table 4: Risk Categorisation System

Category	Risk Profile	Check-up Frequency
0	No sensory neuropathy	Once a year
1	Sensory neuropathy	Once every 6 months
2	Sensory neuropathy with signs of peripheral vascular disease	Once every 3 months
3	Previous ulcer/amputation	Once every 1 to 3 months

Prevention of Diabetic Foot Includes

- Primary prevention: screening of high-risk feet and proper advice on preventive footwear.
- Secondary prevention: management of trivial foot lesions such as callus removal, treatment of nail pathologies, and deroofing blisters, etc.
- Tertiary prevention: prompt referral to specialist for advanced foot lesions.

Majority of patients with neuropathic feet require preventive footwear such as sandals or shoes. They should be strictly instructed to avoid slippers and 'chappals'. Therapeutic footwear are required for minority of patients who have partial foot amputation, Charcot foot, or grossly deformed feet.

Understanding the diabetic foot, proper examination of feet, investigations to classify the foot ulcers and proper management techniques using team approach along with preventive steps, would go a long way in limb salvage and prevention of limb amputation in people with diabetes.

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9.20 Diabetes and Pregnancy

V Seshiah

INTRODUCTION

A new structure develops *de novo* during pregnancy and matures till it is expelled at the completion of the gestational period. The metabolic adaptations that occur during pregnancy are to accommodate a rapidly growing tissue transplant, the conceptus (placenta and foetus). For its own normal growth and development, the conceptus brings about alterations in maternal fuel metabolism and hormones. The placenta facilitates embryogenesis, growth, maturation and survival of the foetus. It has the capacity to synthesise steroid and peptide hormones and to modulate and transport maternal fuel to the foetus, 'an exquisite hormono-metabolic adaptation'.

CLASSIFICATION OF DIABETES IN PREGNANCY

Pregestational Diabetes

This term denotes pregnancy occurring in women who already have established type 1 or type 2 diabetes. They have to be followed-up taking into consideration the age of onset, duration of diabetes, mode of therapy and the existing complications.

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Abnormal glucose tolerance during pregnancy is not only associated with increasing pregnancy morbidity but also increases the likelihood of subsequent diabetes in the mother. Maternal hyperglycaemia has a direct effect on the development of foetal β-cell mass and is associated with increased susceptibility to the development of obesity and diabetes in the offspring (**Figure 1**). This effect on the offspring is independent of other genetic factors. As such GDM has implications beyond the index pregnancy, identifying two generations (mother and her offspring) at risk of future diabetes. The recognition of glucose intolerance during pregnancy is more relevant in the Indian context as Indian women have 11-fold increased risk of developing GDM compared to white women. It is important to detect these GDM cases because, if unrecognised, pregnancy may end in perinatal death and foetal wastage.

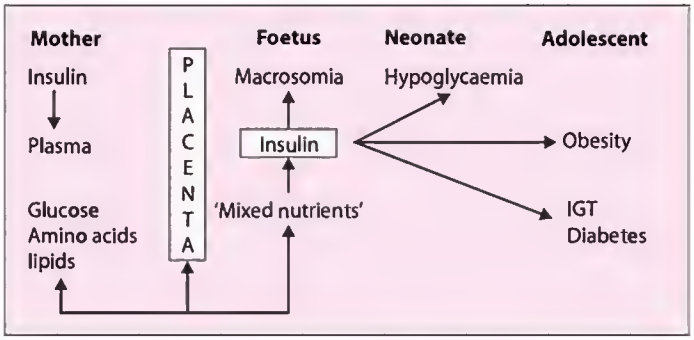


Figure 1: Pedersen/Freinkel hypothesis.

PATHOGENESIS OF GLUCOSE INTOLERANCE DEVELOPING DURING PREGNANCY

During pregnancy, there is an increased elaboration of placental chorionic somatomammotrophin (human placental lactogen or hPL), prolactin and cortisol. The surge of counter hormones results in the insulin resistance and stress the carbohydrate metabolism (diabetogenic stress). Normally a pregnant woman increases her endogenous insulin production by more than 30% from her non-pregnant insulin level. A pregnant woman, who is unable to secrete adequate insulin to compensate for the insulin resistance of pregnancy, develops gestational diabetes. Women with GDM are insulin resistant and have impaired β-cell function.

CONSEQUENCES OF THE CHANGES IN FUEL METABOLISM DURING PREGNANCY ON THE FOETAL DEVELOPMENT

Effect of Maternal Fuels on Foetal Development

The clinical hyperglycaemia-hyperinsulinism hypothesis of Pedersen (**Figure 1**) has been modified to include contributions of other maternal fuels besides glucose that are also responsive to maternal insulin. All of these can influence the growth of the foetus and the maturation of the foetal β-cell and increase in insulin secretion. Within this formulation, growth will be disparately greater in insulin-sensitive tissues (excessive abdominal fat deposition, organomegaly of liver, spleen and heart and accelerated skeletal maturation) than in insulin-insensitive tissues in the foetus.

Consequences of Maternal Hyperglycaemia on Foetus and Neonates

Prevention of foetal morbidity necessarily starts before conception, reflecting the importance of pre-pregnancy counselling in obtaining good glycaemic control and advising folic acid 400 µg per day to prevent neural defects. Consequences of maternal hyperglycaemia are described in **Table 1**.

Table 1: Consequences of Maternal Hyperglycaemia on Foetus and Neonates

First Trimester Foetal Problems	Second Trimester Foetal Problems	Third Trimester Foetal and Neonatal Problems
Malformations Growth retardation Foetal wastage	Hypertrophic Cardiomyopathy Polyhydramnios Erythraemia Placental insufficiency Pre-eclampsia Foetal loss Low IQ	Hypoglycaemia Hypocalcaemia Hyperbilirubinaemia Respiratory distress syndrome Macrosomia Hypomagnesaemia Intrauterine death

Consequences of Diabetes on the Pregnant Mother

Complications of diabetes in pregnancy occur almost exclusively in pre GDM.

- Hypoglycaemia
- Diabetic ketoacidosis
- Retinopathy
- Nephropathy
- Hypertension
- Diabetic gastropathy

DIAGNOSIS

World Health Organization Criteria

World Health Organization (WHO) recommends using a 2-hour 75 g oral glucose tolerance test (OGTT) with a threshold plasma glucose concentration of more than 7.8 mmol/L (140 mg/dL) at 2 hours similar to that of impaired glucose tolerance (IGT) outside pregnancy. This criterion is widely followed in much of the world including India; most suitable for universal screening in high-risk population for diabetes. It will be advantageous to estimate fasting plasma glucose also as this will help in planning treatment strategy.

National Institute for Health and Clinical Excellence (NICE) Guidelines

World Health Organization criteria of 2 hours plasma glucose >140 mg/dL with 75 gm oral glucose load for diagnosing GDM. Do not screen using fasting plasma glucose, random blood glucose or glucose challenge test.

International Association of Diabetes in Pregnancy Study Group

The International Association of Diabetes in Pregnancy Study group (IADPSG) suggest 75 gm glucose load for an OGTT in all clinical settings in or outside of pregnancy. The diagnosis of GDM is made if any one or two glucose value F >92 mg/dL/1 hour >180 mg/dL/2 hours >153 mg/dL, which is almost similar to the existing Carpenter and Couston criteria American diabetes association (ADA) criteria of FPG >95 mg/dL, 1 hour >180 mg/dL and 2 hours >155 mg/dL.

MANAGEMENT

The important predictor of foetal outcome either in pre-gestational or gestational diabetes is the glycaemic control attained immediately before and during pregnancy. The plasma glucose level of normal pregnant women is less than 90 mg/dL and 120 mg/dL, respectively during fasting and post-prandial states. Hence, the best foetal outcome can be expected by maintaining the mean plasma glucose level around 105 mg/dL in a pregnant diabetic woman.

Medical Nutrition Therapy

The expected weight gain during pregnancy is 300 to 400 gm per week and a total weight gain of 10 to 12 kg by term. Hence, the meal plan aims to maintain euglycaemia and to provide sufficient calories to sustain adequate nutrition for the mother and foetus and to avoid excess weight gain and post-prandial hyperglycaemia. Calorie requirement depends on age, activity, pre-pregnancy weight and stage of pregnancy. Approximately 30 to 40 kcal/kg ideal body weight, or an increment of 300 kcal/day above the basal requirement, is needed. Pregnancy is not the time for obesity correction but permitted weight gain is up to 9 kg. Underweight subjects are those not gaining weight as expected, particularly in the third trimester, require admission to ensure adequate nutrition to prevent low birth weight infants.

Insulin Therapy

Gestational diabetes mellitus

Fasting or postprandial plasma glucose exceeding 90 mg/dL or 120 mg/dL respectively after 2 weeks of medical nutrition therapy (MNT), on more than two occasions is an indication for insulin therapy. Human insulin is recommended. The patient may require a small dose of intermittent acting insulin about 4 to 6 units as initial dose given before breakfast. The dose has to be titrated on follow-up. A few of them may require combination of soluble and intermittent acting insulins. Usually, they may not require more than 20 units of insulin per day (the total dose is divided 2/3 in the morning and 1/3 in the evening). Recently short-acting analogues have been found to be safe and approved for use during pregnancy.

Pregestational type 1 diabetes mellitus: Maintenance of normoglycaemia before conception is essential to prevent foetopathy, since the organogenesis is completed by the sixth week after conception, at a time when most of the women are not even aware of their pregnancy. It has been proved in experimental animals and from observations in human pregnancies that glucose has to be normal before conception to avoid congenital malformation.

Two special diagnostic procedures in the first half of the pregnancy are relevant to detect any malformation in the foetus in a pregnant woman who attends the antenatal clinic after conception. Ultrasonography is performed to diagnose anomalies like anencephaly, cardiac and spinal abnormalities. Elevated serum alpha-foetoprotein at 14 to 16 weeks of gestation indicates neural tube defect.

In a pregestational type 1 diabetic woman, the requirement of insulin may fall during the early part of first trimester and increase as the pregnancy advances and plateaus during third trimester. They may require morning and evening 'split and mixed' dose of insulin, i.e. both short and intermittent acting insulins in the morning and evening. A few pregnant women may require less insulin in the last week of pregnancy attributed to foetal handling of maternal glucose. Sudden decrease in requirement of insulin in the third trimester of pregnancy indicates foetal jeopardy.

Type 2 diabetes mellitus in women: Pre-gestational type 2 diabetic women, desiring to become pregnant, should also undergo pre-pregnancy counselling. Pre-pregnancy control of diabetes with insulin is ideal. Sometimes a hitherto undiagnosed type 2 diabetic woman may progress through the early weeks of gestation at the risk of malformation in her offspring or a known type 2 diabetic woman who is already on oral hypoglycaemic agent (OHA) may present to antenatal clinic after conception and at times in second or third trimester of pregnancy. The best course at this juncture is to withdraw OHA and introduce insulin besides monitoring foetal well-being.

Insulin requirement

The insulin requirement varies from person to person, both in type 1 and type 2 diabetic pregnant women. The aim should

be to maintain plasma glucose at an acceptable level and not to unduly worry about the amount of insulin being administered. A few type 2 diabetic women may require very high dose of insulin, even more than 200 units/day compared with pregnant mothers with gestational diabetes. One should not be unduly concerned about the dose of insulin, as the aim during pregnancy is to have optimal glucose control for good foetal outcome.

Insulin Treatment During Delivery

The goal is to maintain the glucose level of 90 to 108 mg/dL to avoid the risk of neonatal hypoglycaemia. Insulin requirement declines after delivery to approximately 60% of the dose prior to pregnancy. Insulin dose has to be adjusted on follow-up.

Role of Oral Hypoglycaemic Agents

Normally, OHAs are not recommended during pregnancy. However, there are instances of women treated with OHAs completing their gestation successfully. A randomised unblended clinical trial compared the use of insulin and glibenclamide in women with GDM who were not able to meet glycaemic goals on meal plan. Treatment with either agent resulted in similar pregnancy outcomes. All these patients were beyond the first trimester of pregnancy at the initiation of therapy.

A randomised controlled study found that in women with GDM, metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin. Metformin has been found to be useful in women with polycystic ovarian disease (PCOD) who failed to conceive. Continuing this drug after conception is still a controversy, but there are a few studies favouring continuation of metformin throughout pregnancy in these women. More studies are required before routinely recommending OHAs during pregnancy.

GESTATIONAL DIABETES MELLITUS LIKELY TO DEVELOP DIABETES

The future risk of developing diabetes for a gestational diabetic is 2-fold, if she becomes overweight, but maintaining the ideal body weight approximately halves the risk. The requirement of insulin in addition to diet to maintain euglycaemia during the index pregnancy is also predictive of future diabetes.

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9.21 Prevention of Diabetes Mellitus

Yash Pal Munjal

INTRODUCTION

Diabetes mellitus has reached pandemic proportions. It is estimated that 285 million people corresponding to 6.4% of the adult population in the world were afflicted with diabetes in the year 2010. This figure is growing at a fast pace and it is expected to touch 438 million by the year 2030 and that will constitute 7.8% of the adult population globally. About 70% of this diabetic population will happen to be living in low and middle income group countries. In India it is estimated that there are 50.8 million patients of diabetes, followed by China which has 43.2 million. Most of these cases occur between the age group of 40 to 59 years which is a decade earlier than the western world. A large pool of diabetics remains undetected, ranging from 70% to 80% in different parts of the world. It is a matter of concern all over the world. Besides this there is a large population with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The prevalence of this group in our country is around 14%. It is estimated that approximately 40% of the patients with IGT shall progress to diabetes in the next 5 years to 10 years. The cost of medicare for managing these patients will be quite staggering for the economy of any country, particularly the developing countries. The progression and onset of diabetes takes 10 years to 15 years, and therefore, provides a good opportunity for prevention of diabetes and thus prevent morbidity. Based on the demographic profile of this disease, prevention can be primary, secondary and tertiary as outlined in **Figure 1**. These preventive measures are based on the correction of the two major pathogenetic mechanisms, i.e. insulin resistance and insulin deficiency. The issue of lifestyle changes and pharmacological interventions are the hallmark in all stages of preventive strategy. In this chapter lifestyle measure and comparative value of pharmacological prevention are discussed in high-risk and IGT/diabetic patients.

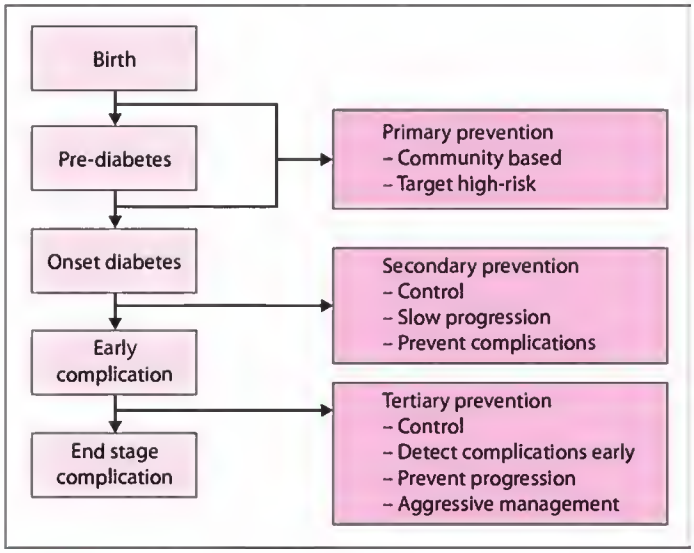


Figure 1: Stages of prevention of diabetes.

STRATEGIES FOR PREVENTION OF DIABETES

Two major strategies have been evaluated for reducing the incidence of type 2 diabetes, i.e. lifestyle interventions and drugs. Surgery (metabolic surgery) is emerging as the third arm of prevention. The first two steps aim at modifying the risk profile for diabetes. The risk factors of diabetes can be classified into modifiable risk factors and non-modifiable risk factors (**Table 1**). The modifiable risk factors are the subject matter of intervention.

Table 1: Risk Factors for Type 2 DM

Modifiable	Non-Modifiable
Overweight and obesity	Ethnicity
Sedentary lifestyle	Family history
Previously identified impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)	Age
	Gender
	History of gestational diabetes mellitus
Metabolic syndrome	Polycystic ovarian disease
Elevated TG, reduced HDL	
Hypertension	
Dietary factors	
Intra-uterine environment	
Inflammation	
Use of drugs like corticosteroids, diuretics	

Lifestyle Interventions

Lifestyle interventions include medical nutrition therapy (MNT) and physical activity (PA). They serve to address the issue of overweight and obesity, improve insulin sensitivity and prevent the progression from IFG and/or IGT and to overt diabetes and control inflammation, an important aspect in prevention of micro- and macrovascular complications.

Obesity or overweight

The present epidemic of diabetes is very significantly fuelled by the growing problem of overweight and morbid obesity. Obesity is again a global problem increasing progressively. Excessive truncal adiposity is very well correlated with the risk for diabetes, hypertension and cardiovascular disease. The changing lifestyle, lack of physical activity and increasing stress are some of the important contributory factors. To sum up, the marked increase in the intake of energy dense food with very little or no physical activity and high level of stress contributes significantly to the progression of the epidemic. The question arises: how and at what level of natural history diabetes can be prevented especially by modifying lifestyle factors? To answer this, a prospective Nurses Health Study of 84,941 female nurses was conducted. They were followed for 16 years and a series of risk factors related to dietary behaviour, physical activity, weight and cigarette smoking were identified and targeted. This was associated with a remarkable 91% reduction in the risk of developing diabetes. Even with a family history of diabetes the risk reduction was 88%. In theory, therefore, diabetes can be

prevented, largely by lifestyle changes despite genetic background. In most of the trials reduction in weight predicts a decrease in incidence of diabetes. It is estimated that *each kilogram of weight loss is associated with approximately 16% reduction in the occurrence of overt diabetes*. Similar results were observed in the Finnish diabetes prevention programme (FDPP) in which weight loss averaging 3 to 4 kg over 4 years in overweight subjects with IGT led to a 58% decline in the occurrence of overt diabetes. A similar result was observed by the diabetes prevention programme (DPP) in the United States in which lifestyle interventions involving exercise and dietary changes in subjects with IGT reduced the occurrence of diabetes by 58%. The results of studies involving lifestyle modifications are shown in **Table 2**.

Table 2: Results of Lifestyle Modifications

Study	Duration (Years)	Relative Risk Reduction (%)
Malmo	6	63
Da Qing	6	42
Finnish DPP	3	58
DPP (USA)	3	58
DPP (Japan)	4	67
DPP (India)	3	28

The results of these lifestyle intervention programmes are quite impressive in the prevention of diabetes but practically lifestyle management is replete with problems. These interventions are labour intensive (one study needed 16 one to one sessions delivered by case managers to achieve target weight reduction and exercise levels). Although lifestyle interventions produced successful results, in research settings they are difficult to replicate even in well funded healthcare systems. After completion of DPP all the participants were offered an intensive lifestyle programme in a group sessions format. Those subjects who opted were enrolled in DPP outcome study (DPPOS). This study was conducted to evaluate whether the effects of diabetes prevention were sustained over a period of time. During the trial phase the training in group session format and follow-up was aggressive during the additional follow-up averaging over 6.8 years in DPPOS. Its results were published in the year 2009 thus giving a mean follow-up of approximately 10 years. In the intensive lifestyle modification (ILS) group, as compared to the other group, a 34% risk reduction was noted. The Japanese and Indian studies have shown similar results. (Though of shorter duration).

In case of over-weight individuals, reduction of weight by restricting calories and increasing exercise is of vital importance. However, it has been observed that it is not necessary to reduce the weight to the level of ideal body weight, but a reduction of about 5% to 10% in the body weight gives substantial reduction. In severely overweight subjects with IGT, gastric bypass surgery led to a weight loss of 22.5 kg (and 28 kg in the Swedish SOS Intervention Study), the incidence of diabetes reduced 30-fold compared with normal patients. Weight loss associated with improvement of gastrointestinal hormones is considered to, contribute in reducing the incidence of diabetes.

Nutrition

Diet: Recommendations for individuals should consider the following maintain calorific intake. The calories are to be distributed in various forms of food constituents.

Distribution of food/calories: This is dealt in Chapter 5 of this section.

Physical activity

Physical activity is an important element in the prevention and management of type 2 diabetes in all its stages. Large and well planned studies have established the importance of exercise. One has to do 30 to 45 minutes of aerobic exercise and resistance exercises for 6 days a week and preferably all the 7 days. The beneficial effects of physical activity are due to the mechanisms given in **Table 3**.

Table 3: Benefits of Physical Activity

Decreases insulin resistance/improve insulin sensitivity
Decreases overall adiposity
Reduces central adiposity
Improves blood glucose levels (glucose tolerance), lipid levels and blood pressure
Desirable changes in muscle mass

Though there are difficulties in implementing lifestyle measures, some of the tips that may help to achieve the goal are given in **Table 4**.

Pharmacotherapy for Prevention

Considerable emphasis has been focused on the prevention of diabetes with the drugs which are used for the treatment of diabetes as well. Table 5 gives the important drug trials and their results. The diabetes prevention programme research group study found a 31% reduction in the incidence of diabetes with metformin (at 2.8 years). Acarbose showed 25% risk reduction over 3 years in STOP NIDDM study. However, sustained effects with acarbose have not been studied. Troglitazone proved to be effective in controlling blood sugar levels but was removed from the market because of serious liver toxicity. In the DREAM

Table 4: Practical Tips for Nutrition and Physical Activity

Calculate Calorie Intake Based on Weight and Activity Profile
Fats – Restrict 20% to 25% of total calories
Increase fibre content (20 to 30 gm per day)
Small frequent meals
Encourage intake of whole grains, beans, fruits, vegetables and nuts
Emphasise on portion size/slow eating
Physical Activity
Set goal – 45 minutes exercise of moderate intensity aerobic and resistance exercise every day
Individual-based exercise programme is useful
May use small gadgets like pedometer
Start slowly and build up gradually
Others
Provide family help and support
Failures be circumvented
Close follow-up

trial rosiglitazone showed risk reduction of 60% over 3 years study period, but due to its cardiovascular side effects the drug has been withdrawn from the market. In case of obese people, orlistat has been shown to reduce the risk of diabetes by 37% as compared with placebo. Pravastatin when given to non-diabetics for cardiac or cholesterol lowering reasons reduced the number of new cases of diabetes. ACE-Inhibitors (ramipril, perindopril) and angiotensin receptor blockers (telmisartan and olmesartan) have shown improvement in glucose tolerance when given to non-diabetics. But these are not substantiated in subsequent well planned trials.

Table 5: Review of Drug Intervention Trials

Study	Drug	Study Duration (Years)	Relative Risk Reduction (%)
DPP	Metformin	3	31
India (IDPPI)	Metformin	3	26
TRI POd	Troglitazone	1	75
STOP NIDDM	Acarbose	3	25
XEN DOS	Orlistat	4	37
DREAM	Rosiglitazone	3	60

Lifestyle measures as compared with pharmacological intervention have shown better results and that is intensive lifestyle changes are two times better than pharmacotherapy.

In a cost benefit analysis discussed in American Diabetes Association Annual Scientific Sessions 2011 it was also demonstrated that though lifestyle measures are more effective in prevention of diabetes, the cost benefit ratio is better in patients being managed on metformin.

BARIATRIC SURGERY

The basic clinical outcome of bariatric surgery is to reduce weight and this in turn has proved to be useful in the prevention of diabetes. It is also postulated that there is a change in the intestinal hormones (incretins) which are known to control diabetes. In one of the prospective Studies of over 2000 patients who underwent various forms of bariatric surgery (the commonest being vertical banded gastroplasty) and compared with a standard-care group, it was demonstrated that the patients who underwent bariatric surgery, the risk of diabetes was reduced by 86% at 2 years and 75% at 10 years follow-up. It was also found out in the sub-group where there was 12% or more of weight loss from the baseline people did not develop diabetes at all.

Bariatric surgery is also reported to induce a remission in diabetic patients. Similarly another randomised control prospective trial of gastric banding versus conventional therapy there was remission in 73% as compared to 13% of control procedures. Gastric banding procedures improve glycaemic control in diabetic patients. The patient selection has to be careful and as compared to morbid obese patients bariatric surgery has to be considered in patients with a body mass index (BMI) of more than 35 kg/m^2 as compared to obese people with BMI of more than 40 kg/m^2. Large scale trials are underway to establish the long-term benefits of the various procedures for control and prevention of diabetes.

PREVENTION OF DIABETES IN THE INDIAN CONTEXT

The Indian Diabetes Prevention Programme 1 (IDPPI) was the first study to show that lifestyle modification was effective in preventing diabetes in native Asian Indians. IDPPI was a multicentre randomised, controlled and 3-year prospective study in subjects with IGT. The study groups were as follows:

Group 1: control group with no intervention (n = 133)

Group 2: subjects advised lifestyle modification (n = 120)

Group 3: subjects treated with 500 mg of metformin (n = 128)

Group 4: subjects treated with both lifestyle modification and metformin (n = 121)

The median follow-up period was 30 months and the 3 years decrease in cumulative incidence of DM was 55%, 39.3%, 40.5% and 39.5% in groups 1 to 4 respectively. The relative risk reduction in lifestyle modification (28.5%; P = 0.018), metformin (26.4; P = 0.029), lifestyle modification and metformin (28.2%; P = 0.022) compared with the control group was very similar. The study showed that progression from IGT to diabetes was high in Indians. Both lifestyle modification and metformin were equally effective and there was no added benefit in combining them.

The study thus showed that primary prevention of DM was possible in a comparatively lean but highly insulin resistant indian population by moderate changes in physical activity and diet. Family history of DM in first degree relatives of Indian diabetics was 45% to 54% compared to 38% in Europeans suggests a strong ethnic genetic susceptibility. Prevalence of overweight among Indian urban children (17.8% boys and 15.8% girls aged 14 to 19 years) with lack of physical activity and high carbohydrate, high fat and high calorie diet would be a forerunner of DM. Intrauterine malnutrition or overnutrition and poor control of gestational DM also increase the chance of future DM. Urbanisation and migration seem to increase the incidence of DM. Screening for glucose intolerance for preventive measures at an early age is a requisite in Indians as they develop hyperglycaemia at a younger age. It is ideal to achieve primary prevention of type 2 diabetes by non-pharmacological intervention in the relatively lean Asians as compared with western population.

Role of Vitamin D in Prevention

Recent studies (Women health study: nurses health study) have drawn attention to the role of vitamin D and calcium homeostasis in the metabolic syndrome. It was observed that low levels of vitamin D are contributory to insulin resistance, reduced calcium mediated insulin secretion and higher incidence of diabetes. Vitamin D along with calcium supplements has shown improvement in insulin resistance and insulin secretion. Asians have high prevalence of vitamin D deficiency and vitamin D with calcium supplements is likely to improve β-cell function.

POPULATION BASED-PREVENTION STRATEGIES

World health organisation and other member countries who are seized with the problem of chronic diseases especially diabetes have formulated a series of guidelines for implementation at the community level for the control and prevention of diabetes. international diabetes federation (IDF) has also given its guidelines. Based on the recommendations of WHO and IDF, the following strategies provide an insight in preventing DM at

community level. The approach with each country and sub-population will vary from place to place. However the basic plan of prevention will remain the same globally.

The prevention strategies can be grouped in three steps:

Identification of People at High-Risk

Large population based surveys for diabetes detection may be an expensive exercise and is not feasible. It is therefore, prudent to identify people at high-risk and screen them. This is more cost effective and beneficial exercise. The people at high-risk can be identified by so called opportunistic screening, by various questionnaire and diabetes risk tests which have been devised by several countries. These risk scores are based on the following:

- High BMI (cut-off values vary from continent to continent)
- IGT/IFG
- Gender
- Family history of diabetes
- Waist measurement
- Dyslipidaemia

India has also formulated its own diabetes risk score. These parameters contribute to one another but are not mutually exclusive. **Table 6** gives the details of the Indian population at risk.

Table 6: Measurement of Risk in Indian Population

Plasma glucose – fasting blood glucose followed by oral glucose tolerance test, if necessary
HbA1C > 6%
Waist circumference (85 cm for female and 90 cm for male)
Cardiovascular disease risk factors
Family history
Body mass index (BMI) more than 23 kg/m^2

Interventions

Based on these parameters the people at risk have been graded into high, medium and low-risk areas. According to the level of their risk grading the interventions can be planned based on their relative risk category. The interventions have to be aggressive especially in high and medium risk population. The possible role of various inventions medical nutrition therapy (MNT), physician assistant (PA), Bariatric Surgery) has been discussed above and need not be repeated. The interventions suggested by IDF and WHO provide the blue print but the exact programme has to be designed on geographical and ethnic basis in each country.

Prevention of Type 1 Diabetes

Type 1 diabetes is a T helper cell mediated autoimmune disease in a genetically susceptible individual. The susceptibility and protection loci are in the short arm of chromosome 6 in the major histocompatibilty complex. Environmental factors like infections including viruses especially coxsackie and rubella, ingestion of bovine milk proteins and nitrosourea compounds during childhood, malnutrition and infection during pregnancy have been attributed as environmental triggers. For an effective prevention strategy there is need for an efficient prediction strategy using genetic and immune markers (Islet cell antibodies, GAD antibodies). First phase insulin response in intravenous glucose tolerance test is also an early marker. Risk groups include first degree relatives of type 1 diabetics and offspring of auto-antibody positive, gestational diabetic parents, children born to older mothers especially in first born children of mothers over 40 years of age and high parental age. The groups more prone to develop type 1 diabetes have been tabulated in **Table 7**. In patients with new onset of diabetes, treatment with Anti CD3 monoclonal antibodies (teplizumab) have recently been shown to slow the decline in C-Peptide levels.

Table 7: Risk Factors in Various Groups

Group	Level of Risk
General population	0.7% to 1.5%
Offspring of diabetic parents (mother/father)	2% to 5%
Siblings	5% to 6%
Monozygotic twins	33% to 50%

From the Table above it is quite apparent that first degree relatives of diabetic patients, siblings and children born to older mothers have a higher propensity to develop diabetes.

Various studies to see the effect of interventional trials in type I diabetes like DPPTI (diabetic prevention trial of north America and European nicotinamide diabetes intervention trial (ENDIT) have been completed and have shown negative results.

Interventions in animal models have shown success in preventing or delaying type 1 DM. Interventions that target the immune system directly are immunosuppression, selective T cell subset deletion and induction of immunologic tolerance to islet proteins. Another approach is to prevent cell death by blocking cytotoxic cytokines or increasing islet cell resistance to the destructive process. However, these interventions have not been successful in preventing type 1 diabetes in humans. The diabetes prevention trial type 1 also concluded that insulin (IV and SC or PO) did not prevent type 1 DM. Therefore, the focus is shifting to develop a vaccine for prevention of type 1 diabetes, and this is being followed vigorously.

CONCLUSION

The evidence base for prevention of type 2 diabetes is quite robust. The cost involved and the benefits accruing may be considered acceptable at government and community level. Every doctor practicing curative medicine should also focus on the preventive aspects of DM. Relatives of patients with overt diabetes, children born to mothers with gestational DM, family history of DM in patients visiting for other ailments and over-weight individuals need to be screened and to be suggested lifestyle measures.

Exercise and nutrition counselling will go a long way in preventing diabetes. Provide healthy food alternatives and encourage physical activity. Use metformin and bariatric surgery wherever appropriate.

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Section 10

Endocrinology

Section Editor: Nikhil Tandon

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10.1 Basic Considerations of Endocrinology

Ashok Kumar Das

INTRODUCTION

The endocrine system consists of ductless glands which, by releasing chemical signals (hormones) in the blood stream, regulate function in distant organs. The endocrine system works closely with the nervous system to maintain homeostasis. The major endocrine glands are pituitary, hypothalamus, thyroid, parathyroid, islets of Langerhans (pancreas), adrenals and gonads (testes and ovaries).

Hormones act on multiple cell types by interacting with cell surface (protein hormones) or nuclear (steroid hormones) receptors. The effects of the hormones are both, short-term, due to enzymatic catalytic reactions within the cell and long- term, due to changes in the expression and upregulation of genes.

In addition to dedicated endocrine glands, there are endocrine cells within the organs whose primary function is not endocrine. These include cells within the heart that produce atrial natriuretic peptide (ANP), liver cells that produce insulin like growth factor type 1 (IGF-1), cells within the kidney that produce erythropoietin (EPO) and numerous cell types within the gastrointestinal tract that produce gastrointestinal hormones.

DEFINITION OF HORMONES

Hormones (endocrine signals) are chemical messengers that are secreted by ductless glands of the endocrine system and act on distant target organs via specific cell receptors resulting in the upregulation of specific second messengers which, in turn, brings about the changes in the cell structure/function.

Hormones secreted by various endocrine organs have been listed in **Table 1**.

CLASSIFICATION

Hormones can be classified based on the location of the target cell.

Autocrine Signals

These are chemical messengers secreted by cells into the extracellular fluid and affect the function of the same cell.

Paracrine Signals

These are chemical messengers secreted by cells which affect neighbouring cells of a different type. For example, glucagon produced by the alpha-cells of the Islets of Langerhans act on the adjacent insulin secreting beta cells.

Table 1: Hormones and Their Sites of Production

Gland	Hormone
Dedicated endocrine glands	
Hypothalamus	Anti-diuretic hormone (ADH), oxytocin, corticotrophin-releasing hormone (CRH), thyrotrophin-releasing hormone (TRH), gonadotrophin-releasing hormone (GnRH), growth hormone regulating hormone (GHRH), somatostatin, dopamine
Pituitary gland	Growth hormone (GH), adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinising hormone (LH), prolactin
Thyroid gland	T3, T4, calcitonin
Parathyroid gland	Parathyroid hormone (PTH)
Islets of Langerhans	Insulin, glucagon, somatostatin
Adrenal gland (cortex)	Cortisol, aldosterone, dehydroepiandrosterone (DHEA)
Adrenal gland (medulla)	Epinephrine, norepinephrine
Ovary	Oestradiol, progesterone, inhibin
Testis	Testosterone, inhibin, anti-müllerian hormone
Organs with primary function other than endocrine	
Brain (pineal gland)	Melatonin
Heart	Atrial natriuretic peptide (ANP)
Kidney	Erythropoietin
Adipose tissue	Leptin, adiponectin
Stomach	Gastrin, somatostatin, ghrelin
Intestines	Secretin, cholecystokinin, GLP-1, GLP-2, gastrin inhibitory peptide, motilin
Liver	Insulin-like growth factor (IGF)
Hormones produced to a significant degree by peripheral conversion	
Lungs	Angiotensin II
Kidney	1, 25$(OH)_2$ Vitamin D
Adipose, mammary glands	Oestradiol-17β
Liver	Testosterone
Genital skin, prostate	5-Dihydrotestosterone

Peptide hormone can remain bound on the membrane of one cell and interact with a receptor on juxtaposed cell. For example, sex steroids in the ovary, angiotensin II (AT II) in kidney and platelet derived growth factor (PDGF) in the vascular wall.

Intracrine

Hormones can act inside the cell without being released, e.g. insulin and somatostatin that can inhibit their own release from pancreatic β and δ cells, respectively.

Neurocrine

These are the hormones secreted by neural cells and they consist of neurotransmitters and neurotrophins. Neurotrophins foster the production of proteins associated with neuronal growth, differentiation and development. Neurotrophins include nerve growth factor, brain derived neurotrophic factor (BDNF), neurotrophin-3, neurotrophin 4/5.

Classification on the Basis of Chemical Structures

Hormones can also be classified based on their chemical structures and on their mechanisms of action. There are three general classes of hormones classified by chemical structure.

Steroid hormones

These hormones are derived from cholesterol and have the basic backbone of the cholesterol molecule, with variations in side chains providing functional specificity. The basic structure of steroid hormones is illustrated in **Figure 1**.

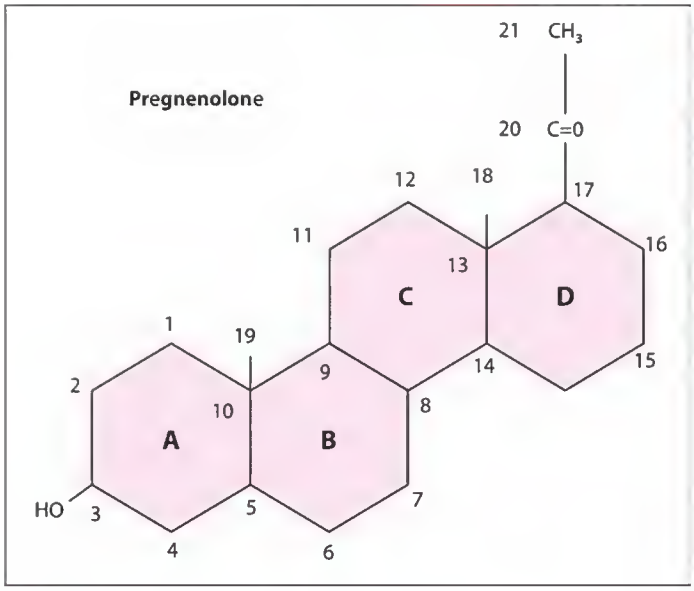


Figure 1: Chemical structure of steroid hormone.

The adrenal cortex and the gonads are the main sources of steroid hormones. The major steroid hormones are glucocorticoids (cortisol), mineralocorticoids (aldosterone), androgens (testosterone), oestrogens (including oestradiol and oestrone), progestogens (e.g. progesterone).

Amino acid derivatives

Amine-derived hormones are derivatives of the amino acids tyrosine and tryptophan. Examples are thyroxine, catecholamines such as dopamine, epinephrine and norepinephrine. The chemical structure of the amino acid derivatives is illustrated in **Figure 2**.

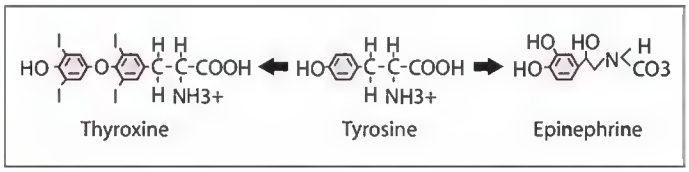


Figure 2: Chemical structure of thyroxine, tyrosine and epinephrine.

Peptide hormones

Peptide hormones are most prevalent and consist of chains of amino acids. Larger peptides are usually referred to as proteins, while complex protein hormones with carbohydrate side chains are called glycoprotein hormones. A summary of the classification based on the chemical structure is given in **Table 2**.

Peptide hormones can be classified into various families as listed in **Table 3**.

Table 2: Classification of Hormones Based on the Chemical Structure

Precursor	Type of compound	Examples
Protein	Protein	Growth hormone
	Peptide	ACTH
	Cleavage of peptide	Thyroxine → Triiodothyronine
	Cleavage of amino acid	Phenylalanine → Catecholamine
Cholesterol	Steroid	Cortisol
		$1,25(OH)_2D3$
Amino acid	Modified amino acid	Epinephrine
	Tripeptide	Thyrotropin-releasing hormone
Fatty acid	Retinoids	Retinoic acid
	Eicosanoids	Prostaglandin E

Table 3: Classification of Peptide Hormones

Growth hormone family	Growth hormone (GH) Prolactin (PRL) Human placental lactogen (hPL)
Glycoprotein hormone family	Gonadotrophins (LH, FSH, CG) Thyroid stimulating hormone (TSH)
Gastrointestinal hormones and peptides	Gastrin family: gastrin, cholecystokinin (CCK) Secretin family: glucagon, secretin, glicentin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide
Proopiomelanocortin (a prohormone)	β Endorphins

MECHANISM OF ACTION OF HORMONES

Peptide Hormones

A peptide hormone binds to a cell-surface receptor, resulting in activation of an enzyme that catalyses the synthesis of cyclic AMP (cAMP) from ATP. Cyclic AMP then serves as a second messenger for perpetuation of hormone action. Other second messengers have been discovered.

Steroid Hormones

Steroid hormones enter the cell and bind to cytoplasmic receptors. The hormone-receptor complex enters the nucleus and activates specific genes, initiating transcription of the message followed by protein translation. Steroid hormones act more slowly than peptide hormones because of the time required to produce new proteins as opposed to activating proteins that are already present.

Hormone Receptors

As mentioned earlier, the two main sites of hormone receptors are: cell surface and nuclear.

Cell surface receptors

Cell surface receptors have ligand recognition domains that are exposed on the outer surface of the cell membrane. Cell surface receptors are of four types:

1. *G protein linked receptors (have seven transmembrane domains):* A common way to translate a signal to a biologic effect inside cells is by way of nucleotide regulatory proteins (G proteins). These are also called serpentine receptors, as the proteins span the cell membrane seven times. Hormones whose action is mediated by these receptors include catecholamines, prostaglandins, adrenocorticotropic hormone (ACTH), glucagon, parathyroid hormone (PTH), thyroid stimulating hormone (TSH) and luteinising hormone (LH).
2. *Receptors with intrinsic ligand regulated enzymatic activities:* These receptors have an intrinsic tyrosine kinase domain. When the ligand binds to the receptor, the tyrosine kinase domain undergoes autophosphorylation. This leads to production of transcription factors in the nucleus that alter gene expression. Hormones whose action is mediated by these receptors include growth factors, atrial natriuretic peptide (ANP), epidermal growth factor (EGF) and platelet-derived growth factor (PDGF).
3. *Cytokine and colony stimulating factor receptors:* These receptors contain a surface exposed amino terminal domain that binds the ligand (i.e. hormone), a single membrane spanning domain and a carboxy terminal effector domain. They initiate tyrosine kinase activity in the cytoplasm. In particular, they activate the so called Janus tyrosine kinases (JAKs) in the cytoplasm. These in turn phosphorylate signal transducer and activator of transcription (STAT) proteins. The phosphorylated STATs move to the nucleus where they act as transcription factors. Hormones whose action is mediated by these receptors include growth hormone (GH) and leptin.
4. *Receptors having serine-threonine kinase activity:* Their effects are mediated by SMADs, intracellular proteins which when phosphorylated move to the nucleus, bind to DNA and initiate transcription of various genes.

Nuclear receptors

These receptors mediate the actions of hormones such as steroid hormones and thyroid hormones. In particular, oestrogen and triiodothyronine (T3) receptors bind hormones in the nucleus. The T3 receptors also bind thyroxine (T4), but with lesser affinity. The glucocorticoid receptor is located mainly in the cytoplasm but migrates promptly to the nucleus as soon as it binds to its ligand. Nuclear receptors also include two families of retinoic acid receptors, RAR and RAX. These receptors have an extensive role to play in foetal development.

Second Messengers

Second messengers are intracellular molecules which link the hormone receptors with the effector pathways in the target cells. Examples of second messengers and the respective hormones have been listed in **Table 4**.

Table 4: Hormones Utilising Second Messengers

Second messenger	Examples of hormones which utilise this system
Cyclic AMP	TSH, FSH, LH, antidiuretic hormone, epinephrine, norepinephrine, glucagon, calcitonin, parathyroid hormone
Protein kinase activity	Insulin, growth hormone, prolactin, oxytocin, erythropoietin, several growth factors
Calcium and/or phosphoinositides	Angiotensin II, antidiuretic hormone, gonadotrophin- releasing hormone, thyrotrophin-releasing hormone
Cyclic GMP	Atrial natriuretic peptide, nitric oxide

Hormones secreted from various principal endocrine organs and their salient effects have been listed in **Tables 5 to 7**. Detailed description of each one of them is given in the respective chapters.

Table 5: Hormones Secreted by the Hypothalamus

	Effect on hormone secretion	Hormones affected
Thyrotrophin-releasing hormone (TRH)	Stimulates	TSH
	Stimulates	Prolactin (PRL)
Gonadotrophin-releasing hormone (GnRH)	Stimulates	LH
	Stimulates	FSH
Dopamine	Inhibits	Prolactin
	Inhibits	LH
Corticotrophin-releasing hormone (CRH)	Stimulates	ACTH
Growth hormone-releasing hormone (GHRH)	Stimulates	GH
Growth hormone-inhibiting hormone (somatostatin)	Inhibits	GH
	Inhibits	TSH
	Inhibits	Insulin

Table 6: Hormones Secreted by Pituitary and Their Physiological Effects

Hormones	Organs	Major functions
Anterior pituitary gland		
Growth hormone (GH)	Liver, adipose tissue	Promotes growth (indirectly), control of protein, lipid and carbohydrate metabolism
Thyroid stimulating hormone (TSH)	Thyroid gland hormones	Stimulates secretion of thyroid
Adrenocorticotrophic hormone (ACTH)	Adrenal gland (cortex)	Stimulates secretion of glucocorticoids
Prolactin (PRL)	Mammary gland	Milk production
Luteinising hormone (LH)	Ovary and testis	Control of reproductive function
Follicle stimulating hormone (FSH)	Ovary and testis	Control of reproductive function
Posterior pituitary gland		
Antidiuretic hormone (ADH)	Kidney	Conservation of body water
Oxytocin	Ovary and testis	Stimulates milk ejection and uterine contractions

Table 7: Hormones Secreted by Other Glands and Their Actions

Gland	Hormones	Major functions
Thyroid	Thyroxine (T4) Triiodothyronine (T3)	Increases the rate of chemical reaction and basal metabolic rate
	Calcitonin	Promotes calcium deposition in bone
Adrenal cortex	Cortisol	Glucose homeostasis, anti-inflammatory effects and many others
	Aldosterone	Na^+, K^+ and water homeostasis
	DHEA, Androstenedione	Androgenic action
Adrenal medulla	Epinephrine Norepinephrine	Same effects as sympathetic stimulation
Pancreas	Insulin and glucagon	Carbohydrate metabolism
Parathyroid	Parathyroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption
Testis	Testosterone	Development of male reproductive system and male secondary sexual characters
Ovaries	Oestrogens Progesterone	Development of female reproductive system, female breasts and female secondary sexual characters
Placenta	Human chorionic gonadotrophin	Promotes growth of corpus luteum
	Human somato-mammotropin	Promotes development of some foetal tissues
Kidney	Renin	Conversion of angiotensinogen to angiotensin
	Erythropoietin	Increases erythrocyte production
Stomach	Gastrin	Stimulates the gastric acid secretion
Small intestine	Secretin	Stimulate pancreatic acinar cells to release bicarbonate
	Cholecystokinin	Stimulate gallbladder contraction
Adipocytes	Leptin	Inhibits appetite
Heart	Atrial natriuretic peptide	Increases sodium excretion by kidneys

CONTROL OF ENDOCRINE ACTIVITY

Hypothalamic anterior pituitary hormones, and those produced by target organs under their influence, are regulated by a classical feedback loops which involve hormonal, neural and direct feedback mechanisms (**Figure 3**). Another category of hormones, such as insulin and PTH, are directly regulated by circulating levels of glucose and calcium.

The concentration of hormone as seen by target cells is determined by three factors:

- Rate of production
- Rate of delivery: dependent of blood flow
- Rate of degradation and elimination

MECHANISMS OF ENDOCRINE DISEASES

Based on the physiological functions, endocrine diseases are classified into three subtypes: hormone excess, hormone deficiency and hormone resistance.

Effects of Hypo- and Hyperfunctioning of Various Endocrine Glands

The various endocrine dysfunctions due to hypo- and hyperfunctioning are depicted in **Table 8**.

LABORATORY DIAGNOSIS OF HORMONAL DISORDERS

The diagnosis of endocrine disorders is based on clinical examination and focused investigations. The basic approach in the diagnosis involves:

- Proving hypo- or hyperfunction of the glands by measurement of serum or urine hormone levels as compared to normal age and sex-matched individuals
- Establishing aetiologic basis by radiological investigations and ancillary tests like FNAC and biopsy in some cases.

The laboratory evaluation is discussed in detail in the chapter on 'Endocrine Disorders: A Clinical Approach', in great detail.

TREATMENT

Treatment of endocrine diseases depends on the functional status of the endocrine glands, degree of disability, age and coexistent morbidities. In general, hypofunctioning glands are treated by replacement of the appropriate hormones in adequate physiological doses with regular follow-up and dose adjustment for stressful conditions. Hyperfunctioning glands need careful evaluation to determine the cause of the excess function. Medical therapy is attempted whenever feasible, using hormone antagonists and receptor blockers. In case of tumours that are not responsive to medical therapy, surgical removal of the glands can achieve cure, however, at the risk of causing iatrogenic hypofunctioning.

Deficiency Disorders

Almost all the hormones are available, either as chemically synthesised entities or as recombinant molecules. Some are oral preparations (T3, T4, steroids) while others are given parenterally (GH, testosterone). Novel systems of delivery are being used like testosterone patches, insulin analogues.

The hormones are usually started in physiological doses and adjusted according to the response. Details of hormone replacement are provided in the relevant chapters discussing individual hormone deficient states.

Hormone Excess States

The treatment of such diseases can be either medical or surgical.

Medical

Medical therapy for hyperfunctioning states includes agents which, either function as antagonists (e.g. somatostatin analogues for GH excess), agonists for endogenous inhibitors (bromocriptine, dopamine analogue for prolactin excess) or enzyme inhibitors (carbimazole and propylthiouracil for hyperthyroidism; metyrapone, ketoconazole for Cushing's syndrome).

Surgical

In addition to medical therapy, hyperthyroid states can also be treated with surgery (thyroidectomy) or radioactive iodine ablation. Primary hyperparathyroidism due to parathyroid adenoma or parathyroid hyperplasia are cured by surgically removing the parathyroid glands. Pituitary micro- and macro-

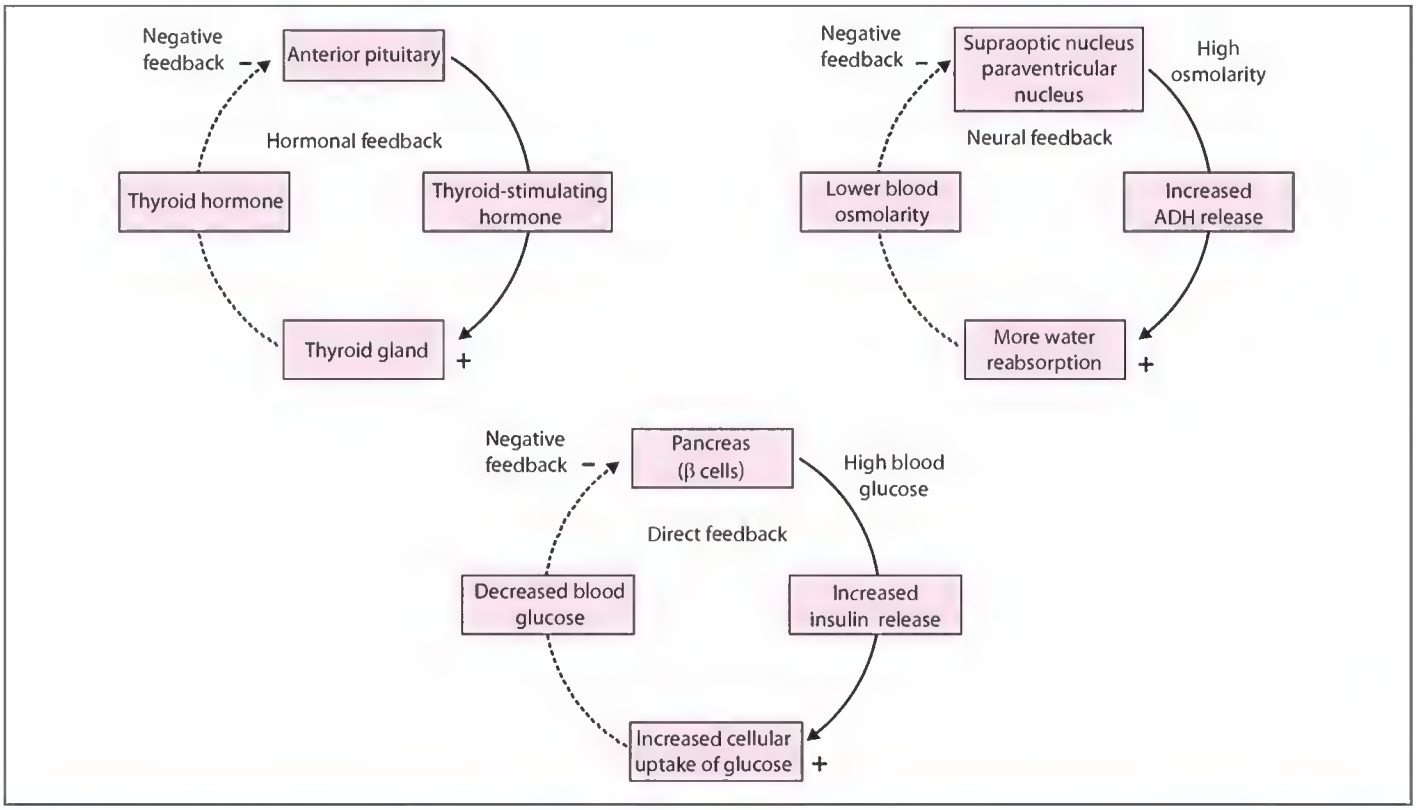


Figure 3: Classic feedback loops for control of hormone secretion.

Table 8: Showing Effects of Hypo- and Hyperfunctioning of Various Endocrine Glands

	Hormones	Hyperfunction	Hypofunction
Anterior pituitary	Growth hormone	Acromegaly and gigantism	Impaired growth and short stature
	Adrenocorticotropic hormone	Cushing's disease	Secondary hypoadrenalism
	Prolactin	Galactorrhoea amenorrhoea syndrome in women; reduced libido and hypogonadal features in men	
	Luteinising hormone Follicle stimulating hormone		Hypogonadotrophic hypogonadism
Posterior pituitary	Anti-diuretic hormone		Diabetes insipidus
Thyroid	Thyroxine (T4) Triiodothyronine (T3)	Hyperthyroidism	Hypothyroidism
Adrenal cortex	Cortisol	Cushing's syndrome	Addison's disease
	Aldosterone	Conn's syndrome	
Adrenal medulla	Epinephrine Norepinephrine	Hypertension (Pheochromocytoma)	
Pancreas	Insulin	Insulinoma	Diabetes mellitus
	Glucagon	Glucagonoma	
Parathyroid	Parathyroid hormone (PTH)	Primary hyperparathyroidism	Hypoparathyroidism: hypocalcaemia
Testis	Testosterone		Hypogonadism
Ovary	Oestrogens Progesterone		Hypogonadism

adenomas can be surgically resected by various surgical approaches in case of compressive symptoms and mass effect or treated with radiation delivered either by conventional means or through a stereotactic approach.

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10.2 Endocrine Disorders—A Clinical Approach

MS Seshadri

INTRODUCTION

Endocrinology is a discipline that deals with hormonal disorders. The term 'hormone' traditionally means a chemical signal produced by a discrete gland which reaches distant target organs and tissues through the blood stream and regulates their function. Glands producing hormones constitute the endocrine system. In addition, cells may also produce other chemical signals, which may either exert an effect on the cell which produces them (autocrine) on adjacent cells (paracrine).

Endocrine glands may be a single discrete gland, e.g. adenohypophysis (anterior pituitary), or multiple discrete glands, e.g. parathyroid glands or could even be scattered throughout an organ, e.g. islets of Langerhans in the pancreas. Further, the same endocrine gland may produce more than one hormone, e.g. production of glucocorticoid, mineralocorticoid and adrenal androgens from the adrenal cortex.

There may be different receptors through which a single hormone exerts its effect such as the receptors for epinephrine and the response of the target tissue may depend on the nature of the receptor that it expresses.

CHEMICAL NATURE OF HORMONES

Hormones may be derived from a single amino acid such as thyroxine or serotonin, from cell membrane lipids as in prostaglandins or from cholesterol, e.g. steroid hormones. They can be polypeptides, e.g. parathyroid hormone (PTH) or glycopeptides, e.g. thyroid stimulating hormone (TSH).

FUNCTIONS OF THE ENDOCRINE SYSTEM

The role of this complex system is to maintain the consistency of the internal environment (*milieu interior*) of all the cells in the intact organism. Hormones also mediate growth, differentiation, sexual maturation and reproduction. Together with the nervous system, the endocrine system helps the organism to cope with changes in the external environment also. At different times in the life of the organism, the same hormone may play different roles, e.g. during intrauterine life, insulin promotes growth but in the extrauterine life it is a powerful regulator of plasma glucose.

MECHANISM OF ACTION OF HORMONES

Hormones act on target cells through receptors which are located on the cytoplasmic membrane, e.g. PTH receptor or in the nucleus, e.g. steroid hormone receptors. A hormonal disorder may be due to abnormal production of the hormone, e.g. overproduction of thyroxine by the thyroid gland in hyperthyroidism. Sometimes, the endocrine disorder is due to abnormalities in the signal transduction through the receptor, e.g. complete androgen insensitivity syndrome where a genotypic male with 46 XY (male) karyotype with normal testosterone production presents phenotypically as a female. The biochemical nature of hormonal resistance is defined in some disorders. For example, in pseudohypoparathyroidism, there is a defect in the G protein coupled to PTH receptor which precludes PTH action on target tissues, resulting in hypocalcaemia despite inappropriately normal or elevated PTH levels. Constitutive activation of the hormonal receptor in spite of normal circulating levels of the hormone can lead to endocrine disorders with clinical features of hormonal over-activity. For example, in McCune Albright syndrome focal activation of the G protein coupled to skeletal PTH receptors leads to lytic bone lesions indicative of excessive PTH action on the skeleton, even though circulating PTH levels are not elevated.

SYNTHESIS OF HORMONES

Synthesis of hormones is an orderly and sequential process and involves the action of a series of enzymes on a defined substrate. Polypeptide hormones are initially produced as preprohormones which are cleaved to prohormones which in turn are converted to the hormone by sequential removal of short peptide fragments. If there is a deficiency of any of the enzymes involved in intracellular hormone synthesis, the concerned hormone will not be produced and a precursor may accumulate, giving rise to clinical symptoms, e.g. in congenital adrenal hyperplasia (CAH), a deficiency of the 21 hydroxylase enzyme leads to decreased production of cortisol leading to hypoadrenalism, while adrenal androgens accumulate and produce virilisation of a female infant. A number of hormones exert their cellular effects by stimulating or suppressing intracellular enzymes.

GENES AND HORMONES

The production of hormones, receptors and enzymes are regulated by genes in the endocrine cell or in the target cell. Therefore, it is not surprising that several endocrine disorders are genetically determined. The clinician therefore needs to elicit a detailed family history in patients with endocrine disorders. The genetic abnormality may involve an entire chromosome as in Turner's or Klinefelter's syndrome or may just involve single gene mutations as in some patients with growth hormone deficiency.

INTERACTIONS BETWEEN ENDOCRINE AND IMMUNE SYSTEMS

There is a close interaction between the endocrine system and the immune system. There may be a primary alteration in the immune system that leads to endocrine gland dysfunction, or a primary alteration in endocrine function that leads to altered immune responses. Further, biochemical changes in the extracellular fluid due to primary endocrine disease may lead to decreased ability to tackle infections.

Several endocrine disorders such as primary thyrotoxicosis, autoimmune hypothyroidism and autoimmune adrenal insufficiency (Addison's disease) are clearly immunologically mediated. The altered hormonal mileau in endocrine disorders

may significantly impair immunity, e.g. hypercortisolism in Cushing's disease suppresses humoral and cell-mediated immune responses and leads to opportunistic infections. In endocrine disorders such as diabetes mellitus the alteration in plasma glucose levels as a consequence of the endocrine disease may alter neutrophil function and predispose to recurrent bacterial infections and non-enzymatic glycosylation of collagen may interfere with proper wound healing.

Some patients with systemic autoimmune disorders such as Sjögren's syndrome or systemic lupus erythematosus may have associated autoimmune endocrine disease leading to hypothyroidism or hypoadrenalism.

Most autoimmune endocrine disorders are caused by organ-specific autoimmune responses, e.g. Type 1 diabetes mellitus and autoimmune thyroiditis. The tendency for familial aggregation of endocrine disorders may therefore be due to heritable abnormalities of the immune system. When autoimmunity is the basis for the development of an endocrine disorder more than one endocrine gland may malfunction, e.g. association of autoimmune thyroid disease with adrenal deficiency or hypoparathyroidism. Other non-endocrine tissues may be affected by the autoimmune process in a patient with autoimmune endocrine disease, e.g. association of atrophic gastritis and B12 malabsorption with autoimmune thyroid disease. Therefore, when a patient presents with one endocrine problem, the clinician may have to look for other associated endocrine and other immunologically mediated non-endocrine disorders. A detailed evaluation of other organ systems may be necessary if the patient has additional symptoms. For instance, in a patient with autoimmune thyroiditis with some symptoms of peripheral neuropathy, a detailed neurologic examination may reveal features of subacute combined degeneration of the cord due to B12 deficiency.

TRANSPORT OF HORMONES IN CIRCULATION

Hormones are carried in the circulation usually bound to plasma proteins and the bound fraction constitutes the major portion of the measured hormone level, e.g. thyroxine bound to thyroxine binding proteins constitutes more than 99% of circulating total thyroxine. However, it is only the free fraction, which is not bound to circulating proteins, that is physiologically active. The concentration of the free hormone is so low that accurate measurement may be very difficult, e.g. free T4 or free cortisol. Therefore, a calculated value for the free hormone level such as free thyroxine index or a free testosterone index is often used. There are many disorders where the concentration of the hormone in serum is altered due to alterations in the concentration of the binding protein. For example, during pregnancy hepatic production of thyroxine binding proteins like thyroxine binding globulin (TBG) increases in response to oestrogen, accounting for increase in Total T4 levels seen in pregnancy. In nephrotic syndrome, the serum albumin is very low because of massive proteinuria and this may lead to low levels of measured Total T4, without affecting free hormone levels.

METABOLIC INACTIVATION OF HORMONES

Hormones are degraded at different sites such as the liver and kidney and major dysfunction of these organs may cause abnormal levels of certain hormones. This in turn may lead to clinical symptoms and signs, e.g. in chronic liver disease there are clinical features of hyperoestrogenism, like gynaecomastia and testicular atrophy in men. Similarly, there may be a sharp decline in insulin requirements in patients with diabetes who develop chronic kidney disease, resulting in frequent hypoglycaemic events unless insulin dose is reduced. Some drugs used in treating endocrine disorders are inactivated or excreted by the liver or kidney. Hence, in the presence of renal or hepatic insufficiency, these agents need to be either withdrawn or their doses reduced. For example, metformin must not be used in people with even mild elevations of serum creatinine (>1.5 mg/dL).

RHYTHMIC NATURE OF HORMONE SECRETION

Several circulating hormones exhibit characteristic biological rhythms. ACTH and cortisol show diurnal variation with peak levels in the early morning while oestrogen and progesterone show cyclical variations during different phases of the menstrual cycle over a period of about one month. Altered rhythmicity of hormone production may be the earliest sign of disease and can be used as a diagnostic test, e.g. loss of diurnal variation in serum cortisol levels is an early abnormality in Cushing's syndrome.

CLINICAL FEATURES OF ENDOCRINE DISORDERS

The clinical features in endocrine disorders can be very common such as weight-gain or very unusual such as hypokalaemic periodic paralysis in thyrotoxicosis. Since, hormones circulate to all parts of the body, symptoms and signs may reflect involvement of a range of organ systems. For example, in a patient with thyroid hormone excess, there may be weight loss, palpitations, dyspnoea, fatiguability, increased appetite, diarrhoea and nervousness suggesting involvement of the cardiovascular, respiratory, musculoskeletal, alimentary and nervous systems. Hence, a detailed general physical examination (e.g. height, weight, heart rate, blood pressure) and evaluation of all major organ systems is mandatory for any patient with suspected endocrine disease. In children height should be recorded at each visit and the height velocity in cm/year calculated annually so that early disorders of growth can be identified, evaluated and treated. In adolescents, the extent of pubertal development (Tanner staging) should be recorded accurately.

The unusual nature of symptoms in endocrine diseases may lead to wrong referrals to a number of different specialists including psychiatrists. Symptoms in a patient with pheochromocytoma may be mistaken for a panic attack or a patient with insulinoma and recurrent hypoglycaemia may land up with a neurologist for 'seizure disorder' or with a psychiatrist for a behavioural disorder. Several endocrine disorders such as primary hypothyroidism and Cushing's syndrome may have psychosis or altered behaviour as a major component of the symptom complex. On the other hand drugs used in psychiatric practice often cause endocrine dysfunction, e.g. hyperprolactinaemia, amenorrhoea and galactorrhoea in patients who are on phenothiazines.

Iatrogenic Endocrine Disorders

Drugs used in endocrine practice are often misused and may result in clinical manifestations of endocrine disease.

Glucocorticoid misuse is the most common cause for Cushing's syndrome in clinical practice. Supraphysiological doses of thyroxine are often erroneously prescribed to obese patients and may result in thyrotoxicosis with osteoporosis or atrial fibrillation. Amiodarone induced thyrotoxicosis, anticonvulsant induced osteomalacia, ketoconazole induced adrenal and androgen deficiency and antipsychotic drug-induced hyperprolactinaemia are other common examples of iatrogenic endocrine disease. It is, therefore, mandatory to elicit a detailed drug history in patients presenting with endocrine disorders so as to avoid expensive investigations and unnecessary procedures.

When Should a Physician Suspect an Endocrine Disorder?

The basis for suspecting an underlying endocrine disorder is given in **Table 1**.

Table 1: Basis of Clinical Suspicion of Endocrine Disorder

Suspect an endocrine disorder in the event of
Rapid changes in body-weight
Unpredictable changes in blood pressure
Hypotension on trivial insults
Unexplained hypertensive response to drugs
Inappropriate responses of body temperature
No fever in the presence of an infection
High fever in the absence of an infection
Unusual reactions to drugs
Hypertension during anaesthesia in unrecognised-pheochromocytoma
Failure to recover from anaesthesia in unrecognised-hypothyroidism
Recent changes in skin pigmentation
Hyperpigmentation in adrenal insufficiency and ACTH producing tumours
Hypopigmentation of usually pigmented areas in hypopituitarism
Disorders of growth and sexual maturation
Disorders of sexual differentiation in an infant
Disorders of menstrual function and reproduction
Inappropriate secondary sexual characters
Gynaecomastia in a male
Hirsutism in a female
Inappropriate biochemical changes
Hyponatraemia in the presence of a high urine spot sodium (SIADH)
Kaliuresis despite hypokalaemia (Conn's syndrome)

LABORATORY TESTS AND THEIR INTERPRETATION

Circulating levels of hormones are usually present in minute concentrations. The methods used for assaying hormones follow some general principles. A fixed concentration of a specific antibody against the hormone is incubated with the serum sample for a defined period of time. Subsequently, a fixed quantity of a labelled hormone is added and incubated for a defined time period. Finally, the antibody-bound and unbound fractions of the hormone are separated by a chemical agent or a second antibody. The concentration of the label is measured in the bound and in the free fraction by a detector. The proportion of labelled hormone bound to antibody is inversely proportional to the quantity of the unlabelled hormone present in the clinical sample. This same process is carried out with known concentrations of highly purified hormone and a standard curve is constructed. The reading of the unknown sample can be read off the standard curve. The label can be a radionuclide (radioimmunoassay) or an enzyme (ELISA) or a fluorescent probe or a chemiluminescent probe (chemiluminescence assay).

All assays of hormones should include appropriate quality controls at low, normal and high levels of the analyte in question so that the reproducibility and accuracy of the test from day-to-day and from assay-to-assay is ensured. It is necessary that the clinician knows whether the laboratory is adhering to these standards and it is better to get the tests done by an accredited laboratory [(The national accreditation board for testing and calibration laboratories (NABL) is the agency responsible for accreditation)]. In the event of a laboratory report not consistent with the clinical picture, the clinician should alert the laboratory about a potential error in measurement so that issues can be sorted out. Similarly, the laboratory should alert the clinician if the report is very abnormal, since an early therapeutic response may be mandated. It is this cross-talk between the clinician and laboratory that ensures that the patient gets the maximum benefit out of the test carried out.

The concentrations of hormones in blood are tightly regulated by trophic hormones secreted by the pituitary or by serum levels of chemicals such as glucose or calcium. If T4 levels are low due to a thyroid problem, TSH, which is the corresponding trophic hormone, would be high. On the other hand if T4 is low and TSH also is low, it implies that the gland secreting the trophic hormone, i.e. pituitary is hypofunctioning. Similarly, in a patient with hypercalcaemia, elevated PTH levels imply that the normal

Table 2: Laboratory Tests in Hormonal Disorders

Suspected hypothyroidism: Free T4 and TSH
Suspected hyperthyroidism: Free T4 and TSH
Primary amenorrhoea: FSH and LH
Secondary amenorrhoea: FSH, LH, prolactin and TSH
Suspected metabolic bone disease: Ca, phosphorus, albumin, globulin, alkaline phosphatase, PTH and 25-OH vitamin D if indicated
Tetany: Ca, phosphorous, albumin, creatinine, Na^+, K^+, HCO_3^-, chloride, PTH and 25-OH vitamin D if indicated
Spontaneous hypoglycaemia: Fasting plasma glucose and fasting insulin
Suspected Cushing's syndrome: Screening plasma cortisol at 8 am after 1 mg dexamethasone administered at 11 pm previous night. If cortisol in more than 1.8 µg % do a formal low and high dose Dexamthasone suppression test
Suspected primary hyperaldosteronism: Na, K, HCO_3 and chloride, serum aldosterone and plasma renin activity
Suspected endocrine hypertension: Na^+, K^+, HCO_3^-, chloride, Ca, phosphorous, creatinine, albumin/globulin, alk phosphatase, 24 hours urine metanephrine and normetanephrine, aldosterone and plasma rennin activity
Suspected Sheehan's syndrome/hypopituitarism: FSH, LH, Free T4, TSH, 8 am cortisol
Virilised female: Testosterone and DHEAS
Suspected polycystic ovary syndrome: Plasma glucose fasting and post-prandial, fasting lipid profile, testosterone, prolactin, TSH
Child with ambiguous external genitalia: 17-OH progesterone, Na^+, K^+, HCO_3^-

regulatory process is not in place and that there is unregulated overproduction of PTH. In contrast, if a hypocalcaemic patient has elevated PTH this is expected and would be interpreted as secondary hyperparathyroidism. Therefore, when tests are ordered both trophic and target hormone should be measured together for proper interpretation.

The clinician ordering the test should know details of collection, e.g. PTH samples and ACTH samples which are thermolabile, should be collected in test tubes placed in a beaker of crushed ice and the serum separated using a refrigerated centrifuge. When FSH and LH are checked in menstruating women it is appropriate to collect the sample on the second or third day of the menstrual cycle, i.e. follicular phase enabling appropriate interpretation in the clinical context. A mid-cycle sample on the other hand may have a very high LH value, and unless the clinician is informed the result may be misinterpreted. In women when tests are ordered one should verify the last menstrual date and if pregnancy is suspected or confirmed, be aware that the serum level of several hormones such as total T4, prolactin and cortisol are higher in pregnancy than in the non-pregnant state.

The common set of tests ordered in typical clinical situations is shown in **Table 2**. These will be the initial tests. Further testing may be needed in individual situations.

STIMULATION AND SUPPRESSION TESTS

These are used in ambiguous situations when the basal level of the hormone has yielded a borderline low or high value indicating that the hormonal abnormality is subtle. By and far these tests need to be validated in each institution as the published 'normal' responses vary.

In general, stimulation tests are used in target organ hypofunction and suppression tests in target gland hyperfunction. For example, in a patient with endogenous overproduction of cortisol from an adrenal adenoma, exogenous administration of high doses of a synthetic glucocorticoid like dexamethasone fails to suppress cortisol levels. This is one of the most common suppression tests used in endocrine practice. Conversely, in patients with symptoms suggestive of adrenal insufficiency, the basal serum cortisol levels are not adequate to discriminate a normal from a deficiency state. Serum cortisol levels <20 µg/dL with dynamic testing using intravenous synthetic ACTH 1-24 (Synacthen), are diagnostic of adrenal insufficiency. Individual situations and the appropriate tests will be discussed in each individual chapter in this section.

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10.3 Disorders of Hypothalamus and Pineal Gland

Abdul Hamid Zargar, Bashir Ahmad Laway

HYPOTHALAMUS

Hypothalamus is the ultimate brain structure that allows maintenance of homeostasis. This neuroendocrine gland, weighing approximately 4 grams, is situated between thalamus above and pituitary gland below. The key functions of hypothalamus are:

1. Reception of sensory inputs like light, pain and temperature from external environment.
2. Receiving information regarding internal environment like blood pressure, osmolality and glucose.
3. Other inputs like feedback, both positive and negative, from hormones such as glucocorticoids, sex hormones and thyroid hormones.

Functionally, hypothalamus and pituitary act in concert as a unit and pituitary could be considered as an extension of hypothalamus. The unit is supplied by a rich network of portal vessels. Hypothalamic neuronal cells synthesise and release specific stimulatory and inhibitory factors directly into the portal system of vessels. This allows reliable transmission of hypothalamic peptides into the pituitary, without any systemic dilution.

The hypothalamic nuclei along with afferent and efferent nerve fibres connect the hypothalamus to various portions of brain and brainstem. The hypothalamus is divided into four regions from anterior to posterior including preoptic, supraoptic, tuberal and mammary regions and three zones namely, periventricular, medial and lateral.

The hypothalamus is responsible for important body functions including water metabolism, temperature regulation, appetite control, sleep-wake cycle, circadian rhythms and control of sympathetic and parasympathetic functions. The neuro-endocrine control of anterior pituitary is the most important function of hypothalamus.

CLINICAL FEATURES OF HYPOTHALAMIC DISORDERS

Disorders of varied aetiologies affecting hypothalamus may give rise to similar clinical features because of small size of the hypothalamus. Common manifestations are headache, vomiting, visual disturbances, signs of pyramidal and extrapyramidal tract involvement and cerebellar signs. Other manifestations include disturbances of puberty, water metabolism and caloric imbalance.

MANIFESTATIONS OF HYPOTHALAMIC DISORDERS

Disorders of Water Metabolism

Central diabetes insipidus

Destruction of anti-diuretic hormone (ADH) producing magnocellular neurons in supraoptic and paraventricular nuclei or defects in the transport of ADH to posterior pituitary results in central diabetes insipidus. Common causes are idiopathic, Langerhans cell histiocytosis, vascular accidents and neuro-surgical trauma. Patients present with polyuria, polydipsia with dilute urine in presence of increased serum osmolality and good response to administration of ADH.

Syndrome of inappropriate ADH secretion (SIADH)

Manifests with hyponatremia. Clinical features depend upon the severity of hyponatremia. Normal serum sodium is 136 to 145 mEq/L. Mild hyponatremia (plasma sodium 125 to 135 mEq/L) presents with nonspecific symptoms in the form of weakness, lethargy, and headache. Severe hyponatremia (plasma sodium <125 mEq/L) presents with confusion, seizures and coma. Diagnosis of SIADH requires presence of hyponatremia with plasma osmolality <270 mosmol/kg (normal plasma osmolality being 285 to 295 mosmol/kg); urinary osmolality of >100 mOsm/kg with elevated urinary sodium (>40 mEq/L) and presence of normal thyroid and adrenal function without any volume overload state.

Disorders of Appetite

Hypothalamic obesity

Almost one fourth of patients with hypothalamic disorders manifest with obesity. Obesity results from involvement of ventromedial nucleus (satiety centre). Common causes include craniopharyngioma, granulomatous disorders, head trauma and infiltrations. Syndrome also presents with headache, visual disturbances, hypogonadism, diabetes insipidus and increased sleep.

Anorexia nervosa

Common disorder affecting women of less than 25 years. These women have distorted body image, exercise excessively and induce vomiting. There is a functional hypothalamic disturbance and many endocrine abnormalities are associated with it. These include amenorrhoea, low serum thyroxine (T4) and adrenocorticotrophic hormone (ACTH). Growth hormone (GH) and prolactin levels are elevated. The manifestations completely reverse with weight gain.

Abnormalities of Sleep-Wake Cycle and Circadian Rhythm

Suprachiasmatic nuclei are responsible for the maintenance of circadian rhythms resulting in sleep-wake cycle, temperature control and cognitive function. Hypersomnolence with or without obesity occur in around 30% of patients with hypothalamic syndrome. Day time sleepiness and night time hyperactivity is common.

Abnormalities of Emotion and Behaviour

Agitation, destructive behaviour with activation of sympathetic nervous system during the episodes is more common in lesions of ventromedial nucleus. Gelastic or laughing seizures are common in hamartoma of tuber cinereum. Abnormalities in EEG are present during the seizures.

Disordered Control of Pituitary

Precocious puberty

Premature activation of hypothalamo-gonadal axis results in precocious puberty in girls (<8 years of age) and boys (<9 years of age). Activation of the axis in girls is mostly idiopathic, but in boys around 50% have hypothalamic lesion, hamartoma being the most common (**Figures 1A and B**). Precocious puberty in these patients is gonadotrophin releasing hormone (GnRH) dependent confirmed by predominant LH rise after GnRH injection.

Specific Hypothalamic Syndromes

Clinical features of common hypothalamic syndromes are summarised in **Table 1**.

disorder is more common in boys causing undescended testes and hypogonadism. Nerve deafness, colour blindness, cleft palate, exostosis and renal abnormalities may also be associated.

Growth Hormone Deficiency

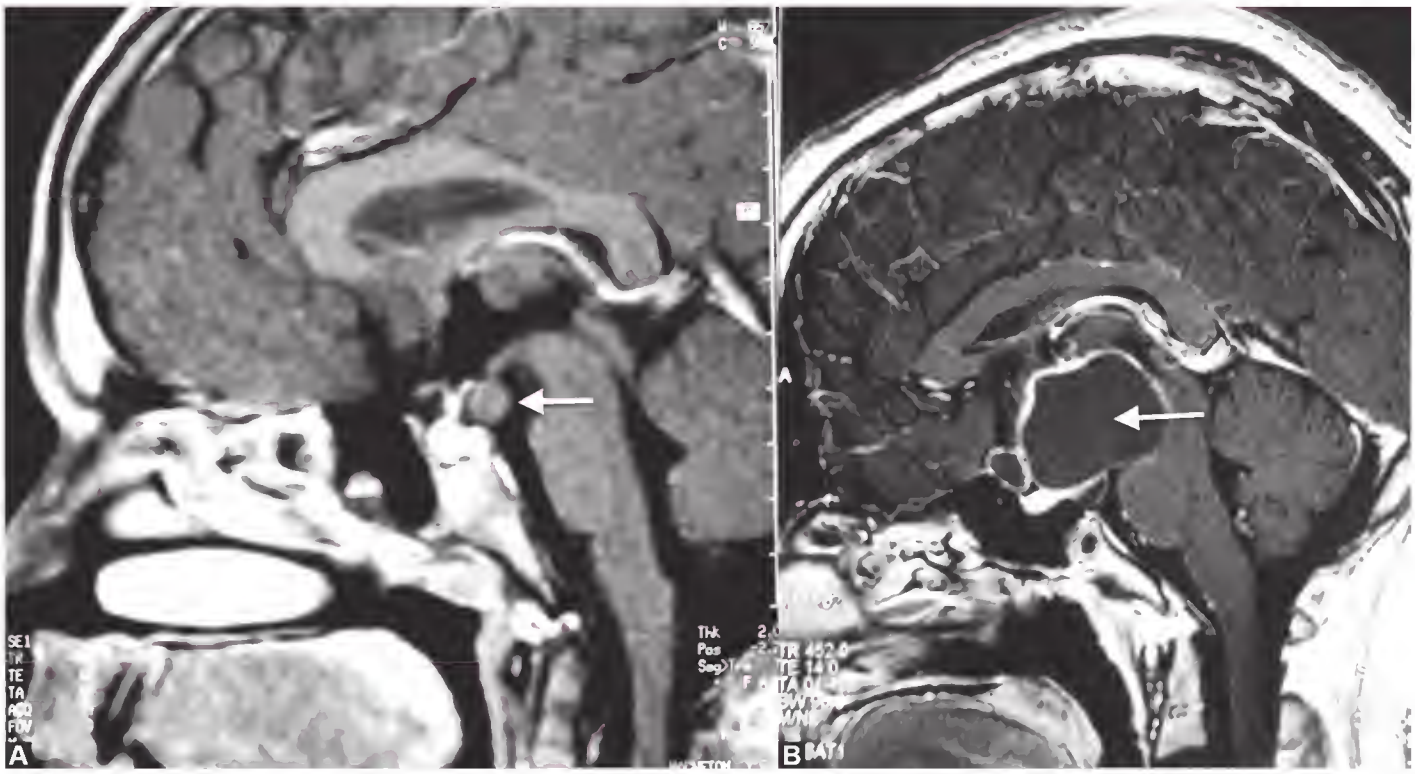
Many congenital defects involving hypothalamus like septo-optic dysplasia, anencephaly may result in GHD. Affected children have normal height and weight at birth with delay in height and bone age at one year of age associated with increased subcutaneous fat and hypoglycaemia.

Congenital ACTH Deficiency

It can occur in septo-optic dysplasia. Children present with vomiting, hypoglycaemia without pigmentation and electrolyte abnormalities.

Table 1: Clinical Features of Common Hypothalamic Syndromes

System	Prader-Willi	Laurence–Moon-Biedl	Cohen	Carpenter	Alstorm
Facial	Narrow forehead, olive shaped eyes, squint, V shaped mouth, high arched palate	Squint	High nasal bridge, open mouth, short philtrum, dysplastic ears	Flat nasal bridge, acrocephaly, high arched palate	—
Skeletal	Short stature, syndactyly, scoliosis, dislocated hips	Short stature, polydactyly, clinodactyly	Short or tall stature	Polydactyly, syndactyly, genu valgum	Short stature
Neuro-muscular	Decreased IQ, hypotonia	Decreased IQ, retinitis pigmentosa	Mild mental retardation	Mild mental retardation	Normal IQ
Endocrine	Hypogonadism, diabetes mellitus, obesity	Hypogonadism, diabetes insipidus, obesity	Hypogonadism, delayed puberty, obesity	Obesity	Hypogonadism in males, obesity
Others	Hyperphagia	Renal abnormalities	—	—	—



Figures 1A and B: (A) Sagittal view T1-weighted pre-contrast MRI in 6-year old boy with central precocious puberty showing hypothalamic hamartoma (arrow); (B) Sagittal view T1-weighted contrast enhanced MRI in a 20-year boy presented with hypogonadism and delayed puberty showing nodular soft tissue component and cyst wall enhancement suggestive of craniopharyngioma (arrow).

HYPOTHALAMIC HYPOFUNCTION SYNDROMES

Kallmann's Syndrome

KAL gene normally directs migration of GnRH neurons from the olfactory placode to hypothalamus. Defective gene causes agenesis of olfactory bulb (and subsequent hypo/anosmia). The

HYPOTHALAMIC TUMOURS

Craniopharyngioma

It constitutes 3% to 5% of all intracranial neoplasms. These arise from Rathke's pouch, are cystic or partially cystic, and are usually located in suprasellar area. Most cases present in childhood with

features of raised intracranial tension, visual disturbances, short stature, delayed puberty and diabetes insipidus. Most of the adults present with visual symptoms; suprasellar calcification in curvilinear, flocculent or granular pattern may be present on skull X-ray. Computed tomography or MRI is the preferred imaging modality (**Figures 1A and B**). Treatment usually involves surgery and radiotherapy.

Hypothalamic Hamartoma

A rare benign brain tumour located near the hypothalamus. It consists of mass of neurosecretory neurons, fibre bundles and glial cells and secretes LHRH. It presents as true isosexual precocious puberty more so in boys before the age of 3 years, and can be associated with laughing seizures if the size is larger than 10 mm. MRI is the preferred imaging and appears as isodense prepontine mass without any enhancement after giving contrast (**Figures 1A and B**). Mass usually does not increase in size on long-term follow up and does not need surgical intervention. Puberty is LHRH dependent and is treated with LHRH agonists.

PINEAL GLAND

The pineal gland is a small central structure and weighs around 100 to 150 mg in humans. The main cellular component is the pinealocyte and it is richly vascularised. Its predominant innervation is sympathetic, arising from the superior cervical ganglion. In humans it gets calcified after puberty. The main function of this gland is to synthesise melatonin. Most synthetic activity occurs during the dark phase, with a major increase in the activity of serotonin-N-acetyltransferase. Melatonin has been traditionally considered to be derived principally from the pineal gland. However, several investigations have now demonstrated that melatonin synthesis occurs also in the retina of several vertebrate classes, including mammals. As in the pineal gland, melatonin synthesis in the retina is elevated at night and reduced during the day.

Physiology of Pineal Gland

Shortly after birth very little melatonin is detectable in body fluids. The melatonin rhythm appears around 6 to 8 weeks of life. The plasma concentration of melatonin increases rapidly thereafter and reaches a life-time peak on an average at 3 to 5 years age. Subsequently steady decline occurs reaching mean adult concentrations in mid to late teens with a major decline prior to puberty. Melatonin is synthesised and secreted during the dark phase of the day. The duration of secretion of melatonin correlates with duration of darkness (night). Even a brief exposure to light of sufficient intensity at night rapidly suppresses melatonin production. It is reasonable to assume that the pineal gland conveys information concerning light-dark cycles for the organisation of seasonal and circadian rhythms in humans. Circadian rhythm disturbance is associated with shift work, jet lag, blindness, insomnia and old age.

Pathology of Pineal Gland

Psychiatry

Abnormalities of circadian function have been postulated in depression and mania. There is evidence to suggest a decrease in the amplitude of melatonin in depression and increase in mania. Most pharmacological anti-depressant treatment stimulates melatonin secretion, acting through increased availability of the precursors (tryptophan and serotonin), or by direct action on serotonin and catecholamine receptors.

Pineal tumours

Pineal tumours are rare and constitute less than 1% of intracranial space-occupying lesions. These tumours originate from three different cell lines: parenchymal cells (pineoblastomas and pineocytomas); germ cells (teratomas, germinomas and mixed germ cell tumours); and supporting stroma (gliomas). The most common symptoms are secondary to hydrocephalus (headache, vomiting and drowsiness) together with visual disturbances, diabetes insipidus and reproductive abnormalities. Germinomas and teratomas occur predominantly in males. There is no consistent information on overproduction or underproduction of melatonin with specific types of tumour.

Clinical Uses of Melatonin

The established role of melatonin in humans is that of phase shifting and resetting of circadian rhythms and melatonin has been used to treat jet lag and disorders of circadian-based sleep disorders. Melatonin has also been shown to regulate sleep in humans. It also has been shown to have a hypnotic effect. It also is believed to be effective in seasonal affective disorders. Scientific evidence in favour of melatonin in sleep disorders is not strong, but the drug is safe if given for less than three months. It is available as an over-the-counter drug.

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10.4 Disorders of Anterior Pituitary

RV Jayakumar

The pituitary gland consists of the anterior pituitary (adenohypophysis), posterior pituitary (neurohypophysis) and the intermediate lobe. It is located inside the sella turcica, a depression in the sphenoid bone in the base of the skull. It is related superiorly to the optic chiasma, hypothalamus and the third ventricle from which, it is separated by the diaphragma sellae, antero-inferiorly to the sphenoid sinus and laterally to the cavernous sinuses on either side. Histologically, anterior pituitary has five different hormone secreting cells. The somatotrophs (secrete growth hormone, GH), lactotrophs (secrete prolactin, PRL), thyrotrophs (secrete thyroid stimulating hormone, TSH), corticotrophs (secrete adrenocorticotropic hormone, ACTH) and gonadotrophs (secrete follicle stimulating hormone, FSH; and luteinising hormone, LH). The release of anterior pituitary hormones is under control of hypothalamic releasing hormones, which have either stimulatory or inhibitory action (**Table 1**). These hypothalamic hormones are carried to adenohypophysis through the portal venous plexus located on the median eminence. The release of hypothalamic hormones is modulated partly by neuronal and chemical inputs and partly by input from higher centres.

Table 1: Hypothalamic Control of Anterior Pituitary Hormones

Hypothalamic factor	Action	Anterior pituitary hormone
Growth hormone releasing hormone (GHRH)	Stimulatory	Growth hormone
Growth hormone releasing inhibiting hormone (GHRIH)/somatotrophin release inhibitory factor (SRIF)	Inhibitory	Growth hormone
Thyrotrophin releasing hormone (TRH)	Stimulatory	Thyroid stimulating hormone (TSH), Prolactin
Gonadotrophin releasing hormone (GnRH)	Stimulatory	Luteinising hormone (LH) Follicle stimulating hormone (FSH)
Prolactin inhibiting factor/dopamine	Inhibitory	Prolactin
Corticotrophin releasing hormone (CRH)	Stimulatory	Adrenocorticotropic hormone (ACTH)
Vasopressin	Stimulatory	ACTH

Anterior pituitary develops from the ectoderm of Rathke's pouch, an upward invagination from the roof of the embryonic stomodaeum. Many pituitary transcription factors have now been identified which temporally regulate the development of anterior pituitary cell lineages. The main factors include LHX 3, HESX 1, Prop 1 and Pit 1. Deficiency of these transcription factors can lead to congenital, isolated or combined, pituitary hormone deficiencies.

ADRENOCORTICOTROPHIC HORMONE (ACTH)

This is a 39 amino acid polypeptide derived from a precursor molecule proopiomelanocortin (POMC). The secretion of POMC is stimulated by CRH, arginine, vasopressin and stress. It is inhibited by glucocorticoids. ACTH stimulates synthesis and secretion of glucocorticoids and androgens from the adrenal cortex. The release of ACTH has a diurnal rhythm, with the highest levels recorded at around 4 am and lowest in the evening. Plasma cortisol release also responds to this rhythm accordingly. In addition to pituitary secretion, ACTH can be produced ectopically from other sources, e.g. small cell carcinoma of lung, medullary carcinoma of thyroid and carcinoid tumours.

Increased production of ACTH from a pituitary adenoma results in Cushing's disease and is the commonest cause of Cushing's syndrome (detailed in the chapter on Adrenal). Such adenomas are usually microadenomas (<10 mm) and are treated by surgical removal. Those not responding to surgery may require radiotherapy. Medical treatment with cabergoline and somatostatin analogues are sometimes beneficial for ACTH secreting pituitary adenomas

Defective production of ACTH results in secondary adrenal insufficiency with predominantly glucocorticoid deficiency in the face of normal mineralocorticoid production, because the latter is under the dominant control of the renin angiotensin system. So classic features of Addison's disease like salt wasting, hyperkalaemia and hyperpigmentation are absent. Treatment involves replacement with glucocorticoids.

THYROID STIMULATING HORMONE (TSH)

This is a glycoprotein hormone having an alpha and a beta subunit similar to other glycoprotein hormones such as FSH, LH and hCG. While the alpha subunit is common for all these hormones, the beta subunit is responsible for specific biological activity. TSH regulates thyroid hormone and release by the thyroid gland. Plasma level of thyroid hormone and TRH regulate the TSH release. It is so finely adjusted that even a slight decrease in circulating thyroid hormone increases pituitary TSH release; hence measurement of plasma TSH is the single most sensitive test to assess primary hypothyroidism.

The tumours of anterior pituitary involving TSH producing cell are extremely rare. They present with hyperthyroidism by chronically stimulating the thyroid gland (central hyperthyroidism). Serum T4 levels are high while TSH levels are inappropriately normal or marginally elevated. The characteristic feature of TSH secreting adenoma is the elevation of alpha subunit in blood. Deficiency of TSH is usually part of a plurihormonal deficiency secondary to neoplasia or vascular conditions.

GONADOTROPHINS

The gonadotrophic hormones, FSH and LH are secreted from the anterior pituitary under the stimulation of pulsatile secretion of GnRH. In males, LH acts on Leydig cells to increase synthesis and

secretion of testosterone, while in females LH activates production of oestrogens, androgens and progesterone from interstitial cells of ovary. Gametogenesis in both sexes is controlled by FSH. Both LH and FSH are under stimulatory control of hypothalamic GnRH (LHRH). In pre-pubertal period, FSH response to LHRH is greater than LH while with onset of puberty, LH response exceeds that of FSH. A decrease in testosterone in males and oestrogens in females increases LH secretion whereas damage to germ cells increase the FSH, contributed by loss of inhibin production from Sertoli cells in males. Functioning gonadotrophic adenomas producing LH and FSH are rare. In adults they usually present with features of a non-functioning pituitary mass lesion.

Patients with isolated gonadotrophin deficiency usually have hypothalamic pathology coming under the group of Kallmann's syndrome with anosmia. Isolated LH deficiency in men is a rare syndrome (fertile eunuch syndrome), in which patients lack secondary sexual characters but have normal sized testes with arrested spermatogenesis.

GROWTH HORMONE

Human growth hormone is a linear polypeptide with 191 amino acids. A significant proportion of it in the serum is bound with GH binding protein. The main biological effect of GH is promotion of linear growth in postnatal life until completion of puberty. In addition, GH, both directly and through release of IGF-1 (Insulin growth factor-1) from the liver, has anabolic effects on protein, lipid and carbohydrate metabolism. The release of GH occurs in a pulsatile fashion. Hypothalamic GHRH stimulates whereas GHIH/SRIF inhibits its release from the pituitary (**Table 2**). Circulating GH, IGF-1 and glucocorticoids also decrease its secretion. GH deficiency in children results in short stature, while that in adults has been correlated to general asthenia.

Table 2: Factors Affecting GH Release

Augment GH release	Suppress GH release
Stages III and IV NREM sleep	REM sleep
Exercise	Obesity
Stress	Emotional deprivation
GHRH	Glucocorticoids
Insulin-hypoglycaemia	Somatostatin
Arginine	Hyperglycaemia
L-Dopa	IGF-1
Clonidine	Hypothyroidism
Oestrogen	Cyproheptadine
Glucagon	

Gigantism and Acromegaly

Excess production of GH prior to closure of skeletal epiphysis leads to gigantism while in adults it causes acromegaly. In nearly 98% of such patients, excess GH release is from a pituitary somatotroph adenoma. In exceptional cases, it may be secondary to excess release of GHRH from a hypothalamic tumour or due to ectopic secretion of GHRH from a bronchial carcinoid, pancreatic islet cell tumour or phaeochromocytoma.

Clinical Features

Patients with gigantism have abnormally tall stature (**Table 3**). In acromegaly (**Figures 1 and 2**), there is acral (hand and feet)

Table 3: Causes of Tall Stature

Gigantism
Marfan's syndrome
Hyperthyroidism in childhood
Homocystinuria
Cerebral gigantism
Sexual precocity

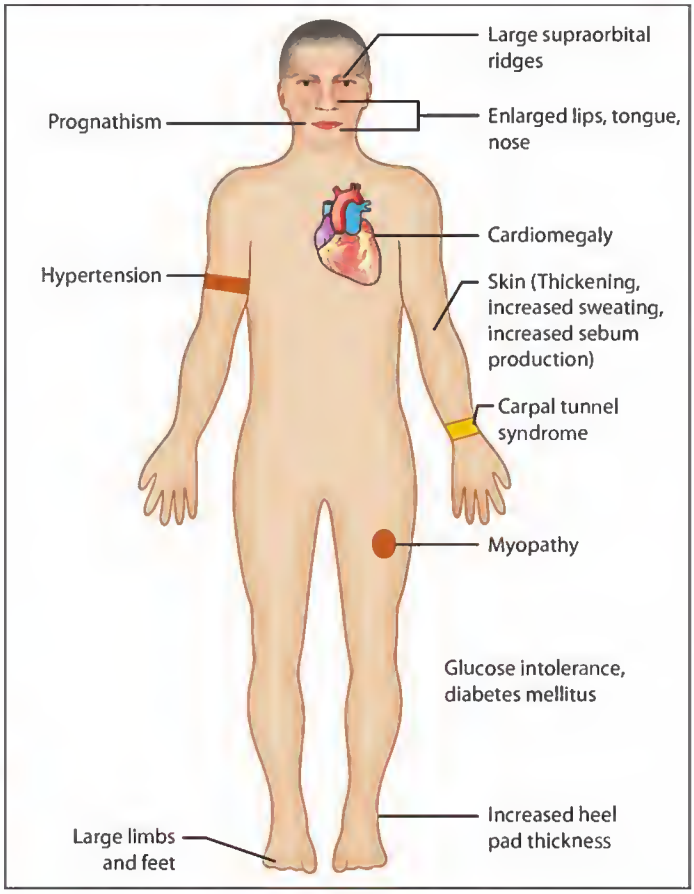


Figure 1: Clinical features of acromegaly.



Figure 2: Broad hands in acromegaly.

and soft tissue enlargement leading to facial disfigurement (bulbous nose, prominent supra-orbital ridge, prognathism, thick lips, malocclusion and splaying of teeth causing difficulty in biting food and macroglossia). There may be cutaneous gyratus on the scalp and thick heel pad.

Other cutaneous manifestations include thick skin, prominent palmar creases, forehead furrows, increase in skin tags, acanthosis nigricans, hirsutism, acne, increased sweating and malodourous sebum secretion. Patients may notice increase in size of ring, shoes and hat. Enlargement of visceral organs like liver, spleen, heart and thyroid are common, but this may not always be clinically apparent. Enlargement of larynx and paranasal sinuses lead to thick sonorous voice. Cardiovascular diseases like cardiomyopathy, hypertension and congestive heart failure are the major cause for excess mortality in these patients. Respiratory disturbances including central and obstructive sleep apnoea are common. Synovial oedema often leads to entrapment neuropathies like carpal/tarsal tunnel syndrome. Arthralgia, degenerative arthritis and hyperextensibility of joints are common and are directly related to the severity and duration of GH excess. An excess cancer risk, putatively mediated through IGF-1 excess, has been suggested, but the issue is far from settled. In view of this, close follow-up including surveillance for colonic polyps is indicated in patients with acromegaly. Rarely, some patients may have galactorrhoea with or without associated hyperprolactinaemia. Enlarging pituitary macroadenoma may cause bitemporal headache, visual field defect (bitemporal hemianopia) and signs of raised intracranial tension. In 15% to 25% of patients there may be impaired glucose tolerance or frank diabetes mellitus.

Diagnosis

The diagnosis of acromegaly can be made on the basis of the characteristic clinical appearance. However, as the changes may be subtle and slowly progressive, diagnosis is often delayed for more than 10 years from onset of the disease and serial photographs provide a good evidence for clinical diagnosis.

For GH secretory status, failure of GH suppression after an oral glucose load is considered diagnostic. In normal subjects, GH levels after glucose load fall to <1 ng/mL, whereas in acromegaly, GH levels remain unsuppressed. Serum IGF-1 levels are also elevated and can be used in the diagnosis, but more importantly in the follow-up of acromegaly. Nearly 30% of patients may have associated hyperprolactinaemia, while secretion of other pituitary hormones such as gonadotrophins, TSH and ACTH may be decreased.

MRI, with gadolinium enhancement, is the gold standard for detecting a pituitary somatotroph adenoma (**Figure 3**); imaging of chest and abdomen for ectopic production of GHRH or GH is rarely required. Radiological studies of skull reveals thickness of calvarium, enlarged air sinuses and mastoid air cells, sellar enlargement (deep and wide sella, occasionally having double floor) and nuchal ligament calcification. X-ray hand shows tufting of terminal phalanx with soft tissue swelling whereas X-ray foot reveals heel paid thickness (>20 mm). X-ray spine may show scoliosis with calcification of spinal ligament. Rarely acromegaly occurs as part of familial syndromes like MEN 1 (parathyroid adenoma and pancreatic tumours) or Carney's complex or McCune Albright syndrome.

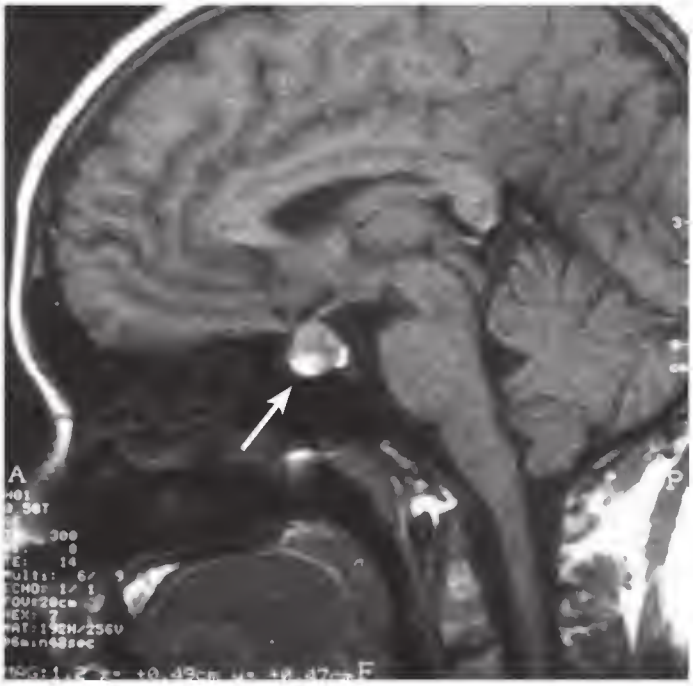


Figure 3: MRI scan showing pituitary GH secreting microadenoma.

Prognosis

The mortality in acromegaly is about four times greater than in general population. The high mortality is due to cardiovascular, cerebrovascular, pulmonary and neoplastic disorders. The post treatment GH level is the significant determinant of mortality in patients with acromegaly.

Treatment

Treatment of acromegaly should aim to normalise GH and IGF-1 levels, remove tumour mass effect and preserve normal pituitary function. The general consensus about the criteria for cure is to achieve a mean growth hormone level of less than 2.5 ng/mL and a glucose suppressed GH <1 ng/mL, with a normal IGF-1 which is associated with survival rates equal to those of general population. Trans-sphenoidal surgery, pharmacological therapy and various forms of radiation therapy are used to treat GH secreting adenomas.

Surgery

Trans-sphenoidal surgery for the pituitary adenoma is the accepted first line therapy in patients with a somatotroph adenoma. Surgery alleviates acromegalic symptoms, removes the tumour mass, relieves optic tract pressure effects and regularises GH level in about 70% of patients. The most important determinant of a successful surgical outcome is the experience of the surgeon. Better results are obtained in microadenomas (90%) while less than 50% of macroadenomas respond to surgery alone.

Radiotherapy

Pituitary irradiation is a mode of therapy for pituitary adenomas but the slow biochemical response rate of 20% cure in 10 years time, qualifies it as a follow-up therapy after inadequate surgical removal rather than as a primary form of treatment. External

radiotherapy aims to give 4500-5000 rads to the pituitary gland, Proton beam therapy, giving heavy particle pituitary radiation, achieves higher cure rates. Stereotactic ablation of GH secreting adenoma by gamma knife radiosurgery or linear accelerator are newer forms of treatment for acromegaly. However, these are available only in few centres and the initial long-term results are favourable.

Treatment

Somatostatin analogues constitute the main medical modality of treatment for acromegaly. They mainly bind to somatostatin receptor subtypes 2 and 5 (SSTR2 and 5) expressed on somatotrophs and inhibit secretion of GH 45 times more potently than endogenous somatostatin. Previously, octreotide a synthetic analogue of somatostatin used to be given as subcutaneous injection in doses of 50 to 200 mcg, eight hourly to normalise GH; GH is normalised in more than 70% of patients by this drug. Presently, several long acting preparations of somatostatin analogues are available for treatment and their long-term efficacy is also well established. The commonly used drugs are octreotide LAR and lanreotide. A monthly injection of 20 mg octreotide LAR or a fortnightly injection of 30 mg Lanreotide will effect persistent suppression of GH in more than 60% to 70% of acromegalic patients. These agents are relatively safe, side effects being transient gastrointestinal symptoms and increased incidence of gall stones. Recently, the new somatostatin analogue SOM 230 (Pasreotide) which acts on more types of somatostatin receptors has been found to be useful in tumours unresponsive to the conventional somatostatins. Because of their cost, in the Indian scenario, these somatostatin analogues are used while waiting for the radiotherapy to be effective or after insufficient surgical removal of pituitary adenoma, even though primary medical treatment with these agents are becoming common in the West. Dopamine agonists like bromocriptine have been used for several years to reduce GH levels. However, GH normalisation occurred in less than 15% patients on a dose of 10 to 30 mg per day in divided doses. Cabergoline, a long acting dopamine agonist, is also used at a dose of 0.5 mg daily but the long-term efficacy is the same as that of bromocriptine.

Another form of medical treatment of acromegaly is the use of growth hormone receptor antagonist called pegvisomant which antagonises the action of GH on GH receptor and decrease the IGF-1 levels. This agent has no effect on tumour size, and may even be associated with an increase in size.

PROLACTIN

Prolactin is a single chain 198 amino acid polypeptide, which is essential for production of milk from the mammary gland in lactation and pregnancy. It is mainly under the inhibitory control of PIF, which is dopamine. The major stimulus for prolactin secretion is suckling, but its level can go up with stress, sleep and hypoglycaemia. Administration of oestrogens, phenothiazines and TRH increases its serum levels. Excess circulating prolactin in females results in amenorrhoea-galactorrhoea syndrome, while in men it manifests as loss of libido and sexual dysfunction. Its deficiency is not symptomatic in males and non-lactating women, whereas in post-partum period and in lactating women its deficiency produces absence of lactation.

Hyperprolactinaemia and Prolactinomas

Persistent elevation of serum prolactin level in the absence of pregnancy and lactation indicates hypothalamo-pituitary dysfunction. The elevation of prolactin may be physiological, pathological or secondary to drug therapy (**Table 4**).

The hyperprolactinaemic syndrome is commoner in women, which may be explained by their exposure to oestrogen. Prolactinomas are a frequent cause of organic hyperprolactinaemia, and they form about 40% to 50% of all pituitary adenomas. About 65% to 70% of prolactinomas are microadenomas (<10 mm in size) which are frequently present in females whereas macroadenomas (>10 mm in size) are seen with equal frequency in both the sexes.

Table 4: Causes of Hyperprolactinaemia

Physiological	Pathological
Sleep, stress, pregnancy and nursing	Hypothalamo-pituitary tumours, inflammatory and granulomatous diseases
Pharmacological	Pituitary stalk lesions prolactinomas
Dopamine receptor blockers, phenothiazines, haloperidol, metoclopramide, domperidone	Plurihormonal adenomas empty sella
Dopamine synthesis inhibitor methyl dopa	Primary hypothyroidism Polycystic ovarian syndrome
Catecholamine depletors, reserpine	Chronic kidney disease Liver cirrhosis Idiopathic
Ranitidine,cimetidine, fluoxetine, amitriptyline, oestrogens	

Clinical Manifestations

The frequent clinical presentations of hyperprolactinaemia in women are amenorrhoea, galactorrhoea and infertility. The alteration of menstrual cycle may vary from oligomenorrhoea to amenorrhoea, and rarely no menstrual dysfunction may be seen. Galactorrhoea, occurs in about 60% to 80% of hyperprolactinaemic women and may be the only finding in a patient presenting with infertility. Seborrhoea and moderate hirsutism may be present due to increased adrenal androgen production. In men with hyperprolactinaemia, the common presenting complaints are progressive loss of libido and sexual potency. Galactorrhoea or gynaecomastia are present in 15% to 25% of patients. Fluid retention with increase in body weight is seen in both sexes. Headache is present in patients with both micro- and macroadenomas and has no correlation with the size of adenoma. Defects in visual fields and hypopituitarism can occur in macroadenomas.

Diagnosis

Diagnosis of hyperprolactinaemia is confirmed by measuring basal levels of prolactin from multiple pooled samples. Sometimes, a high prolactin level may be revealed only by doing the test in dilution (Hook effect) and conversely prolactin levels may be falsely elevated by the presence of biologically inactive prolactin called macroprolactin. Thyroid function tests should be done in all cases of hyperprolactinaemia as primary hypothyroidism can cause elevation of PRL, mediated by the high TRH levels. In all cases of macroprolactinomas other

pituitary hormones should be carefully evaluated to assess accompanying deficits. A prolactin of >100 ng/mL in a non-pregnant woman is generally due to a pituitary adenoma. Imaging of the hypothalmo-pituitary area is very important in such situations, with contrast enhanced dynamic MRI being the preferred method. Using high resolution scans, microadenomas as small as 2 to 3 mm can be detected.

Treatment

The aim of treating hyperprolactinaemia is to normalise prolactin level, relieve symptoms and shrink the tumour. In this regard, the efficacy of dopaminergic drugs is well established and it is accepted as the first-line therapy with prolactinomas. Other treatment modalities available are pituitary surgery and radiation. Pituitary surgery is indicated mainly for those who are intolerant and resistant to dopamine-agonists, and for those macroprolactinomas that do not shrink adequately with medical therapy.

The most extensively used dopamine agonists are ergot derivatives bromocriptine and cabergoline. These drugs should be started in low doses (e.g. 1.25 mg at night for bromocriptine and 0.5 mg cabergoline once a week) and slowly increased in step-wise manner. The usual dose of bromocriptine is 2.5 mg to 20 mg per day in two or more divided doses. It causes reduction of prolactin level to normal in 60% to 100% cases. Clinical symptoms are relieved in 1 to 3 months, and tumour shrinkage occurs in 70% to 90% cases. Cabergoline is a long acting ergot derivative and at a dose of 0.5 mg to 1 mg, prolactin levels are suppressed for 7 to 14 days; hence weekly dose is sufficient. Once prolactin levels are normalised and sexual functions have improved and tumour has reduced in size, the dose of dopamine agonists can be reduced and a supervised trial off therapy can be given especially in microprolactinomas.

The common adverse effects of dopamine agonists are nausea and postural hypotension which can be circumvented by starting the drug at a smaller dose given at night after meals. It can also exacerbate underlying psychosis. Other rare but serious side effects are hepatic dysfunction, CSF rhinorrhoea, cardiac arrhythmias and valvular stenosis. During pregnancy, prolactinomas can enlarge and cause visual impairment. This is more common in macro- than microprolactinomas. Hence, dopamine agonists are discontinued when a lady with microprolactinoma conceives, and they are closely monitored for headache and signs of visual field defects. Macro-prolactinomas may need treatment during pregnancy. Bromocriptine has been the most widely used dopamine agonist in pregnancy with no reported adverse effects on the mother and baby; cabergoline also appears safe in pregnancy even though experience with its use in pregnancy is limited.

PITUITARY INSUFFICIENCY (HYPOPITUITARISM)

This is a clinical condition characterised by deficiency of one or more of the pituitary hormones. While selective deficiency of one or two hormones is either congenital or idiopathic, multiple hormone deficiencies usually result from tumours or destructive lesions. Causes of hypopituitarism are varied (**Table 5**). Common causes include non-hormone secreting pituitary tumours, pituitary surgery and cranial iradiation.

Table 5: Aetiology of Hypopituitarism

Pituitary and para-pituitary tumours; craniopharyngioma and chromophobe adenoma
Radiotherapy
Surgery
Trauma: Skull fracture and perinatal
Vascular: Apoplexy, Sheehan's syndrome, post-snake bite, sickle cell disease
Infiltration: Sarcoidosis, histiocytosis, haemochromatosis
Lymphocytic hypophysitis
Infection: Basal meningitis and encephalitis
Congenital and genetic disorders: Pit 1, Prop1, HESX 1, LHX 3 mutations
idiopathic

Clinical Features

Clinical features of hypopituitarism depend on the type (single or plurihormonal) and extent of hormone deficiency, speed of onset and local pressure effects of the pituitary lesion. The clinical features of pituitary mass lesions include bi-temporal headache, visual field defect (bi-temporal hemianopia), features of raised intracranial pressure, rarely cranial nerve palsies, CSF rhinorrhoea (when the mass erodes the sellar floor), temporal lobe epilepsy and hypothalamic features. In slowly progressive pituitary lesions like that following radiation or vascular insult, e.g. Sheehan's syndrome or post-snake bite hypopituitarism, a characteristic pattern is present. Secretion of growth hormone fails first, followed by gonadotropins, TSH and lastly, ACTH. Prolactin deficiency is rare, except in Sheehan's syndrome. Generally, hyperprolactinaemia is the rule. This may be due to release of lactotrophs from the tonic inhibition of dopamine or due to secretion from a prolactinoma. Diabetes insipidus is not a feature of anterior pituitary disease; its presence denotes hypothalamic or stalk lesion. The clinical features of individual hormone deficiencies are given in **Table 6**.

Table 6: Clinical Features of Hormone Deficiency

Hormone	Age group	Manifestations
Growth hormone	In children	Short stature
	In adults	Abnormal body composition, reduced sense of well being and performance, low bone mass
Gonadotropins	In males	Poor libido, impotence, reduced facial hair, atrophic testes, infertility
	In females	Amenorrhoea, infertility, breast atrophy
TSH	In children	Growth retardation, dry skin, constipation
	In adults	Myxoedema, slow relaxation of deep tendon reflexes
ACTH		Weakness, tiredness, postural hypotension and giddiness, pallor and hypoglycaemia
Prolactin		Lactation failure

For diagnosis of pituitary failure, clinical examination is important. In children, documentation of height, weight and pubertal status are necessary. Blood pressure should be checked

for postural drop and visual fields documented by perimetry. It is a good guide to suspect pituitary deficiency in the following situations: post-partum failure of lactation, hyperinvolution of uterus, and involution of breast; sparse pubic and axillary hair, in patients with unexplained amenorrhoea, features of ACTH or TSH deficiency and raised intracranial pressure; women with unexplained anaemia and asthenia; males with decreased libido and sexual potency.

Diagnosis

The diagnosis of hypopituitarism is based on endocrine tests ranging from measuring basal levels of all hormones, to stimulatory tests of individual hormones. Insulin tolerance test is the gold standard to assess the pituitary GH and ACTH reserve. LHRH and TRH tests are done to assess the reserve of gonadotropins and TSH, respectively. MRI of the hypothalamo-pituitary area should be done to look for structural lesions. Congenital mutations in pituitary transcription factors can be associated with small anterior pituitary, absent stalk and an ectopic posterior pituitary bright spot.

Treatment

The treatment of hypopituitarism includes therapies directed at the underlying disease process and hormone replacement therapy (**Table 7**) which should aim at improving symptoms, while avoiding over-treatment and should mimic the normal hormonal milieu as far as possible. Replacement is usually given with the target hormones rather than pituitary hormones.

Table 7: Endocrine Replacement Therapy for Hypopituitarism

Hormone deficiency	Replacement	Dose
Growth hormone	Growth hormone	0.25 to 0.7 mg/d S/C
Gonadotrophin	Women	
	Oestradiol valerate	1 to 2 mg/d
	Conjugated oestrogens/	0.625 to 1.2 mg/day
	Ethinyl oestradiol	20 to 30 mcg/day
	Progesterone	Cyclical therapy
	Men	
	Testosterone enanthate or propionate	250 mg every 3 weeks IM
TSH	L-thyroxine	50 to 200 µg/d oral
ACTH	Hydrocortisone	15 to 20 mg/d oral
Prolactin	None	None

In combined deficiency of TSH and ACTH, steroid replacement should always precede thyroid replacement. In patients on steroid replacement therapy the importance of increasing the dose of steroid during stress should be emphasised. Acute adrenal crisis will require parenteral steroids. Replacement of growth hormone in AGHD (adult growth hormone deficiency) is known to improve lean body mass and bone mass and improve cardiovascular risk. In hypogonadal patients desirous of fertility, treatment with gonadotropins (recombinant HCG and FSH) are indicated. There is now evidence that hypopituitarism is associated with excessive mortality as compared to normal population. It is possible that with proper hormone replacement therapy, this mortality can be reduced. Lastly, as hypopituitarism requires complex drug regimens, every effort should be made to prevent its occurrence by avoiding unnecessary and extensive radiation or surgical therapy.

NELSON'S SYNDROME

This entity results from an aggressive ACTH producing adenoma in a patient who has undergone bilateral adrenalectomy for Cushing's syndrome. These patients present with headache, visual field defects and external ophthalmoplegia, all suggestive of pituitary mass lesion. The high circulating ACTH levels produce hyperpigmentation due to its MSH-like action. This condition represents enhancement of tumour growth, by removal of negative feedback of high cortisol secretion from adrenal gland. This is shown to be preventable by external pituitary irradiation in some patients. Once established, transsphenoidal decompression and radiotherapy are the modalities of treatment. In order to identify Nelson's syndrome early, periodic pituitary imaging is recommended in all patients who have undergone bilateral adrenalectomy for Cushing's syndrome.

PITUITARY APOPLEXY

This is a life-threatening clinical situation arising from acute infarction of the pituitary gland. A haemorrhagic infarction usually arises in the presence of pituitary tumour, while ischaemic infarction can occur in normal gland following obstetric haemorrhage or anticoagulant therapy. This usually causes anterior pituitary hypofunction, which can be permanent or transient. The degree of hypopituitarism depends on the extent of pituitary destruction. Clinically, pituitary apoplexy presents with severe headache, sudden change of sensorium, ophthalmoplegia, visual loss and prostration. Once suspected, it should be treated immediately with glucocorticoid supplementation and other supportive measures to reduce pressure effects. Deterioration in sensorium and visual impairment are indications for surgical decompression.

CRANIOPHARYNGIOMAS

These tumours, which are often cystic, arise from the Rathke's pouch remnants. They constitute 3% to 5% of intracranial tumours and majority are diagnosed when children present with growth failure or sexual infantilism. There may be associated diabetes insipidus. The treatment of choice is surgery followed by radiation.

EMPTY SELLA SYNDROME

This is a clinical condition similar to a pituitary tumour, and occurs when a defect in the diaphragma sellae results in subarachnoid space herniation into the sellar space. Pressure on the bony walls of the sella causes subsequent remodeling, sellar enlargement and flattening of the pituitary gland. Though the exact pathogenesis remains unclear, raised intracranial pressure in a subject with a diaphragmatic defect is thought to predispose to the empty sella syndrome. This is frequently detected when a patient with obesity and headache is investigated by pituitary imaging (**Figure 4**). Though clinically uncommon, this is seen in 20% of women at autopsy. It can cause diagnostic difficulty when it mimics the radiological appearance of a pituitary tumour. Treatment is

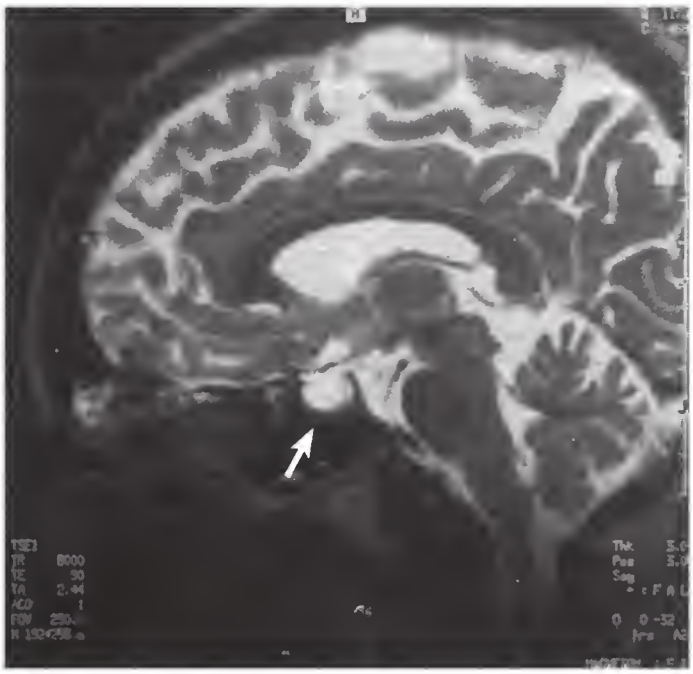


Figure 4: Sagittal view MRI showing empty sella (white arrow).

symptomatic for primary empty sella, and those with a secondary cause should receive appropriate therapy of the underlying disease process.

LYMPHOCYTIC HYPOPHYSITIS

This occurs usually in the post-partum period and patients present with headache, visual disturbance, hyperprolactinaemia, diabetes insipidus or hypopituitarism. It is thought to be autoimmune in origin and it is difficult to differentiate it from pituitary adenoma. Patients may have antipituitary antibodies and other organ and non-organ specific autoantibodies. Treatment is with steroids and surgery is usually not necessary except for a tissue diagnosis. It may remit spontaneously also.

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10.5 Disorders of Posterior Pituitary

GR Sridhar

The posterior pituitary develops from neural ectoderm of the forebrain and secretes the hormones vasopressin and oxytocin. Vasopressin or anti-diuretic hormone (ADH) is produced by hypothalamic supraoptic nucleus and *oxytocin* by paraventricular nucleus. They traverse with neurophysins to posterior pituitary, from where they directly enter systemic circulation. ADH regulates water balance in the kidney. It is released in late sleep to prevent dehydration and enuresis. Oxytocin primarily affects uterine contraction and post-partum milk ejection, although it could influence cognition.

DISORDERS OF POSTERIOR PITUITARY

ADH deficiency (impaired production or end organ resistance) leads to diabetes insipidus. Inappropriate secretion causes SIADH (syndrome of inappropriate ADH).

DIABETES INSIPIDUS (DI)

Epidemiology and Clinical Features

Diabetes insipidus is uncommon (3:100,000 general population) but, when it occurs, must be identified and promptly corrected. It presents as polyuria (>3 litres of urine daily of dilute urine), leading to thirst that may disturb sleep. It can occur at any age and in both sexes. Its occurrence in adults depends on the aetiology; it often occurs as a result of pathological insults to the hypothalamic-pituitary axis. In children, organic central DI should be suspected in children presenting after the age of five years, and with features of anterior pituitary insufficiency, such as growth retardation.

Urine specific gravity (SG) is <1.010 and serum sodium exceeds 145 mEq/L. Polyuria may be less severe when ADH deficiency is partial or when other endocrine diseases coexist, such as hypothyroidism or Addison's disease.

Aetiology

DI may result from deficient ADH production from the hypothalamus-pituitary (central DI) or from renal end-organ resistance to ADH action (nephrogenic DI) (**Table 1**).

Hereditary DI results from mutations of genes: arginine vasopressin gene, arginine vasopressin receptor gene, and vasopressin sensitive water channel gene.

Clinical Features

Polyuria, depends on the degree of ADH deficiency. Daily urine volume may vary from a few litres to nearly 18 litres. Nocturia is invariable, unlike in primary polydipsia.

If water is denied, hypertonia leads to irritability, fever, mental dullness, prostration and death. If DI is due to primary pituitary lesion, neurological abnormalities coexist. Children may present with poor feeding, failure to thrive and irritability.

Post pituitary-surgery DI is often transient. When permanent, persistent polyuria begins about 10 to 14 days postoperatively.

Table 1: Causes of Diabetes Insipidus (DI)

- **Central DI**
  - Tumours of hypothalamo-pituitary region
    - Craniopharyngioma
    - Suprasellar extension of pituitary tumours
    - Germinoma
    - Pinealoma
    - Metastasis
  - Infiltrative lesions
    - Sarcoidosis
    - Histiocytosis X
    - Tuberculosis
    - Leukaemias
  - Pituitary or hypothalamic surgery
  - Severe head injury (stalk section)
  - Ruptured cerebral aneurysm
  - Idiopathic
  - Familial
- **Nephrogenic DI**
  - Congenital or familial
  - Acquired
    - Chronic renal diseases
    - Acute tubular necrosis
    - Primary aldosteronism
    - Chronic hypercalcaemia
    - Drug-induced (lithium, demeclocycline)

Modalities of Diagnosis

Firstly polyuria (>3 L/d) should be demonstrated by measuring 24 hours fluid intake and urine output. In diabetes insipidus hypertonicity occurs if water loss cannot be corrected by fluid ingestion. In the presence of polyuria, hypertonicity and the absence of other causes of polyuria, the diagnosis of diabetes insipidus can be made. In the face of unambiguous features, water deprivation may not be performed. Further investigations may be needed to differentiate DI from primary polydipsia, identify partial forms of DI and to evaluate for the cause of DI.

Water deprivation test

This test, done under supervision, is started early in daytime; the earlier the better. The subject is weighed, 97% baseline weight calculated and noted prominently, for termination if this is reached during the test. In those who are already on replacement with desmopressin, it must be stopped 24 hours earlier, while steroids (for other indications, e.g. hypopituitarism are not stopped).

Fluid is withheld until one of the following occurs: orthostatic hypotension and postural tachycardia appear, $\geq$ 5% of the initial body weight has been lost, or the urinary concentration does not increase >0.001 SG or >30 mOsm/L. Serum osmolality is determined and 5 units of aqueous vasopressin injected SC. Urine for SG or osmolality measurement is collected 60 min after the injection before allowing fluids to be ingested.

A normal response produces maximum urine osmolality after dehydration (often >1.020 SG or >700 mOsm/L), exceeding the plasma osmolality; osmolality does not increase more than an additional 5% after injection of vasopressin.

Interpretation

A plasma osmolality of more than 288 mOsmol/kg before vasopressin injection denotes sufficient dehydration. In a normal person, vasopressin results in <9% rise of urine osmolality, in contrast to central DI, where the rise is more than 9%. Nephrogenic DI shows little change in urine osmolality with dehydration and little further increase with vasopressin. Psychogenic polydipsia requires prolonged fluid deprivation before plasma osmolality reaches 288 mOsm/kg; though vasopressin results in less than 9% increase.

Differential Diagnosis

In primary polydipsia, rather than nocturia, modest daytime polyuria occurs; acquired nephrogenic DI has less polyuria compared to primary nephrogenic DI or central DI. Hypernatraemia with normal serum creatinine and low urine sodium with polyuria suggests water diuresis (e.g. DI) than osmotic diuresis. On MRI a 'bright spot' is shown by normal posterior pituitary; it is absent in central DI, although some 'normal individuals', i.e. without diabetes insipidus could also have absent bright spot. Coexistence of DI with pituitary mass suggests the mass is likely malignant or infiltrative.

Management, Course and Prognosis

Central DI is treated by desmopressin, a long acting vasopressin analogue. Ambulatory replacement is started with intranasal administration (5 to 10 µg) at bedtime, and the dose titrated by control of nocturia. Oral desmopressin preparations are available; although there is no single fixed dose, it can be started at one oral tablet of DDAVP (0.1 mg) per 8 hours. The antidiuretic dose-equivalence ratio for intranasal to oral desmopressin is 1:18.

An intact thirst mechanism is an important defense against complications. When unconscious (e.g. postoperative period, following head injury), 1 µg of DDAVP is injected; although some if residual vasopressin exists, potentiators such as chlorpropamide (100 to 500 mg/d), clofibrate (500 mg 6 hourly) or carbamazepine (400 to 600 mg/d) are used. Carbamazepine and vasopressin are best not used together.

Annual follow-up is necessary. DI should not be considered idiopathic till four years later.

Nephrogenic DI is treated with thiazide diuretics (hydrochlorothiazide 25 to 50 mg/d) and low salt intake. Thiazide diuretics impair sodium chloride co-transporter in renal distal convoluted tubule. Increased renal sodium excretion causes antidiuretic effect. Rarely, indomethacin or high dose vasopressin may be needed.

Rarely when diabetes mellitus and diabetes insipidus coexist, the latter can be suspected by the low specific gravity in an individual with diabetes mellitus.

SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

In SIADH, hyponatraemia occurs due to excess water relative to solute. There is no oedema. Causes are listed in **Table 2**. Clinical features are due to hyponatraemia: anorexia, nausea, vomiting, cramps, weakness and coma. SIADH is diagnosed by hypotonic hyponatraemia, urine osmolality >100 to 150 mmol/kg, without extracellular depletion. Systemic conditions such as dysfunction of thyroid, adrenal, heart, liver and kidney, head injury, malignancy or lung infection should be excluded.

Table 2: Causes of SIADH

Pulmonary disorders
Pneumonia
Tuberculosis
Lung abscess
Pneumothorax
Positive pressure ventilation
Bronchogenic carcinoma
CNS disorders
Encephalitis, meningitis, brain abscess
Vascular injury
Trauma
Guillain-Barré syndrome
Brain tumours
Endocrine disorders
Myxoedema
Adrenal insufficiency
Anterior pituitary insufficiency
Ectopic ADH production
Drugs
Stimulation of ADH release (clofibrate, vincristine, cyclophosphamide)
Enhancement of ADH action (chlorpromazine)
Unknown (morphine, carbimazine)

It is treated by correcting the cause and depends on the severity: restriction of free water by 500 to 1000 ml/d may only be needed. Demeclocycline (600 to 1200 mg/d) is needed uncommonly.

OXYTOCIN

The other posterior pituitary hormone, oxytocin, has two actions: it contracts uterine myometrium, and stimulates breast milk ejection. It also affects social and emotional bonding. There is no clinical condition of excess oxytocin.

RECENT ADVANCES

Vasopressin is also used in treatment of cardiac arrest and in vasodilatory shock. Newly developed vasopressin antagonists are useful in treating hyponatraemia of heart failure. Oxytocin use may improve communication in autism. Potential roles for oxytocin are being studied as a regulator of bone mass.

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10.6 Disorders of Thyroid Glands

Nikhil Tandon, Gunjan Garg

STRUCTURAL EMBRYOLOGY

Thyroid tissue is present in all vertebrates, and is first recognised in humans about 1 month after conception. The primordium begins as thickening of epithelium in the pharyngeal floor. This forms a diverticulum which later is displaced caudad assuming a bi-lobate shape. It remains attached to pharyngeal floor by the thyroglossal duct, the lower portion of which differentiates into pyramidal lobe of the gland. Rest of the thyroglossal duct undergoes dissolution and fragmentation by about second month of conception, leaving behind a small depression at the junction of the middle and posterior thirds of the tongue (foramen caecum). Persistence of this duct can form thyroglossal cyst. About 10% of the thyroid, the parafollicular or C cells, develops from the ultimobranchial bodies originating from 4th and 5th pharyngeal pouches. A number of proteins are known to be crucial for normal thyroid gland development. These include the thyroid-specific transcription factor PAX8, as well as thyroid transcription factors 1 and 2 (TTF1 and 2).

FUNCTIONAL ONTOGENY

Thyroid follicular cells acquire capacity to form thyroglobulin (Tg) by 29th day of gestation, while the ability to concentrate iodine and initiation of hormonogenesis occurs by the 11th week of gestation. Thyroxine-binding globulin (TBG) is detectable in serum by 10th gestational week and increases subsequently, enabling a progressive increase in circulating thyroid hormone levels to term.

ANATOMY AND HISTOLOGY

The thyroid is one of the largest of endocrine organs, weighing about 15 to 20 gm in adults, with each lobe being approximately 4 cm (height) × 2 cm (width) × 2 to 2.5 cm (thickness). The two lobes are connected by the isthmus, which is approximately 2 cm in height and width, and 0.5 cm in thickness. The gland is supplied by the superior and inferior thyroid arteries. The gland is formed of follicles, which are filled with colloid. From the apex of follicular cells, numerous microvilli extend into colloid. It is at or near this surface of the cell that iodination, exocytosis and the initial phase of hormone secretion occur. Colloid contains Tg molecules in which thyroid hormones are present. The lining cells of the follicle are cuboidal in the inactive phase and columnar in the active phase. About 20 to 40 follicles are grouped to form a lobule, which is demarcated by connective tissue septa and supplied by a single artery. The parafollicular cells (C cells) secrete calcitonin, which participates in calcium metabolism.

SYNTHESIS AND SECRETION OF THYROID HORMONES

The thyroid secretes two iodine containing hormones, tetraiodothyronine (T_4) and triiodothyronine (T_3). Active uptake of iodine by the follicular cell, against a concentration gradient, is mediated by the NaI symporter (NIS), which is expressed at the basolateral margin of the cell. NIS enables the entry of one iodine atom against the downhill transport of two Na atoms. The NIS also transports TcO_4^-, ClO_4^-, and SCN^-, which has allowed these agents to be used for thyroid scanning and blocking iodine uptake. The NIS is also present in non-thyroidal tissues e.g. breast, salivary gland. Another protein involved in iodine transport is pendrin, which is a product of the PDS gene. Mutation in NIS and PDS genes are associated with congenital hypothyroidism.

After uptake, iodine is oxidised by the enzyme thyroid peroxidase (TPO), followed by iodination of tyrosine molecules in Tg, a process called organification. TPO is now recognised to be the major component of what was previously called thyroid microsomal antigen. Monoiodotyrosine (MIT) and diiodotyrosine (DIT) are then coupled in varying proportion to form T_3 and T_4, a reaction also catalysed by TPO. There are 3 to 4 T_4 molecules on each molecule of Tg, while only 20% of Tg molecules contain T_3. Tg is then processed in lysosomes to release T_4 and T_3 in circulation, while the uncoupled MIT and DIT are deiodinated by dehalogenase thereby recycling iodine. The thyroid gland contains enough stored hormone to maintain a euthyroid state for at least 6 to 8 weeks.

REGULATION OF THYROID HORMONE SECRETION

Thyroid stimulating hormone or thyrotrophin (TSH), released from the anterior pituitary, stimulates all steps in the formation and release of thyroid hormones, and the conversion of T_4 to T_3. TSH itself is under the positive regulation of the hypothalamic tripeptide, thyrotropin releasing hormone (TRH). Somatostatin, glucocorticoids, cytokines such as IL-1 and TNF-α, phenytoin and dopamine suppress TSH secretion. In turn, TSH and TRH secretion is inhibited by T_4, forming a negative feedback loop that keeps free T_4 levels within a narrow range.

While T_4 is solely secreted directly by the thyroid, about 80% of T_3, which is the active hormone, is generated by 5' monodeiodination of T_4. T_4 to T_3 conversion is impaired by fasting, systemic illness or acute trauma, oral contrast agents and variety of medications (e.g. propylthiouracil (PTU), propranolol, amiodarone, glucocorticoids).

THYROID HORMONE TRANSPORT AND ACTION

Thyroid hormone exists in circulation in both free and bound form. About 75% to 80% of thyroid hormone is bound to thyroxine binding globulin (TBG). Other proteins to which thyroid hormone is bound are transthyretin (TTR), and albumin. Only the free-fraction enters cells and produces biological effect by binding to a nuclear DNA bound thyroid hormone receptor (TR), for which T_3 has a 15-fold higher binding affinity than T4. There are two TR genes, TRα and TRβ. The coded protein has three major functional domains, one to bind ligand, one to bind DNA, and the other for transcriptional activation.

Resistance to thyroid hormones (RTHs) occurs because of mutation in TRβ gene. Patients with RTH may have features of

hypothyroidism if resistance is severe and generalised, while in some instances they may have features of hyperthyroidism if resistance is predominantly in the hypothalamic-pituitary axis and not in peripheral tissues. Treatment is difficult and is directed towards suppression of TSH using thyroid hormone analogues such as TRIAC (3, 5, 3' triiodo-thyroacetic acid).

CLINICAL EVALUATION

History and physical examination should be tailored to evaluate for presence of a thyroidal enlargement: size, shape, symmetry, nodularity, consistency, associated lymphadenopathy, fixity, retrosternal extension, and auscultation for a bruit; presence of the features of hypothyroidism or hyperthyroidism. In case of Graves' disease, associated features of thyroid associated ophthalmopathy and infiltrative dermopathy must also be sought.

During clinical examination the exact dimensions of the thyroid gland can be documented, while in epidemiological studies goitre can be graded as follows:

Grade 0: No visual or palpable goitre.

Grade 1: A goitre that is palpable, but not visible when the neck is in the normal position. Thyroid nodules in a thyroid which is otherwise not enlarged are included in grade 1.

Grade 2: A swelling in the neck that is clearly visible when the neck is in normal position and is consistent with an enlarged thyroid when the neck is palpated.

Goitre is said to be present when each lateral lobe has a volume greater than the terminal phalanx of the thumb of the subject being examined.

IODINE DEFICIENCY DISORDERS (IDDs)

Iodine is the key trace element required for thyroid hormonogenesis. The recommended dietary allowance (RDA) for iodine in a non-pregnant adult is 150 mcg/day, while that in a pregnant female is 200 mcg/day. Iodine content in food and water depends critically on the iodine content of the soil. Soil iodine content is increased by plants that concentrate iodine, colloids that absorb iodine and by an acid pH, while it is decreased by repeated flooding and by an alkaline pH. Sea food and sea weed are rich sources of dietary iodine.

Iodide in the plasma is taken up via active transport into the thyroid follicular cells, a process which becomes more efficient in the iodine deficiency state. Iodine deficiency results in enlargement of the thyroid to enhance the ability of the glands to trap iodine. The term endemic goitre is used to describe goitre seen in a population with iodine deficiency. An area is defined to be endemic if more than 5% of children, between 6 to 12 years of age, are found to have goitre. The stages of goitre formation include an initial diffuse parenchymatous goitre, followed by diffuse colloid goitre, hyperplastic nodular goitre, nodular parenchymatous goitre and nodular colloid goitre. The first two stages are most likely to disappear after making region iodine replete, while later stages are unlikely to involute.

Other manifestations of iodine deficiency depend on the severity and age at exposure. Endemic cretinism is a state of severe congenital hypothyroidism occurring in an endemic area. Two clinical types are recognised: neurological cretinism characterised by mental retardation, abnormal speech and hearing, diplegia, and strabismus; myxoedematous type, characterised by prominent features of hypothyroidism, mental retardation and short stature. Learning disability has been described even in euthyroid children living in endemic areas. Exposure to iodine deficiency during pregnancy is also associated with abortions, stillbirths, increased foetal anomalies and perinatal mortality.

Magnitude of the Problem in India

Results of sample surveys conducted in 325 districts covering all the States/Union Territories revealed that 263 districts are endemic, where the prevalence of iodine deficiency disorders is more than 10%. It is estimated that more than 71 million persons are sufferring from goitre and other iodine deficiency disorders.

To address this public health problem, the Government of India, has implemented the National Iodine Deficiency Disorders Control Programme (NIDDCP) formerly known as National Goiter Control Programme (NGCP). This is a 100% centrally assisted programme with a focus on the provision of iodised salt, IDD survey/resurvey, laboratory monitoring of iodised salt and urinary iodine excretion, health education and publicity. Government of India has banned the sale of non iodated salt in the entire country for direct human consumption under Prevention of Food Adulteration Act (1954), with effect from 17th May, 2006.

For effective implementation of the programme at the State level, the Ministry of Health is providing financial assistance to all the States/UTs for establishment of an IDD Control Cell, and IDD Monitoring Laboratory, in addition to assistance for conducting surveys and health education and publicity for consumption of iodated salt by the population.

HYPERTHYROIDISM

Thyrotoxicosis is the hypermetabolic condition associated with elevated levels of free thyroxine (FT_4) and/or free triiodothyronine (FT_3). Hyperthyroidism includes diseases that are a subset of thyrotoxicosis, that are caused by excess synthesis and secretion of thyroid hormone by the thyroid.

The common causes of thyrotoxicosis are shown in **Table 1**. It is important to remember that all causes of hyperthyroidism, except iodine-induced hyperthyroidism, are associated with an increased radioactive iodine uptake (RAIU). Thyrotoxicosis without hyperthyroidism is not associated with an increased RAIU.

Table 1: Common Causes of Thyrotoxicosis

Conditions causing hyperthyroidism
Graves' disease
Toxic multinodular goitre
Toxic adenoma
Iodide-induced hyperthyroidism
Trophoblastic tumour
Increased TSH secretion: thyrotrophinoma
Conditions causing thyrotoxicosis not associated with hyperthyroidism*
Thyrotoxicosis factitia
Subacute thyroiditis
Post-partum thyroiditis
Chronic thyroiditis with transient toxicosis
Ectopic thyroid tissue (struma ovarii, functioning metastasis of Ca thyroid)

** These conditions are associated with decreased radioactive iodine uptake.*

Clinical Features

The common symptoms and signs of thyrotoxicosis can be explained on the basis of an increased metabolic rate and sympathetic activity (**Table 2**). The latter are observed despite no change in circulating levels of catecholamines and could result from a heightened sensitivity at the receptor level. The symptom profile depends on the severity and duration of thyrotoxicosis and the age of the patient. Patients commonly complain of weight loss despite an increased appetite, irritability, palpitation, tremors, increased sweating, hyperdefaecation, weakness and fatiguability.

Table 2: Common Symptoms and Signs of Thyrotoxicosis

System	Symptoms	Signs
CVS	Palpitation, dyspnoea	Tachycardia, atrial fibrillation, cardiac failure, wide pulse pressure
CNS	Restlessness, irritability, tremors, insomnia	Tremors, proximal muscle weakness, periodic paralysis
GIT	Increased appetite, hyperdefaecation	Exaggerated bowel sounds, pernicious anaemia
Eye	Foreign body sensation, prominence of eyes*, diplopia*, diminished vision*	Stare, lid lag, globe lag, proptosis*, extraocular muscle involvement*, exposure keratitis*, lagophthalmos*
Reproductive system	Short menstrual cycles, loss of libido	Gynaecomastia
Thyroid	Neck swelling	Goitre, bruit
General	Weight loss, weakness, heat intolerance, hyperpigmentation pruritus	Weight loss, warm and moist skin, onycholysis, palmar erythema

**Reported only in infiltrative ophthalmopathy in Graves' disease (and not routinely, in other causes of thyrotoxicosis).*

On examination, the common signs are: goitre, tachycardia, rhythm disturbances like atrial fibrillation, widened pulse pressure, warm and moist skin, bruit over thyroid, and eye signs. Hair and nails may be soft and friable. Eye signs common to all thyrotoxic states include: lid retraction (retraction of the upper eyelid with a rim of sclera visible between lid and limbus); lid lag, globe lag, and fine tremors of lightly closed eyelids. A typical thyrotoxic face is depicted in **Figure 1**. Proximal muscle wasting disproportionate to the weight loss, thyrotoxic myopathy, can be disabling. Untreated thyrotoxicosis can lead to osteoporosis. Menstrual disturbance, commonly hypo- or oligomenorrhoea or even amenorrhoea, and loss of libido, erectile dysfunction and gynaecomastia have been described.

Older patients may present with 'apathetic thyrotoxicosis' where typical adrenergic features are lacking and they may present instead with depression or apathy, weight loss, atrial fibrillation, worsening angina pectoris or congestive heart failure.

Diagnosis

Approach to the diagnosis of a patient with clinical suspicion of thyrotoxicosis is shown in **Figure 2**. Elevated serum total and FT_4 and suppressed TSH are seen in patients with thyrotoxicosis. Some patients may have normal T_4 and an isolated elevation of T_3, a state called T_3 toxicosis. As mentioned above, increased RAIU



Figure 1: Thyrotoxic facies.

is seen in all patients with hyperthyroidism except those with iodide-induced hyperthyroidism. On a thyroid scan in a hyperthyroid patient, uniform tracer distribution suggests Graves' disease, patchy distribution suggests toxic MNG and unifocal activity corresponding to a nodule, with suppression of the rest of the thyroid gland, suggests a toxic adenoma.

GRAVES' DISEASE

This is the most common cause of hyperthyroidism in iodine replete parts of the world and is characterised by the triad of diffuse toxic goitre, infiltrative ophthalmopathy and infiltrative dermopathy. It is a part of the spectrum of autoimmune thyroid disease which also includes Hashimoto's thyroiditis and atrophic thyroiditis. Peak presentation occurs in the 3rd and 4th decades, while the disease is rare in the first decade and in the elderly. While data from the Western world suggests a female: male ratio of 7-10:1, most reports from India describe only a 2- to 3-fold excess of female disease. The immunopathogenesis of Graves' disease involves the formation of autoantibodies which stimulate the TSH-receptor and can activate adenylate cyclase as TSH agonists. Evidence for genetic susceptibility to Graves' disease is provided by a high concordance rate in monozygotic twins and is possibly mediated through the HLA and CTLA-4 locus. It is currently believed that immune response directed against an antigen common to the thyroid and orbital tissue or skin can be responsible for ophthalmopathy and dermopathy respectively. Precipitation of autoimmunity may be caused by infection and stress, though this has never been unequivocally proven.

Clinical Features Specific to Graves' Disease

In addition to those common to all causes of thyrotoxicosis, certain clinical features are observed exclusively in Graves' disease due to its autoimmune aetiology.

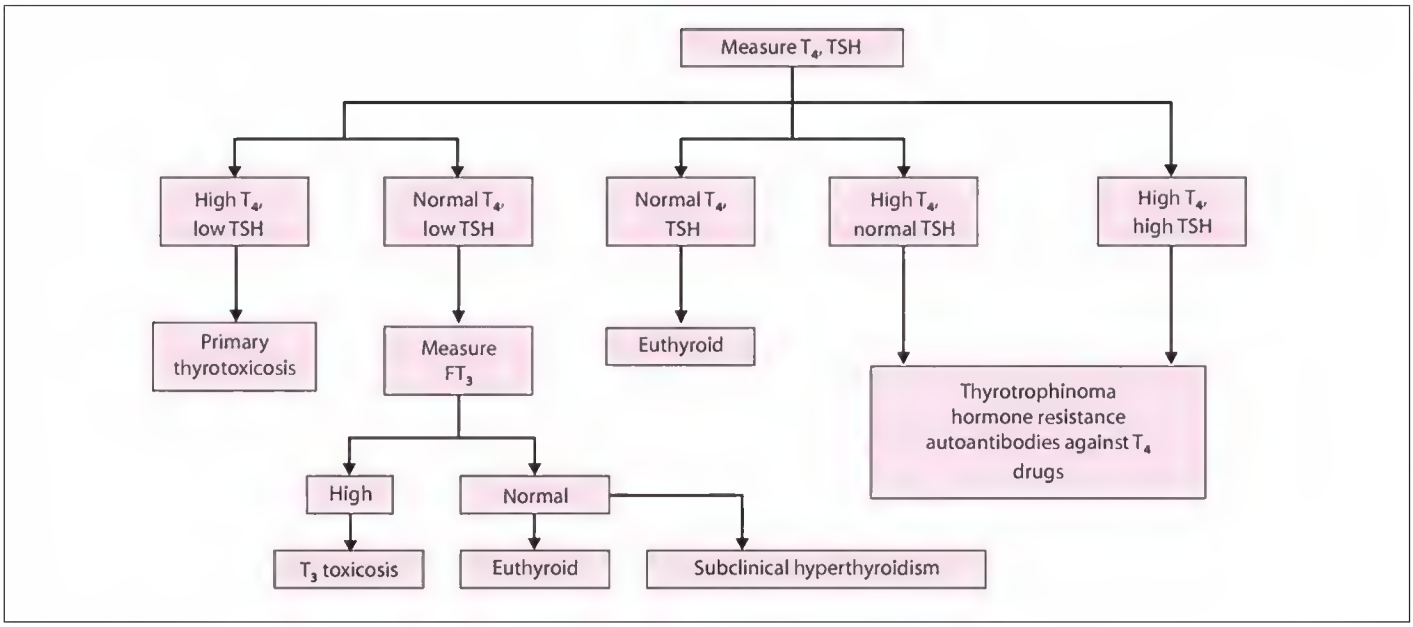


Figure 2: Approach to a patient with clinical features suggestive of thyrotoxicosis.

Coeliac disease and gastric achlorhydria may coexist with Graves' disease. Up to 3% patients may have pernicious anaemia. Myasthenia gravis may occur in approximately 1% of patients with Graves' disease, while 3% to 5% of patients with myasthenia may have Graves' disease.

Infiltrative ophthalmopathy

Extraocular and orbital adipose tissue are inflamed and swollen by the accumulation of glycosaminoglycans (GAGs) secreted by fibroblasts under influence of cytokines. Smoking is considered an important risk factor for development of ophthalmopathy in Graves' disease. Early symptoms include foreign body sensation, conjunctival congestion and periorbital swelling. Exophthalmos, which can be asymmetric, may prevent eyelid closure during sleep, a condition called lagophthalmos. Diplopia due to extraocular muscle involvement, corneal ulceration due to exposure keratitis and loss of vision are extreme manifestations. The American Thyroid Association has classified thyroid-associated ophthalmopathy (**Table 3**), which can be remembered by the mnemonic NOSPECS based on the first letter of each category.

Table 3: The NOSPECS Classification of Thyroid Associated Ophthalmopathy

Class	Description
N	No eye symptoms or signs
O	Only signs, no symptoms (upper eye lid retraction, stare, lid lag, proptosis <22 mm)
S	Soft tissue involvement (signs and symptoms)
P	Proptosis >22 mm
E	Extraocular muscle involvement
C	Corneal involvement
S	Sight loss (optic nerve involvement)

An overall activity score (0 to 7) is helpful in the follow-up of such patients and can be determined by assigning 1 point each for the presence of spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, or eyelid oedema or fullness.

Infiltrative dermopathy

This occurs in 5% to 10% of white patients with Graves' disease and is invariably accompanied by severe ophthalmopathy. It is rarely reported in Indian patients with Graves' disease. Lesions are non-pitting, indurated areas of skin on legs commonly on shins (pretibial myxoedema), but can occur at other sites, often as nodular lesions (**Figure 3**). Clubbing has been reported in long standing disease and is called thyroid acropachy. The hypermetabolic state leads to axial bone destruction, presumably secondary to enhanced osteoclast activity.



Figure 3: Severe dermopathy.

Laboratory investigations in Graves' disease

Like all causes of thyrotoxicosis, Graves' disease is associated with elevated T_4 and T_3 and suppressed TSH. Elevation of T_3 is proportionately to a greater extent than T_4. TPO antibodies are present in 80% patients. Thyroid scan will show a diffusely enlarged gland with uniformly increased radiotracer uptake. By definition, TSH-receptor autoantibody should be present in all patients, though they are not recommended for routine clinical use. CT or MRI of the orbits usually reveal thickening of extra-ocular muscles with sparing of tendons.

Treatment

Three main therapeutic modalities are available for the management of Graves' disease: medical therapy with antithyroid drugs; radioactive iodine ablation; and surgery.

Medical therapy

Thionamides (methimazole, carbimazole and propylthiouracil) are the preferred agents used for medical therapy. All these agents inhibit thyroid hormone synthesis, with the organification step being most sensitive to their action. In addition, propylthiouracil (PTU) also inhibits extrathyroidal conversion of T_4 to T_3. Carbimazole is entirely converted to methimazole (half-life is 6 hours), which is the active agent. The usual dose for carbimazole is 30 to 45 mg/day, initially given in three divided doses. Once euthyroid state is achieved, the dose can be gradually reduced to a maintenance dose of approximately 10 mg, which can be given as a single daily dose. PTU, due to a shorter duration of action (half-life is 1.5 hours), is given as a dose of 50 to 100 mg at 8 hourly intervals. If T_4 levels do not fall after 4 to 8 weeks, the dose should be increased. Later dose is adjusted to maintain T4 levels in normal range. There is no consensus about the duration of treatment which is usually given for 12 to 18 months. In addition to the titration regimen described above, an alternate regimen is the block-replacement regimen, which is currently not preferred because of a concern of increase in side effects.

The likelihood of long-term remission with a full course of antithyroidal agents is about 50%. Once a patient relapses, there is no advantage in repeating another full course of medical therapy because the chance of a relapse is nearly 100% in this situation.

Minor side effects including cutaneous reactions, arthralgia, and gastrointestinal adverse events, occur in approximately 5% of patients and tend to be mild or transient. Agranulocytosis is the most feared adverse effect requiring drug withdrawal. Recently, serious hepatic adverse effects including acute liver failure have been reported with propylthiouracil in children.

Current guidelines recommend that methimazole be used as the first line therapy in treatment of patients with hyperthyroidism and that the use of propylthiouracil should be reserved for individuals in the first trimester of pregnancy, patients with life-threatening thyrotoxicosis or thyroid storm and patients who have experienced adverse effects of methimazole (except agranulocytosis).

Other agents occasionally used to treat hyperthyroidism include lithium, which decreases thyroid hormones release. Dexamethasone, in a dose of 2 mg 6 hourly, inhibits secretion of hormone, T_3 neogenesis and has immunosuppressive effects. It has been used in patients with severe thyrotoxicosis or thyroid storm. Inorganic iodine (as in Lugol's solution or SSKI) acutely reduces the synthesis and release of T_4 and T_3, and also reduces the vascularity of thyroid gland. Iodine is used to prepare patient rapidly for surgery or as an adjunctive measure in patient with thyroid storm. Typical doses are Lugol's solution 3 to 5 drops tid and SSKI one drop tid. Iodine containing medications like sodium ipodate and iopanoic acid have also been used in those with side effects to thionamides.

Symptomatic therapy with beta-adrenergic antagonists is used to relieve symptoms like palpitations, tremors and anxiety. Propranolol (20 to 40 mg qid) or atenolol (25 to 50 mg OD) are the preferred agents.

Radioactive iodine ablation

Pregnancy should be excluded immediately before RAI therapy is planned in potentially fertile women. Thionamide therapy should be stopped at least 3 to 7 days prior to RAI therapy. In recent years, the trend is favouring a simple fixed dose regimen. Most patients with Graves' disease are treated with 5 to 10 mCi. These doses are effective in 90% to 95% of patients. Even with small doses of radioiodine, permanent hypothyroidism will occur in about 40% patients within 10 years. Pregnancy should be deferred for at least 6 months after I^{131} ablation. In patients with moderate to severe Graves' ophthalmopathy, RAI therapy may worsen the eye disease and thus shall be avoided. If RAI therapy is used in such patients, they should stop smoking and receive a course of oral corticosteroids immediately after the radioiodine treatment.

Surgery

Surgery is usually preferred in patients with very large goitre causing compressive symptoms or patients with significant eye involvement, or in those having severe adverse reaction to antithyroid drugs. Surgery is also indicated if there are suspicious or proven malignant nodules. Patients should be euthyroid before surgery to decrease the risk of arrhythmias during induction of anaesthesia and risk of post-operative thyroid storm. The surgical procedure of choice is bilateral subtotal thyroidectomy taking care to avoid potential complications, hypoparathyroidism and recurrent laryngeal nerve injury and bleeding into the operative site.

OTHER CAUSES OF THYROTOXICOSIS

Two other important causes, in addition to Graves' disease, are toxic MNG and toxic adenoma.

Toxic Multinodular Goitre (MNG)

Toxic MNG is usually reported in a person with a long-standing MNG, in which one or more nodules become functionally autonomous. It usually occurs in older individuals, 4th-5th decade, and in addition to the usual features of thyrotoxicosis may also have obstructive symptoms due to a large goitre. Further, cardiovascular manifestations may be prominent because of the older age of patients. Patients with mild toxic MNG are also at risk for developing iodine-induced thyrotoxicosis (Jod-Basedow effect) after exposure to intravenous contrast or treatment with amiodarone.

Radioisotope scans show a combination of hyper- and hypofunctioning areas. Medical therapy should be used to attain euthyroidism following which either radioiodine ablation (25 to 30 mCi) or surgery should be performed as definitive therapy.

Toxic Adenoma

The disorder is usually caused by a benign single adenoma that is palpable as a solitary nodule and hence is sometimes referred to as *hyperfunctioning solitary nodule* or *toxic nodule*. The basic pathogenesis of a large fraction of these tumours, is one of several somatic point mutations in the TSHR gene, commonly in the third transmembrane loop. This condition occurs in a younger age group than does toxic multinodular goitre, typically in patients in their 30s or 40s.

Patients develop features of thyrotoxicosis only when the adenoma achieves a diameter of 2.5-3 cm. Radioisotope scan shows a hyperfunctioning 'hot' nodule, with suppression of the remainder of the gland. Radioiodine ablation of the adenoma is the treatment of choice, since usually the remaining thyroid tissue does not take up radioiodine. Larger adenomas may require surgery.

Figure 4 provides the approach to making an aetiological diagnosis in a patient with thyrotoxicosis.

Thyroid Storm (Thyrotoxic Crisis)

Thyroid storm is a life-threatening condition, with features of severe thyrotoxicosis, including fever (38.5°C), tachycardia out of proportion to the fever, confusion, agitation, nausea and vomiting, hypertension, congestive cardiac failure, increased transaminases, with biochemical evidence of thyrotoxicosis.

It is unusual for untreated hyperthyroidism to present as thyroid storm, as there are usually precipitating events such as surgery, sepsis, burns injury, cardiovascular accident, parturition, status epilepticus, I^{131} treatment.

The treatment principles are to decrease the production and release of thyroid hormones, to block the effects of circulating T_4 and T_3, to deal with the underlying precipitants, and to provide general support.

Large doses of antithyroid drug (PTU 300 to 400 mg every 4 hourly) are given by mouth, by nasogastric tube, or if necessary, per rectum. PTU is preferred to methimazole due to its additional effect of inhibiting the peripheral conversion of T4 to T_3. SSKI (5 drops every 6 hours), ipodate (500 mg twice daily) or Lugol's solution (3 to 5 drops tid) acutely retard the release of hormone from the thyroid gland.

If patients are allergic to iodine, lithium carbonate (300 mg every 6 hours, with twice daily lithium levels checked until a therapeutic dose of 1 mmol/l is attained) can be used instead. Intravenous steroid will also block the conversion of T_4 to T_3 and so dexamethasone 4 mg four times daily intravenous (or hydrocortisone 100 mg four times daily) is recommended. If there are no contraindications to beta-blockers, then the choice is propranolol 80 mg three times daily (orally or via nasogastric tube), or 1mg/min intravenously. If beta-blockers are contra-indicated, the possible alternatives would include calcium channel blockers or digoxin.

Supportive measures include correction of dehydration and hypernatraemia, if present, and administration of glucose. Salicylates should be avoided and hyperpyrexia should be managed with paracetamol, cold sponging, fans or ice packs.

SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism is a condition of chronically suppressed serum TSH levels and normal levels of circulating free thyroid hormone. Subclinical hyperthyroidism may accelerate bone loss in postmenopausal women and is associated with a higher incidence of atrial arrhythmia including atrial fibrillation in elderly patients. It can occur either because of excessive supplementation with thyroxine or because of evolving thyrotoxic state. Treatment by titrating thyroxine therapy should be done to ensure that serum TSH remains in the mid-normal range. In endogenous causes of subclinical hyperthyroidism, therapy should be planned if a resultant tissue effect is evident, such as a low bone mineral density or arrhythmias. In other situations, patients can be followed up to assess disease evolution before committing to any definitive therapy.

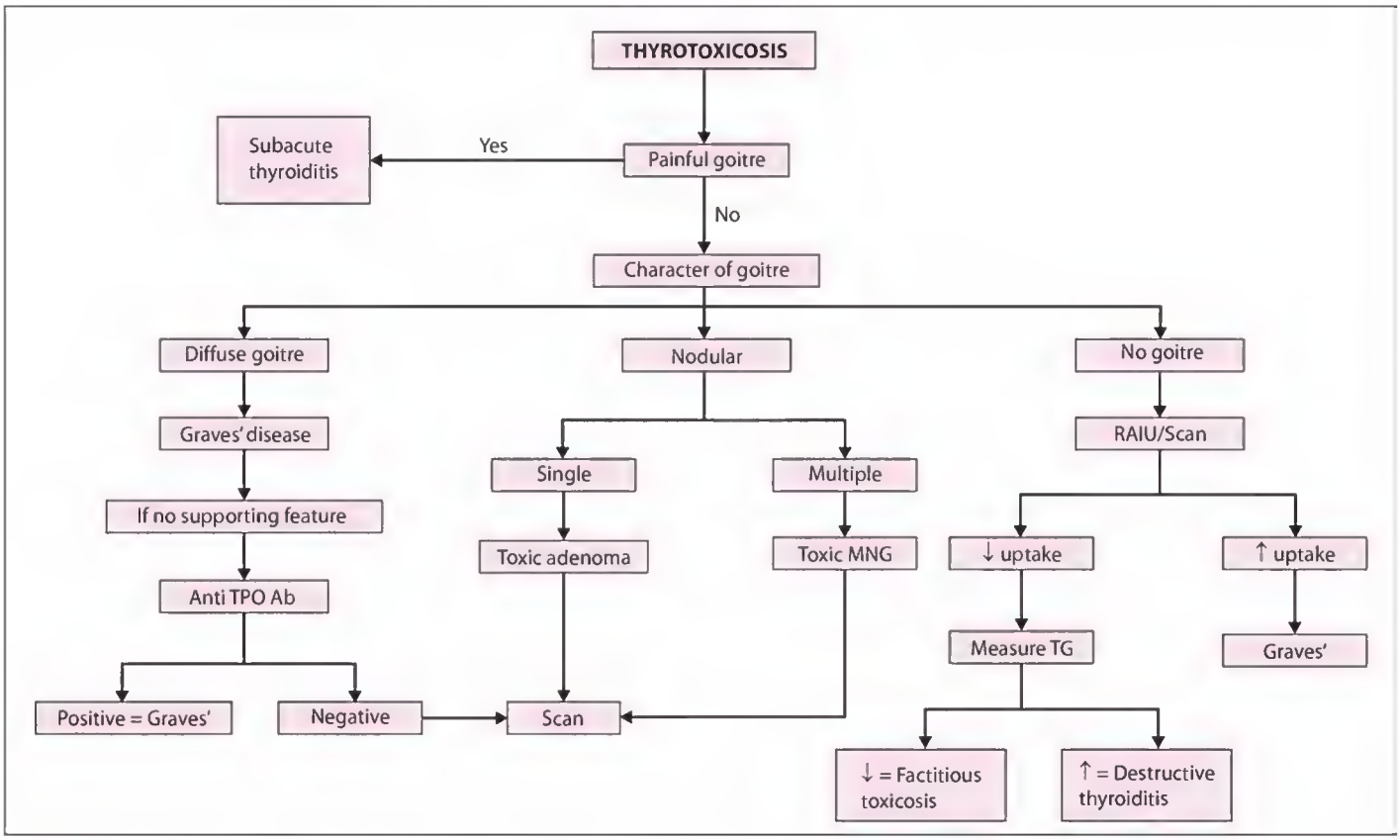


Figure 4 : Approach to establish aetiology in a patient with thyrotoxicosis.

HYPERTHYROIDISM IN PREGNANCY

If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology during pregnancy and hyperemesis gravidarum, which may also be associated with suppressed TSH with or without elevated serum FT_4 levels. Differentiation of Graves' disease from gestational thyrotoxicosis is supported by evidence of autoimmunity, a goitre, and presence of TSH receptor antibodies.

Rise in TBG levels during pregnancy, results in increase in total T4 levels. Therefore either free T_4 levels should be measured or one can use the normal (non-pregnant) range for the serum total T_4 concentration multiplied by 1.5.

Medical therapy with antithyroid drugs (ATDs) is advocated at the lowest possible dose to ensure a euthyroid state with FT_4 near the upper limit of normal. As methimazole may be associated with congenital anomalies propylthiouracil should be used as a first-line drug, especially during first-trimester organogenesis. TSH receptor-stimulating antibodies freely cross the placenta and can stimulate the foetal thyroid. These antibodies should be measured before pregnancy or by the end of the second trimester in mothers with current Graves' disease, or with a history of Graves' disease.

In women with elevated TRAb or in women treated with ATD, foetal heart rate monitoring, and assessment of foetal thyroid size by ultrasound should be performed to assess foetal thyroid status. Surgery is best avoided, but if it becomes essential it should be performed in the second trimester. Neither radioactive iodine ablation nor iodine/iodine-containing agents should be considered for therapy in pregnancy.

HYPOTHYROIDISM

Reduced production of thyroid hormone is the central feature of the clinical state termed *hypothyroidism*.

Primary hypothyroidism is due to disease of thyroid itself. It accounts for approximately 99% of cases, with < 1% being due to TSH deficiency known as central or secondary hypothyroidism. Primary hypothyroidism can be further subclassified depending on whether it is associated with goitre or an atrophic gland, and each of these entities can either be congenital or acquired in aetiology (**Table 4**).

Clinical Features

In adult hypothyroidism, clinical features can largely be explained by the reduced metabolic rate and deposition of glycosaminoglycans (GAG) in different body compartments. Symptoms of hypothyroidism develop gradually. The term myxoedema refers to the boggy appearance of the skin and subcutaneous tissues in the patients in a severe hypothyroid state. Peripheral manifestations of hypothyroidism are less manifest in patients with secondary hypothyroidism.

Skin is pale and cool, and reduction in sweat and sebaceous secretion causes dryness and coarseness. Capillary fragility causes easy bruisability. Scalp and body hair become dry and brittle and tend to fall. GAG deposition in the pharynx and larynx contributes to hoarseness of voice.

Cardiovascular involvement includes decreased cardiac output, narrowing of pulse pressure and increased systemic vascular resistance causing diastolic hypertension and decrease in exercise tolerance. Pericardial effusion may occur in severe primary hypothyroidism, while a small heart size is common in central hypothyroidism. ECG changes include sinus bradycardia and low voltage complexes with ST-T wave abnormalities. Cold intolerance occurs due to diminished blood supply and vasoconstriction. Pleural effusion and obstructive sleep apnoea may occur as well.

Table 4: Causes of Hypothyroidism

Primary hypothyroidism with goitre

Acquired
- Hashimoto's thyroiditis
- Iodine deficiency disorders
- Goitrogen exposure
- Antithyroid drug treatment

Congenital
- Iodide transport or utilisation defect
- Defects in thyroid hormonogenesis

Primary hypothyroidism with atrophic gland

Acquired
- Atrophic thyroiditis
- Post-ablative hypothyroidism (radioiodine therapy, surgery)

Congenital
- Thyroid agenesis
- Thyroid dysplasia

Transient primary hypothyroidism

After thyroiditis: silent, subacute or post-partum thyroiditis

Central hypothyroidism

Acquired
- Pituitary or hypothalamic disease, e.g. tumour, haemorrhage, granulomatous disease, hypophysitis

Congenital
- TSH deficiency or TSH receptor defects

Resistance to thyroid hormone action
- Generalised resistance to thyroid hormone action

Modest weight gain despite reduced appetite and constipation, due to reduced gut peristalsis, are common complaints. Myxoedema megacolon and myxoedema ileus are uncommon. Neuromuscular manifestation include slowed physical and mental functions, lethargy, somnolence, agitation ('myxoedema madness') or depression, deafness, carpal tunnel syndrome and 'hung-up' reflexes may also be present.

In adult women, hypothyroidism may be associated with diminished libido, failure of ovulation, polymenorrhoea, menorrhagia, and reduced fertility. In men, hypothyroidism may cause reduced libido, impotence and oligospermia. These disturbances in the reproductive system are often associated with hyperprolactinaemia (since prolactin is also under the control of TRH) and rarely can also be associated with pituitary enlargement due to thyrotroph hyperplasia. Energy metabolism is reduced leading to a decrease in appetite, cold intolerance, reduced protein synthesis and lipid accumulation (elevated TG and LDL-cholesterol).

A child with congenital hypothyroidism is sluggish and may present with prolonged physiological jaundice, meconium ileus, umbilical hernia, feeding difficulty, dry scaly skin and a large tongue. Unless diagnosed and treated early, irreversible neurological impairment can occur. Severe hypothyroidism in infancy is called cretinism.

During infancy, in addition to constipation, hoarse cry, and somnolence, there is delay in eruption of deciduous teeth and reaching physical and mental milestones. Persistence of untreated hypothyroidism will cause impaired linear growth, resulting in dwarfism and delay in closure of fontanelles. X-ray pelvis will reveal dysgenesis of femoral capital epiphysis, which is pathognomonic for hypothyroidism in infancy and childhood.

Clinical features of hypothyroidism beginning in childhood, juvenile hypothyroidism, are a combination of those seen in infantile and adult hypothyroidism. Retarded linear growth, delayed sexual maturation and poor intellectual performance are important.

Diagnosis

Plasma TSH is the best initial diagnostic test, and a normal value excludes primary hypothyroidism. Low T_4 with elevated TSH confirms the diagnosis of primary hypothyroidism, while normal T_4 with isolated elevation of TSH leads to the diagnosis of subclinical hypothyroidism. Individuals with subclinical hypothyroidism who have elevated anti-TPO antibodies are more likely to progress to overt hypothyroidism than antibody negative individuals.

Central hypothyroidism is characterised by a low T_4 and an inappropriately normal TSH. Evaluation for other pituitary hormone deficiency is recommended to confirm the diagnosis and guide therapy. Imaging to look for pituitary-hypothalamic disease using MRI should also be performed.

In severe non-thyroidal illness also, total plasma T_4 and T_3 are low. These may revert to within normal range in 3 to 6 months after recovery from illness.

ACQUIRED CAUSES OF PRIMARY HYPOTHYROIDISM

Hashimoto's Thyroiditis/Chronic Lymphocytic Thyroiditis

It is the most common cause of goitrous hypothyroidism in iodine sufficient parts of the world. It is more common in women. It is characterised by intrathyroidal lymphocytic infiltration with germinal centre formation, follicular damage or destruction and fibrosis. Goitre develops gradually, and is firm in consistency. Presence of anti-TPO antibodies and thyroglobulin autoantibodies favours the diagnosis. History of autoimmune endocrinopathies and other autoimmune diseases like rheumatoid arthritis should be ascertained in the individual and first degree relatives. Immunogenetic predisposition, exposure to excess iodine, therapy with interferon and pregnancy or post-partum state are known risk factors for Hashimoto's thyroiditis.

Iodine Deficiency Disorders

(Already Discussed)

Primary Idiopathic Hypothyroidism

Several authors use the term autoimmune thyroiditis to include the goitrous (Hashimoto's thyroiditis) and non-goitrous variants (primary idiopathic hypothyroidism/atrophic thyroiditis). The lack of goitre in atrophic thyroiditis is attributed to antibodies that block the action of TSH. Clinical manifestations are the same as for Hashimoto's thyroiditis except for the absence of goitre.

Post-ablative Hypothyroidism

Hypothyroidism after thyroidectomy depends on the extent of the surgery. The incidence is 100% after total/near total thyroidectomy for cancer but can also occur with less complete forms of thyroidectomy depending on the amount of tissue left behind. Hypothyroidism after destruction of thyroid tissue with radioiodine is common and is the one established disadvantage of this form of treatment for hyperthyroidism in adults. Its frequency is determined, in large part, by the dose of radioiodine. The incidence of post-radioiodine hypothyroidism increases with time. Even when doses are calculated to render a patient euthyroid, approximately 10% of patients are hypothyroid at the end of the first year and a further 2% to 3% become hypothyroid every year, over the next decade.

Drugs

Lithium and amiodarone are commonly used drugs which are associated with hypothyroidism.

CONGENITAL CAUSES OF PRIMARY HYPOTHYROIDISM

In addition to thyroid agenesis or dysplasia, iodide transport defects (NIS or pendrin mutations) and defects in thyroid hormone genesis can cause goitrous primary hypothyroidism. Pendred's syndrome is characterised by sensorineural hearing loss.

Therapy

Since primary hypothyroidism inevitably requires life long replacement therapy, it is advisable to reconfirm the diagnosis by repeating thyroid function tests, if the clinical features are equivocal, before starting therapy.

Adults

Levothyroxine is the drug of choice and most adult patients require a daily dose of 75 to 150 µg (1.7 µg/kg/day). The initial dose depends on the degree of hypothyroidism, age and general health status of the patient. Therapy in young healthy subjects can be initiated with the full dose. In elderly patients, average replacement dose is slightly lower and treatment should be started with a small initial dose. The recommended starting dose in the elderly is 25 µg/day, which is then increased by 12.5 to 25 µg at monthly intervals. In pregnancy, thyroxine requirement increases by 25 to 50%. If any patient is requiring a dose >150 µg/day, compliance should be assessed. The dose should be given as a single dose, on an empty stomach, in the morning. Absorption of thyroxine is hampered by iron preparations and antacids containing aluminium and these preparations should not be given at the same time as thyroxine. Aim of treatment is to keep TSH in the mid-normal range. Keeping in mind the time required by the pituitary-thyroid axis to reset, TSH should be measured no sooner than 6 to 8 weeks after initiating therapy or making a dose change. Once an individual becomes euthyroid on a stable dose of thyroxine, an annual TSH is adequate for monitoring. Over treatment, as indicated by suppressed TSH levels, should be avoided due to risk of osteoporosis and atrial fibrillation.

Subclinical hypothyroidism may be treated if any of the following are present: goitre, high titres of anti-TPO antibodies or pregnancy. In the absence of these findings, patients may be kept under follow-up, with repeat thyroid function tests at 6 monthly intervals to look for progression to overt hypothyroidism.

Infants and children

A dose of approximately 50 µg/day, is advocated in congenital hypothyroidism with the aim of maintaining T_4 levels at about

10 µg/dL. The pituitary feedback mechanism matures at 2 years of age, and the target of therapy then can be normal TSH level.

Secondary hypothyroidism: Since corticotroph failure may co-exist, glucocorticoid replacement must be initiated before starting T_4 therapy. Monitoring is with serum T_4 levels.

Myxoedema Coma

Myxoedema coma is the ultimate stage of severe long-standing untreated hypothyroidism, most often in elderly subjects and frequently in cold winter months.

Myxoedema coma can be the first presentation of new hypothyroidism, often precipitated by infection, stroke, myocardial infarction, sedative drugs or exposure to cold. Treatment is initiated on the basis of clinical suspicion, especially in non-responsive patients with a history of hypothyroidism, although blood should be taken for thyroid function tests and cortisol first. Initially, the precipitating illness needs to be identified and treated and general supportive treatments instituted. Functional adrenal insufficiency should also be treated with intravenous hydrocortisone.

The important clinical features are altered sensorium (or coma), subnormal temperature, bradycardia, manifestations of severe myxoedema and hypotension. The core temperature must be checked using a low reading thermometer, as the mortality of this condition is related to the severity of the hypothermia.

If intravenous thyroxine is available, a single dose of 500 µg T_4 can replete the hormone pool and can be followed by 100 µg IV daily. Alternatively, 500 µg thyroxine can be administered through a nasogastric tube, followed by 100 to 200 µg/day. Glucocorticoid replacement with IV hydrocortisone (5 to 10 mg/hour) should also be given. No hypotonic fluids should be given. Respiratory support using ventilator may be required. No external heating should be done because it may cause cutaneous vasodilatation and increase the strain on the heart. Despite aggressive intensive care, a high mortality rate of up to 50% is reported.

THYROIDITIS

The term thyroiditis indicates inflammation of the thyroid gland. Causes of thyroiditis include chronic autoimmune (Hashimoto's) thyroiditis, subacute thyroiditis, postpartum thyroiditis, Riedel's thyroiditis, amiodarone-induced thyroiditis (all of the above conditions are painless) and also acute infectious thyroiditis, radiation thyroiditis and traumatic (e.g. surgery, palpation, FNAB), thyroiditis (all of which are painful).

Subacute Thyroiditis (de Quervain's Thyroiditis, Viral Thyroiditis, Granulomatous Giant Cell Thyroiditis)

It is most likely viral in origin. It commonly presents with neck pain, which may radiate to ear or mandible. Hoarseness, dysphagia and signs of thyrotoxicosis may be present. Patients may also complain systemic features like lassitude and weakness. Thyroid gland is very tender and firm. The characteristic feature on histopathological examination is a well developed follicular lesion that comprises of a central core of colloid, surrounded by multinucleate giant cells. On evaluation, ESR is usually high and RAIU is suppressed to extremely low levels (0 to 5%). Serum TSH is suppressed and serum T_4 and T_3 levels are high. This condition is nearly always self-limiting, but can pass through a transient hypothyroid phase before reverting to euthyroidism. Using propranolol 10 to 20 mg, orally 3 to 4 times daily, controls symptoms of thyrotoxicosis. NSAIDs can be used for pain relief, though severe cases may require glucocorticoid therapy.

Postpartum Thyroiditis

Postpartum thyroiditis is the occurrence of thyrotoxicosis, hypothyroidism, and/or thyrotoxicosis followed by hypothyroidism in the first postpartum year in women without overt thyroid disease before pregnancy.

It occurs in 8% to 10% of women in postpartum period and up to 30% of those who were anti-TPO antibody positive in pregnancy. The thyroid gland does not show fibrosis as in Hashimoto's thyroiditis or giant cell infiltration as in subacute thyroiditis. The condition is painless. These patients are very likely to experience a recurrence following a subsequent pregnancy. Course of this disease in majority is self-limiting. The clinical manifestations can include an initial thyrotoxic phase (3 to 6 months after delivery) followed by a hypothyroid phase lasting for a few months before returning to euthyroid state.

Symptomatic treatment with beta-blockers is needed in the toxic phase and thyroxine replacement in the hypothyroid phase. Reassessment of thyroid function tests should be performed after stopping thyroxine therapy, one year after delivery to check for return to the euthyroid state.

Women with a history of postpartum thyroiditis have increased risk of developing permanent primary hypothyroidism in the 5- to 10-year period following the episode of postpartum thyroiditis. An annual TSH level should be performed in these women.

Since hypothyroidism is a potentially reversible cause of depression, women with postpartum depression should be screened for hypothyroidism, even though there is limited evidence supporting an association between postpartum depression and postpartum thyroiditis.

Riedel's Thyroiditis

This rare cause of thyroiditis is characterised by fibrosis of the thyroid and adjacent structures and occurs primarily in middle aged women. Patients usually present with a stony hard, immobile goitre resulting in pressure symptoms due to compression of trachea, oesophagus and recurrent laryngeal nerve. The presence of eosinophils on fine needle aspiration specimens has been demonstrated histologically, suggesting a unique autoimmune response to fibrous tissue.

One-third of the patients have hypothyroidism. When symptoms of obstruction are present, surgical removal of gland is indicated.

Glucocorticoids have been used for treatment because they reduce inflammation. Tamoxifen, 20 mg twice daily, has been successful in some patients. The proposed mechanism of action is the induction of transforming growth factor beta (a potent inhibitor of fibroblast proliferation).

Non-Toxic Goitre

Simple, non-toxic or euthyroid goitre represents any thyroid gland enlargement that is not associated with either hyperthyroidism or hypothyroidism and which does not occur

due to inflammation or neoplasia. The diagnosis of euthyroid gland is based on palpation and imaging of thyroid gland or on evaluation of thyroid functions. Thyroid enlargement may be diffuse or multinodular or there may be a solitary nodule. Each nodule contains a collection of thyroid follicles. Larger nodules may develop a fibrous capsule by compressing surrounding parenchyma.

Most affected patients do not exhibit clinical symptoms and signs of thyroid dysfunction and usually seek medical attention for thyroid enlargement. Large goitre may cause symptoms of dysphagia, dysphonia, or hoarseness by compressing local structures like oesophagus, trachea, or the recurrent laryngeal nerve.

Suspicion of malignancy is higher if the nodule occurs in the very young or elderly, shows rapid progression in size, is hard in consistency, has restricted mobility, associated lymphadenopathy or hoarseness.

The incidence of multinodular goitre (MNG) is more common in women and increases with age. Most patients are asymptomatic and do not require any therapy. Intervention is required if hyperthyroidism results (toxic MNG) or an enlarging MNG causes pressure symptoms. Surgery is the best option for these situations. A dominant nodule in a MNG has the same biological behaviour and chance of harbouring a malignancy as a solitary thyroid nodule.

Investigations

Fine needle aspiration cytology

Fine needle aspiration cytology (FNAC) is the investigation of choice in nodular goitre. In case of an inconclusive aspiration, a repeat FNAC should be performed. If even that is inconclusive, an ultrasound-guided FNAC increases the likelihood of reaching a diagnosis. Multiple sites should be aspirated to improve the diagnostic yield. A satisfactory specimen contains at least five or six groups of 10 to 15 well-preserved cells.

Thyroid function tests

A suppressed TSH, with or without elevated T_4 is suggestive of an autonomously functioning nodule/s.

Radionuclide scan

A pertechnetate scan is often used to make a functional diagnosis of a nodular goitre. Nodule showing no uptake of radioactivity is called a 'cold' nodule, while that with an uptake similar to the rest of the thyroid is called a 'warm' nodule. Nodules which take up increased amount of radioactivity along with suppressed uptake in the rest of the gland are called 'hot' nodules. Initially it was considered that only 'cold' nodules harboured malignancy. However, current evidence suggests that all types of functional nodules can contain malignancy.

Ultrasound

This is a useful modality to differentiate solid from cystic nodules. A purely cystic nodule is unlikely to contain a neoplasm. However, most nodules have both a solid and a cystic component. Ultrasound can be used to guide the FNAC from the solid component of such nodules.

Management of a solitary thyroid nodule (Figure 5)

'Hot' nodules with a suppressed TSH should be treated with radioiodine ablation or with surgery if they are large in size. Other emerging treatment alternatives are percutaneous ethanol and laser treatment.

If FNAC is suggestive of a malignancy or is suspicious, patient should be managed surgically with appropriate follow-up. If the

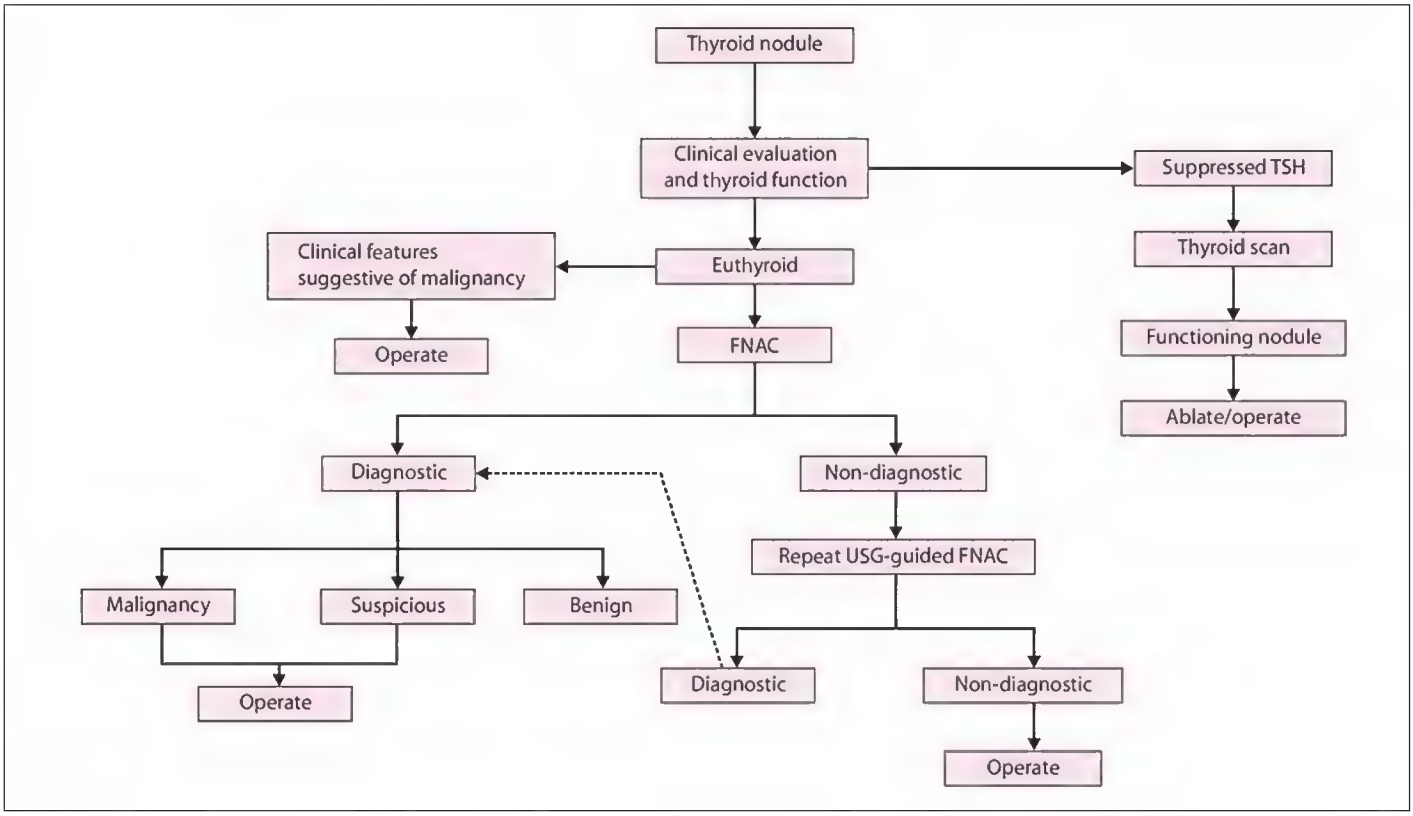


Figure 5: Approach to a patient with a solitary thyroid nodule.

FNAC suggests a benign disease, the patient can be followed up without any intervention. Suppressive regimens with levothyroxine have been tried with non-significant trend towards 50% reduction in nodule size. The disadvantage with this approach is the likelihood of causing subclinical thyrotoxicosis and its attendant complications.

Table 5: Classification of Thyroid Neoplasia

Primary epithelial tumours
- Tumours of follicular cells
  - Benign tumours: Follicular adenoma
  - Malignant tumours: Papillary carcinoma, follicular carcinoma, poorly differentiated cancer, undifferentiated cancer (anaplastic cancer)
- Tumours of C cells
  - Medullary thyroid cancer
- Mixed tumours
  - Mixed medullary–follicular cancer

Non-epithelial tumours
- Lymphomas
- Others

If FNAC is non-diagnostic, even after an ultrasound-guided aspirate, surgery is the preferred option.

Thyroid Neoplasia

Thyroid tumours are the most common endocrine neoplasm. Most of these are benign hyperplastic (or colloid) nodules or benign follicular adenomas but approximately 5% to 10% of these are carcinomas. The likelihood of malignancy is high if the lesion occurs in the young (<20 years) or elderly (>70 years), male, history of external neck radiation in childhood/adolescence, recent onset of compressive features and a family history of thyroid cancer. FNAC is the investigation of choice, as described in the section above. A classification of thyroid neoplasia is provided in **Table 5**.

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10.7 Disorders of Parathyroid Glands

Ambrish Mithal, Beena Bansal

There are four parathyroid glands located posteromedial to the thyroid gland. The upper two glands develop from the fourth branchial arch, while the lower two develop from the third branchial arch, but migrate caudally with the thymus. Anomalies in migration may result in glands in ectopic positions, like the mediastinum.

There are two types of cells in parathyroid glands—chief cells, which secrete parathormone (PTH) and oxyphil cells, which are considered non-secretory.

PARATHORMONE

PTH is a single chain polypeptide with 84 amino acids. The principal role of PTH is tight regulation of extracellular calcium levels.

Parathyroid glands have calcium sensing receptors (CaSRs) on the cell membrane and vitamin D receptors in the nucleus. The parathyroid gland is exquisitely sensitive to calcium—it is said that that the chief cell can virtually 'sniff' calcium!

Point mutations associated with loss of function cause a syndrome, familial hypocalciuric hypercalcaemia (FHH). On the other hand, gain-of-function mutations cause autosomal dominant hypocalcaemia hypercalciuria (ADHH).

Low calcium and low vitamin D will stimulate PTH synthesis, secretion and also increase number of chief cells. Prolonged hypocalcaemia and hypovitaminosis D can therefore lead to secondary hyperparathyroidism and enlarged parathyroid glands.

PTH ACTIONS

PTH acts through cell surface receptors PTH1R and PTH2R. PTH1R is the classic PTH receptor expressed in bone and kidney.

Bone

(a) PTH releases calcium from bone and increases remodelling.
   i. It acts directly on the osteoblasts through its receptors. The action on osteoclasts is indirect (through cytokine release from osteoblasts which then stimulate osteoclasts).
   ii. Continuous exposure to PTH (as in hyper-parathyroidism) increases osteoclast mediated bone resorption leading to osteoporosis. On the other hand, intermittent exposure to PTH increases net bone formation and therefore synthetic PTH (1-34) called teriparatide is given for treating osteoporosis.

Kidneys

(a) PTH increases calcium reabsorption in renal tubules and increases phosphorus excretion.

(b) It stimulates 1-α hydroxylase which converts 25(OH) vitamin D to active $1,25(OH)_2$ vitamin D, which in turn stimulates calcium absorption from the gut.

PRIMARY HYPERPARATHYROIDISM

This is a disorder characterised by increased PTH secretion by the gland. The causes are outlined in **Table 1**.

Table 1: Causes of Primary Hyperparathyroidism

Adenomas
- Solitary
- Multiple
  - Isolated
  - Part of hereditary syndromes
    - MEN-1
    - MEN-2A
    - Hyperparathyroidism-jaw tumour syndrome (HPT-JT)

Chief cell hyperplasia

Clinical Features

The effects of primary hyperparathyroidism are mainly seen on bone and kidneys. *Typically, in India, the disease very much resembles the description by Fuller Albright in 1930s—a disease of 'bones, stones and groans'. This is thought to be related to the widespread vitamin D deficiency in Indians. Some form of bone involvement is seen in 80% to 100% of cases in India.* Patients present with bone pains, skeletal deformities and pathologic fractures. The distinctive bone manifestation othef primary hyperparathyroidism seen in 50% to 90% of Indian patients is brown tumours (on radiograph) or osteitis fibrosa cystica (histologically). Clinically palpable bony swellings may be present. On histopathology, the pathognomonic features are increase in giant multinucleated osteoclasts in scalloped areas on the bone surface (Howship's lacunae) and a replacement of the normal cellular and marrow elements by fibrous tissue. Other radiological findings include subperiosteal resorption of phalanges and salt and pepper appearance of the skull.

Kidney involvement, due to deposition of calcium in renal parenchyma (nephrocalcinosis) is seen in 5% to 10% cases and recurrent nephrolithiasis in 10% to 40% of Indian patients.

Proximal muscle weakness and atrophy of muscles may be so striking as to suggest a primary neuromuscular disorder.

The patient who suffers a combination of severe bone disease and profound myopathy can be rendered immobile and has been referred to as a 'parathyroid cripple'.

Neuropsychiatric manifestations, mild gastrointestinal symptoms, pancreatitis, chondrocalcinosis, pseudogout, pancreatitis and hypertension are associated with primary hyperparathyroidism.

Rarely, the patient may present in hypercalcaemic crisis. The symptoms are general malaise, anorexia, polyuria, thirst, vomiting, constipation, abdominal pain, depression, confusion, progressing to stupor and coma.

In the West (North America and Europe), the majority of patients with hyperparathyroidism are asymptomatic and diagnosed during routine biochemical screening. Such cases are now increasingly seen in India as well.

Diagnosis

In a patient with hypercalcaemia, the diagnosis is established by demonstrating elevated PTH levels. With the exception of lithium, thiazide use and familial hypocalciuric hypercalcaemia (FHH), virtually all other causes of hypercalcaemia are associated with suppressed PTH (**Table 2**).

Table 2: Differential Diagnosis of Hypercalcaemia

High PTH
- Primary hyperparathyroidism
- Lithium therapy
- Familial hypocalciuric hypercalcaemia

Hypercalcaemia of malignancy
- Local osteolytic hypercalcaemia
  - Multiple myeloma
  - Breast cancer
- Humoral hypercalcaemia of malignancy

High vitamin D levels
- Vitamin D intoxication
- Increased $1,25(OH)_2D$: sarcoidosis and other granulomatous diseases
- Idiopathic hypercalcaemia of infancy

High bone turnover
- Hyperthyroidism
- Immobilisation
- Thiazides
- Vitamin A intoxication

Renal failure
- Severe secondary hyperparathyroidism
- Aluminium intoxication
- Milk-alkali syndrome

Management

Management of hypercalcaemic crisis

If a patient presents with hypercalcaemic crisis, immediate management of hypercalcaemia followed by definitive treatment of hyperparathyroidism is needed.

1. *Hydration, increased salt intake, mild and forced diuresis:*

   Many hypercalcaemic patients are dehydrated because of vomiting, and/or hypercalcaemia induced polyuria. The first principle of treatment is to restore normal hydration. Calcium levels start decreasing within hours.

   Under life-threatening circumstances, up to 6 litres of isotonic saline plus frusemide in doses up to 100 mg every 1 to 2 hours may be required. Careful monitoring of central venous pressure and serum electrolytes should be done.

2. *Bisphosphonates:*

   IV pamidronate 30 to 90 mg or zolendronate 4 to 8 mg reduces calcium levels over 24 to 48 hours. Flu like reactions are common. Rarely, these drugs can precipitate renal dysfunction, so proper hydration is essential.

Management of symptomatic primary hyperparathyroidism

Parathyroidectomy is the treatment of choice in all symptomatic cases after preoperative localisation by ^{99m}Tc-sestamibi scintigraphy or ultrasonography.

Postoperative management: Serum calcium declines within 24 hours after successful surgery. Acute postoperative hypocalcaemia is seen if:

- Severe bone disease is present preoperatively
- The patient is vitamin D deficient
- There is associated hypomagnesaemia
- There is injury to all the parathyroid glands or their blood supply during surgery.

Parenteral calcium replacement is indicated if:

- There are signs of hypocalcaemia; or
- Serum calcium is less than 8 mg/dL

An infusion of 0.5 to 2 mg/kg/h of 1 mg/mL solution of calcium gluconate in dextrose (not saline) usually suffices to relieve symptoms.

Magnesium deficiency impairs the secretion of PTH, so hypomagnesemia should be corrected whenever detected.

Management of asymptomatic primary hyperparathyroidism

The National Institutes of Health (NIH) sponsored Third Workshop in 2009 recommends surgery only if significant hypercalcaemia, renal dysfunction or osteoporosis is present (**Table 3**). It is also recommended in young individuals and in whom medical surveillance would be difficult. All other cases should be appropriately monitored (**Table 4**).

Table 3: Guidelines for Parathyroid Surgery in Asymptomatic Primary Hyperparathyroidism (PHPT)

- Serum calcium 1 mg/dL above upper limit of normal
- Creatinine clearance <60 mL/min
- Bone mineral density T-score < -2.5 at any site and/or a previous fragility fracture
- Age <50 years
- Patients in whom medical surveillance is neither desired nor possible

Table 4: Asymptomatic Primary Hyperparathyroidism Patients Who Do Not Undergo Parathyroid Surgery

Asymptomatic patients should be monitored regularly:
- Serum calcium biannually
- Serum creatinine annually
- Bone density every 1 to 2 years (lumbar spine, hip, forearm)

Bisphosphonates can be given to individuals with PHPT for whom skeletal protection is the primary reason for intervention whereas the calcimimetic cinacalcet can be used to lower serum calcium and PTH levels during long-term therapy in PHPT.

HYPOPARATHYROIDISM

Hereditary or acquired hypoparathyroidism presents with chronic hypocalcaemia. The differential diagnosis of

hypocalcaemia is given in **Table 5**. The so called 'idiopathic hypoparathyroidism' is probably autoimmune in origin, and autoantibodies to the calcium sensing receptor have been demonstrated in patients, including Indians.

Table 5: Causes of Hypocalcaemia

PTH absent

- Hereditary hypoparathyroidism
  Idiopathic hypoparathyroidism
  Syndromes associated with hypoparathyroidism
  – DiGeorge syndrome, Kenney Caffey syndrome, etc.
  Polyglandular autoimmune type 1 deficiency
  Autosomal dominant hypocalcaemia hypercalciuria (ADHH)
- Acquired hypoparathyroidism
  Surgery
  Radiation
- Hypomagnesemia

PTH ineffective

- Chronic renal failure
- Active vitamin D lacking
  Decreased dietary intake or sunlight exposure
  Defective metabolism
  – Anticonvulsant therapy
  – Vitamin D dependent rickets type 1
  Active vitamin D ineffective
  – Intestinal malabsorption
  – Vitamin D dependent rickets type II
  Pseudohypoparathyroidism

PTH overwhelmed

- Severe acute hyperphosphatemia
  Tumour lysis
  Acute renal failure
  Rhabdomyolysis

Osteitis fibrosa after parathyroidectomy

Clinical Features of Hypoparathyroidism

Symptoms include muscle spasms including the classic carpopedal spasms, facial grimacing and in extreme cases, laryngeal spasm, convulsions and respiratory arrest. Increased intracranial pressure occurs in some patients with long standing hypocalcaemia, often in association with papilloedema. Mental changes include irritability, depression and psychosis. The QT interval on electrocardiogram may be prolonged. Arrhythmias occur and effect of digitalis may be reduced. Intestinal cramps and chronic malabsorption may occur. Chvostek's and Trousseau's signs may be positive. *Trousseau's sign* is the development of carpal spasm when sphygmomanometer cuff is kept inflated at a pressure 30 mmHg above systolic blood pressure for 2 minutes. *Chvostek's sign* manifests as twitching of facial muscles when the facial nerve is tapped anterior to the ear.

Basal ganglia calcification is common and extrapyramidal syndromes are seen occasionally. Brittle hair and nails and lenticular cataracts can also be present. Alopaecia and candidiasis are associated with autoimmune polyglandular failure.

Treatment

Treatment involves replacement with vitamin D or $1,25(OH)_2D_3$ (calcitriol) combined with calcium supplementation. For most patients, 0.5 to 1 µg calcitriol combined with 1g elemental calcium is satisfactory. The wide dosage range reflects the variation encountered from patient-to-patient; precise regulation of dose is required. Since the urinary calcium excretion is high in these patients, care must be taken to avoid excessive urinary calcium excretion after calcium and vitamin D therapy; otherwise, kidney stones can develop. A thiazide diuretic especially along with a low sodium diet is beneficial in mitigating hypercalciuria and easing the daily management of these patients.

PSEUDOHYPOPARATHYROIDISM

Pseudohypoparathyroidism (PHP) is a hereditary disorder characterised by symptoms and signs of hypoparathyroidism, typically in association with distinctive skeletal and developmental defects. The hypoparathyroidism is due to deficient end organ response to PTH. Hyperplasia of the parathyroids, a response to hormone resistance, causes elevation of PTH levels. Four types of PHP exist; PHP I, subdivided into a and b, PHP II and pseudoPHP (PPHP). PHP Ia, PHP Ib and PHP II have hypocalcaemia and hyperphosphataemia. Pseudo-pseudohypoparathyroidism (PPHP) has normal calcium and phosphorus levels.

Albright's hereditary osteodystrophy (AHO) phenotype is present in PHP Ia and PPHP. AHO phenotype consists of short stature, round face, skeletal anomalies (brachydactyly - short fourth and fifth metacarpals and metatarsals) and heterotopic calcification. Basal ganglia calcification is seen in half of these patients.

Treatment of PHP is similar to that of hypoparathyroidism, except that the doses of vitamin D and calcium are usually lower than those required in true hypoparathyroidism.

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10.8 Disorders of Adrenal Glands

Eesh Bhatia, Vijayalakshmi Bhatia

INTRODUCTION

The adrenal glands are divided into two major parts: the cortex and medulla. In this chapter only function and disorders of the adrenal cortex will be considered.

The adrenal cortex secretes three main sets of hormones: the glucocorticoids (cortisol), mineralocorticoids (aldosterone) and androgens (dehydroepiandrosterone, DHEA). The steroid hormones are synthesised from cholesterol through a series of enzymatically catalysed steps. The enzymes are differentially expressed in differing zones of the cortex. Thus, the outermost zona glomerula secretes mineralocorticoids, while the remaining zones (fasiculata and reticularis) secrete cortisol and androgens. A simplified diagram showing the synthesis of the adrenal hormones is shown in **Figure 1**. Cortisol is required for an adequate stress response, intermediary metabolism and immune functions. Aldosterone regulates plasma volume, blood pressure and electrolytes. The adrenal androgens are important for secondary sexual characteristics in females.

Glucocorticoids

The synthesis of cortisol is regulated by adrenocorticotrophin hormone (ACTH), which is synthesised and stored in corticotrophes of the anterior pituitary. The secretion of ACTH is regulated by three influences: positive signals [from hypothalamic hormones, corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP)], extrinsic signals (e.g. stress) and negative feedback by cortisol (**Figure 2**). Through signals from the hypothalamus, ACTH (and hence cortisol) is secreted with a circadian rhythm, being highest in the early morning and lowest at midnight. Cortisol exerts a feedback effect both at the level of the pituitary and the hypothalamus. Thus, a deficiency of cortisol resulting from an enzyme block or destruction of the adrenal gland leads to an elevation of ACTH.

Aldosterone

While aldosterone secretion is increased by ACTH in the short-term, its regulation is predominantly under the effect of the renin-

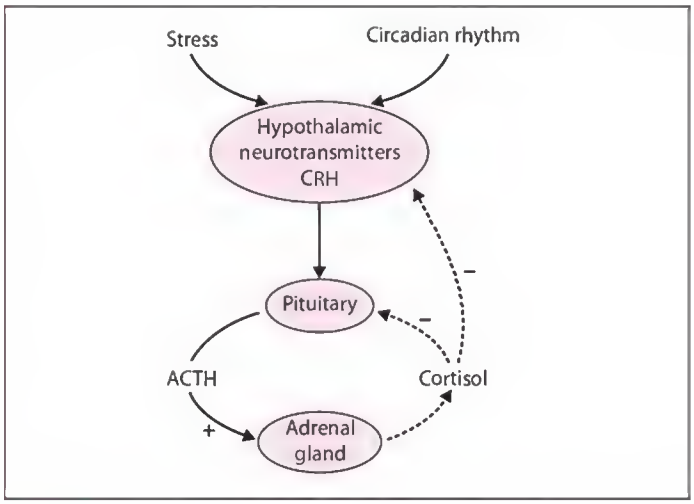


Figure 2: Regulation of hypothalamic-pituitary-adrenal axis.

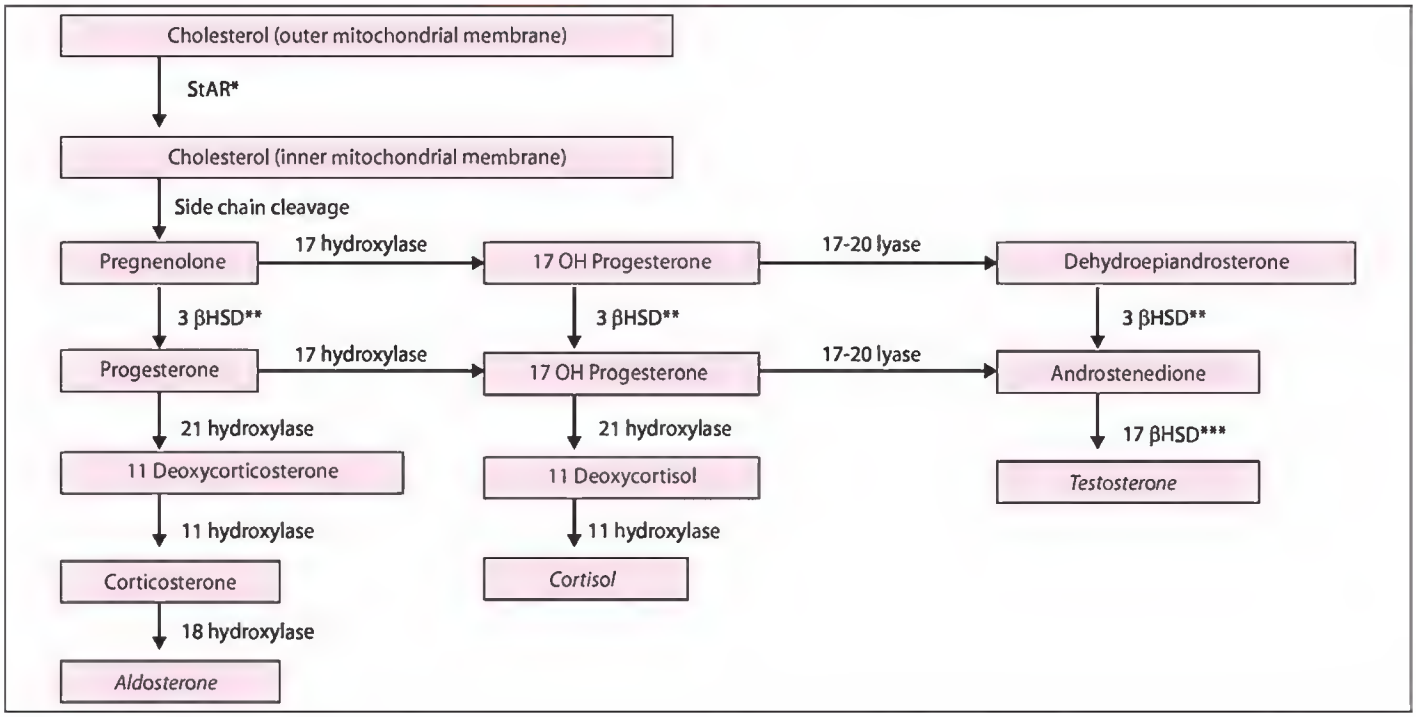


Figure 1: Adrenal steroid hormone synthetic pathways.
(*StAR: steroidogenic acute response protein; **3 βHSD: 3 β-hydroxysteroid dehydrogenase; ***17 βHSD: 17 β-hydroxysteroid dehydrogenase).

angiotensin system (**Figure 3**). A decrease in plasma volume stimulates the secretion of renin from the juxtaglomerulus apparatus cells surrounding the afferent arterioles in the kidney. Renin cleaves angiotensinogen to angiotensin I, which is then converted by the angiotensin converting enzyme (ACE) to angiotensin II. The latter then stimulates aldosterone release, sodium retention and increase in plasma volume. In addition, potassium ions directly stimulate the secretion of aldosterone.

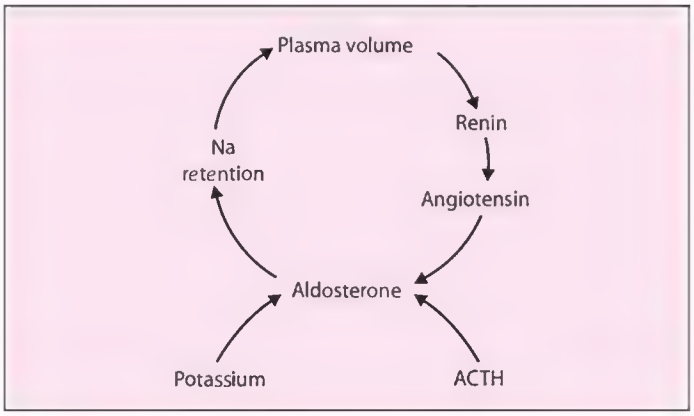


Figure 3: Regulation of aldosterone secretion.

Adrenal Androgens

These include predominantly androstenedione and DHEA. They are relatively weak androgens in comparison to the end product, testosterone and consequently have minimal effects in males. In contrast, in females, over-secretion can lead to virilisation. Adrenal androgens are regulated by ACTH.

HYPERFUNCTION OF THE ADRENAL CORTEX

Cushing's Syndrome

Cushing's syndrome (CS) was named after Sir Harvey Cushing who described the syndrome in 1912. Excessive production of adrenal glucocorticoids results in a characteristic combination of clinical features. Though CS is an uncommon illness, it has a high morbidity and mortality if untreated. This is mainly due to an increased risk of cardiovascular disease as well as infections. Therefore, early diagnosis and treatment is essential.

Aetiology

CS results from an excess of corticosteroids, either endogenous or exogenous. The various causes for CS are shown in **Table 1**. In clinical practice, the excessive use of steroids with glucocorticoid activity is the most common aetiology of CS (exogenous CS). In contrast, CS due to endogenous causes is relatively uncommon.

Certain medical conditions, such as depression, alcoholism, severe obesity and pregnancy may closely mimic clinical features of CS ('pseudo-Cushing's'). This occurs as a result of activation of the hypothalamic-pituitary-adrenal axis and increased secretion of CRH. In such conditions, the levels of cortisol are elevated and other diagnostic tests may also be falsely positive. The features of CS remit with the resolution of the basic medical problem.

Clinical features

The clinical features of CS result from the effects of excessive levels of glucocorticoids on the body. There is an increased body fat, mainly in a truncal distribution: marked central obesity with abdominal fat, rounding of face (moon face) and fat deposition in the neck (buffalo hump). Protein catabolism results in reduced muscle mass of the limbs, thinning of the skin, broad (>1cm) and reddish-violet striae (**Figure 4A**), easy bruising without trauma and proximal muscle weakness. These features are important in distinguishing CS from exogenous obesity. Growth retardation is an important sign in children. Other frequent features, though not specific for CS, include hypertension, glucose intolerance or diabetes, depression and other changes in mood, and hirsutism, oligomenorrhoea or amenorrhoea in women. Fungal skin infections are common. Osteoporosis, most severely affecting the lumbar spine, is frequent and may result in pathological fractures.

Table 1: Aetiology of Cushing's Syndrome

Aetiology	Comment
ACTH-dependent	***80%***
Pituitary adenoma	Most common aetiology of endogenous Cushing's syndrome; mostly microadenomas (<10 mm diameter)
Ectopic ACTH	Small cell carcinoma lung (most common), bronchial adenoma, bronchial and thymic carcinoids, medullary thyroid carcinoma, pheochromocytoma
Ectopic CRH	Rare
ACTH-independent	***20%***
Adrenal adenoma	Small, homogeneous tumour
Adrenal carcinoma	Large adrenal mass, rapid course, poor prognosis
Primary adrenal hyperplasia	May be micronodular or macronodular
Oral or parenteral steroids	Most common aetiology of Cushing's syndrome; cortisol and ACTH are undetectable (in case of most synthetic steroids)

CRH = Corticotrophin releosing hormone; ACTH = Adrenocorticotrophin hormone. The common oetiologies of endogenous Cushing's syndrome ore pituitory odenomo, ectopic Cushing's syndrome ond odrenol tumours.

Specific aetiologies of CS have characteristic clinical features. Cushing's disease (CD) is more common in females of the age groups 20 to 40 years and the course is often slowly progressive. Hyperpigmentation may be noted. Ectopic ACTH syndrome, due to a slow growing malignant tumours, such as small cell carcinoma lung present with weight loss, marked hyperpigmentation, hypokalaemia and muscle weakness. In contrast, ectopic ACTH syndrome due to a slow growing tumours such as bronchial carcinoid or cortisol-secreting adrenal adenoma may be indistinguishable from CD. In contrast, adrenal carcinomas have a rapid course, palpable abdominal mass and, in case of females, may lead to virilisation.

Diagnostic evaluation

The diagnostic evaluation of CS is done in two parts. First, the diagnosis is confirmed and then the aetiology determined (**Figure 5**). To confirm the diagnosis of CS, cortisol levels in serum, urine or saliva are measured. Alternatively, testing for the lack of suppression of serum or urine cortisol after supraphysiological doses of dexamethasone is utilised. Unfortunately, no single test is more than 95% sensitive, and hence a battery of tests needs to be conducted. Screening tests include the overnight 1 mg dexamethasone suppression test, 24-hour urine cortisol and midnight salivary cortisol (not commonly available in India) (**Figure 5**). The 2-day low-dose dexamethasone



Figures 4A to C: Clinical features of adrenocortical disorders. (A) Broad violaceous striae in a patient with Cushing's disease; (B) Addison's disease: hyperpigmentation of the hands; (C) Addison's disease: hyperpigmentation of gums and buccal mucosa).

suppression test (0.5 mg 6 hourly over 48 hours followed by serum cortisol measurement) is often used as a confirmatory test. Recent guidelines suggest that at least 2 of the above 4 tests need to be positive to diagnose CS.

To determine the aetiology of CS, plasma ACTH levels are measured. In case plasma ACTH is undetectable (<10 pg/mL) a CT scan of the adrenal glands is performed for an adrenal tumour (**Figures 6A to C**). If ACTH is elevated or normal, the most likely aetiologies are a pituitary adenoma or ectopic ACTH syndrome. In this case, an MRI of the pituitary with contrast is performed. In case a pituitary adenoma is clearly visible no further tests are required (**Figure 6**). However, if no tumour is seen, the best option is to proceed to inferior petrosal sinus sampling to directly measure ACTH secretion from the pituitary, preferably after injecting CRH intravenously. If ACTH is higher in either petrosal sinus compared to a peripheral vein, this suggests a pituitary aetiology. On the other hand, if there is no gradient it indicates an ectopic ACTH source. A CT of the chest and abdomen can then be performed to visualise any tumour. Alternatively, since petrosal sinus sampling can only be performed in advanced referral centres, in many centres if a

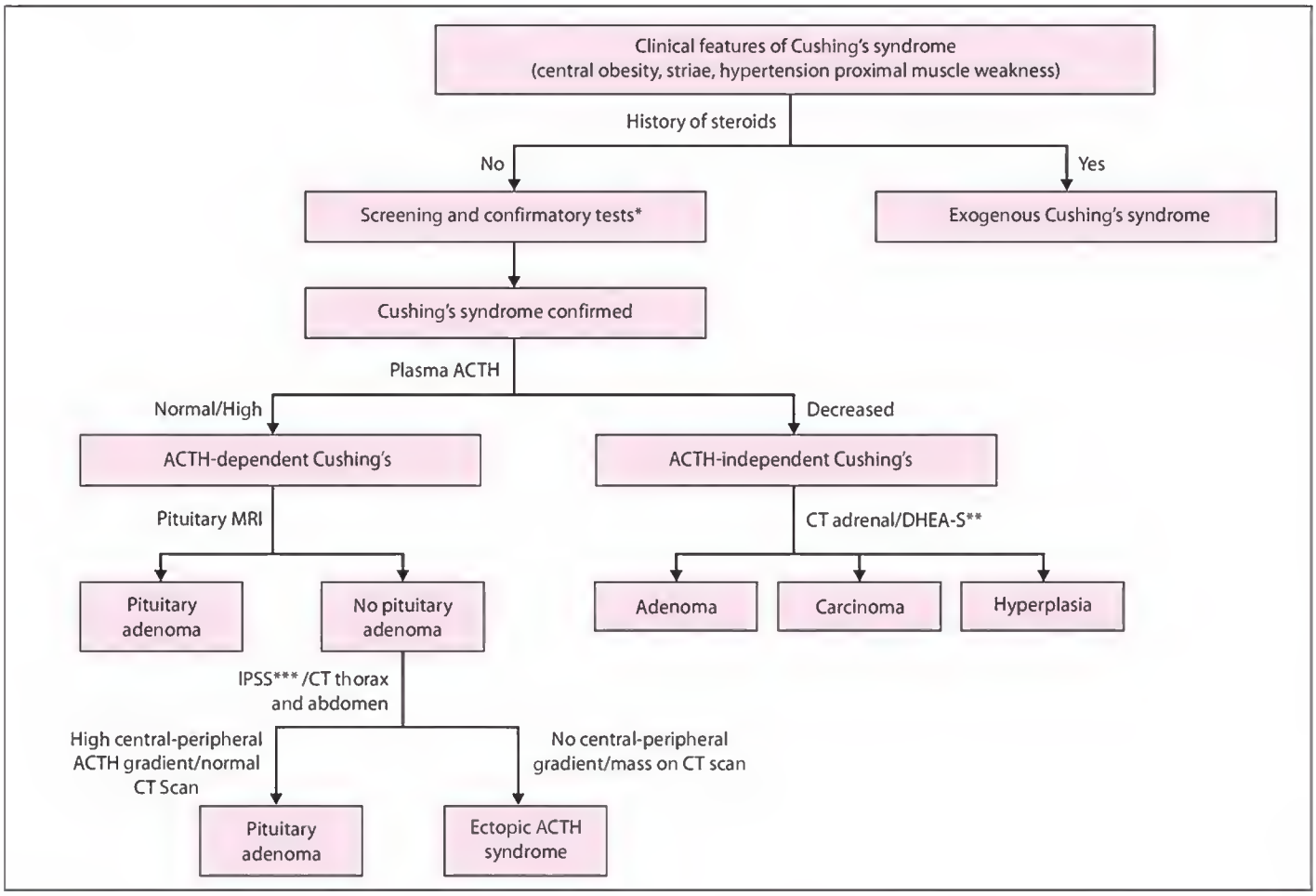
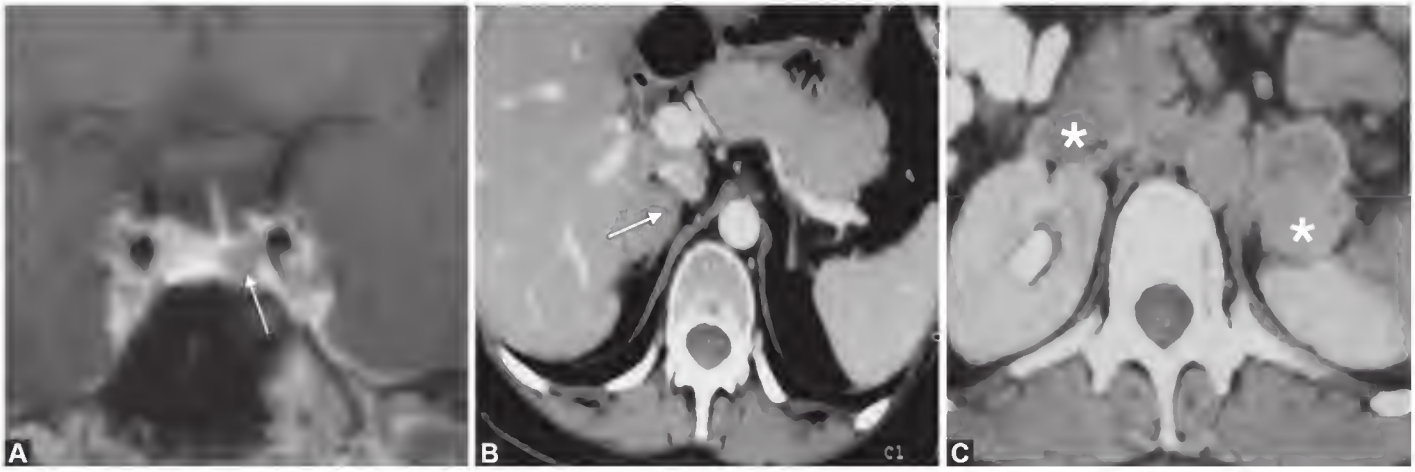


Figure 5: Approach to a patient with Cushing's syndrome.
**Screening tests: Overnight dexomethosone suppression test (8 om cortisol >1.8 µg/dL after 1 mg of dexamethosone at midnight); 24 hours urine cortisol >50 mg. Confirmatory test: 48 hours dexamethosone suppression test (serum cortisol >1.8 µg/dL after 0.5 mg dexamethasone 6 hourly for 2 days). **DHEA-S = Dehydroepiandrostenedione; ***IPSS = Inferior petrosal sinus sampling (for ACTH).*



Figures 6A to C: Radiological features in adrenal disorders. (A) T1- weighted MRI image of microadenoma of the pituitary [arrows]; (B) Contrast CT scan of right adrenal adenoma [arrow]; (C) Contrast enhanced CT scan of bilateral adrenal tuberculosis [asterix].

pituitary MRI does not show an adenoma, a CT scan of the chest/abdomen is directly performed. Detailed evaluation of CS is a specialised task and is best carried out by an experienced endocrinologist in a referral hospital.

Management

Cushing's disease

Different modes of treatment include trans-sphenoidal resection of the tumour, bilateral adrenalectomy, focused radiotherapy and medical treatment with drugs which block adrenal steroidogenesis. The primary treatment modality is trans-sphenoidal surgery with an operating microscope using a sub-labial or transnasal approach. This should always be performed by a neurosurgeon experienced in this technique so as to obtain optimum results. Since most patients harbour microadenomas (size <10 mm), a complete resection is feasible without damaging the normal pituitary. Immediate remission rates are close to 70% to 90% while long-term remission is 60% to 70% in most centres. Undetectable postoperative cortisol (< 1.8 µg/dL) shortly after surgery suggests greater chance of long-term remission. Patients need to be on life-long follow-up since relapses of the disease (15% to 20% over 10 years), as well as new pituitary hormone deficiencies, may occur at any time point. In case of failure of initial surgery or relapse, a repeat trans-sphenoidal surgery is attempted or bilateral adrenalectomy or pituitary radiotherapy can be utilised.

Bilateral adrenalectomy is nearly always successful in the treatment of CD. However, the morbidity and mortality of the surgery is significant and life-long replacement with glucocorticoids and mineralocorticoids is necessary. In addition, the pituitary tumour may increase in size after surgery and lead to elevated ACTH, hyperpigmentation and local tumour invasion (Nelson's syndrome) in nearly 15% to 20%. Fractionated external beam radiotherapy or stereotactic radiosurgery is effective in reducing ACTH levels but the effect is slow. Control can be achieved in approximately 50% to 60% within 5 years. Side effects such as hypopituitarism are frequent and occasionally damage to adjoining structures can occur. Finally, medical therapy with drugs such as ketoconazole or metyrapone (not available in India) can be utilised to block adrenal steroidogenesis. While the drugs are effective, they have numerous side-effects and are frequently used for only for short-term control, such a prior to surgery or awaiting the results of radiotherapy.

Other Aetiologies

The treatment for ectopic ACTH syndrome involves surgical removal of the neoplasm or, if not feasible, chemotherapy or radiotherapy of the primary tumour. Adrenal adenomas are cured after unilateral adrenalectomy. In contrast, the prognosis of adrenal carcinoma is poor. Treatment involves resection of the tumour and then treatment with mitotane (o,p'-DDD), an adrenolytic agent.

PRIMARY ALDOSTERONISM

Excessive aldosterone production by the adrenal cortex results in a syndrome characterised by hypertension, hypokalaemia and metabolic alkalosis, known as primary aldosteronism (PA). This needs to be differentiated from the more common secondary aldosteronism, where the stimulus to aldosterone production is an increased rennin secretion due to causes such renal artery stenosis or malignant hypertension.

Prevalence

Earlier studies reported that less than 1% of patients with hypertension who were screened by presence of hypokalaemia had PA. More recently, studies in certain series of hypertensive patients, suggest that more than 10% are secondary to PA.

Aetiology

Causes of PA are shown in **Table 2**. An important treatable cause of PA is a unilateral aldosterone-producing adenoma (Conn's

Table 2: Aetiology of Aldosteronism

Aetiology	Comment
Primary	
Adenoma	Small homogeneous tumour
Carcinoma	Very uncommon
Hyperplasia	Common; may be unilateral or bilateral
Familial hyperaldosteronism (types I and II)	Autosomal dominant; type I is also known as glucocorticoid remediable aldosteronism
Miscellaneous (ingestion of licorice)	Both aldosterone and PRA are low
Secondary	
Malignant hypertension, renal artery stenosis	Both PRA and aldosterone elevated

PRA = Plasma rennin activity; aldosterone secreting adenoma and adrenal hyperplasia are most frequent causes. All other aetiologies are rare.

syndrome). Such adenomas are commonly unilateral, benign and less than 2 cm in diameter. Aldosterone secreting carcinomas are very rare. Cortical nodular hyperplasia of the adrenal gland is far more common than an adenoma. The hyperplasia may be unilateral or bilateral. Hereditary forms of hyperaldosteronism (familial aldosteronism types I and II) are autosomal dominant disorders. The former is also known as glucocorticoid-remediable aldosteronism and can be ameliorated by small doses of glucocorticoids.

Clinical Features

Patients present with sustained hypertension, which may be severe. The hypertension may require two or more drugs for its control. Hypokalaemia and/or increased urine potassium excretion is found in one-third of patients with PA (more commonly in adenomas). Hypokalaemia may be associated with muscle weakness (and in severe cases can lead to periodic paralysis), polyuria and mild hyperglycaemia. The frequency of cardiovascular accidents and hypertensive cardiomyopathy are higher in PA when compared to essential hypertension, probably due to the adverse effects of high aldosterone on target tissue.

Diagnosis

The diagnosis should be suspected in patients with severe hypertension, poor control with 2 or more drugs, onset <30 years, family history of early-onset hypertension, associated hypokalaemia or association with early cardiovascular events. A flow chart for confirming the diagnosis is shown in **Figure 7**. The best screening test is the ratio of plasma aldosterone (in ng/mL)/plasma renin activity (in ng/mL/hour). Before performing this test drugs such as diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be stopped for four weeks. An elevated value (>30) is highly suggestive of PA. A high ratio should be followed a confirmatory test for PA, which aims to assess non-suppression of aldosterone after salt loading and increasing plasma volume. Once PA is confirmed, a CT scan of the adrenals is performed. In case a single adenoma is visualised, and the patient is <40 years of age, surgery can be advised. In all other cases (bilateral adenomas, hyperplasia) if surgery is desired, it is recommended that bilateral adrenal venous sampling for aldosterone should be performed to determine the side of aldosterone production. This last test carries some risk of haemorrhage into the adrenal gland and requires special expertise.

Management

In case of adenoma or unilateral hyperplasia, a unilateral adrenalectomy, performed laparoscopically, improves both hypokalaemia and hypertension. However, hypertension which is long-standing, or requiring more than 2 drugs for control prior to surgery, may persist though control will improve. If medical

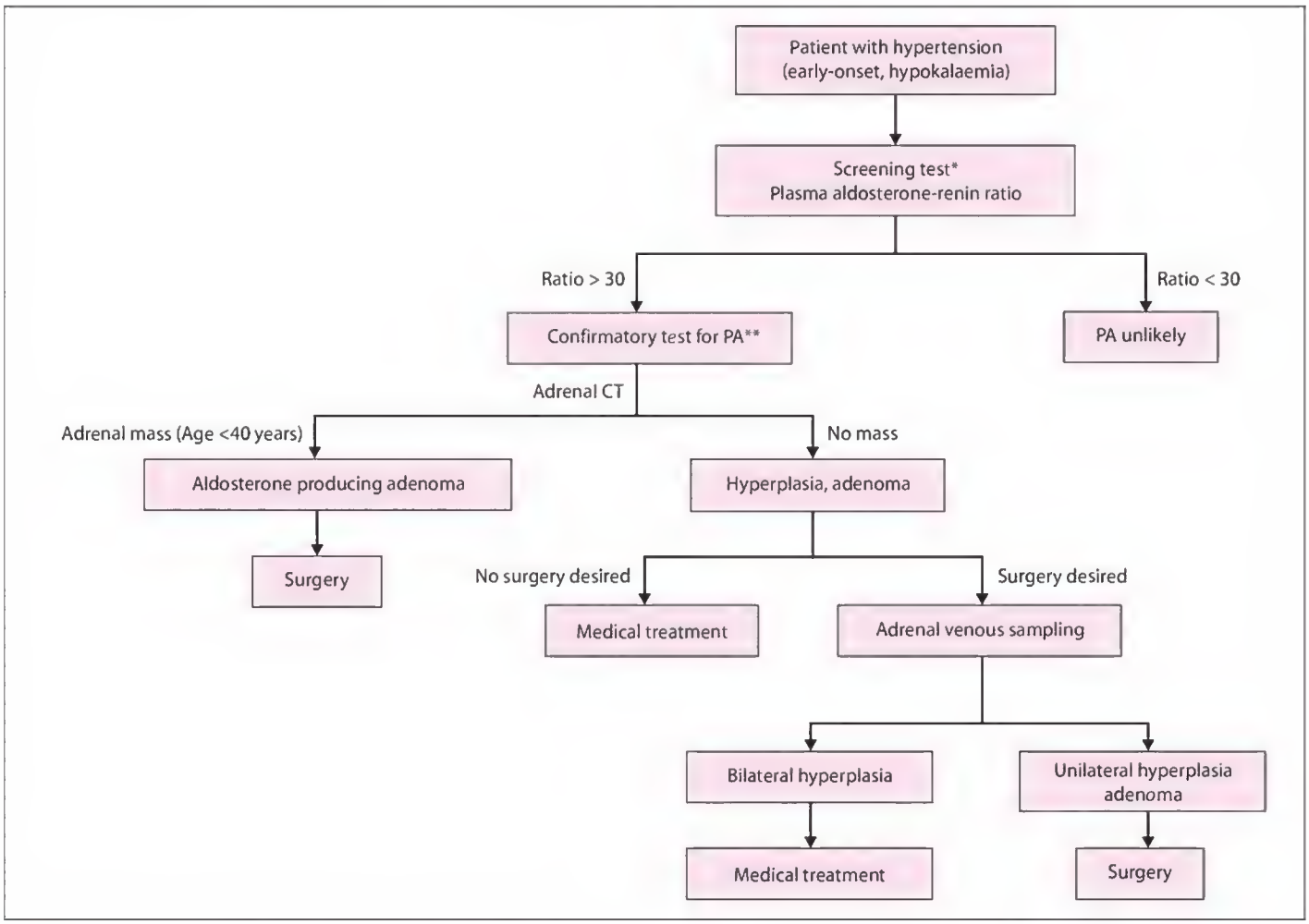


Figure 7: Approach to a patient with suspected primary aldosteronism.

**Screening test: Morning plasma aldosterone (measured in ng/mL) and plasma renin activity (measured in ng/mg/hour) ratio >30; **Confirmatory test: Infusion of 2 litres of 0.9% saline over 4 hours; serum aldosterone >10 ng/dL. (not to be performed in uncontrolled hypertension or cardiac impairment).*

therapy (bilateral lesions, patient preference) is opted for, mineralocorticoids receptor blockers (spironolactone, eplerenone) and potassium-sparing diuretics (triamterene, amiloride) are effective.

ASYMPTOMATIC ADRENAL MASSES

In recent years, due to the easy availability of ultrasound and CT imaging, adrenal masses are often detected incidentally ('incidentaloma'). In autopsy studies, the frequency of adrenal adenomas is 6%, with an increasing prevalence with age. The prevalence of adrenal carcinoma, however, is low. The management of such masses depends upon the evidence of malignancy at other sites, the functional activity of the tumours and their size and radiological characteristics (**Figure 8**).

For the evaluation of such masses, screening for functional tumours (urine or plasma metanephrines, overnight 1 mg dexamethasone suppression test for cortisol) should be performed. In addition, in case the patient is hypertensive, the ratio of plasma aldosterone to plasma renin should be measured. If the mass is found to be functionally active, it should be undergo resection. In case it is non-functional, in subjects with evidence of malignancy elsewhere, fine needle aspiration cytology (FNAC) to rule out a metastatic lesion should be performed. In addition, if an infective aetiology (tuberculosis, histoplasmosis) is suspected, FNAC and other relevant tests should be undertaken. In other cases the radiological characteristics of the mass should be considered. Masses >4 cm in diameter, having an irregular margin, heterogeneity or non-enhanced CT scan attenuation >10 Hounsfield units have a greater chance of malignancy and should be removed. Other tumours can be followed up by CT scan and by functional assays after six months and then annually for 4 to 5 years for any change in size. If their size increases they should undergo surgery.

ADRENAL INSUFFICIENCY

Adrenal insufficiency (AI) can result from either destruction of both adrenal cortices (primary AI) or from a deficiency of ACTH (secondary AI). Patients with primary AI (Addison's disease) may present acutely in shock (adrenal crises) or more indolently, with increased pigmentation, weakness and postural hypotension. Once diagnosed, the disease has an excellent prognosis with appropriate replacement of steroids and most patients have a normal life-expectancy.

Prevalence

The overall prevalence of AI (primary, secondary due to hypothalamic and pituitary tumours, and congenital adrenal hyperplasia) is approximately 5 per 10,000. The prevalence of Addison's disease in Western countries, primarily of autoimmune aetiology, is 125 to 280 per million. However, its prevalence in India is not known.

Aetiology

AI develops after approximately 90% of the adrenal cortex is destroyed. In Western countries the most common aetiology is an autoimmune destruction of the adrenal cortex (**Table 3**). However, in developing countries such as India, infectious disorders such as tuberculosis constitute nearly half the cases. Less frequently encountered are fungal infections, mainly histoplasmosis.

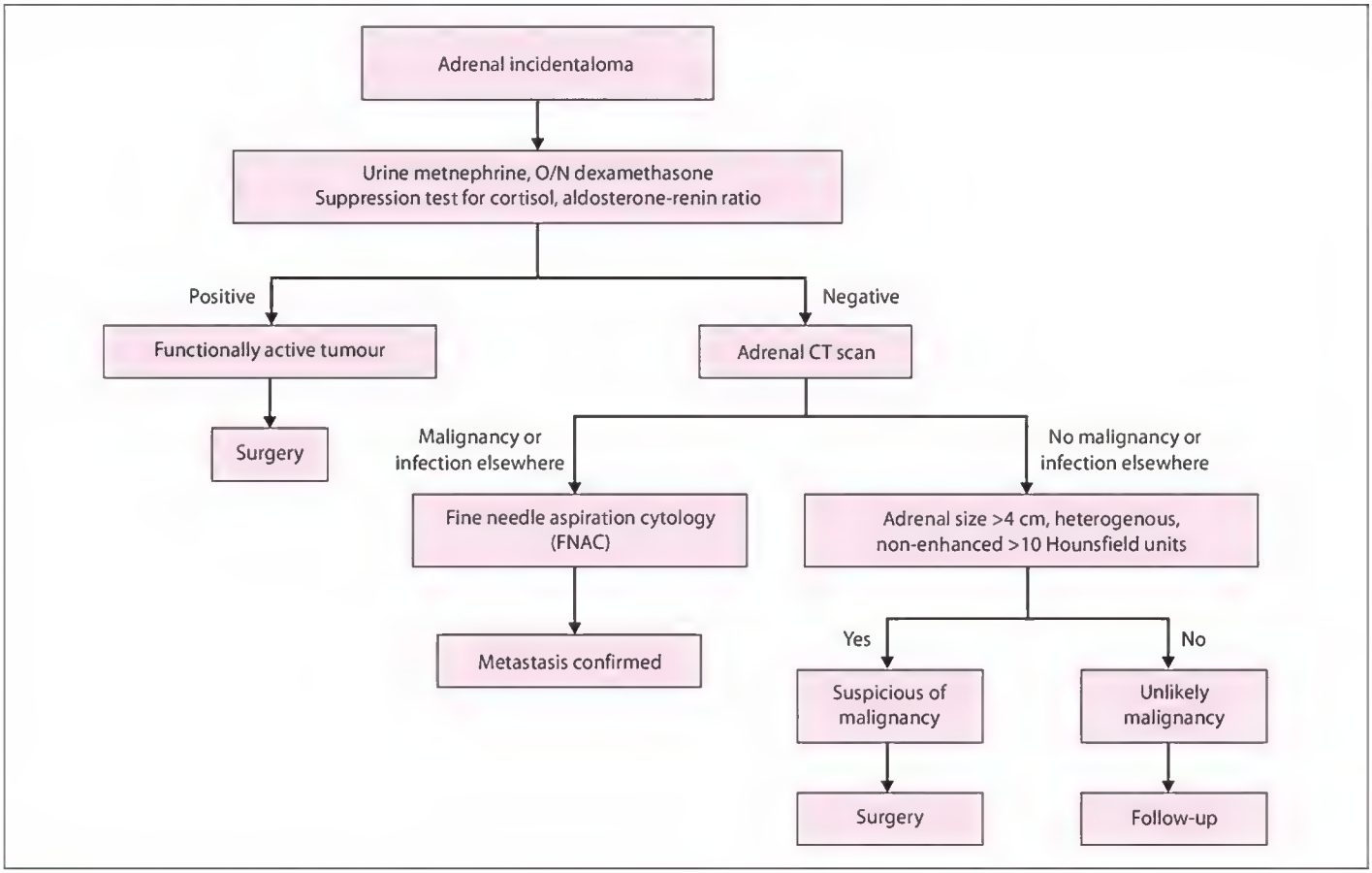


Figure 8: Approach to a patient with incidentally detected adrenal mass.

Table 3: Aetiology of Adrenal Insufficiency

Aetiology	Comment
Primary	
Autoimmune	Frequency 80-90% in industrialised nations, approximately 50% in Indians
Infections	
Tuberculosis	Frequency 50% in Indians
Fungal	Histoplasmosis
Viral (HIV-AIDS)	Cytomegalovirus
Adrenomyeloleucodystrophy and adrenoleukodystrophy	X-linked, males involved, associated neurological degeneration, accumulation of very long chain fatty acids
Malignancy	Lymphoma, metastases
Infiltration	Haemochromatosis, amyloidosis, sarcoidosis
Haemorrhage	Septicaemia, antiphospholipid syndrome
Secondary	
Pituitary and hypothalamic tumours, infiltration, surgery, radiation, haemorrhage	–
Steroid withdrawal	Common after prolonged supra-physiological steroids usage

Autoimmune and tubercular aetiologies are equally common in Indians; all other aetiologies of primary adrenal insufficiency are uncommon.

Autoimmune AI may occur independently or be associated with other disorders of organ-specific autoimmunity, (known as autoimmune polyglandular syndromes, APS). APS type 1 consists of mucocutaneous candidiasis, hypoparathyroidism and AI. Multiple other autoimmune disorders are frequent. APS type 1 results from recessive mutations in the autoimmune regulator gene (AIRE) which codes for a transcription factor important for central tolerance. APS type 2 consists of AI, autoimmune thyroid disease and/or type 1 diabetes. It is far more frequent than APS 1.

Clinical Features

Acute AI can result from overwhelming sepsis, most commonly due to *Neisseria meningitides* (Waterhouse-Friderichsen syndrome), oral anti-coagulants, bilateral thrombosis of the adrenal veins or the phospholipid syndrome. Patients present with abdominal pain and unexplained shock which is unresponsive to fluids or vasoconstrictors, hyperkalaemia, hyponatraemia and metabolic acidosis.

Chronic AI is far more common than acute adrenal failure. Patients present with lassitude, weakness, weight loss and postural hypotension of variable duration. Abdominal complaints (vomiting, pain) may be prominent. Hyperpigmentation of the skin (palm creases, nipples, and nails) and oral mucosa (gums, buccal mucosa, and tongue) is characteristic (**Figures 4B and C**). In patients with an autoimmune aetiology, skin pigmentation and vitiligo may coexist. Evidence of other autoimmune disorders (hypothyroidism, Graves' disease, premature ovarian failure, coeliac disease) may be present or develop subsequently. Androgen deficiency may be apparent in females leading to loss of pubic and axillary hair and decrease in libido. Some patients may present in acute adrenal crises after a predisposing illness or stress.

Diagnosis

Routine tests reveal hyponatraemia, hyperkalaemia and mild metabolic acidosis. The diagnosis is confirmed by the measurement of serum cortisol after stimulation with 250 ug of intramuscular synthetic aqueous 1 to 24 ACTH (Synacthen®) (**Figure 9**). A serum cortisol <18 µg/dL, measured 30 or 60 minutes after ACTH injection, indicates inadequate adrenal

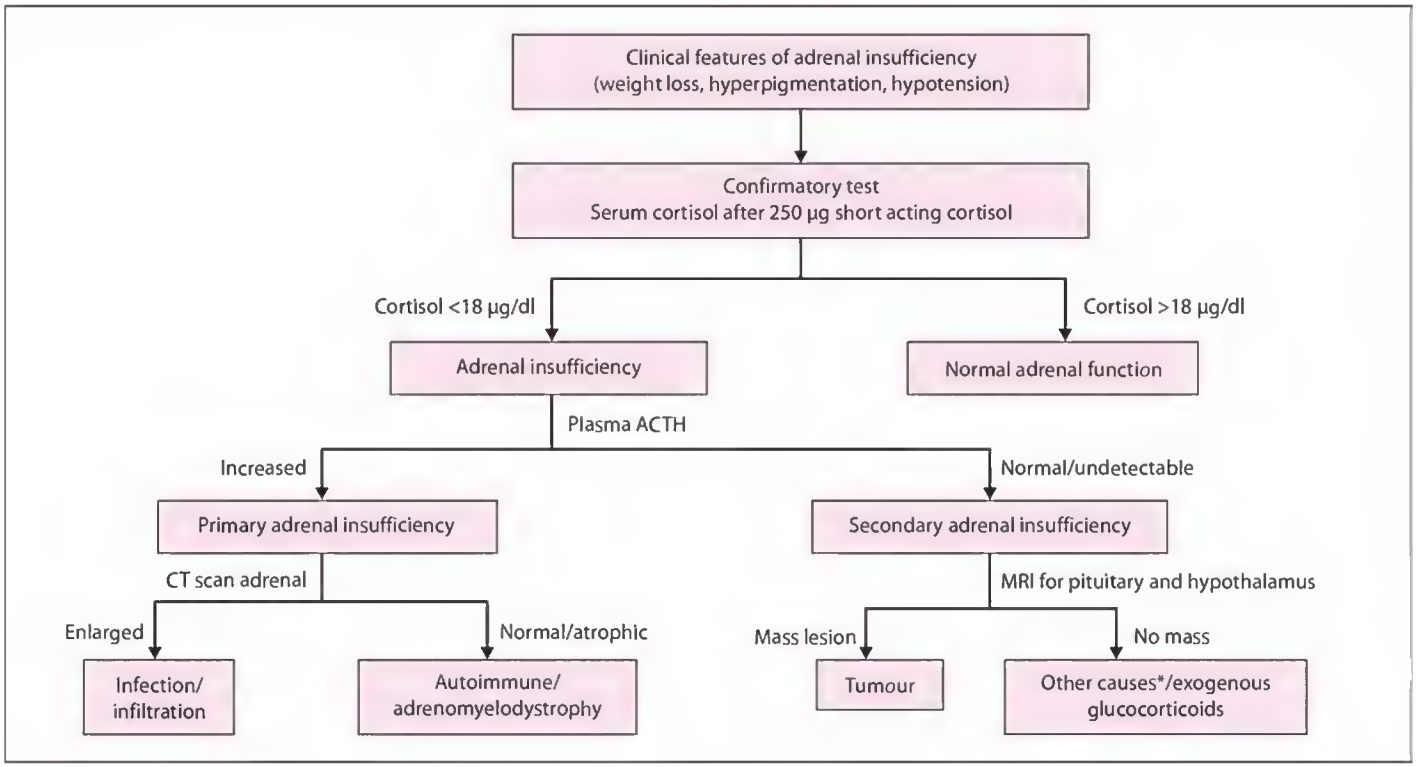


Figure 9: Approach to a patient with adrenal insufficiency.

** Other causes: see **Table 3***

function. A simultaneous plasma ACTH sample is elevated, usually >100 pg/mL. To determine the aetiology of Addison's disease, a CT scan or MRI of the adrenal glands is performed. In the case of infections such as tuberculosis and histoplasmosis, one or both adrenal glands are usually enlarged, heterogeneous and with calcifications. In case of normal or atrophic glands, adrenal antibodies may be measured, but this test is not available in India. Thyroid function should be tested at onset in patients suspected to have an autoimmune aetiology.

Management

Acute AI

If strongly suspected, it is not necessary to confirm the diagnosis of the illness prior to starting treatment when the patient is critically ill. A random sample for cortisol can be obtained and parenteral fluids and steroids are immediately started. Replacement with normal saline or dextrose-saline should be started at a fast rate, and monitored closely. Parenteral hydrocortisone 100 mg intravenously and should be followed by 8 to 10 mg/hour hydrocortisone by continuous intravenous infusion. In case it is not feasible to give intravenous steroids by infusion, intravenous or intramuscular hydrocortisone should be given in a dose of 50 mg 6 hourly. The precipitating cause must be sought and appropriate treatment, e.g. antibiotics should be instituted. Once the patient is recovering the dose of hydrocortisone can be gradually tapered and oral hydrocortisone or prednisolone can be substituted. Once the dose of hydrocortisone is <50 mg/day, fludrocortisone in a daily dose of 0.1 mg should be added.

Chronic AI

Patients with long-standing AI require replacement with both glucocorticoids and mineralocorticoids. The glucocorticoids commonly used are hydrocortisone (12 to 15 mg/m^2 in two or three divided doses) or prednisolone (2.5 to 5 mg/day in two divided doses). The larger portion of the steroid is taken as early in the morning as feasible and second dose at 2 to 4 pm. Hydrocortisone tablets may be difficult to procure in some cities. The dose of steroids should be adjusted depending upon features of under-replacement (weight loss, lack of energy and increasing pigmentation) or over-treatment (weight gain, striae, and hypertension). The dose of fludrocortisone is 0.05 to 2.5 mg/day taken as a single morning dose. The dose can be adjusted depending upon blood pressure, oedema and electrolytes. A normal salt intake is advised, but salt and fludrocortisone dose may need to be increased in summer months. Replacement with adrenal androgen, DHEA, may be useful in some women with features of androgen deficiency such as dry itchy skin and loss of libido.

The aetiology of AI should be sought and treated. While there is no specific treatment known to reverse features in patients with an autoimmune (idiopathic) aetiology, these patients need to be tested at onset and subsequently at yearly intervals for development of autoimmune thyroid disorders (hypothyroidism or Graves' disease). Other organ-specific autoimmune disorders develop less frequently, but should be kept in mind. Infectious causes (tuberculosis, histoplasmosis) should be appropriately treated, though recovery of adrenal function after treatment is unlikely.

Stress doses: Stress doses should be emphasised in all patients with AI. In less severe forms of stress (fever, infections and surgery under local anaesthesia) the dose of the glucocorticoid should be increased to 2 to 3 times of daily dose for the duration of the stress. In case of severe stress (e.g. surgery under general anaesthesia, severe infections, major accident) higher doses of glucocorticoids should be provided parenterally. A dose of hydrocortisone 150 to 200 mg/day in four equal doses intramuscular or intravenous should be given initially, and gradually tapered when the stress subsides. All patients should be provided an identification card to keep, which provides information on their disease and emergency measures in case of crises. Their family members should be taught to inject hydrocortisone or dexamethasone if required.

Glucocorticoid-Induced Adrenocortical Deficiency

Prolonged glucocorticoid use, whether for therapeutic reasons, intention abuse, or inadvertently due to spurious admixture with other drugs, leads to suppression of the hypothalamo-pituitary-adrenal (HPA) axis and adrenal cortex. This is most likely to occur with use of more potent glucocorticoids which have longer duration of action, e.g. dexamethasone, high doses, prolonged use and oral/parenteral administration. It is unlikely after inhalational or topical steroids, though rare instances of adrenal insufficiency have been noted. The use of prednisolone in doses of more thant 20 to 30 mg/day for more thant 1 week, or in lower doses for less thant 1 month, is likely to lead to significant suppression. However, glucocorticoids in physiological amounts (prednisolone ≤5 mg/day, hydro-cortisone 15 to 20 mg/day), especially if given early morning, are unlikely to lead to adrenal cortical suppression.

A small proportion of patients who receive prolonged high doses of glucocorticoids may develop clinically apparent secondary AI if the steroids are withdrawn abruptly. This is most likely to occur in the setting of acute stress such as infection, serious injury or major surgery. The AI occurs due to suppressed levels of ACTH, as well as due to an inability of the atrophied adrenal gland to respond to ACTH (**Figure 2**). Such patients, despite having certain physical features of CS due to chronic steroid excess, present with many of the signs and symptoms seen in primary AI. However, they are not hyperpigmented. Serum cortisol is low or undetectable (except if the patient is ingesting hydrocortisone or prednisolone) and plasma ACTH is also suppressed. The response of serum cortisol after injecting 250 ug soluble 1 to 24 ACTH (rapid ACTH stimulation test), or after insulin hypoglycaemia, is subnormal. The former test can be used to monitor the recovery of the HPA axis.

As a general principle, the smallest dose of glucocorticoids should be used for the shortest period of time to obtain a required therapeutic effect. The steroid should be given as a single dose in the morning or on alternate days, if feasible. It should be tapered to physiological doses (≤5 mg/day prednisolone or 10 to 12.5 mg/m^2 hydrocortisone/day) as soon as feasible to allow the HPA axis to recover and then stopped. The problems which may arise on tapering glucocorticoids include flare up of the original illness and adrenal insufficiency. Overall recovery of the HPA axis may take weeks to >1 year and is longer with a higher dose and

longer duration of treatment. For higher doses given for prolonged periods, it is recommended that glucocorticoid be withdrawn over weeks or months. The dose can be reduced weekly or two weekly by 10 mg if the daily dose of prednisolone is >30 mg, and 5 mg once the daily dose is <30 mg. After a dose of <20 mg/day is reached slower reduction, e.g. by 2.5 mg every 2 to 4 weeks, can be done. After reaching physiological doses, the glucocorticoid can be given on alternate days, thus allowing the HPA axis to recover faster. At this time, the adrenal recovery should be studied by measuring the basal cortisol or more accurately by using the short ACTH stimulation test (described earlier). An 8 am serum cortisol or stimulated cortisol of >20 ug/dL, suggests normal adrenal function and glucocorticoids can be discontinued. Testing may have to be done on more than one occasion until recovery is documented.

CONGENITAL ADRENAL HYPERPLASIA

As discussed earlier, the production of adrenal steroids requires numerous enzymes, several belonging to the cytochrome P450 family (**see Figure 1**). When any of these enzymes is deficient (e.g. due to a genetic mutation), cortisol production is decreased and there is release of the negative feedback on the corticotrophs of the pituitary. The resulting elevated ACTH drives growth of the adrenal glands (causing hyperplasia) as well as hyperfunction of several enzymes in steroid synthesis. Biochemical precursors proximal to the enzymatic block are massively elevated and shunted into the pathways which may have a block, such as the mineralocorticoid or androgen pathways. This gives rise to typical clinical characteristics as well as a diagnostic steroid profiles in serum and urine.

21-Hydroxylase Deficiency

Deletions or mutations in the CYP 21A gene encoding the 21 hydroxylase enzyme are responsible for 95% of congenital adrenal hyperplasia (CAH). It is a relatively common genetic disorder, with a worldwide prevalence of approximately 1:15,000 births. It is characterised by deficiency of cortisol. Proximal to the block, the elevated serum precursor 17 hydroxyprogesterone (17 OHP), is shunted into the androgen pathway to produce excess of dehydroepiandrosterone, androstenedione and testosterone. The latter brings about virilisation of the female foetus *in utero*, and virilisation in both genders postnatally. Thus, the labia in a female newborn may resemble a scrotum, the clitoris may resemble a small penis, and the perineum may be partially or completely fused, obliterating the external vaginal opening. In the most severe degree of masculinisation, the genitalia will resemble those of a completely normal male baby but with apparent bilateral cryptorchidism. Pigmentation can be appreciated on the genitalia and nipples in addition to the skin. If the enzymatic block is severe, features of mineralocorticoid deficiency will also be present (salt-wasting variety). In contrast, the simple virilising type does not affect mineralocorticoid production much.

Newborn female babies can be diagnosed at birth, due to the abnormal genitalia. However, male babies will only come to light during salt wasting episodes which may start from about 1 week of age. These are characterised by diarrhoea, vomiting, lethargy and hypotension and may be mistaken for ordinary diarrhoeal episodes. The typical electrolyte pattern of hyponatraemia, hyperkalaemia and metabolic acidosis should alert the physician. Untreated, salt-wasting CAH is associated with morbidity and mortality. Further, in childhood, the effects of postnatal adrenal androgen production result in peripheral precocious puberty in boys and heterosexual precocity or virilisation in a girl. Certain mutations of the CYP 21A gene give rise to a mild variety of disease called late onset congenital adrenal hyperplasia (LOCAH). This presents in the peripuberted age with hirsutism, menstrual irregularity, anovulation and, less commonly, male pattern scalp hair loss, muscular habitus and clitoromegaly.

Diagnosis

The diagnosis of classic 21 hydroxylase deficiency is made by measurement of serum 17 OHP or its urinary metabolite pregnanetriol. Serum 17 OHP is >10,000 ng/dL and plasma renin activity is elevated. Supportive tests include electrolytes and blood gas analysis. LOCAH on the after hand, has lower levels of 17 OHP, necessitating stimulation by ACTH to establish a firm diagnosis. Basal 17 OHP (done at 8 to 9 AM) is usually > 200 ng/dL and stimulated 17 OHP ranges from 1500 to 2000 ng/dL.

Treatment

This is aimed at replacing cortisol, with hydrocortisone or prednisolone, which will also bring about the suppression of precursors and thereby androgen formation. Simultaneously, fludrocortisone is administered. Added salt must be provided in the first year of life, till the baby starts getting salt from table foods.

Treatment of LOCAH includes glucocorticoids for suppressing androgen and bringing about ovulation. Spironolactone may be added to give better relief of hirsutism and estrogen – progesterone pills may be needed for regularisation of menstrual cycles.

Other CAH

P450 oxido-reductase deficiency is the latest in the list of P450 enzyme mutations that can cause a disorder of sexual differentiation. Other enzyme deficiencies include 3 β hydroxysteroid dehydrogenase, 11 hydroxylase and 17 hydroxylase. The last two may cause hypertension as well cortisol deficiency.

RECOMMENDED READINGS

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10.9 Disorders of Puberty

AC Ammini

INTRODUCTION

Puberty is the transitional period between childhood and adulthood when rapid linear growth, sexual maturation and reproduction capacity are attained. It is an extremely important phase in the physical and psychosocial development for both girls and boys. Initiation of puberty is brought about by a complex series of inter-related endocrine events leading to activation of the hypothalamo-pituitary-gonadal axis (**Figures 1 and 2**).

There has been a positive secular trend in adult height since mid 19th century in most European countries. Adult height is increased by 1.5 to 2 cm per decade during this period up to 1960. This was believed to be due to improvements in nutrition, hygiene and health care. During this period, age at menarche decreased from 17 years to 13 years.

Energy balance exerts a critical influence on puberty and reproductive functions. The neuroendocrine mechanisms involved in the coupling between energy homeostasis and puberty onset are not clear. This possibly involves several metabolic hormones and neuropeptides, which involve/interact at the brain/hypothalamic centres regulating reproduction. Some of the metabolic hormones could be insulin, leptin and ghrelin. These may act as links between energy store, like adipose tissue and reproductive system, indicating if adequate energy stores are present for normal reproductive functions.

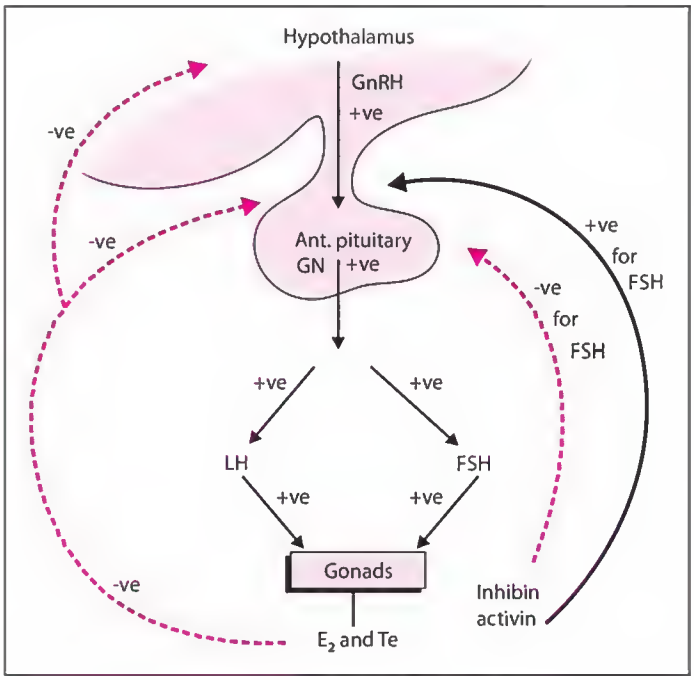


Figure 1: LH, FSH feedback mechanism.

E_2 = Oestradiol; Te = Testosterone; LH = Luteinising hormone; FSH = Follicle stimulating hormone; GN = Gonadotrophin.

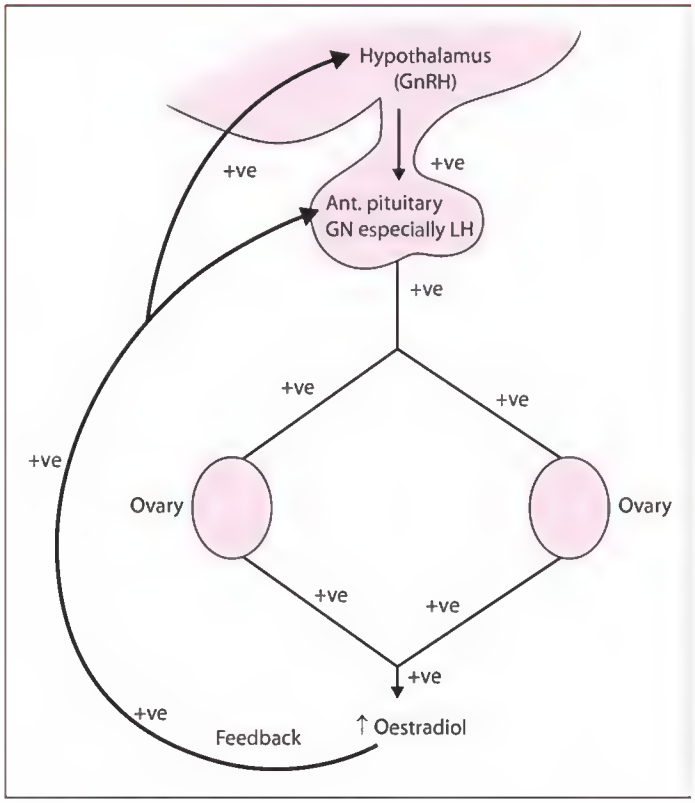


Figure 2: Midcycle positive feedback effect of oestradiol on hypothalamic-anterior pituitary axis.

Kisspeptin (product of Kiss 1 gene) acting through its receptor (G protein coupled receptor 54) has been shown to have an important role in the regulation of the gonadotrophic axis and reproduction. Mutations (in human) and deletions (genetically targeted mutations in mice) of either Kiss 1 or Kiss 1 receptor (GPR54) cause hypogonadotrophic hypogonadism. Neurones that express Kiss 1/Kisspeptin are found in discrete nuclei in the hypothalamus and other brain areas. Kisspeptin neurones stimulate gonadotrophin-releasing hormone (GnRH) neurones, the final common pathway, through which brain regulates reproduction. Kisspeptin neurones express both oestrogen and androgen receptors, and these neurones are believed to be direct targets for the action of gonadal steroids. This may be involved in triggering and guiding tempo of sexual maturation at puberty, preovulatory GnRH/LH surge, seasonal control of reproduction, etc. It also has functions outside the realm of reproductive endocrinology like in vascular dynamics, metastasis, placental physiology, etc.

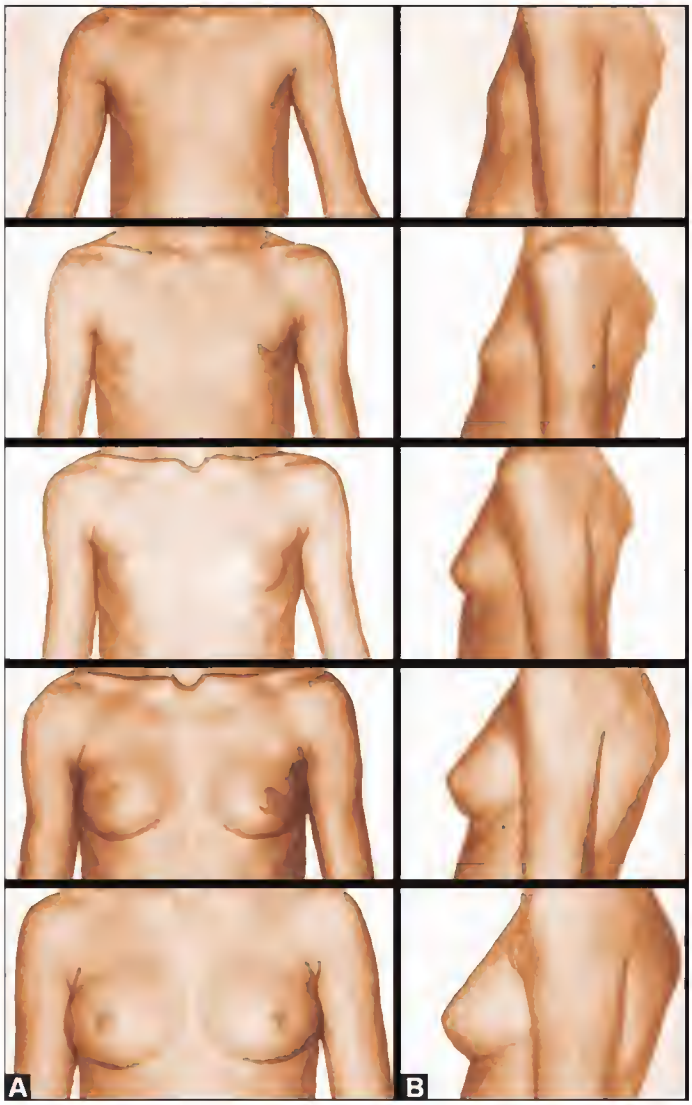
PINEAL GLAND

The status of the pineal gland has evolved from 'the seat of human soul' (Descartes, 17th century) to that of a neuroendocrine transducer with isolation of melatonin. It transforms the information about light received from retina to an endocrine response by synthesis and release of melatonin. Melatonin is a powerful neurotransmitter which makes the pineal gland, a

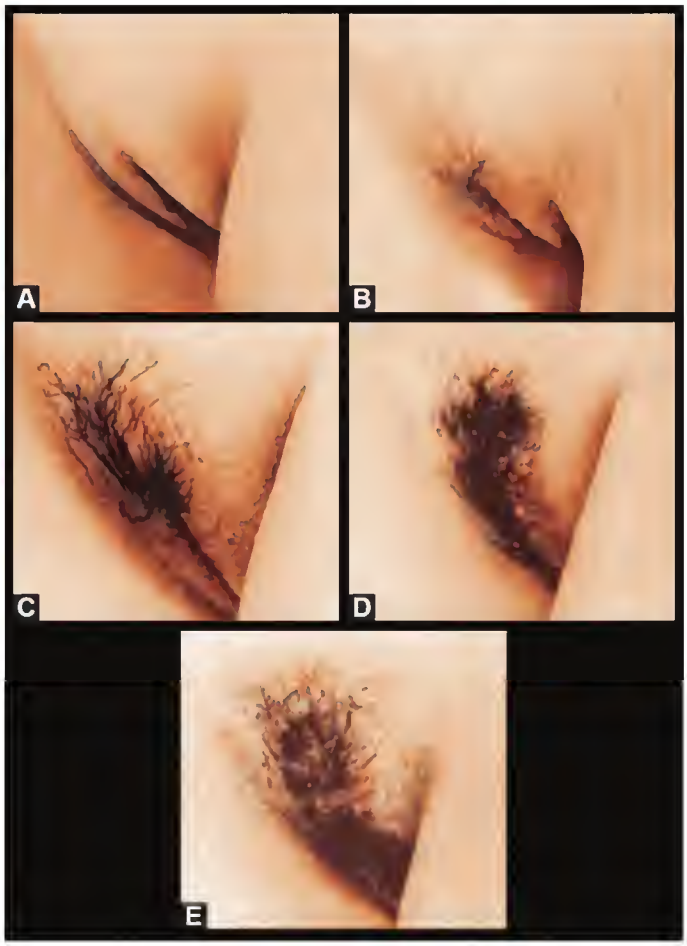
'biological clock'. Melatonin also has an antigonadotrophic effect in most animals. The seasonal changes in the number of hours per day that melatonin is secreted, mediate the temporal coupling of reproductive activity to seasonal changes in day length.

Increase in GnRH pulse frequency and amplitude triggers a cascade of events starting from increase in luteinising hormone (LH), follicle stimulating hormone (FSH) and sex steroids and this brings about the manifestations of puberty, both external (breast development, genital enlargement) and internal (uterus, ovaries, testes). Pubic hair develops largely through the effects of androgens secreted by the adrenal glands.

Sexual maturity scoring is used to describe different phases of puberty. The most widely used description of pubertal events in boys and girls is that of Marshall and Tanner who examined groups of English girls and boys as they went through puberty. The different phases of external pubertal development in girls are designated as Tanner stages, B1 through B5 for breast development (**Figures 3A and B**) and PH1 through PH6 for pubic hair growth (**Figures 4A to E**). It takes about 4 years from B2 (palpable breast bud under the nipple) to adult breast development. Breast development before the age of 8 years is considered precocious while no breast development till 13 years of age is considered delayed.



Figures 3A and B: Stages in normal breast development in female [front (A) and lateral view (A)].



Figures 4A to E: Stages of normal pubic hair development in female.

Pubertal development in boys begins with increase in testicular size (**Figures 5A to E**). Later pubic hair appears, penile size increases and voice breaks. Spermatozoa first become detectable around 13 to 14 years of age.

TIMING OF PUBERTY

Signs of puberty before the age of 8 years in girls and 9 years in boys are considered early or premature; while no signs of puberty till the age of 13 in girls and 14 in boys are defined as delayed puberty. Diagnostic evaluation is aimed at differentiating pathological conditions from normal variants. The normal variants include constitutional delay or acceleration of growth and development, premature thelarche, premature pubarche and pubertal gynaecomastia.

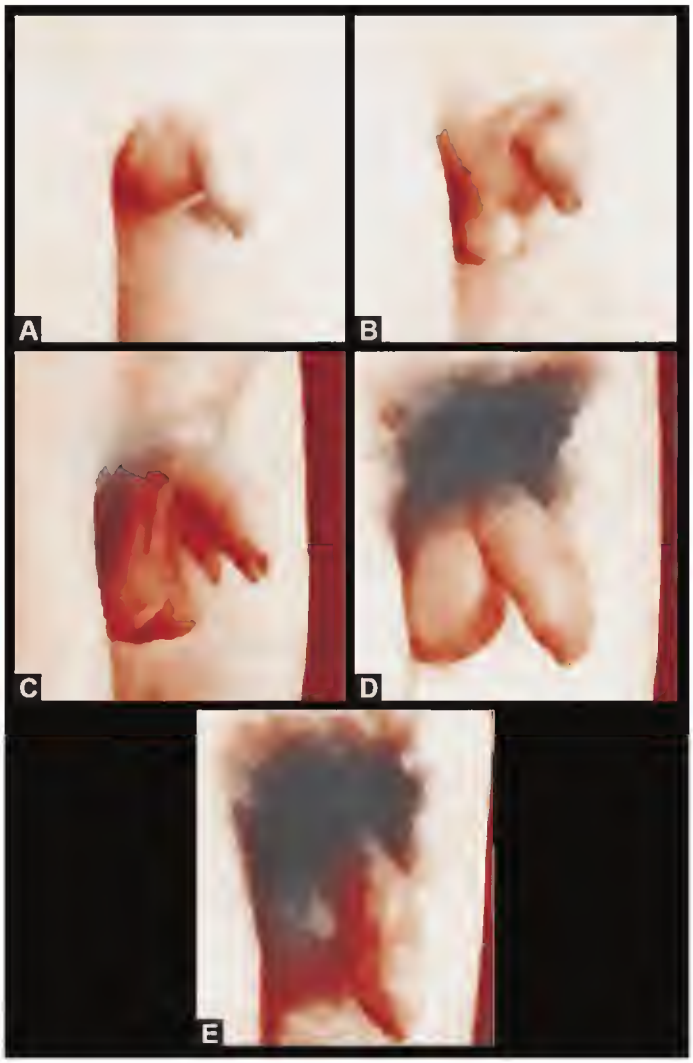
In constitutional delay of growth and development, there is spontaneous pubertal development, more than 2 SD, later than the mean age at onset of puberty. Growth is slower, but final adult height is often in the target range.

Premature Thelarche

Breast tissue develops early, sometimes during the first 2 years of life, occasionally in neonatal period and then persists till the time of puberty. It is an isolated event without signs of accelerated growth or skeletal maturation.

Premature Pubarche

It is the development of pubic or axillary hair (before age 8 in girls and 9 in boys). The adrenal androgen levels are normal, there is no increase in growth and skeletal age is comparable



Figures 5A to E: Stages in normal genital and pubic hair growth development in male.

to chronological age or slightly advanced. Premature pubarche is to be differentiated from premature adrenarche where adrenal androgens are elevated, like in congenital adrenal hyperplasia or androgen secreting tumour.

Pubertal Gynaecomastia

Some degree of gynaecomastia can be observed in over 50% of boys. In most cases, it is only a small induration under the nipple which regresses in 6 to 18 months. In some cases, it is more pronounced and persists longer. In such cases, medical/surgical intervention may be required. Rarely pubertal gynaecomastia can be due to increased oestrogen production or other conditions like Klinefelter's syndrome, partial androgen insensitivity syndrome, true hermaphroditism, etc.

Pathological conditions, which lead to early puberty, can be divided into gonadotrophin dependent (true precocious puberty) or gonadotrophin independent (precocious pseudopuberty) disorders.

GONADOTROPHIN DEPENDENT EARLY PUBERTY (TRUE PRECOCIOUS PUBERTY)

It is initiated by premature activation of hypothalamo-pituitary-gonadal (HPG) axis and is more common in girls. Prevalence is estimated to be 1 in 5000 to 1:10,000. It follows the normal sequence of events in pubertal development. The cause remains unidentified in 40% to 60% of cases, more so in girls. Lesions in pituitary hypothalamic area (hypothalamic hamartoma, glioma, astrocytoma, germinoma), internal hydrocephalus, earlier episodes of meningitis, radiotherapy, traumatic brain injury, etc. can cause true precocious puberty. The magnetic resonance imaging of brain is indicated in all cases of true precocious puberty.

GONADOTROPHIN INDEPENDENT PRECOCIOUS PUBERTY (PRECOCIOUS PSEUDOPUBERTY)

It starts before and independently of the HPG axis maturation. Appearance of secondary sexual characteristics is due to the increased production of sex steroids. HPG axis is suppressed due to the abnormally elevated sex steroids. Oestrogens produce isosexual puberty in girls and heterosexual puberty in boys. Similarly, androgens produce isosexual puberty in boys and heterosexual puberty in girls. There are several causes for precocious pseudopuberty including hormone secreting tumours of the central nervous system, adrenal gland, gonads and liver; testotoxicosis; McCune Albright syndrome; steroid biosynthetic disorders, like congenital adrenal hyperplasia.

Germ cell tumours secrete human chorionic gonadotrophin (hCG) which in turn stimulate LH receptors in testes which produce testosterone. These tumours can arise from the CNS (pituitary, pineal), liver, retroperitoneal or posterior mediastinum. Gonadal and adrenal tumours produce testosterone.

Familial Testotoxicosis

There is early Leydig cell maturation and testosterone production due to an activating mutation of the LH receptor. It is an autosomal dominant disorder, affecting only boys.

McCune Albright Syndrome

This syndrome manifests with café-au-lait spots, fibrous dysplasia and follicular cysts with precocious pseudopuberty. The cause is a somatic mutation in the alpha subunit of the G protein resulting in pathological over secretion of a variety of hormones. In addition to precocious pseudopuberty, patients may manifest with hyperthyroidism, Cushing's syndrome or increased growth hormone secretion.

Congenital adrenal hyperplasia is the most common cause for premature adrenarche. These patients may develop precocious true puberty after starting glucocorticoid therapy.

Absence of puberty could be due to disturbances in hypothalamus, pituitary or gonads (**Tables 1 and 2**). Plasma LH and FSH are low when it is pituitary or hypothalamus (hypogonadotrophic hypogonadism), while these are high when there is primary gonadal failure called hypergonadotrophic hypogonadism (**Table 3**). Sex steroids are low and follicular maturation or sperm production does not occur in both situations.

Table 1: Hypothalamic Causes for Absent Puberty

Migration disorder of the GnRH neurone (Kallman syndrome)
Disturbances of GnRH secretion
Mutations of GnRH receptor gene
Mutations in leptin/leptin receptor gene
Mutations in Kiss 1/GPR54 gene

Table 2: Pituitary Causes for Hypogonadism (Congenital or Acquired)

Congenital	
	Mutations in pituitary transcription factors
	Mutations of the gene for LH or FSH subunit
	Mutations of LH or FSH receptor gene
	Congenital midline defects
Acquired	
	Tumours of the hypothalamic pituitary region
	Pituitary surgery/radiation
	Hypophysitis and infiltrative disorders
	Post-traumatic

Table 3: Causes of Hypergonadotrophic Hypogonadism

Girls	Boys
Turner's syndrome and variants	Klinefelter's syndrome
Pure gonadal dysgenesis	Disorders of testosterone biosynthesis
Damage to ovaries	Testicular damage
– Oophoritis	– Radiation
– Radiation	– Chemotherapy
– Chemotherapy	– Torsion
– Surgical ablation	– Trauma

Absence of signs of puberty (breast development in girls or testicular volume less than 3 mL in boys) by 15 years requires evaluation. The major cause still will be constitutional delay in growth and development.

Functional hypothalamic hypogonadism refers to a reversible dysfunction usually associated with anorexia nervosa, severe emotional stress or participation in intense physical training.

Primary amenorrhoea in a girl with normal secondary sexual development should raise the possibility of congenital malformation of the genital tract (Müllerian duct). Cases of complete androgen insensitivity also present with primary amenorrhoea with normal breast development. Absence of pubic and axillary hair, and the presence of gonads in the labia are clues to diagnosis of this syndrome.

Children with disorders of sexual development also have problems of pubertal development. Congenital adrenal hyperplasia (CAH) is the most common cause for disordered sexual development in girls. Appropriately treated children enter puberty normally. However, some girls, especially those with simple virilising forms of CAH who did not receive medical attention during neonatal period, may present at puberty with masculinisation and primary amenorrhoea. 46 XY disorder of sexual differentiation (DSD), e.g. partial androgen insensitivity syndrome, disorders of testosterone biosynthesis, gonadal dysgenesis, etc. will also require appropriate treatment for proper pubertal development. It is a bigger challenge in our country as many of these may not have been diagnosed or treated during childhood.

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10.10 Disorders of Growth and Development

Nalini S Shah

Growth is a unique and complex process that is affected by multiple factors. However, children normally grow in a remarkably predictable manner. Deviation from a normal growth pattern can be the first manifestation of a wide variety of disease processes, including endocrine and non-endocrine disorders.

Clinical assessment using parameters like height measurement, growth velocity, use of appropriate growth charts, mid-parental height, body proportions and stage of puberty can generate valuable clues for differential diagnosis of growth disorders.

MEASUREMENT OF HEIGHT

Accurate serial height measurements documented over time on a growth chart are important for the diagnosis of growth abnormalities. During first 2 to 3 years of life, length should be measured with an infantometer (**Figure 1A**). It contains a firm horizontal platform, an attached yardstick, a fixed head plate, and a movable foot plate. During measurement, one person supports the child's head and ensures that the head is positioned in the Frankfort horizontal plane (lower margin of the bony orbit and upper margin of the external auditory meatus in the same horizontal line). A second person can align the child's legs by placing one hand with gentle pressure over the knees. With the other hand, foot piece is slided to rest firmly against the soles of the feet which are flexed perpendicular against the foot piece (**Figure 1B**). After 2 to 3 years of age, height should be measured on a wall-mounted, well-calibrated ruler with an attached horizontal measuring bar fixed at 90 degrees [e.g. a stadiometer (**Figure 1C**)]. The child should stand erect with the back of the head, back, buttocks area and heels touching the vertical bar of the stadiometer; the horizontal measuring bar is lowered to the child's head to obtain the measurement (**Figure 1D**). The height can be expressed as standard deviation scores (SDS or Z scores). Z score is calculated using the formula: (Child's height – mean height for age from a reference chart) ÷ 1 SD of height for that age and sex in the reference chart. The Growth Monitoring Guidelines Consensus Meeting of the Indian Academy of Paediatrics recommends the use of Agarwal *et al*, growth charts as reference charts for Indian children.

In addition to height, weight measurement will provide clues towards the aetiology of short stature. Normal or elevated weight SDS points towards endocrine disorders like Cushing's syndrome or pseudohypoparathyroidism while low weight SDS points towards systemic illnesses.



Figures 1A to D: (A) Infantometer; (B) Method of measuring length with an infantometer; (C) Stadiometer; (D) Method of measuring height with a stadiometer.

HEIGHT VELOCITY AND GROWTH PATTERN

Assessment of height velocity is an essential part of evaluation of a short child. Length of an average Indian child at birth is 50 cm. During infancy, the average height gain is 25 cm reaching 75 cm by first birthday. During second year, the growth rate is 12.5 cm followed by 6 to 7 cm during third and fourth years. After that, the growth rate is approximately 5 cm per year till pubertal spurt. A growth spurt is observed during pubertal period which may be up to 11 cm/year in girls and 12 cm/year in boys. Average total height gain during the pubertal period is 24 to 25 cm and 27 to 29 cm in girls and boys respectively. The majority of mean height difference between adult men and women results partly from the height difference at the age of pubertal onset, with boys being taller at their later age of takeoff than girls and partly from greater gain in height of boys during the pubertal growth spurt.

The growth pattern of a child should be recorded on a growth chart to have a longitudinal assessment of growth. Intrauterine environment affects the size of a baby at birth. During first 18 to 24 months of life, children pass through an important phase of growth, often called catch-up or catch-down growth. It is characterised by moving up or down on the growth chart which depends on the height of parents so that most children achieve their genetically determined height percentiles by 2 years of age. Thereafter, growth typically proceeds along the same percentile until the onset of puberty. Children with constitutional delay of growth and puberty (CDGP) grow at a rate parallel to but below the 3rd percentile, whereas children with conditions such as growth hormone deficiency or systemic illnesses have a growth pattern that progressively falls further below the 3rd percentile or crosses percentiles. Growth patterns of few common disorders causing short stature are shown in **Figure 2**.

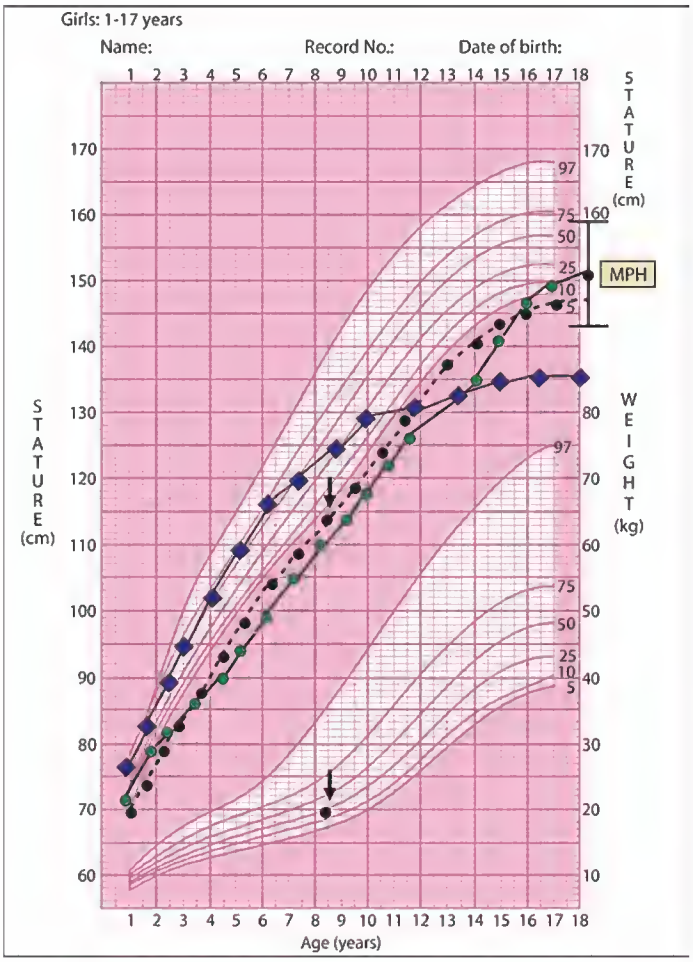


Figure 2: It Illustrates charting of height and weight of an 8½ years old short girl (height below 5th percentile line and weight at 25th percentile) marked by arrows. It also illustrates extension of height percentile parallel to 5th percentile line till 18 years of age (black circles) and compares it with mean parental height (MPH) and target height range which helps to differentiate familial short stature (black circles) from pathological short stature (blue diamonds). The figure also shows typical growth patterns of a child with constitutional delay in growth and puberty (green circles).

GENETIC POTENTIAL

Most commonly used but a crude method to assess the genetic potential is to calculate the midparental height (Target height). The midparental height is a child's expected adult height based on the heights of the parents. It is calculated by the formula: average of mother's height and father's height plus or minus 6.5 cm for boys and girls respectively. It is important to measure the parents' heights in the office, rather than use their reported height to avoid over-or underestimation of midparental height. A rough estimate of the child's projected height, without taking skeletal maturation or pubertal tempo into account, can be determined by extrapolating the child's growth along his or her own height percentile to the corresponding 18-year point. If the estimated final height is within 8 to 10 cm of the midparental height, the child's current height is appropriate for the family. However, if the projected height differs from the midparental height by more than 8 to 10 cm, a variant growth pattern or a pathologic cause should be considered.

BODY PROPORTIONS

The evaluation of upper-to-lower body segment ratios in short children helps to differentiate causes of disproportionate short stature like skeletal dysplasia from causes of proportionate short stature. Lower segment is determined by measuring the distance from the top of symphysis pubis to the floor in a child standing in erect position. The lower body segment is subtracted from the child's height to obtain the upper body segment value. The upper-to-lower body segment ratio (US:LS ratio) is then derived by dividing the upper body segment value by the lower segment value. Body proportions vary with age of a child. The average US:LS ratio is 1.7 at birth and decreases to 1.3 at 3 years, 1.1 at 6 years and 1.0 at 10 years of age. Children with achondroplasia have a normal sized trunk with short limbs, while children with spondyloepiphyseal dysplasias will have short trunk with normal limbs.

Measuring the arm span is also crucial in the evaluation of body proportions. The arm span is the distance between the tips of the left and right middle fingers when a child is standing against a flat wall with arms outstretched as far as possible, creating a 90 degree angle with the torso. Arm span is shorter than height by 2.5 cm at birth and equals height by 10 years of age. Children with long limbs like Klinefelter's syndrome and short trunk like scoliosis may have a disproportionately higher arm span than height.

PUBERTAL ASSESSMENT

Pubertal assessment has an important role in the diagnosis of short stature. Onset of puberty is followed by height spurt which

is seen during adolescence. Hence, onset and progression of puberty will affect the stature in the peri- and post pubertal periods. The stage of puberty is assessed by the Tanner's method of sexual maturity rating. Orchidometer is used for accurate measurement of testicular volume.

BONE AGE ASSESSMENT

Bone age estimation is an important investigation in the evaluation of short child. This is conventionally done from X-rays of wrist and hand. The bone age is estimated from the appearance of epiphysis, size and shape of bones using Greulich-Pyle atlas or Tanner-Whitehouse method. A child with delayed bone age has a better prognosis for future height gain than those with appropriate or advanced bone age. Children with familial genetic short stature have bone age appropriate for chronologic age whereas CDGP children have slightly delayed bone age. Children with endocrine causes such as growth hormone deficiency or hypothyroidism are likely to have markedly delayed bone age. Adult height can be predicted with the help of Bayley-Pinneau charts by using chronologic age and bone age.

SHORT STATURE

Short stature is defined as height that is two standard deviations below the mean height for age and sex (less than the 3rd percentile) or more than two standard deviations below the midparental height. A growth velocity disorder is defined as an abnormally slow growth rate, which may manifest as height deceleration across two major percentile lines on the growth chart. Many children with height SDS less than 2 SD may not be pathological and hence, evaluation for short stature may be limited to children with following features:

1. Severe short stature [height (Ht) SDS < -3SD)]
2. Severe growth deceleration [height velocity (HV) SDS < -2 SD over 12 months]
3. Ht SDS < -2 SD and HV SDS < -1SD over 12 months
4. Ht SDS < -1.5 SD and HV SDS < -1.5 SD over 2 years.

Causes of short stature are listed in **Table 1**. **Table 2** summarises the points to be focused during history-taking physical examination of a short child. **Figure 3** represents an algorithm for the evaluation of a short stature. **Figures 4A to H** shows few children suffering from one of the common disorders leading to short stature.

Table 1: Causes of Short Stature According to the ESPE Classification

A. Primary Growth Disorders

1. ***Clinically defined syndromes***
   - Turner syndrome
   - Cornelia de Lange syndrome
   - DiDeorge syndrome (velocardiofacial syndrome)
   - Down's syndrome
   - Noonan's syndrome
   - Prader-Willi-Labhart syndrome
   - Neurofibromatosis type 1
   - Silver-Russell syndrome
2. ***Small for gestational age with failure of catch-up growth***
   - IGF-I deficiency, IGF resistance
   - Due to known cause, e.g. prenatal infections, drugs, smoking, alcohol
   - Idiopathic
3. ***Skeletal dysplasias***
   - Achondroplasia
   - Hypochondroplasia
   - Dyschondrosteosis (Leri-Weil and other defects in the SHOX gene)
   - Osteogenesis imperfecta I-VI
   - Mucopolysaccharidosis (type IH, IS, II-VII)
   - Mucolipidosis (type II and III)
4. ***Dysplasias with defective mineralisation***
   - Hypophosphatasia
   - X-linked hypophosphataemic rickets

B. Secondary Growth Disorders

1. ***Insufficient nutrient intake (malnutrition)***
2. ***Disorders in organ systems***
   - Cardiac disorders
   - Pulmonary disorders, e.g. cystic fibrosis
   - Liver disorders
   - Intestinal disorders, e.g. Crohn's disease, malabsorption syndromes
   - Short bowel syndrome
   - Renal disorders, e.g. Fanconi syndrome, renal acidosis chronic anaemia, e.g. thalassaemia
3. ***Growth hormone deficiency (Secondary IGF-1 deficiency)***
   - Idiopathic
   - Genetic (HESX1, PROP1, POU1F1, LHX3, LHX4, GHRHR, GH)
   - Associated with syndromes of cerebral or facial malformations, e.g. septo-optic dysplasia, empty sella syndrome
   - Associated with perinatal conditions, e.g. Rubella
   - Acquired (craniopharyngioma, other pituitary tumours, e.g. germinoma, hamartoma)
   - Head trauma
   - Central nervous system infections
   - Granulomatous disease, e.g. histiocytosis
4. ***Other disorders of the growth hormone-IGF axis (primary IGF-I deficiency and resistance)***
   - Bio-inactive growth hormone
   - Abnormalities of the growth hormone receptor (growth hormone insensitivity syndrome)
   - Abnormalities of GH signal transduction, e.g. STAT5B defect
   - ALS (acid-labile subunit) deficiency
   - IGF-I deficiency
   - IGF resistance (IGF1R defects, postreceptor defects)
5. ***Other endocrine disorders***
   - Cushing syndrome
   - Hypothyroidism
   - Leprechaunism
   - Diabetes mellitus (poorly controlled)
   - Short adult stature caused by accelerated bone maturation, e.g. precocious puberty, hyperthyroidism, CAH, exogenous oestrogens or androgens
6. ***Metabolic disorders***
   - Disorders of calcium and phosphorus metabolism
   - Disorders of carbohydrate metabolism
   - Disorders of lipid metabolism
   - Disorders of protein metabolism
7. ***Psychosocial***
   - Emotional deprivation
   - Anorexia nervosa
   - Depression
8. ***Iatrogenic***
   - Systemic glucocorticoid therapy
   - Local glucocorticoid therapy (inhalation, intestinal, others)
   - Other medication
   - Treatment of childhood malignancy
   - Total body irradiation
   - Chemotherapy
   - Other specified iatrogenic causes

C. Idiopathic Short Stature

1. ***Familial (idiopathic) short stature***
2. ***Non-familial (idiopathic) short stature***

Table 2: Points to be Focused during History-taking and Evaluation of a Short Child

History	Comments
Birth size (length, weight, head circumference) and gestational age	To identify small for gestational age (symmetric vs asymmetric)
Birth history (breech delivery, asphyxia, jaundice, hypoglycaemia)	Associated with pituitary dysfunction
Previous growth information	May provide clues about the aetiology
Onset and progression of puberty	Has significant impact on stature
Current and previous medical history	***Identify organic or iatrogenic causes***
Cardiac: dyspnoea, anasarca, cyanosis	Cardiac failure, cyanotic heart disease
Pulmonary: chronic cough, dyspnoea	Cystic fibrosis, bronchial asthma, tuberculosis
Intestinal: abdominal distension, diarrhoea	Malabsorption syndromes like coeliac disease
Renal: polyuria, vomiting, fatigue	Chronic kidney disease, RTA
Neurological: headache, vomiting, focal neurological deficits	Neurotuberculosis, sellar or perisellar tumours, brain tumours treated with radiotherapy
Previous surgeries: intestinal resection	Short bowel syndrome
Medications like glucocorticoid	Glucocorticoid induced growth suppression
Feeding history (feeding difficulties, total calorie and protein intake)	Feeding difficulties during first year in PWS and poor nutrition affects growth (weight > height)
Parental height	Required to assess genetic potential to grow
Tempo of puberty in parents	To look for familial pattern of delayed puberty
Family history	To look for a genetic cause
Delayed milestones, mental retardation	Genetic syndromes and metabolic disorders
Social environment	To look for emotional deprivation
Physical examination	
Underweight	Malnutrition, malabsorption, hypocortisolism, metabolic disorders, SGA
Obesity	Hypothyroidism, Cushing's syndrome, IGF-1 deficiency, Pseudohypoparathyroidism
Microcephaly	Birth asphyxia, symmetric SGA, syndromes
Macrocephaly	Hydrocephalus, achondroplasia, storage disorders
Short trunk or short limbs	Skeletal dysplasias
Dysmorphic features	Primary growth disorders (syndromes)
Frontal bossing, mid-facial hypoplasia	IGF-1 deficiency
Round facies, facial plethora, virillisation	Cushing's syndrome
Pharyngeal examination	Look for adenotonsillar hypertrophy
Bradycardia, dry skin, goiter	Hypothyroidism
Hypertension	Kidney disease, Cushing's syndrome
Hepatosplenomegaly	Hepatic or metabolic disorder
Pubertal stage	Early, normal or late puberty
Micropenis	Hypogonadism, hypopituitarism
Fundoscopy, visual field defect	Central nervous system pathology
Signs of neglect or abuse	Emotional deprivation

MANAGEMENT

Identification and appropriate management of the systemic illnesses improves growth in most of the disorders. Chronic infections like tuberculosis should be treated with appropriate (anti-tubercular) medications. Haemolytic anaemias like thalassaemia should be treated with regular blood transfusions and iron chelating agents. Gluten free diet is the treatment of choice for coeliac disease. Nutritional rickets is treated with supplementation of vitamin D and calcium. Hypophosphataemic rickets is treated with phosphate supplementation and calcitriol while vitamin D dependent rickets are managed with normal to high doses of calcitriol. Distal renal tubular acidosis is treated with Shohl's solution and potassium supplementation while proximal renal tubular acidosis is treated with sodium bicarbonate and potassium supplementation. Hypothyroidism should be treated with L-thyroxine. Conditions which have received FDA approval for growth hormone (GH) therapy and the doses of GH advocated in these disease states are shown in **Table 3**. Growth hormone is given as daily subcutaneous injections before bedtime. IGF-1 treatment is effective in GH insensitivity.

Table 3: Indications and Doses of Growth Hormone Therapy in Children

Indication	Dose of GH (mg/kg/wk)
Growth hormone deficiency	0.18 to 0.3
Chronic kidney disease	0.35
Turner syndrome	0.375
SGA children with failure to catch up growth	0.47 to 0.48
Idiopathic short stature	0.48 to 0.37
Prader Willi syndrome	0.24
Noonan syndrome	0.46
SHOX gene haploinsufficiency	0.35

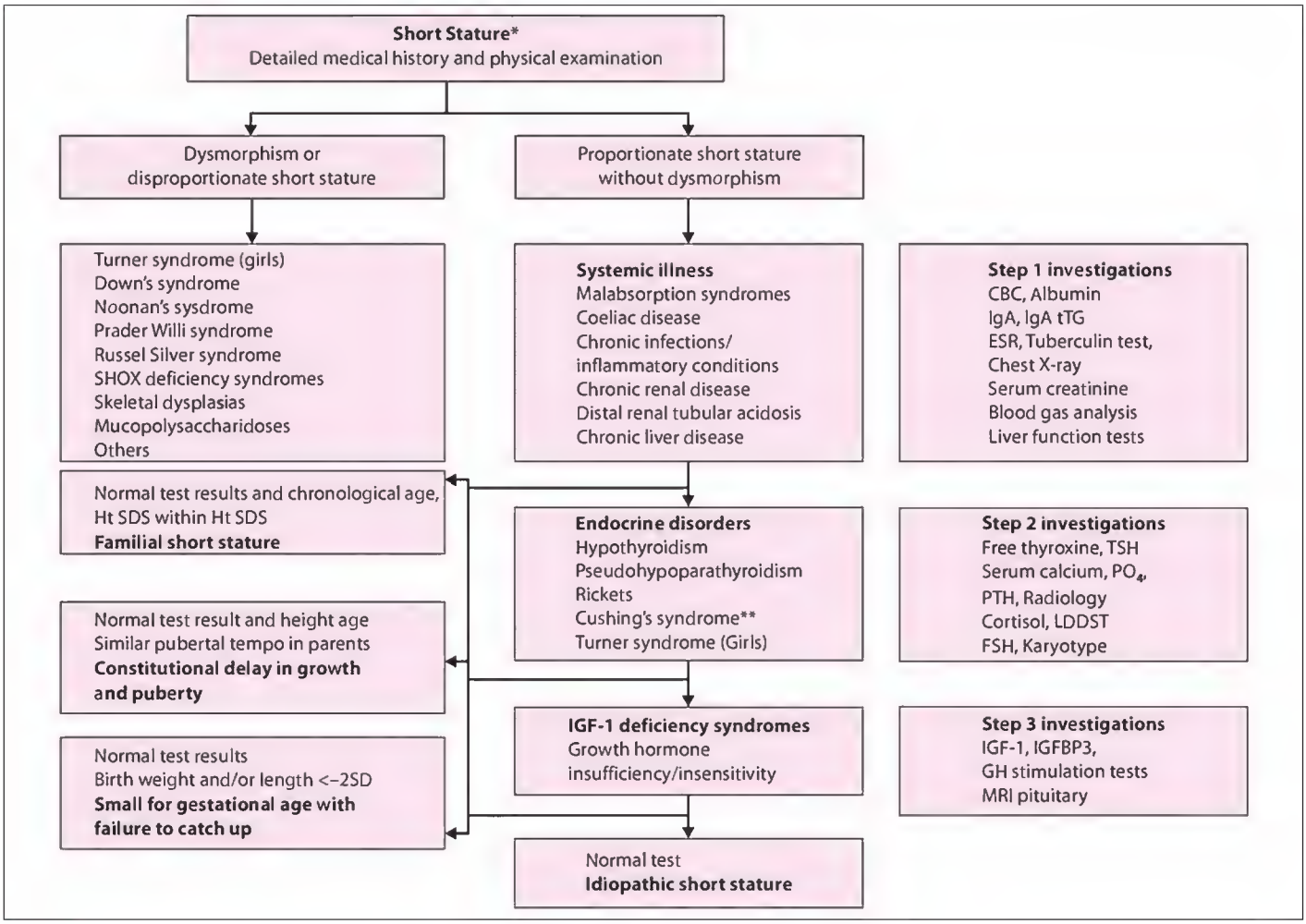


Figure 3: An algorithm depicting approach to a child with short stature.

**Consider psychosocial dwarfism at any step if features of abuse/neglect are identified; **Only if clinical features are suggestive. CBC = Complete blood count; ESR = Erythrocyte sedimentation rate; FSH = Follicle stimulating hormone; GH = Growth hormone; IgA tTG: IgA antibodies to tissue transglutaminase; IGF = Insulin-like growth factor; LDDST = Low dose dexamethasone suppression test; IGFBP3 = IGF binding protein-3; MRI = Magnetic resonance imaging; PO_4 = Phosphorous; SD = Standard deviation; SDS = Standard deviation score.*



Figures 4A to H: Children suffering from one of the common disorders leading to short stature.

A = Cushing's syndrome; B = Prader Willi syndrome; C = Primary hypothyroidism; D = Nutritional rickets; E = Growth hormone insufficiency; F = Pseudoparathyroidism type 1a; G = Turner syndrome; H = Coeliac disease.

TALL STATURE

Tall stature is defined as a height that is 2 SD above the mean for age and sex. Excessive growth could also manifest as height acceleration across two major percentile lines on the growth chart. It is important to distinguish the pathological causes from physiological causes of tall stature. Though only few tall children have a defined pathology, tall stature or height acceleration may be the initial manifestation of serious underlying diseases, such as congenital adrenal hyperplasia. Causes of tall stature are listed in **Table 4** and an algorithmic approach to a tall child is depicted in **Figure 5**.

Management of Tall Stature

Reassurance of the family and the patient is the key to the management of normal variant tall stature. Hypogonadism is treated by replacement with appropriate sex steroids. For eugonadal, extremely tall children whose parents feel strongly about treatment, a trial of sex steroid may be considered. However, it should be restricted to patients with predicted adult height more than 3 SD above the mean. Since, sex steroids act by accelerating puberty and epiphyseal fusion, initiation of therapy in prepubertal or early pubertal phase has better results.

Children with excess GH status are managed with one or more of the following modalities of treatment viz, excision of pituitary adenoma, somatostatin analogues (Octreotide LAR, Lanreotide),

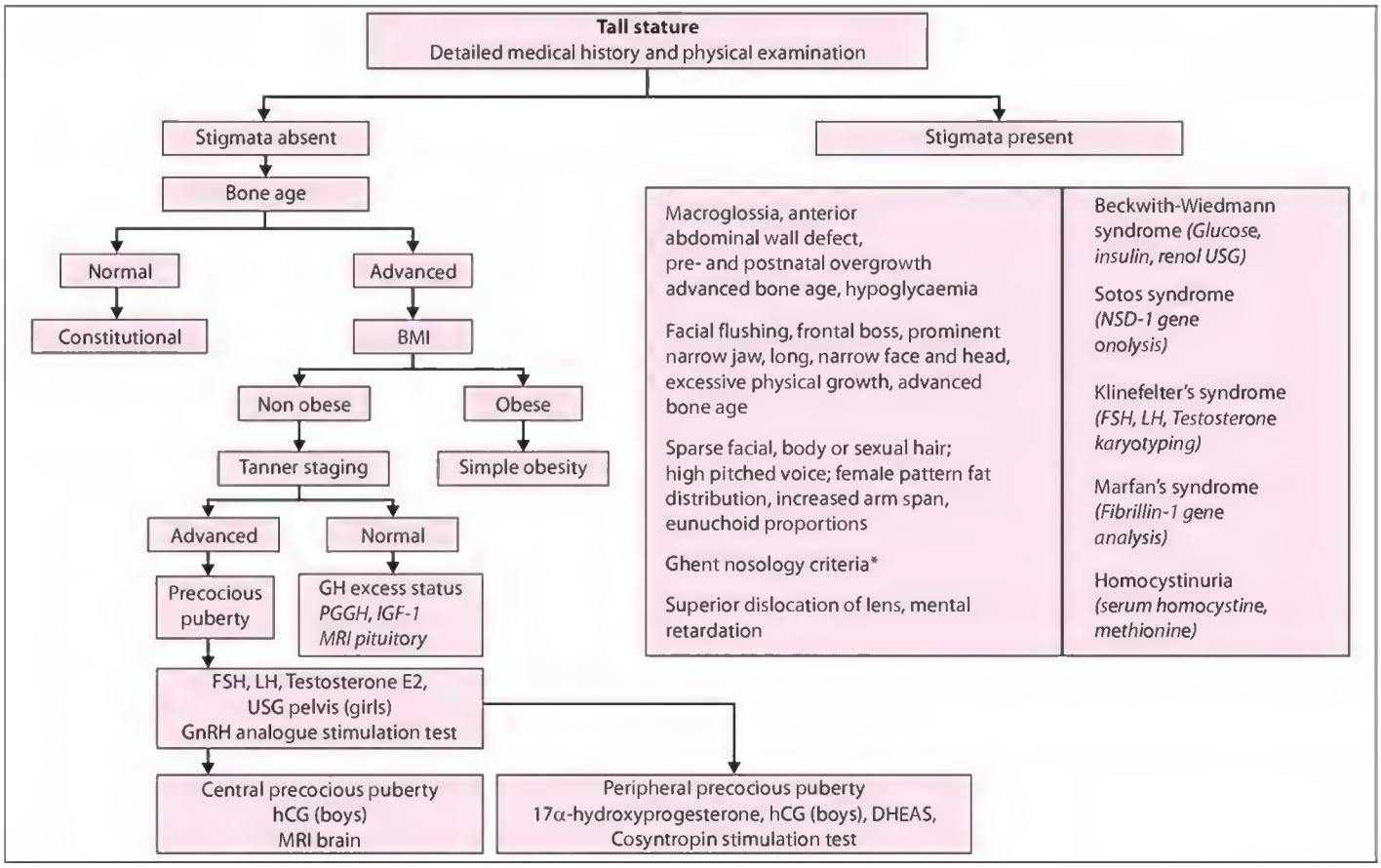


Figure 5: An algorithm depicting approach to a child with tall stature.

BMI = Body mass index; DHEAS = Dehydroepiandrosterone sulphate; E2 = Oestrodiol; FSH = Follicle-stimulating hormone; GH = Growth hormone; GnRH = Gonadotropin-releasing hormone; hCG = Human chorionic gonadotropin; IGF-1= Insulin-like growth factor-1; LH = Luteinising hormone; MRI = Magnetic resonance imaging; PGGH = Post-glucose growth hormone; USG = Ultrasonography.
**The clinical criteria for the diagnosis of Marfan syndrome, which requires a combination of findings in different organ systems.*

Table 4: Causes of Tall Stature

Foetal overgrowth
Maternal diabetes mellitus
Cerebral gigantism (Sotos syndrome)
Weaver syndrome
Beckwith-Wiedemann syndrome
Other IGF-2 excess syndromes

Post-natal overgrowth leading to childhood tall stature
Familial (constitutional) tall stature
Cerebral gigantism
Beckwith-Wiedemann syndrome
Exogenous obesity
Excess GH secretion (Pituitary gigantism)
Precocious puberty
Marfan syndrome
Klinefelter's syndrome
Weaver syndrome
Fragile X syndrome
Homocystinuria
XYY
Hyperthyroidism

Post-natal overgrowth leading to adult tall stature
Familial (constitutional) tall stature
Androgen/oestrogen deficiency or estrogen resistance in males
Testicular feminisation
Excess GH secretion
Marfan syndrome
Klinefelter's syndrome
XYY

GH receptor antagonist (Pegvisomant) or radiotherapy. Suppression of adrenal androgens with appropriate replacement of glucocorticoids (hydrocortisone, prednisolone or dexamethasone) with or without mineralocorticoids (fludrocortisone) forms the essential treatment of precocious puberty with congenital adrenal hyperplasia. Central precocious puberty is treated with GnRH analogues (Leuprolide acetate).

CONCLUSION

Disorders of growth, especially short stature are common problems in paediatric age group. Thorough clinical assessment using auxological parameters can lead to correct differential diagnosis and hence appropriate evaluation and management. Prudent use of endocrine tests can clinch diagnosis in most of the patients. Management options largely rest on correct diagnosis. Monitoring of therapy with appropriate dosage schedule modification and patient education to ensure compliance are keys to long-term success.

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10.11 Disorders of Gonads

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Gonadal disorders in females are treated by gynaecologists. Hence only gonadal disorders which occur in males are discussed here.

PHYSIOLOGY

Testosterone is the primary male hormone, not only responsible for normal development of the male characteristics and maintenance of bone and muscle, but also due to its positive effect on mood, energy levels and sexual drive. Testosterone is mainly produced in the Leydig cells located in the interstitial spaces of the testes. Normal adult men produce 4 to 10 mg of testosterone per day in a circadian pattern, with maximal plasma levels reached in early morning and minimal levels in the evening. Testosterone is the principal androgen of which 95% is made in testes, 5% in adrenals. It is synthesised from cholesterol at approximately 6 mg/day and metabolised by liver and excreted in urine. Testosterone can be bioconverted into two other steroids at target tissues—dihydrotestosterone and oestradiol.

Dihydrotestosterone (DHT) binds more readily to androgen receptors. Conversion takes place in the prostate, seminal vesicles and pubic skin. DHT is 10 times more powerful than testosterone, thus conversion amplifies the action of testosterone. DHT may be responsible for male pattern baldness and benign prostatic hypertrophy.

Oestradiol is an oestrogen of which 25% is made by testes and 75% bioconverted in the liver and the brain from testosterone. It is responsible for aggressiveness in men.

HYPOGONADISM

Hypogonadism is defined as 'inadequate gonadal function, as manifested by deficiencies in gametogenesis and/or the secretion of gonadal hormones'.

General Manifestations

Hypogonadism may manifest with testosterone deficiency, infertility, or both conditions. Symptoms of hypogonadism depend primarily on the age of the male patient at the time of development of the condition. Hypogonadism is seldom recognised before the age of puberty unless it is associated with growth retardation or other anatomic or endocrine abnormalities. When hypogonadism develops before the age of puberty, the manifestations are those of impaired puberty (**Table 1**).

Table 1: Pre-Pubertal Hypogonadism

Small testes, phallus, and prostate scant pubic and axillary hair
Disproportionately long arms and legs (from delayed epiphyseal closure)
Reduced male musculature
Gynaecomastia
Persistently high-pitched voice

Post-pubertal loss of testicular function results in slowly evolving subtle clinical symptoms and signs. In ageing men, these symptoms and signs may be difficult to appreciate because they are often attributed to 'getting older'. The growth of body hair usually slows, but the voice and the size of the phallus and prostate remain unchanged. Temporal hair recession and balding usually do not occur and would not be expected to prompt a patient to seek medical attention. Patients with hypogonadism may have the following findings (**Table 2**).

Table 2: Post-Pubertal Hypogonadism

Progressive decrease in muscle mass
Loss of libido
Impotence
Oligospermia or azoospermia
Occasionally, menopausal-type hot flushes (with acute onset of hypogonadism)

The risk of osteoporosis and attendant fractures is increased. Many cases of hypogonadism are disclosed during the course of infertility evaluations.

Evaluation

A comprehensive history should be elicited and a complete physical examination should be performed to help determine the cause and extent of the hypogonadism.

History

Any history of loss of libido, sexual dysfunction, or impotence should be generally noted. A history of use of medications, herbal preparations, or home remedies and any history of possible exposure to oestrogens should be elicited.

A history of anosmia or hyposmia, midline defects, or cryptorchidism may be suggestive of Kallmann's syndrome or other types of hypogonadotrophic hypogonadism. A family history may indicate an underlying genetic basis.

Primary testicular failure is usually associated with genetic syndromes such as Klinefelter's syndrome or congenital disorders such as anorchism. Testicular failure may also be associated with a history of testicular trauma, certain surgical procedures in the area, cryptorchidism, mumps orchitis, and, occasionally, toxic exposures, radiation treatment or chemotherapy.

A post-pubertal onset of hypogonadotrophic hypogonadism, generally manifesting as loss of libido, sexual dysfunction, or impotence, should suggest the likelihood of a pituitary tumour. Indications of other endocrine deficiencies such as central hypothyroidism or secondary adrenal insufficiency, visual field disturbances, headaches, or seizures may also be associated findings.

Physical Examination

The amount and distribution of body hair, including beard growth, axillary hair, and pubic hair, should be noted, as should the presence of a male pattern escutcheon. (The ethnic origin of the patient should be considered in this assessment. Some communities are more hairy than others).

The presence and degree of gynaecomastia should be recorded. The presence of galactorrhoea would suggest pronounced hyperprolactinaemia.

The testes should be measured (length and width) by using a Prader orchidometer or callipers. Some testicular disorders may selectively affect production of sperm without influencing production of testosterone. These disorders may sometimes be detected by careful physical examination, including determination of testicular size and consistency. Because approximately 85% of testicular mass consists of germinal tissue, a reduced germinal cell mass would be associated with a reduced testicular size and a soft consistency. Testicular growth is a reliable index of pubertal progression in peri-pubertal boys, in whom hypogonadism may frequently be difficult to distinguish from delayed puberty (**Table 3**).

Table 3: Approximate Ranges of Testicular Size

Age	Testicular volume (ml)	Testicular length (cm)	Testicular width
Pre-pubertal	3 to 4	<3	<2
Peri-pubertal	4 to 15	3 to 4	2 to 3
Adult	20 to 30	4.5 to 5.5	2.8 to 3.3

Testicular consistency should be noted. If the germinal epithelium was damaged before puberty, the testes are generally small and firm. If post-pubertal damage occurred, the testes are usually small and soft.

On examination of the scrotum, the presence of any masses or varicocoeles should be noted for further evaluation. For assessment of any potentially significant varicocoele, the patient should be asked to perform a Valsalva manoeuvre.

In prepuberty, the length of the stretched penis is about 4 to 8 cm, and the width is less than 2 cm in a flaccid state. In the adult, the length of the penis ranges from about 10 to 17 cm, and the width in the flaccid state is more than 3 cm.

With prepubertal onset of hypogonadism, the stature may assume eunuchoidal proportions, with a crown-to-pubis divided by a pubis-to-floor ratio of <1 and an arm span more than 6 cm greater than the height.

Laboratory Investigations

Testosterone

Testosterone levels vary from hour to hour; an overall diurnal rhythm is also present, and the highest levels of circulating testosterone occurring in the early morning hours. Therefore, testosterone levels should be determined in the morning, and patients with subnormal levels should have repeated studies, especially those with no definite signs or symptoms of hypogonadism. For a reliable testosterone determination, use of three pooled morning testosterone samples will minimise errors attributable to the variation in testosterone levels.

Testosterone circulates principally in bound form, mainly to sex hormone-binding globulin (SHBG) and albumin. It tightly binds to SHBG and is not biologically available, whereas the testosterone fraction associated with albumin is weakly bound and can dissociate to free, active testosterone. Only about 2% of testosterone is in the free form, 30% is bound tightly to SHBG, and 68% is weakly bound to albumin.

Although a testosterone determination is the threshold test in the evaluation of suspected male hypogonadism, the total testosterone concentration may be within the normal range in men with primary testicular disorders such as Klinefelter's syndrome. Low production of testosterone stimulates production of SHBG from the liver. Male patients with hypogonadism often have high SHBG levels because of enhanced production of oestradiol from increases in intratesticular aromatisation. Therefore, if the clinical findings indicate that hypogonadism is present and the total testosterone levels are normal or borderline low, an SHBG or free testosterone level should be determined. Free testosterone assays are method-dependent and may be difficult to interpret. Because albumin binds testosterone weakly, the amount of free testosterone measured will vary with the technique. Equilibrium dialysis free testosterone measurements are used to determine the amount of testosterone not bound to SHBG, but are generally not available.

Conversely, a low testosterone level may also be misleading under some circumstances. Slightly subnormal levels of total testosterone may occur in men with low levels of SHBG and normal circulating levels of free testosterone. A low SHBG level may be associated with hypothyroidism, obesity, or acromegaly. SHBG or free testosterone levels may be helpful for clarifying the underlying disorder, especially when the clinical findings are not suggestive of hypogonadism.

Gonadotropins

If a low testosterone level has been established, further laboratory testing is used to determine whether the hypogonadism is related to a primary testicular disorder (hypergonadotrophic hypogonadism) or to pituitary disease (hypogonadotrophic hypogonadism). The primary feature of hypogonadotrophic hypogonadism is the failure of a reciprocal increase in gonadotropins in the setting of a sub-stantially decreased testosterone level. In patients with signs and symptoms indicative of hypogonadism, determining luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels together with the initial testosterone level in a single sample is usually most efficient.

FSH and LH may have variable biologic activity, depending on their carbohydrate content. Unlike standard radioimmuno-assays, highly sensitive, two-site radioimmunometric assays for gonadotropins yield results that generally correlate well with biologic assays. Because the biologic to radioimmunologic ratio of activity of gonadotropins may vary in aging and various disease states, the most accurate results will be obtained with these highly sensitive assays. Assays for gonadotropins currently lack the sensitivity to detect values below the normal range. Additional studies, such as gonadotropin-releasing hormone (GnRH) testing, by an endocrinologist may help in the further assessment of these patients.

Both FSH and LH are secreted in short pulses. FSH has a longer half-life than does LH and is more likely to provide adequate results on a single blood sample. In addition, most patients with progressive hypogonadism will have increased FSH levels well before LH levels increase. Because LH has a shorter half-life than does FSH, errors may be introduced in measurements made on single samples. Pooled samples for LH done 20 to 30 minutes apart are more accurate than single-sample determinations (albeit less convenient). Persistent borderline values may be further evaluated with dynamic endocrine testing. These tests may include the GnRH stimulation test, the clomiphene stimulation test, and the human chorionic gonadotropin (hCG) stimulation test. These specialised, dynamic studies should be conducted and interpreted by an endocrinologist and may have limited clinical value.

Dynamic Tests

GnRH stimulation test

In the GnRH stimulation test, intravenous injection of 100 mg of GnRH causes serum LH levels to increase three-fold to six-fold during a period of 30 to 45 minutes and FSH levels to increase between 20% and 50%. Various degrees of primary testicular failure cause higher than expected peak values for LH and FSH. Men with hypothalamic or pituitary disease may have a reduced or normal response that is often inadequate for distinguishing between a pituitary and a hypothalamic disorder. If the pituitary gland is primed with repeated doses of GnRH, the stimulation test may provide a more sensitive and reliable result.

Clomiphene stimulation test

In the clomiphene stimulation test, 100 mg of clomiphene citrate is given for 7 days as an evocative test of the hypothalamic-pituitary axis. Clomiphene acts by interrupting the negative feedback loop and thereby stimulating release of gonadotropin from the pituitary. A doubling of LH and a 20% to 50% increase in FSH are normal results indicative of an intact hypothalamic-pituitary response.

hCG stimulation test

Various protocols are used for hCG stimulation testing. In general for post-pubertal male patients, a single dose of hCG (5,000 IU intramuscularly) is administered, and pre-therapy and 72-hour post-therapy testosterone measurements are done (some protocols use 1,000 to 4,000 IU of hCG or multiday dosing). Generally, a post-therapy testosterone level of > 100 ng/dL is considered normal.

Prolactin level

In men with acquired hypogonadotrophic hypogonadism, who usually have a reduced libido and impotence, a prolactin level should be determined to evaluate for a prolactinoma or other cause of hyperprolactinaemia. About 5% of men who complain of impotence will have an increased prolactin level. Further endocrinological evaluation with magnetic resonance imaging (MRI) scanning of the pituitary gland is indicated for unexplained hyperprolactinaemia.

Semen analysis

A semen analysis is the primary test to assess the fertility potential of the male patient. Semen should be collected by masturbation after 2 to 5 days of abstinence and evaluated within 2 hours. Variability between specimens is common; with low or borderline samples, follow-up consisting of evaluation of three or more samples should be done during a 3-month period. A fertile sample is usually associated with a motility of more than 50% and a count that exceeds 20 million/mL. In general, semen volume should range from 1.5 to 6 ml. Morphologic features should be examined for abnormalities.

A fructose test should be done on a semen sample showing azoospermia. Because fructose is secreted by the seminal vesicles, absence of fructose may indicate complete obstruction of the ejaculatory ducts or congenital absence of the vas deferens and ejaculatory ducts.

Most often, a semen analysis is done in an otherwise asymptomatic man during the course of an infertility evaluation. Of note, in the evaluation of infertility of a couple, a semen analysis should be done early to determine appropriate further evaluation and therapeutic options.

Other Studies

Bone densitometry

Because hypogonadism frequently results in low bone density, osteoporosis, and future increased fracture risk, a baseline bone densitometry study should be performed to assess the initial situation and allow future interventions to be based on any deterioration in bone density that may occur overtime. Treatment options to maintain bone mass may include testosterone therapy, calcitonin, or bisphosphonates, in addition to the standard regimen of calcium, exercise, and vitamin D. From 1 to 2 years after therapy is initiated, a follow-up bone density study should be done to determine whether bone mass is being appropriately maintained.

Pituitary imaging

In cases of acquired hypogonadotrophic hypogonadism (low testosterone with low-normal FSH and LH) not clearly attributable to a specific cause, pituitary imaging studies with MRI or computed tomography may be needed to evaluate for structural lesions in the hypothalamic-pituitary region. MRI generally provides better pituitary images, but bony changes in the sella may be better characterised by computed tomography. In general, MRI done with and without a contrast agent is recommended as the initial pituitary imaging study in patients requiring delineation of a pituitary pathologic condition.

Genetic studies

Patients with hypergonadotrophic hypogonadism and impaired pubertal development associated with small, firm testes and often with gynaecomastia are likely to have Klinefelter's syndrome or a variant. Classically, a buccal smear was done to establish the diagnosis by revealing Barr bodies. Currently it is recommended to do genetic karyotype testing to confirm the diagnosis in a patient with these findings at initial assessment. Fluorescent *in situ* hybridisation (FISH) studies increase the sensitivity of detecting Klinefelter's syndrome associated with mosaicism.

Testicular biopsy and scrotal exploration

Since the advent of sensitive FSH assays, germinal cell function is now most often assessed through the FSH assay alone rather than testicular biopsy. In general, however, men with

azoospermia, normal FSH levels, and normal testicular size should usually undergo testicular biopsy and scrotal exploration to determine whether a germinal cell abnormality, an obstruction, or a congenital abnormality of the vas, is present.

Testicular ultrasonography

Testicular ultrasound examination should be done in patients with clinical findings suggestive of a scrotal or testicular mass.

Differential Diagnosis

The differential diagnosis of hypogonadism includes a large and diverse group of disorders affecting the testicles directly or affecting hypothalamic-pituitary regulation of the testes. The clinical setting, history, physical examination, and clinical judgement will, to a large degree, determine which possible aetiologic factors are present.

The different causes are listed in **Table 4**.

Table 4: Aetiology of Male Hypogonadism

Gonadal defects
Genetic defect—Klinefelter's syndrome, myotonic dystrophy, Prader-Willi syndrome
Polyglandular autoimmune failure syndromes (e.g. Schmidt syndrome)
Anatomic defects
Toxins—cytotoxic agents, spironolactone, alcohol
Radiation
Orchitis—usually due to mumps
Hypopituitarism
Idiopathic
Tumour
Other causes
Hyperprolactinaemia
Usually due to pituitary adenoma
Idiopathic increased prolactin production
Hormone resistance
Androgen insensitivity
Luteinising hormone insensitivity
Gonadotrophin deficiency
Hypogonadotrophic hypogonadism
Isolated congenital idiopathic GnRH deficiency
GnRH deficiency with anosmia—Kallman syndrome
Acquired GnRH deficiency is very uncommon
Respond to pulsatile GnRH administration
Hypothalamic insufficiency
LH or FSH deficiency
Systemic diseases
Chronic diseases
Malnutrition/starvation
Massive obesity
AIDS/HIV

The common syndromes are briefly discussed below. They can be broadly classified into hyper- and hypogonadotrophic.

Hypergonadotrophic Hypogonadism Situations

Klinefelter's syndrome

Klinefelter's syndrome (**Figure 1**) is caused by extra X chromosomes present in the male karyotype and occurs in about 1 in every 400 men. The most common karyotype is 47/XXY; mosaicism is sometimes present (in about 1 in every 400 men). Men with Klinefelter's syndrome classically have small, firm testes (generally <2 ml), gynaecomastia, eunuchoid habitus,



Figure 1: Tall stature and gynaecomastia in a patient with Klinefelter's syndrome.

and increased gonadotropin levels. Although production of testosterone is low, high levels of SHBG may result in normal-range testosterone levels in about 40% of patients with Klinefelter's syndrome. These patients have azoospermia, but those with mosaicism may have some spermatogenesis and may produce some pregnancies early in their reproductive lives. Virilisation may begin with puberty but frequently fails to progress. Gynaecomastia is often present and frequently necessitates surgical therapy. Bone density is significantly low. Autoimmune disorders are present with increased frequency in patients with Klinefelter's syndrome and may respond favourably to testosterone therapy.

47/XYY syndrome

The 47/XYY karyotype, which occurs in about 0.1% of males, has been thought to be associated with aggressive behaviour in some men with the disorder. Affected patients may have azoospermia

in association with maturation arrest of the germinal epithelium. Usually, serum FSH levels are increased, but Leydig cell function is normal, as are testosterone and LH levels.

Dysgenetic testes

Dysgenetic testes may occur in conjunction with mosaicism; the patient may have an XO karyotype, a mixed XO/XY karyotype, or pure XY with streak gonads. Occurrence of pure gonadal dysgenesis in conjunction with an XY karyotype and streak gonads imposes an increased risk of malignant disease, which necessitates gonadectomy. Such patients generally have genital ambiguity.

Androgen receptor defects

Patients with androgen receptor defects have an XY genotype and variable phenotype, depending on the degree of receptor defect. Such syndromes include testicular feminisation, Reifenstein's syndrome, and other partial defects, as discussed in the following paragraphs.

Testicular feminisation

Patients with testicular feminisation have a female phenotype but a blind vaginal pouch. Testosterone receptor is non-functional or absent. Laboratory testing shows normal to high male range testosterone and increased gonadotropin levels. The testes should be removed after puberty because of an increased risk of a malignant lesion. Administration of testosterone yields no response.

Reifenstein's syndrome

In Reifenstein's syndrome, patients have a male phenotype with variable pseudohermaphroditism. A partial androgen receptor defect is present; testosterone and gonadotropin levels are increased. Abdominal testes should be removed because of the risk of a malignant lesion. If hypospadias is present, surgical correction of the genitalia may be needed. Any significant gynaecomastia may also need surgical correction. Patients may respond to high doses of testosterone.

Other syndromes

Some male patients with gynaecomastia or oligospermia may have partial androgen insensitivity in association with mild increases in testosterone and gonadotropin levels.

5-alpha reductase deficiency

An autosomal recessive condition, 5-alpha reductase deficiency is associated with an XY genotype. The patients, however, have genital ambiguity until puberty, when increasingly male features develop. The diagnosis is based on clinical manifestations and an increased testosterone/dihydrotestosterone ratio both after puberty and in response to hCG before puberty. Sexual assignment is an issue, and patients may need corrective surgical procedures that necessitate speciality consultation.

Myotonic dystrophy

Myotonic dystrophy occurs only in male patients, by transmission from father to son. Because testicular failure usually occurs around age 40 years, patients often have children at risk for the disease.

Cryptorchidism

Unilateral or bilateral cryptorchidism can occur. The incidence of this condition is 3% to 4% at birth, but most testes ultimately descend. Thus, the 1-year incidence is about 0.8 per cent. Because normal testicular descent requires normal pituitary function and dihydrotestosterone levels, the incidence of cryptorchidism is increased in patients with Kallmann's syndrome. Problems associated with the management of cryptorchidism include distinguishing between cryptorchidism and retractile testes and recommending medical treatment with hCG or surgical therapy in an infant. Generally, the objective is to bring the undescended testicle into the scrotum before 1 to 2 years of age—to decrease the risk of gonadal malignant lesions associated with abdominal testes and to improve fertility potential. In pre-pubertal boys, hCG treatment should generally be used initially for 4 weeks to determine whether descent occurs before operative intervention is considered. Discussion of these problems is beyond the scope of these guidelines; appropriate specialty consultation should be obtained.

Vanishing testes syndrome (congenital anorchism or pre-pubertal functional castrate)

The initial manifestation of the vanishing testes syndrome is sexual immaturity in a male patient. The cause is unclear, but the syndrome may be due to testicular torsion during foetal life after sufficient testosterone exposure to produce masculinisation of the reproductive tract. Impalpable testes suggest the possibility of cryptorchidism. FSH and LH levels are increased, and testosterone levels are low. If the LH levels are only minimally increased, hCG stimulation testing of the gonad should be done. With vanishing testes syndrome, no response would be demonstrated. A response to hCG stimulation would raise the possibility of intra-abdominal testes, which would necessitate further evaluation because of the possibility of malignant transformation. In this setting, an MRI is recommended to assess the possibility of a retained intra-abdominal dysgenetic gonad because this would be associated with an increased risk of a malignant lesion and would necessitate removal.

Haemochromatosis

Iron overload may lead to primary gonadal failure or sometimes hypothalamic-pituitary dysfunction that results in secondary gonadal failure. The diagnosis is made in the setting of associated findings of haemochromatosis in conjunction with an increased ferritin level and is generally confirmed with a liver or bone marrow biopsy.

External Testicular Insults

Trauma

The patient may have a history of direct traumatic injury. Testicular torsion sometimes is associated with a 'bell-clapper' abnormality in which the testes lie horizontally because of incomplete closure of the surrounding tissues.

Mumps orchitis

In patients with postpubertal mumps, a 25% risk of orchitis exists. More than 50% of those with orchitis will be infertile. Increased FSH concentrations and oligospermia or azoospermia are present. Mumps orchitis can progress to produce low testosterone and high LH levels in some men.

Radiation treatment or chemotherapy

With irradiation or chemotherapy, testicular exposure can occur from treatment of another disease or inadvertently. A dose-

dependent recovery potential and variable Leydig cell dysfunction have been noted. Pretreatment sperm banking is possible if future 'fertility' is desired and sperm counts are normal.

Autoimmune syndromes

Anti-Leydig cell antibody-associated disorders or conditions associated with anti-sperm antibodies are autoimmune syndromes related to hypogonadism. These syndromes are poorly characterised, and further research is needed to determine diagnostic criteria and possible treatment options.

Sertoli cell only syndrome

The absence of germ cells in patients with small testes, high FSH levels, azoospermia, and normal testosterone levels should suggest the presence of Sertoli cell only syndrome. The diagnosis can be made only by testicular biopsy. The cause is currently unknown.

Hypogonadotrophic Hypogonadism Situations

Kallmann's syndrome

Classic Kallmann's syndrome is a congenital disorder inherited as an X-linked recessive trait manifesting as prepubertal hypogonadism with an incidence of about 1 in 10,000 male births. Low testosterone levels are present because of an impaired release of LH and FSH as a result of variable GnRH deficiency. LH and FSH are released in response to priming followed by stimulation with GnRH. The gene on the X chromosome for classic Kallmann's syndrome and associated anosmia has been identified and cloned. Autosomal recessive and autosomal dominant variants of hypogonadotrophic hypogonadism also exist and are referred to as idiopathic hypogonadotrophic hypogonadism.

Classically, Kallmann's syndrome is associated with anosmia as a result of defective development of the olfactory tract in the brain. The GnRH-containing neurones originate in the developing olfactory tract and therefore do not develop properly in this syndrome. This defective development of the olfactory tract can be diagnosed by MRI scanning. In some cases, other defects such as cerebellar dysfunction, cleft palate, and congenital deafness are present. Cryptorchidism may occur because gonadotropins contribute to normal testicular descent. The pre-pubertal testes in patients with Kallmann's syndrome tend to be larger than in patients with Klinefelter's syndrome and are appropriate for age up to puberty, in as much as normal initial amounts of germinal tissue are present. Partial pubertal development may be present in patients with partial defects; thus, Kallmann's syndrome may be difficult to distinguish from delayed puberty up through the teenage years. Once a patient with Kallmann's syndrome has been identified, other family members at risk (on the basis of mode of inheritance) should be assessed, if possible.

Other related syndromes

Congenital hypogonadotrophic syndromes are associated with secondary hypogonadism and other somatic findings. Prader-Willi syndrome is characterised by hypogonadism, short stature, mental retardation, hypotonia at birth, and obesity. Laurence-Moon-Bardet-Biedl syndrome is an autosomal recessive trait characterised by mental retardation, retinitis pigmentosa, polydactyly, and hypogonadism. These syndromes may be due to a hypothalamic deficiency of GnRH.

Fertile eunuch syndrome

Hypogonadotrophic hypogonadism in patients who have modest FSH secretion and selective LH deficiency is known as the fertile eunuch syndrome. Fertility may be present in some of these patients.

Pituitary disorders

Acquired hypogonadotrophic hypogonadism may indicate the presence of pituitary insufficiency or a pituitary tumour. Unless the reason for the pituitary defect is clear, imaging studies of the pituitary gland are indicated to determine whether a pituitary tumour is present. Hypothalamic tumours, metastatic tumours, granulomas, abscesses, and haemochromatosis may also be discovered.

Hyperprolactinaemia is a potential cause of hypogonadotrophic hypogonadism and generally, manifests with a low libido and impotence. A prolactin level should be determined in men with acquired hypogonadotrophic hypogonadism. High prolactin levels are usually associated with a prolactinoma, but certain medications may also cause hyperprolactinaemia.

Hypogonadotrophic hypogonadism from pituitary disease may also occur with granulomatous and infiltrative disorders, cranial trauma with or without stalk transection, irradiation, and hypophysitis.

Haemochromatosis

See earlier discussion in hypergonadotrophic hypogonadism section.

Serious illness, acquired immunodeficiency syndrome and stress

Transient hypogonadotrophic hypogonadism may occur in patients with serious disorders or malnutrition. Acquired immunodeficiency syndrome (AIDS) may be associated with low testosterone levels and generally low gonadotropin levels (consistent with hypothalamic-pituitary involvement). In some patients with AIDS, gonadotropin levels are increased (consistent with testicular disease).

Ageing, andropause or male menopause

Considerable controversy exists over the concept of a male climacteric. Growing evidence indicates that some aging men have reduced production of testosterone associated with decreased libido, impotence, decreased growth of body hair, decreased muscle mass, increased risk of myocardial infarction, and decreased bone mass in conjunction with osteoporosis. Measurements of free testosterone or SHBG with total testosterone are usually needed to demonstrate the abnormality. Often the FSH and LH levels are mildly increased; an indication that a primary testicular disorder may be present in conjunction with a secondary abnormality in LH burst frequency. Dynamic testing may disclose more subtle abnormalities of hypothalamic function. Data from long-term research studies are desperately needed to clarify the criteria for therapy considerations in aging men. Currently, men with symptomatic hypogonadism and clearly low testosterone levels (free or total, in consideration of SHBG) are potential candidates for therapy, although no specific recommendations can be given.

Short-term research studies have demonstrated improved lean body mass, increased haematopoiesis, decreased low-density

lipoprotein (LDL) levels with a constant LDL to high-density lipoprotein (HDL) ratio, improved libido, and improved well-being in men with low testosterone levels after treatment with testosterone. Generally, prostate size does not change in comparison with otherwise normal men, but prostate-specific antigen (PSA) levels have been found to increase in some men.

Treatment Options

The goals of therapy are to restore sexual function, libido, well-being, and behaviour; produce and maintain virilisation; optimise bone density and prevent osteoporosis; possibly normalise growth hormone levels in elderly men; potentially affect the risk of cardiovascular disease; and restore fertility in cases of hypogonadotrophic hypogonadism.

Testosterone therapy in adult male patients with hypogonadism

Ideally, testosterone therapy should provide physiologic range of testosterone (between 300 and 1,200 ng/dL) and physiologic range of dihydrotestosterone and oestradiol levels, which would allow optimal virilisation and normal sexual function. Testosterone therapy is used in the male patient with hypogonadism who is not interested in fertility or not able to achieve fertility. In late teenage male patients with delayed puberty, testicular size should be monitored for evidence of onset of puberty. In this setting, testosterone therapy should be withdrawn to determine whether spontaneous puberty will occur.

The following preparations of testosterone may be used: long-acting intramuscular preparations, short-acting intramuscular preparations, pellets, scrotal patches or transdermal patches.

Orally administered testosterone is quickly metabolised by the liver and cannot achieve sufficient blood levels overtime to be useful. The orally administered alkylated androgen preparations currently available are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects, such as haemorrhagic liver cysts, cholestasis, and hepatocellular adenoma. Testosterone undecanoate may be a more acceptable oral alternative, but erratic testosterone levels, frequent dosing, high dihydrotestosterone levels, and occasional gastrointestinal side effects may limit the usefulness of this preparation. Testosterone pellets are sometimes used, and further study may prove them to be suitable for many men. For patients with hypogonadotrophic hypogonadism wishing fertility, hCG with or without human menopausal gonadotropin (FSH), or pulsatile GnRH therapy and hCG with or without assisted reproduction are options.

Parenteral testosterone preparations

These are the mainstay of therapy for all practical purposes. Testosterone enanthate and testosterone cypionate are long-acting testosterone esters suspended in oil to prolong absorption. Peak levels occur about 72 hours after intramuscular injection and are followed by a slow decline during the subsequent 1 to 2 weeks.

For complete androgen replacement, the regimen should be between 75 mg, 150 mg and 250 mg of testosterone enanthate or cyprionate administered intramuscularly every 7 to 10 to 21 days, which will allow relatively normal levels of testosterone throughout the time interval between injections. Longer time intervals are more convenient but are associated with greater fluctuations in testosterone levels. Higher doses of testosterone produce longer-term effects at the expense of higher peak levels and wider swings between peak and nadir circulating testosterone levels; the result is fluctuating symptoms in many patients. The use of 100 to 200 mg every 2 weeks is a reasonable compromise. Use of 250 to 300 mg injections every 3 weeks is associated with wider fluctuations of testosterone levels. With use of these longer-interval regimens, many men will have pronounced symptoms during the week preceding the next injection. In such instances, a smaller dose at closer intervals should be tried. As a guide, testosterone levels should be above the lower limit of normal, in the range of 250 to 300 ng/dL, just before the next injection.

When full androgen replacement is not required, lower doses of testosterone are used. One such category includes adult male patients with pre-pubertal onset of hypogonadism who are going through puberty for the first time on therapy and who often may require psychologic counselling, especially when a spouse is involved as well. In these patients, testosterone therapy should be begun at 50 to 100 mg every 3 to 4 weeks with a gradual increase during subsequent months, as tolerated, up to full replacement within 1 year. Men with appreciable benign prostatic hypertrophy who have hypogonadism and symptoms may be given 50 to 100 mg every 2 weeks as an initial regimen and maintained on this dosage with careful monitoring of urinary symptoms and prostate examinations; therapy can be withdrawn, if necessary.

Attaining full virilisation in the patient with hypogonadism may take as long as 3 to 4 years. Follow-up intervals should be between 4 and 6 months to monitor progress, review compliance, and determine whether any complications or psychologic adjustment problems are present.

Transdermal testosterone therapy

Transdermal testosterone delivery system—normal skin: A testosterone patch with permeability enhancement allows testosterone delivery through normal skin. Daily evening application generally results in normal-range testosterone levels, which mimic the normal diurnal changes in testosterone in normal men. In contrast to the situation with use of the scrotal patch, dihydrotestosterone levels remain within the normal range. Oestradiol and bioavailable testosterone levels also remain within the normal range. Skin irritation may be a problem in some patients. Therapy consists of two patches applied to normal skin. As with scrotal patches, treatment is more expensive than injections, but convenience of use, maintenance of normal diurnal testosterone levels, and elimination of office visits for injections may make this form of treatment useful in many patients.

Scrotal patch testosterone delivery system: Scrotal testosterone patches are available in 40 and 60 cm^2 sizes, which deliver, respectively 4 and 6 mg of testosterone daily. The patch is applied to the scrotal skin after preparation of the scrotum with dry shaving. The patch is non-adhesive, and a new patch is applied each morning. The testosterone levels mimic the diurnal rhythm present in normal men. Because genital skin contains high concentrations of 5-reductase, the dihydrotestosterone levels in treated patients increase initially but may return to

normal in some men. The cost of using the scrotal patch is greater than for testosterone injections, but the convenience of use may make this therapeutic option acceptable for many patients.

Side effects of testosterone therapy

Periodic follow-up of patients receiving testosterone therapy is recommended. During the first year of therapy, the patient should have the progress and the side effects monitored at 3 to 4 month intervals. Examination of the prostate should be done routinely. PSA levels should be determined annually in older men receiving testosterone replacement therapy, and the haematocrit should be determined at least yearly. An initial lipid profile should be recorded, and a follow-up profile should be done after 6 to 12 months of therapy. Testosterone, and especially dihydrotestosterone, stimulates the growth of the prostate and seminal vesicles.

Gynaecomastia may result from the aromatisation of testosterone to oestradiol and changes in SHBG levels. The use of aromatase inhibitors, such as testolactone, or surgical therapy may be considered for some patients.

Supraphysiologic levels of testosterone stimulate the bone marrow production of erythrocytes. The result is an increased haematocrit with the possibility of hyperviscosity side effects.

Lipid disturbances in testosterone treated male patients are generally not a problem because of the aromatisation of testosterone to estradiol. The HDL: total cholesterol ratio generally remains constant. Anabolic steroids that are not aromatised increase LDL and lower HDL levels and could increase cardiovascular risk.

Sleep apnoea may also be a problem in some men, and testosterone therapy should be discontinued until the sleep apnoea problem can be adequately addressed.

Gonadal Stimulation in Hypogonadotrophic Hypogonadism

Because gonadotrophin or GnRH therapy is effective only in hypogonadotrophic hypogonadism, this diagnosis must be firmly established before consideration of therapy. Although these agents may also be used to induce puberty in boys and to treat androgen deficiency in hypogonadotrophic hypogonadism, the major use of these preparations is in the initiation and maintenance of spermatogenesis in hypogonadotrophic men who desire fertility.

Gonadotrophin therapy in androgen deficiency

hCG binds to Leydig cell LH receptors and stimulates the production of testosterone. Peri-pubertal boys with hypogonadotrophic hypogonadism and delayed puberty can be treated with hCG instead of testosterone to induce pubertal development. The initial regimen of hCG is usually 1,000 to 2,000 IU administered intramuscularly two to three times a week. The advantages of hCG over testosterone in this setting include the stimulation of testicular growth, which may be an important issue for some men. hCG may also yield greater stability of testosterone levels with fewer fluctuations in hypogonadal symptoms. In addition, hCG treatment is necessary for stimulating enough intratesticular testosterone to allow the initiation of spermatogenesis. Problems with hCG include the need for more frequent injections and the greater cost.

Gonadotrophin therapy for induction of spermatogenesis

Males with pre-pubertal onset of hypogonadotrophic hypogonadism have not completed pubertal development and have testes generally smaller than 5 ml. These patients usually require therapy with both hCG and human menopausal gonadotropin (or FSH) to induce spermatogenesis. Men with partial gonadotropin deficiency or who have previously (peri-pubertally) been stimulated with hCG may initiate and maintain production of sperm with hCG alone. Men with post-pubertal acquired hypogonadotrophic hypogonadism and who have previously had normal production of sperm can also generally initiate and maintain spermatogenesis with hCG only. Fertility may be possible at sperm counts much lower than what would otherwise be considered fertile. Counts of less than 1 million/mL may be associated with pregnancies under these circumstances. It is imperative that the female partner undergo assessment for optimal fertility before or concurrently with consideration of therapy in the man.

GnRH therapy

In patients with hypogonadotrophic hypogonadism, GnRH can be given in a pulsatile fashion sub-cutaneously through a pump every 2 hours. GnRH therapy is monitored by measuring LH, FSH, and testosterone levels every 2 weeks until levels are in the normal range, at which point monitoring can be adjusted to every 2 months. GnRH can be used to initiate pubertal development, maintain virilisation and sexual function, and initiate and maintain spermatogenesis. In most patients, these effects may take from 3 to 15 months to achieve sperm production. As with gonadotropin therapy, fertility can be achieved with very low sperm counts—often in the range of 1 million/mL. GnRH may be more effective than gonadotropin stimulation in increasing testicular size and initiating spermatogenesis in many patients with hypogonadotrophic hypogonadism.

Contraindications to Testosterone, GnRH, and Gonadotrophin Therapy

Testosterone replacement, pulsatile GnRH therapy, and gonadotrophin therapy are contraindicated in men with prostate cancer or male breast cancer. Treatment with these medications can stimulate tumour growth in androgen-dependent neoplasms. Careful examination of the male breast and prostate is required initially and at follow-up visits. In addition to prostate examination, baseline and follow-up PSA levels should be determined in older men at increased risk for prostate cancer. Sleep apnoea and hyperviscosity states are relative contra-indications to the use of testosterone therapy.

Other Treatment Considerations

Anti-oestrogen therapy in oligospermia

Long-term use of low-dose clomiphene citrate at 25 mg daily or tamoxifen to increase pituitary stimulation of testicular function has often been attempted in men with oligospermia with limited success.

Assisted reproductive technology

The ability to perform *in vitro* fertilisation (IVF) with intracytoplasmic sperm injection (ICSI) directly into the egg has revolutionised the approach to male sub-fertility. A single sperm or immature form retrieved from the testicle is sufficient to

fertilise an egg and give a reasonable chance at pregnancy. *In vitro* fertilisation with intracytoplasmic sperm injection may be a viable option in many men with hypogonadism who cannot otherwise be induced to produce enough sperm to result in pregnancy as well as in the presence of a female factor that may further make pregnancy by the couple difficult or impossible. The procedure is expensive and seldom covered by health insurance; therefore, this technology will generally not replace conventional gonadal stimulation protocols. Intrauterine insemination (IUI) may also be a low-cost option in suitable women when the man has mild-to-moderate oligospermia.

Pituitary tumours

Patients with acquired hypogonadotrophic hypogonadism require assessment for a pituitary tumour with appropriate pituitary imaging studies, such as MRI, and determination of a prolactin level. Depending on the presence or absence of a tumour, other hormonal testing may be indicated, including thyroid and adrenal function tests. Further evaluation and treatment options would depend on what hormonal deficits are present, the size and site of the tumour, the operability of the tumour, and the patient's preferences in specific circumstances. If a prolactinoma is present, therapy would be directed toward correcting this problem before initiation of other therapy. Medical therapy with bromocriptine or pergolide may effectively reduce prolactin levels sufficiently to allow gonadal function to resume or allow stimulation with gonadotropins. Even when prolactin levels cannot be normalised, hCG therapy alone or in conjunction with human menopausal gonadotropin (or FSH) therapy may stimulate spermatogenesis and result in pregnancies. Surgical therapy should especially be considered for significant pituitary tumours that are not prolactin-secreting adenomas. Surgical treatment may also be an option in prolactin-secreting adenomas, if patients have severe side effects from medications or prefer this approach after being appropriately informed of the risks and benefits of medical versus surgical management.

Gynaecomastia

Many men have psychologic problems resulting from gynaecomastia. This problem should be taken seriously and discussed with the patient. Aromatase inhibitors, such as testolactone, tamoxifen or even clomiphene citrate may be helpful in some patients. Consultation with a plastic surgeon may be necessary in appropriate cases.

Psychologic counselling

Men with hypogonadotrophic disorders frequently have associated mood disturbances, including depression, aggression, poor self-esteem, and learning problems. In such cases, psychologic counselling is often needed to allow proper identification and treatment of these problems. Counselling should also include parents, spouse and relatives, if possible.

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Section 11

Dermatology

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11.1 Introduction and Principles of Diagnosis in Dermatology

Vibhu Mendiratta

SKIN AS A VITAL ORGAN

Skin or the integument is the largest organ of the body and constitutes 16% of the body weight. It is composed of skin and appendages (sweat glands, sebaceous glands, hair and nails). It is not merely a covering for internal organs but is an active, functional organ that performs diverse functions, such as, protection from noxious environmental factors, as a sensory organ, participates in immunological defence mechanisms (skin has antigen presenting cells, and skin associated lymphoid tissue), endocrine functions (synthesis of vitamin D) and thermoregulation through sweating. The appendages of skin (nails, hair, sweat and the sebaceous glands) also perform various functions.

STRUCTURE OF SKIN

Skin is composed of three distinct zones — the epidermis, dermis and the subcutis (**Figure 1**). The epidermis is the outer layer of skin and is composed of keratinised stratified squamous epithelium. The dermis is mesodermally derived and consists of collagenous connective tissue that lies below epidermis and interdigitates with it. The hypodermis contains loose connective tissue with varying amounts of adipose tissue.

Epidermis

Epidermis is the outermost visible layer. The thickness is variable (0.05 mm on eyelids and the thickest on the palms and soles at 1.5 mm). Epidermis is thrown into folds over dermis in order to increase the area of absorption and for stronger cohesion to the dermis. Epidermis is composed of keratinocytes, melanocytes, Langerhans cells. It bears receptors for touch, pressure, temperature and free nerve endings. Epidermis is further composed of four sublayers, as described below:

1. Stratum corneum

It is the outer layer which consists of keratinised epithelial cells. The cells are flattened and anucleated. Thickness of the layer varies from 5 to 10 layers. *Stratum corneum* is regularly shed of and it renews itself every 14 to 30 days.

2. Stratum granulosum

Measures 3 to 5 cell layers of keratinocytes and contains keratohyaline granules. These granules are involved in the process of keratinisation.

3. Stratum spinosum

It is the thickest layer of epidermis and measures 5 to 8 layers.

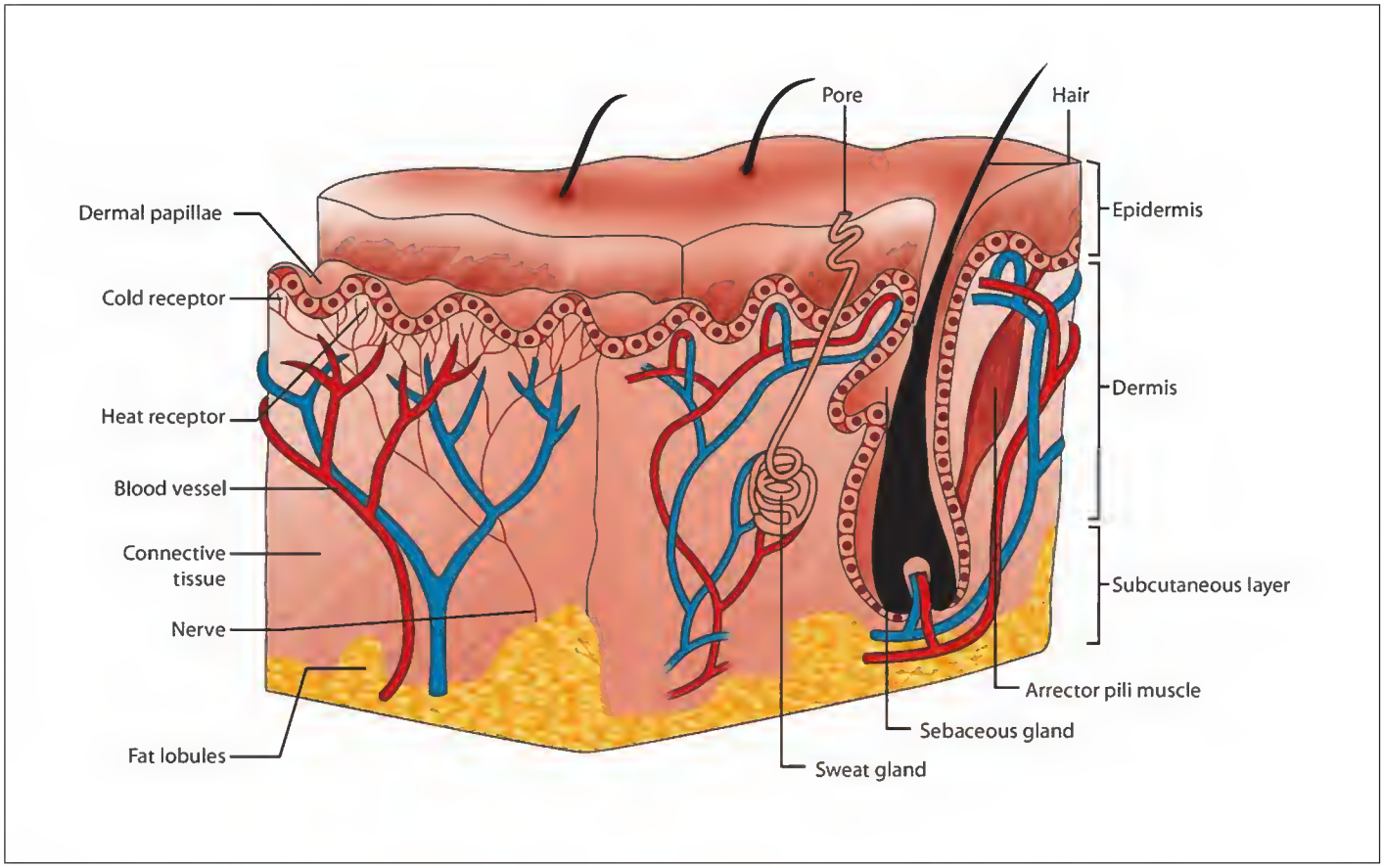


Figure 1: Skin structure with three distinct zones—epidermis, dermis and subcutis.

It is composed of cuboidal cells and appears more flattened than the underlying stratum basale.

4. Stratum basale

It is the lower most layer of the epidermis, which is composed of a single layer of cells that are columnar in shape, proliferate actively and lie interspersed with other cells. Stratum basale also has cells with dendritic processes which produce pigment (melanin). These are called the melanocytes. They remain in contact with keratinocytes. Langerhans cells also bear dendritic processes and belong to the macrophage-monocyte series. They lie in the living layers of the epidermis and perform the important task of antigen presentation to the T-lymphocytes. Merkel cells are special cells that are found in the basal layer of epidermis and act as touch receptors.

Dermis

Thickness of dermis is variable and measures 0.3 to 3 mm. It comprises of elastin, collagen and glycosaminoglycans. It contains extensive vasculature, neurones, smooth muscle, fibroblasts, sweat and the pilosebaceous apparatus with their ducts. It is the principal mechanical barrier of skin. Its network of elastic fibres functions to support the epidermis and binds the skin to the deeper hypodermis. The dermis contains two layers, the papillary layer and the reticular layer. The papillary layer is loosely woven, contains superficial connective tissue and interdigitates with the epidermal ridges and the deeper reticular layer. The dermal ridges contain Meissner's corpuscles, encapsulated nerve endings, and capillary loops that provide nutrients to the avascular epidermis. Dermis provides tensile strength, elasticity, and thickeness to the skin.

Subcutaneous Tissue/Hypodermis

It is the deepest part of skin composed of adipose tissue. The hypodermis provides insulation, shock absorption, energy storage, and the ability of skin to slide over joints. It also contains the major blood vessels of the skin.

PRINCIPLES OF DIAGNOSIS

Skin is the largest organ of the body. It reflects the state of internal organs. Various lesions based on their morphology are classified as primary or secondary lesions. A step-wise approach aids in correct diagnosis and includes the following steps:

History

History of drug intake, atopy, sexual history, recent travel, type of house, emotional status, illicit drug use and family history of skin diseases should be sought. Systemic diseases such as tuberculosis, diabetes, hypertension, hepatitis, blood transfusion, hospitalisations and major operative procedures should be recorded. History of local treatment, associated symptoms like pruritus, pain, stinging, burning, or anaesthesia should be enquired about.

Examination

Examination is performed in a well lit room. Skin, hair, nails, and mucous membranes should be examined. The clinician should recognise the primary lesions of a skin rash, determine pattern of distribution, and arrangement of eruption.

Identification of primary lesions of a skin rash

Primary lesions arise on the previously normal skin and have been classified further into various subtypes (**Table 1**).

Table 1: Different Types of Cutaneous Lesions (Primary/Secondary)

Primary lesions	Secondary lesions
Macule	Erosion
Patch	Crust
Papule	Ulcer
Plaque	Scale
Nodule	Lichenification
Vesicle	Atrophy
Bulla	Scar
Pustule	
Wheal	
Burrow	
Comedone	
Telangiectasia	

1. *Macule:* It is a flat, circumscribed area of skin showing an alteration in the skin colour, e.g. melasma, pityriasis and vitiligo (**Figure 2**).
2. *Patch:* A larger macule (>1 cm) is referred to as a patch. Patches are seen in leprosy, vitiligo and purpura (**Figure 3**).



Figure 2: Depigmented macules over tips of fingers in vitiligo.



Figure 3: A large purpuric patch over thigh in autosensitisation syndrome.

3. *Papule:* It is a circumscribed, raised elevated lesion which measures less than 0.5 cm, e.g. acne papules, lichen planus, *molluscum contagiosum* (**Figure 4**).
4. *Plaque:* A circumscribed area of skin which shows a change in the consistency of skin (**Figure 5**). Plaques are seen in lichen planus, psoriasis and neurodermatitis.
5. *Nodule:* An elevated, palpable lesion with greater depth than its height or width (**Figure 6**).
6. *Vesicle:* It is a clear fluid containing lesion measuring < 0.5 cm. Vesicles are seen in herpes zoster (**Figure 7**).
7. *Bulla:* A fluid filled lesion which measures more than 1 cm (**Figure 8**). The bullae are seen in pemphigus.
8. *Pustule:* A tiny lesion containing pus measuring less than 0.5 cm in size (**Figure 9**).
9. *Wheal:* Constitutes an erythematous, oedematous, transient, itchy papule or plaques seen in urticaria (**Figure 10**).
10. *Burrow:* It is a linear, thread like lesion in the web spaces of fingers, flexural folds of wrists, ankles and constitutes the primary lesion of scabies (**Figure 11**).
11. *Comedone:* It is a dark papule filled with keratin debris. Closed comedone is white in colour (**Figure 12**). Comedone is the primary lesion of acne.
12. *Telangiectasia:* Are the superficial, dilated capillaries, appear as wavy, thin, reddish blue lines (**Figure 13**). They are seen in connective tissue diseases.



Figure 6: Nodule over cheek (arrow).



Figure 4: Raised papule of acne over cheek.



Figure 7: Vesicles in herpes zoster.



Figure 5: Scaly plaque over the lower back in psoriasis.



Figure 8: A large fluid filled bullae in erythema multiforme.



Figure 9: Multiple pustules over knee and legs in pustular psoriasis.



Figure 10: Wheals. Erythematous, raised, itchy lesions over back in urticaria.



Figure 11: Burrows. Curvilinear, thread like structures over palms(arrows) burrows in scabies.



Figure 12: Comedone. Greyish-black, tiny, dark papules over cheeks in acne.



Figure 13: Telangiectasia. Multiple telangiectasia over nose and cheeks in systemic sclerosis.

Secondary lesions

Secondary lesions are changes in the primary lesions due to scratching, infection or treatment.

1. *Excoriations:* These are linear marks caused by scratching of skin (**Figure 14**). Excoriation marks are seen in scabies, dermatitis herpetiformis.



Figure 14: Excoriations. Linear marks with oozing of blood and crusting due to scratching in prurigo.

2. *Erosion:* Partial loss of epidermis constitutes an erosion (**Figure 15**). Erosions are seen in toxic epidermal necrolysis (TEN).
3. *Ulcers:* Loss of epidermis and partial loss of dermis forms ulcer (**Figure 16**). Ulcers arise secondary to trauma, burns, ischaemia or lack of nerve supply.



Figure 15: Erosion. Partial loss of epidermis causing a raw area in pemphigus.



Figure 16: Ulcer. Loss of epidermal cover with partial loss of dermis in an ulcer.



Figure 17: Scales in hand eczema.

4. *Scales:* Shedding of stratum corneum cells forms scales (**Figure 17**). Scale may be silvery, dry and abundant as in psoriasis.
5. *Crust:* Drying up of the exudates forms crust (**Figure 18**). A crust may be purulent, honey-coloured as seen in impetigo contagiosa, chocolate coloured in ecthyma.
6. *Lichenification:* Skin is thickened, leathery, pigmented with accentuated skin markings. It occurs in chronic eczema such as lichen simplex chronicus or neuro-dermatitis (**Figure 19**).
7. *Atrophy:* Decrease in the thickness of skin leads to atrophy. Epidermal atrophy is seen as smooth, shiny and wrinkled skin with easily visible dermal blood vessels. Dermal and subcutaneous tissue atrophy leaves behind a pit on the skin (**Figure 20**).
8. *Scar:* Destruction of skin and the underlying dermis results in scar which appears as a wrinkled area with loss of normal skin markings. It can be an atrophic (**Figure 21**) or hypertrophic scar. Atrophic scars are seen in acne, morphoea, post-burn. Keloid is a scar which is raised beyond the original lines of injury.



Figure 18: Crusts. Dried up exudate.



Figure 19: Lichenification.



Figure 20: Atrophy in linear morphoea.



Figure 21: Scar. An atrophic scar over leg.

Distribution of lesions

Lesions can be localised (limited to a discrete area) or generalised (widespread/affecting many areas). Distribution can be extensor (as in psoriasis) or flexural (neck, axillae, sub-mammary folds, groins). Intertrigo and candidal infections involve the flexural surfaces. Photosensitive disorders (systemic lupus erythematosus, photo-allergic dermatitis, polymorphous light eruptions) show photo distribution over the face, nape and V of the neck, extensor aspect of arms and dorsum of hands.

Identification of arrangement/configuration of lesions

Arrangement of lesions may vary. It may be linear, grouped, annular, targetoid, zosteriform, geographic, reticulated, and serpiginous.

Linear: Lesions arranged along a line as in linear lichen planus, linear psoriasis (**Figure 22**).

Grouped/Herpetiform: Lesions are closely clustered together, e.g. Herpes.

Annular: Arrangement in the form of a ring-plaques in borderline leprosy (**Figure 23**).

Targetoid: Lesion in concentric circles forming a target board that mimics the various zones of a target as in erythema multiforme (**Figure 24**).

Zosteriform or segmental: Distribution along one side of the body along a dermatome (area on the skin which is supplied by a dermal nerve) (**Figure 25**).



Figure 22: Linear lesions (in linear lichen planus on face).



Figure 23: Annular lesions in borderline leprosy.



Figure 24: Targetoid lesions in erythema multiforme.



Figure 25: Zosteriform lesions in herpes zoster.



Figure 26: Geographic tongue showing map-like pattern.



Figure 27: Reticulate lesions in livedo reticularis.

Geographic: Refers to large, bizarre lesion which have a map - like irregular outline. Borderline: borderline leprosy, geographic tongue (**Figure 26**).

Reticulated: Refers to a net work like distribution—oral lichen planus, cutis marmorata (**Figure 27**).

Serpiginous: Running along a zig-zag track like a snake-cutaneous larva migrans (**Figure 28**).

Blaschkoid: Along the lines of Blaschko as in epidermal naevi (**Figure 29**).



Figure 28: Serpiginous lesions in cutaneous larva migrans.



Figure 29: Blaschkoid lesions in hypomelanosis of Ito.

Final Categorisation of Skin Rash

Based on the morphological type of lesions the best way to categorise rashes would be presented as in **Table 2**.

Table 2: Morphological Types of Cutaneous Eruptions

Papulosquamous—As seen in psoriasis, pityriasis versicolour, lichen planus and *P. rosea*
Vesiculobullous—Herpes zoster, chickenpox, pemphigus vulgaris, bullous pemphigoid
Maculopapular—Drug rash, measles, rubella, toxic shock syndrome
Urticarial rash—Urticaria, erythema multiforme, vasculitis
Purpuric rash—Thrombocytopenia, drug hypersensitivity, vasculitis
Nodular rash—Syphilis, lepromatous leprosy
Pustular rash—Psoriasis, candidiasis, drug eruptions
Eczematous rash—Atopic dermatitis, seborrhoeic dermatitis, contact dermatitis

LABORATORY TESTS/LABORATORY TESTS AND PROCEDURES

The various tests are discussed below and summarised in **Table 3**.

Table 3: Common Investigative Procedures for Skin Diseases

KOH	Fungal infections, candidiasis
Gram's staining	Pyodermas, pustular lesions
Tzanck smear	Viral diseases, autoimmune bullous diseases
Skin biopsy	All kinds of rashes
Slit-smear preparation (Ziehl-Neelsen's staining)	Leprosy Mycobacteria (Tuberculosis and leprosy)
Immunofluorescence	Autoimmune bullous disease, connective tissue disease

KOH Examination

In case of itchy scaly lesions, the most active part of the lesion, (generally the border) is scraped gently with the help of a sterile, no. 14 blade and the scrapings are transferred onto a clean glass slide over which a drop of KOH (10%) is placed. Examination under the light microscope shows fungal hyphae as branching, septate, refractile filaments. *Candida* is seen as short, pseudo-hyphae which may show budding at places.

Wood's Lamp Examination

Wood's lamp contains a barium trisilicate filter that filters out all light except 311 nm. The lamp is used for examining the hair in suspected cases of tinea capitis as some causative dermatophytes fluoresce under ultraviolet light. It serves as a useful tool in the diagnosis of fungal infection of scalp. It is also used for examining the urine and teeth in certain congenital porphyrias and erythrasma.

Tzanck Smear

Fresh blister is de roofed using a sterile blade after cleaning it with spirit swab. Fluid is drained. The base of the blister cavity is scraped gently and smear is made on a clean glass slide. The smear is air dried and heat fixed and stained with Geimsa stain (1%). The smear is examined under the oil immersion lens of the light compound microscope. Multinucleate giant cells, acantholytic cells can be demonstrated in chickenpox and pemphigus group of diseases, respectively.

Gram's Stain

Smear is prepared from the pus filled lesions. It shows Gram-positive and negative cocci in pyodermas. It also demonstrates Gram-positive pseudohyphae of *Candida*. Absence of bacteria in the smear from a pus filled lesion indicates sterile pustules as in pustular psoriasis and drug-induced pustular eruptions.

Skin Biopsy

Histopathological examination of skin is carried-out by taking a tiny bit (0.4 to 0.6 mm) of the affected skin. Biopsy is taken with biopsy punche which come in various sizes (0.3 to 0.6 mm). Size of the punch is selected based on the depth of specimen required. An incisional biopsy is taken after administering local anaesthesia. It is an outdoor procedure. The specimen is transported in formalin (1%) for sectioning and staining.

Immunofluorescence

The technique is used in the diagnosis of autoimmune blistering diseases and autoimmune connective tissue diseases like systemic lupus erythematosus.

Slit-Smear Examination

It is a useful procedure to demonstrate the presence of *Mycobacterium leprae* in the skin. It is prepared from the ear lobes, eyebrows or from skin lesions. The site is cleaned with the help of sterile spirit swab, and kept pinched between the thumb and fingers for half a minute. A small nick (2 to 3 mm) is given with the help of a sterile surgical blade (No. 13-14). The area is gently scraped from the blunt margins of the blade. A smear is prepared on a clean glass slide. It is air dried and heat fixed and then stained with Ziehl-Neelsen stain. It is examined under the oil emersion lens for mycobacteria.

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11.2 Cutaneous Infections

Vineet Kaur, Gurmohan Singh

BACTERIAL INFECTIONS OF SKIN (PYODERMAS)

The skin of newborn baby is sterile. Virgin skin is immediately colonised with non-pathogenic bacteria which include staphylococci, micrococci and diphtheroids. *Staphylococcus aureus* may also get colonised in neonatal period. Resident flora inhibits colonisation by pathogenic bacteria (bacterial interference). Hydration of skin promotes bacterial growth and desiccation limits the number of bacteria.

Impetigo Contagiosa

It is a superficial infection of the skin caused by *S. aureus* and/or *Streptococcus* beta haemolyticus. It is highly contagious in infants and young children. It is more frequent in hot and humid climates.

Staphylococci produce exotoxins which provoke inflammation of even intact skin. Streptococci can only infect the inflamed or traumatised skin.

It starts as vesicles on an erythematous base, containing clear fluid which becomes turbid in a day or two. In staphylococcal impetigo vesicles enlarge and become bullae and rupture after few days. In streptococcal impetigo, vesicles rupture fast, forming a honey coloured, loosely adherent crust (**Figure 1**). There may be regional lymphadenitis.

Diagnosis is straightforward. In recurrent cases one has to look for pre-existing skin condition like pediculosis capitis, mosquito bites or atopic eczema. Culture is seldom done unless it is not responding to treatment or is recurrent.



Figure 1: Impetigo contagiosa.

Good hygiene and regular baths in summer are helpful in prevention. Some cases of streptococcal impetigo may develop glomerulonephritis after 2 to 4 weeks.

Ecthyma

It is a deeper variant of impetigo occurring in older children with poor hygiene, malnutrition and repeated trauma, usually as a secondary infection. The crusts are thick chocolate coloured, more adherent with indurated base and surrounding erythema. It occurs mostly on lower extremities.

Folliculitis

It is staphylococcal infection of the hair follicle (**Figure 2**). It may be superficial or deep depending on the part of the hair follicle involved. Follicles may be infected after epilation or after oil massage. Deep folliculitis involves the whole depth of follicle. It commonly occurs on beard area (sycosis barbae) or neck (sycosis nuchae). Infection occurs through abrasions on shaving. Generally there is no destruction of hair follicles.



Figure 2: Folliculitis.

Furunculosis (Boils)

There is extended involvement of hair follicles including the perifollicular region in the dermis. It is caused by *S. aureus*. The boils are common during adolescence and early adulthood and are common during rainy season. Generally subjects are otherwise healthy but have poor hygiene or are carriers of *S. aureus*. In older patients factors like diabetes mellitus and intake of corticosteroids may be responsible for their increased frequency and greater severity.

Carbuncle

It is a group of boils which show deep infection of contiguous follicles with *S. aureus*. Infection spreads from one follicle to the other through subcutaneous tissue. Common sites are back of neck, shoulders, hip and thighs. It is usually associated with diabetes mellitus, exfoliative dermatitis or prolonged steroid therapy.

Erysipelas

It is streptococcal infection of the skin, mainly upper subcutaneous tissue and lymphatic vessels. The organism enters through a wound, injury or even a subclinically traumatised skin. Usually, there is a history of antecedent streptococcal throat infection. Skin is tense, erythematous, oedematous and lesions spread peripherally. Margins are sharply defined. Sites of involvement are abdominal wall in infants and face in children.

Cellulitis

It is a deeper variant of erysipelas and may be acute, subacute or chronic. The borders are less well defined. There may be associated systemic symptoms of malaise and fever.

Secondary Bacterial Infection

Staphylococcus aureus and streptococci can complicate any skin disorder.

Management of pyodermas

1. Improvement of local hygiene
2. Identification and elimination of immunocompromising factors, if any suspected
3. Avoidance of insect bites in children
4. Staphylococcal carrier sites (anterior nares) be treated with twice a day application of fusidic acid or mupirocin ointment for 3 months
5. Topical antibiotics may be useful in preventing streptococcal pyoderma when applied three times a day for minor skin trauma in children. In crusted lesions the crusts must be removed gently
6. Local application of heat is beneficial in cases of boils.

Topical treatment

Superficial localised skin infections like impetigo and superficial folliculitis may respond to rigorous topical treatment with antibiotic creams like fusidic acid or mupirocin. 1% gentian violet is a cheap but effective option. Bacitracin, polymyxin and neomycin are available in various preparations, often in combinations.

Systemic treatment

These are needed for all but the most localised infections. *Streptococci* are relatively easily amenable to treatment with antibiotics. Penicillin group of drugs are effective. *Staphylococcus* has developed resistance to many anti-microbials.

Empirically one can start with tetracyclines (including doxycycline), or cotrimoxazole. Hospital acquired infections are more often resistant and need treatment with cloxacillin, azithromycin or cephalosporins. Duration of treatment is 5 to 7 days for superficial infections and up to 3 weeks for deep infections.

DISORDERS DUE TO OVERGROWTH OF CORYNEBACTERIA (DIPHTHEROIDS)

These are commensals but persons who sweat more may develop malodorous axillae and trichomycosis axillaris (fine yellowish deposits on axillary hair). In those who have prolonged immersion of hands and feet in water develop pitted keratolysis.

FUNGAL INFECTIONS OF SKIN

There are two main groups of fungal infections of superficial skin: (i) those due to dermatophytes and (ii) those due to yeasts. A few fungi invade deeper tissues. These are the deep mycoses.

Dermatophytoses (Tinea/ Ringworm)

These are classified according to sites affected. They are often self treated or wrongly treated with topical steroids which may confuse the picture (tinea incognito).

Tinea Capitis (Scalp Tinea)

Usually a disease of pre-adolescents. Fungi may be contracted from family members having tinea anywhere on body, or school-mates with tinea capitis or from infected animals. There is patchy loss of hair (only broken hair) with variable degrees of inflammation (to differentiate from alopaecia areata in which there is no inflammation and total loss of hair from the root). There may be inflammatory tinea with boggy swelling (kerion) (**Figure 3**). This is usually acquired from animals and is often misdiagnosed as pyoderma.



Figure 3: Tinea capitis (Kerion).

Tinea Corporis

The lesions are itchy, erythematous and scaly patches with well-defined borders. The borders are more prominent and often have papules and pustules. There may be central clearing so that annular or circinate patterns are formed (**Figure 4**).

Tinea Cruris

It involves groins and buttocks. It is more common in adult males. Recurrence is usually due to autoinfection from other sites like tinea pedis. Tight clothing and humidity are predisposing factors.

Tinea Pedis and Tinea Manum

These are common and often associated with tinea unguium (**Figure 5**). There are three distinct forms.



Figure 4: Tinea corporis.

1. Tinea interdigitale. There is scaliness or maceration in the interdigital space.
2. Vesicles on sides of feet, extending to rest of soles.
3. Dry and scaly type, often treated as eczema or psoriasis. Presence of typical tinea lesions on the dorsum of the foot and other parts of body may assist in diagnosis. In tinea manum, the scales are powdery and start in creases.

Tinea manum is most often unilateral.

Tinea Unguium

Toe nail infection is common as isolated tinea or associated with tinea pedis. Free edge of nail becomes yellowish, crumbly, then developing subungual hyperkeratosis and separation of nail from its bed (**Figure 5**). Usually starts with one or two nails, but rarely all are affected. Finger nail involvement is less common and less severe and is always associated with tinea manum.



Figure 5: Tinea unguium.

Tinea Barbae

It is invasion of hairs of beard by fungus, resulting in inflammatory lesion with follicular pustules. Usually due to unhygienic shaving by road side barbers.

Tinea Faceii

It is infection of face outside the beard area. Face is involved if a person has tinea of other sites or due to sharing towels with another family member with tinea.

Treatment

Topical treatment alone is indicated when the disease is of limited extent and only one site is involved. Clotrimazole, miconazole, and terbinafine creams applied twice daily for 4 to 6 weeks are effective. On palms and soles where there are hyperkeratotic lesions, Whitfield's ointment is more effective.

Systemic treatments include griseofulvin, triazoles and terbinafine. Griseofulvin is the drug of choice for tinea capitis in doses of 15 to 20 mg/kg body weight for 8 weeks. Triazoles include itraconazole and fluconazole. Itraconazole 200 mg to be given twice per day for 7 days for tinea cruris and corporis and for tinea unguium 400 mg daily for 7 days every month for 3 months. Fluconazole 150 mg once or twice a week for 4 weeks for tinea cruris and corporis and for 6 months for tinea unguium. Terbinafine is given as 250 mg daily for 2 weeks in tinea cruris, corporis and manum; 3 months for tinea unguium of finger nails and 6 months for toe nails.

YEAST INFECTIONS

Most yeasts are true commensals and only invade skin under certain conditions.

Pityriasis Versicolour

Pityrosporum orbiculare, the causal organism, is a normal inhabitant, grows profusely in humid climates and on certain skin types. As the organisms are normal inhabitants, it is not a contagious disease. It commonly affects upper chest, back and upper arms. Some patients may have mild itching. Even after treatment the hypopigmentation may take a long-term to clear. Recurrences in humid season are common.

Treatment

Topical treatment with selenium sulphide and/or clotrimazole once weekly for few weeks. Oral fluconazole 400 mg single dose is an alternative.

Candidiasis

Candida albicans is an opportunistic pathogen, found naturally in the oral cavity and lower intestinal tract and vagina in half of the normal population. Predisposing factors for symptomatic invasion include obesity, high humidity, diabetes, pregnancy, use of contraceptive pills, topical or systemic steroids or systemic antibacterials. Its clinical picture varies with the site.

Oral

It is most common in children or the elderly. Persons on oral antibacterials or immunosuppressants are also more prone. It presents as thrush, which are white adherent patches that leave an erythematous or bleeding surface on wiping off. There may be angular cheilitis.

Flexures

The areas commonly involved are inframammary, axillae, groins and between fingers. There is glazed erythema and maceration. There may be satellite pustules. Often there is some burning sensation.

Genital

White curdy discharge with erythema and pruritis are the features of candidial vulvovaginitis. This may be associated with inguinal candidiasis. Conjugal infection in males results in balanitis (in circumcised) or balanoposthitis. The glans becomes erythematous and the prepuce is inflamed, indurated and becomes whitish. There is difficulty in retracting the prepuce. On forcible retraction fissures may develop on the prepucial orifice.

Nail folds

Common in bakers and housewives working with water. Proximal nail fold and later lateral nail folds get inflamed and swollen. On pressing the nail fold, some cheesy material may be extruded. This is called chronic paronychia. *Proteus* or *Pseudomonas* may be co-pathogens. Staphylococci or streptococci may secondarily infect producing acute paronychia (**Figure 6**).



Figure 6: Paronychia.

Treatment

Topical gentian violet 1%, clotrimazole and miconazole and oral fluconazole are effective. Dryness of the affected part needs to be maintained.

DEEP MYCOSES

There are many deep fungal infections but the most common among these is mycetoma.

Mycetoma (Madura foot)

It is caused by either filamentous bacteria (*Actinomyces* spp.) or fungi which are introduced by a penetrating injury. Indurated nodules develop which enlarge and soften. These are often neglected and the process extends to deeper tissues and may even involve bone. The nodules burst on the surface producing multiple sinuses discharging pus which is granular. The granules are colonies of infecting organisms. These are diagnostic.

Treatment

Bacterial mycetomas respond to high doses of penicillin, streptomycin, cotrimoxazole, tetracyclines, dapsone and saturated solution of potassium iodide given for long periods of time.

Fungal mycetomas respond to ketoconazole 200 mg twice a day, or itraconazole 200 mg a day for 6 to 9 months.

VIRAL INFECTIONS

Viral Warts (Verrucae)

Caused by human papilloma virus (HPV). A few of these have oncogenic potential. Clinically they present variously depending on the site involved.

Common Warts

Rounded or irregularly shaped papules with rough and hyperkeratotic surface, on hands and feet. These may spread by autoinoculation and may be in a linear pattern. In severe immunosuppression they may be generalised. These are painful, if present around or under the nail. Lesions on the neck are often pedunculated (filiform warts).

Plantar Warts

Warts on the soles are only slightly raised, even when they assume large size. These may or may not be present on pressure sites. Corns occur only on pressure points. Both are painful particularly on walking. Warts if present only on pressure points can be distinguished from corns by paring, when oozing capillary loops can be observed in warts.

Plane Warts

These are flat topped, smooth, skin coloured or slightly dark, usually present on the face in children. Lesions arranged along scratch lines, if present, help in diagnosis.

Anogenital Warts

These are mostly sexually transmitted. Rarely these may result from autoinoculation from warts on other parts of the body. Lesions increase in number and size and coalesce to become cauliflower like. In women these may also affect the vagina and cervix. Other sexually transmitted infections (STIs) should be excluded. In children with anogenital warts, sexual abuse should be considered.

Treatment

Topical treatment

Keratolytics: In plane warts, topical tretinoin 0.05% to 0.1% applied at night for few months may be effective. In common and plantar warts, 'wart lotions' or 'corn lotions' which contain salicylic acid and lactic acid may be used only on the lesions, protecting the surrounding normal skin, preferably after paring the affected skin. Trichloracetic acid (TCA) may be applied on the lesions. In anogenital warts, 50% TCA may be applied once or twice a week. On plane warts, this may be applied on the wart with a sharp wooden toothpick.

Cytotoxic agents: Podophyllum 20% is applied on the lesion and washed after 2 to 4 hours and repeated once a week. Podophyllotoxin is safer to apply.

Formaldehyde 5%: Soles or palms can be soaked for 10 to 15 minutes per day.

Destruction: Electrosurgery, cryotherapy or scalpel excision.

Topical immunotherapy: Sensitisation with DNCB, topical imiquimod.

Systemic therapy: Immunomodulators like levamisole.

Cellular modifying agents like oral retinoids.

Molluscum Contagiosum

It is a common skin infection in school children. It is transmitted by direct contact and rarely through swimming pools. In adults lesions near genitals are often sexually transmitted. Large lesions on the face may indicate immunosuppression.

The lesions are globular whitish or yellow papules which develop a central depression (umbilication). Cheesy material can be expressed from a well developed lesion.

Treatment

Options include topical application of phenol, TCA or 10% KOH with a toothpick, curettage with a hypodermic needle or cryotherapy.

Herpes Simplex

It is caused by herpes simplex virus, which has 2 strains HSV1 and HSV2. HSV1 causes lesions around the oral orifice but genital lesions are generally caused by HSV2. The disease is acquired by direct contact with an infected person. Once infection is acquired it persists in the nerve ganglion all through life. Recurrence is more common in genital herpes.

The first infection is often asymptomatic and passes off unnoticed in most people. In some children, however, there may be acute gingivostomatitis characterised by multiple vesicles and ulcers. There is regional lymphadenitis. In genital herpes, a similar picture may be seen. After the primary herpes simplex infection, the virus becomes latent and may remain so or may get activated and present as recurrent herpes. The precipitating factors include stress, fever, common cold, excessive exposure to sunlight and trauma.

Recurrent herpes I lesions usually occur on the same sites. There is tingling or burning followed few hours later by erythema on which tense grouped vesicles appear. Vesicles dry and crust or erode. These heal in 7 to 10 days. In genital herpes, lesions are painful. The recurrent, grouped vesicles on erythematous base make diagnosis straightforward. Antibody titres do not rise with recurrent infections and are of no diagnostic significance.

Treatment

As it is self-limiting, no treatment is indicated. Topical application of surgical spirit keeps it dry and prevents secondary infection. Anti-viral drugs like acyclovir reduce viral replication and shorten attacks. However, these are only effective if started at the first sign of recurrence. Acyclovir (5%) needs to be applied every 4 to 5 hourly after removing the roof of the vesicles. Oral acyclovir 200 mg five times a day after food for 5 days may be given. Suppressive therapy is given in cases getting more than 6 recurrences a year. Acyclovir 400 mg twice a day for a year is recommended. Other antivirals for herpes simplex are valacyclovir and famciclovir.

Varicella (Chickenpox)

It is caused by varicella-zoster virus, which spreads by droplet infection. Incubation period is around 2 weeks. Constitutional symptoms, which are absent or mild in children, are followed by appearance of itchy papules which rapidly turn into vesicles. These become pustular in 3 to 4 days and finally get crusted. Lesions appear in crops. The lesions are maximum on the trunk. The patient is infectious from prodrome to formation of crusts.

Treatment

This is only symptomatic. Acyclovir is indicated only for severe attacks and for immunocompromised patients.

Herpes Zoster

It is reactivation of V-Z virus lying in a latent phase in the sensory nerve ganglion. It may, however, transmit the virus to others and result in varicella in non-immune subjects.

Initial symptoms are burning sensation and pain, which is followed by typical herpetic lesions. These are unilateral and distributed dermatomally. The lesions become pustular and then crusted in 2 to 3 weeks. It may leave depressed scars on healing. If the ophthalmic division of trigeminal nerve is involved, corneal ulcers may develop. If there are vesicles on side of nose, it indicates the involvement of the above nerve. There may be persistent neuralgic pain after the lesions subside. This is usually seen in the elderly (post-herpetic neuralgia).

Treatment

As secondary bacterial infections are common, topical antibacterials may be used. Treatment is symptomatic, using analgesics. In older people with higher risk of post-herpetic neuralgia and in ophthalmic zoster, oral acyclovir can be given. The dose of acyclovir is 4 times that used in herpes simplex, i.e. 800 mg 5 times a day. It is useful only if given within first two days of the attack. If post-herpetic neuralgia develops, this can be managed with long-term use of tricyclic compounds (amitryptiline 25 mg BD) or gabapentine 300 mg to 900 mg daily.

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11.3 Infestations and Insect Bites

Devinder Mohan Thappa, Laxmisha Chandrashekar

INTRODUCTION

Infestation refers to the state of being invaded or overrun by parasites. It can also refer to parasites living in or on a host. A parasite is defined as an organism that depends upon a living host for one or more of its essential metabolic requirements. Cutaneous lesions may result from direct damage by or presence of the parasite. Scabies, pediculosis and papular urticaria are caused by ectoparasites; patients usually present with itching.

SCABIES

There are two main types—human scabies and animal scabies.

Human Scabies

It is a contagious disease caused by the mite *Sarcoptes scabiei* var. *hominis* contracted through close personal contact or contaminated clothing. Over-crowding and poor hygiene helps its spread.

Sarcoptes scabiei var. *hominis* has an ovoid body, flattened dorsoventrally. The adult female measures approximately 0.4 mm long by 0.3 mm broad, and the smaller male 0.2 mm long by 0.15 mm broad. There are 4 pairs of short legs; the anterior 2 pairs end in elongated peduncles tipped with small suckers. In the female, the rear 2 pairs of legs end in long bristles (setae) (**Figure 1**). The adult male mite dies after copulation with adult female mite. After copulation the fertilised female mite excavates a burrow in the stratum corneum. Approximately 40 to 50 eggs are laid by each female during a lifespan of 4 to 6 weeks, during which time she does not leave the burrow. Six-legged larvae emerge from the eggs after 3 to 4 days and escape from the burrow by cutting through its roof. The larvae then dig short burrows (moulting pockets) in which they transform into nymphs. After further moults, adult males and females develop. On an average, an adult has 12 mites and an infant 20 mites.

First episode may take 3 to 4 weeks time to manifest. However, reinfection provokes immediate symptoms both due to immediate and delayed type hypersensitivity.

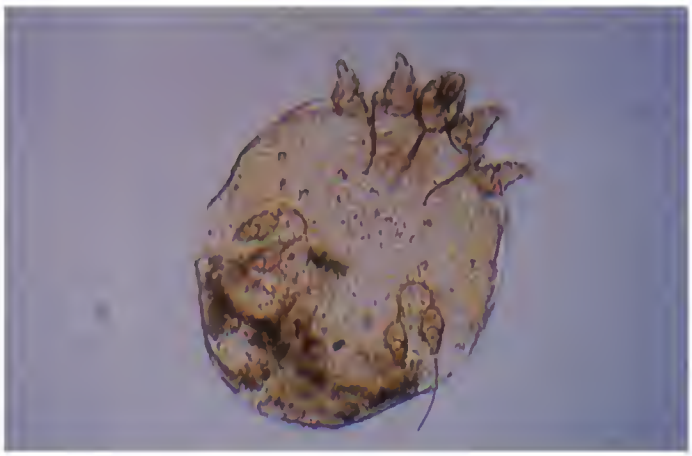


Figure 1: *Sarcoptes scabiei* var. *hominis* mite.

Clinical features

Often suspicion of scabies is based on nocturnal itching and family history of scabies. The pathognomonic lesions of scabies are burrows, which appear as fine, tortuous 'S' shaped slightly scaly blackish threads a few millimitres long. Sometimes, a papulovesicle is visible near the blind end of the burrow adjacent to which is the female mite. The burrows and associated papules and vesicles are directly related to the presence of the *Sarcoptes* whilst the generalised rash is related to the development of sensitisation.

Most worrying to the patient is the papular pruritic eruption, which is the result of hypersensitivity reaction to the mites and mite's products. Sites of predilection (**Figure 2**) include the finger web spaces (**Figure 3**), borders of hands, sides of fingers, feet particularly the instep, wrists, axillae, areolae, umbilicus (**Figure 4**), lower abdomen, genitals, buttocks (**Figure 5**). An imaginary circle intersecting the main sites of involvement—axillae, elbow flexures, wrists and hands and groins has long been called the 'circle of Hebra'. This predilection may be due to the fact that mites prefer non-hairy skin and areas of low sebum production. The involvement of genitalia of males (**Figure 6**) and itching of nipples in females are important clues.

In babies, the presentation may be slightly different with vesicles and vesiculopustular eruption on palms and soles, extensive

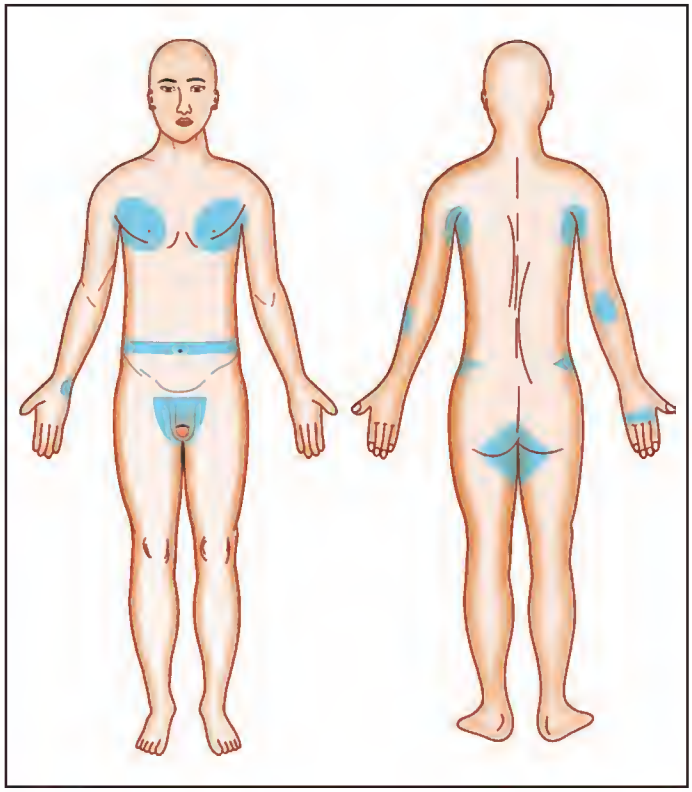


Figure 2: Characteristic distribution of scabies lesions over the body in adults.

distribution of burrows and crusted nodules including over the trunk and limbs, and extensive eczematisation is seen. Unlike in adults, the scalp and face may be involved in infants. In clean individuals only few scattered papules may be seen and itching may be mild.



Figure 3: Finger web spaces involved by papular and excoriated lesions.



Figure 4: Papular eruption of scabies around umbilicus.



Figure 5: Papular and excoriated lesions over the buttocks.

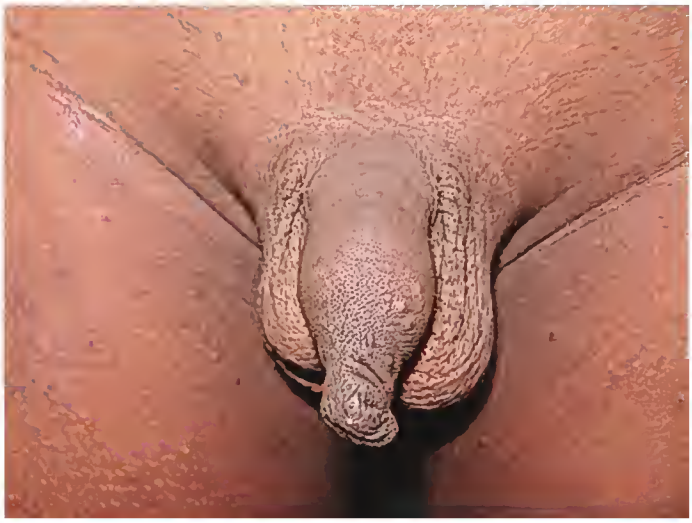


Figure 6: Typical burrows of scabies along with papules over the shaft of the penis.

Variants of scabies include nodular scabies and crusted scabies. Bullous pemphigoid like eruption and cutaneous vasculitis are unusual presentations. Secondary changes may confuse the clinical picture frequently. Secondary infection manifests as folliculitis and impetigo and infection with beta haemolytic streptococci may be responsible for secondary sepsis and post-streptococcal glomerulonephritis. Eczematous changes are common and severe.

Diagnosis

Scabies can be easily diagnosed based on history of nocturnal itching, family history of itching and typical localisation of lesions. Confirmation of diagnosis if desired may be accomplished by demonstration of burrows, mites (**Figure 1**) and mite's products like scybala, eggs, etc. from skin scrapings or epiluminescence microscopy. To identify burrows quickly, a drop of India ink or gentian violet can be applied to the infested area, and then removed with alcohol. Thin thread-like burrows retain the ink.

Anti-scabietic agents used in the treatment include:

Topical Agents

- Permethrin 5% cream
- Lindane (gamma benzene hexachloride) 1% lotion or cream
- Benzyl benzoate 10% and 25% lotion or emulsion
- Malathion 0.5% lotion
- Monosulfiram 25% lotion
- Crotamiton 10% cream
- Precipitated sulphur 2% to 10% ointment
- Esdepallethrine 0.63% aerosol
- Ivermectin 0.8% lotion

Oral drugs

In infants and pregnant women, sulphur ointment and crotamiton is preferred. The 5% permethrin cream may be used in infants over 2 months of age. In adults and children over 5 years of age, 5% permethrin cream is standard therapy for scabies. In children less than 5 years of age, the cream must be applied to the head and neck, as well as the body.

Single overnight application with permethrin is sufficient. However, gamma benzene hexachloride lotion needs to be kept on the body for 8 to 12 hours. Benzyl benzoate if used, 3 applications need to be given at 12 hourly interval without intervening bath. Sulphur ointment though messy is thought to be most effective treatment given once daily for 3 days. Similarly, crotamiton may be used. Additional advantage with crotamiton is its antipruritic effect. Monosulfiram is available as soap. Now even, gamma benzene hexachloride is marketed as soap. Ivermectin, an antihelminthic agent can be given in a single oral dose (200 µg/kg body weight, adult dose is 12 mg). Side-effects include headache, pruritus, pain in the joints and muscles, fever, maculopapular rash, and lymphadenopathy. It is contraindicated in patients with an allergy to ivermectin and central nervous system disorders. It is increasingly being used in the treatment of scabies in India.

Symptomatic relief of itching can be achieved with antihistamines. The older sedative antihistaminics are to be preferred over newer non-sedative ones. Prior to anti-scabietic treatment, secondary pyoderma and eczematisation should be treated appropriately. Treatment of other family members is important. Clothing and bedding can be laundered and put in sunlight.

Nodular Scabies

In some cases, itching nodules persist for several months on the genitalia. They are found most commonly on the scrotum. Topical therapy, intra-lesional steroids, tars or excision are methods of treatment. Histologically, it may suggest lymphoma.

Crusted Scabies (Norwegian or Hyperkeratotic)

It is found in immunocompromised or debilitated patients, including those with neurologic disorders, Down's syndrome, organ transplants, graft-versus-host disease, adult leukaemia, leprosy, or AIDS. It is characterised by psoriatiform or warty lesions accompanied by nail hyperkeratosis but no burrows and minimal itching is present. The average number of mites in these cases is 2 million; it is highly contagious and may be the source of epidemics. Ivermectin is the treatment of choice in addition to keratolytics.

Scabies incognito occurs on inappropriate use of topical steroids as steroids suppress the inflammation to the mites and reduce itching, so there is less scratching and destruction of burrows.

Animal Scabies

Various itch mites affect animals with which man comes in close contact. These animals are dogs, cats, birds, etc. Itchy papular eruption is localised to site of contact of animal with human skin. The eruption is self-limiting, with no burrows. Animals need to be treated with anti-scabietic agents and symptomatic treatment is given to the person concerned.

PEDICULOSIS

Infestation with lice is called pediculosis. Lice are called ectoparasites because they live on the body. Close personal contact or contact with objects shared by others helps in the transmission of lice. They are classified as wingless insects because they have three pairs of legs. Three kinds of lice infest humans: *Pediculus humanus* var. *corporis* (body louse), *Pediculus humanus* var. *capitis* (head louse) and *Phthirus pubis* (pubic or crab louse) (**Figure 7**). The body louse is the largest and the crab louse is the smallest with a short oval body with prominent claws resembling sea crabs. Lice feed by piercing the skin with their claws, injecting irritating saliva and sucking blood. The female lays approximately 6 eggs or nits each day. The egg hatches in 8 to 10 days and reaches maturity in approximately 18 days. Nits are glued to the bases of hair shafts (**Figure 8**). The incubation period of pediculosis is about 30 days.

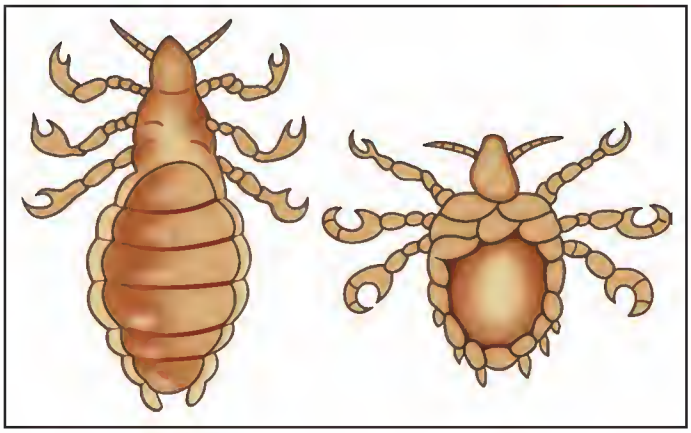


Figure 7: *Pediculus humanus* var. *capitis* (head louse) and *Phthirus pubis* (pubic or crab louse).

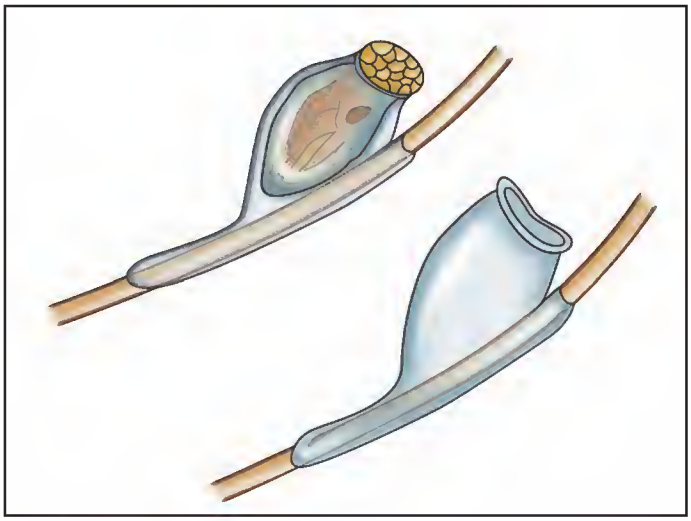


Figure 8: Viable nit (top left) and non-viable nit, empty egg case (bottom right) glued to hair.

Pediculosis Capitis

Lice infestation of the scalp is most common in children especially girls with long hairs. Itching and secondary pyoderma in the scalp are presenting manifestations. The diagnosis is made by seeing the lice in the scalp or more often, nits glued to the hair shaft (**Figure 9**) in the retro-auricular and occipital region of the scalp. Ova close to the scalp are only viable; along the distal hair shaft are empty egg cases. Peripilar keratin hair casts are remnants of inner root sheath that encircle the hair which can be mistaken for nits. While nits are firmly cemented to the hair, casts move freely along the hair shaft.

Pediculocidal treatment with 1% permethrin rinse or gamma benzene hexachloride lotion/shampoo may be instituted. Malathion, crotamiton and lindane have also been found to be effective. Combing with a metal or plastic comb after conditioner (8% formic acid solution) is an adjunctive measure.

In case of secondary infection of the scalp, cotrimoxazole may do the dual function of treating pyoderma and killing all adult lice. Repeat treatment with pediculocidal agents may be necessary after 1 week, as they may not kill nits. Shaving the head will cure head lice but has poor patient compliance. Orally, ivermectin has also been used. Family members and contacts should be treated.



Figure 9: Nits glued to scalp hair.

Pediculosis Corporis (Vagabond's Disease)

Pediculosis corporis is a disease of the unclean. Body lice live and lay their nits in the seams of clothing and return to the skin surface only to feed. It induces pruritus that leads to scratching, copper coloured macules, wheals, lichenification and secondary infection. The diagnosis is positively established by finding the lice or nits in the seams of clothing. Body lice are vectors for relapsing fever, trench fever and epidemic typhus.

Treatment is directed at clothing and bedding. Simple laundering and ironing is successful. Permethrin or malathion spray can be used to disinfect clothing.

Pediculosis Pubis

Phthirus pubis infestation is found in the pubic region, as well as hairy areas of legs, abdomen, chest, axillae, arms and also eyelashes (pediculosis palpebrum) and scalp rarely. Itching or crawling sensation of something are the complaints in the majority of patients. It is transmitted by close sexual contact, hence a screening for sexually transmitted diseases should be done. Diagnosis is made on seeing black speck like bodies attached to the root of hair at an angle—the crab lice. Occasionally, in fair skinned individual, one may encounter gray blue macules (maculae caeruleae) varying in size from 1 to 2 cm in the groin, inner thighs and sides of trunk. They are probably caused by altered blood pigments.

Gamma benzene hexachloride lotion or permethrin may be used topically for pediculosis pubis. For eyelash involvement a thick layer of petrolatum can be applied twice daily or fluorescein can be used. Shaving of pubic hairs is another alternative treatment. Sexual partners should be treated simultaneously.

PAPULAR URTICARIA

Definition

Papular urticaria is a term used to describe a chronic or recurrent eruption of pruritic papules, often grouped in irregular clusters, frequently seasonal in incidence, and affecting predominantly children between the ages of 2 and 7 years. Adult cases are seen but are less common than childhood cases.

Aetiopathogenesis

Papular urticaria is an allergic hypersensitivity reaction to arthropod bites. The role of arthropods in papular urticaria gradually gained support because of the following observations:

1. The lesions usually appear in the summer months;
2. The disease is more common in lower socioeconomic groups; and
3. Papular urticaria is seen with greater frequency among households with pets.

The most commonly implicated arthropods are the mosquitoes, bed bugs and the fleas.

Clinical Features

The condition consists of small, 3 mm to 10 mm diameter, pruritic, urticarial papules, sometimes surmounted by a vesicle, that are present on exposed areas of the body (**Figure 10**). The papules may last from weeks to months and, in some cases, years. They form in clusters and are characteristically distributed on the extensor surfaces of the arms and legs.



Figure 10: Papular excoriated lesions over the lower limb of a child.

The genital, perianal and axillary regions are not usually involved. Excruciating pruritus frequently leads to excoriations, which may become secondarily impetiginised. The lesions generally persist for 2 to 10 days and may result in temporary hyper-pigmentation once they resolve.

Differential Diagnosis

Differential diagnosis includes:

- Scabies,
- Prurigo simplex,
- Urticaria,
- Atopic dermatitis,
- Papular drug reaction,
- Miliaria rubra and
- Allergic contact dermatitis.

Treatment

The treatment is based on identification and removal of the cause. Mild topical steroids and oral antihistamines can be used to control pruritus. Oral antibiotics can be used for secondary infections. Disinfection of all pets along with fumigation of the home in recommended. Patients should use insect repellent creams on the skin before venturing outdoors.

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11.4 Eczemas

Ashok Kumar Bajaj

INTRODUCTION

Eczema or dermatitis is a group of inflammatory skin diseases provoked by a wide variety of stimuli, i.e. direct injury from toxic chemicals, mechanical trauma and immunological reactions. The word eczema is derived from the Greek word 'eczein' meaning 'to boil over' or 'to effervesce'. The terms, dermatitis and eczema are often used as synonyms, but the term eczema is preferably used for exudative dermatitis.

Depending upon the clinical manifestations, eczema can be subdivided into the following three stages:

Acute Eczema

It represents wet dermatitis characterised by intense pruritus, erythema, oedema, papules, vesicles, oozing, crusting, and even blister formation.

Subacute Eczema

It is characterised by diffuse erythema, oedema and scaling. In this stage, oedema, vesiculation and oozing components come down. The lesion starts scaling.

Chronic Eczema

It is represented by severe itching, hyperkeratosis and lichenification (thickening, hyper-pigmentation and accentuated skin markings).

Just like clinical features, histopathology varies with the stage of eczema. In the acute stage, there is spongiosis (intercellular oedema) and intraepidermal spongiotic vesicle formation. Features that predominate in the chronic stage are acanthosis (thickening of stratum malpighii with elongation of rete ridges), hyperkeratosis (thickening of stratum corneum) and parakeratosis (nuclei seen in stratum corneum). In the subacute stage, there is combination of these two reaction patterns.

CLASSIFICATION

Eczematous disorders are classified according to the aetiology (**Table 1**) as follows:

Table 1: Classification of Eczema

Endogenous eczema	Exogenous eczema
Atopic dermatitis	Irritant contact dermatitis
Seborrhoeic dermatitis	Allergic contact dermatitis
Nummular eczema	Photodermatitis
Pompholyx (Dyshidrotic eczema)	Infectious eczematoid dermatitis
Asteatotic eczema	
Stasis dermatitis	
Juvenile plantar dermatitis	
Lichen simplex chronicus	

Endogenous Eczema

In this type of eczema, the course of the problem arises mainly from the patient's inherent constitutional factors and partly due to the superimposed environmental factors.

Exogenous Eczema

When the patient develops eczema as a result of the exposure of the patient's skin to environmental noxious agents.

In many cases both external and internal factors contribute to the pathogenesis of eczema.

ATOPIC DERMATITIS (ATOPIC ECZEMA)

Atopic dermatitis is a common form of endogenous eczema and its incidence is increasing in India. The exact aetiology is unknown but genetic and environmental factors are probably equally important in the development of atopic dermatitis. A family history of asthma, hay fever (rhinitis and conjunctivitis), atopic dermatitis and even urticaria is common in patients with this condition. Around half of the children with atopic dermatitis go onto develop asthma or hay fever or both. These disorders are inherited as autosomal dominants with incomplete penetrance. The environmental factors which act as triggers for atopic dermatitis are climatic changes, food items (eggs, dairy products, nuts, etc.), bacterial infection and dry skin.

Clinical Features

Atopic dermatitis usually develops around the age of 3 months and is labelled as infantile eczema. It classically affects the cheeks, scalp and extensor surfaces of the limbs and trunk (**Figure 1**). There is erythema, oedema and papulovesicular oozing lesions with severe itching. It is the itch which produces the lesions rather than the lesions which cause itching. The affected children may sleep poorly and may be hyperactive. After a variable course of relapses and remissions the disease subsides in over 80% of the children by the age of 18 months. In the rest of them it continues into *childhood phase* which is characterised by itchy papular lesions in the cubital and popliteal fossae, ankles, wrists, and sides of the neck. The skin may also become thickened and rough



Figure 1: Atopic dermatitis (infantile eczema).

(lichenification). Patients often have fairly dry skin. Multiple scratch marks and abrasions are seen in patients with severe itching. It affects the school and social life of such children.

In about two-thirds of the childhood eczema patients, the disease subsides by the age of puberty, and in the remaining it continues on to the *adult phase*. The distribution in the adult phase is similar to childhood phase with morphology of subacute or chronic eczema. Relapses and remissions depend upon the activation of various trigger factors like mental and physical stress, climatic changes, secondary infection, etc.

Common complications include secondary bacterial infection with staphylococci and viral infections. Most patients of atopic eczema are colonised by *Staphylococcus aureus* all the time with or without apparent evidence of infection and anti-staphylococcal therapy frequently leads to improvement. This emphasises the role of bacteria in perpetuation of dermatitis. Common viral infections complicating atopic eczema are molluscum contagiosum and herpes simplex which can become widespread. Kaposi's varicelliform eruption (eczema herpeticum) is disseminated herpes simplex infection in an atopic dermatitis patient and it can be life-threatening if it is primary infection by the herpes virus.

Management

There are hardly any confirmatory laboratory investigations for the diagnosis of atopic eczema. The classical morphological pattern, i.e. dry skin, severe itching, clinical course, history of atopy in the family/patient, and raised IgE serum levels strongly suggest the diagnosis. The management has to be individualised depending upon severity, age, complications and associated disorders.

General principles

(a) Avoid aggravating external factors like extreme variations of temperature, contact with woollen and synthetic clothes.

(b) Skin barrier should be restored by using mild neutral pH soaps and liberal use of emollients.

(c) Food items like dairy products, nuts, eggs, fish, etc. may be avoided though their role is questionable.

Pharmacotherapy

The pharmacotherapy is aimed at controlling the acute attacks and keeping the disease under control till remission. Various effective topical and systemic agents are:

(a) Topical corticosteroids of appropriate potency taking into consideration the age of the patients and extent of involvement. Prolonged use of topical steroids should be discouraged to minimise side effects like skin atrophy and side effects due to systemic absorption. Potent corticosteroids are quite affective but should be used in short bursts to overcome acute attacks and then followed-up by low potency steroids and other agents.

(b) Topical immunomodulators like tacrolimus 0.03 to 0.1%, pimecrolimus are effective alternatives for topical corticosteroids especially for the face and flexural skin due to their minimal side effects, except initial burning and irritation. Pimecrolimus can be used under the age of 2 years while tacrolimus should be preferred for older age groups.

(c) Oral antihistamines with sedative effects such as diphenhydramine, promethazine hydroxyzine and doxepin should be preferred to relieve pruritus.

(d) Oral antibiotics like dicloxacillin, cephalexin and other cephalosporins are useful in improving dermatitis by controlling colonisation and secondary infection by staphylococci.

(e) In severe recalcitrant cases, to improve the quality of life, systemic steroids, cyclosporine, azathioprine, mycophenolate mofetil, low-dose methotrexate have been found to be effective. Interferon gamma, narrow band ultraviolet B (UVB) and psoralen and ultraviolet A (PUVA) have also been advocated in such cases.

Atopy means a genetically determined state of hypersensitivity to environmental allergens and includes asthma, hay fever and dermatitis. Early age of onset, severe itching, face and flexural involvement, family or personal history of atopy, dry skin and raised IgE are suggestive of atopic dermatitis.

SEBORRHOEIC DERMATITIS

Seborrhoeic dermatitis is a common chronic inflammatory disorder with a characteristic distribution of lesions in the areas rich in sebaceous glands. The exact cause of the disorder is as yet unresolved, but overgrowth of the yeast *Malassezia furfur/ Pityrosporum ovale* has been implicated as a causative factor. This is further supported by increased incidence of seborrhoeic dermatitis in acquired immune deficiency syndrome (AIDS) patients with extensive involvement. Seborrhoeic dermatitis has a bimodal occurrence and can manifest in early infancy (infantile seborrhoeic dermatitis); or adult life (adult seborrhoeic dermatitis), but the two are not related.

Infantile Seborrhoeic Dermatitis

It generally appears in the first three months of life. The areas affected are the scalp, face, axillae, and napkin areas. The scalp shows erythema and sticky scales (cradle cap). The napkin area may be sore and weepy but there is no itching unlike atopic eczema. It usually remits in a couple of months. Oil applications, mild shampooing may suffice in most of the cases, but some may require application of steroid and antifungal agents topically.

Adult Seborrhoeic Dermatitis

Occurs commonly in the age group of 20 to 40 years. Pityriasis capitis (dandruff) is probably the mildest form of the disease. In severe cases there is marked erythema, scales, and even exudation on the scalp. Red, somewhat greasy-looking scales are also seen on other areas rich in sebaceous glands like the face, nasolabial folds, front and back of the upper chest, retroauricular areas, eyebrows, and eyelids (blepharitis). Some patients develop lesions in the axillae and groins which may be mild or quite troublesome. Though the severity of the disease may fluctuate, the tendency persists throughout life. Dandruff is treated with shampoos containing selenium sulphide, zinc, pyrithione, tar, ketoconazole or fluconazole. To treat mild to moderate cases of seborrhoeic dermatitis, mid-potency topical steroids and topical antifungal agents are sufficient. More severe cases may require oral ketoconazole or fluconazole and systemic steroids. Oral antibiotics and antihistamines can be prescribed as and when required. *Isotretinoin* in smaller doses of 20 mg on alternate days is also quite effective in treating seborrhoeic dermatitis.

Seborrhoeic dermatitis commonly affects the face, scalp, front and back of chest of adults in the 20 to 40 years age group.

NUMMULAR ECZEMA (DISCOID ECZEMA)

Nummular eczema is a chronic and recurrent endogenous eczema of unknown aetiology. Many cases have an atopic background. It manifests as itchy, multiple, sharply demarcated, coin shaped or oval lesions with papulovesicles (**Figure 2**) or papules and scales on an erythematous base. It is more commonly seen in the elderly with dry skin and usually affects the extensor aspects of extremities. The course of the disease varies from a few months to a few years with recurrences and remissions. Treatment consists of avoidance of contact with irritants, mid-potency topical steroids, and resistant cases may require systemic steroids, antibiotics and sedating anti-histamines.



Figure 2: Nummular eczema.

POMPHOLYX (DYSHIDROTIC ECZEMA)

Pompholyx is a distinctive, chronic relapsing, vesicular eczematous dermatitis of unknown aetiology. It affects young adults and is characterised by sudden crops of highly pruritic, deep-seated sago-like vesicles on the palms, sides of fingers and/or soles (**Figure 3**). The disease may be isolated, asymmetrical or bilaterally symmetrical. Summer aggravation is common and lesions frequently get secondarily infected. Vesicles resolve slowly over 1 to 3 weeks. In patients with bilateral symmetrical lesions, fungal infection of the feet should be ruled-out by KOH examination and contact sensitivity should be ruled-out by patch testing. Nickel and chromate as well as neomycin and quinoline contact sensitivity have been implicated to produce pompholyx lesions. Ingestion of nickel, chromate and cobalt can elicit lesions even if the patch tests are negative. The acute form is treated with soaks and compresses of potassium permanganate and topical steroids. Subacute and chronic stages are treated with topical steroids and dapsone. In severe cases oral steroids and even methotrexate (15 to 20 mg weekly) may be required. Majority of patients who are sensitive to metals improve markedly on low nickel diet (avoid canned foods, beans, mushroom, onions, corn, spinach, tomatoes, peas, whole grain flour, cocoa, chocolate, baking powder, etc.).



Figure 3: Pompholyx (dyshidrotic eczema).

ASTEATOTIC ECZEMA (WINTER ECZEMA; ECZEMA CRAQUELE)

Asteatotic eczema is an endogenous eczematous disorder that is caused by excessive dryness and chapping of the skin. Factors leading to dryness are reduced skin surface lipid, low humidity and decreased water binding capacity of the stratum corneum. It is a form of subacute eczema that is low grade with aggravation in winter season. Clinically, it is characterised by dry scaling and cracking giving the skin a fissured appearance (**Figure 4**). Later, the skin may become red and inflamed. It commonly affects the lower limbs, trunk, arm, and hands of elderly males but the face and moist flexural areas are often spared. Rarely, similar changes may be widespread requiring exclusion of underlying lymphoid malignancy. Treatment of asteatotic eczema involves the removal of underlying aggravating factors and rehydration of the skin surface by advocating the use of greasy emollients, bath oils and emollient cleansers. Mild or mid-potency topical steroids for a short period may be required, but oral steroids should be avoided.



Figure 4: Asteatotic dermatitis.

STASIS DERMATITIS (GRAVITATIONAL ECZEMA/VARICOSE ECZEMA)

Stasis dermatitis is a chronic relapsing eczema that occurs secondary to venous incompetence and hypertension. It commonly affects middle-aged or elderly individuals. It usually begins as pruritic, dry scaling skin on the medial aspect of the leg above the ankle that later becomes fissured, erythematous and hyperpigmented (**Figure 5**). The skin may become thin

and atrophic. Fibrosis may lead to tight, bound-down, indurated skin prone to chronic ulceration. Secondary spread of eczematous eruptions to distant sites is common and may indicate allergic contact sensitivity to topical medicaments which is not uncommon in varicose eczema. The management requires rest, elevation of the legs, and use of elastic bandages or stockings. Only mild topical steroids should be used to relieve irritation and to minimise atrophy. Surgical intervention may be helpful in some cases.



Figure 5: Stasis dermatitis.

JUVENILE PLANTAR DERMATOSIS (DERMATITIS PLANTARIS SICCA)

It is a common dermatosis of childhood characterised by shiny, dry, fissured skin of the soles with loss of the epidermal ridge pattern. The sites affected are the weight-bearing areas particularly the forefeet and undersides of the toes. The toe webs and instep are spared. It is thought to be due to excessive sweating and blockade of sweat ducts due to occlusive footwear. Some consider the condition to be a manifestation of atopy. The condition is usually worse during winter and sometimes during dry summer season. It usually subsides during late teens.

The treatment consists of avoiding occlusive footwear, and preferably to use cotton socks. Emollients are usually effective but topical steroids of mid potency may be required in patients with itching and discomfort.

LICHEN SIMPLEX CHRONICUS

Lichen simplex chronicus also known as neurodermatitis, it is a localised patch of chronic eczematous inflammation which is created by habitual scratching in predisposed individuals. The initiation and perpetuation of the lesions is due to the development of an 'itch-scratch' cycle. It is characterised by a lichenified plaque and many of these patients have an atopic diathesis. The areas most commonly involved are those that are conveniently reached. These sites are nape of the neck, ankles, legs, forearms, wrists, and genitalia (scrotum or mons pubis). Emotional factors have an exacerbating effect.

The treatment consists of use of potent topical steroids alone or in combination with keratolytic agents under occlusion except in cases with genital involvement. Anxiolytics and sedating antihistamines are helpful. PUVA, UVB therapy and sometimes immunosuppressants may help some patients.

CONTACT DERMATITIS

Contact eczema develops as a result of contact with injurious material. These materials may injure by direct toxic action (irritants) or may induce immunological reaction of delayed hypersensitivity type (allergens). The first type of reaction is known as irritant contact dermatitis whereas the latter is termed as allergic contact dermatitis.

Irritant Contact Dermatitis

This type of dermatitis occurs due to contact with irritants like detergents, acids, alkaline chemicals, oils, organic solvents, oxidants, and reducing agents. The intensity of the inflammation is related to the concentration of irritant and the exposure time. Mild irritants cause dryness, fissuring and erythema (cumulative irritant dermatitis; wear and tear dermatitis) and strong irritants may produce an immediate reaction characterised by burning, erythema, oedema, blistering, and possibly ulceration of skin (**Figure 6**). Housewife's eczema, diaper dermatitis and industrial dermatitis are common examples of cumulative irritant contact dermatitis. Housewife's dermatitis and industrial/occupational dermatitis commonly affect the hands.

Treatment of acute irritant dermatitis requires washing quickly with water or a weak neutralising solution or frequent wet compresses, followed by the application of a bland or antibacterial with mid-potency steroid cream. For chronic cases, removal of all adverse chemical and physical factors and the use of bland barrier creams and mid potency topical steroids are necessary along with protective gloves.



Figure 6: Irritant dermatitis.

Allergic Contact Dermatitis

It is a type IV delayed type hypersensitivity reaction mediated by T-lymphocytes against certain chemicals coming in contact with the skin. In India, the common sensitisers are metals (nickel, chromium), plants (parthenium, also known as congress grass), antibacterial agents (neomycin, nitrofurazone), rubber chemicals (mercaptobenzothiazole, thiuram) and hair dyes/*Kali Mehndi* (paraphenylenediamine), etc. The eczematous rash

often develops at the sites of skin contact with the allergen but an irritant dermatitis eruption can develop at distant sites. Moreover, autoinoculation of the antigen can lead to widespread lesions. Parthenium dermatitis is the most common and severe type of allergic contact dermatitis seen in India. It is caused by a weed *Parthenium hysterophorus* (**Figure 7**) which grows wild along roads, railway tracks and in the fields. It commonly manifests as air-borne contact dermatitis affecting mainly the face including the eyelids, neck, flexures of the extremities, and sometimes the whole body surface may be involved (**Figure 8**). Distribution of lesions on sun-exposed areas is not uncommon. There is worsening during summer and rainy season while the lesions undergo partial or complete remission during winter.



Figure 7: *Parthenium hysterophorus*.



Figure 8: Parthenium dermatitis.

Nickel sensitivity is quite common and manifests as dermatitis due to ear rings (**Figure 9**), bangles, necklace, zips, metal buttons, and safety pins. Occupational nickel sensitivity affects the hands. Chromium allergy is also quite common and is usually due to leather footwear, cement and ink. Footwear dermatitis (**Figure 10**) is another common type of allergic contact dermatitis in our country due to the hot and humid weather. Rubber and leather are the most common causes. Topical medicament dermatitis (**Figure 11**) is commonly due to nitrofurazone and neomycin. Neomycin sensitivity is quite often superimposed on varicose and footwear eczema, and remains



Figure 9: Ear ring dermatitis.



Figure 10: Footwear dermatitis.

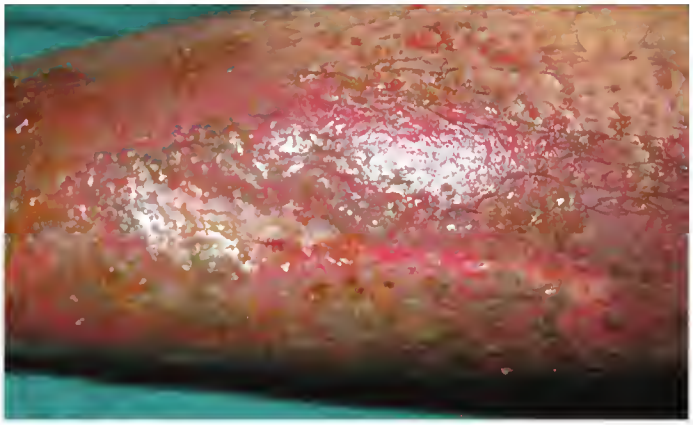


Figure 11: Topical medicament dermatitis.

undetected due to its use with topical steroids. Hair dye dermatitis is also not uncommon and it is becoming common due to high concentrations of paraphenylenediamine (PPD) in *Kali Mehndi* (black henna) (**Figure 12**). Other types of allergic contact dermatitis peculiar in our country are bindi dermatitis (**Figure 13**), black henna dermatitis (**Figure 14**), and tooth powder dermatitis (**Figure 15**).



Figure 12: Hair dye dermatitis.



Figure 13: Bindi dermatitis.



Figure 14: Black henna dermatitis.

Diagnosis of allergy is confirmed by patch testing. Management includes detection and avoidance of contact sensitisers, use of barrier creams and topical steroids of appropriate potency. For severe attacks, systemic steroids, azathioprine, methotrexate and even cyclosporine can be used. Azathioprine is quite effective in parthenium dermatitis as a steroid-sparing agent.



Figure 15: Tooth powder dermatitis.

The common allergens in India are metals (nickel, chromium), rubber chemicals (mercaptobenzothiazole), Parthenium (a weed), medicaments (nitrofurazone, neomycin) and hair dye (PPD).

Medicament dermatitis is fairly common in patients of stasis dermatitis, footwear dermatitis and atopic dermatitis.

PHOTODERMATITIS

It is the result of exposure of skin to sunlight following the topical or systemic administration of certain photosensitising agents (drugs and chemicals). Photodermatitis could be either phototoxic or photoallergic and is mainly distributed over the sites exposed to light. For further details, refer to the chapter titled 'photosensitivity dermatoses'.

INFECTIOUS ECZEMATOID DERMATITIS

Infectious eczematoid dermatitis or infective eczema or bacterial eczema is caused by an allergic reaction to micro-organisms or their products. It manifests as advancing erythema with exudation and predominantly affects the retroauricular areas, scalp, legs and areas around the discharging sinuses and wounds. The eczema responds to treatment with appropriate topical and systemic antibiotics.

AN APPROACH TO A CASE OF ECZEMA

Diagnosis of eczema is based on the clinical features (especially morphology and distribution). The predominant features depend upon the stage: lesions in acute eczema are often exudative while chronic eczema is associated with severe pruritus, scaling and lichenification. The next important step is to differentiate between endogenous and exogenous eczema.

Clinical features suggestive of an endogenous eczema are bilaterally symmetrical distribution of lesions and well established patterns of lesions, e.g. atopic dermatitis or seborrhoeic dermatitis. Clinical features suggestive of an exogenous eczema are asymmetrical distribution, linear or rectilinear configuration of lesions, history of contact with irritant and/or allergens, and improvement on change of environment.

INVESTIGATIONS

Although clinical examination is quite sufficient to suggest the diagnosis of eczema, as a general rule it is advisable to treat acute eczemas without investigations. On the other hand, chronic and recurrent eczemas should be investigated thoroughly to find the cause of eczema.

Patch Testing

It is the only scientific method available to confirm the diagnosis of allergic contact dermatitis but is not useful for irritant contact dermatitis as it detects the allergens responsible for type IV allergy only. It should be performed after the acute stage subsides. A series of allergens in adequate concentration are applied on the back with adhesive tape and left on for 2 days. The readings are taken on day 2 and day 4. The offending allergens will produce erythema and papulovesicles at the site of application. A good patch test should indicate contact sensitisation and produce no false positive reactions.

Photopatch Testing

These tests are performed to find the cause of photo allergic contact dermatitis. It should be performed in photo distributed dermatitis. In photopatch testing also, the patches of chemicals are applied as for ordinary patch testing, except that they are applied in duplicate and after 24 hours one set of patches is removed and the underlying skin is irradiated with ultraviolet light. After irradiation, the patch sites are covered again and evaluated at day 2 and day 4.

Prick Testing

These are performed to detect the type I hypersensitivity reactions. Relevance of positive prick tests in establishing the cause of the eczema is questionable.

Serological Testing

Estimation of total serum IgE and IgE antibodies specific to certain antigens are useful diagnostic criteria for atopic dermatitis. Radio-allergosorbent test (RAST) is helpful to detect specific dietary environmental allergens, which could be aggravating the dermatitis, especially in atopics.

Skin Biopsy

A skin biopsy is rarely required to diagnose the eczema and histopathological findings will depend upon the stage.

TREATMENT

Successful management of dermatitis requires a multipronged approach. Apart from the specific therapy, appropriate general measures are very helpful in treating the eczemas.

GENERAL MEASURES

Identification of any offending allergen, irritant or triggering factor is very important. Adequate measures to avoid the offenders may help in treating the dermatitis.

Eczemas like atopic dermatitis and asteatotic dermatitis are associated with dry skin and hence increased susceptibility to irritants. Maintaining proper hydration of the skin is important in treating dry eczema.

Topical Treatment

Wet compresses with a solution of either potassium permanganate (0.01%/light pink colour) or aluminium sulphate (0.65%) followed by application of steroid lotion/cream is best in the oozing stage of eczema. These compresses help by suppressing inflammation, removal of crusts, have antibacterial action and cause drying of the lesions.

In the subacute stage, wet compresses should be discontinued and only mid-potency topical steroid cream can be prescribed.

Chronic eczema requires potent steroid in ointment base for topical application. In lichenified lesions, a topical steroid can be combined with keratolytic agents like salicylic acid or urea. For secondary bacterial infection a topical antibiotic can be combined with a steroid.

Systemic Treatment

A short course of systemic steroids may be needed for extensive lesions and when an irritant dermatitis eruption (spread of an acute inflammatory dermatitis to distant sites is termed irritant dermatitis eruption or autosensitisation) develops in acute eczema.

Systemic antibiotics are required for infected lesions.

Oral antihistamines may be prescribed, as and when required, but may not be helpful in contact dermatitis. Steroid sparing agents like methotrexate in small weekly doses, azathioprine, and even cyclosporine may be required in recalcitrant cases like atopic dermatitis, parthenium dermatitis, etc.

RECOMMENDED READINGS

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11.5 Drug Reactions

M Ramam

INTRODUCTION

A fairly large number of drug reactions present with a skin rash. Patients who are taking medicines and develop a skin eruption pose an important clinical challenge because a decision needs to be taken whether the drug can be continued safely or should be changed.

A simple way to avoid this problem would be to stop using those drugs that cause reactions. But if we look at the list of drugs causing reactions, we find that these are medications which are commonly used (**Table 1**). Unfortunately, there is no way of predicting which patient will develop a reaction and which patient will not and so there is no good way of preventing drug reactions. We will continue to be faced with this problem as long as we use drugs to treat our patients.

Table 1: Drug Groups Usually Causing Eruptions

Nonsteroidal anti-inflammatory drugs
Antibiotics
Anti-tuberculosis drugs
Anti-convulsants

A genetic suspectibility to certain drug eruptions has been identified, e.g. HLA B*1502 is associated with carbamazepine reactions and in South-Asian populations where this allele is frequent, it is recommended that HLA typing be performed before prescribing the drug. The presence of certain infections make drug eruptions more likely, e.g. infectious mononucleosis and human immunodeficiency virus infection. However, in the vast majority of patients there are no identifiable factors that can be used to predict (and prevent) the development of drug eruptions. At the level of a community, the strongest determinant of which drugs cause reactions appears to be the prescription practices of its physicians. The most robust method of preventing drug reactions is to use drugs only when required.

Typically, drug reactions do not occur at first exposure to a drug. Usually, the drug has to be first taken for about a month before a reaction develops. However, once a reaction has developed, subsequent exposure to the drug will lead to a reaction within a few hours after re-exposure. Stopping the drug leads to improvement of the eruption over the next few days. Development of a drug eruption after the drug has been stopped is distinctly unusual and indicates that the diagnosis may be incorrect.

Drug eruptions can be suspected if a widespread, symmetric, itchy, rapidly progressive rash develops in a patient taking medications. In such a situation, it is wise to stop the drugs being taken and seek an urgent medical/dermatological consultation. If the rash is accompanied by fever, a feeling of being ill, or blisters and ulcers in the skin and mouth, a severe drug reaction is likely. Less severe drug eruptions may manifest as localised areas of redness and inflammation.

All eruptions that develop following drug intake are not drug eruptions. The eruption may be related to the underlying disease and may have manifested itself later in the course of the illness after medication was begun, e.g. viral exanthems or rashes of connective tissue disease. Or, the eruption may be due to an unrelated disorder of the skin that developed during treatment for another illness, e.g. pityriasis rosea developing in a child on anticonvulsant therapy or scabies in a man receiving antituberculosis therapy.

TYPES OF ACUTE CUTANEOUS DRUG ERUPTIONS

It is commonly stated that drug eruptions are great mimics and that any eruption can be caused by drugs. Fortunately, there is a limited number of ways in which the vast majority of important drug eruptions present and this is helpful in recognising them. But it is good to remember that eruptions that closely resemble drug eruptions can be caused by other agents including viral infections, connective tissue diseases and other skin diseases, among other causes.

Urticaria and Anaphylaxis

This is probably the most common type of drug reaction and presents with itchy wheals. Typically, the wheals are irregular and amoeboid in shape. Individual lesions last a few minutes to hours but new wheals often continue to appear leading some patients to state that the wheals do not subside. If the reaction is severe, wheals may be widespread and accompanied by hypotension, bronchospasm, abdominal pain and syncope. Non-steroidal anti-inflammatory drugs are a common cause.

Exanthematous Eruptions (Figure 1)

This is also a common type of drug eruption. Exanthematous or morbilliform rashes present as symmetrical, generalised, itchy, erythematous, small and large inflamed papules with a



Figure 1: Exanthematous (or maculo-papular) drug rash. Symmetrical, extensive, itchy erythematous eruption.

tendency to coalesce. In the early stages, it may be difficult to differentiate the oedematous papules of an exanthem from a wheal, but persistence of individual lesions for longer than 24 hours excludes urticaria.

Erythroderma

Persistent exanthematous eruptions evolve into erythroderma or exfoliative dermatitis. Some eruptions begin as erythroderma from the beginning. There is redness and scaling over most of the skin surface accompanied by severe itching.

Photosensitive Drug Eruptions (Figure 2)

Some drugs produce an eruption only on areas exposed to sunlight. The appearance of the rash can range from erythema to papules and blisters. The distribution of the rash predominantly on exposed skin with relative or complete sparing of covered areas is the most important clue to this type of reaction.



Figure 2: Photosensitive eruption. Erythema and oedema in a butterfly distribution. The patient was taking doxycycline.

Vesicular/Bullous/Pustular Eruptions

When inflammation is severe, fluid-filled lesions may develop leading to clear vesicular eruptions. Some eruptions consist predominantly of pustules (which are typically sterile). Constitutional symptoms often accompany these eruptions.

Erythema Multiforme/Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

This group of disorders is characterised by necrosis of the skin of varying extent. In erythema multiforme, there are erythematous papules and small plaques which show central darkening due to necrosis. Stevens-Johnson syndrome shows similar skin lesions accompanied by severe mucosal erosions and fever. Toxic epidermal necrolysis is characterised by dark brown necrosis of large areas of the skin accompanied by fluid collection and erosions (**Figure 3**). The mucosae of the eyes, mouth and genitals is often affected and bronchial mucosa may also be involved. These patients are usually very ill.

Fixed Drug Eruption

In fixed drug eruptions, intake of a drug leads to inflammation of the skin and or mucosae at exactly the same sites in every episode (**Figure 4**). In the acute phase, there is redness accompanied by blistering and erosions if the reaction is severe.



Figure 3: Toxic epidermal necrolysis. Extensive, confluent, superficial brown necrosis of the skin.



Figure 4: Fixed drug eruption. Circumscribed, pigmented, inflamed macule.

The lesions tend to be circular and to be limited in number but some patients may develop widespread lesions that may be difficult to differentiate from Stevens-Johnson syndrome or toxic epidermal necrolysis. Lesions subside with a characteristic brown-black pigmentation that is very persistent. Subsequent exposures to the drug lead to inflammation of all previously affected sites and may be accompanied by the development of new lesions.

SUBACUTE/CHRONIC DRUG ERUPTIONS

These eruptions develop over a longer period of time and can take long to subside, in spite of the causative drug having been stopped. Such eruptions include lichen planus-like drug eruptions, lupus erythematosus-like drug eruptions and pemphigus and pemphigoid-like eruptions. The resemblance of the eruption to the idiopathic disease can be remarkably close on clinical, histopathological and immunological criteria. The diagnosis is usually made on careful history-taking and subsidence of the eruption on discontinuing the causative drug (though this may be delayed).

SYSTEMIC MANIFESTATIONS

Severe drug eruptions may be accompanied by constitutional symptoms, signs, and laboratory abnormalities. Fever, pneumonitis, eosinophilia and transaminitis are frequently noted. Typically, they resolve along with the drug eruption though subsidence may be delayed till after the rash has subsided.

LABORATORY TESTS

There are no laboratory tests that reliably help to diagnose an eruption as a drug rash or to identify the causative drug. Haematological, biochemical, and radiological investigations provide information on the involvement of other organ systems, such as the liver, lungs and bone marrow.

TREATMENT

Once an eruption is confirmed or strongly suspected as being a drug eruption, the first principle of treatment is stopping the causative drug. Unfortunately, there are no reliable methods to identify the causative drug quickly in the setting of an acutely ill patient with a drug reaction. It is common practice to stop the most recently introduced drug in the belief that it is the most likely causative drug, but this may not be correct. Similarly, educated guesses about which one of the several drugs caused the eruption can be mistaken. In view of this, when the reaction is severe, all but absolutely essential drugs should be stopped. Essential drugs should be substituted by chemically unrelated drugs, if these are available. When the reaction is less severe and it would be difficult to stop all drugs, one or a few drugs that are suspected to be the cause can be stopped and the patient closely monitored. If the rash improves, it is likely that the causative drug was correctly identified. However, if the rash does not improve, or it worsens, other drugs will also need to be stopped.

The second principle of the treatment of drug eruptions is suppression of inflammation. If the reaction is mild or diagnosed early, stopping the drug may be enough to achieve this goal. In urticarial eruptions characterised by the development of wheals, anti-histamines are specifically and highly effective in controlling the eruption. However, other types of drug eruptions are not mediated by histamine and antihistamines are not as effective and provide only some relief in itching. They should not be considered 'anti-allergic' drugs useful in all types of drug reactions. Other measures to relieve symptoms of itching and burning include the use of cold compresses. Anaphylactic reactions require adrenaline injections along with other measures used in the treatment of urticarial eruptions.

In severe reactions, systemic corticosteroids are required, and are usually administered as a short, sharp course that is tapered rapidly over 2 weeks. There is controversy about the use of systemic corticosteroid therapy in toxic epidermal necrolysis but most workers believe that the drugs are effective in the early, inflammatory stage of the disease. Slower tapering over about 4 weeks is recommended in exanthematous drug eruptions and even longer therapy is required in drug-induced erythroderma.

Supportive care is paramount in the treatment of severe drug eruptions as these may lead to reduced intake and painful micturition because of oral and genital erosions, fluid and electrolyte imbalances, renal failure, pneumonitis following bronchial mucosal erosions and transaminitis as a consequence of liver involvement.

DRUG THERAPY DURING AND FOLLOWING A DRUG REACTION

Which drugs are safe in a patient who has had a drug reaction? This question comes up while caring for patients suffering from a drug reaction (and also after they have recovered from the reaction but require treatment for another illness). The simple answer is that all drugs are safe except the causative drug. There is no need to prescribe 'safe' drugs that are reported to cause eruptions less frequently. To spell this out, there is no safe antibiotic, anti-convulsant, nonsteroidal anti-inflammatory drug or anti-tuberculosis drug that can be uniformly given to a patient who has developed a drug reaction. The list of drugs that are safe will vary from one patient to another depending on the drugs taken before the onset of the reaction.

In real life, this situation is complicated by the fact that a large number of drugs may be suspected to be the cause. In such cases, the group of drugs suspected to be the cause of the eruption should be avoided; drugs from chemically dissimilar groups can be used. Additional challenges include the multiplicity of brand names under which a particular molecule is sold in different markets. This makes it difficult to identify the drug even when the patient is carrying a prescription. Over-the-counter (OTC) dispensing of medications without a prescription or other record by chemists, practitioners of alternative systems of medicines, and even doctors, is another hurdle in evaluating drug eruptions. Hostility to the prescriber of drugs that caused a reaction also makes it difficult to find out the medicines that were prescribed. A phone call to the prescribing physician is a simple technique that can provide much useful information.

Techniques to identify the causative drug include intradermal testing, patch tests and *in vitro* tests using the lymphocyte transformation test or the lymphocyte toxicity assay, but there are problems with the availability, applicability and reliability of these tests. Challenge or provocation tests consist of the administration of a small dose of the drug under medical supervision in an in-patient setting where reactions can be diagnosed and treated early. The goal of challenge testing may be to identify the causative drug, or more conservatively and pragmatically, it can be used to generate a list of drugs that can be safely taken. The procedures and the precautions

required are similar but the risks are lower with the latter goal. If a drug is strongly suspected to be the cause of an eruption, it is not administered. The risk of adverse effects during supervised administration is relatively small. When assessing the utility and safety of challenge testing, it should be remembered that adverse effects are likely to be significantly more severe if a patient who does not know the causative drug is inadvertently prescribed the drug and takes it in full doses at home.

In exceptional circumstances, it may be considered imperative to administer a drug that the patient has reacted to. Desensitisation protocols have been described that allow successful re-administration of the drug but the procedure must be undertaken with due care and caution.

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11.6 Abnormal Vascular Responses

AK Jaiswal, TS Nagesh

The phenomenon of abnormal cutaneous vascular response plays an important role in the aetiopathogenesis of many dermatoses. This chapter aims at providing a brief overview of some of the common dermatological conditions with abnormal vascular response.

URTICARIA AND ANGIOEDEMA

Definition

Urticaria is a vascular reaction pattern characterised by transient, erythematous, oedematous papules or plaques (wheals) of varying sizes and shapes which are usually pruritic. Angioedema is the same process but involves the deep dermis, subcutaneous and submucosal tissues.

Epidemiology

Around 20% of the population suffers from this condition once in their lifetime. Common in young adults (female > male). In children it is frequently associated with infection.

Classification

The simplest classification of urticaria and angioedema is according to their aetiology (**Table 1**).

Table 1: Aetiological Classification of Urticaria and Angioedema

Drugs	Aspirin, penicillin, nonsteroidal anti-inflammatory drugs (NSAIDs), sulphonamides and others
Ingestants	Nuts, eggs, fish, milk, wheat and others
Inhalants	Pollens, house dust, animal dander, fungi
Injectants	Vaccines, serum, blood
Infections	Foci of bacterial, viral, parasitic and fungal infections
Contactants	Cosmetics, animal and plant products
Physical urticarias (15%)	Dermographism (4% to 5%) Heat Cold Pressure Solar Cholinergic Aquagenic
Hereditary	Angioneurotic oedema Vibratory angioedema
Other conditions	
Systemic	Collagen vascular diseases, thyroid disorders, polycythemia vera, uraemic states
Dermatologic	Pemphigoid, dermatitis herpetiformis, urticaria pigmentosa
Psychogenic	

Clinical Features

Urticaria can be acute (<6 weeks) or chronic (>6 weeks) depending on the duration of episodes. Clinically urticaria manifests as wheals of varying sizes and shapes which are transient, well defined, erythematous or pale swellings of the dermis (**Figure 1**). The lesion may appear pale centrally during the initial stage of fluid collection. Very rarely, a vesicle or a bulla can develop in an urticarial plaque. Individual wheals rarely persist longer than 12 to 24 hours. No mark is usually left behind when wheals resolve. The lesions are usually pruritic and stinging and often preceded by pricking sensation. Urticarial lesions may be localised or generalised.



Figure 1: Urticaria showing wheals of varying sizes.

Angioedema is the term used to describe giant wheals or wheals involving mucous membrane surface lasting longer that urticaria. Angioedematous swelling may occur over the face (primarily periorbital area, lips, tongue), an entire extremity or within a vital organ system (**Figure 2**). Urticaria and angioedema may coexist in 50% of cases. Systemic symptoms like malaise, abdominal pain, dizziness, arthralgia, hoarseness, syncope or even anaphylaxis may sometimes be associated with urticaria and angioedema.



Figure 2: Angioedema of the eyelids.

Variants of urticaria with distinctive clinical features:

Dermographism

It is characterised by the rapid appearance of linear itchy wheals with a surrounding bright red flare at sites of scratching or rubbing (**Figure 3**). The prevalence is 4% to 5%.



Figure 3: Dermographism.

Cholinergic urticaria

One of the most common physical urticaria.Usually induced by exercise.The lesions are characterised by extremely pruritic, small 2 to 3 mm scattered wheals surrounded by large erythematous flare.

Pathophysiology

Histamine and chemokine release from mast cells and basophils is the basic pathogenetic mechanism in urticaria and angioedema.These chemical mediators act on the blood vessels causing vasodilatation (erythema), sensory nerve stimulation (itch), increased vascular permeability and leakage of fluid into the skin leading to dermal oedema.

The activation of mast cells and basophils may be both immunologic and nonimmunologic. Immunologic activation involves Type I—Type IV hypersensitivity reactions depending upon the cause, whereas nonimmunologic activation happens due to direct degranulation of mast cells by certain agents (drugs—morphine,codeine;foods—strawberries and shell fish).

Diagnosis

The diagnosis of urticaria and angioedema is essentially based on clinical observation and detailed history.If a complete review of systems is normal and physical urticarias are ruled-out, it is often futile to carry-out extensive laboratory investigations to determine the offending agent in chronic urticaria. However, investigations like complete blood count (CBC), stool and urine examination, thyroid function tests, hepatitis screening, anti-nuclear antibodies (ANA), total IgE, skin prick test, serological ELISA test,autologous serum skin test and ultrasonography may be carried-out if any underlying illness is suspected.

Management

- The goal of managing urticaria is to identify and then remove the offending agent/cause.
- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may aggravate urticaria and should be avoided.
- Soothing lotions (calamine) and cool compresses are given for relieving pruritus.
- A trial of elimination diet or a course of antibiotic,antifungal and antihelmintic drugs may be useful in some cases.
- H_1 anti-histaminic drugs (AHD) are the mainstay of treatment. Algorithm for the pharmacologic management is shown in **Figure 4**.

Key Points

- Urticaria and angioedema are easily identifiable symptoms, not a disease.

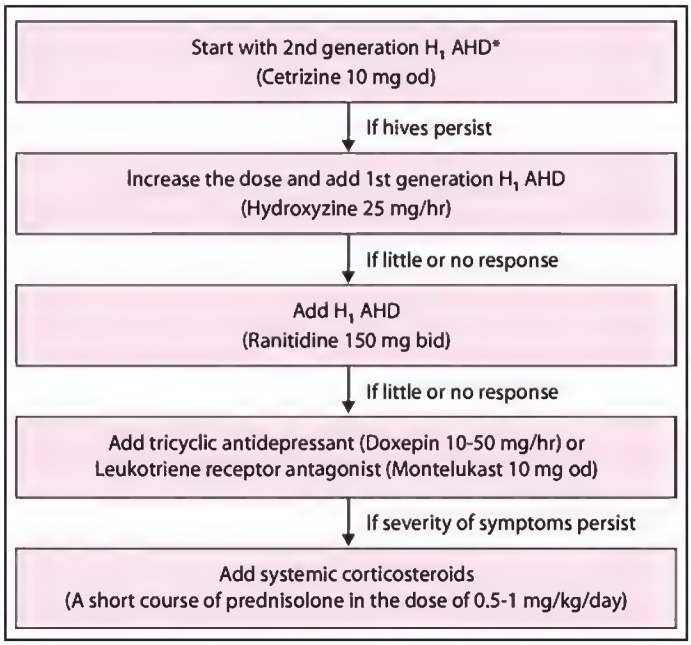


Figure 4: Pharmacologic therapy of chronic urticaria and angioedema.

- Meticulous history helps in determining the cause of urticaria more than any tests.
- Cyproheptadine 2 to 4 mg tid is the treatment of choice in cold urticaria.
- Epinephrine should be used for acute attacks in the presence of angioedema of the respiratory tract.

INTERESTING HISTORICAL HIGHLIGHT

In 1772, Herbeden described urticaria as follows: "the little elevations upon the skin in the 'nettle' rash often appear involuntarily, especially if the skin be rubbed or scrubbed and seldom stay many hours in the same place, and sometimes not many minutes. There is nobody exempt from 'them' and by far the greatest number experience no other evil from it besides the intolerable anguish arising from the itching....". This appropriately designed description of urticaria holds good even after more than 200 years.

ERYTHEMA MULTIFORME

Definition

Erythema multiforme (EM) is an acute, self-limiting, usually mild, often recurrent inflammatory syndrome characterised by symmetrically distributed erythematous papular, urticarial and typical iris/target shaped lesions. This classic form of EM is currently defined as EM minor.The more severe variant with extensive mucous membrane involvement and constitutional symptoms is called EM major (Stevens-Johnson Syndrome).

Epidemiology

EM affects primarily children and young adults (male > female). Mostly seen in spring and fall.

Aetiopathogenesis

EM appears to be a symptom complex secondary to many triggering agents causing the responsible hypersensitive phenomenon.

The common causes are:

Infections—Herpes simplex, *Mycoplasma, Streptococci*,

Drugs—Antibiotics, anti-convulsants.

Idiopathic (up to 50%)—Probably also due to undetected herpes simplex or *Mycoplasma* infections.

Clinical Features

The lesions of EM are predominantly erythematous papular, macular urticarial and *classical iris* or *'target' lesions*. The lesions appear suddenly in crops for 2 to 3 weeks and are usually symmetrical with a predilection for palms, soles and extensor surface of limbs. The characteristic iris (target) lesion is urticarial with a dusky center that may blister and have successive bright red bordering rings (**Figure 5**). There is little or no mucous membrane involvement. Vesiculobullous lesions may be seen at times.



Figure 5: Erythema multiforme with typical target lesions.

Diagnosis

The diagnosis is usually not difficult in the presence of symmetrical distribution of typical target lesions.

Treatment

As majority of cases of EM resolve spontaneously in 2 to 3 weeks, treatment is only symptomatic in the form of oral antihistamines and topical corticosteroids. The underlying precipitant cause, when appreciated, should be treated. A short course of prednisolone (0.5 to 1 mg/kg/d) may be given in patients with extensive skin lesions. Recurrences can be suppressed with long-term treatment for herpes simplex infections (acyclovir 400 mg bid).

Key Points

- Herpes simplex infection is the most common cause of recurrent EM.
- Classical target or iris lesions are characteristic of EM.

VASCULITIS

The term vasculitis is used to describe a group of diseases characterised by an idiopathic primary inflammation and necrosis of blood vessels, having many common clinical features. The primary cutaneous lesion in vasculitis is *palpable purpura*.

Classification

The vasculitis has extensively been discussed in section Rheumatology chapter "The Vasculitides".

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11.7 Papulosquamous Disorders

K Pavithran

Papulosquamous disorders are a group of unrelated skin diseases that share the morphological feature of scaly papules and plaques. Important conditions in the group are psoriasis, lichen planus, and pityriasis rosea.

PSORIASIS

Psoriasis is one of the common skin diseases characterised by scaly papules and plaques. Prevalence of psoriasis in different parts of the world varies from 0.1% to 3%. Onset of psoriasis is most common in the second to fourth decades of life though it can appear just after birth or in old age. A high familial occurrence of psoriasis (7% to 36%) suggests that genetic factors play a role in its aetiology. Psoriasis occurs in equal frequency in males and females.

Aetiopathogenesis

Genetic factors

Twin and population genetic studies support the hypothesis of multifactorial inheritance which requires both polygenic and environmental factors for its clinical expression.

The immunologic basis of psoriasis

T-lymphocyte mediated T-helper cell (Th-1) type of immune response is responsible for psoariasis. Unidentified triggers or infective agents like bacteria, HIV, drugs, etc. induce antigens which are presented to T-lymphocytes by Langerhans cells of skin leading to T-cell activation. Activated T-cells secrete cytokines that promote dermal inflammation and resultant hyperproliferation of the epidermis.

Triggering factors

Psoriasis is a chronic disease marked by periods of remissions and exacerbations. Remissions may last for a few weeks to many years. Triggering factors may be local or systemic and include trauma (Koebner phenomenon), season (worsens in winter), emotional stress, upper respiratory tract infections and drugs like beta-blockers, lithium and chloroquine. Withdrawal of systemic steroids can lead to precipitation of pustular psoriasis.

Histopathology

Characteristic histopathological features of psoriasis are regular elongation of rete-ridges, parakeratosis, hypogranulosis, and presence of Munro's microabscesses in the horny layer and spongiform pustules of Kogoj. The psoriatic epidermis shows rapid transition of epidermal cells in as fast as 2 days as compared to 13 days in normal epidermis.

Clinical Features

Psoriasis is characterised by the development of erythematous, well-defined, dry, scaly papules and plaques of sizes ranging from a pinhead to palm-sized or larger. The scales are abundant, loose, dry and slivery white or micaceous. On skin scraping, capillaries at the tips of elongated papillae are torn leading to multiple bleeding points (Ausptiz sign).

Psoriasis: Key Diagnostic Points

1. Erythematous scaly plaques
2. Well-defined border
3. Scales dry loose and micaceous
4. Koebner phenomenon seen
5. Auspitz sign positive
6. Regular, circular pits on nail plates
7. Involvement of distal interphalangeal joints of fingers and toes
8. Histopathological: Spongiform pustules of Kogoj

Koebner phenomenon is more common during the acute or eruptive stage of psoriasis or in patients with florida or progressive psoriasis. Psoriasis as a Koebner phenomeon may develop at sites of mechanical, physical, chemical or allergic trauma.

Clinical Variants of Psoriasis (Table 1)

Guttate psoriasis

This is usually seen in children, follows streptococcal infection and tends to resolve spontaneously. Pinhead to pea-sized erythematous papules erupt abruptly and are distributed bilaterally symmetrically all over the body.

Table 1: Various Clinical Types of Psoriasis

Guttate psoriasis
Chronic plaque psoriasis (psoriasis vulgaris)
Exfoliative psoriasis (psoriatic erythroderma)
Pustular psoriasis
Generalised—Von-Zumbusch type
Exanthematic type
Annular type
Localised pustular psoriasis
Psoriasis unguis
Mucous membrane lesions in psoriasis
Psoriatic arthritis
Classical type
Rheumatoid type
Arthritis mutilans
Oligoarticular arthritis
Psoriatic spondylitis
Follicular psoriasis
Psoriasis verrucosa
Linear psoriasis

Chronic plaque psoriasis

This common type of stable psoriasis manifests as coin-sized to large palm-sized well defined erythematosquamous plaques-distributed bilaterally on extensors of body (**Figure 1**). The extensor surfaces of the body, the elbows and knees lumbosacral area and back are commonly involved.



Figure 1: Chronic plaque psoriasis, erythematosquamous lesions.

Palmoplantar psoriasis

This common form usually affects only the palms or soles but may extend to the dorsa of hands and feet or occasionally may evolve into psoriasis vulgaris.

Flexural psoriasis

Affliction of axillae and groins may simulate dermatophyte infection or erythrasma. Rapid response to topical steroids is a rule.

Nail psoriasis

Nails are commonly affected in psoriasis. Pitting, thickening of nail plate, subungual hyperkeratosis, onycholysis and oil spots are some of the frequent nail findings in psoriasis.

Exfoliative psoriasis (psoriatic erythroderma)

It is a generalised form of the disease and is characterised by erythema and scaling of more than 90% of the body surface area (**Figure 2**).

Pustular psoriasis

When tiny, superficial, sterile pustules top a plaque of psoriasis, it is called pustular psoriasis. Pustular psoriasis is broadly classified into a localised form and a generalised form. Localised form may affect only the palms and soles or may be more widespread.

Generalised pustular psoriasis is the most severe form of pustular psoriasis. The skin lesions start abruptly as multiple erythematous, tender plaques which soon become studded with pinhead-sized, tiny sterile pustules that appear in waves. Features of systemic toxicity such as fever, chills, polyarthralgia and malaise may be associated. Geographic tongue and hypocalcaemia may be associated. The disease may last for weeks or even months.

Psoriasis in HIV-infected persons

The prevalence of psoriasis seems not to be increased in HIV-infected patients. But psoriatic arthritis, dactylitis and enthesitis are more common in them.

Psoriatic arthritis

Psoriatic arthritis (**Figure 3**) is an inflammatory arthritis associated with psoriasis usually with a negative test for rheumatoid factor. Arthritis occurs in about 5% to 0% of patients



Figure 2: Psoriatic-erythroderma, involving more than 90% of body surface area.



Figure 3: Psoriatic arthritis; multiple small skin distal joint uncolourment.

with psoriasis. Onset of arthritis is concurrent with the skin disease in 10% of cases but may precede it. There are 5 clinical patterns of psoriatic arthritis: classical psoriatic arthritis affecting distal interphalangeal joints; rheumatoid type of psoriatic arthritis; arthritis mutilans; oligoarticular arthritis (commonest type) and psoriatic spondylitis.

Treatment

Psoriasis usually has a chronic but unpredictable course with periods of remissions and exacerbations. The aim of psoriasis therapy is to control the disease, to improve quality of life, rather than to cure it. Avoiding alcohol and reducing weight, help in better control of psoriasis (**Table 2**).

Table 2: Treatment of Psoriasis

Topical therapy
Emollients
Topical corticosteroids
Dithranol
Tars
Salicylic acid
Vitamin D analogues—Tacalcitol, calcipotriol
Tazarotene
Tacrolimus and pimecrolimus

Systemic therapy
Oral retinoids
Methotrexate
Cyclosporine
Hydroxyurea
Mycophenolate mofetil
Razoxane
Corticosteroids
Biologicals
- Alefacept
- Etanercept
- Infliximab
- Efalizumab

Other drugs
Gold
Colchicine
Dapsone
Methimazole
Tacrolimus
Sulfasalazine
Fumaric acid

Other forms of therapy
UVB phototherapy
Photochemotherapy
Excimer laser
Treating psychological factors
Photodynamic therapy
Surgical treatment
Hyperthermia (Balneotherapy)
Sea bathing
Diet control

Topical therapy

Majority of the cases of psoriasis can be controlled with topical therapy. Emollients like white soft paraffin and liquid paraffin form the mainstay of topical psoriasis therapy but are best suited for unstable psoriasis cases who cannot tolerate other topicals. Stable plaque psoriasis responds well to strong topical steroids and keratolytics, like salicylic acid. Efficacy of topical steroids can be improved by occlusion therapy or by intra-lesional injection. Use of strong topical steroids like clobetasol, betamethasone, over large areas of body can lead to systemic absorption with its resultant side-effects. Modern topical steroids like mometasone or fluticasone in ointment form are preferred as they do not cause much skin atrophy or systemic absorption.

Non-steroidal topical options for psoriasis include topical tar and dithranol. Tazarotene, a topical synthetic retinoid is used for the treatment of plaque psoriasis. It has a rapid onset of action and its beneficial effect is sustained for up to 12 weeks after cessation of therapy. Tazarotene's potency is comparable to that of mid-to-high-potency corticosteroids. This drug should not be given to pregnant or lactating women or women not practicing adequate contraception. But they can sometimes exacerbate psoriatic lesions. Topical calcipotriol, a vitamin D derivative is free of serious side-effects but is expensive.

Systemic therapy

The systemic drugs commonly used for the treatment of psoriasis include oral retinoids, methotrexate and photochemotherapy (PUVA) and narrow band UVB phototherapy. Availability of cyclosporine and biological agents like etanercept or infliximab has increased options but these drugs are still prohibitively expensive for most patients. Systemic corticosteroids, although dramatic in short-term effectiveness are contraindicated in psoriasis as they cause rebound increase after stoppage.

Oral retinoids: Acitretin, a second-generation oral retinoid, is useful in severe unstable disease, including pustular and erythrodermic psoriasis. Elevation of transaminases and triglycerides need to be watched for during the 3 to 6 months required for complete response. Oral retinoids are absolutely contraindicated in women of childbearing potential.

Methotrexate: Methotrexate improves psoriasis by its action on T-cells. It is indicated in disabling or widespread psoriasis unresponsive to topical therapies, pustular psoriasis and erythrodermic psoriasis. Methotrexate is also helpful to control psoriatic arthritis. Contraindications include pregnancy or those who desire to get pregnant, moderate-to-severe hepatic or renal compromise, blood dyscrasias, peptic ulcer and chronic alcoholism. Cytopaenia occurs in 10% to 20% of patients on long-term methotrexate therapy (> 6 weeks) for psoriasis and manifests as leucopaenia, thrombocytopaenia or pancytopaenia. Hepatotoxicity is a major concern, with a 7% overall risk of severe fibrosis/cirrhosis in psoriatics. It is administered as 7.5 to 22.5 mg in 3 equally divided weekly oral doses at 12 hourly intervals or a single dose of 10 to 25 mg methotrexate every week.

UVB phototherapy and PUVA therapy

Modern narrow band UVB phototherapy has its emission almost exclusively in the narrow band between 311 nm and 313 nm. This minimises the potential for causing skin cancer and avoids skin effects associated with the use of oral psoralens in PUVA therapy. Patients with extensive stable psoriasis are candidates for UVB phototherapy.

PUVA therapy consists of administration of 8-MOP, 0.6 mg/kg/body weight, on alternate days followed by exposure to ultraviolet rays 2 hours later. Nausea, vomiting, headache, vertigo, erythema, pruritus, blistering and worsening of psoriasis may occur as side-effects of PUVA therapy. Long-term side-effects include cataracts, and in white skinned persons, skin cancers.

LICHEN PLANUS

Lichen planus (LP) is a pruritic disease affecting the skin, mucous membranes and hair follicles. The characteristic primary lesions are tiny, shiny, violaceous, flat-topped, polygonal papules. Surface shows scant adherent scales. Koebner phenomenon may occur. Sites commonly affected are the front of wrists, shins, trunk, medial thighs and glans penis. The cutaneous lesions (**Figure 4**) are intensely pruritic and the lesions on legs may become hypertrophic. The oral

mucosal lesions of LP may be reticular, annular, atrophic, or erosive. The buccal mucosa is commonly affected though tongue and gingiva may also be involved (**Table 3**).



Figure 4: Lichen planus purple, papulosquamous flat topped lesions.

Table 3: Lichen Planus: Key Diagnostic Features

Intense pruritus
Erythematous-to-violaceous colour for early lesion
Flat topped polygonal papules
Intense black pigmentation on healing
Koebner phenomenon present
Lace-like pattern for oral lesions

Nail changes occur in 5% to 10% patients and manifest as pterygium, longitudinal streaks and atrophy. Clinical variants of LP include linear, annular, ulcerative, hypertrophic (**Figure 5**) and bullous forms (**Table 4**).

Table 4: Lichen Planus: Clinical Types

Annular
Linear
Atrophic
Hypertrophic
Eruptive (Guttate)
Follicular (Lichen planopilaris)
Lichen planus pigmentosus
Vesicular/Bullous
Erosive/Ulcerative
Actinic
Inverse

The exact aetiology of LP is not fully understood. Some cases are associated with HCV infection. LP may co-exist with many diseases with an immunologic basis for their aetiopathogenesis, e.g. lupus erythematosus thymoma. The immunologic reaction in LP is mediated by T-cells.

The course of the disease is unpredictable. The spontaneous remission is known but the period is variable with different types of lichen planus. Treatment include antihistamines, topical steroids, intralesional steroids, topical PUVA in localised cases



Figure 5: Hypertrophic lichen planus.

and low dose systemic steroids or oral pulse steroids, dapsone, anti-malarials, oral retinoids, systemic PUVA and mycophenolate mofetil in generalised lichen planus. Topical tacrolimus is used to treat cutaneous, oral and genital erosive lichen planus. Appearance of new lesions, increase in size of existing lesions and Koebner's phenomenon indicate the activity of the lesions and requires therapy. Long standing lesions run a small risk of developing squamous cell carcinoma.

PITYRIASIS ROSEA

Pityriasis rosea (PR) is an exanthem characterised by oval, or circinate salmon-coloured macules that are covered with finely crinkled epidermis which often desquamates leaving a collarette of scaling. Sometimes the eruption may be papular, purpuric, urticarial, lichenoid, bullous, or vesicular. The exanthem is often preceded by a single herald plaque which is much larger than the succeeding lesions. The eruption has a characteristic 'bathing suit' distribution (trunk and proximal parts of limbs). Mild pruritus is often present and the rash persists for 6 to 8 weeks and subsides spontaneously. Recurrence may occur in 2% of the cases.

The exact aetiology of PR is not known though HHV-6 and -7 have been implicated.

There is no specific treatment of PR. Antihistamines may relieve pruritus. UVA and UVB therapy and oral erythromycin and acyclovir also are reported to be beneficial. Topical emollients often relieve pruritis.

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11.8 Autoimmune Bullous Disorders

KK Raja Babu

Autoimmune bullous disorders are a group of immunobullous diseases of unknown aetiology where circulating antibodies target specific components in the epidermis and the adhesion complex that links the epidermis and dermis.

INTRAEPIDERMAL AUTOIMMUNE BULLOUS DISORDERS

Pemphigus

Pemphigus is the most common and also potentially the most severe immunobullous disorder involving the skin and mucous membranes. The disease has a worldwide distribution with an incidence of 0.1 to 0.5 per 100,000 population. Circulating IgG autoantibodies targeting antigens in the intercellular attachment plaques (desmosomal complexes) of the epidermal keratinocytes, identified as desmogleins, lead to acantholysis and cell separation, and intraepidermal blister formation. The reason for this anomalous antibody activity is not known. HLA-linkage analysis suggests that there may be some genetic predisposition.

Broadly two types of pemphigus are recognised, each with one variant: *Pemphigus vulgaris* and its variant, pemphigus vegetans; and pemphigus foliaceous and its variant, pemphigus erythematosus. In *P. vulgaris* blisters occur in the immediate suprabasal layers, and in pemphigus foliaceous they develop subcorneally. Desmoglein1 is the target antigen in pemphigus foliaceous and desmoglein 3 and less frequently desmoglein 1 are the target antigens in *P. vulgaris*. The clinical phenotype of pemphigus is defined by the anti-desmoglein antibody profile.

Pemphigus vulgaris is a very common disease in India and young adults of both sexes are preferentially affected. In more than 50% of cases, the disease begins with oral erosions and 90% have oral lesions at some stage of their life. Oral erosions are painful and tender and heal very slowly. They frequently occur on the buccal and palatine mucosae. Conjunctival, nasal, pharyngeal, laryngeal, anal and genital mucous membranes are uncommonly affected. Skin lesions are generalised flaccid blisters of varying sizes that quickly rupture to leave large denuded raw areas which crust and continue to spread without further blistering at the same site. Blisters frequently appear on a normal looking skin without any background erythema. Scalp, face, axillae and groins are the common sites of involvement. Tangential shearing pressure on the unaffected skin may cause separation of the epidermal layers and denudation of skin. This is called Nikolsky's sign. Lateral or perpendicular pressure applied on intact blisters may lead to their extension and is called bulla spreading or Asboe-Hansen's sign.

Pemphigus vegetans is a much milder disease compared to pemphigus vulgaris, and intertriginous involvement is common. The disease may begin either as vesicles and blisters or as pustules and eventually evolve into hypertrophic, granulomatous or vegetative lesions. Oral lesions may occasionally occur.

Pemphigus foliaceous presents as very superficial blisters and erosions in a seborrhoeic distribution. Intact blisters are rarely found. Nikolsky's sign is strongly positive. Extensive disease may present as erythroderma. Oral lesions are rarely seen. Fogo selvagem is a special form of pemphigus foliaceous that is endemic to Brazil and other South American countries. The affected skin has a burnt appearance and patients experience a painful burning sensation in the lesions (fogo selvagem = wild fire).

Pemphigus erythematosus presents with erythematous, scaling plaques over the nose and malar skin, upper part of the back, chest and intertriginous areas closely mimicking the rash of systemic lupus erthyematosus (SLE).

Other important variants of pemphigus are drug-induced pemphigus and paraneoplastic pemphigus. Drugs with highly reactive sulfhydryl groups like penicillamine and captopril can induce pemphigus. Enalapril, penicillin, cephalosporins and rifampicin are other drugs that are occasionally responsible. Both immunological and non-immunological mechanisms operate in the occurrence of drug-induced pemphigus. Most examples of drug-induced pemphigus are of the foliaceous type. Eighty percent of patients show direct immunofluorescence positivity.

Paraneoplastic pemphigus is characterised by severe, persistent and painful mucosal erosions and a polymorphic skin eruption that is resistant to treatment. The underlying malignancies are generally lymphoproliferative and approximately 80% of cases are linked to non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and Castleman's disease.

Light microscopy reveals acantholytic intraepidermal blisters. Direct immunofluorescence of the perilesional skin is of singular value in the diagnosis of pemphigus. A fish net-like intercellular fluorescence is characteristic. Indirect immunofluorescence detects circulating IgG antibodies directed against antigens of the desmosomal complex. Recently ELISA tests that can detect IgG autoantibodies to desmoglein 1 and 3 have been developed and these have paved the way for a rapid diagnosis of different forms of pemphigus.

General supportive measures, attention to fluid and electrolyte balance and control of infection are of paramount importance in the management of fulminant forms of pemphigus. Systemic corticosteroids (prednisolone 1-2 mg per kg body weight per day) along with cytotoxic immunosuppressive agents like cyclophosphamide or azathioprine (1 mg/kg/day) are the mainstay drugs in the treatment of pemphigus, especially of the severe forms. Cyclophosphamide pulse therapy or cyclophosphamide+steroid pulse therapy have been found to be beneficial for severe and recalcitrant examples of pemphigus vulgaris. Topical and intralesional steroids help milder forms.

With appropriate treatment, most cases of pemphigus go into extended remissions. Untreated pemphigus vulgaris carries significant morbidity and mortality.

SUBEPIDERMAL AUTOIMMUNE BULLOUS DISORDERS

Bullous Pemphigoid

Bullous pemphigoid (BP) (**Figures 1 and 2**) is an autoimmune, subepidermal blistering disorder of the elderly. Men are likely to be affected twice as frequently as women. BP is mediated by IgG autoantibodies directed against hemidesmosame-associated proteins. Two pathogenetically important BP antigens are recognised: BP 230 and BP180. Though BP230 is the principal antigen, serum levels of antibodies to BP 180 correlate well with disease activity. Association between HLA DQ7 and DRB1 and susceptibility to BP has been reported. Recent studies reveal that a small, nonetheless significant, association between BP and visceral malignancy exists. Drugs sometimes induce pemphigoid-like eruptions. Examples are frusemide, sulphasalazine, penicillamine, penicillins, captopril and PUVA therapy. BP has also been reported to be associated with a variety of disorders like SLE, multiple sclerosis, diabetes mellitus, rheumatoid arthritis, psoriasis and lichen planus. Bullous pemphigoid also shares many immunopa-thological characteristics with pemphigoid gestationis and cicatricial pemphigoid.



Figure 1: Bullous pemphigoid. Erythematous oedematous plaques, tense blisters and erosions.

Large, tense blisters arising on an erythematous and oedematous background are typical of BP. The blisters are filled with thick, fibrinous fluid and can occasionally be haemorrhagic. The common sites of involvement are the lower abdomen, inner thighs, groins and the flexor aspects of the limbs. Nikolsky's sign is negative, and so is Asboe-Hansen's sign. Blisters do not quickly rupture. Additionally patients may also have erythematous macules, papules and urticarial plaques. Occasionally eczematous eruptions occur. All these clinical lesions may sometimes precede blisters by weeks or months (Prodromal bullous pemphigoid). Mucosal lesions are uncommon. Pruritis is often present but may range in severity. Ruptured blisters heal rapidly leaving behind post-inflammatory pigmentary changes. Scarring does not occur.

Several clinical variants of BP exist.

Histologically, BP manifests as a subepidermal blister with a mixture of inflammatory cells. Direct immunofluorescence (DIF) demonstrates a linear pattern of IgG and C3 deposition across the basement membrane zone (BMZ). On indirect immunofluorescence, approximately 70% of patients have circulating anti-BMZ IgG antibodies. DIF of biopsy samples of perilesional skin that have been incubated in 1 molar saline skin-splitting buffer at 4 °C for 36 to 72 hours results in a split in the lamina lucida of the BMZ. In BP, the IgG deposits are mostly found on the epidermal (roof) surface of the blister while in epidermolysis bullosa acquisita, the antibodies are detected on the dermal side (floor) of the blister.



Figure 2: Bullous pemphigoid. Tense blisters and erosions.

Localised disease can be treated with topical or intralesional steroids. Systemic steroids are indicated for a generalised disease. Moderate doses (prednisolone 30 to 40 mg per day) are enough to control the disease unlike in pemphigus vulgaris. Azathioprine, cyclophosphamide or methotrexate can reduce steroid dependency. Tetracycline or erythromycin along with nicotinamide has been found to help some patients of BP in whom corticosteroid use is contraindicated.

Cicatricial Pemphigoid

Cicatricial pemphigoid (CP) is another subepidermal blistering disorder and primarily affects the mucous membranes of the mouth, eyes and genitalia. Occasionally oesophagus, pharynx and larynx are involved. Scarring and its attendant sequelae are frequent. Skin lesions are uncommon and are predominantly seen on the head and neck. Both scarring and non-scarring lesions occur on the skin.

BP180 is the most frequently recognised autoantigen. Direct immunofluorescence findings are similar to those seen in BP. On indirect immunofluorescence, circulating IgG anti-BMZ antibodies in low titres are detectable in 10% to 25% of patients.

Localised oropharyngeal lesions are treated with topical or intra-lesional steroids. Systemic steroids (0.5 to 1 mg/kg per day of prednisolone) are indicated in more severe disease. Dapsone or azathioprine help resistant cases. Surgical intervention is required in the presence of scarring and strictures of vital structures.

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is a rare (at least in India), chronic, intensely itchy papulovesicular disease associated with gluten-

sensitive enteropathy. The enteropathy is mostly asymptomatic. Less than 10% of patients with DH have gastrointestinal symptoms suggestive of coeliac disease. Some patients manifest diarrhoea, steatorrhoea, abdominal distension and weight loss. Both the skin lesions and the enteropathy respond to a strict gluten-free diet, and recur when gluten-containing products are ingested. Gluten is present in wheat, barley, oats and rye but not in rice and corn. The enteropathy is believed to be due to non-allergic sensitivity to the gliadin fraction of gluten. Circulating IgA2 antibodies directed against gliadin and connective tissue autoantigens (reticulin and endomysium) are found in the sera of DH patients. There is a strong association between HLA B8, DRw17 and DQw2 and DH.

DH most often is seen in the second and third decades. The disease is slightly more common in males. The skin eruption is characteristically polymorphic although at any given time, only one type of lesions (papules, vesicles, wheals or bullae) predominater. The lesions are typically grouped or herpetiform. Itching is intense and excoriations are common. Lichenification may follow chronic scratching. The areas of predilection are the elbows, knees, shoulders, buttocks, sacrum and scalp. Facial involvement is uncommon and mucous membranes are rarely affected. Iodides exacerbate the disease. Patients with DH manifest a high incidence of autoimmune abnormalities. There is an increased risk of developing lymphomas, especially of the gastrointestinal treat.

Histologically, neutrophilic microabscesses at dermal papillary tips are typical of DH. Eventually unilocular subepidermal blisters form. On direct immunofluorescence of the perilesional skin, granular deposits of IgA are found in the dermal papillae. No circulating anti-BMZ antibodies are detectable by indirect immunofluorescence.

Gluten-free diet and dapsone therapy are the mainstay treatment of DH. In most cases, with an initial dose of 100 mg of dapsone per day, burning and itching ceases within 24 hours. If there is no response after 2 weeks, the dose should be increased by 50 mg every 2 weeks. Doses higher than 300 mg per day are rarely required. Once the disease is under control, a maintenance dose of dapsone (as low as 50 mg once a week) is all that is needed. Patients who are intolerant of dapsone may respond to sulfasalazine (500 mg three times a day, increased to 2.0 g per day). Cochicine (0.6 mg three times a day) may occasionally be helpful.

Linear IgA Bullous Dermatosis

Linear IgA bullous dermatosis (LAD) is a rare subepidermal blistering disorder characterised by a linear deposition of IgA along the dermoepidermal junction. Chronic bullous disease of childhood (CBDC) although clinically distinctive, is the childhood variant of LAD. The best characterised antigen in LAD is a 97 kDa antigen and this reacts with IgA1 subclass of antibodies.

The onset of CBDC is rather abrupt with large tense bullae filled with clear or haemorrhagic fluid on or near genitalia. The eruption gradually extends to involve such areas as buttocks, scalp and face, particularly the perioral and periocular areas. Clustering of blisters is common. New, small, tense blisters may appear around a crusted, healing, erythematous plaque giving a 'string of jewels' appearance. Mucosal lesions are sometimes found.

LAD generally has its onset in the fifth decade. There is considerable variation in the morphology and distribution of lesions. Flexural and truncal involvement with scattered vesicles and tense blisters, as in BP, is common. Bullae occasionally are linear and sausage-shaped. DH-like eruptions may appear in some patients. Oral lesions, though mild, are frequent. There is increased incidence of lymphoproliferative disorders in patients of LAD. Drug-induced LAD has been reported following vancomycin, diclofenac and captopril use.

Histologically, a subepidermal blister is seen. Direct immunofluorescence of uninvolved skin demonstrates linear deposition of IgA along the BMZ. Circulating anti-BMZ antibodies are demonstrable in 30% of adults and 80% of children.

Dapsone in a dose of 1.5 to 2 mg/kg per day is a very useful drug for both children and adults, and has to be given for a long time. Some patients additionally require prednisolone (0.5 to 1 mg/kg per day) to control their disease. In two-thirds of children, remission occurs by the time they reach their puberty. In others, the disease may persist into adult life. In adults, the disease is chronic but eventually remits.

Other Subepidermal Autoimmune Bullous Diseases

Other important autoimmune bullous disorders are pemphigoid gestationis that occurs in pregnancy and puerperium, epidermolysis bullosa aquisita, and bullous systemic lupus erythematosus which develops in a setting of SLE.

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11.9 Disorders of Pigmentation

Bhushan Kumar

Normal human skin colour is produced by skin pigments – red (haemoglobin), yellow (carotenoids), brown (melanin). Of these, melanin which is produced by melanocytes forms the major component of the skin colour. Normal human skin colour is primarily related to size and the arrangement of melanosomes in melanocytes.

MELANIN SYNTHESIS

Melanocytes originate from neural crest and then migrate to populate the skin, inner ear, choroid, iris, leptomeninges, mucous membranes and the hair. The skin melanocytes are located in the epidermal basal layer and project their dendrites into the malpighian layer of the epidermis where a melanocyte secretes melanosomes into a finite number of neighbouring keratinocytes (approximately 36); this partnership of a melanocyte and a neighbouring group of keratinocytes is called an epidermal melanin unit. Melanocytes in the hair follicle provide the melanin for hair shaft pigmentation. The major differentiated function of melanocytes is to synthesise melanin in specialised organelles within the melanocytes, the melanosomes, and to transfer melanosomes to neighbouring keratinocytes to provide protection from ultravoilet (UV) irradiation. Pigmentation, the synthesis and distribution of melanin in the epidermis, involves several steps. Disruption in any of these steps results in hypopigmentation. Melanin in the melanocytes is produced in two forms—the brown black, eumelanin and the light coloured red, yellow, pheomelanin. Tyrosinase, a melanocyte specific copper binding enzyme catalyses the oxidation of catechols to their corresponding quinones. *In vivo* tyrosinase converts tyrosine through DOPA and various precursors to brown or yellow/red melanin.

MELANIN PIGMENTARY DISORDERS

Broadly there are three categories of melanin pigmentary disturbances:

1. Hypomelanosis or lighter than individual's skin colour or complete loss—leucoderma,
2. Brown hypermelanosis (melanoderma), and
3. Gray, slate or blue hypermelanosis (ceruloderma).

All these disorders for the purposes of better understanding can be described under the heading as melanotic, melanocytotic and non-melanocytotic. Classification of various disorders of pigmentation is given in **Tables 1 and 2**.

Table 1: Hypopigmentation: Clinicopathologic Classification

Aetiologic factors	Melanocytopaenic (Melanocytes decreased or absent)	Melanopaenic (Melanin decreased or absent)	Non-melanotic (No melanin defect)
Chemical	Catechols	Arsenicals, Chloroquine, Glucocorticoids,	—
	Monobenzylether of hydroquinone	Hydroxychloroquine, Hydroquinone, Retinoids	—
	Para-substituted phenols		—
	Sulphydryls		
Endocrine	—	Addison's disease, Hypopituitarism, Hypothyroidism	—
Genetic	Ataxia telangiectasia	Albinism	Naevus anemicus
	Piebaldism	Chediak-Higashi syndrome	—
	Vitiligo	Homocystinuria	—
	Vogt-Koyanagi-Harada syndrome	Fanconi's syndrome	—
	Waardenburg syndrome	Hypomelanosis of Ito, Naevus depigmentosus	—
	Xeroderma pigmentosum	Tuberous sclerosis	—
Inflammatory	Actinic reticuloid	Leprosy, Pityriasis alba, Post-inflammatory	Woronoff's ring (hypopigmentation around psoriasis lesions)
	Mycosis fungoides		—
	Onchocerciasis		—
	Pityriasis lichenoides chronica	(Discoid lupus, Eczema, psoriasis),	—
	Pinta		—
	Yaws		—
		Post-Kala-azar, Sarcoidosis,	
		Syphilis: (endemic, secondary), Pityriasis versicolour	—
Neoplastic	Halo naevus	Melanoma	—
	Leucoderma acquisitum centrifugum	Halo around primary or metastatic lesions	—
Nutritional	Vitamin B12 deficiency	Chronic protein loss— Kwashiorkor, Malabsorption,	—
		Nephrosis—Ulcerative colitis	—
Physical	Burns (Ionising, Thermal, UV)	Post-dermabrasion	—
	Trauma	Post-laser	—
Miscellaneous	Alopaecia areata, Scleroderma	Canities, Idiopathic guttate hypomelanosis	Anaemia oedema

Table 2: Epidermal Hypermelanoses: Clinicopathologic Classification

Epidermal factors	Melanocytotic (Increase in number of melanocytes)	Melanotic (Increase in melanin)	
Heritable or developmental	Lentigines, neurodysraphic Centrofacial lentiginosis Peutz-Jegher syndrome PUVA therapy	*Cafe-au-lait* macule, Neurofibromatosis, Albright's syndrome, Bloom's syndrome, Becker's melanosis, Naevus spilus, Ephelides (freckles)	Neurocutaneous melanosis Familial periorbital hyperpigmentation Dowling-Degos disease Dyskeratosis congenita Acropigmentation of Dohi Reticulate acropigmentation of Kitamura
Metabolic		Porphyria cutanea tarda Haemochromatosis, Gaucher's disease, Niemann-Pick disease	
Endocrine		Melasma, ACTH- and MSH-producing tumours, Exogenous ACTH therapy,Pregnancy, Addison's disease, Oestrogen therapy	
Chemicals and drugs		Arsenicals, Busulfan, Photochemical agents (psoralens, tar), Berloque dermatitis	5-fluorouracil, cyclophosphamide nitrogen mustard, topical bleomycin
Nutritional		Kwashiorkor, Pellagra, Sprue Vitamin B12 deficiency	
Physical	Lentigo, solar, ultraviolet (radiation tanning)	Ultraviolet radiation- (sun tanning), Thermal radiation, Ionising radiations Trauma (e.g. chronic pruritus)	
Inflammation and infection		Post-inflammatory melanosis (exanthems, drug eruptions) Discoid lupus erythematosus	Lichen simplex chronicus, Atopic dermatitis, Psoriasis, Lichen planus
Neoplastic		Melanoma, Mastocytosis, Acanthosis nigricans with or without, adenocarcinoma and lymphoma	
Miscellaneous	Lentigines, eruptive lentigo	Systemic scleroderma, Chronic hepatic insufficiency Whipple's syndrome	

HYPOMELANOSIS

Table 1 shows that pigmenatry disturbances may be congenital or acquired, localised or generalised and the loss of colour is either partial (hypomelanosis) or complete (amelanosis). De-pigmentation is applied for the condition when there is complete loss of pre-existing normal pigmentation. Localised or circumscribed hypomelanosis refers to islands of hypopigmented/depigmented skin amidst clinically normal skin. Hypopigmentation here may be amelanotic and progressive (vitiligo, chemical leucoderma), amelanotic congenital and stable (piebaldism, Waardenburg syndrome), hypomelanotic and progressive (pityriasis versicolour, post-inflammatory) or hypomelanotic and stable (tuberous sclerosis, naevus depigmentosus).

Certain features in circumscribed hypomelanotic macules facilitate diagnosis, which include size, shape, hue, arrangement, etc. Small 1 to 2 mm macules may be seen in vitiligo, chemical leucoderma, and tuberous sclerosis. Lesions of *Pityriasis alba* and post-inflammatory hypopigmentation are larger but have fuzzy, indistinct margins, unlike the sharp margins in idiopathic guttate hypomelanosis. Convex borders are usually seen in vitiligo or chemical leucodema. The lance ovate shaped white lesions are characteristic of tuberous sclerosis. Macules of vitiligo and piebaldism are milky or chalk white as compared to the off white colour of naevus depigmentosus (**Figure 1**), tuberous sclerosis or post-inflammatory hypopigmentation. *Vitiligo:* It is a common acquired disorder characterised by milky white macules with the likely incidence between 1% to 2%. All races are affected. Both sexes are affected equally. Vitiligo occurs more commonly on the sun exposed areas and in darker skin types. Vitiligo may develop at any age—birth to 81 years of age. A typical vitiligo macule has a chalk or milky white colour, round to oval in shape often with convex margins which are usually well defined, varying from few millimetres to many centimetres in diameter. Trichrome vitiligo refers to the presence of an intermediate colour (uniform tan colour), an interface between the white lesions of vitiligo and the normally pigmented skin. Quadrichrome refers to fourth colour—perifollicular or marginal pigmentation seen in some cases of re-pigmenting vitiligo. Inflammatory vitiligo has an erythematous raised border similar to the one sometimes seen in pityriasis versicolour.

CLASSIFICATION AND TYPES OF VITILIGO

Focal, segmental, generalised and universal are the most common patterns of vitiligo. Vitiligo is also classified as



Figure 1: Naevus depigmentosus.

segmental, acrofacial, generalised and universal or by pattern of involvement as focal, mixed and mucosal.

Focal Vitiligo

There is either a single or few macules limited in both size and number. About 20% of the children have this pattern.

Segmental Vitiligo

The lesions are distributed in a dermatomal or quasi-dermatomal pattern. This is earlier in onset but is considered a stable type of vitiligo.

Generalised Vitiligo

It is the most common type of vitiligo and is characterised by few to many to widespread macules. The lesions are often symmetrical and involve extensor surfaces, areas over small and large joints. Periungual involvement may occur alone or with simultaneous involvement of lips, distal penis and nipples. The names lip tip and acrofacial vitiligo are given to this peculiar distribution of lesions (**Figure 2**).



Figure 2: Generalised vitiligo.

Universal Vitiligo

It indicates almost total involvement of the body with few remaining areas of pigmentation and has been associated with various endocrinopathy syndromes. Koebner's phenomenon is not uncommon and on sites of burns, injury or laceration, the depigmentation appears in that shape. Mucosal involvement is not infrequent, genitalia, lips, gingiva are often involved. Involvement of palms and soles though uncommon does occur. Vitiligo may be associated with leukotrichia, prematurely gray hair, halo nevi, and alopaecia areata. Depigmented hair are often found in isolated vitiligo lesions. Leucotrichia (poliosis) has been reported in up to 45% of cases of vitiligo. Rarely vitiligo patients may have pigmentary abnormalities in iris and retina. Many authors have reported an association of vitiligo and thyroid function abnormalities. Pernicious anaemia though uncommon occurs with increased frequency in patients with vitiligo. Association with systemic lupus erythematosus, diabetes mellitus, Addison's disease, inflammatory bowel disease, rheumatoid arthritis, etc. is well known.

Aetiology and Pathogenesis

Though vitiligo is mostly a single entity, the aetiology is complex. Several hypothesis to explain its aetiopathogenesis have been propounded which include-genetic, autoimmune, self destruct, neural and composite hypothesis. Familial cases of vitiligo are common, suggesting a genetic basis. However, the transmission is more complex, most likely polygenic. In the self destruct hypothesis, formation of hydrogen peroxide (H_2O_2), certain tyrosine analogues and intermediates in melanin synthesis are thought to cause the destruction of melanocytes. In the autoimmune hypothesis, presence of antibodies against the melanocytes, various melanocyte antigens and transcription factors have been cited as the evidence. Diagnosis is easy in the presence of progressive chalk white macules in typical sites. Wood's lamp examination may help.

Differential Diagnosis

The picture is mostly classical but it should include chemical leucoderma, leprosy (**Figure 3**), post-inflammatory hypo-pigmentation, pityriasis alba, pityriasis versicolour, tuberous



Figure 3: BT leprosy.

sclerosis (**Figure 4**), piebaldism, etc. Small lesions of naevus depigmentosus, and idiopathic guttate hypomelanosis have to be considered when the vitiligo lesions are focal.



Figure 4: Ash leaf macules of tuberous sclerosis.

Treatment

Most patients require reassurance and an understanding of their affliction. Re-pigmentation is the basic aim of the treatment. Currently available options include psoralens, topical calcineurin inhibitors (tacrolimus, pimecrolimus), topical and systemic corticosteroids, topical and systemic PUVA, narrow band UVB, immunosuppressives and skin grafting according to the type of vitiligo.

Topical steroids are probably first-line therapy for most patients with limited disease. Topical tacrolimus (0.03% and 0.1%) ointment has been found to be safe and effective in childhood vitiligo. Narrow band UVB is currently considered the treatment of choice for generalised vitiligo. Surgical techniques include skin grafting, cultured/non-cultured melanocyte grafting, punch grafting, etc.

Albinism

Albinism refers to genetic abnormalities of melanin synthesis (in hair, skin and eye) associated with normal number and structure of melanocytes. Characteristic ocular changes include nystagmus, iris translucency, reduced melanin in the retinal pigment epithelium. It results in a characteristic albino with white hair, white skin and blue eyes.

Piebaldism

This is an uncommon, autosomal dominant, congenital, stable leucoderma characterised by chalk or milk-white macules like that of vitiligo and a typical white forelock.

Chemical Leucoderma

Acquired hypomelanosis is due to repeated exposures to specific chemical compounds particularly phenols and sulphydryl compounds. Monobenzylether of hydroquinone (MEBH) was the first compound identified producing leucoderma in tannery workers. The lesions of chemical leucoderma resemble lesions of vitiligo, but usually do not have sharp margins. They appear not only at the site of contact with the offending compound but also remotely. The sites affected may be specific or very odd which come in contact with these chemicals due to footwear, watch straps, waist bands of undergarments, condoms, purses left in contact with the breast, bindi and hair dye, etc.

Post-Inflammatory Hypopigmentation

A number of inflammatory dermatoses may be associated with or resolve to leave hypopigmented lesions corresponding to areas of involvement and are seen commonly after healing of a lesion of dermatitits and psoriasis, etc.

Pityriasis Alba

It usually affects young children of both sexes equally. The macule is pale or light brown with indistinct margins. Erythema if present fades over weeks to leave behind off-white or tan-white macule with fine scales. All parts of the face, forehead, malar prominences, around the mouth are common sites. Pityriasis alba is probably a non-specific eczematous dermatosis with post-inflammatory hypomelanosis.

Pityriasis Versicolour (Tinea Versicolour)

It is caused by lipophilic yeast *Malassezia furfur.*

Typical lesion is a round, scaly, hypomelantoustic macule, which sometimes may be raised and has erythematous raised margins. Affected sites are the upper back and chest but also occur on upper arms, neck and even face. The lesions are more extensive in patients living in tropics. The lesions can be tan, hyperpigmented and erythematous or a mixture with the hypopigmented lesions. Various topical and systemic antifungals are effective in treating this condition.

HYPERMELANOSIS

Table 2 shows that hypermelanosis may be melanotic or melanocytotic in origin which may be congenital or due to nutritional, hormonal, chemical factors or due to neoplasia or post-inflammatory. Epidermal hypermelanosis refers to brownish pigmentation due to increased melanin in the epidermis (**Figure 5**). Some of the hypermelanoses may be associated with a dermal component (mixed hypermelanoses) characterised by melanin in dermal macrophages. Hypermelanosis may be diffuse or localised (ephelids, *café- au-lait* spots, Dowling-Dego disease).

Lentigines

These are small (usually less than 0.5 cm in diameter), circumscribed, brown to dark brown to black, variegated to uniformly coloured



Figure 5: Becker's naevus.

macules. They may be found as isolated macules or multiple lesions mostly on sun-exposed areas. Mucosal lesions are localised to lips, oral mucosa, palate and tongue in Peutz-Jeghers syndrome. Although most of the hamartomatous polyps are benign, there is a chance of them turning malignant.

Café-au-lait macules (CALMs)

These are discrete, well-circumscribed, 2 to 20 mm, uniformly pale brown macules characterised by serrated or irregular margins, appearing at or soon after birth. CALMs are common cutaneous findings but can be markers for multisystem disease such as neurofibromatosis.

Melasma

It is an acquired symmetric hypermelanosis, with light brown to gray brown macules or patches on sun exposed areas of the skin. The most common sites involved are centrofacial pattern affecting the cheeks, forehead, upper lip, nose, and chin (**Figure 6**). It is much more common in women and is seen more often in people with dark skin. Important aetiologic factors are genetic predisposition, UV radiations (sun exposure), endocrine disorders, nutritional deficiencies, female sex hormones and certain drugs. The majority of cases appear related to pregnancy or oral contraceptives. Melasma like hyperpigmentation has been described in HIV disease. High expression of α-MSH in the lesional keratinocytes may play an important role in the melanisation of skin. Increased number of melanocytes have been reported in the lesions. Use of sun block and bleaching forms the mainstay of treatment though majority of the times the treatment is unsuccessful and the relief is temporary as long as the treatment lasts. The sun screen must be a broad-spectrum, chemical sunscreen (both UVA and UVB protecting) or an opaque physical (zinc oxide, titanium dioxide). Topical hydroquinone (2% to 4%) with retinoids and or steroids is the usual treatment. Steroids should be used with care.

Post-inflammatory hyperpigmentation

In many dermatoses, pigmentation follows the healing of the lesions. Eczemas and various dermatoses can lead to post-inflammatory hyperpigmentation (**Figure 7**). The pigmentary



Figure 6: Melasma.



Figure 7: Lichen planus pigmentosus.

macules are discrete, with hazy feathered margin corresponding to the primary eruption.

DERMAL HYPERMELANOSIS (CERULODERMA)

This results from the presence of pigment in the dermis. Circumscribed dermal melanocytotic melanoses are generally developmental and mostly occur among Asians like Mongolian spots, naevus of Ota, naevus of Ito, etc. Circumscribed dermal melanotic hyperpigmentation are—incontinentia pigmenti, macular amyloidosis, etc.

Fixed Drug Eruption

This is a very special type of process where the lesions occur repeatedly on the same spot and the pigment darkens every time.

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11.10 Disorders of Skin Appendages

Raj Kubba, Tanvi Pal

Hair follicles, sebaceous glands (pilosebaceous units), eccrine (sweat) glands and nails are the key appendages of the skin. This section identifies and describes the solitary, most relevant disease entity in each of these, namely, miliaria, acne vulgaris, rosacea, and alopaecia areata.

MILIARIA

Definition

Miliaria results from blockage of the acrosyringium, the long thin duct that carries sweat from the coiled secretory portion located in the reticular dermis and the subcutaneous fat to the skin surface, with secondary leakage of sweat in the epidermis and papillary dermis.

Aetiopathogenesis

Immaturity of the acrosyringium is the most likely reason for miliaria in newborns. Sudden, excessive, unaccustomed sweating and febrile illnesses are some of the known triggers in both children and adults. Miliaria affected skin is reported to have three fold greater counts of bacteria such as *Staphylococcus epidermidis* and *Staphylococcus aureus*, suggesting yet another aetiologic factor.

Clinical Features

Depending upon the level of the blockage, three sub-types of miliaria are recognised. The details are given below:

Miliaria crystallina

The acrosyringium is blocked superficially—in the stratum corneum—resulting in sheets of uniform, delicate, 1 mm sized, vesicles with clear serous contents on the scalp, face, neck, and upper torso. This subtype is seen mostly in newborns.

Miliaria rubra

Also known as 'prickly heat', this subtype is clinically characterised by uniform, non-follicular, 1 to 3 mm, erythematous papules, occurring in sheets with a predilection for back, flexures and frictional areas. Itching is intense and there is a propensity for secondary bacterial infection as impetigo and 'boils'.

Miliaria profunda

When the acrosyringium is blocked at a deeper level the sweat leaks into papillary dermis producing 1 to 3 mm, flesh coloured papules that are typically non-itchy. The anatomic distribution is similar to *Miliaria rubra*.

Treatment

Physical readjustment, in the form of confining to a cooler environment, avoiding known triggers, frequent cold baths and applying a soothing lotion containing calamine, menthol or boric acid is all that is required to treat a typical case of *Miliaria rubra*. Topical antibiotics and topical steroids are required for complicated cases. There are no sequelae. Recurrences are common.

ACNE VULGARIS

Acne vulgaris (literally meaning common acne) is a chronic inflammatory disorder of sebaceous follicles, predominantly seen in adolescence. It affects 80% of the population in the age group of 11 to 30 years. Acne has a major impact on the quality of life (QOL).

Aetiopathogenesis

Acne is hormonal in origin. Acne results from a complex interplay of increased sebum production, ductal hypercornification, follicular colonisation with *Propionibacterium acnes*, and inflammation. Acne lesions begin with the microcomedo, a microscopic lesion not visible to the naked eye. With time, the follicle fills with lipids, bacteria and cell fragments. Ultimately, a clinically apparent lesion occurs, either a non-inflammatory lesion (open or closed comedo) or an inflammatory lesion. Comedogenesis is unique to acne and ductal hypercornification is a key step in it. There is hyper proliferation and abnormal cellular differentiation in the follicular infundibulum, resulting in accumulation of excess and sticky keratinocytes that turn into plugs (comedones). *Propionibacterium acnes*, a Gram-positive, rod-like bacterium, resides in sebaceous follicles and contributes to comedogenesis and inflammation in acne through production of lipases and proteases, through elaboration of cytokines (TNF-α, IL-1α, IL-8), and through activation of toll-like receptor 2 (TLR 2).

Clinical Features

Acne is readily recognised by its age of onset, anatomic distribution, and folliculocentric morphology. However, it displays considerable range and variation. Typically, it precedes puberty by a year or two, peaks between 14 and 16 years in females, and 17 and 19 years in males. Acne displays cephalocaudal evolution. The first lesions, usually comedones, develop on the forehead (pre-adolescent acne). At its peak, acne covers the entire face (adolescent acne), and in mature adults (25 years plus) it settles on the jaw area and the adjacent neck (persistent acne/adult acne). Acne is reportedly more common in males, 55% versus 45% for females, although the latter frequently seek consultation from dermatology clinics. Also, our female patients have more severe acne, often with added stigmata of cutaneous hyperandrogenism, namely, seborrhoea, hirsutism, and alopaecia.

Typically, face is the only site of involvement or is distinctly more involved. Less commonly, back is more involved (acne corporis) (**Figure 1**), and such cases represent greater severity. Acne corporis also involves the chest, shoulders and upper arms, and rarely, buttocks and thighs.

Acne is a polymorphic condition showing an array of comedones, inflammatory lesions and sequelae. Besides open comedones (blackheads) (**Figure 2**), and closed comedones (whiteheads) (**Figure 3**), there are macro-comedones (larger



Figure 1: Acne vulgaris on back. Erythematous conical papules.



Figure 2: Acne vulgaris. Numerous blackheads (open comedones) and a few inflamed nodules.



Figure 3: Acne vulgaris. Inflammatory papules and pustules, 'closed comedones' pitted and ice-pick scars.

than 1 mm). A diagnosis of acne in the absence of comedones is not tenable. However, 10% of acne patients may not show comedones at first clinic visit. Inflammatory lesions include macules, papules, pustules, papulopustules, nodules, pseudo cysts, and sinus tracts (**Figure 4**). Only larger inflammatory



Figure 4: Severe acne vulgaris. Several inflammatory nodules, cysts and sinuses.

lesions are painful or tender. Acne may be associated with itching. Sequelae include post-inflammatory pigmentation and scars. There are several grading systems. An easy to use acne grading system is described in **Table 1**.

Table 1: Grading of Acne

Grade 1: Mild acne Predominance of comedones	Comedones < 30 Papules < 10 No scarring
Grade 2: Moderate acne Predominance of papules	Comedones any number Papules > 10 Nodules < 3 Mild scarring ±
Grade 3: Severe acne Predominance of nodules/cysts	Comedones any number Papules any number Nodules/cysts > 3 Extensive scarring

Acne tends to aggravate in hot and humid weather, under stress, and by injudicious use of oils and oily skin care products. Premenstrual flares are common and indicate hormonal imbalance. In time, acne remits, usually before the age of 25 years. Increasingly, it may persist longer, in some instances beyond the age of 50 years. There are also individuals who develop acne for the first time after the age of 25 years (adult acne).

Diagnosis

Acne is diagnosed clinically. Laboratory tests are only done to evaluate for hormonal imbalance and to screen and monitor for certain treatments. Differential diagnosis includes acneiform drug eruptions, folliculitis, and rosacea.

Treatment

Acne treatment plans are based on severity, and presence of associated features such as cutaneous hyperandrogenism. Combination treatments are preferred. Available modalities and their respective mode of actions are listed in **Tables 2 and 3**. First line treatments for all forms of acne are topical retinoid and benzoyl peroxide. Moderate acne often requires systemic antibiotics. Severe acne should be treated with oral isotretinoin. Acne in the context of cutaneous hyperandrogenism requires antiandrogens. Topical agents should be applied on the entire susceptible area, for example, the entire face. Topical retinoids are photoreactive and are best applied at bedtime. Adapalene

is the least irritating topical retinoid and also has anti-inflammatory effect. Topical antibiotics should never be used as monotherapy for risk of bacterial resistance. Oral isotretinoin has potential for serious adverse effects and should only be administered under expert supervision. An algorithmic approach to management of acne is described in **Figure 5**.

Table 2: Topical Treatment Options in Acne

Predominantly anticomedonal
- Adapalene 0.1%
- Tretinoin 0.25% and 0.05%
- Tazarotene 0.05% and 0.1%
- Azelaic acid 10% and 20%

Predominantly antimicrobial
- Benzoyl peroxide 2.5% and 5%
- Clindamycin 1%
- Erythromycin 4%, clarithromycin 2%

Combinations
- Adapalene/clindamycin
- Benzoyl peroxide/erythromycin

Table 3: Systemic Treatment Options in Acne

Antibiotics (antimicrobial, anti-inflammatory)
- Tetracycline 500 mg bid
- Doxycycline 100 mg od
- Minocycline 100 mg od

Retinoids (sebosuppressive, anti-comedonal, anti-inflammatory, anti-microbial)
- Vitamin A 50,000 units bid
- Isotretinoin 0.5 to 1.0 mg/kg

Anti-androgens (sebosuppressive, anti-comedonal)
- Combination OCP (cyproterone acetate 2 mg + ethinyl oestradiol 35 µg)
- Combination OCP (drospirenone 3 mg + ethinyl oestradiol 30 µg)
- Spironolactone 25 to 50 mg bid

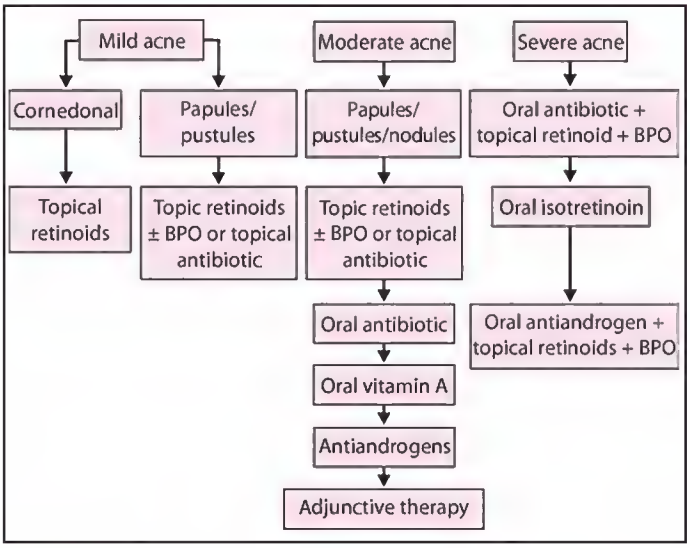


Figure 5: Acne treatment algorithm.

BPO= Benzoyl peroxide.

DRUG-INDUCED ACNE

Acne can be triggered or aggravated by androgens, progestogens, anabolic steroids, topical and oral corticosteroids, halogens, isoniazid, diphenylhydantoin, phenytoin, thiouracil, cyclosporine A, disulfiram, lithium, vitamin B12, and PUVA therapy. Steroid acne refers to the sudden onset of an asymptomatic, monomorphic, papular or pustular eruption on the upper torso in a post-pubertal individual, with or without previous acne, who has received systemic steroids. It does not scar and tends to resolve spontaneously or with mild topical acne medications after the steroids have been withdrawn.

ROSACEA

Rosacea is a chronic, waxing and waning, vascular reaction pattern, involving the central area of the face, occurring in mature adults. It is characterised by episodic flushing, erythema, telangiectasia, recurrent papules and pustules.

Aetiopathogenesis

Hypotheses include potential roles for vascular abnormalities, environmental factors, and micro-organisms such as *Demodex folliculorum* and *Helicobacter pylori*. Steroid rosacea refers to a rosacea-like clinical state, induced by prolonged use of topical steroids.

Clinical Features

Four clinical patterns are recognised: Erythemato-telangiectatic, papulopustular, phymatous, and ocular. Rosacea typically involves the central face viz. glabella, nose, cheeks and chin. Besides central location, later onset, and flushing, rosacea is distinguished from acne by the absence of comedones. However, acne and rosacea may co-occur (acne rosacea). Ocular changes are irritation, lacrimation, blepharitis, episcleritis, keratitis, corneal vascularisation, and iritis. Rhinophyma describes a sequel where the hypertrophied nose shows craggy, bulbous swelling with prominent follicular ostia filled with keratinous debris.

Treatment

Metronidazole 0.75% gel and/or oral antibiotics are the first-line treatments. Doxycycline 100 mg once daily; minocycline 100 mg daily; or clarithromycin 250 mg twice daily or 500 mg once daily, for 4 to 12 weeks are all effective. However, the condition tends to relapse.

ALOPAECIA AREATA

Human skin bears approximately 5 million hair follicles of which around 100,000 hair follicles are located on the scalp. The hair grow in a cyclical manner and exhibit four phases: Growth (anagen), regression (catagen), resting (telogen), and shedding (exogen). Hair disorders may result from defects in hair cycle, or hair growth (excess—hirsutism; sparse—hypotrichoses), and from hair follicle destruction by per follicular inflammation (Lichen planus, Lupus erythematosus).

Definition

Alopaecia areata (AA) is the most notable example of non-scarring, non-patterned alopaecia, characterised by sudden/rapid appearance of circumscribed, circular/ oval bald patches in hair bearing areas especially the scalp (**Figure 6**). The alopaecia results from arrest of hair follicles in late anagen phase.

Epidemiology

The prevalence in general population is 0.1% to 0.2%; life-time risk for developing AA is 1.7%, and it comprises 0.7% to 3% of all patients seen by dermatologists. A positive family history has been recorded in 10 to 20%. AA can occur at any age but the highest susceptibility has been observed in the age group 15 to 29 years.



Figure 6: Alopaecia areata. Circumscribed patchy alopaecia with no inflammation or scarring.

Aetiopathogenesis

AA is postulated to be a T-cell mediated autoimmune disease directed against hair follicles in late-anagen phase. AA is believed to be a polygenic condition with environmental and life-style factors acting as triggers and causing aggravation. AA is associated with atopy, type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune polyendocrinopathy syndrome, vitiligo, pernicious anaemia, inflammatory bowel disease and Down's syndrome.

Clinical Features

Alopaecia areata is common in both men and women. A solitary patch is the initial presentation in 80%, and spontaneous re-growth in 3 to 6 months is the rule. The natural course is variable and unpredictable. Recurrences are common and, with each recurrent episode, the severity tends to increase and probability of spontaneous re-growth diminish. The presence of 'exclamation mark hair' at the margin of the alopaecia is indicative of activity. Re-growth in AA patches commences from the centre and progresses centrifugally. AA patches are typically skin coloured and asymptomatic.

Based on distribution and severity, several clinical patterns are recognised, namely, focal, reticular, ophiasis (band-like hair loss in the occipital and temporal scalp), sisaipho (predilection for parietal scalp mimicking androgenetic alopaecia), totalis (loss of all scalp hair), and universalis (loss of all scalp and body hair). Nail involvement, mostly as pitting, has been noted in 6.8 to 49.4%. AA significantly impacts the quality of life.

Diagnosis and Prognosis

AA is a clinically distinctive disease. The prognosis is variable, being good in mild disease and initial episodes. However, recurrent disease, severe disease (particularly ophiasis, totalis and universalis), early age at onset, nail involvement, and co-morbidities such as atopy, are adverse prognostic signs.

Treatment

A wide range of therapeutic options are available for management of AA. First choice modalities include topical steroids, intralesional steroids (triamcinolone acetonide 2.5 to 5 mg/ml), and 5% minoxidil lotion. For active/spreading AA systemic therapy with levamisole (50 to 150 mg on two consecutive days each week for 3 to 6 months) and/or prednisolone as oral minipulse (0.5 mg/kg dose on two consecutive mornings each week) are popular in our country. Aggressive systemic steroids, as daily dosing for limited periods, may be justifiable for severe and psychologically disabling disease. Systemic steroids are therapeutically very effective but relapses are a rule when they are withdrawn.

NAIL CHANGES

Nails, another skin appendage, are subject to abnormalities both internally as well as by disorders of the skin. Understanding the biology and anatomy of the nail allows the treating physician to ascertain the location of pathology and treat accordingly. The nail unit comprises of the proximal and lateral nail folds, nail matrix, nail bed, and hyponychium (**Figures 7 and 8**). Described

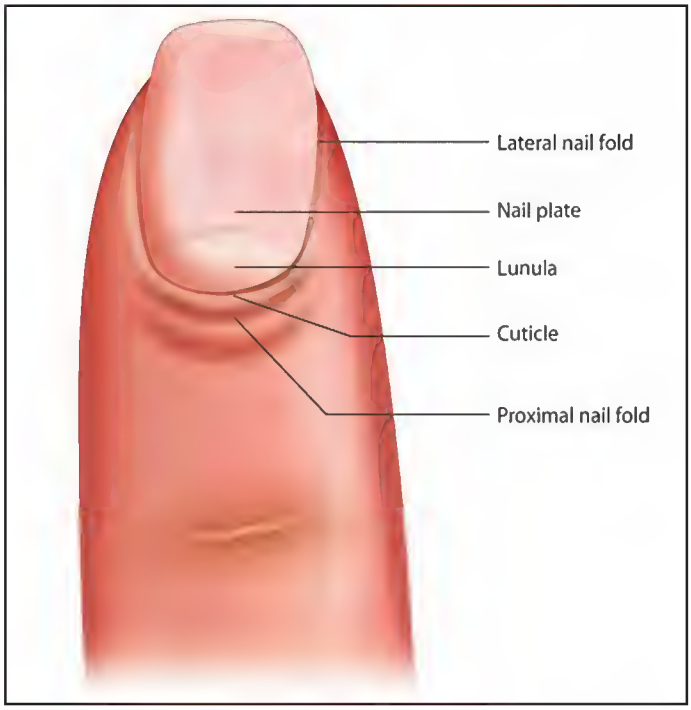


Figure 7: Diagramatic presentation of nail structure.

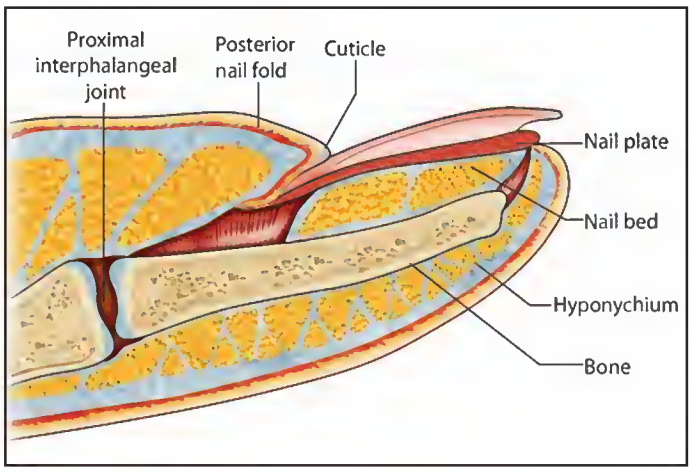


Figure 8: Nail unit in cross-section.

below are few of the common nail signs affecting the nail plate, nail bed, and nail folds.

Koilonychia

It is spooning of the nails, where the lateral edges of the nail plate are elevated above a depressed centre. Endocrinological diseases such as hypothyroidism and iron deficiency anaemia are the main causes way.

Pitting

Pitting occurs in response to a defect in the nail matrix, mainly the proximal matrix. They are shallow depressions in the surface of the nail and can be regular, irregular, large, or small depending on the duration and extent of pathology. Most common causes of pitting are psoriasis, alopaecia areata and eczematous conditions.

Clubbing

It is a over-curvature of the nail, with or without hypertrophy of the soft tissues and cyanosis. Clubbing is characterised by an increase in the angle (> 180°) between the proximal nail fold and nail plate, and it is mostly seen in cardiovascular, gastrointestinal and familial disorders.

Beau's Lines

A growth disruption in the nail matrix results in horizontal (transverse) depressions in the nail plate (**Figure 9**). Any systemic disease or event that is severe enough to cause disturbance of nail growth can result in Beau's lines.



Figure 9: Beau's lines. Transverse depressions in the nail plate.

Paronychia

Paronychia means inflammation of the nail folds. It is categorised into acute and chronic. Acute form is one of the most common infections of the hand, with *Staphylococcus aureus*, Streptococci and *Pseudomonas* being the likely pathogens. Chronic paronychia is caused by repeated trauma to the nail folds either physical (excessive manicuring) or chemical (water, contact irritants).

Tinea Unguium

The infection of the nail unit with dermatophytic fungi is known as *Tinea unguium*. Dermatophytes are keratinolytic fungi and normally invade keratins of skin, hair and nails, most common being *Trichophyton rubrum* and *T. mentagrophytes* (**Figure 10**). Toenails are infected 25 times more than the finger nails.



Figure 10: Distal onychomycosis showing yellow-brown discolouration.

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11.11 Cutaneous Responses to Physical Factors

S Criton

Sun is the perennial source of energy and it sustains life on earth. Though it has beneficial effects, at times sunlight can cause harmful effects to man. This may range from trivial transient pigmentation to lethal cutaneous as well as systemic malignancies.

Sunlight has many components such as gamma rays, X-rays, ultraviolet rays, infrared light and radio waves. Common harmful effects of sunlight are due to ultraviolet rays. The ultraviolet rays have three components such as ultraviolet A (320 nm to 400 nm), ultraviolet B (290 nm to 320 nm) and ultraviolet C (200 nm to 290 nm). When light falls on skin some are reflected and some are absorbed. The penetration into skin is dependent on the wave length (the longer wavelengths penetrate more). As the rays penetrate, part of it is absorbed by chromophores, part is transmitted and part is reflected back. Once the energy is absorbed, the chromophores become excited and form photoproducts. These photoproducts are responsible for the skin changes.

CUTANEOUS EFFECTS OF ULTRAVIOLET EXPOSURE

The cutaneous effects of ultraviolet ray, exposure may be divided into early and late effects. The early effects are inflammation, tanning, hyperplasia, immunological changes, vitamin D synthesis and photo onycholysis. The late effects of ultraviolet exposure include pseudoporphyria, photoageing, photocarcinogenesis.

Skin Phototypes

Fitzpatrick developed the concept of skin types based on the person's responses to sunlight. Based on this, the skin is typed as Type I through VI. Persons with types I and II usually burn more easily. The types V and VI individuals tan easily and have least propensity to develop skin cancers. Type III individuals have moderate susceptibility to sun burn and good tanning ability; whereas type IV skin has low sun burn susceptibility but very good tanning potential.

MECHANICAL INJURY

Mechanical injuries are common on human skin due to pressure and shearing force. This may occur as a consequence of occupation, recreational activity or due to deformities. Constant friction produces callosities, corns and calluses. It can also lead to bullae. Corns are circumscribed areas of hard skin in the shape of a nodule commonly seen over the dorsal surface of toes. Calluses are more diffuse. Pressure ulcer is due to localised area of ischaemia and necrosis following prolonged compression of soft tissues over a bony prominence. Suction can also produce 'suction blister', which is a mechanical injury due to negative pressure.

'Computer palms' and 'mouse fingers' are emerging injuries due to mechanical stress to palms and fingers. Pressure, shear, moisture and friction are attributed factors causing these injuries. 'Spectacle frame acanthoma' is another entity developed following pressure and friction of the spectacle and moisture at the site where spectacle is coming into contract.

Vibration can cause vibratory angioedema and hand-arm vibration syndrome. Vibratory angioedema is a form of physical angioedema which disappears when the stimulus is withdrawn. In 'hand-arm vibratory syndrome', initially there is tingling and numbness. As the disease progresses, anaesthesia occurs. This is followed by blanching. As the disease progresses further, there is reduction in touch sensation and difficulty in doing fine work. The condition may be improved with use of nefedipine and α-andrenoreceptor antagonist.

THERMAL INJURIES

Thermal injuries include burn, electric injury and lightening injury. The spectrum of burn may be trivial and inconsequential to very severe leading to death. The type, depth, extent, age of the patient, associated illness, time elapsed between burn and treatment and general status of the patient either singly or in combination determine the outcome of burn. While treating the patient with burn cardiac status, renal status, the infection and coagulation abnormalities are monitored and corrected appropriately. Once the acute phase is over, long-term complications such as scarring and contracture are addressed.

Electricity can produce burns. This may be divided into high tension and low tension burns. With high tension injury, there will be injuries at the entry site as well as at the exit point. The management of electric burn include general supportive care and specific wound management.

When lightening strikes, focal entry and exit wounds are lacking in many. In some at the site of entry, there may be superficial streaking burns, known as 'lightening figures', and at the exit site there may be a charred defect.

COLD INJURIES

Cold environment is harmful to human body. Inherently body has developed protective mechanisms from cold injuries. When body is exposed to cold, a number of responses occur such as cutanenous vasoconstriction, increase in viscosity of blood, change in platelet adhesiveness, diminished conduction velocity in cutaneous nerves and slowing of dissociation of oxyhaemoglobin to haemoglobin. These factors will help the body to maintain its core temperature. Prolonged cutaneous vasoconstriction leads to ischaemia and later necrosis. This is prevented by subsequent vasodilatation which is known as *'hunting reaction of Lewis'*.

Disease of Cold Injury

The type and gravity of cold injuries depend on various factors such as absolute temperature, duration of exposure, individual susceptibility and altitude at which injury occurs. The factors controlling individual susceptibility are physical injury, body mass, physical fitness level, fatigue, sickness, trauma, peripheral circulation status as well as clothing and age of the patient.

Habits like alcohol consumption, smoking and use of psychotropic drugs will add onto cold injuries.

Classification of Cold Injury

The cold injuries may be broadly divided into freezing and nonfreezing injuries.

Frostbite

Frostbite is a type of cold injury caused by acute freezing of tissues on exposure to extreme degrees of cold. Frostbite has four phases such as pre freeze (vasospastic) phase, freeze thaw phase, stasis phase and ischaemic phase.

Frostbite usually affects fingers, toes, nose or cheeks. Depending on the tissue involved it may be graded into first through fourth degree. The first degree frost bite presents with blanched anaesthetic skin. In second degree, there will be oedema and blister formation. In third degree, the bullae become haemorrhagic, while in fourth degree, there will be necrosis.

Treatment

The principle in the management of frostbite is rapid rewarming and avoidance of further trauma. Rapid rewarming is done by immersion in water at 40 to 42° C for 20 minutes. The damaged part should be elevated and blisters should be left intact. Liberal use of analgesics are recommended for relief of pain. Early administration of heparin and infusion of low molecular weight dextran are suggested as effective modalities. Oxpentifylline and hyperbaric oxygen therapy are other recommendations.

Trench Foot (Immersion Foot)

Trench foot results by prolonged exposure to low temperature without freezing.

Clinical features

It start as numbness and tingling. The skin becomes erythematous initially but later it becomes pale and mottled. If the condition persists there may be pain, ulceration and sometimes gangrene.

Treatment

Rewarming the area and other supportive measures like rest to the part, analgesics, and antibiotic. The part should not be massaged, rubbed and exposed to extreme heat.

Pernio (Chilblains)

Chilblain is characterised by localised, tender, inflammatory, erythematous, pruritic lesions which blister or ulcerate. The predisposing factors to chilblains include genetic susceptibility, inadequate nutrition, focal sepsis, hormonal changes and systemic diseases such as dysproteinaemia, myelodysplastic disease and anorexia.

Clinical features

The characteristic lesions are blue-red oedematous, sharply bordered nodules. They are distributed on dorsal aspect of fingers and toes, shins, inner aspect of knees and thighs, heels, nose, ears or occasionally on breasts. Some of the lesions may ulcerate. On warming they become pruritic and later painful. The lesions may persist for 3 weeks or rarely more.

Treatment

The various drugs used are calcium channel blockers viz. nifedipine and diltiazem, vasodilators such as nicotinic acid esters as well as pentoxyfylline.

Acrocyanosis

Acrocynosis is a persistent cyanotic or erythrocyanotic-discolouration of skin with mottled pigmentation. It mainly affects the hands; feet and face are also affected in some.

Acrocyanosis may be idiopathic phenomenon or secondary to some diseases and drugs. The diseases causing acrocyanosis include autoimmune disorders, neoplastic diseases, eating disorders, neurological disorders, psychiatric illnesses and chronic arsenic poisoning.

There is no effective treatment for idiopathic condition. But if it is secondary to diseases, appropriate treatment may help to improve.

Livedo Reticularis

Livedo reticularis is a mottled cyanotic discolouration of the skin with network pattern, which is accentuated with cold. It may be physiological, idiopathic or secondary to intravascular obstruction or vessel wall diseases.

Cold Urticaria

This is characterised by development of wheals on rewarming at the site of localised cooling. It may be *acquired cold urticaria* or *familial cold urticaria*. In acquired variety there may be wheals with constitutional features on exposure to cold; while familial cold urticaria is an autosomal dominant condition. The diagnosis of cold urticaria may be made with 'ice cube test'. This may be negative in familial cold urticaria.

Cold panniculitis

In children on exposure to cold, there will be erythematous, tender subcutaneous nodules which persist for 2 to 3 weeks.

Winter Xerosis

Patients may present with itching during winter. The itching may be generalised; it may be more over legs. Predisposing factors include atopic dermatitis, ichthyosis, old age, hypothyroidism and excessive washing with soap.

Photodermatoses: Abnormal Cutaneous Effects of Ultraviolet Radiation Exposure

Photodermatoses can be divided into four categories such as (1) acquired idiopathic photodermatosis, e.g. polymorphic light eruption; (2) DNA – repair defective photodermatoses, e.g. Xeroderma pigmentosum; (3) photosensitisation by exogenous or endogenous drugs or chemicals, e.g. sulphonylureas, porphyrias; and (4) photoexacerbated dermatoses, e.g. lupus erythematosus.

Acquired idiopathic photodermatoses include polymorphic light eruption (PLE), actinic prurigo, hydroavacciniforme, chronic actinic dermatitis and solar urticaria.

Polymorphic (Polymorphous) Light Eruption (PLE)

This is a common form of idiopathic photodermatoses characterised by itching and polymorphous skin lesions such as papules, vesicles, plaques, papulovesicles, and erythema multiforme-like lesions. Though the lesions are polymorphic, in a given individual, they are monomorphic. The lesions are distributed in sun exposed areas of the body.

The treatment includes sun protection, topical steroid and antimalarials. The disease has a good prognosis.

Actinic Prurigo

A seasonal dermatitis characterised by itching, nodular and eczematous lesions over legs. It may begin at any age. The face and distal limbs are commonly affected. Treatment is mainly photoprotection. Systemic thalidomide is found to be useful.

Chronic Actinic Dermatitis

This is a syndrome encompassing photosensitive eczema, photosensitivity dermatitis, actinic reticuloid and persistent light reaction. The disease is reported world wide and affects chiefly the elderly. It presents as papules and plaques on a normal or erythematous skin over sun exposed areas. The disease may persist for a long time and in some there may be transformation to lymphoma.

The treatment includes avoidance or reduction of sun exposure and photoprotection. Systemic steroid, cyclosporine and azathioprine may be used in the treatment with some benefit. Very resistant cases PUVA (Psoralen and UVA) or NB UVB (Narrow Band UVB) may be useful.

Solar Urticaria

Solar urticaria (SU) is characterised by the appearance of wheals on exposure to sunlight. It may be primary or secondary. Solar urticaria is considered as Type I hypersensitivity reaction; while secondary solar urticaria is due to drug photosensitivity, cutaneous porphyria or lupus erythematosus.

Drug and Chemical Induced Photosensitivity

This may mimic sunburn. A number of patterns may help to suspect this entity such as pricking and burning sensation, immediate erythema on exposure to sun, oedema and urticaria, hyperpigmentation, exaggerated sunburn, telangiectasia and angioma, blisters, increased skin fragility and delayed erythema. Drugs such as sulphonamides, sulphonylureas, phenothiazines, furocoumarins, fragnances, sun screens, NSAIDs are considered important in causing drug-induced photosensitivity.

CLINICAL EVALUATION OF THE PATIENT WITH SUSPECTED CUTANEOUS PHOTOSENSITIVITY

While evaluating the patient with photosensitivity, the following points are noted: the age, sex, occupation, recreational activity, prior history of photosensitivity, family history of photosensitivity, history of seasonal changes, interval between exposure and onset of symptoms, history of medication for the disease or any other diseases, application of topical agents, the pattern of dress and aggravating and/or relieving factors.

The morphology of lesion and site of involvement are important diagnostic clues. The characteristic lesions are patches or papules. Pinhead sized hypopigmented papules may suggest PLE. Blisters with scarring may be of porphyria. Persistent excoriated papules over sun-exposed areas are suggestive of actinic prurigo; eczematous lesions may be due to chronic actinic dermatitis. Wheals on exposure to sun may suggest solar urticaria.

The sites of involvement such as malar area, and tip and bridge of nose, anterolateral forearm, rim of ears, 'V' area of chest, sides of neck and dorsum of hands may suggest photodermatitis (these are common sun-exposed areas). In photodermatitis some areas are not usually involved such as submental area, behind the pinna, sun protected areas, web space of fingers are some among them. Sparing of these areas in the dermatitis in question may also help to make a diagnosis of photodermatitis.

Laboratory investigations may help to establish the underlying cause of photodermatitis, e.g. estimation of porphyrin, antinuclear antibodies in lupus erythematosus. Photo testing and photopatch testing are some useful tools in evaluation of photodermatitis.

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11.12 Genodermatoses

Vibhu Mendiratta

DEFINITION

Genodermatoses are a group of diseases which are transmitted genetically from parents to children. Genodermatoses have well-defined cutaneous features whose recognition plays a key role in its diagnosis and management.

AETIOPATHOGENESIS

The disorders arise due to defect or alteration in a single or multiple genes (polygenic disorders), or these may also arise due to alterations in chromosomal structure. Factors that may give rise to genetic defects include mutagens such as radiation, drugs, cytotoxic agents, chemicals, ultraviolet (UV) light, and viral infections. Single gene disorders have a clear mode of transmission which may be autosomal dominant, recessive, X-linked recessive or dominant. The genetic defect may affect specific protein which may be keratin, DNA or enzymes required for various metabolic processes. Some common genodermatoses, namely neurofibromatosis, tuberous sclerosis, icthyosis, palmoplantar keratoderma, xeroderma pigmentosum shall be outlined in detail.

NEUROFIBROMATOSIS (SYN. VON RECKLINGHAUSEN'S DISEASE)

Epidemiology

It is one of the most commonly encountered genetic disorder which affects both men and women equally. The prevalence is estimated to be 1 case per 3,000.

Aetiopathogenesis

An autosomal dominant disorder with a defect on the long arm of the chromososme 17. Children of one affected parent have a 50% chance of getting the disease. Severity in the affected individuals is variable, some have all the features, while others are only mildly affected.

Clinical Features

Neurofibromas are skin coloured, soft, fleshy, nodules distributed on various areas. Some neurofibromas are subcutaneous lumps (**Figure 1**). Neurofibromas increase in number with age. Plexiform neurofibroma are soft, doughy, subcutaneous swelling having a bag of worm feeling and run along nerves. Presence of multiple, brownish macules (*Café au lait* macules) and tiny specks of brownish macules in the axilla (axillary freckling) constitute some diagnostic features (**Figure 2**). There are multiple bony abnormalities in the form of scoliosis, *spina bifida*. Examination of the eyes shows Lisch nodules which are brownish iris hamartomas (**Figure 3**). Neurofibromatosis (NF-1) has bony abnormalities like scoliosis, *spina bifida*. Phaeochromocytoma, precocious puberty, tumours of the central nervous system (CNS), seizures and mental retardation may be associated. Neurofibromatosis type 2 has bilateral acoustic neuromas of the vestibulocochlear nerve leading to hearing loss. The diagnostic criteria are enlisted in **Table 1**.



Figure 1: Multiple nodules (neurofibromas) on face.



Figure 2: Multiple *café au lait* macules and freckling in neurofibromatosis.

Complications

Pressure effects on nerves, seizures, malignant change in neurofibroma.

Treatment

Single plexiform neurofibromas can be removed with the help of laser or excision. Genetic counselling should be held for the patient.



Figure 3: Iris hamartomas on the surface of iris.

Table 1: Diagnostic Criteria for Neurofibromatosis Based on the Clinical Criteria

1. Two or more neurofibromas on the skin or under the skin or one plexiform neurofibroma
2. Freckling of the groin or the axilla
3. *Café au lait* spots. Six or more measuring 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals
4. Skeletal abnormalities, such as sphenoid dysplasia or thinning of the cortex of the long bones of the body
5. Lisch nodules (iris hamartomas, freckling in the iris)
6. Tumours on the optic nerve also known as an optic glioma
7. A first-degree relative with a diagnosis of neurofibromatosis-1

TUBEROUS SCLEROSIS (SYN. BOURNEVILLES DISEASE)

Definition

Tuberous sclerosis is a genetic disorder with an autosomal dominant pattern of inheritance, and variable penetrance. Two-thirds of tuberous sclerosis (TSC) cases result from sporadic genetic mutations. Hence, there may not always be presence of an affected member in the family.

Epidemiology

Tuberous sclerosis occurs in all races, genders and ethnic groups. The prevalence is estimated to be between 10 to 13 cases per 100,000.

Clinical Features

The physical manifestations of tuberous sclerosis are due to formation of hamartomas. Hamartomas are present in the brain (in the form of cortical tubers). Characteristic cutaneous findings appear as multiple, brown, soft, grouped papules present in the perinasal area and cheeks in a butterfly distribution (**Figure 4**). These are called facial angiofibromas (misnamed as adenoma sebaceum). Their number increases with age. Subependymal nodules in the brain are diagnostic. Patient often presents with seizures at an early age, developmental delay and behavioural problems. About 50% of patients with tuberous sclerosis (TSC) have learning difficulties. Between 60 and 80% of the patients have tumours (angiomyolipomas) in kidneys, lung cysts, and cardiac rhabdomyomas. Ungual or subungual fibromas, (known as Koenen's tumours) are small fleshy tumours that grow around and under the toenails or fingernails and may need to be surgically removed if they enlarge or cause bleeding. Hypomelanotic macules ('ash leaf spots') are white- or light-coloured patches on skin that may appear anywhere on the body. These are usually the only visible sign of tuberous sclerosis at birth. Shagreen patches are areas of thick leathery skin which is dimpled like an orange peel and is usually found on the lower back or nape of the neck (**Figure 5**). *Café au lait* macules can be seen.



Figure 4: Multiple, brown small, grouped, fleshy papules around nose (angiofibromas) in tuberous sclerosis.



Figure 5: Shagreen patch and ash leaf macules on the back in tuberous sclerosis.

Approach to the Diagnosis of Tuberous Sclerosis

1. Taking a personal and family history
2. Examining the skin under Wood's lamp
3. Cranial imaging with non-enhanced CT or preferably MRI (for cortical tubers and subependymal nodules)
4. Renal ultrasound (angiomyolipoma or cysts)
5. An echocardiogram in infants (rhabdomyoma)
6. Fundoscopy (retinal nodular hamartomas or achromic patch).

Management

Management is symptomatic. Seizures require anti-epileptic drugs. Mental retardation should be managed in the developmental clinics. Facial angiofibromas can be removed with the help of electrosurgery or lasers.

Prognosis

The prognosis for individuals with tuberous sclerosis depends on the severity of symptoms. Leading causes of death include renal disease, brain tumour, lung cysts and status epilepticus.

ICTHYOSIS

Definition

The ichthyosiform dermatoses are a diverse group of hereditary skin disorders characterised by the accumulation of 'fish-like' scales resulting from abnormal epidermal cell kinetics. Severity of individual types ranges from mild to life-threatening icthyosis. Based on the mode of inheritance icthyosis can be autosomal dominant which includes: Icthyosis vulgaris, X-linked icthyosis (seen in boys only) and autosomal recessive icthyosis which includes the lamellar icthyosis and icthyosiform erythroderma. Recessive forms of icthyosis tend to be more severe than the dominant types.

Epidemiology

Icthyosis vulgaris is the most common type of icthyosis affecting around 1 in 250 people. Non-bullous icthyosiform erythroderma, bullous icthyosis and lamellar icthyosis are more severe forms but are uncommon.

Aetiopathogenesis

Icthyosis arise as a result of mutation in the gene regulating the keratin synthesis.

Clinical Features

All icthyosiform dermatoses present with dry, scaly skin which shows fish-like or plate-like scales in variable pattern of distribution. Icthyosis vulgaris begins in the first year of life and shows dry, scaly skin over the extensor aspects of the arms and legs. The scales are larger over the lower extremities and presence of mild keratoderma or (thickening of the skin over the palms and soles) is noted. The dryness becomes worse during winters and improves in summers and humid weather. Some patients also bear a tendency to develop atopic dermatitis.

X-linked icthyosis affects boys only. The scales are dirty brown in colour and affect both the extensor and flexural surfaces of the extremities with prominent involvement of the neck and trunk (**Figure 6**). Severe icthyosis exhibit widespread scaling, scales are more diffuse and distributed over both the extensor and flexures of the body. Scales are larger and plate-like (**Figure 7**). Associated features, such as thickening of skin of palms and soles, nail changes, eye abnormalities like ectropion, reduced sweating and redness of skin are some of the other associated features.



Figure 6: X-linked icthyosis showing dirty dark brown, big fish like scales on extremities.



Figure 7: Large, dark scale in lamellar icthyosis.

Differential Diagnosis

Drug induced icthyosis, icthyosis secondary to lymphomas.

Diagnosis

Distribution of scales, colour and severity of scaling offer important clues to the diagnosis. A family history is very useful. In some cases, a skin biopsy is done to help confirm the diagnosis. In some cases, genetic testing and prenatal testing may be helpful in making the diagnosis.

Treatment

Treatment for icthyosis includes application of creams and emollients in the form of petroleum jelly and vegetable oils for hydrating the skin. Oral retinoids are used for severe icthyosis. Exposure to sunlight may improve or worsen the condition. Systemic complications need symptomatic and supportive treatment.

Prognosis

Autosomal dominant icthyosis improves with age and the severity lessens with time. Weather also affects the severity and icthyosis improves in summers.

XERODERMA PIGMENTOSUM

Definition

Xeroderma pigmentosum or XP, is an autosomal recessive disorder of DNA repair.

Epidemiology

It is a very rare disorder. Affects both men and women. Parents already with a child with XP have a 1 in 4 chance of having another child with XP.

Pathogenesis

There is a genetic defect in the repair of DNA damaged by UV light. The most common defect in XP is an autosomal recessive genetic defect in which nucleotide excision repair (NER) enzymes are mutated. Patients with XP are at a higher risk of developing skin cancers such as the basal cell carcinoma.

Clinical Features

Disease presents early in life in the infantile period (around 3 to 6 months) with the history that the child cries on exposure to

the light. Skin turns erythematous on exposure to sun and there may be photophobia. Development of freckles and lentiginosis on the exposed area of the body, such as the extensor aspect of arms, face and the neck are early signs. With the passage of time actinic keratoses, seborrhoeic keratosis, keratitis, corneal ulcers and pre-malignant lesion appear on the skin and the conjunctiva (**Figure 8**). The skin appears dry and pigmented. Later by adulthood squamous cell carcinoma, basal cell carcinoma, and malignant melanoma may form, and constitute the common causes of death.



Figure 8: Multiple actinic keratoses, lentiginosis and conjunctival erythema in xeroderma pigmentosum.

Diagnosis

Diagnosis is based on the recognition of symptoms and skin signs of photosensitivity, dry, pigmented skin with multiple freckles, lentiginosis, pre-malignant and malignant skin lesions. There may be presence of affected members in the family. Identification of the severity of the enzyme defect is based upon demonstration of defective excision repair of DNA bases on exposure to the ultraviolet light.

Management

Patients should be counselled strictly to avoid sun light by wearing hats, goggles and full sleeved garments. Potent, broad spectrum sun screens should be advised. Oral retinoids have been used as chemopreventive agents against the development of skin cancers. Patients should be examined regulary in the clinic and any suspicious, noduloulcerative lesion should be biopsied to exclude the possibility of malignant transformation.

Prognosis

Prognosis is poor in severe cases. Early preventive measures in the form of strict avoidance of sun exposure might delay the development of skin cancers.

EPIDERMOLYSIS BULLOSA

Definition

It is a mechanobullous disorder which is caused by an inherited defect in the keratin formation and is characterised by the presence of multiple blisters and erosions over the trauma prone areas of the body.

Epidemiology

It occurs in a frequency of 1 in 50,000. Epidermolysis bullosa is more common in communities where consanguineous marriages are common. It is common in South India.

Clinical Features

Epidermolysis bullosa presents at or soon after birth. Depending on the keratin defect and the depth of bulla formation there can be divided into three types: (i) E. bullosa (simplex), (ii) junctional; and (iii) dermal or dystropic variant. Simplex varieties are more common, milder and show improvement in the severity of blistering with time. Junctional and the dystrophic variants are more severe and show mucosal blisters, erosions and deformities in the form of contractures. The disease is characterised by the formation of blisters on gentle rubbing or on minimal skin trauma especially over the trauma prone sites such as the buttocks, elbows, hand, feet, arms and legs (**Figure 9**). The blisters rupture to form erosions and crusted lesions which may be slow to heal and get infected. Severe variants with mucosal blistering interfere with feeding. There may be blisters in the pharynx, larynx, eyes and the genital mucosa. There may be contractures and mitten like deformities of hands in the severe variants (**Figure 10**). Pyloric stenosis and development of squamous cell carcinoma are some of the other associated complications.

Diagnosis

Diagnosis is made on the basis of presence of early, spontaneous blistering of skin on trauma prone sites and a positive family history. Confirmation of the diagnosis is by performing electron microscopy on skin biopsy obtained from the blister.

Treatment

The disease requires a multi-dimensional, multi-speciality approach. Treatment is symptomatic with care of the eroded skin using potassium permanganate compresses (1:8000)



Figure 9: Leg contracture and mitten like deformities in epidermolysis bullosa.



Figure 10: Erosions on neck, hands in a newborn in epidermolysis bullosa.

dilution and application of topical antibiotics like mupirocin cream to prevent superimposed infections. Prolonged walking and tight foot wear should be avoided to prevent blisters over feet in localised cases. Severe blistering involving the mucosae and skin can be improved by administering systemic steroids or other immunosuppressive agents, such as cyclophosphamide or cyclosporine. Reconstructive surgery is required for deformities.

Prognosis

Epidermolysis bullosa is a lifelong disease which does not have a cure. Epidermolysis bullosa simplex has the best prognosis as the disease tends to improve a little with age. Limb deformities, oesophageal stenosis, malnutrition, squamous cell carcinoma are some of the complications which develop sometime during the course of the disease and the latter may be an important cause of death.

PALMOPLANTAR KERATODERMA

Definition

Palmoplantar keratoderma are a group of heterogenous disorders some of which are inherited defects due to mutations in the enzymes involved in the synthesis of keratin. They can be autosomal dominant or autosomal recessive.

Epidemiology

These are uncommon.

Clinical Features

The onset of keratoderma is usually seen in childhood. Skin over palms and soles becomes hard, thick, dry and hyperkeratotic. There may be fissures and cuts in the skin (**Figures 11 and 12**). Sometime, the keratoderma may show involvement of the dorsum of hand and feet with areas of thickened skin. The condition is usually asymptomatic but it may interfere with daily activities. Severe variants show abnormal teeth and thickening of nails also.



Figure 11: Diffuse thickening of skin over soles with fissures in hereditary palmoplantar keratoderma.



Figure 12: Keratoderma over palms.

Diagnosis

Skin biopsy and presence of familial occurrence of the disease help in differentiating it from other acquired causes such as psoriasis, hyperkeratotic eczema.

Treatment

Liberal application of emollients are advised along with specific agents in the form of high concentrations of salicylic acid (3% to 12%) depending on the severity of thickening. Oral retinoids are also employed for severe cases.

RECOMMENDED READINGS

1. Harper JI, Trembath RC. Genetics and genodermatoses. *Rook's Textbook of Dermatology*; 7th Ed. Blackwell Science: 2004; pp 12.
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11.13 Skin in Connective Tissue Diseases

Sandipan Dhar

This group of diseases is characterised by inflammation of connective tissues in various parts of the body. These are also labelled as 'Collagen Vascular Diseases'. However, there is little evidence that collagen is primarily involved in causation of these diseases. Most of the entities have multisystem involvement and are characterised by distinct histopathological features and positivity of a number of immunological tests in the blood, known as 'collagen profile'. Various connective tissue diseases with significant cutaneous involvements are shown in **Table 1**.

Table 1: Various Types of Connective Tissue Diseases with Significant Cutaneous Involvement

Lupus erythematosus
Systemic lupus erythematosus
Discoid lupus erythematosus
Subacute lupus erythematosus
Scleroderma
Progressive systemic sclerosis
Morphea or localised scleroderma
Scleredema
Lichen sclerosus *et atrophicus*
Dermatomyositis
Mixed connective tissue disease

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Lupus erythematosus encompasses a group of disorders characterised by chronic inflammatory vasculopathy involving the skin and almost all the systems of the body. Skin involvement is the most common clinical manifestation after joint inflammation and is found in up to 70% of patients during the course of the disease and about 25% patients present with cutaneous lesions for the first time.

Clinical Features

The most frequent cutaneous manifestations of SLE are malar rash (58%), photosensitivity (45%), discoid rash (10%), livedo reticularis (14%), and subacute cutaneous lesions (6%). The malar rash presents over the butterfly area of the face as an erythematous, mildly scaly patch involving the cheeks and bridge of the nose (**Figure 1**). The lesions are quite photosensitive and continued exposure to ultraviolet light leads to increased synthesis of antinuclear antibodies (ANAs) in the circulation.

Mucous membrane lesions in the form of gingivitis, mucosal ulceration and haemorrhage are also seen in this form of the disease.

Diagnosis

Serologic tests are quite useful not only in the diagnosis but also in evaluation of the disease severity and its systemic involvement. Various serologic tests carried-out are antinuclear antibody (ANA), deoxyribonucleic acid, dsDNA, antihistone antibody. ANA titre of more than 1:160 is quite suggestive of active SLE. A positive anti-dsDNA is confirmatory of SLE. 'Lupus band test' requires direct immunofluorescence testing of skin biopsy sample from the affected skin, exposed unaffected skin and covered skin.



Figure 1: Systemic lupus erythematosus scaly patch involving the cheeks and bridge of the nose.

Treatment

Oral corticosteroids are the mainstay of treatment. The dose of steroid is decided according to the severity of the disease, i.e. organ system involvement. The usual starting dose is 30 to 40 mg of prednisolone per day. Steroid dosage is then tapered slowly over a period of 3 to 6 months as per activity of the disease. To prevent osteoporosis, oral vitamin D and calcium supplementation are given as a routine to all patients. Various immunosuppressives used as steroid-sparing agents are azathioprine, cyclophosphamide, methotrexate, chlorambucil, etc. Newer agents used for this are mycophenolate mofetil, tumour necrosis factor (TNF) inhibitors, etc. Use of a good sunscreen is mandatory throughout the day in all patients with lupus erythematosus.

Prognosis

The prognosis of SLE has improved drammatically over the past few decades because of availability of systemic corticosteroids and cytotoxic drugs.

DISCOID LUPUS ERYTHEMATOSUS (DLE)

Epidemiology

It is thought to be seven-fold commoner than SLE and is generally seen between 20 to 40 years of age. Females are more commonly affected with a female to male ratio of 3:1.

Clinical Features

The discoid lesions of DLE are characterised by well-circumscribed, erythematosus, indurated plaques with adherent

scales, patulous follicular openings and telangiectasia (**Figure 2**). The lesions, when heal, produce atrophy, scarring, hyperpigmentation and/or depigmentation. The lesions are most commonly found over the face (**Figure 3**), head (**Figure 4**) and neck. However, the involvement of chest, upper arm, back, buttock, thighs, legs are not infrequent. Lips are often affected by DLE and sometimes lichen planus and lupus erythematosus may coexist over lips, mostly lower lip and known as LE-LP overlap syndrome.



Figure 2: Typical discoid lesion of systemic lupus erythematosus on back of patient.



Figure 3: Discoid lupus erythematosus lesion on the face.



Figure 4: Discoid lupus erythematosus lesion on the scalp.

Diagnosis

Diagnosis of DLE is confirmed by histopathological examination of the skin.

Treatment

For few isolated lesions of DLE, topical moderately potent to potent corticosteroids are used for a period of 3 to 6 weeks. For disseminated lesions, oral chloroquine or hydroxychloroquine is given for a period of 3 to 6 months depending upon the response. Prior eye examination and cardiac check-up including electrocardiogram (ECG) are to be carried out in each patient. Other drugs used with variable success are dapsone and clofazimine. When present over photoexposed areas, regular use of a sunscreen lotion is a must.

Prognosis

Up to 25% to 40% of DLE patients remit spontaneously; 20% with generalised DLE and 5% with localised DLE go onto develop SLE.

SUBACUTE LUPUS ERYTHEMATOSUS

Subacute lupus erythematosus presents as annular/polycyclic lesions or psoriasiform lesions mostly over the trunk and upper extremities.

SCLERODERMA

Scleroderma is a chronic disease of unknown aetiology that affects the microvasculature and loose connective tissues and is characterised by fibrosis of the skin and internal organs. Various diseases of importance under this heading are progressive systemic sclerosis, localised scleroderma/morphea and scleroderma.

Progressive Systemic Sclerosis (PSS)

It is a generalised disease of the skin, lungs, heart, gastrointestinal tract, joints and kidneys. The diagnosis of PSS is made on the basis of some criteria as shown in **Table 2**.

Table 2: Diagnostic Criteria for Progressive Systemic Sclerosis

Major Criteria
Sclerodermatous alterations
Raynaud's phenomenon
Minor Criteria
Capillary microscopy changes
Vascular changes
Gastrointestinal involvement
Renal involvement
Cardiac involvement
Muscle involvement
Joint/tendon involvement
Serology

Clinical Features

The skin changes are characterised by diffuse and progressive induration and hardening of the skin. Often the process starts over the face and acral areas (acrosclerosis). The face looks hide-bound and expressionless with pinched nose, pursed mouth and mat-like telangiectasiae (**Figure 5**). Often there are pigmentary changes over the face and neck in the form of hyperpigmentation and depigmentation (pepper-salt pigmentation) (**Figure 6**). Changes over the fingers show



Figure 5: Typical facies in progressive systemic sclerosis.



Figure 6: Pepper-salt pigmentation in progressive systemic sclerosis.



Figure 7: Sclerodactyly and pitted scars on fingertips.

sclerodactyly or sausage shaped fingers with taut skin over the fingers and thimble pitted scars over fingertips (**Figure 7**). Raynaud's phenomenon is almost a constant feature in cases of PSS. On exposure to cold, patients complain of pain, burning, pallor, cyanosis, tingling and hyperhidrosis. It commonly affects fingers and toes. At the early stage of the disease, patients often complain of arthralgia and limited joint mobility. Patients often complain of weight loss, fatigue, reflux and dyspepsia, muscle weakness and dyspnoea. Pulmonary involvement is a major



Figure 8: Sclerodactyly and telangiectasia.

cause of mortality and more than 50% of the patients with PSS show restrictive lung changes. A variant of scleroderma is known as CREST syndrome which is an acronym for calcinosis, Raynaud's phenomenon, oesophageal hypomotility, sclerodactyly and telangiectasia (**Figure 8**).

Diagnosis

Histopathological examination of the skin and detection of anti scl-70 (anti DNA topoisomerase) and anti-centromere antibodies are most important and useful tests.

Treatment

Treatment of PSS entails a host of systemic care. General measures include avoidance of factors leading to vasospasm (tension, fatigue, stress, cold weather, smoking) and minimising trauma to the hands. For Raynaud's phenomenon, nifedipine or pentoxphylline is used. For arthritis, nonsteroidal, anti-inflammatory drugs (NSAIDs) are used and omeprazole/pantoprazole is used for reflux oesophagitis. In the early oedematous stage of the disease, oral corticosteroids are useful. Prednisolone is given in a dose of 30 to 40 mg/day for 2 to 3 weeks followed by definitive therapy of the disease. D-penicillamine has been found to be useful in some patients. Methotrexate and cyclosporine have also been used with variable success for long-term control of the disease.

Prognosis

The prognosis of PSS is variable and depends on the involvement of organ system(s) and rate of progression of the disease. The cause of death is usually cardiac or respiratory failure. It usually follows a relatively benign course and in such cases anti-centromere antibody is positive.

Pregnancy and Systemic Sclerosis

Systemic sclerosis is considered to be a high risk factor for pregnancy because of higher chances of miscarriage, premature birth and other complications.

MORPHOEA (LOCALISED SCLERODERMA)

Morphoea is a localised type of scleroderma characterised by localised induration and hyperpigmentation of skin.

Clinical Features

It can be subdivided into five types, e.g. plaque, generalised, linear, guttate and deep, according to clinical presentation and depth of tissue involvement. In case of 'guttate morphea', the lesions

are 1 to 3 mm sized indurated papules. In 'linear scleroderma' there may be involvement of the face and/or forehead manifesting as Parry-Romberg syndrome and *'en coup de sabre'*. Linear scleroderma involving frontal and frontoparietal regions of the scalp is called *'en coup de sabre'*. It presents as a depressed sclerotic groove over the frontal/frontoparietal region of the scalp, usually unilateral. The groove may extend downwards to involve cheek, nose, upper lip, and at times mouth, gum, chin or neck. Rarely, the localised scleroderma may involve the subcutaneous tissue, muscle and bone and is known as 'disabling pansclerotic morphea'. Sometimes, the morphea lesions may have overlying lichen sclerosus *et atrophicus* (LSA) lesions.

Plaque-type morphea presents as one or few hyperpigmented indurated papules of 0.5 to 15 cm diameter. The areas usually affected are back, buttock, abdomen, thigh and rarely the face (**Figure 9**). The lesions resolve with hyperpigmentation and sometimes atrophy (**Figure 10**).

Diagnosis

Skin biopsy helps in diagnosis of morphea and localised scleroderma of all types. ANA positivity occurs in approximately 25% to 65% of cases with linear scleroderma and generalised morphea. Rheumatoid factors are positive in 25% to 40% cases and eosinophilia is seen in a good number of cases. Recently, anti-topoisomerase II antibodies have been detected in 76% of patients with localised scleroderma and in 85% of cases of generalised morphea. These antibodies, in contrast to anti-topoisomearse I/scl-70 antibodies have been found in 14% of the patients with systemic scleroderma.

Treatment

Treatment of morphea and linear scleroderma is not very rewarding. Topical and intralesional corticosteroids help in resolution of the lesions. Topical calciprotriol has been shown to help resolution of the lesions particularly when used under occlusion and at early stage of the disease. For generalised morphea and linear scleroderma, oral corticosteroids are given initially for 2 to 3 weeks followed by methotrexate for a period of 3 to 6 months which may help resolution of the lesions. Other therapeutic options are oral calcitriol, cyclosporine and D-penicillamine. These treatment modalities are, however, chosen for very selective patients. Physiotherapy and corrective surgeries are adjunctive treatment modalities.



Figure 9: Plaque-type hyperpigmented lesions on back.



Figure 10: Plaque-type hyperpigmented lesions on the back.

Prognosis

Plaque type of morphoea tends to improve within 3 to 5 years. However, the residual hyperpigmentation and hypo-pigmentation and occasional atrophy may persist for long periods of time. Lesions of linear scleroderma also tend to improve with time. However, the residual atrophy and pigmentary changes may remain for indefinite period of time.

SCLEREDEMA

Scleredema is a rare disorder that manifest as large area of induration of skin and subcutaneous tissue that must be distinguished for more commonly occurring scleroderma. The condition most commonly occurs in adult diabetics (scleredema *adultorum of Buschke*). However, children often suffer from this disorder usually after an episode of streptococcal upper respiratory tract infection. The skin changes often start over the neck and spread in a cephalocaudal direction to involve the upper trunk and occasionally the face and arms. It manifests as slow and insidious onset of non-pitting oedema and induration. Usually, the patients are asymptomatic, but in some patients a prodrome of fever and malaise may precede the skin changes by 2 to 4 weeks. The condition is by and large benign, but involvement of skeletal and cardiac muscles have been reported. The pathogenesis of scleredema is unknown. The condition usually resolves spontaneously over a variable period of a few months to 2 years or so.

LICHEN SCLEROSUS ET ATROPHICUS

Lichen sclerosus *et atrophicus* (LSA) is a disease of unknown aetiology which is mostly seen in females, although, males are also affected.

Clinical Features

The disease is characterised by sharply defined small pink to ivory coloured papules which coalesce to form plaques of variable sizes (**Figure 11**). As the lesions progress, follicular plugging and atrophy becomes more prominent (**Figure 12**). The lesions are asymptomatic and can develop on any part of the body. Lesions often tend to develop over the sites of trauma, irritation and surgical scars (Koebner's phenomenon).



Figure 11: Lichen sclerosus *et atrophicus* showing plaques of variable sizes.

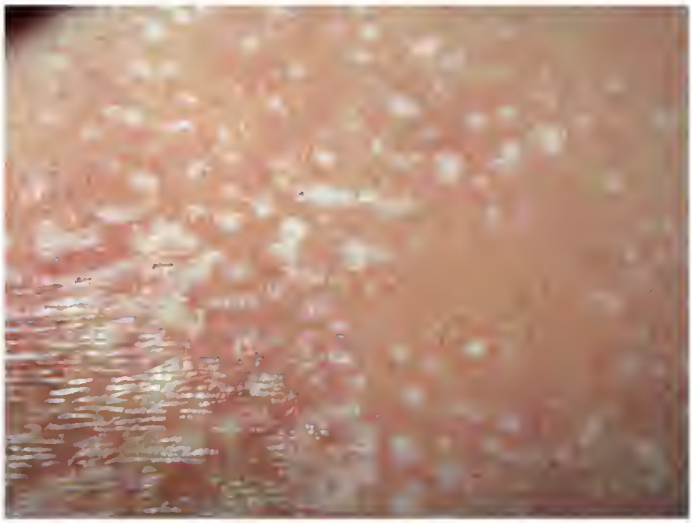


Figure 12: Lichen sclerosus *et atrophicus* showing follicular plugging and atrophy.

The lesions of LSA may top the lesions of plaque-type of morphea. Lesions often develop over the genital areas both in females and males. In females, the lesions of LSA lead to the development of kraurosis vulvae. Here the lesions are distributed over the genital and perianal area in an hourglass configuration or figure of eight pattern (**Figure 13**). The lesions are symptomatic and produce pruritus, burning sensation and bleeding from vulvar and perianal area on urination and defaecation. There may be vaginal discharge, purpuric lesions, blistering and excoriation over labia minora and clitoris. In males, the lesions are known as 'balanitis xerotica obliterans' (BXO).

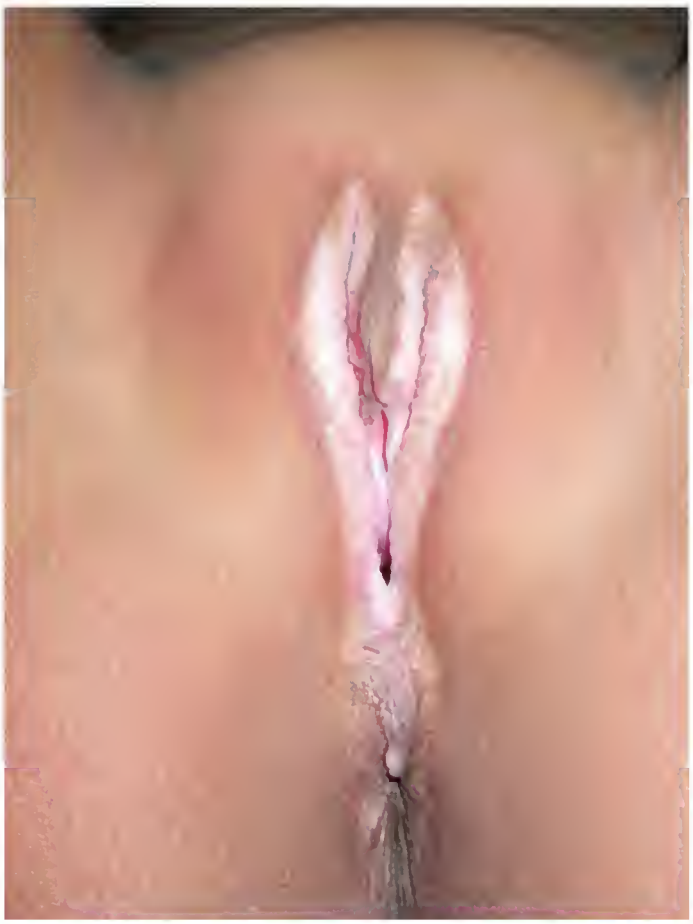


Figure 13: LSA showing lesions over the genital and perianal area.

Diagnosis

Skin biopsy and histopathological examination clinches the diagnosis as the condition has some unique histopathological features.

Treatment

Topical corticosteroids are the treatment of choice. Moderately potent to superpotent topical corticosteroids used for a period of 6 to 8 weeks help to resolve the lesions. Topical tacrolimus (0.1%) and premecrolimus (1%) have recently been found to be quite helpful. Surgical options like circumcision, plastic reconstruction and corrective surgeries may be required along with medical therapy to improve the quality of life of the patients.

Prognosis

Some of the lesions may improve spontaneously, particularly the lesions over the skin. Lesions over the genitalia, however, show little tendency to resolve spontaneously. Instead, ulceration, urethral stricture, anal and vaginal stenosis may occur. In females, carcinoma may develop over longstanding vulvar LSA.

DERMATOMYOSITIS

It is an idiopathic inflammatory myopathy of striated muscles along with the characteristic cutaneous findings, hence it has got both cutaneous and muscular components. Disease has got racial predilection. Females are affected twice as commonly as males. Though it can occur at any age but two peaks are seen, one between 5 to 10 years and another is 50 years of age.

Aetiopathogenesis

The exact cause of dermatomyositis is unknown, but certain factors have been implicated like genetic factor linked to human leucocyte antigen (HLA) DR3, DR5, DR7. Infectious agents like coxsackievirus, parvovirus, echovirus, HTLV-1, human immunodeficiency virus (HIV), toxoplasma and borrelia can be a trigger factor. Various drugs like hydroxyurea, penicillamine, statins, quinidine and phenylbutazone, etc. can cause dermatomyositis.

Clinical Features

Various types of dermatomyositis are enumerated in **Table 3**.

Table 3: Various Clinical Types of Dermatomyositis

Dermatomyositis
Polymyositis
Dermatomyositis associated with malignancy
Dermatomyositis associated with connective tissue disorders
Juvenile dermatomyositis

The pathognomonic cutaneous features are heliotrope rash (periorbital confluent macular mauve or violaceous erythema) and Gottron's papules (papules having violaceous hue overlying the dorsolateral aspect of interphalangeal or metacorpophalangeal joints). Other cutaneous features are malar erythema, poikiloderma (variegated telangiectasia along with atrophy and hyperpigmentation) (**Figure 14**), periungual and cuticular changes (cuticular hypertrophy with haemorrhagic infarcts) and mechanics hands (fingertip erythema and scaling). Calcinosis cutis are also seen, which are firm yellow or flesh coloured nodules extruding calcium through the skin though seen only in 4% of children and adolescents (**Figure 15**).



Figure 14: Dermatomyositis on the face of a child.

Muscle findings are proximal muscles weakness like difficulty in rising from chair or bed, climbing the stairs, combing hair, difficulty in swallowing; but walking may be normal as distal muscles are unaffected. Systemic features which include joint swelling associated with pulmonary and gastrointestinal involvement make the prognosis worse. It should be differentiated from lupus erythematosus, MCTD, steroid myopathy, cutaneous vasculitis, etc.

Diagnosis

Diagnosis is basically clinical and can be made from the skin changes. Muscle enzymes are abnormal during the course of dermatomyositis except in the amyotrophic variety. Most sensitive enzyme is CPK (creatine phosphokinase). Apart from this, aldolase, AST, LDH, may also be abnormal. Magnetic resonance imaging (MRI) is a useful tool as it not only shows the presence of inflammatory myopathy but also helps to differentiate it from steroid myopathy. It can also serve as a guide in selecting the muscle biopsy site.



Figure 15: Calcinosis cutis showing extruding calcium.

Treatment

It includes general measures, treatment of involved skin, affected muscles, and treatment of complications. General measures include bed rest for severe muscle inflammation, programmed physical therapy to avoid contractures and joint complications. Goal of pharmacotherapy is to reduce morbidity and to prevent complications. Mainstay of the treatment are systemic corticosteroids. It has been observed that most patients develop corticosteroid-induced myopathy. Therefore, it is prudent to use immunosuppressive agents like methotrexate, azathioprine and cytotoxic agents (mycophenolate mofetil) as steroid sparing agents. Apart from these, intravenous immunoglobulin for at least 6 months has proved beneficial. Rituximab is another effective option.

Therapy for cutaneous lesions is difficult. Education, avoidance of sun and broad-spectrum sunscreens are helpful in photosensitive patients. For the treatment of calcinosis cutis, calcium channel blockers (diltiazem) shows gradual resolution.

Prognosis

The disease may spontaneously remit in the juvenile variety of cases, but relapses can be seen. Prognosis also depends upon the degree of systemic involvement. In adults, it is mandatory to search for underlying malignancy, successful treatment of which can reduce the mortality to a greater extent. Majority of the patients survive but may develop residual weakness and disability.

RECOMMENDED READINGS

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11.14 Skin in Systemic Diseases

Uday Khopkar

Skin is a mirror of health and disease and reflects almost all systemic disturbances. The skin is available for examination to any physician who cares to pay attention to it.

CUTANEOUS SYMPTOMS AND SIGNS OF INTERNAL DISEASES

Pruritus

Pruritus (itching) in the absence of skin lesions can be a symptom of internal disease and may even be a presenting manifestation of it. Patients with infective hepatitis or evolving renal disease may occasionally present with generalised pruritus without any skin rash. Generalised dry itchy skin may be a feature of Hodgkin's lymphoma. Pruritus in a case of polycythaemia gets worse after bath.

Exanthem and Enanthem

Skin rashes (exanthem) and mucosal rashes (enanthem) are well recognised since ages as signs of systemic viral and occasionally bacterial infections. Chickenpox, smallpox, measles, rubella, hand, foot and mouth disease have characteristic morphology and distribution of their rashes. The confluent rash of dengue fever gives an appearance of 'islands of normal skin in a sea of red'; is late to appear in the course of disease and may be missed due to its asymptomatic nature.

Purpura

Thrombocytopaenia and disorders of coagulation result in non-inflammatory purpura (petechiae, purpura, ecchymosis, haematoma), damage to blood vessels in small vessel vasculitis results in inflammatory purpura (palpable purpura). Palpable purpura is seen as red oedematous papules, which fail to blanch on diascopy.

Ischaemic Necrosis and Ulcers

Cutaneous infarcts may occur due to vascular occlusion resulting from a variety of internal diseases like diabetes, atherosclerosis, Berger's disease, vasculitis, collagen vascular diseases, disseminated intravascular coagulation, coumarin necrosis, antiphospholipid antibody syndrome or calciphylaxis. Cutaneous ulcers may be a manifestation of diverse conditions like sickle cell disease or ulcerative colitis, Crohn's disease or even septicaemia or fungaemia. While taking care of the immediate consequences of such lesions, it is important to detect and correct the underlying cause.

Skin Nodules

Nodules on the skin may occur due to plethora of internal causes like erythema nodosum, erythema nodosum-leprosum, panniculitis, metastasis of internal malignancy, lymphomas, sarcoidosis or systemic infections like cryptococcosis, penicilliosis, histoplasmosis, leishmaniasis, bacillary angiomatosis or cysticercosis.

Papular Lesions

Systemic infections like cryptococcosis, miliary tuberculosis, neoplastic conditions like leukaemia and histiocytosis X may present with papular lesions. Tuberculids like papulonecrotic-tuberculid and lichen scrofulosorum present as papular rashes due to hypersensitivity to tubercular antigen.

SYSTEMIC DISEASES AND THEIR SKIN MANIFESTATIONS

For the purpose of this discussion, internal diseases that manifest onto the skin may be grouped into: HIV infections; internal malignancies; multisystem diseases; individual organ diseases; specific skin signs of diseases affecting individual organs; and non-specific signs of organ failure (**Table 1**).

Human Immunodeficiency Virus (HIV) Infection

With a very high prevalence of HIV infection in India, familiarity with cutaneous manifestations of HIV infection has become a necessity for all physicians.

Since HIV infection is sexually transmitted in most instances, other sexually transmitted infections like herpes simplex, condyloma-acuminata, syphilis and chancroid tend to occur more frequently in the HIV-infected. These infections are also more severe in terms of extent, morphology, speed of progression, time to healing and complications. Details of various cutaneous manifestations are covered in the chapter on 'Sexually Transmitted Infections and HIV'.

Skin in Multisystemic Diseases

Several multisystem diseases involve the skin in a variety of ways. Frequently many of these manifestations are subtle or asymptomatic and are therefore not complained of by the patient. Seeking these actively will certainly add an edge to the clinical acumen of a physician. Lupus erythematosus in its localised form (discoid lupus erythematosus, **Figure 1**) and systemic form [systemic lupus erythematosus (SLE), **Figures 2 to 4**], systemic sclerosis (**Figures 5 and 6**), dermatomyositis (**Figures 7 and 8**) and sarcoidosis (**Figure 9**) are some of the prominent diseases in this category of multisystem diseases.

Cutaneous Markers of Internal Malignancies

Apart from cutaneous metastases and their side-effects like lymphoedema, internal malignancy may manifest onto the skin through the immune suppression (candidiasis) or malnourishment (dry skin) associated with advanced malignancies. Besides, internal neoplasms in genetic diseases may be associated with skin signs.

It is common for lymphoproliferative diseases like lymphomas and leukaemias to manifest onto the skin at some stage of the disease. Moreover, several skin signs presage development of internal malignancies. Some of these may result from the effects of hormones secreted by the tumour while still others occur through hitherto undiscovered mechanisms (paraneoplastic dermatoses). Some of the skin manifestations of internal malignancies are tabulated in **Table 2**.

Table 1: Examples of Skin Manifestations of Systemic Infections

Bacterial infections	
Bacterial endocarditis	Palmar erythema and nodules
Anthrax	Malignant pustule over face
Tuberculosis	
Miliary tuberculosis	Brown-red papules
Scrofuloderma	Nodules and sinuses overlying involved organs
Tuberculids	Demonstrable tuberculous focus, no acid fast bacili (AFB) in skin lesions, strong Mantoux test and tuberculoid granuloma on biopsy
Erythema induratum	Tender nodules and ulcers over calves of young ladies
Papulonecrotic tuberculid	Papulopustular lesions healing with scarring
Lichen scrofulosorum	Grouped follicular micropapules
Erythema nodosum	Tender, erythematous nodules and plaques over shins
Septicaemia	
Septic vasculitis	Palpable purpura, haemorrhagic vesicles, skin infarcts
Disseminated intravascular coagulation	Skin infarcts and gangrene of digits
Purpura fulminans	Large skin infarcts lead to deep punched out ulcers
Meningococcaemia	Palpable purpura, haemorrhagic vesicles over limbs
Pseudomonas septicaemia	Necrotic ulcers with yellow-green discharge (ecthyma gangrenosum)
Viral infections	
Viraemia due to many viruses	Maculopapular or papulovesicular exanthem and enanthem
Hepatitis B	Cutaneous vasculitis
Spirochetal infections	
Secondary syphilis	Symmetric non-pruritic scaly rash
Leptospirosis	Rash over shins
Borreliosis	Erythema chronicum migrans expanding rings over limbs
Fungaemia	
Cryptococcosis	Papules, nodules and ulcers over face and limbs
Histoplasmosis	Nodules and ulcers over mucosae and mucocutaneous junctions
Parasitic infestations	
Post-kala-azar dermal leishmaniasis	Generalised symmetric hypopigmented macules, nodules and diffuse erythema of face
Cysticercosis	Asymptomatic subcutaneous nodules over trunk



Figure 1: Disseminated discoid lupus erythematosus. Erythematous dyspigmented plaques.



Figure 2: Discoid lupus erythematosus. Extensive confluent discoid lesions.



Figure 3: Systemic lupus erythematosus. Malar rash with erythema and oedema over lips and upper chest.

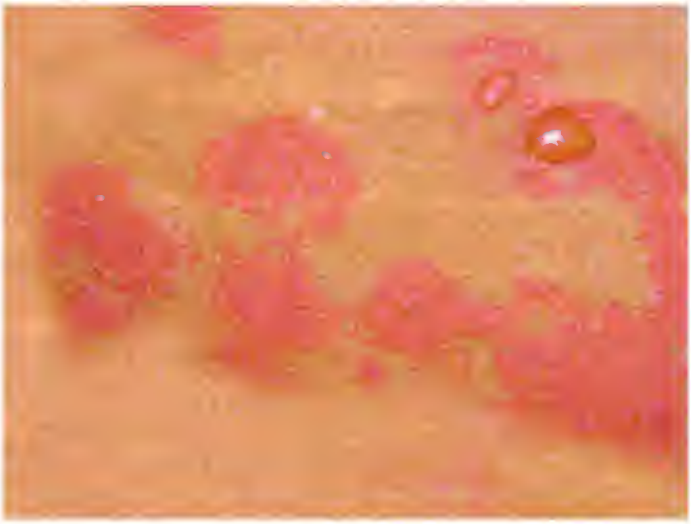


Figure 4: Bullous lupus erythematosus. Vesiculobullous lesions on erythematous base.



Figure 7: Dermatomyositis. Diffuse violaceous erythema of face with affection of upper eyelid.



Figure 5: Systemic sclerosis. Re-pigmenting vitiligo like patches over hidebound skin.



Figure 8: Gottron's papules. Erythematous lichenoid papules in dermatomyositis.



Figure 6: Systemic sclerosis. Acrosclerosis with scarring and resorption of tips of digits.



Figure 9: Sarcoidosis. Reddish brown shiny plaque.

Table 2: Skin Changes Associated with Internal Malignancies

Direct effects of malignant neoplasms	
Carcinomas	Cutaneous metastases
Haematological malignancies	Specific skin infiltrates
Visceral malignancy	Infiltration or ulceration of contiguous skin
Effects of infiltration	Sclerosis, lymphoedema, lymphangiectasia
Effects of debility	Candidiasis, herpes zoster, dry, lusterless skin and hair, hyperpigmentation, xerosis
Genodermatoses with associated internal malignancy	
Gardner's syndrome	Cutaneous lipoma and osteomas are pointers of colonic polyposis and malignancy in future
Neurofibromatosis	Phaeochromocytoma, gliomas, haematological malignancies
Peutz-Jeghers syndrome	Lentigines on lips associated colonic polyps with predisposition for malignancy
Paraneoplastic signs of internal malignancy	
Acanthosis nigricans	Brown-back velvety plaques over neck and flexures
Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Tender, red plaques over limbs and face in a middle-aged lady
Acquired ichthyosis	Dry fish-like skin most commonly in Hodgkin's lymphoma
Clubbing	Severe grades of clubbing with lung carcinoma
Dermatomyositis	Up to 10% cases have associated with internal malignancy
Erythema gyratum repens	Concentric rings of erythema and scaling over trunk
Hypertrophic osteoarthropathy	Subperiosteal new bone formation
Migratory thrombophlebitis	Highly malignant lesion with metastases
Myeloma-associated amyloidosis	Skin nodules and purpura
States associated with endocrine neoplasms	
Addisonian pigmentation	Adrenal corticotropin hormone (ACTH) secreting neoplasms
Hirsutism	Coarse hair in females in male distribution
Androgenetic alopaecia in females	Virilising tumours
Necrolytic migratory erythema	Expanding rings of erythema and vesiculation with glucagonoma
Carcinoid tumours	Flushing of face and upper trunk

Skin in Diseases Affecting Individual Systems or Organs

The skin is involved in this group of diseases in two ways. The more common skin manifestations are those that are caused due to individual organ failure and are therefore not part of a specific aetiopathologic entity. Hence, the dryness of skin seen in renal failure is not specific for any of the causes of renal failure and is therefore not helpful to reach an aetiopathologic diagnosis. On the other hand, cutaneous inflammatory lesions in a case of Crohn's disease are specific for the condition and are helpful to reach the diagnosis.

Endocrine Disorders

With the probable exception of keratinocytes almost every component of the skin is influenced by the endocrine system. Hence, careful examination of the skin is an integral part of the workup in endocrinology. Hyper- or hypofunction of individual endocrine gland is accompanied by several skin alterations that provide clues to the diagnosis. Some of these are enumerated in **Table 3**. Additionally common autoimmune skin diseases like vitiligo, alopaecia areata or lichen planus may occur together with autoimmune endocrine disorders.

Acanthosis nigricans

This important marker of endocrine disease is characterised by symmetrical velvety hyperpigmented plaques in neck and flexures (**Figure 10**). Acanthosis nigricans has been classified into the five following types: hereditary, pseudoacanthosis nigricans, benign, drug-induced and malignant. The last two types are rare. The hereditary benign type is dominantly transmitted, presents during childhood and is not associated with any internal malignancy or endocrine disorder.

Acanthosis nigricans is most commonly seen in obese persons who may have subclinical insulin resistance. The skin changes are reversible on weight reduction. The benign type occurs in association with various endocrine disorders or syndromes. They include acromegaly, Cushing's disease, hypothyroidism, insulin-resistant diabetes mellitus, Addison's disease, Stein-Leventhal syndrome, etc. The triad of hyperandrogenism, insulin-resistance and acanthosis nigricans in women is known as HAIR-AN syndrome. Correction of endocrine abnormalities may slowly revers the skin changes.

Cardiocutaneous Diseases

Although it is not common for heart diseases to be associated with skin lesions several multisystem diseases frequently manifest with cardiac and cutaneous findings. These include SLE, rheumatic fever, dermatomyositis, systemic sclerosis, rheumatoid arthritis, behçet's disease, periarteritis nodosa, Reiter's disease and sarcoidosis. Bacterial endocarditis may present with splinter haemorrhages in the nails or palmar erythema or nodules. In addition, several specific cardiocutaneous associations have been identified. These are listed in **Table 4**.

Skin Changes in Gastrointestinal Diseases

Several gastrointestinal symptoms or syndromes have specific dermatologic associations (**Table 5**, **Figure 11**). In addition to these, pancreatic and liver diseases frequently manifest themselves onto the skin. Moreover, some common skin diseases are associated with asymptomatic but significant gastrointestinal affection. Prominent amongst them are dermatogenic enteropathy, dermatitis herpetiformis and pyoderma gangrenosum. Dermatogenic enteropathy indicates

Table 3: Endocrine Disorders and the Skin

Pancreas	
Diabetes mellitus	(Please refer to the chapter on Metabolic and Nutritional Disorders of the Skin)
Glucagonoma	Necrolytic migratory erythema (expanding rings of superficial vesicopustules and scaly papules over face, trunk or flexures)
Pancreatitis	Cutaneous haemorrhage, enzymatic panniculitis
Pancreatic carcinoma	Migratory thrombophlebitis
Pituitary	
Acromegaly	Skin is coarse, leathery, oily and dark, hypertrichosis, cutis verticis gyrata and acanthosis nigricans are other features
ACTH secreting tumours	Cutaneous features of Cushing's syndrome and addisonian pigmentation
Hypopituitarism	Lack of axillary and pubic hair, pallor of skin and nipple
Thyroid	
Myxoedema	Skin of the face and acral areas is thick and boggy (non-pitting oedema)
Hypothyroidism	Skin is dry, cool and pale yellow (due to carotenaemia), hairs are dull, coarse and brittle, loss of lateral third of eyebrows, nails are thin, striated and brittle
Graves' disease	Pretibial myxoedema (waxy papules or plaques with 'peau de orange' look) may affect hands and feet, thyroid acropachy (drumstick clubbing)
Hyperthyroidism	Skin is flushed, moist and smooth, velvety to touch, hair are thin and friable and alopaecia is common, nails are soft, friable or show koilonychia or onycholysis, generalised pruritus
Adrenal cortex	
Cushing's syndrome	Skin is thin, fragile with purpura and striae, redistribution of body fat leads to truncal obesity, moon facies, buffalo hump and thin limbs. Acne, hirsutism and acanthosis nigricans are other features
Addison's disease (primary hypoadrenalism only)	Generalised diffuse brown-black pigmentation of skin and mucosae with accentuation over exposed areas (face, hands, forearms), flexures (axillae, groins), bony prominences (knuckles, knees, elbows), normally pigmented areas (palmar creases, nipples, genitalia, pre-existing melanocytic nevi), frictional areas (e.g. beltline), mucosae (blue black colour esp. over oral mucosa), pigmented bands on nails
Sex hormones excess	
Defeminising and virilising syndromes	Hirsutism and male pattern alopaecia, thick, oily, hyperhidrotic skin with acne and acanthosis nigricans
Deficiency	
Hypogonadism (pituitary)	Features hypopituitarism, juvenile scalp hair pattern in adult males
Hypogonadism	Absence of sparsity of axillary and pubic hair in males or female type body hair distribution in male.

Table 4: Cardiocutaneous Diseases

Heritable diseases	
Progeria (childhood and adulthood)	Atherosclerosis with premature ageing of skin
Neurofibromatosis	Hypertension due to pheochromocytoma with coarctation of aorta
Marfan's syndrome	Striae with valve disease or aneurysm of aorta
Pseudoxanthoma elasticum	Yellowish papules over neck and flexures with hypertension, peripheral vascular disease
Infective diseases	
Bacterial endocarditis	Palmar erythema, septic vasculitis, Osler's nodes, Janeway lesions, subungual splinter haemorrhages
Lyme disease	Myocarditis and erythema chronicum migrans in *Borrelia burgdorferi* infection
Syphilis	Aortic aneurysms, penile scar, gumma
Viral and rickettsial infections	Myocarditis and maculopapular or haemorrhagic rash
Connective tissue disorders	
Systemic lupus erythematosus	"Libman-Sack" endocarditis, pericardial effusion, congenital heart blocks in neonatal lupus erythematosus
Scleroderma	Conduction blocks, cardiomyopathy
Metabolic diseases	
Hyperlipidaemias	Tuberous and planar xanthomas in coronary artery disease due to hypercholesterolaemia
Amyloidosis	Cardiomyopathy and skin infiltration and purpura
Haemochromatosis	Cardiomyopathy with hyperpigmentation
Fabry's disease	Generalised angiokeratomas with hypertension and ischaemic heart disease

malabsorption associated with extensive skin disease like exfoliative dermatitis. The intestinal villi are atrophic and general indicators of malabsorption are present Gluten-sensitive enteropathy occurs in association with dermatitis herpetiformis though this is probably uncommon in Indian patients with dermatitis herpetiformis. Skin ulcers in pyoderma gangrenosum are sometimes associated with inflammatory bowel disease.

Hepatic Diseases and the Skin

Chronic liver disease manifests itself on the skin with many signs. Icterus is associated with yellowish discolouration of skin and pruritus. Spider angiomas occur over the face, neck and upper trunk in hepatic failure. The nails become clubbed and white and the palms show erythema and Dupytren's contracture. The face turns red initially and later dark and the skin becomes thin with telangiectasia (paper-money skin) and purpura. There is gynaecomastia and loss of axillary and pubic hair. Prominent veins around the umbilicus (caput medusae) and over chest are a sign of portal hypertension. Viral hepatitis may act as a trigger for autoimmune phenomena in the skin like leucocytoclastic vasculitis.

Cutaneous Manifestations of Renal Diseases

Renal failure due to any cause leads to dry, pruritic, scaly skin with a tendency to develop purpura or ecchymoses on minor trauma. Besides, the skin is pale yellow due to associated anaemia and

Table 5: Gastrointestinal Diseases and the Skin

Diarrhoea	
Gluten-sensitive enteropathy	Dermatitis herpetiformis
Ulcerative colitis	Pyoderma gangrenosum, aphthae, pyoderma vegetans, pyostomatitis, erythema nodosum
Crohn's disease	Pyoderma gangrenosum, perianal fistule, mucocutaneous granulomas, erythema nodosum
Mastocytosis	Urticaria pigmentosa
Pellagra	Photodermatitis over neck, hands and forearms, glossitis, erythema of other mucosae
Gastrointestinal bleeding	
Henoch-Schönlein purpura	Palpable purpura
Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu)	Spider-like angiomas of skin and mucosa
Pseudoxanthoma elasticum	Small, soft, yellowish papules over neck and axillae
Gastrointestinal polyposis	
Peutz-Jeghers syndrome	Acral and periorificial lentigines
Gardener's syndrome	Lipomas, sebaceous cysts, osteomas
Gastrointestinal neoplasms	
Glucagonoma	Necrolytic migratory erythema
Pancreatic adenocarcinoma	Migratory thrombophlebitis
Carcinoid syndrome	Flushing of face, upper torso, pseudoscleroderma
Metastatic carcinoma	Umbilical nodule due to metastasis of stomach carcinoma
Malabsorption	Diffuse hyperpigmentation, dry scaly skin, lusterless fragile hair, thin brittle nails, pruritus, acquired ichthyosis
Pancreatitis	Enzymatic panniculitis: purpura over periumbilical region (Cullen's sign) or flanks (Grey Turner's sign). Hyperlipemic xanthomatosis is associated with pancreatitis
Skin lesions in liver cell failure	Icterus, paper-money skin, spider angiomas, palmar erythema, hyperpigmentation, white nails, gynecomastia, loss of axillary and pubic hair, caput medusae if poral hypertension

pitting oedema as well as accumulation of urochrome or carotene pigments. High blood urea levels may reflect onto the skin by deposition of urea crystals on the nose and malar area forming 'uraemic frost'. Other non-specific indicators of renal failure include acquired perforating dermatoses like perforating folliculitis or Kyrle's disease and loss of hair from limbs, all of which result from persistent rubbing and scratching of the skin. Secondary hyperparathyroidism due to renal failure is probably responsible for persistent pruritus in some cases. Calcinosis cutis and pseudoporphyria cutanea tarda are other non-specific signs of renal failure. Half and half nails in chronic renal failure show brown red discolouration of their distal half. Occasionally, skin and kidneys may be affected by the same pathological process. Some of these instances are enlisted in **Table 6**.

Haematological Disorders and the Skin

Many haematologic diseases display skin lesions at some stage of the disease evolution (**Figure 12**). Some of them like those of T-cell lymphoma or systemic mastocytosis are of diagnostic importance whereas others like purpura in leukaemia are not



Figure 10: Acanthosis nigricans. Velvety hyperpigmented plaque.



Figure 11: Peutz-Jeghers syndrome. Lentigines on lips and face.

Table 6: Renocutaneous Diseases

Hereditary diseases	
Fabry's disease	Angiokeratomas, sphingolipid deposits in kidneys
Sickle cell disease	Leg ulcers and pigmentation
Tuberous sclerosis	Shagreen plaque, adenoma sebaceum, ash-leaf macules
Metabolic disorders	
Gout	Cutaneous and subcutaneous yellowish nodules (tophi) that contain urate crystals
Primary and myeloma associated amyloidosis	Papules, nodules, purpura

specific for the disease (**Table 7**). Occasionally, skin diseases may be associated with haematologic disturbances. Amongst these are anaemia induced by persistent exfoliative dermatitis or, leucocytosis seen in generalised pustular psoriasis or Sweet's syndrome.

Respiratory Diseases and the Skin

Most of the multisystem diseases like SLE or sarcoidosis or vasculitides display both skin and respiratory system involvement. Tuberculosis of lungs or other organs may be occasionally associated with skin lesions (**Table 1**). The skin may be directly affected due to tuberculous infection or may show features of hypersensitivity to circulating tuberculous antigens. The latter condition is termed as a tuberculid to distinguish it from actual tuberculous infection.

Skin Lesions in Diseases of Bones and Joints

Most of the multisystem diseases including collagen vascular diseases are associated with arthritis or arthralgias. Besides



Figure 12: Digital gangrene in antiphospholipid antibody syndrome.

those, about 5% psoriatics have arthritis whereas about 5% of patients with arthritis have psoriasis. Type II lepra reaction in lepromatous leprosy may occasionally present with arthritis. Erythema nodosum, hepatitis B, secondary syphilis, Lyme disease and Sweet's syndrome are other instances where skin rashes are accompanied by joint pains.

Keen observation of skin lesions frequently provides a decisive clue to diagnosis of an internal disease. Hence, familiarity with

Table 7: Skin Manifestations of Some Haematologic Disorders

Erythrocyte disorders and haemoglobinopathies	
Iron deficiency anaemia	Koilonychia, atrophic glossitis, alopaecia
Pernicious anaemia	Addisonian hyperpigmentation, vitiligo, glossitis, cheilitis
Haemolytic anaemia	Sickle cell anaemia, thalassaemia—Leg ulcers
Polycythaemia	Pruritus or flushing after bathing, erythermalgia, urticaria
Meth/sulph/carboxy haemoglobinaemia	Violet or brown discolouration of skin, especially face and hands
Porphyrias	Photosensitivity and skin fragility
Leucocyte disorders	
Leukaemia	Chloromas are greenish blue nodules in acute myeloblastic leukaemia. Leukaemia cutis (papules, nodules or plaques) are specific lesions. Non-specific lesions include purpura, Sweet's syndrome, pyoderma gangrenosum, eczematous eruptions or pruritus. Moreover, opportunistic infections like candidiasis, herpes zoster, molluscum contagiosum or cryptococcosis occur
Chediak-Higashi syndrome	Pigment dilution of skin and hair
Platelet disorders	Livedo reticularis, chilblain-like lesions, leg ulcers, gangrene
Consumptive coagulopathy	Skin infarcts, gangrene
Lymphocyte diseases	
Cutaneous T-cell lymphoma (Sézary syndrome)	Scaly, poikilodermic patches or plaques and infiltrated erythematous nodules, ulcers or erythroderma
B-cell lymphoma	Secondary cutaneous infiltrates (nodules or plaques) occur in late stages.
Plasma cell disease	
Multiple myeloma	Skin nodules.
Myeloma-associated systemic amyloidosis	Macroglossia, indurated purpuric, nodules or plaques
Mast cell disease	Mastocytosis sysndrome (diarrhoea, abdominal pain), urticaria pigmentosa (hyperpigmented itchy plaques with positive Darier's sign)
Cryoglobulinaemia	Cold urticaria, Raynaud's phenomenon or skin lesions resembling vasculitis
Antiphospholipid syndrome and macro or hyperglobulinaemia	Raynaud's phenomenon, livedo reticularis, purpura, skin infarcts, gangrene

skin signs of systemic diseases will work as an asset to the clinical acumen of a physician.

Neurocutaneous Disorders

The integumentary system and the nervous system are both derived from the ectoderm. Hence, it is not surprising that many nervous system disorders are associated with skin changes. Some of these neurocutaneous disorders also involve eyes and are called as phacomatosis that include genodermatoses like neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, phacomatosis pigmentovascularis, etc. Skin manifestations are obvious pointers to the correct diagnosis in this group. Other conditions where skin and nervous system may be affected simultaneously include autoimmune disorders and infections (Table 8).

Nutritional Deficiencies

Protein energy malnutrition (PEM)

Children with PEM show numerous skin changes. Kwashiorkor presents with dry, scaly skin (flaky paint dermatosis) that is oedematous and tends to crack with criss-cross fissures (crazy pavement dermatosis). The face is swollen and pale with dry skin. In marasmus, the skin is dry, thin and wrinkled. There is near-absence of subcutaneous fat with lax skin giving a wizened 'old man' look to the face. The hair are thinner and lighter in colour, sometimes with variation in colour of hair along their length (flag sign).

Phrynoderma

The skin of the elbows and knees becomes rough (toad skin) due to follicular keratoses. The conical keratotic papules with central plug are also seen over buttocks, lateral aspects of thighs and arms. Deficiency of vitamin A and essential fatty acids is causative. Night blindness and conjunctival and corneal xerosis may be associated.

Pellagra

Deficiency of niacin leads to pellagra. Most common predisposing factor for pellagra in the Indian setting is alcohol abuse, expecially in the absence of protein supplementation. However, niacin deficiency may also occur in people on a staple diet of maize or jowar. Rarely pellagra like lesions occur due to drugs (INH, ethionamide). Photosensitivity leading to brownish red erythematous patches and sharply circumscribed plaques over sunexposed areas characterise the condition. Forearms and neck are preferentially affected. Sharply outlined brownish plaques around the neck lead to the typical 'Casal's necklace'. Less frequently, bony prominences, flexures and frictional areas get affected. The tongue is smooth and red.

Riboflavin deficiency

Riboflavin causes oral, ocular and cutaneous changes. The oral mucosa is red and the tongue magenta red and smooth. The nose, eyebrows and other seborrheic areas of face show yellowish powdery scales (seborrhoea). Riboflavin deficiency commonly co-exists with pellagra in the setting of alcohol abuse.

Table 8: Neurocutaneous Disorders

Genetic disorders or nevoid anomalies	
Neurofibromatosis	Neurofibromas, Café au lait macules, iris hamartoma, gliomas, vestibular neuromas
Tuberous sclerosis	Adenoma sebaceum, ash-leaf macule, shagreen patch, mental retardation, epilepsy, cortical tubers
Cerebriform congenital	Over scalp with leptomeningeal melanocytosis melanocytic naevus
Sturge-Weber syndrome	Port wine stain, retinal and intracranial vascular malformation
Infections	
Tuberculosis	Miliary tuberculosis involving skin and nervous system
Cryptococcosis	Cryptococcal meningitis, umbilicated white papules over skin
Cytomegaloviruses (CMV) infections	Encephalitis - with perianal ulcers, CMV retinitis
Toxoplasmosis	Encephalitis and retinitis
Syphilis	Meningovascular or parenchymal involvement, tabes dorsalis, cerebral form – General paralysis of the insane (GPI)
Bacterial infection of the dangerous area of face	Cavernous sinus thrombosis
Neurocysticercosis	Cutaneous cysts in neck area, seizures
CNS haemorrhage	
Severe thrombocytopaenia	Petechiae, subarachnoid or intra-cranial bleeding
Autoimmune	
Antiphospholipid antibody syndrome	Non-inflammatory palpable purpura, seizures, abortions, positive anti-phospholipid antibodies
Systemic lupus erythematosus	Cognitive dysfunctions, seizures, early stroke, malar rash
Periarteritis nodosa	Painful subcutaneous nodules along arteries, vasculitic ulcers, peripheral neuropathy
Wegener's granulomatosis	Medium sized vasculitis affecting skin, kidney, upper and lower respiratory tract, peripheral neuropathy
Behçet's disease	Oro-genital ulcers, arthritis, positive pathergy test, meningoencephalitis, brainstem involvement, cranial nerve palsies, cerebral venous sinus thrombosis

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11.15 Leprosy

BK Girdhar

DEFINITION

Leprosy (Hansen's disease) is a chronic infectious disease caused by *Mycobacterium leprae*. The organism mainly affects the skin and the peripheral nerves.

EPIDEMIOLOGY

The case load has drastically come down with the worldwide application of multi-drug therapy. Though new patients continue to be detected, the recent (2007) prevalence rate across the globe is very small with all but four countries (Brazil, Democratic Republic of the Congo, Mozambique and Nepal) having achieved elimination, i.e. having prevalence less than one per 10,000 population. Within the India, seven states (Bihar, Chattisgarh, Jharkhand, Maharashtra, Orissa, Uttar Pradesh and West Bengal) continue to have higher prevalence of the disease and contribute two thirds of the patients.

AETIOLOGY AND BACTERIOLOGY

Leprosy is caused by *M. leprae*, a Gram-positive bacillus which is weekly acid-fast and stains bright red with carbol-fuschin.

TRANSMISSION

Man is the only natural host and reservoir of this infection, though a few animals caught in wild have been found to have the infection. It is mainly the untreated lepromatous patients who are infectious and spread the disease in the community. The route of exit of bacilli from the body is mainly from nose and mouth. Aerosol and close contact are important source of transmission. The organisms enter the healthy contacts either through microscopic breaches in the skin or more likely through upper respiratory tract, in particular the nasal mucosa.

PATHOGENESIS

The incubation period ranges from six months to more than 20 years (in most instances 2 to 5 years. In a small proportion of infected individuals (less than 1% to 5%), the disease develops due to impairment of specific cell-mediated immunity (CMI). The type of disease that the patient develops depends upon the degree of impairment of cellular immunity (**Figure 1**).

CLINICAL MANIFESTATIONS

Based on the outcome, determined by individual's specific cellular immunity, six defined types of leprosy have been classified.

Indeterminate Leprosy (IL)

This is the earliest diagnosable manifestation of the disease. The lesions are small, asymptomatic, vague macules, 1 to 3 in number and are hypopigmented, may be with mild redness (**Figure 2**). Some impairment of sensations may be found on careful testing for fine touch (with cotton wool or pointed paper) and temperature (hot and cold).

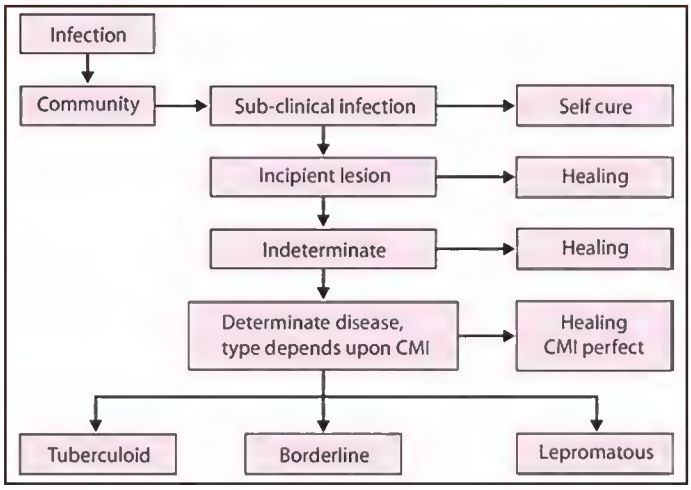


Figure 1: Pathogenesis of leprosy.

CMI = Cell-mediated immunity



Figure 2: Indeterminate leprosy: Small vague lesion on the elbow.

Tuberculoid Leprosy (TL)

This type of disease develops in those who have good CMI (**Figure 3**). Here the disease remains localised to one anatomical area with 1 to 3 patches which are usually medium to large in size and are well defined. Two types of lesions, one raised and red plaques and the other well-defined hypo-pigmented flat

macules are seen which have loss of hair, and impairment of sensations. Local or regional nerve thickening may be there. Skin smears are negative but lepromin test is strongly positive (**Table 1**).

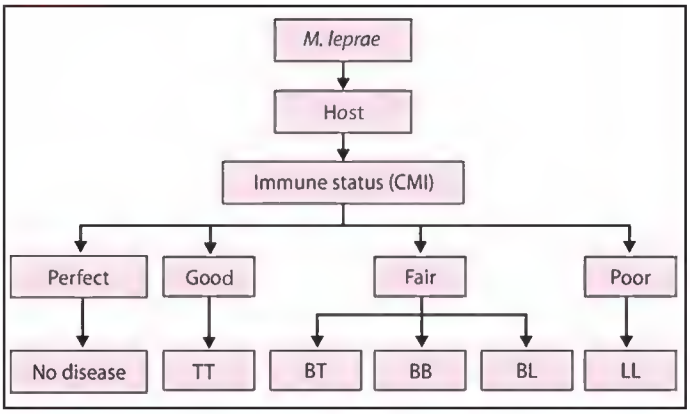


Figure 3: Conceptual representation of spectrum of leprosy.

CMI = Cell-mediated immunity; TT = Tuberculoid leprosy; BT = Borderline tuberculoid; BB = Mid borderline; BL = Borderline lepromatous; LL = Lepromatous leprosy.

(Reproduced with permission from L.K. Bhutani. Colour Atlas of Dermatology)

Lepromatous Leprosy (LL)

Lesions can be macules, plaques, and nodules which appear in generalised symmetrical fashion affecting the extensors more than the flexors (**Table 1**). Early lepromatous disease may present only as shine, due to smoothening of creases by infiltration, over the face and/or back. Papules and nodules appear on the ear, especially the rim of the external ear (**Figure 4**), forehead, cheeks and chin and on the extensors of the body. Lesions are symmetrically placed, small, ill-defined, smooth shiny and devoid of any sensory impairment.



Figure 4: Lepromatous leprosy. Infiltration with nodularity of the ear rim.

The eyebrows may be lost starting from the lateral side. In the absence of treatment, appearance of thicker infiltration in the form of nodules on the face may give the face a leonine look (**Figure 5**). Sheets of infiltration may appear on the distal parts of the extremities (**Figure 6**). There is peripheral anaesthesia of glove and stocking type (**Figure 7**).



Figure 5: Lepromatous leprosy. Leonine facies.



Figure 6: Lepromatous leprosy. Infiltration and shiny skin of hands.

In untreated cases, skin smears are positive in all sites, often with large number of organisms in all microscopic fields. In contrast to tuberculoid disease, lepromin test is uniformly negative.

Borderline Leprosy (BT, BB and BL)

This is a large group with variable and unstable immune system. Depending upon the closeness to the tuberculoid type, the patients are grouped as borderline tuberculoid (BT), while those with features more akin to the lepromatous form are designated as borderline lepromatous (BL). Patients with some manifestations of both the types are called mid borderline (BB). Lesions are relatively more localised, fewer, often larger with

Table 1: Clinical Features of Leprosy

Feature	Tuberculoid (TT)	Borderline tuberculoid (BT)	Mid borderline (BB)	Borderline lepromatous (BL)	Lepromatous (LL)
No. of lesions	1 to 3	Few	Many	Numerous	Innumerable
Distribution	Localised	Localised or distant, mostly regional	Widespread	Generalised asymmetrical	Generalised symmetrical
Size	Usually large	Usually large with satellites	All sizes	Mostly small	Small with sheets of infiltration
Margin/edge	Well-defined	Partly well-defined	Ill-defined, inner edge abrupt in annular lesions	Vague	Vague, infiltration
Surface	Dry, hair loss +	Dry, hair loss +	Some dry, some smooth	Mostly smooth	Smooth, shiny or oily
Sensations	Impaired or lost	Impaired, intact in satellite lesions	Impaired in some, intact in others	Mostly intact	Intact in lesions, peripheral anesthesia ±
Nerves thickening	Limited local and/or regional	Limited local and/or regional	Many regional or distant	Many, often symmetrical	Many, symmetrical
	Firm	Abscess ± Firm	Firm/normal	Normal/soft	Soft and smooth
Skin smears	Negative	Negative	May be positive in some lesions (+/++)	Positive, usually moderately	Positive, often highly
Lepromin	+++	+++	+/–	–	–



Figure 7: Lepromatous leprosy. Acquired ichthyosis and oedema feet.



Figure 8: Borderline tuberculoid leprosy. Well-defined erythmatous plaque with central clearing.

definite sensory impairment in patients toward the BT group (**Figure 8**) and progressively wide spread, more in number, smaller and vague with partial or no loss of sensations as one goes towards the BL type (**Figure 9**). Likewise the number of affected nerves increases and the nerves become softer with disease progression (**Table 1**).



Figure 9: Borderline lepromatous leprosy. Bilateral, small, vague erythmatous macules and plaques over the trunk.

Neuritic Leprosy (NL)

In NL there are no skin manifestations (apart from signs and symptoms of nerve damage) but only nerve thickening. There may be only one nerve thickening (mono-neuritis) or multiple nerves may be clinically involved (mono-neuritis multiplex).

ORGAN INVOLVEMENT

Organ involvement is mainly seen in patients with lepromatous type of disease.

Of the internal organs, liver and kidneys are commonly affected. Kidney involvement is common, especially in those who have had repeated attacks of type 2 erythema nodosum leprosum (ENL) reactions. Glomerulonephritis, interstitial nephritis, less commonly pylonephritis and amyloid deposits can occur resulting in proteinuria, cells and cast in the urine.

Testes being the cooler organ are frequently involved in lepromatous patients. The disease may *per se* produce testicular atrophy with loss of normal testicular sensations. Oligo/

Azoospermia and decreased testosterone levels may result in sterility and loss of libido. Acute painful orchitis may occur in some patients during reactions.

Lymphnodes may get mildly enlarged in a significant proportion of lepromatous patients.

Bone and muscle affection is seen in a small proportion of untreated lepromatous disease of many years. Specific involvement of the eyes due to bacillary spread with appearance of lepromas in the iris and cornea, resulting in insidiously appearing granulomatous uveitis and keratitis respectively, is not uncommon in patients with advanced lepromatous disease and can reduce vision partially or completely. In patients with type 2 (ENL) reaction, eyes may suddenly become painful and red. In the nose there is ulceration of the septal and turbinate mucosae, resulting in blood stained nasal discharge and crusting. Following repeated or prolonged ulceration, bone and cartilage may get affected and destroyed with consequent perforation of septum and collapse of nasal tip.

It is noteworthy that brain, spinal cord, heart, lungs and gastro-intestinal tract have not been observed to have any significant affection.

DISABILITY AND DEFORMITY

Disability means the diminished ability of a person to perform normal movements and do his/her normal work. Deformity is defined as any deviation of appearance of any part or parts of the body. Nerve damage is the main cause for the above. Deformities are called primary, if these are due to direct damage by the disease process, e.g. muscle paralysis, nasal deformity, eye damage, etc. (**Figures 10 and 11**). Secondary deformities are a consequence of sensory loss and thereby loss of tissue due to burns, trauma and secondary infection, e.g. post-burn blisters, ulcers, scars, contractures and loss of digits on hands, trophic ulcers on feet and corneal ulcers due to affection of trigeminal nerve (**Figures 12 and 13**). Disabilities occurring due to damage to various nerves are detailed in **Table 2**.

Table 2: Clinical Effects of Nerve Damage

Site	Nerves	Features
Face	Trigeminal	Loss of sensation over the face corneal anaesthesia if ophthalmic division affected
	Facial	Facial palsy. If only zygomatic branch affected – lag ophthalmos on the affected side
Hand	Ulnar	Loss of sensations and sweat over the little and medial half of ring finger. Clawing of little and ring finger initially and later of long and index fingers
	Median	Loss of sensations and sweat over the thumb, index, long and lateral half of ring fingers. Loss of abductor and opponence function of thumb and later its clawing
	Ulnar and median	Loss of sensations and sweat over whole of palm and medial half of dorsum of hand. Clawing of all fingers
	Radial	Sensory and sweating loss over lateral half of dorsum of hand. Wrist drop
Foot	Common peroneal	Loss of sensations and sweat over lower half of leg. If only superficial affected, sensory loss over dorsum of foot. Foot drop
	Posterior tibial	Loss of sensation and sweat over the sole of foot. Claw toes

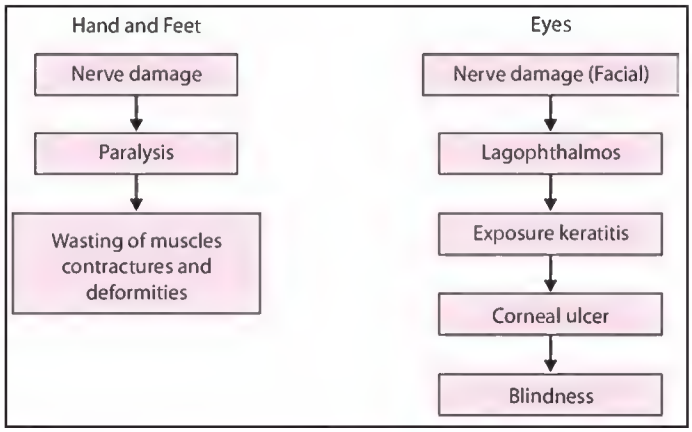


Figure 10: Development of primary disabilities.



Figure 11: Claw hand with trophic ulcers (post-burn blister, ulcers and scars).

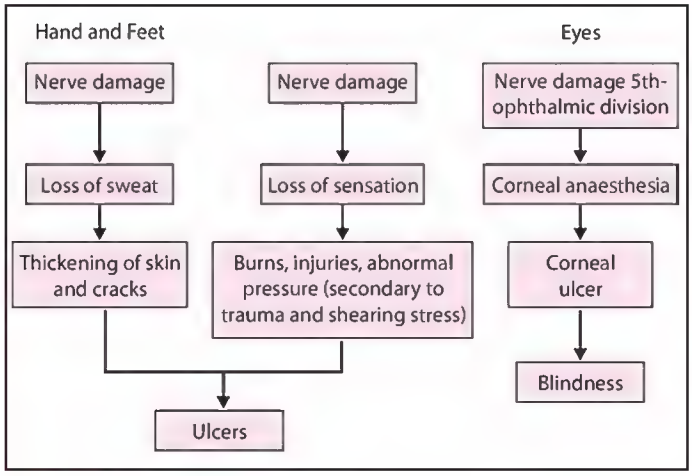


Figure 12: Development of secondary disabilities.

DIAGNOSIS OF LEPROSY

The diagnosis of leprosy is based on the following three cardinal signs: (i) hypopigmented or erythematous patch with definite impairment of sensations, (ii) involvement of peripheral nerve(s), demonstrated by palpable thickening of cutaneous (**Figure 14**) and/or regional nerve trunks and (iii) finding of acid-fast bacilli (AFB) in the skin smears from lesion. For the definite diagnosis either the first two or the third alone need to be present.



Figure 13: Trophic ulcers. Deep punched ulcers over the pressure points of fore feet.



Figure 14: Thickened greater auricular and transverse cervical nerves.

For testing pain, tip of fine ball-pen can be used. Thermal sensation can be tested using test tubes containing hot and cold water. Peripheral nerve trunks and local cutaneous nerves should be palpated for thickening, tenderness and consistency. Nerve function assessment includes, testing for sensations in the lesions and area supplied by the nerve and assessment of power in the muscles supplied by the nerve(s) (the voluntary muscle testing).

Bacteriological Examination (Skin Slit Smears)

This involve making a nick in the suspected lesion and taking a small amount of blood free dermal tissue on to a glass slide and staining the same for AFB using 5% sulphuric acid or 1% acid (hydrochloric acid) alcohol. Skin smears as above are taken from a number of sites including ear lobules and lesions. The stained slides are examined, under oil immersion for number of pink stained bacilli per field, averaging after examination of almost hundred microscopic fields. An average of at least four sites is the bacteriological index (BI). The BI reflects the quantum of bacillary load in the body. The BI, in log scale, is usually 4 to 6+ in untreated lepromatous patients, while it may be hard to find the bacilli towards the tuberculoid end.

Skin Biopsy

Histological examination is often required for confirmation of doubtful cases and for accurate classification of the disease.

Nerve Biopsy

This is required only in a very few cases, especially in those who do not have any skin signs.

Lepromin Test (Mitsuda/Dharmendra)

Lepromin test has no diagnostic value, particularly in endemic areas and where BCG vaccination is practised. Though important for assessing the degree of specific cellular immunity of the patients and useful for immunological classification, presently its role is limited to academics and research only.

Other Laboratory Tests for Diagnosis

Serological tests for leprosy (fluorescent antibody absorption test, PGL-1 antibody and monoclonal antibody based tests) are all positive in high proportion (92% to 100%) of highly bacillated lepromatous cases.

DIFFERENTIAL DIAGNOSIS

As mentioned, careful sensory testing and nerve examination in suspected cases confirms or rules out leprosy. However, in patients with hypopigmented patches/conditions like birth marks (especially, naevus achromicus), pityriasis alba, pityriasis versicolour, vitiligo, post-inflammatory hypopigmentation and lesions of post-kala-azar dermal leishmaniasis (PKDL) need to be differentiated. Nutritional deficiencies, alcoholism, diabetes and heavy metal effects should be considered in patients suspected to have leprosy. Entrapment neuropathies involving the main trunks of the limbs, including that of lateral cutaneous nerve of the thigh (resulting in meralgia paresthetica or Bernhardt's syndrome), and those of trigeminal and facial nerves may occasionally cause confusion in diagnosis.

REACTIONS IN LEPROSY

Occurrence of acute episodes in leprosy have been called reactions. Basically there is a rapid change in the host response with temporary increase in T-cell reactivity. In many patients, this is precipitated by intercurrent problems like stress, pregnancy, acute or chronic infections and anti-leprosy drugs.

Reactions occurring in borderline patients (called type 1 or reversal reactions) are mostly the result of increased cellular hypersensitivity and present as lesions becoming suddenly swollen, angry red and may even ulcerate (**Figure 15**). New lesion may suddenly appear. Nerves may become acutely painful, tender, swollen with increased nerve damage leading to motor deficit. Steroids constitute the main treatment.

In lepromatous and some BL patients, the reactions are on account of antigen-antibody (immune) complexes—either formed or deposited locally. This type of reaction is known as type 2 or ENL reaction. Patients have febrile episodes together with crops of painful red papules or plaques over the face, trunk and the extensors of the limbs (**Figure 16**). These episodes are often associated with acute neuritis, peripheral oedema, lymphadenitis, bone pains, arthritis, acute uveitis and/or orchitis. Swollen and necrotic lesions may also occur.



Figure 15: Borderline tuberculoid leprosy in type I reaction: Swollen, erythmatous and oedematous plaque.



Figure 16: Erythema nodosum leprosum (type II lepra reaction): Erythmatous tender plaques.

MANAGEMENT

Simultaneous administration of two or more drugs, called the multi-drug therapy (MDT) has been the recommended therapy since 1982 (**Table 3**). Dapsone, a sulphonamide derivative, continues to be basic drug. Clofazimine is mildly bactericidal. Having a different mode of action and anti-inflammatory properties has been recorded with this drug. The main component of MDT is rifampicin.

In addition to the above, several new compounds includes fluoroquinolones, in particular ofloxacin, sparfloxacin and moxifloxacin, minocycline.

Multi-Drug Therapy (MDT)

A combination of drugs is routinely advocated to prevent drug resistance. For the purpose of treatment, based on the quantum of the infecting organisms within the body of the patients, all leprosy patients are divided into pauci-bacillary and multi-bacillary groups. Earlier BI was taken as the guide, presently the number of skin lesions is the criteria for this classification. For field treatment, set guidelines have been provided by the World Health Organization (WHO) and adopted by the Government of India. The regimens are detailed in **Table 3**.

All other patients, lepromatous, borderline lepromatous (BL), mid-borderline (BB), borderline tuberculoid (BT) patients with more than 5 lesions are considered multi-bacillary. As expected, almost all of them show AFB positivity in skin smears, though to a variable extent. The MDT for multi-bacillary patients has been recommended for presently 12 months but the dwrofrai can be increased up to 18 months (**Table 3**).

Table 3: WHO Regimens for Leprosy

Group	Drugs	Doses (mg)			Regimens	Duration
		Adult	Children			
			6-14 (years)	0-5 (years)		
PB	Rifampicin	600	450	300	Once a month supervised	6 monthly pulses in maximum of 9 months
	Dapsone	100	50	25		
MB	Rifampicin	600	450	300	Once a month supervised	12 monthly pulses in a maximum of 18 months
	Clofazimine	300	150	100		
	Dapsone	100	50	25	Daily self-administered	
	Clofazimine	50	50 AD	50 BW		

mg = Milligram; PB = Pauci-bacillary; MB = Multi-bacillary; AD = Alternate days, BW = Twice a week

As in tuberculosis, it is mandatory that patients should be kept under surveillance following completion of regimens. This is not only to diagnose and provide care for reaction and/or nerve damage, that can occur even after completing the regimens but also to look for relapses, which are mostly late to appear. All pauci-bacillary patients, including single lesion cases, should be seen at least once a year for 2 years and all multi-bacillary patients should be followed up yearly for at least 5 years.

Management of Lepra Reactions

The type 1 reactions, which are the consequence of changes (more often increase) in cellular hypersensitivity, result in sudden increase in inflammation in skin and nerves in borderline patients. Oral corticosteroids are the mainstay for this type of reactions. An initial daily dose of 30 mg to 40 mg

prednisolone equivalent is sufficient in most cases. After 4 to 8 weeks when the condition improves, as evidenced by decrease in lesional redness and swelling, nerve pain and tenderness or improvement in sensory and motor recovery, the steroids are tapered gradually.

Type 2 (ENL) reactions are the result of local and systemic immune complex deposition or formation and are seen in lepromatous patients. As stated above, attempt should be made to identify and manage precipitating cause, if any, like concomitant infections, physical or psychological stress etc. Addressing the precipitating factors often relieves the patient of reactions. Patients having mild reactions, i.e. with only a countable few skin lesions (with or without mild fever), usually respond to rest, aspirin and/or chloroquine in 5 to 10 days. However, those with severe reactions, presenting with wide-spread skin lesions with fever, acute nerve problems, acute lymphadenitis, arthritis, periostitis, uveitis or orchitis need to be given steroids. Unlike type 1 reactions, here the steroids are required to be given in short courses and rapidly tapered off.

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11.16 Sexually Transmitted Infections

Vinod K Sharma, Naresh Jain

Sexually transmitted diseases (STDs) represent a major public health problem causing acute illness, chronic disability and long- term consequences in men, women and children. STDs have a tremendous impact at individual and community level. STDs are responsible for significant proportion of maternal morbidity, ectopic pregnancy, infant illness and death, malignancies, infertility and increased transmission of HIV infection. Sexually transmitted infections (STIs) include all STDs and other infections that may not cause clinical disease of genitals but can be transmitted by sexual intercourse, e.g. hepatitis B, HIV, HTLV-1, etc. STDs most commonly affect people aged 15 to 44 years, the most economically productive group. The emergence of HIV has led to changes in the epidemiological patterns of various sexually transmitted bacterial and viral infections. The different aetiological agents for STDs, diseases caused and complications are listed in **Table 1** and incubation period of common STDs is summarised in **Table 2**.

Table 1: Sexually Transmitted Agents and Diseases

Agents	Disease or syndrome	Complications
Bacteria		
Neisseria gonorrhoeae	Urethritis, epididymitis, bartholinitis, cervicitis, endometritis, salpingitis, proctitis, pharyngitis	Infertility, ectopic pregnancy, chorioamnionitis, premature rupture of membranes, premature delivery, conjunctivitis, PID, disseminated gonococcal infection (DGI)
Chlamydia trachomatis (D-K)	Urethritis, epididymitis, bartholinitis, cervicitis, endometritis, salpingitis, proctitis, pharyngitis	Same as in N. gonorrhoeae, except DGI, Reiter's syndrome, pneumonia
Chlamydia trachomatis (L1, L2, L3)	Lymphogranuloma venereum	Esthiomene, ano-recto-genital syndrome, proctocolitis, skin rashes, pneumonia, hepatitis, meningoencephalitis
Treponema pallidum	Syphilis-primary and/or secondary, latent neurosyphilis, cardiovascular syphilis	Abortions, dementia, death
Haemophilus ducreyi chancroid	Phimosis, sclerosis, meatal stenosis	
Calymmatobacterium granulomatis	Donovanosis	Phimosis, sclerosis, SCC
Mycoplasma hominis	Non-gonococcal urethritis, cervicitis, salpingitis	PID, post-partum fever
Ureaplasma urealyticum	Non-gonococcal urethritis, cervicitis, salpingitis	Chorioamnionitis, low birth weight
Gardnerella vaginalis and others	Bacterial vaginosis	
Group B *β-haemolytic Streptococcus*	Neonatal sepsis, neonatal meningitis	
Viruses		
Herpes simplex virus 1, 2	Primary and recurrent genital herpes	Aseptic meningitis, neonatal herpes and associated mortality or neurological sequelae, spontaneous abortion, premature delivery
Human papilloma virus	Condyloma acuminata	Laryngeal papilloma in infants, squamous epithelial neoplasia of cervix, anus, vagina, vulva and penis
Hepatitis B virus	Acute, chronic and fulminant hepatitis B	Cirrhosis, hepatocellular carcinoma
Cytomegalovirus	Infectious mononucleosis	Congenital infection, birth defects, infant mortality, cognitive impairment (mental retardation, sensorineural deafness), variable manifestations in immunocompromised host
Molluscum contagiosum virus	Genital *molluscum contagiosum*	Infection, eczematoid dermatitis, erythema annulare centrifugum
Human immunodeficiency virus	AIDS and related conditions	Opportunistic infections, death
Human T-lymphotropic virus	T-cell leukaemia, lymphoma, tropical spastic paraparesis	Death
Protozoa		
Trichomonas vaginalis	Urethritis, balanitis, vaginitis	
Fungus		
Candida albicans	Vulvovaginitis, balanitis, balanoposthitis	
Ectoparasites		
Phthirus pubis	Pubic lice infestation	
Sarcoptes scabiei	Scabies	Norwegian scabies in immunocompromised host

Table 2: Incubation Period of Common STDs

STDs	Incubation Period (mean)
Primary chancre	9 to 90 days (21 days)
Chancroid	One to several weeks (5 to 8 days)
Donovanosis	9 to 50 days (17 days)
Lymphogranuloma venereum	5 to 30 days (10 days)
Herpes genitalis (primary)	5 to 7 days (5 days)
Genital warts	1 to 8 months (3 months)
Gonococcal urethritis	1 to 14 days (2 to 5 days)
Non-gonococcal urethritis	7 to 21 days (10 days)

Syphilis, herpes genitalis and anogenital warts are discussed in separate chapters.

CHANCROID

Aetiology

Chancroid is a sexually transmitted ulcerative disease associated with inguinal adenitis (bubo) caused by *Haemophilus ducreyi*, a Gram-negative, facultative anaerobic bacillus, arranged in chains of 2 to 4 giving the typical appearance of a *'school of fish or rail road track'. H. ducreyi* is a fastidious organism and culture is difficult.

Epidemiology

Chancroid is most common in many of the world's poorest regions, such as areas of Africa, Asia, and the Caribbean. The prevalence of chancroid is higher in lower socioeconomic groups.

Clinical Features

After an incubation period that ranges from 1 to 14 days, a small inflammatory papule surrounded by erythema develops on genitalia, which rapidly progress to pustules followed by ulceration. The ulcers are multiple, painful, sharply circumscribed with ragged undermined edge (**Figure 1**). The ulcer base is composed of granulation tissue that bleeds on manipulation. Characteristically, the base of the ulcer is non-indurated. The ulcers are located primarily on the prepuce, frenulum or glans penis in males and labia, fourchette and cervix in females. Unilateral painful inguinal adenitis (bubo) in 30% to 60% of the patients within 1 to 2 weeks of the development of ulcer. The nodes become enlarged, tender and then matted.

Diagnosis

Besides the clinical clues, the main tool for definite diagnosis for chancroid is bacterial culture of *H. ducreyi* and direct examination of *H. ducreyi* from the genital ulcer by Gram-stain. Polymerase chain reaction (PCR) and indirect immunofluorescence using monoclonal antibodies are recent techniques. Histopathological examination also helps in the diagnosis.

Treatment

Azithromycin 1 g orally in a single dose or ceftriaxone 250 mg intramuscularly in a single dose or ciprofloxacin 500 mg orally twice a day for 3 days or erythromycin base 500 mg orally three times a day for 7 days. Ciprofloxacin is contraindicated for pregnant and lactating women. Fluctuant bubo should be aspirated using a wide bore needle. In the presence of bubo, the antimicrobial agents may have to be continued for a longer period till the bubo heals. Sexual contacts within 10 days before the onset of patient's symptoms should be examined and treated, even in the absence of symptoms in view of the known asymptomatic carriage.

Follow-up

After starting the treatment, patients should be reviewed at day 3 and day 7.

DONOVANOSIS

Aetiology

Donovanosis (*granuloma inguinale*) is indolent, progressive, ulcerative and granulomatous skin disease caused by *Calymmatobacterium granulomatis*. The organism has an appearance similar to a safety pin.

Epidemiology

Donovanosis is endemic in tropical and subtropical regions. In India donovanosis is endemic along the East Coast, i.e. Orissa (7.5%), Andhra Pradesh (1.12%) and Tamil Nadu (4.7%).

Clinical Features

The incubation period may range from 3 days to 3 months. The primary lesion may be a skin-coloured to erythematous papule, which ulcerates to form well-defined granulomatous ulcer (**Figure 2**). The ulcer is usually painless, beefy-red in colour and bleeds easily on touch. In men, the penis, scrotum and glans are most commonly affected and in females, the labia minora, mons-veneris and fourchette are most common sites. True adenopathy is rare. The disease spreads by satellite inoculation and daughter lesions and thereby these spread slowly to the inguinal region where it can mimic a bubo (pseudobubo).



Figure 1: Chancroid-ulcer with ragged edges.



Figure 2: Donovanosis-fleshy ulcer.

During its progression it leads to the destruction of lymphatics resulting in lymphoedema and elephantiasis of the genitalia. Persistent untreated lesions over years can lead to malignant transformation.

Diagnosis

Besides history and clinical appearance, a touch or crush preparation stained with Wright's or Giemsa's stain from a punch biopsy specimen which shows deeply staining, bipolar, safety pin rods in the cytoplasm of macrophages (Donovan bodies). The culture of organism is difficult but PCR can help in the diagnosis.

Treatment

Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed. Azithromycin 1 g orally once per week or ciprofloxacin 750 mg orally twice a day or erythromycin base 500 mg orally four times a day or trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day are alternatives. Therapy should be continued for at least 3 weeks and until all lesions have completely healed. All sex partners (within 60 days of onset of patient's symptoms) should be examined and offered therapy.

Follow-up

Review is preferably monthly for first 3 months.

LYMPHOGRANULOMA VENEREUM

Aetiology

Lymphogranuloma venereum (LGV) is a sexually transmitted disease affecting primarily the lymphatic system, caused by *Chlamydia trachomatis* serovars L1, L2 and L3. *Chlamydia* are Gram-negative, intracellular, obligate parasites, measuring from 0.3 to 1.0 micron in size.

Epidemiology

LGV has a worldwide distribution but is endemic in India and South-East Asia.

Clinical Features

The incubation period is usually around a week (3 to 12 days). The portal of entry and the initial symptoms are determined by the nature of sexual act. The clinical features can be divided into primary stage, secondary (inguinal stage) and a tertiary stage (complications).

Primary Lesion

The primary lesion is 5 to 8 mm soft, erythematous, painless erosion that heals spontaneously in a few days.

Inguinal Syndrome (Bubo)

Secondary inguinal lymphadenopathy (bubo) begins 1 to 2 weeks after the primary lesion as discrete, movable, tender nodes that later coalesce to form a firm, fist-sized, elongated, immovable mass. Nodes are bilateral in one-third of cases. These may occur above and below Poupart's ligament, giving rise to the "groove" sign. Rupture of the lymph nodes leads to chronic sinus formation. At time of rupture of the bubo, patients might have constitutional symptoms.

Anogenital Rectal Syndrome

Early manifestation of this disease is mucoid rectal discharge following over weeks to months by fever, rectal pain and tenesmus. At this stage they have multiple superficial ulcers with irregular borders. As the disease progresses, crypt abscesses and fistulas are formed resulting in rectovaginal fistula, fistula in ano, etc. Ultimately they heal with fibrosis and lymphatic obstruction, resulting in rectal stricture and lymphoedema of the genitals (ram-horn penis, saxophone penis) leading to genital elephantiasis (esthiomene). Carcinoma of the rectum develops in 2% to 5% cases of rectal stricture due to LGV. The ano-rectal syndrome is more common in women.

Diagnosis

LGV can be confirmed by: (i) serological procedures like complement fixation test, counter immunoelectrophoresis, radio immunoprecipitation test, etc.; (ii) demonstration of chlamydial antigens by immunofluorescence; and (iii) isolation of *Chlamydia* by tissue culture.

Treatment

Treatment cures infection and prevents ongoing tissue damage. Buboes might require aspiration through intact skin or incision and drainage to prevent the formation of inguinal/femoral ulcerations.

Recommended regimen to doxycycline 100 mg orally twice a day for 21 days, or alternatively, erythromycin base 500 mg orally four times a day for 21 days.

Sexual contacts within the 60 days before the onset of patient's symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated with standard *Chlamydia* regimen (azithromycin 1 g orally stat or doxycycline 100 mg orally twice a day for 7 days).

Follow-up

Patients should be followed clinically until signs and symptoms have resolved. Differential diagnosis of genital ulcer disease is discussed in **Table 3**.

URETHRITIS

Urethritis, inflammation of the urethra can be classified into two types—gonococcal and non-gonococcal urethritis. The former is caused by *Neisseria gonorrhoeae*, a Gram-negative intracellular diplococci and it measure 1 to 2 μ in size. The adjacent surface of the cocci is flattened and long axis of the bean-shaped organisms are parallel. They are cultured on Thayer-Martin medium. Non-gonococcal urethritis is caused by variety of organisms, *Chlamydia trachomatis* being the most common. Other organisms that are responsibile for non-gonococcal urethritis are *Ureaplasma urealyticum, Mycoplasma, Trichomonas vaginalis, Candida albicans,* HSV, etc.

Epidemiology

The disease is spread mainly by sexual activity. The commercial sex workers are the main source of infection in a developing country like India. Urethritis constitutes 14% to 20% of patients attending STD clinic in India.

Clinical Features

After a period of 2 to 10 days of exposure, the disease manifests as acute burning sensation of urethra with copious purulent discharge. Approximately 25% of males will develop gonorrhoea after a single exposure. Meatal erythema, dysuria,

Table 3: Clinical Features of Common Genital Ulcer Disease

Characteristics	Syphilis	Herpes	Chancroid	LGV	Donovanosis
Primary lesions	Papule	Vesicle	Pustule	Papule, pustule or vesicle	Papule
Number of lesions	Usually one but in 1/3 more than 1	Multiple and may coalesce	Usually multiple and may coalesce	Usually one	Variable
Diameter	5 to 15 mm	1 to 2 mm	Variable	2 to 10 mm	Variable
Edges	Sharply demarcated elevated, round or oval	Erythematous, polycyclic	Undermined, ragged, irregular	Elevated round or oval	Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Smooth non-purulent covered with serious exudates	Erythematous	Purulent, bleeds easily	Variable	Red and velvety, bleeds readily
Induration	Button-like	None	Soft	Occassionally firm	Firm
Pain	Uncommon, but tender on firm pressure	Frequently tender	Usually very tender	Variable	Uncommon
Lympha-denopathy	Firm, non-tender, bilateral, and in 1/3 cases it may be tender	Firm, tender, often bilateral with initial episode	Tender, may suppurate, loculated, usually unilateral, occasional cord like lymphangitis	Tender, may suppurate, loculated usually unilateral	None, may be pseudobuboes
Recurrence	No	Yes, in 80%	No	No	No

Adapted from: Sharma VK, Kumar U. Sexually Transmitted Diseases; 2nd edition. New Delhi: Viva Books; 2009. Table 45.3; Page 771.

abnormal bleeding or increased discharge can be seen in females. In addition to urethritis, 1% of male patients develop other complications like tysonitis, periurethral abscess, Cowperitis, epididymorchitis and prostatitis. Disseminated form is seen in immunocompromised patients. Complications like pelvic inflammatory disease, bartholinitis, perihepatitis, and urethral strictures can develop.

Non-Gonococcal Urethritis

Non-gonococcal urethritis (NGU) can occur alone or more often (45%) in association with gonococcal urethritis. They present after a long incubation period of 3 weeks. The symptoms are mild and they have scanty mucopurulent/mucoid discharge. In females, untreated NGU can lead to pelvic inflammatory disease with its consequences.

Diagnosis

Gram stained preparation helps in the diagnosis and in distinguishing between gonococcal and non-gonococcal urethritis. A diagnosis of urethritis is made if there were more than 5 pus cells present per high power field (1 x 1000). In case of gonococcal urethritis, there are sheets of pus cells with Gram-negative intracellular dipococci. In case of non-gonococcal urethritis, there are only scanty pus cells with no intracellular Gram-negative diplococci.

Treatment

Uncomplicated gonococcal infections of the cervix, urethra, and rectum – ceftriaxone 125 mg IM in a single dose or cefixime 400 mg orally in a single dose or ciprofloxacin 500 mg orally in a single dose or ofloxacin 400 mg orally in a single dose or levofloxacin 250 mg orally in a single dose *plus* treatment for *Chlamydia*, if chlamydial infection is not ruled out (Cap. Doxycycline 100 mg bid for 7 days or tab. erythromycin 500 mg qid for 7 days).

HIV and STDs

Sexually transmitted diseases and HIV infection have a symbiotic relationship. Genital ulcer increases the acquisition of HIV infection 2 to 5 times. Because of large ulcerated area and the presence of inflammatory CD4+ cells, which act as receptors of HIV, the genital ulcers (**Figure 3**) provide an ideal route for transmission by shedding HIV virus. On the other hand, HIV infection by immunosuppression can lead to large, non-healing genital ulcers or treatment resistant genital ulcers. Clinical features and treatment of different STDs with HIV are summarised in **Tables 4 and 5**.

Table 4: Variations in Syphilis Presentation in Individuals with HIV Infection

Clinical finding	
Primary syphilis	Painless ulcer becomes painful due to superinfection, giant chancre, multiple ulcers (in up to 25%)
Secondary syphilis	Lues maligna — secondary syphilis with vasculitis manifested by fever, malaise, headache, nodules, indurated plaques with ulceration is more frequent
Latent and tertiary syphilis	Shorter latent period with rapid progression to tertiary disease within the first year of infection
Serological response to syphilis	VDRL and treponemal antibody test in blood and CSF may be false negative due to prozone phenomenon. Failure to drop VDRL titers by one year despite adequate treatment (serofast phenomenon)
Diagnosis	If VDRL is negative, dark field microscopy, biopsy of the lesion and direct fluorescent antibody staining of material from the lesion of polymerase chain reaction may be helpful
Treatment	Syphilis treatment is relatively unchanged in HIV co-infected patients, but regular follow-up is required because of increased rates of treatment failure

Adapted from: Kar HK. Sexually Transmitted Diseases; 2nd Edition. New Delhi: Viva Books; 2009. Table 11.2; Page 224.

Table 5: Variations in Other STDs Presentation in Individuals with HIV Infection

Chancroid	
Clinical findings	Genital ulcers tend to be larger and persist longer. Multiple inguinal buboes. Frequent occurrence of giant and phagedenic ulcer
Treatment	Treatment failure can occur with single-dose therapy with azithromycin and ceftriaxone, so erythromycin, 500 mg 6 hourly for 7 days is preferred
Herpes genitalis	
Clinical findings	As immunosuppression progresses,lesion may persist or progress to chronic enlarged painful non-healing ulcers with raised margin, ulcer may bleed
Treatment	Treatment might be extended if healing is incomplete after 7 to 10 days of therapy.For severe HSV disease, initiating therapy with acyclovir 5 to 10 mg/kg body weight IV every 8 hours might be necessary. Suppressive therapy includes acyclovir 400 to 800 mg bid or tid
Granuloma inguinale	
Clinical findings	Lesion may be larger,extensive,pseudobubo formation which may burst producing ulceration; slow response to the treatment
Treatment	Doxycycline 100 mg orally bid or erythromycin 500 mg orally qid for 2 to 3 weeks. If no improvement, add gentamicin 1 mg/kg intravenously
LGV	
Clinical findings	Acute inflammation with bilateral inguinal bubo which may burst into ulceration
Treatment	Same regimen (doxycycline, 100 mg orally bid or erythromycin, 500 mg orally qid for 21 days, but prolonged therapy may be required

Adapted from: Kar HK. Sexually Transmitted Diseases; 2nd edition. New Delhi: Viva Books; 2009. Table 11.3; Page 229.

SYNDROMIC APPROACH TO STD MANAGEMENT

The main motive under this approach is to diagnose and treat patients on the basis of groups of symptoms or signs



Figure 3: Non-healing ulcer of genital herpes in a HIV-positive patient.

(syndrome) rather than for a specific STD. A genital ulcer, which is a symptom of both chancroid and syphilis, is treated for both chancroid and syphilis in an area where both are prevalent. The urethritis is treated by covering for both gonococcal and chlamydial infection. The '4C's of syndromic approach are counselling, condom usage, compliance and contact tracing. The main drawback of syndromic approach is wastage of resources, use of multiple drugs and development of drug resistance. As laboratory tests are expensive, time consuming and not available at the primary level, the syndromic approach is validated. It also helps in prompt treatment of STD at primary health centre and reduce transmission of STDs including HIV infection.

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11.17 Premalignant Conditions and Malignant Tumours of the Skin

Arun C Inamadar, Aparna Palit

INTRODUCTION

Premalignant and malignant skin lesions are commoner among white races. Malignancies like primary cutaneous melanoma are extremely rare among Indians.

Exposure to solar and artificial ultraviolet rays (UVRs) and contact with carcinogenic chemicals are few of the predisposing factors for development of cutaneous malignancies.

Genetic susceptibility to the development of skin malignancies is well known. High-frequency, low-penetrant genes are responsible for sporadic occurrence of skin cancers whereas rare, low-frequency, high-penetrant genes are associated with familial cancer predisposition syndromes. Immunosuppressed state [organ-transplant recipients and human immunodeficiency virus (HIV) infection] confers a susceptibility to non-melanoma skin cancers.

Common premalignant skin lesions are actinic keratosis and leucoplakia.

ACTINIC KERATOSIS

These are hyperkeratotic lesions with malignant potential occurring on photodamaged skin of elderly individuals.

Fair-skinned outdoor workers are common sufferers and occurrence is directly related to the degree of UVR exposure. The common sites are scalp, face and dorsa of hands. The lesions are multiple, asymptomatic, brownish macules or papules (1 mm to >2 cm) with rough, scaly surface. There may be pain and traumatic bleeding.

Histopathologically there are features of dysplasia. Many lesions may undergo spontaneous resolution or may progress (< 0.1%) to invasive squamous cell carcinoma (SCC). Management includes restricting outdoor activities, use of sunscreen and destruction of existing lesions with 5-fluorouracil (5-FU) cream, cryotherapy or photodynamic therapy.

LEUCOPLAKIA

Leucoplakia is a white patch or plaque on the mucous membrane which is not removable by rubbing, cannot be attributed to any specific underlying cause by its morphology and requires a diagnosis by exclusion (WHO). Some leucoplakias have premalignant potential and may slowly progress to malignancy (2 to 5%) over several years.

Various causes of leucoplakia have been presented in **Table 1**. It is common in elderly with an incidence rate of about 1%. Oral mucosa is the most common site, involving palate, tongue or floor of the mouth. Clinically the lesions are asymptomatic diffuse, speckled or striated, fixed white plaques with or without reddish reticulation on the surface (erythroplakia).

All lesions should be biopsied to rule-out dysplasia. Moderate to severe dysplasia indicate higher risk for malignancy. Such lesions should be managed by topical bleomycin (0.5%), surgical excision or laser ablation. Risk factors must be avoided.

Table 1: Causes of Leucoplakia

Aetiology	Types	Risk of malignancy
Infective origin	Chronic Candidal leucoplakia	Increased risk but malignancy uncommon
	Syphilitic leucoplakia (tertiary stage)	Rare condition, high malignant potential
	Oral hairy leucoplakia (Epstein Barr virus)	Malignancy not recorded
	Leucoplakia associated with chronic renal failure (Epstein-Barr virus)	Slow progression to SCC over decades
	Proliferative verrucous leucoplakia (Human Papilloma virus)	
Chronic irritation	Smoking Tobacco chewing Chewing of Betel leaves and areca nut Snuff-dipping	Higher risk, but rare
Idiopathic	—	—
Paraneoplastic (in association with internal malignancy)	May occur in association with visceral malignancies, specially those of upper aerodigestive tract.	—
In association with genetic disorders	Dyskeratosis congenita Olmsted syndrome	

MALIGNANT EPIDERMAL TUMOURS

Common malignancies of epidermal origin are SCC, basal cell carcinoma (BCC) and primary cutaneous melanoma. These skin tumours constitute part of some of the genodermatoses like Bloom's syndrome, xeroderma pigmentosum (XP), Gorlin's syndrome, Muir-Torre syndrome, Bazex's syndrome, etc.

Squamous Cell Carcinoma

Cutaneous SCC is the malignant proliferation of the epidermal keratinocytes.

Aetiopathogenesis

Exogenous risk factors for SCC include chronic exposure to UVR, carcinogenic chemicals like tar, arsenic and physical agents like ionising and thermal radiation. Latent infection with human papilloma virus is a factor precipitating SCC.

Clinical features

The sites of predilection are photodamaged areas of face and neck, burn scar, keloid, non-healing ulcer, existing pre-malignant lesions or any site with long-term infection (lupus vulgaris) or inflammation. It starts as indurated areas or irregular, raised, painless nodules on such lesions. It enlarges rapidly with variegated/ulcerated surface, bleeding easily. In late stage, the lesion becomes cauliflower-like (**Figure 1**) and malodorous.



Figure 1: Cauliflower like fungating lesion of squamous cell carcinoma.

There are regional and distant lymphadenopathies. Visceral metastasis occurs through lymphatics.

Clinical variants

Intraepidermal, *in situ* SCC with a small potential for invasiveness are Bowen's disease and erythroplasia of Queyrat on genitalia. In India (Kashmir), prolonged contact with Khangri (pot with coal fire) in winter season is one of the precipitating factors causing SCC on abdominal wall (Khangri cancer). SCC that arises from chronically scarred skin is known as Marjolin ulcer.

Key diagnostic points

Histopathologically, the lesions may be well-differentiated (individual cell keratinisation and horny pearls), or poorly differentiated (anaplastic keratinocytes invading the dermis; "windblown" appearance).

Differential diagnosis

Early lesions of SCC may be mistaken with actinic keratosis or BCC.

Treatment

Treatment include topical 5-FU, photodynamic therapy, Mohs micrographic surgery, surgical excision with wide margin (high-risk lesions <1 cm and any lesion >2 cm), radiotherapy, chemotherapy or combination of these.

Basal Cell Carcinoma

BCC is the most common cutaneous malignancy worldwide, accounting for about 90% of malignant tumours. Commonly known as rodent ulcer, it arises from basal cells of the epidermis. It is locally invasive and metastasises very rarely.

Aetiopathogenesis

Predisposing factors include exposure to UVR [mostly ultraviolet B or medium wave (UVB)], occupational contact with tar, pitch and ingestion of arsenic. UV-induced mutations in the *TP53* tumour-suppressor gene (chromosome 17p), have been implicated in some cases of BCC. Multiple, early onset BCC may be seen in familial cancer syndromes.

Clinical features

It occurs in the elderly, fair-skinned individuals, predominantly in the periorbital region (lower eyelid 70%, followed by inner canthus, upper eyelid and outer canthus). The initial lesion is a small, raised, translucent, pearly papule with or without pigmentation and prominent blood vessels. These are slow growing with a rolled-out border, gradually destroying the underlying tissue (**Figure 2**). Neglected, advanced lesions may invade eye, underlying lacrimal duct and sinuses, facial and skull bones and even meninges, known as 'ulcus terebrans' (penetrating ulcer).



Figure 2: Large lesion of basal cell carcinoma with rolled-out border and distortion of inner canthus of eye.

Clinical variants

Various morphological patterns of BCC include:

- Noduloulcerative (most common)
- Cystic
- Morphoeic (cicatricial)
- Superficial spreading (multicentric)
- Pigmented.

Key diagnostic point

Histopathological picture includes islands of dark blue basal cells with peripheral palisading, invading the dermis. Mitotic figures and apoptotic bodies are seen in plenty.

Differential diagnosis

The lesions have to be distinguished from keratoacanthoma, early SCC, seborrhoeic keratosis and melanoma.

Treatment

Different treatment modalities for BCC are topical imiquimod (5%) cream, 5-FU, interferon-α, surgical excision, Mohs micrographic surgery, radiotheraphy, cryotherapy, curettage, cautery and photodynamic therapy. There are chances of recurrence or appearance of new lesions.

Cutaneous Malignant Melanoma

This is a malignant tumour of epidermal melanocytes resulting from UVR exposure in genetically susceptible individuals. This malignancy occurs exclusively among white races. There is a gradual increase in melanoma in Australia, New Zealand and different parts of United States. Primary cutaneous melanoma is extremely rare in Indian skin.

Aetiopathogenesis

Intermittent, unaccustomed or recreational solar exposures are the risk factors for cutaneous melanoma rather than chronic exposure. Other risk factors include positive family history (2%), presence of multiple benign melanocytic naevi and past history

of melanoma. Mutation of the tumour suppressor gene *CDKN2A* (chromosome 9p21) is found in 10 to 30% patients, particularly in familial cases. Mutation of *CDK4*, melanocortin 1 receptor (*MC1R*) gene (chromosome 17) polymorphism and presence of oncogene *BRAF* are other susceptibility factors.

Clinical variants

- Superficial spreading melanoma (most common),
- Nodular melanoma (rapid growth, poor prognosis)
- Lentigo maligna melanoma (Hutchinson's lentigo)
- Acral lentiginous melanoma (Darker races)
- Subungual melanoma
- Mucosal melanoma
- Secondary melanoma without detectable primary site.

Clinical features

Common body sites involved are the trunk in men and lower legs in women. This malignancy affects younger people than other cutaneous carcinomas. Head and neck melanoma may result from cumulative solar exposure in older people.

In nodular melanoma, melanin pigment may be sparse. Lentigo maligna melanoma is very slow-growing, occurring on the face of elderly patients as brownish-black, irregular, flat lesions. Acral lentiginous melanoma occurs on palms and soles as a central raised area surrounded by a pigmented macule. Subungual melanoma is commonly misdiagnosed as other benign conditions and definitive diagnosis is usually late.

Key diagnostic points

A naevus with erratic behaviour (increased size, change in shape/colour) is suspicious. The 'ugly duckling' sign, as proposed by some French authors is that 'a naevus different from its 'brother' naevi can be a melanoma'. Suspected lesions should be biopsied with 1 to 2 mm of surrounding clinically normal skin. Histopathologically, invasion of the dermis by malignant melanocytes is the diagnostic feature.

There are systems to aid clinical diagnosis of melanoma; the American ABCDE (A = asymmetry, B = irregular border, C = irregular colour, D = diameter >1 cm, E = evolution) and Glasgow seven-point check-list are commonly used. The latter includes 3 major and 4 minor features as follows:

Major features:

- Change in size
- Change in shape
- Change in colour.

Minor features:

- Diameter more than 5 mm
- Inflammation
- Oozing/bleeding
- Mild itching/altered sensation.

In adult patients, presence of one major feature is an indication of removal of the lesion, and additional minor features are additive to the clinical suspicion.

Pathological prognostic guides include depth of invasion of tumour cells as expressed by the:

- Breslow's tumour thickness (distance between granular layer and the deepest invasive area of primary lesion in mm).
- Clark's levels (five levels, starting from *in situ* to invasion into fat, indicating extent of penetration of primary lesion).

Several prognostic factors in cutaneous melanoma have been presented in **Table 2**.

Table 2: Prognostic Factors in Primary Cutaneous Melanoma

Factors	Prognosis
Clinical	
Age	Increasing age, worse prognosis
Gender	Female, better prognosis
Location of tumour	Proximal extremity lesions have better prognosis than trunk lesions. Those on head, neck and acral location have worst prognosis
Histopathological	
Cell type	Presence of amelanotic cells, signet ring cells, naevoid cells and small cells indicate worse prognosis Spindle cells have better prognosis
Cellular atypia	Marked cellular atypia worsens prognosis
Angiotropism, vascular invasion and neurotropism	Presence of any of these factors worsens prognosis
Ulceration	Worsens prognosis
Mitotic figures	Increased mitotic figures, worse prognosis
Tumour vascularity	Increased vascularity, worsens prognosis
Breslow's tumour thickness	Increasing thickness, worse prognosis
Clark's level	Increasing level, worse prognosis
Radial and vertical growth phase	Vertical growth is worse than radial growth
Tumour volume	Higher tumour volume, worse prognosis

Differential diagnosis

Benign melanocytic naevi in young adults and seborrhoeic and actinic keratosis in older age group are to be differentiated from melanoma.

Treatment

Tumour node metastasis (TNM) staging system is followed to make decisions on treatment.

Management includes surgical excision, sentinel lymph node biopsy in case of thicker primary lesion and adjuvant chemotherapy/radiotherapy in the advanced stage of disease. Primary preventive measures include awareness campaigns regarding sun protection and identification of early lesions.

Several vaccines for melanoma are in the process of development. These are used in affected melanoma patients instead of prophylactic use. Interferon α 2b and anti-CTLA-4 antibody (iplimumab, ticlimumab) are under trial for the treatment of melanoma.

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11.18 Therapy of Dermatological Diseases

MK Singhi

Dermatology, as with all fields of medicine, is continuously evolving. Introduction of newer drugs, surgical procedures and lasers have revolutionised the treatment of various skin diseases. Dermatological therapies can be divided in three parts:

1. Topical therapy
2. Systemic therapy
3. Surgery

TOPICAL THERAPY

Topical therapy remains the mainstay for the treatment of most of skin diseases. Treatment by topical methods lead to intimate contact between the drug and skin and the risk of systemic side-effects is minimised. In topical therapy the drug is first incorporated into a vehicle before application. A clinician must know the appropriate vehicle that should be used for a particular dermatosis. **Table 1** gives the vehicles used in dermatology.

Wet Therapy

Wet dressings and baths are used to clean the wounds and for dressing purposes. A wide variety of solutions are used for these purposes, viz. aluminium acetate lotion, Burow's solution, Eusol, and potassium permagnate solution.

TOPICAL STEROIDS

Topical steroids are the most widely used therapeutic agents for the treatment of inflammatory skin disease (**Table 2**).

Mechanism of Action

Topical corticosteroids (TCS) are known to act in four ways:

Anti-inflammatory and immunosuppressive effects

TCS reduce the recruitment of neutrophils and monocytes in the affected area and inhibit phagocytosis. They also inhibit capillary proliferation, fibroblast proliferation, collagen deposition. They also cause inhibition of phospholipase A_2 and thereby decreasing the formation of prostaglandins and leukotrienes and hence decreasing the inflammatory process.

Antimitotic effects

TCS affect cell differentiation and have been found to be antimitotic to several tissues.

Table 1: The Various Vehicles and their Use

	Ointments	Creams	Gels	Lotions
Composition	Water in oil emulsion	Oil in water emulsion	Semisolid emulsion in alcohol base	Powder in water (sometimes oil)
Potency	Strong	Moderate	Strong	Low
Hydration property	Hydrating	Some hydration	Drying	Drying
Sensitisation risk	Very low	High	High	High
Irritation risk	Low	Low	High	Moderate
Used on body sites	Non-intertriginous	All sites	Hairy areas	Intertriginous, scalp
Stage of dermatitis treated	Chronic	Acute to subacute	Acute to subacute	Acute

Table 2: Potency of Topical Corticosteroids (TCS) and Considerations for their Use

Potency	Type of dermatoses	Amount of TCS and duration of usage	Location of dermatoses	Usage in children	State of epidermis
Superpotent Clobetasol Halobetasol	Dermatosis resistant to high potency TCS	Use TCS for short duration and avoid extensive application (>50 gm/week)	Do not use on atrophogenic area such as face, axillae, groins and submammary area	Avoid use in children <12 years of age	Best for thick, lichenified or hypertrophic skin, avoid with thin skin
High potency Halcinonide Betamethasone Mometasone Methylprednisolone	Severe	Use TCS for short duration and avoid extensive application (>50 gm/week)	Do not use on atrophogenic area such as face, axillae, groins and submammary area	Avoid use in children <12 years of age	Best for thick, lichenified or hypertrophic skin, avoid with thin skin
Medium potency Hydrocortisone butyrate Triamcinolone acetonide Fluocinolone	Moderate	Used for extensive use in adults	Best on trunk and extremities	Do not use for extended periods (1 to 2 weeks only)	Use for short duration on thin skin, less effective on thick skin
Low potency Desonide Hydrocortisone	Steroid sensitive	Used for treatment of large areas and for long-term use	Best choice for atrophogenic area	Best for infants and children	Best for thin skin, not effective on thick skin

Vasoconstrictor effect

TCS inhibit histamine, bradykinin and prostaglandins and potentiate norepinephrine leading to vasoconstriction. This vasoconstriction potentiates anti-inflammatory effect.

Effects on mast cells and immediate reactivity

TCS on prolonged use decrease the histamine content of the mast cells. Histamine levels did not decline until after 3 weeks of treatment.

Indications of Topical Corticosteroids

- Dermatitis and papulosquamous disorders such as atopic dermatitis, lichen planus, lichen simplex chronicus, psoriasis.
- Bullous dermatoses such as bullous pemphigoid, pemphigus foliaceous.
- Behcet's syndrome, vitiligo, sarcoidosis, alopaecia areata.

Adverse Effects of Topical Corticosteroids

Systemic

- Suppression of hypothalamic-pituitary-adrenal axis
- Cushing syndrome
- Growth retardation in children

Local

Epidermal atrophy- shiny, wrinkled skin with hypopigmentation, telangiectasia, striae, purpura.

Hypertrichosis, contact dermatitis, folliculitis, increased susceptibility to infections, perioral dermatitis, rosacea, acne, delayed wound healing, glaucoma, cataracts.

TOPICAL ANTIBACTERIALS IN DERMATOLOGY

Topical antibiotics are divided into two categories – drugs used for wound care and drugs used for acne and rosacea. Topical use helps to achieve high local drug concentration with minimal systemic absorption, thereby reducing adverse effects.

Drugs used for wound care include bacitracin, neomycin, gentamicin, silver sulphadiazine, mupirocin, fusidic acid and nadifloxacin. They are used for wound care, skin infections such as impetigo, folliculitis, burns, leg ulcers, bruises and lacerations.

Topical drugs used for acne and rosacea include benzoyl peroxide, clindamycin, erythromycin, clarithromycin, metronidazole, azelaic acid. Benzoyl peroxide (BP) is non-specific oxidising agent, is bactericidal for *Propionibacterium acnes* and decreases inflammation of acne lesions. Combination therapy of BP with topical antibiotic is more effective and decreases antibiotic resistance. BP may cause erythema, burning, peeling and dryness and may cause bleaching of hair and clothes. Metronidazole is indicated in the treatment of rosacea.

ANTIFUNGALS

Various antifungals used in dermatology, their mechanism of action and spectrum are listed in **Table 3**.

TOPICAL AND INTRALESIONAL ANTIVIRALS

Antiviral drugs used in dermatology are divided into three main categories-viricidal drugs, immunoenhancing drugs and cytodestructive drugs. The major drugs in these categories are listed in **Table 4**.

TOPICAL RETINOIDS

Retinoids are a group of compounds that have biological activity as that of vitamin A. Topical retinoids currently used in india are tabulated in **Table 5**.

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids are synthetic derivatives of the natural steroid, cortisol, which is produced by the adrenal glands. They are called 'systemic' steroids if taken by mouth or given by injection as opposed to topical corticosteroids, which are applied directly to the skin (**Table 6**).

Mechanism of Action

Corticosteroids bind to the receptor on the cell membrane, translocate to the nucleus and act as agonist or antagonist to multiple genes. They inhibit NFκB and AP-1 genes leading to decreased production of multiple cytokines such as IL-1, TNF,

Table 3: Antifungals and their Route of Administration

Drugs	Mechanism of action	Spectrum
Polyenes Nystatin (topical)	Binds to cell membrane sterols and causes change in cell permeability and cell leakage	Yeasts *(Candida)*
Azoles Topical: miconazole, clotrimazole, oxiconazole, sertaconazole Topical and oral: ketoconazole, flucanazole, itraconazole	Inhibits lanosterol demethylase leading to inhibition of ergosterol synthesis	Dermatophytes, *Candida, M. furfur*
Allylamines Terbinafine (oral and topical), Naftifine (topical)	Inhibit squalene epoxidase leading to inhibition of ergosterol synthesis	Dermatophytes, *Candida* (only Terbinafine)
Benzylamines Butenafine (topical)	Inhibit squalene epoxidase leading to inhibition of sterol synthesis	Dermatophytes, *Candida* (weak activity)
Griseofulvin (oral)		Dermatophytes, mainly *tinea capitis*
Ciclopirox olamine (topical)	Interferes with membrane transport of essential molecular precursors, cell membrane integrity and cell respiratory process	Dermatophytes, *Candida, M. furfur*
Selenium sulphide (topical)	Cytostatic effect on epidermal cells leading to shedding of fungi	Used for treatment of tinea versi-colour and *seborrhoeic capitis*

Table 4: Antiviral Drugs

Group	Drugs	Mechanism of action	Spectrum	Clinical uses	Adverse effects
Viricidal	Acyclovir	Inhibits viral DNA polymerase	HSV-1, HSV-2, VZV	Herpes genitalis and Herpes labialis	Mild pain, burning, stinging
	Cidofovir (under research for topical use)	Inhibits viral DNA synthesis	HSV, MCV, HPV	Herpes genitalis and Herpes labialis, codyloma acuminate, verruca vulgaris, Molluscum contagiosum	Headache, nausea, rash, pain, ulceration, paraesthesia
Immunoenhancing	Imiquimod	Immunomodulator, inducer of IL, TNF, IFN	HPV, HSV, MCV	External genital and perianal warts	Erythema, erosions, oedema, burning, stinging, rash, flu like symptoms
Cytodestructive	Podophyllin	Antimitotic, arrests cells in metaphase		Condyloma acuminate	Erythema, erosions, burning, contraindicated in pregnancy
	Trichloroacetic acid	Causes hydrolysis of cellular proteins leading to cell death		Genital warts, molluscum contagiosum	Local pain, ulceration
	Salicylic acid	Keratolytic		Warts located on hands and feet	Nausea, vomiting, tinnitus, delirium

Table 5: Retinoids

Retinoid	Mechanism of action	Therapeutic effects	Clinical uses	Adverse effects
Tretinoin Isotretinoin	Affects cellular differentiation and proliferation, normalises follicular epithelial differentiation	Comedolysis, epidermal thickening, dermal regeneration, pigment lightening	Acne vulgaris, fine wrinkle, mottled hyperpigmentation	Irritation, erythema, desquamation, pruritis, burning, worsening of psoriasis (tazoretene)
Adapelene	normalises follicular epithelial differentiation	Comedolysis	Acne vulgaris	
Tazarotene	Modulates the expression of genes that regulate cell differentiation, proliferation and inflammation	Normalises proliferation and differentiation of cells in psoriasis, comedolysis	Psoriasis (< 20% of body surface), Acne vulgaris	

Table 6: Classification of Systemic Corticosteroids

Drug	Equivalent dose (mg)	Glucocorticoid potency	Mineralocorticoid potency
Short acting			
Cortisone	25	0.8	2+
Hydrocortisone	20	1	2+
Intermediate acting			
Prednisone	5	4	1+
Prednisolone	5	4	1+
Methylprednisolone	4	5	0
Triamcinolone	4	5	0
Long acting			
Dexamethasone	0.75	20 to 30	0
Betamethasone	0.75	20 to 30	0

cause lymphocyte and eosinophil apoptosis, alter signal transduction by inhibiting phospholipase A_2 leading to decreased production of various prostaglandins, leucotrienes and other inflammatory mediators. They also have inhibitory effect on various white blood cells subsets leading to decreased cellular and humoural immunity. Corticosteroids also cause vasoconstriction, decreased angiogenesis and decreased vascular permeability.

Indications

Systemic corticosteroids are indicated in various bullous dermatoses, autoimmune connective tissue disease, vasculitis, contact dermatitis, papulosquamous disease such as lichen planus and neutrophilic dermatoses.

Contraindications

Absolute contraindications are systemic fungal infection, herpes simplex keratitis. Relative contraindications are hypertension, CHF, depression, previous pyschosis, active TB, diabetes, osteoporosis, pregnancy, cataract, glaucoma and gastric ulcer disease.

Side Effects

Hypothalamic-pituitary adrenal (HPA) axis suppression, addisonian crisis, Cushing's syndrome, hyperglycaemia, increased appetite, hypertension, CHF, hypokalaemia, hypertriglyceridaemia, hypocalcaemia, osteoporosis, avascular nacrosis of head of femur, peptic ulcer disease, cataract, glaucoma, infections, pyschosis, depression, myopathy, pseudotumour cerebri and peripheral neuropathy.

ANTIHISTAMINICS IN DERMATOLOGY

Antihistaminics represent the standard approach for the management of various allergic disorders. They block the effects of the histamine by blocking the H_1 receptors. Major group of antihistaminics are listed below in **Table 7**.

Mechanism of Action

These drugs competitively block the action of histamine at the level of H_1 receptors. They block histamine induced

Table 7: Group of Antihistaminics

First generation antihistaminics

Highly sedative—Diphenhydramine, Promethazine, Hydroxyzine

Moderately sedative—Pheniramine, Cyproheptadine, Meclizine, Buclizine

Mild sedative—Chlorpheniramine, Dimethindene, Mebhydrolin, Cyclizine, Clematine

Second generation antihistaminics

Terfenadine, Fexofenadine, Astemizole, Loratidine, Cetirizine, Mizolastine, Ebastine

Tricyclic antihistaminics

Doxepin

bronchoconstriction, smooth muscle contraction and triple response-wheal, flare and itch. Type I hypersensitivity reactions are suppressed. Urticaria, itching and angioedema are controlled. Many H_1 blockers antagonise muscarinic effects of acetylcholine.

Side Effects

First generation H_1 antihistaminics cross the blood-brain barrier (BBB) and cause sedation, impaired cognitive function, drowsiness. Anticholinergic activity leads to dryness of mouth, urinary hesitancy, blurring of vision, constipation. Tachycardias and dysrhythmias may occur. Second generation antihistaminics have significantly less CNS depressant property and no cholinergic side effects.

Drug Interaction

Erythromycin, clarithromycin, ketoconazole, itraconazole, HIV-1 protease inhibitors, selective serotonin reuptake inhibitors (SSRI) inhibitors increase the risk of torsades de pointes when used along with terfenadine or astemizole.

Uses

Treatment of allergic disorders such as itching, urticaria, hay fever, dermographism, pruritides.

ANTI-MALARIALS IN DERMATOLOGY

Hydroxychloroquine and chloroquine are anti-malarial medications used in the treatment of dermatological disorders. The exact mechanism by which chloroquine acts is not known they are believed to act by their effects on light filtration, immunosuppressive actions, anti-inflammatory actions and DNA binding.

Dose

Hydroxychloroquine: 200 to 400 mg per day, maximum 6.5 g per day

Chloroquine: 250 to 500 mg per day, maximum 4.0 g per day.

Indications

DLE, SLE, photosensitivity disorders pleomorhic light eruptions (PLE) and Porphyria cuternea tarda (PCT), lepra reaction type II. Hydroxychloroquine is used much more frequently than chloroquine, as chloroquine is more likely to cause irreversible retinal damage.

Adverse Effects

Visual disturbances include halos, blurred vision, photophobia, corneal deposits, retinopathy, agranulocytosis, pancytopaenia, nausea, vomiting, diarrhoea, irritability, mood swing, headache, vertigo, tinnitus, pyschosis, bleaching of hair, bluish grey pigmentation of skin, exacerbation of psoriasis, morbilliform rash.

Contraindications

Relative contraindications are pregnancy and lactation, hepatic dysfunction, neurological defects, psoriasis, visual field defects, psychosis, blood disorder, myasthenia gravis, intermittent porphyria or variegate porphyria, Glucose-6-phosphate dehydrogenase deficiency.

SYSTEMIC RETINOIDS

The retinoids are a class of chemical compounds that are related chemically to vitamin A. Systemic retinoids are divided into three groups: First generation (isotretinoin, tretinoin), second generation (etretinate, acitretin) and third generation (bexarotene). Isotretinoin and acitretin are available in India.

Mechanism of Action

Retinoids exert their effect by activating nuclear receptors and regulating gene transcription. Isotretinoin causes inhibition of sebaceous gland differentiation, proliferation, reduce the size of sebaceous gland and suppression of sebum production. It also causes normalisation of follicular epithelial desquamation. Etretinate and acitretin exert antipsoriatic effects by inducing cellular differentiation, antiproliferation, antikeratinisation and anti-inflammation. Bexarotene regulates cellular differentiation and proliferation.

Indications

Psoriasis (acitretin): Erythrodermic psoriasis, pustular psoriasis, severe plaque psoriasis and recalcitrant psoriasis, acne vulgaris (isotretinoin), Mycosis fungoides (bexarotene), other indications are Gram-negative folliculitis, rosacea, hidradenitis suppurativa, Darier's disease, pityriasis rubra pilaris and lichen planus.

Dose

Dose of isotretinoin is 0.5 to 2 mg per kg per day and that of acitretin is 25 to 50 mg per day.

Adverse Effects

Systemic retinoids have potentially serious side-effects. They are highly teratogenic and may cause retinoic acid embryopathy and spontaneous abortions. Women of childbearing age should practice complete contraception during and one month after therapy with isotretinoin and acitretin. Systemic retinoids also cause xerosis, palmoplantar desquamation, telogen effluvium, paronychia, dry eyes, cheilitis, epistaxis, headache. They also cause hypercholesterolaemia, premature epiphyseal closure, myopathy and pseudotumour cerebri and depression. Bexarotene may in addition cause leucopaenia, hypothyroidism and agranulocytosis.

CYTOTOXIC DRUGS

The common cytotoxic drugs used in dermatology are listed in **Table 8**.

SURGICAL PROCEDURES IN DERMATOLOGY

Cryotherapy

Cryotherapy is a commonly used in-office procedure for the treatment of a variety of benign and malignant lesions. The

Table 8: Cytotoxic Drugs

Drug	Mechanism of action	Indication	Side-effects	Contraindication	Dose	Note
Methotrexate	Inhibits dihydrofolate reductase,causes inhibition of cell division in S phase of cell cycle	Psoriasis (pustular, erythrodermic, extensive plaque psoriasis,psoriatic arthritis), Sezary syndrome	Hepatotoxicity, pancytopaenia, malignancy (lymphoma),acute pneumonitis, nausea,anorexia, alopaecia, fatigue	Absolute: Pregnancy and lactation. Relative:alcoholism patient,hepatic disease.	0.3 mg/ kg/week in divided doses	Folic acid 5 mg daily reduces of incidence pancytopaenia and GI side effects
Azathioprine	Active metabolite is 6-thioguanine which inhibits DNA and RNA synthesis leading to decreased T- and B-cell function	Photodermatosis, pemphigus and bullous pemphigoid, contact dermatitis, atopic dermatitis, SLE, connective tissue disease	Malignancy (lymphoma), pancytopaenia, infections, hypersensitivity syndrome, nausea, vomiting	Pregnancy	Up to 2 to 2.5 mg/kg/day	Use cautiously with concomitant allopurinol use
Cyclopho-sphamide	Active metabolite is aldophosphamide and phosphamide mustard. Cell cycle nonspecific. Inhibits B- and T-cell function	Mycosis fungoides, pemphigus, pemphigoid, histiocytosis, vasculitis	Haemorrhagic cystitis, dysuria, urgency, pancytopaenia, increased risk of lymphoma and bladder carcinoma, hair fall, nausea, hepatotoxicity	Absolute: pregnancy and lactation, bone marrow depression Relative: impaired hepatic or renal function	1 to 3 mg/ kg/day	Take plenty of fluids. Mesna decreases the risk of haemorrhagic cystitis
Cyclosporine	Inhibits calcineurin leading to decreased production of IL-2 which causes decreased T-cell proliferation. Also causes decreased production of pro-inflammatory cytokines	Psoriasis, lichen planus, bullous dermatosis, trichosis, connective tissue disease, atopic dermatitis	Renal dysfunction, hypertension, tremors, headache, hyper-gingivial hyperplasia, myalgia,hyperkalaemia, hyperuricaemia, hyperlipidaemia	Uncontrolled hypertension, decreased renal function	2.5 to 5 mg/ kg/day	

mechanism of destruction in cryotherapy is necrosis, which results from the freezing and thawing of cells. Treated areas re-epithelialise. Liquid nitrogen is preferred to other common refrigerants because of its lower boiling point, ease of use and relative safety.

Indications

Benign lesions such as acne, acne Keloidalis, cherry angiomas, keloids, lentigenes, molluscum contagiosum, seborrhoeic keratosis, skin tags, warts and xanthomas.

Premalignant and malignant lesions such as actinic cheilitis, Bowen's disease, leucoplakia, basal and squamous cell carcinoma, and Kaposi's sarcoma.

Complications

1. Acute complications include headache, pain, oedema and blister formation.
2. Delayed complications include haemorrhage, infection and excessive granulation tissue formation.
3. Prolonged-temporary complications include milia, hyperpigmentation and altered sensory nerve function.
4. Permanent complications include alopaecia, atrophy, keloids, scarring, hypopigmentation and ectropion formation.

Relative contraindications to cryotherapy include cold intolerance, cold urticaria, cryoglobulinaemia, history of pyoderma gangrenosum and Raynaud's disease.

Absolute contraindications include the use of cryotherapy near the eye margins.

ELECTROCAUTERY

Electrocauterisation is the process of destroying tissue using heat conduction from a metal probe heated by electric current. Since the heat does not penetrate deeper then papillary dermis, electrocautery is best used for very superficial lesions such as flat seborrhoeic keratosis or acrochordons.

DERMABRASION

Dermabrasion involves resurfacing the skin, from the epidermis, through the papillary dermis, maximum up to the junction of upper and mid reticular dermis either manually, with electrical abraders or CO_2 laser. The wound is allowed to heal by secondary intention, so as to achieve levelling effect, making the scar less conspicuous. The common indications for dermabrasion are acne scars and other facial scars, stable vitiligo, hypertrophic lichen planus, lichen simplex chronicus hypertropicus, actinic keratosis, fine wrinkles, tattoo removal and various tumours.

Adverse effects

Pain, oedema, crusting, hyperpigmentation/hypopigmentation, keloids and hypertrophic scars.

LASERS IN DERMATOLOGY

LASER stands for light amplification by the stimulated emission of radiation. The various types of skin disorders treated by lasers along with type of laser are indicated below:

1. Vascular lesions—vascular malformations, telangiectasias, haemangiomas (Pulsed dye laser).
2. Pigmented lesions—birth marks, Freckles (PDL, Q switched ND-YAG, Q switched Ruby).
3. Hair removal (800 diode, 1,064 long pulsed ND-YAG, IPL).
4. Keloids, hypertrophic scars, warts, seborrhoeic keratosis (CO_2 laser).

DERMAL FILLERS

Although soft-tissue augmentation is not a new cosmetic procedure, the discovery of new materials, suitable for injection into subcutaneous tissue and more refined techniques has enabled many defects to be corrected very well. The materials commonly used for augmentation are silicone, bovine collagen, autologous fat, hyaluronic acid, fibrel, new fill, etc.

Indications

Furrows, wrinkles, depressed scars, lip augmentation and shaping, profile defects of the face.

HAIR TRANSPLANTATION

Hair transplantation is a surgical technique that involves moving skin containing hair follicles from one part of the body (the donor site) to bald or balding parts (the recipient site). It is primarily used to treat male pattern baldness. It is also used to restore eyelashes, eyebrows, and beard hair, and to fill in scars caused by accidents and surgery. The various methods of hair transplantation consist of punch grafts, mini-and micrografts, single hair grafts and follicular unit grafts. Punch grafting causes fibrosis and paddy field appearance and is generally not preferred now a days. Follicular unit grafts give natural and fuller look and is considered to be the best method of hair transplantation.

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Section 12

Cardiology

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12.1 Basic Considerations in Cardiology

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CARDIAC ANATOMY

Location

Heart is an irregularly conical hollow muscular organ, lying obliquely in the middle mediastinum. Right atrium (RA) forms the right heart border, left ventricle (LV) mainly forms the left border and the inferior border is formed mainly by the right ventricle (RV). Anterior surface is mostly formed by the RV, while the inferior surface consists of the right and left ventricles. The posterior surface is quadrilateral, formed mainly by the left atrium (LA). The base is oriented superiorly while the apex points leftward, anteriorly, and slightly inferiorly (levocardia). The heart is retrosternal, two-thirds to the left of the centreline.

The left heart border is formed from above downward by a part of descending thoracic aorta (aortic knuckle on chest radiograph), the pulmonary artery, the left atrial appendage and the LV. The right heart border, mostly retrosternal, is formed by RA with contribution from the venae cavae. The LV apex generally forms the true apex of the heart.

Measurements

The adult heart weighs approximately 325 ± 75 g in men and 275 ± 75 g in women. It measures about 5 inches from base to apex and is 3 inches in width.

The Pericardium

The heart and the origins of the great arteries are enclosed in the conical fibrous pericardium. Within this inelastic fibrous layer lies the serous pericardium. The visceral layer closely adheres to the heart, the parietal layer lines the fibrous pericardium. Between the two layers is a potential space (pericardial space) that contains 10 to 25 cc of fluid. The pericardium maintains the position of the heart within the mediastinum, lubricates the cardiac surfaces and forms a barrier against infection.

The Cardiac Chambers

The RA is a capacitance chamber that receives blood superiorly from the superior vena cava (SVC) and inferiorly from the inferior vena cava (IVC), and its Eustachian valve directs blood flow towards the fossa ovalis. The coronary sinus returns blood from the heart itself and its orifice is partially guarded by the Thebesian valve. Chiari net describes large and fenestrated Thebesian and Eustachian valves. The Thebesian veins directly drain cardiac blood into the heart via multiple orifices. Running almost vertically between the venae cavae is a 'C'-shaped muscular ridge (Crista terminalis) that separates the smooth-walled posterior RA (derived from sinus venosus) from the rough-walled anterior portion, which is prolonged into the triangular auricular appendage. Tendon of Todaro is a fibrous band located between the valves of the IVC and coronary sinus. Between the tendon of Todaro and the tricuspid annulus, is the triangle of Koch; the apex of this triangle overlies the AV node and bundle of His.

The RV is the most anterior heart chamber. Its free wall is about one-third the thickness of the LV. The RV consists of an inlet portion, a trabeculated apical portion and a smooth outflow tract (infundibulum or conus portion). The RV walls show a lattice-work of muscle fibres (trabeculae carneae). The RV contains three papillary muscles, from which extend chordae tendineae, attaching to the leaflet edges. The moderator band is an intracavitary muscle bridge connecting the RV free wall and the distal interventricular septum. It conveys the right bundle branch to the ventricular muscle.

The LA forms the left upper and posterior chamber of the heart. It is a cuboidal structure and receives four pulmonary veins. It is smaller than RA, has thicker walls (3 mm) and higher pressure. Internally it is smooth-walled and does not contain pectinate muscles except in the left atrial appendage. The LA appendage overlies the left circumflex artery and is smaller, longer, windsock shaped structure.

The LV is a high pressure chamber, thicker than the RV (2 to 3 times). Structurally, it contains the inflow tract, the apical zone and the left ventricular outflow tract (LVOT). The ventricular heart muscle is tri-layered (epicardium, myocardium and endocardium). The outer two-thirds of the myocardium has compact muscle layers that twist and spiral from apex to base during contraction. The LV contains two papillary muscles (anterolateral and posteromedial) from which chordae tendineae arise and attach to mitral valve leaflet edges. The chordae check leaflet excursion and prevent valve prolapse. False chordae do not attach to the mitral valve but attach to septum or free wall.

Cardiac Valves

Tricuspid valve is the largest, having three leaflets (anterior, posterior and septal). The mitral valve is funnel shaped (**Figure 1**),

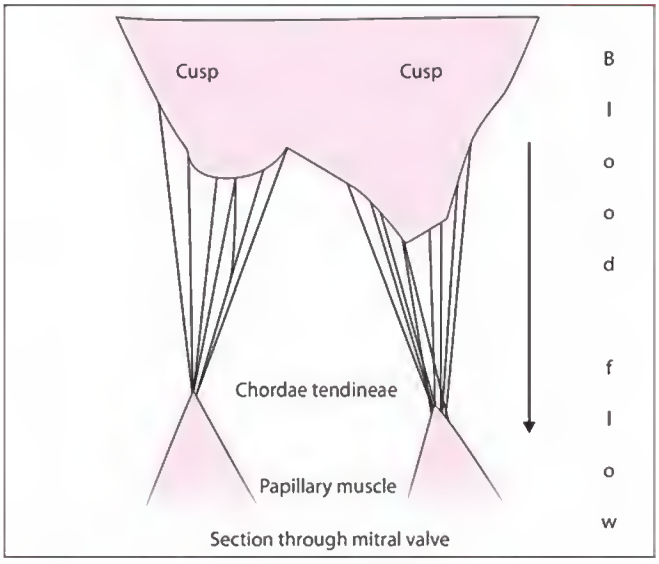


Figure 1: Schematic section through the mitral valve.

with two leaflets forming the apex and protruding into the LV. The posterior leaflet is crescent shaped, longer, narrower and attaches to over two-thirds of the annulus. It has three scallops. The anterior mitral valve is semicircular or oval shaped. The mitral chordae do not have insertions into the septum.

The aortic valve, the thicker and stronger of the semilunar valves (**Figures 2A and B**), consists of annulus, three cusps and a commissure. Approximately 2% of aortic valves are bicuspid. The nodules of Arantius are small fibrous mounds at the centre of the free edge of each cusp. Aortic valve has no tensor apparatus. Behind each cusp the wall bulges outward to form sinus of Valsalva. The aortic cusps are named as right, left and non-coronary (posterior); the right and left sinuses give rise to the corresponding right and left coronary arteries. Pulmonary valve is a mirror image of the aortic valve with similar but thinner cusps.

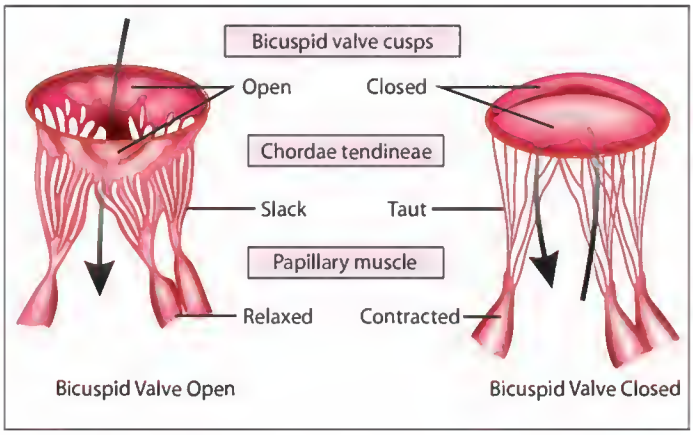


Figure 2A: Tensor apparatus of semilunar valve.

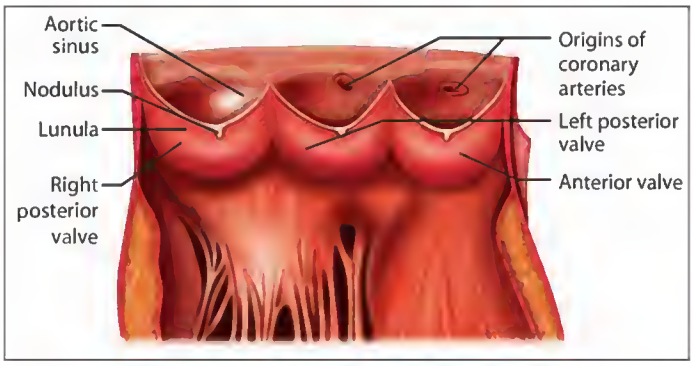


Figure 2B: Aorta cut open to reveal the aortic valve.

At the base of the heart, the fibrous cardiac skeleton encircles the four cardiac valves (annuli, fibrous trigones, intervalvular fibrosa and conus ligament). The fibrous scaffold is firmly anchored to the ventricle. It electrically insulates atria from the ventricles, supports the cardiac valves and provides a firm foundation against which the ventricles may contract.

CORONARY CIRCULATION

The coronaries are the first branches arising from the aorta (**Figure 3**). The right coronary artery (RCA) is located in the right atrioventricular groove and bifurcates at the crux into the posterior descending artery (PDA) and posterior left ventricle branches (PLBs). A dominant RCA provides the PDA and the PLBs; A co-dominant RCA provides the PDA, but the left

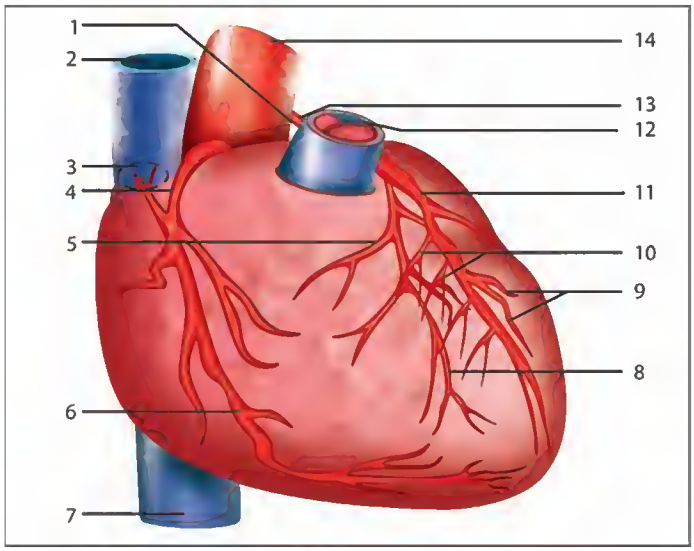


Figure 3: Coronary arteries and their branches.

1 = Left coronary artery; 2 = Superior vena cava; 3 = Sino-atrial node; 4 = Right coronary artery; 5 = Circumflex artery; 6 = Posterior descending artery; 7 = Inferior vena cava; 8 = Obtuse marginal; 9 = Diagonal branches; 10 = Septal perforator; 11 = Left anterior descending artery; 12 = Pulmonary artery and valve; 13 = Left main coronary artery; 14 = Aorta.

circumflex artery supplies the PLBs. A non-dominant RCA is small and does not reach the crux. The RCA dominates in three fourths of cases.

The left main trunk is 1 to 4 cm in length and bifurcates into the left anterior descending artery (LAD) and the left circumflex artery (LCX). In 30% cases, a third branch arises between the two (ramus intermedius). The LAD supplies blood to the ventricular septum (through four to seven septal perforators) and the anterolateral wall (through one to three diagonal branches). The LCX supplies the lateral wall of LV and LA.

The venous system of the heart consists of coronary sinus, cardiac veins and the Thebesian veins. The bulk of the venous drainage of the heart is carried out by veins accompanying coronary arteries and which drain into the RA via coronary sinus. The rest of the blood drains via venae cordae minimae directly into the cardiac cavity.

The electrocardiogram (ECG) can fairly well localise areas of ischaemia or infarction supplied by individual coronary arteries. The coronary blood flow is maintained remarkably constant over a wide range of blood pressures. Any increase in myocardial oxygen demand must be met by increased coronary blood flow.

THE CONDUCTION SYSTEM

It consists of the sino-atrial node (SA node), the atrio-ventricular (AV) node, the bundle of His, the right and left bundle branches and the Purkinje fibres (**Figure 4**). The heart beat is initiated in the SA node (the heart pacemaker), situated in the upper part of the crista terminalis (just to the right of the SVC-RA junction). It spreads down via the AV node into the ventricles. The RCA supplies the SA node (65% cases) and the AV node (80% cases). The nerve supply of the heart is derived from the vagus (cardio-inhibitory) and the cervical and upper thoracic sympathetic ganglia (cardio-accelerator). The transplanted heart is completely denervated and responds only to circulating substances and not to impulses of the autonomic system.

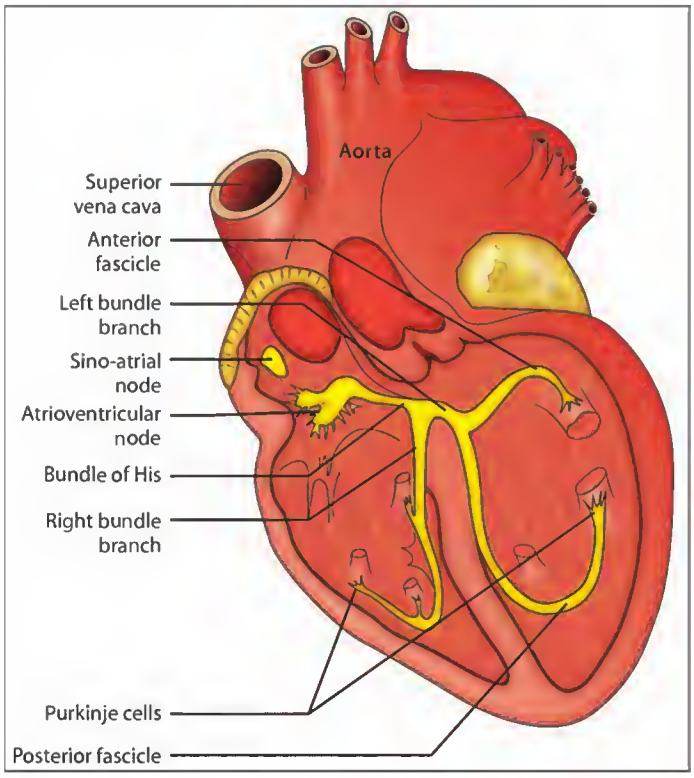


Figure 4: Conduction system of the heart.

CARDIOVASCULAR PHYSIOLOGY

The Circulation

The RA receives deoxygenated blood from the SVC and IVC, and discharges blood to the RV, which in turn pumps it into the pulmonary artery. Blood passes through the pulmonary arterial and alveolar capillary bed where it is oxygenated, then drains via four pulmonary veins into the LA. This in turn fills the LV, which delivers blood into the aorta (**Figure 5**). During ventricular contraction (systole), the tricuspid valve in the right heart and the mitral valve in the left heart close and the pulmonary and aortic valves open. In diastole, the pulmonary and aortic valves close and the two AV valves open. Collectively, these atrial and ventricular events constitute the cardiac cycle of filling and ejection of blood from one heart beat to the next (**Figure 6**).

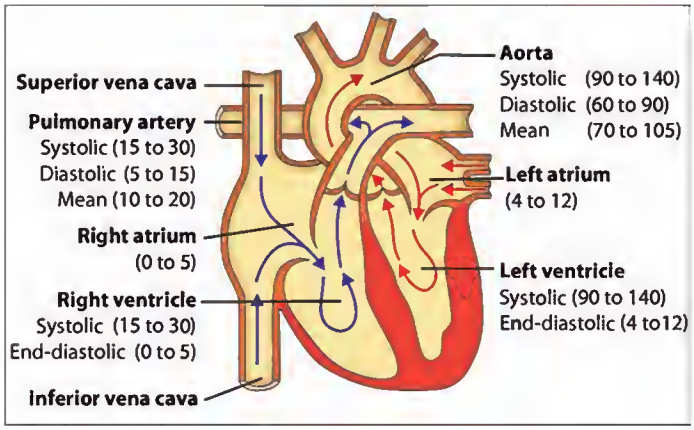


Figure 5: Direction of blood flow through the heart. The blue arrows show deoxygenated blood moving through the right heart to the lungs. The red arrows show oxygenated blood moving from the lungs to the systemic circulation. The normal pressures are shown for each chamber in mm Hg.

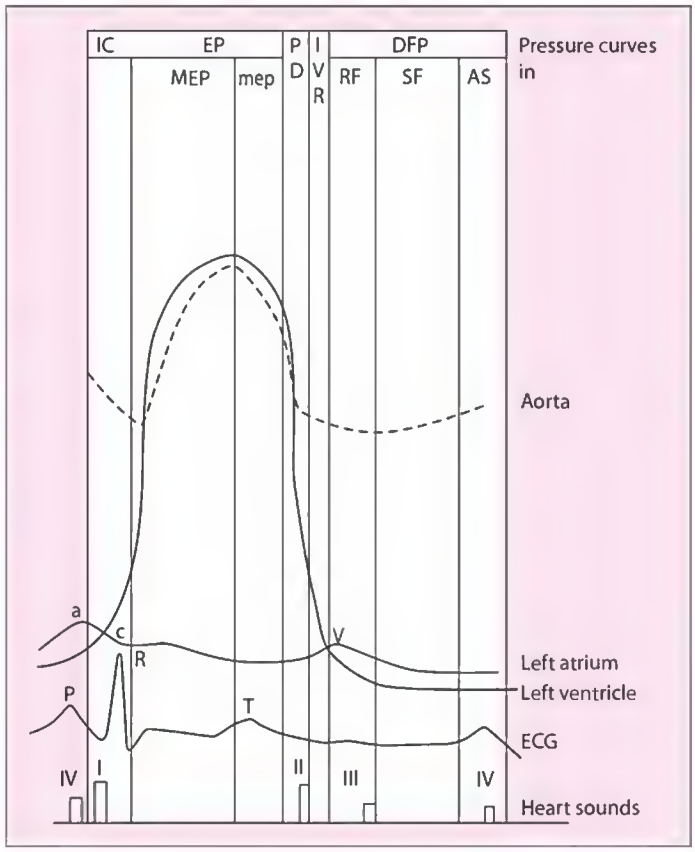


Figure 6: The cardiac cycle.

EP = Ejection period; DFP = Diastolic filling period; IC = Isovolumic contraction; MEP = Maximum ejection phase; mep = Minimum ejection phase; PD = Protodiastole; IVR = Isovolumic relaxation phase; RF = Rapid filling; SF = Slow filling; AS = Atrial systole.

The Determinants of Cardiac Output

Ejection fraction is the percentage of ventricular volume ejected by the ventricle per beat whereas cardiac output is the volume of blood pumped by ventricle per minute. Cardiac output is a paramount physiological variable that is adjusted as per body requirements. It is a product of stroke volume and heart rate. Influences on stroke volume will impact cardiac output, and stroke volume can be altered by changes in preload, contractility, and afterload. Preload is the haemodynamic load (stretch) on the myocardial wall fibres at end-diastole. Clinically, the end-diastolic volume (EDV) is the best measure of LV preload. Changes in ventricular preload operate via Frank-Starling law of the heart. This law states that, 'with all factors equal, stroke volume increase as cardiac filling increases'. Several factors determine preload including intra-thoracic pressure, venous return, body position, skeletal muscle pump function, total blood volume, intra-pericardial pressures and atrial contractility. Contractility is the intrinsic ability and degree of contraction of the cardiac muscle. Ejection fraction is an approximate guide to the degree of contractility. Important factors determining cardiac contractility include sympathetic activity, circulating/exogenous inotropes, cardio-depressant drugs, hypoxia, acidosis, and ischaemia. Sympathetic stimulation increases muscle shortening, and therefore, increases stroke volume by decreasing end-systolic volume (ESV). Myocardial contractility is understood well by the LV pressure-volume curve (**Figure 7**). The curve shifts upwards when cardiac contractility

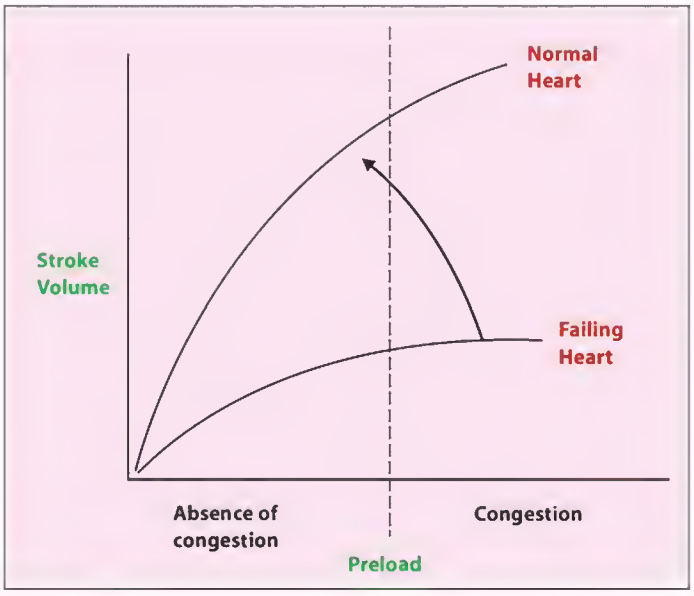


Figure 7: Pressure-volume curve of the normal and failing heart.

is enhanced. In heart failure, the curve is plateau. Afterload is the resistance against which the ventricle is contracting. It is also defined as the wall tension generated during cardiac contraction. The common measures of afterload are: aortic pressure, systemic arterial resistance, arterial impedance, myocardial peak wall stress and LV pressure. An abnormally high afterload decreases stroke volume by decreasing ESV.

Pressure-Volume Loops

These can be constructed in the catheterisation laboratory using high fidelity catheters. When the ventricular volumes during one cardiac cycle are plotted against simultaneous pressures within the ventricle, a pressure-volume loop is generated. End-diastolic pressure-volume relationships (EDPVR) and end-systolic pressure-volume relationship (ESPVR) are the key components of a pressure-volume loop. The cardiac muscle length tension behaviour is the underlying basis for ventricular function. The physiologic measurements obtainable from pressure-volume loop are: volumes (EDV and ESV), pressures (end-systolic and end-diastolic pressures), compliance, elastance, stroke work and contractility.

Compliance is the change in volumes for a given change in pressure (Reciprocal of EDPVR). Compliance is greater at lower volumes. Structural and pressure changes in heart, pericardium and thorax affect changes in compliance. Elastance is the linear relationship between the change in pressure for a given change in volume at end-systole. Stroke work is represented by the area of the pressure-volume loop and represents the work of the heart during each heart beat. Contractility is an intrinsic attribute independent of loading conditions.

Cardiac Energetics

The myocardial adenosine triphosphate (ATP) pool turns over every 10 seconds. In adults, 60% to 90% of ATP is derived from fatty acids, whereas in foetus and neonates, glucose and lactate are the main ATP sources. In advanced heart failure, the cardiac energetics shift back to the faetal form. Cardiac energy requirement is derived primarily from aerobic metabolic pathways such that cardiac work is tightly related to myocardial oxygen consumption. A simple index of the energy demands of the heart is obtained by the product of peak systolic arterial pressure and heart rate. Determinants of myocardial oxygen consumption include myocardial muscle mass, wall stress, contractility and heart rate.

Normal LV diastolic function implies LV filling to a normal EDV, on exercise, as well as rest, without elevating mean LA pressure above 13 mm Hg. Diastolic dysfunction may be seen in several conditions, including systemic hypertension, LV hypertrophy, restrictive cardiomyopathies and pericardial diseases (e.g. constrictive pericarditis). Diastolic dysfunction eventually leads to heart failure with preserved ejection fraction.

The vascular endothelium has been called the cardiovascular endocrine organ. It produces various compounds (e.g. nitrous oxide, endothelin, prostacyclin, endothelial-derived hyperpolarising factor, vascular endothelial growth factor and adhesion molecules). A number of enzymes are located on the surface that control the levels of circulating compounds such as angiotensin, bradykinin and serotonin. It also plays regulatory roles (control of vasomotion, thrombotic status, immune response modulation and vascular cell growth).

RECOMMENDED READINGS

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12.2 Cardiovascular Diseases—A Clinical Approach

GS Sainani

To evaluate a patient with cardiovascular disorder, one has to elicit a proper history, carry out clinical examination, and routine investigations such as roentgenogram of the chest, electrocardiogram, pertinent biochemical and haematological tests. However, a definitive diagnosis is not made on the basis of these; further investigations like echocardiography (M-mode, 2-dimensional, colour Doppler), treadmill exercise test, Holter ambulatory ECG monitoring, radionuclide tests (multigated blood pool studies, thallium exercise test), digital subtraction angiography, cardiac catheterisation and coronary angiography may also be needed.

HISTORY

A patient may be asymptomatic and unaware of his underlying cardiac disease. The common symptoms are:

Dyspnoea

This is a subjective feeling of difficulty in breathing and is due to passive congestion in pulmonary veins and pulmonary capillaries secondary to left-sided cardiac failure.

Dyspnoea has been graded by the New York Heart Association (NYHA) into 4 grades in the presence of cardiac disease.

Grade I : No dyspnoea on any work

Grade II : Dyspnoea on ordinary work

Grade III : Dyspnoea while doing less than accustomed work

Grade IV : Dyspnoea at rest

Dyspnoea may manifest as exertional dyspnoea, paroxysmal nocturnal dyspnoea, orthopnoea or acute pulmonary oedema. *Orthopnoea* is the stage when a patient feels breathless while he lies flat and is relieved by sitting up. In *paroxysmal nocturnal dyspnoea,* the patient gets sudden attacks of dyspnoea during sleep; these wake him up and force him to sit upright. The attack may pass off in a few minutes. In acute pulmonary oedema, which occurs as a result of acute left ventricular failure, the patient gets a sudden attack of dyspnoea and cough with white or pink frothy sputum, sweating, tachycardia and cyanosis.

Cough

Cough of pulmonary venous hypertension is irritating, non-productive and worse at night. In some cases, such dry cough occurring during exertion may first raise the suspicion of underlying cardiac disease.

In severe pulmonary venous hypertension and pulmonary infarction, blood-tinged sputum is seen while in pulmonary oedema, the sputum is pink and frothy.

Oedema

Oedema occurs over the dependent parts (feet in an ambulatory person). In advanced cases, there is generalised oedema with ascites. **Table 1** gives other causes of oedema.

Table 1: Important Causes of Oedema Feet

Congestive cardiac failure
Nephrotic syndrome
Liver cirrhosis
Hypoalbuminaemia (nutritional, protein-losing enteropathy)
Venous insufficiency (obesity, old age)
Chronic lymphatic obstruction
Drug induced (steroids, NSAIDs, nifedipine)
Idiopathic

Pain in Right Upper Abdomen

This is due to congestive hepatomegaly. Due to systemic venous congestion, the liver becomes enlarged and tender. The patient may present with pain in the upper abdomen.

Oliguria and Nocturia

Due to oedema, the patient complains of oliguria particularly during the day. At night, due to redistribution of fluid, the patient's renal perfusion improves and he gets nocturia, with the result that oedema becomes less in the morning.

Palpitation

Palpitation is consciousness of heart beating. This may be due to an enlarged, hyperdynamic left ventricle as seen in mitral and aortic incompetence, or may occur due to arrhythmias like extrasystole, sinus tachycardia and paroxysmal tachycardias.

Chest Pain

Angina pectoris is chest pain due to impaired coronary flow. The classical features are shown in **Figure 1**.

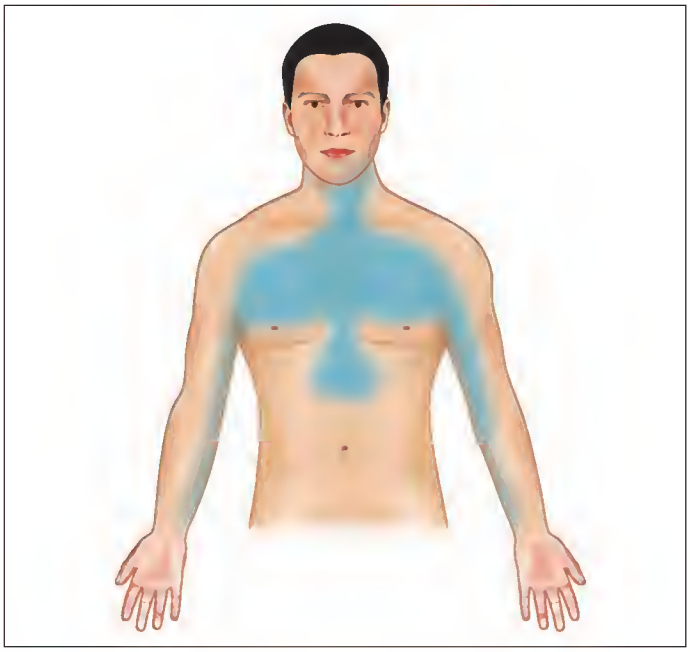


Figure 1: Location of pain in angina pectoris.

1. *Site of pain:* Retrosternal.
2. *Character:* Constricting/crushing.
3. *Radiation:* Across the chest, both arms and shoulders (more commonly left-sided), interscapular region, neck, jaw, fingers and epigastric region.
4. *Duration:* Exertional angina lasts 1 to 5 minutes, emotion-induced angina, 5 to 15 minutes; any pain which lasts for a few seconds is not ischaemic in origin.
5. *Precipitating factors:* Exertion, climbing stairs or uphill, anger, excitement, sudden exposure to cold.
6. *Relief:* Rest, sublingual nitroglycerine or isosorbide dinitrate relieves the pain. This is a stable angina.

Unstable angina occurs at any time, even at rest, without obvious precipitating factors. The pain lasts for several minutes.

In acute myocardial infarction, the characteristics of the pain are the same but it lasts longer, is more severe and is accompanied by sweating, breathlessness and even circulatory collapse. In pericarditis, pain is constant, not related to exertion, pricking in character and localised to the mid praecordium.

Syncope

Syncope is a transient loss of consciousness due to impairment of cerebral perfusion. In heart disease, due to low output, there is cerebral underperfusion.

Fatigue

This is caused by low cardiac output leading to poor blood supply to the muscles. Low cardiac output is due to defective pumping action of the heart which is secondary to myocardial muscle disease, valvular heart disease, coronary artery disease or even pericardial disease (constrictive pericarditis and pericarditis with effusion).

Cyanosis

Though patients may complain of cyanosis, usually this is observed by the physician. Cyanosis may be peripheral or central.

Peripheral cyanosis is restricted to the distal parts of the extremities, i.e. fingers, toes, nails and tip of the nose and ears. It occurs in low cardiac output states with peripheral vasoconstriction.

Central cyanosis occurs in the mucous membranes (tongue, lips) and nails where it is usually associated with clubbing. The hands are warm in contrast with peripheral cyanosis in which the hands are cold.

It is due to shunting of blood from the venous to the arterial side at the ventricular, atrial or aortopulmonary level. Another cause of central cyanosis is inadequate ventilation and impaired oxygenation as seen in interstitial pulmonary fibrosis and gross obesity (Pickwickian syndrome). It must be remembered that in patients with severe anaemia, with haemoglobin of 5 g/dL or less, cyanosis will not be perceptible because for central cyanosis to appear, capillary content of reduced haemoglobin should be more than 5 g%.

Differential cyanosis is a rare situation in which cyanosis is restricted to the lower extremities. This is seen in patients with patent ductus arteriosus and pulmonary hypertension with a right-to-left shunt.

Squatting

The squatting position is assumed by cyanotic children, particularly those with tetralogy of Fallot. By squatting, arterial resistance is increased, thus diverting greater volume of blood to the pulmonary circulation for better oxygenation. This relieves the anoxic spells.

GENERAL EXAMINATION

The child may be underdeveloped and short statured due to long-standing valvular heart disease or congenital heart (particularly cyanotic) disease. In adults, chronic congestive heart failure may lead to cachexia. Some congenital heart diseases are associated with systemic disorders related to the musculoskeletal system (**Table 2**), endocrine system (**Table 3**), metabolic and chromosomal disorders (**Table 4**), and connective tissue disorders (**Table 5**). One should therefore look for non-cardiac features.

Table 2: Syndromes Associated with Cardiac and Musculoskeletal Manifestations

Syndrome	Cardiac Abnormality	Non-cardiac Findings
Holt-Oram	Atrial septal defect	Hypoplastic thumb and radius
Ellis-van Creveld	Atrial septal defect	Dwarfism, polydactyly
Noonan's	Pulmonary valve dysplasia	Webbed neck, pectus excavatum
Kartagener's	Dextrocardia	Sinusitis, bronchiectasis
Laurence-Moon-Biedl-Bardet	Variable defects	Polydactyly, obesity

Table 3: Endocrine Disorders with Cardiac Manifestations

Disorder	Cardiac Findings	Non-cardiac Findings
Hypo-thyroidism	Pericardial effusion, congestive heart failure	Dry thick skin, dry hair, loss of lateral eyebrows, slow relaxation phase of tendon jerk
Hyper-thyroidism	Sinus tachycardia, atrial fibrillation	Asthenic build, tremors, exophthalmos, etc.
Cushing's	Hypertension	Moon face, obesity, striae, etc.
Addison's	Hypotension	Pigmentation of skin and oral mucosa, generalised wasting
Phaeochromo-cytoma	Labile hyper-tension	Neurofibromata
Acromegaly	Hypertension, cardiomyopathy	Tall stature, prognathism, visceromegaly

Pulse

Brachial arterial pulse is better felt, but conventionally the radial artery is examined. To assess the volume of the pulse, the palpating finger should compress the artery with pressure just sufficient to obliterate it during diastole. Thus, the artery can re-expand against the palpating finger during systole. Other arteries, e.g. the opposite radial, femorals, dorsalis pedis, posterior tibials, carotids, subclavians and temporals should be palpated and compared for any delay or difference in volume. In coarctation of the aorta, the volume of the femoral pulse is not only lower than the radial but the femoral pulse is also delayed.

Table 4: Metabolic and Chromosomal Disorders with Cardiac Manifestations

Disorder	Cardiac Findings	Non-Cardiac Findings
Mucopolysaccharidosis, e.g. Hurler's and Hunter's syndromes	Multivalvular disease	Growth and mental retardation, etc.
Chromosomal disorders		
Down's syndrome	Endocardial cushion defects	Mongoloid facies, mental retardation, etc.
Turner's syndrome	Coarctation of aorta	Short female, broad chest, webbed neck, etc.

Table 5: Connective Tissue Disorders with Cardiac Manifestations

Disorder	Cardiac Findings	Non-Cardiac Findings
Marfan's	Aortic dilatation, aortic and mitral regurgitation	Tall thin built, arachnodactyly, etc.
Ehlers-Danlos	Mitral regurgitation	Hyperelastic skin and joints
Pseudoxanthoma elasticum and elastic fibres	Arterial disease	Angioid streaks, degeneration of skin
Osteogenesis imperfecta	Aortic regurgitation	Fragile bones, blue sclera

The pulse is described under the following headings: rate, rhythm, volume, character, condition of arterial wall.

1. *Rate*

The normal rate in an adult varies from 60 to 90 per minute. A rate below 60 per minute is called bradycardia and above 90 per minute is tachycardia.

2. *Rhythm*

Normally the pulse is regular except for a slight increase in rate on inspiration and slowing on expiration (sinus arrhythmia). An irregular pulse may be regularly irregular (as in ectopic beats which are unifocal and come at fixed intervals) or irregularly irregular (e.g. multiple, multifocal ectopics or atrial fibrillation with varying ventricular response).

3. *Volume*

It is the amplitude of pulse wave as judged by the palpating finger. It depends on pulse pressure and is graded as high, normal, small and poor.

A. *High-volume pulse* (water hammer, collapsing or Corrigan's pulse) is caused by: (a) leakage of blood from the aorta (aortic regurgitation, patent ductus arteriosus) or from the left ventricle (mitral incompetence, ventricular septal defect); (b) high output states (anaemia, hyperthyroidism, beriberi, Paget's disease, arteriovenous fistula); and (c) increased stroke volume (complete heart block). Large volume causes high systolic pressure and escape of blood during diastole causes low diastolic pressure, resulting in large pulse pressure.

B. *Low-volume pulse*: Here the amplitude of pulse wave is small; this is due to low systolic pressure or raised diastolic pressure (secondary to peripheral vasoconstriction) or both.

It is caused by low stroke volume; all stenotic lesions (mitral, aortic, tricuspid, pulmonary), cardiogenic shock, tachycardias, dilated cardiomyopathy and heart failure have low stroke volume. The pulse in mitral stenosis is low volume but ill sustained (pulsus parvus), whereas in aortic stenosis it is low volume, well sustained and late peaking (pulsus parvus et tardus).

C. *Varying volume pulse:*

(a) Pulsus alternans is regular pulse (sinus rhythm) but alternating beats are strong and weak. It is difficult to appreciate pulsus alternans by palpating fingers. It is diagnosed while measuring blood pressure. When the mercury is being lowered, the stronger beats are heard first, and on further lowering, the weaker beats also become audible, thus suddenly doubling the number of audible beats. Pulsus alternans is seen in left ventricular failure.

(b) Pulsus paradoxus is an exaggeration of the normal phenomenon of low-amplitude pulse during inspiration and better amplitude during expiration (normal fall by <10 mm Hg on inspiration). Thus, the name 'paradoxus' is a misnomer.

Pulsus paradoxus is caused by:

(i) Restriction in diastolic filling of ventricles (constrictive pericarditis, massive pericardial effusion). Limitation in the diastolic filling of the right atrium and right ventricle during inspiration results in lowering of left ventricular stroke volume.

(ii) Advanced right ventricular failure. Increase in lung volume during inspiration accommodates the reduced right ventricular stroke volume, which in turn results in low left ventricular stroke volume.

(iii) Increased respiratory effort (severe asthma). During inspiration, owing to enhanced intrathoracic negative pressure, there is pooling of blood in pulmonary veins resulting in lowered left ventricular stroke volume. Various types of pulses are shown in **Figures 2A to J**.

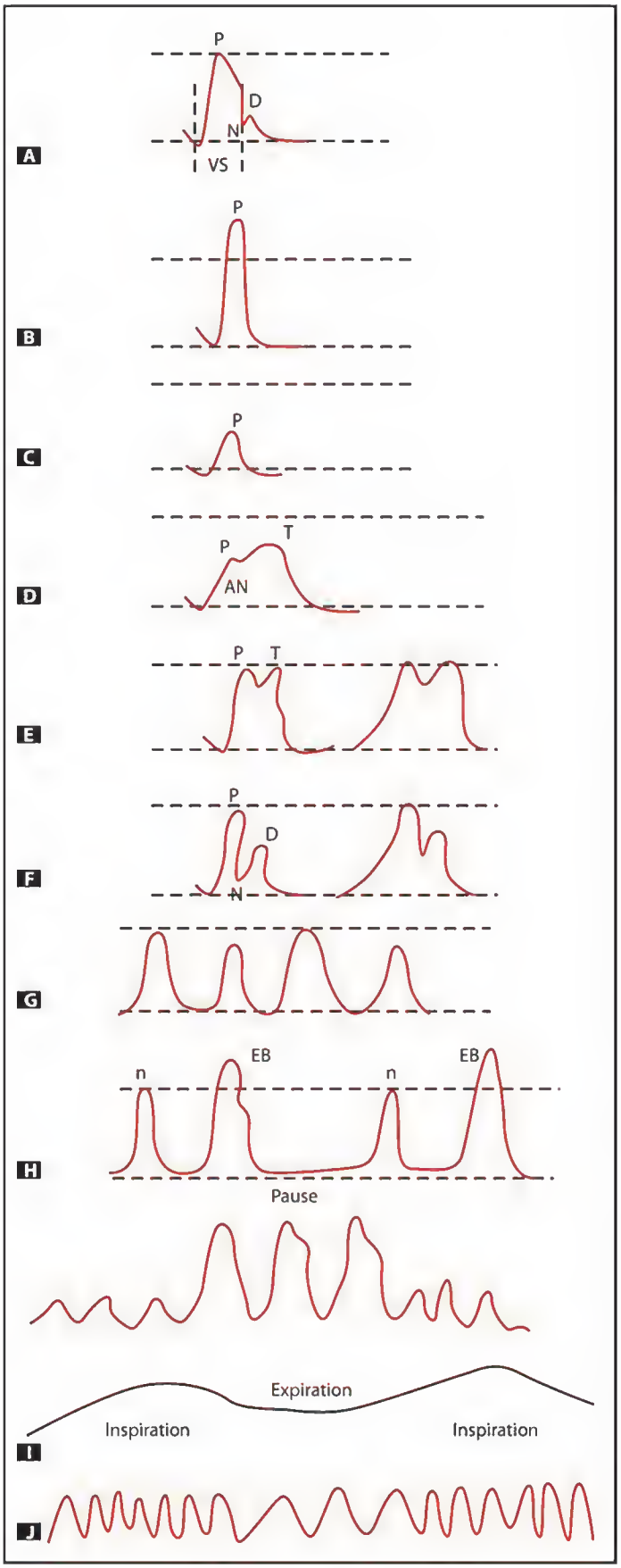
4. *Character*

Some classical characteristics of pulse can provide clues to certain cardiac conditions:

A. *Water hammer or collapsing pulse*: The water-hammer character is due to a steep rising, forceful, high-amplitude percussion wave which gives a sharp tap to the palpating hand similar to the feeling of a water hammer (a hermetically sealed toy glass tube half-filled with water). The collapsing character is attributed to a sudden disappearance of the pulse wave from the palpating hand and is due to the descending limb of the pulse wave. This is classically seen in aortic incompetence.

B. *Anacrotic pulse* is a slow rising, small-volume, well sustained pulse, seen classically in aortic stenosis. There is a distinct anacrotic notch between the slowly rising percussion and tidal waves.

C. *Pulsus bisferiens* is a double-peak pulse during systole. It is seen in combined aortic stenosis and aortic regurgitation.



Figures 2A to J: Type of pulses: (A) normal pulse wave; (B) collapsing (water hammer) pulse; (C) pulsus parvus (D) anacrotic pulse; (E) pulsus bisferiens; (F) dicrotic pulse; (G) pulsus alternans; (H) pulsus bigeminus; (I) pulsus paradoxus; (J) sinus arrhythmia.

P = Percussion wave; T = Tidal wave; D = Dicrotic wave; N = Dicrotic notch; VS = Ventricular systole; AN = Anacrotic notch); EB = Extra beat; N = Normal beat.

The first peak is due to a quick rising percussion wave and the second peak is due to a delayed tidal wave, with a notch in between. Thus, it is a double-peak pulse of the same amplitude during systole.

D. *Dicrotic pulse* is due to accentuation of the normal dicrotic wave, giving the feeling of two impulses with each beat. One impulse comes during systole and is due to the percussion wave, while a second, lower amplitude impulse comes during diastole and is due to accentuated dicrotic wave. It is seen in high-grade fever.

E. *Pulsus bigemini* or *trigemini* or *quadrigemini:* Here the pulse is regularly irregular and is due to fixed unifocal extrasystoles coming after every normal beat or after every two or three normal beats, with the usual pause after the extrasystole.

5. *Condition of arterial wall*

This is appreciated by rolling the radial artery with fingers against the underlying bone. In young persons, it feels soft and elastic; in the elderly, it may be hard and tortuous.

6. *Comparison of other arterial pulses*

Delayed and lower amplitude femoral artery pulse compared to the radials could be due to coarctation of aorta (post-subclavian), aorto-arteritis, or saddle embolus. Unequal radial pulses (right having better volume than left) are due to aortic coarctation (pre-subclavian). Unequal carotid pulses could be due to atheromatous plaque in one of the arteries.

Blood Pressure

This is the pressure at which blood is flowing in the arteries. It is due to pressure exerted by the intravascular blood column laterally on the vascular wall. Systolic blood pressure depends mainly on the cardiac output and diastolic blood pressure depends on peripheral resistance.

Clinically, blood pressure is measured by a mercury sphygmomanometer. The standard cuff (14 cm width) is for the average sized upper arm. For children a small sized (10 cm width) cuff, and for obese persons a large sized (16 cm width) cuff should be used to avoid wrong readings. In a patient with hypertension, blood pressure should ideally be taken in the supine, sitting and standing positions.

Jugular Venous Pressure (JVP)

Examination of jugular veins is of paramount importance to study right heart events. Since there are no valves between the right atrium and internal jugular veins, right atrial pressure is reflected in these veins. Carotid artery pulsations can sometimes be mistaken for the jugular venous pulsation (**Table 6**). The vertical distance from the top of the venous column to the sternal angle is a measure of the venous pressure. For measurement, 3 rulers are used; two are held horizontally, one at the upper level of the blood column in the right internal jugular vein and the other at the angle of Louis. The third ruler is used to measure the vertical distance between the first two, corresponding to the JVP (**Figure 3**). The normal mean pressure when the patient is supported on a backrest or pillow at 45° to the horizontal is 0 to 4 cm. In CCF, JVP is raised with pulsatile veins, whereas, in superior vena cava obstruction JVP is raised but non-pulsatile.

Table 6: Differences between Jugular Venous and Carotid Arterial Pulsations

Venous	Arterial
Visible but not palpable	Visible and palpable
Obliterated by pressure at root of neck	Not obliterated
Two peaks in each cycle	Single
Varies with breathing and position of patient	No change
Abdominal pressure causes rise in hepato-jugular reflux	No effect

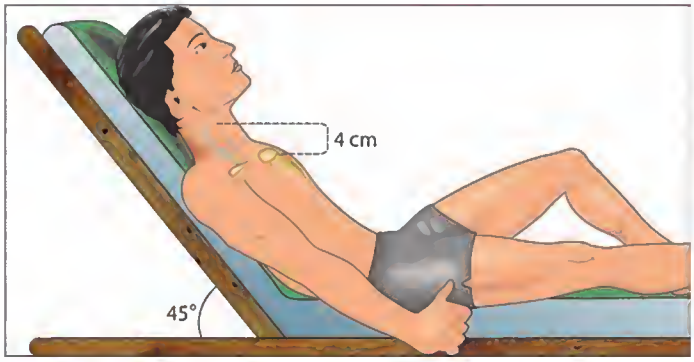


Figure 3: Measurement of jugular venous pressure. Patient's chest, neck and head are at an inclination of 45° to the horizontal. The patient lies with a backrest so that the neck muscles are relaxed.

Jugular veins usually depict 3 positive waves (a, c, v) (**Figure 4**). The *a* wave is due to atrial systole. The *c* wave is due to ballooning of the tricuspid valve into the right atrium during systole. It is also due to transmitted carotid pulse. At the bedside, it is very difficult to identify the *a* and c waves separately. The *a* and c waves are usually fused as an *ac* complex. The *a* wave disappears in atrial fibrillation; it is prominent (giant) in pulmonary stenosis or hypertension, tricuspid stenosis, tricuspid atresia, and Ebstein's anomaly. Cannon waves which are giant '*a*' waves occur when atrial contraction occurs against a closed tricuspid valve. These are seen intermittently in complete heart block and ventricular tachycardia when atrial and ventricular

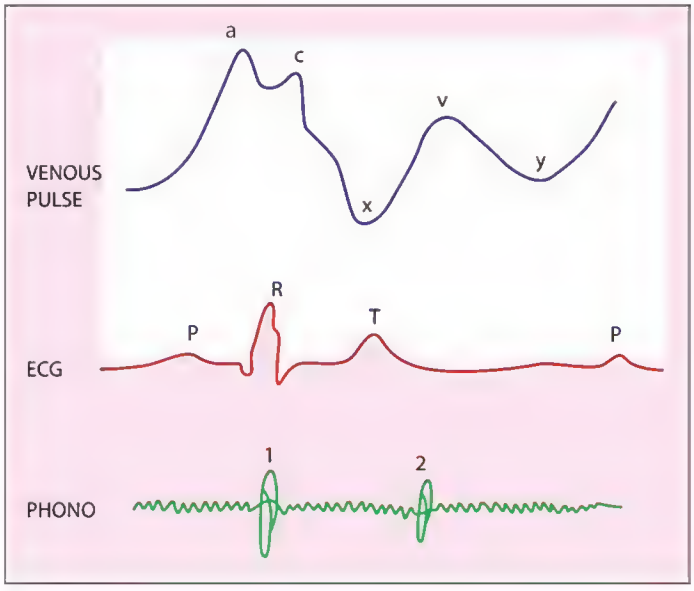


Figure 4: Venous pulse wave.

systole coincide. The x trough is due to atrial relaxation. The x descent is absent in atrial fibrillation and tricuspid insufficiency. The *v* wave that follows the x descent is the wave of venous filling of the right atrium during ventricular systole. It is exaggerated in tricuspid incompetence, heart failure and constrictive pericarditis. The trough that follows is the y descent which is due to emptying of the right atrium. The y descent is accentuated in heart failure, constrictive pericarditis and tricuspid insufficiency.

Oedema

It may be localised or generalised. Localised oedema is due to lymphatic or venous obstruction. The causes of generalised pitting oedema include cardiac, hepatic and renal disorders, beriberi, and severe anaemia with hypoproteinaemia. Myxoedema causes generalised non-pitting oedema, while filariasis causes localised non-pitting oedema.

Cardiac oedema is seen mostly on dependent parts, i.e. over the legs in ambulatory patients and the sacral area and posterior aspects of the thighs in recumbent patients; the oedema in kidney disorders occurs first over the eyelids and is more when the patient wakes up. In cirrhosis of the liver, ascites is the first presentation of fluid collection.

Clubbing

This is usually classified into 4 grades:

1. *Mild (early):* Obliteration of the normal angle between the nail and the dorsum of the finger.
2. *Moderate:* In addition to obliteration of the angle, longitudinal curving of the nails.
3. *Severe:* Drumstick appearance of the terminal phalanges due to swelling of soft tissues (**Figure 5**).
4. *Gross:* In addition to severe clubbing of the finger and toe nails, there is thickening and enlargement around the wrists and ankles due to thickening of the distal ends of bones.

Icterus

This is seen in patients with chronic hepatic congestion, as in chronic heart failure and constrictive pericarditis. In pulmonary infarction, icterus may occur due to lysis of RBCs with release of bilirubin.

Rheumatic Nodules

A patient with active rheumatic carditis may have subcutaneous, painless, mobile rheumatic nodules on the dorsal aspect of fingers, wrists and elbows.

Osler's Nodes

These are small, red, painful cutaneous nodules usually seen over the pulp of fingers in cases with infective endocarditis.

EXAMINATION OF PRAECORDIUM

The term praecordium refers to the aspect of the chest which overlies the heart. The angle of Louis corresponds to the second costochondral junction. Traditionally, praecordial examination is carried out under the following heads:

Inspection

1. Look for praecordial bulging which is seen in long-standing cases of cardiomegaly or pericardial effusion.

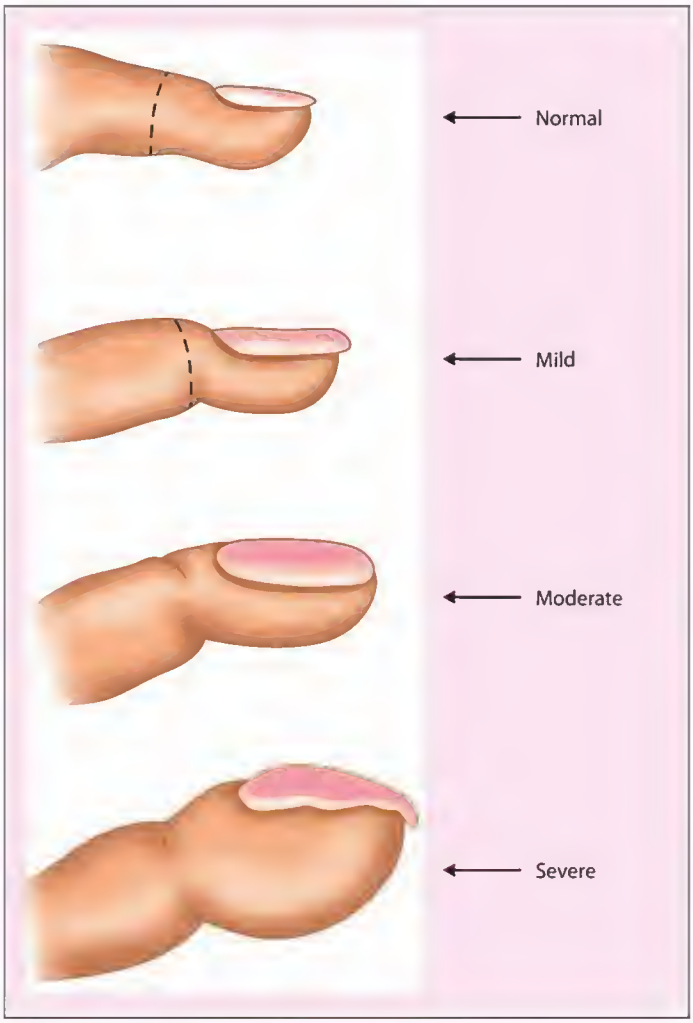


Figure 5: Various grades of clubbing.

2. The apex beat is the lowermost and outermost point of cardiac impulse and is formed normally by the left ventricle.
3. Look for right ventricular pulsations in the left 3rd and 4th intercostal spaces in the parasternal area and in the epigastric region.
4. Pulsations of a prominent pulmonary artery are visible in the left second space parasternally and those of the aorta in the suprasternal notch or sometimes in the right second space parasternally.

Palpation

1. First palpate and define the apex beat. This is best done by the flat of the palm and accurately localised with the tip of the middle finger. This outermost and lowermost point of cardiac impulse gives maximum uplift to a palpating finger kept perpendicular to the chest wall. The apex beat is normally localised in the left 5th intercostal space 1 cm inside the left midclavicular line. Ascertain the character of the apex beat and feel for a thrill. Thrills are palpable vibrations (purring sensation) corresponding to loud murmurs. One may occasionally feel a loud opening snap or third heart sound.

   A tapping or slapping apex beat which is characteristic of mitral stenosis is an ill-sustained, low-amplitude apex beat. It represents a palpable loud first heart sound. An abrupt, forceful or hyperkinetic apex beat is indicative of a diastolic-overload type of left ventricular hypertrophy as seen in aortic incompetence, mitral incompetence, ventricular septal defect and patent ductus arteriosus. A sustained heaving apex is suggestive of a systolic-overload type of left ventricular hypertrophy as seen in aortic stenosis, hypertension and coarctation of aorta. The apex may not be palpable if it is lying under a rib and in emphysema or obese persons.

2. Feel for mid praecordial right ventricular pulsations or heave in the left 4th space in the parasternal plane. A sustained powerful heave indicates systolic-overload type of right ventricular hypertrophy as in pulmonary stenosis and pulmonary hypertension. An abrupt, forceful and hyperkinetic pulsation indicates diastolic-overload type of right ventricular hypertrophy, e.g. tricuspid incompetence.
3. Feel for pulsations in the left second space; these are indicative of enlarged pulmonary artery. Aortic pulsations due to aneurysmal dilatation or unfolding of the aorta are appreciated in the suprasternal notch and right second space. In pulmonary hypertension, a loud pulmonary second sound is palpable as a diastolic shock in the pulmonary area.

Percussion

First percuss the left border of the heart, starting from the left anterior axillary line and proceeding medially with the plexiimeter finger kept parallel to the left border. Defining the right border formed by the right atrium is difficult unless there is gross enlargement of this atrium. One should first find out the upper border of liver dullness and start percussion one space above it from the right mid clavicular plane towards the right sternal plane. Percuss over the left second space and right second space parasternally for dull note in case of pulmonary artery and aortic dilatation.

Auscultation

This is done over the mitral, tricuspid, pulmonary and aortic areas. The mitral area overlies the apex beat; the tricuspid area is over the 5th intercostal space just left of the sternum. The pulmonary area is over the left 2nd space along the lateral sternal border; the aortic I area is over the right second space along the lateral sternal border and the aortic II area (Erb's area) is over the left 3rd space parasternally (**Figure 6**).

Heart Sounds

The first and second heart sounds should be identified, and their intensity and splitting determined. The *first heart sound* is mainly due to closure of the mitral and tricuspid valves. This sound coincides with the R wave on the ECG and the beginning of left ventricular pressure rise.

The *second heart sound* is produced by closure of the aortic and pulmonary valves. The aortic closure sound (A2) corresponds to the incisura of the aortic pressure pulse, and the pulmonary closure sound (P2) corresponds to the incisura of the pulmonary pressure pulse. Both A2 and P2 occur at the end of the T wave on ECG.

The *third heart sound* is due to stretching of the papillary muscle and chordae tendineae during the maximum filling phase of

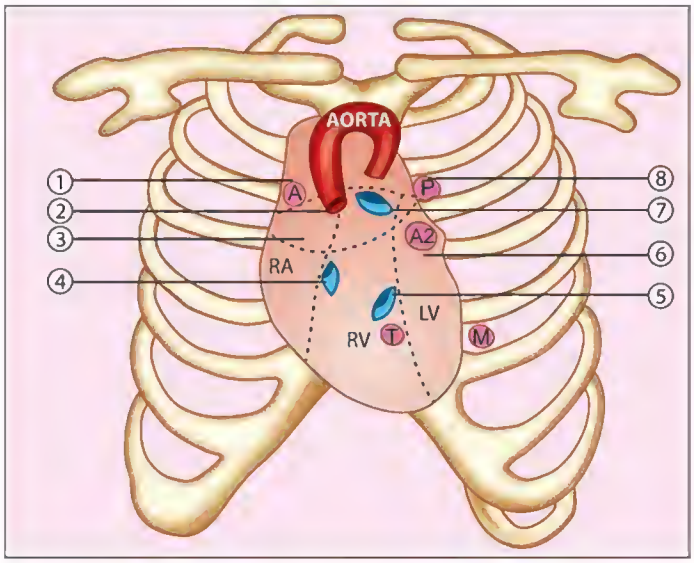


Figure 6: Position of cardiac valves and chambers.

1 = Superior vena cava; 2 = Aortic valve; 3 = Base of the heart; 4 = Tricuspid valve; 5 = Mitral valve; 6 = Left atrial appendage; 7 = Pulmonary valve; 8 = Pulmonary artery, Auscultatory areas; M = Mitral area; T = Tricuspid area; A = Aortic area; A2 = Erb's area; P = Pulmonary area.

diastole. It may be heard normally as a soft sound in children 0.16 s after the aortic component of the second sound. The fourth heart sound is produced during atrial systole by tensing of the mitral or tricuspid cusps; it is not heard normally.

The *opening snap* of the mitral valve is a sharp snappy sound due to abrupt opening of this valve under pressure in mitral stenosis. It occurs 0.06 to 0.12 s after the aortic component of the second sound. *Ejection click* is a sharp sound due to a sudden opening of the semilunar valves under pressure, as in aortic or pulmonary stenosis. It is heard 0.06 s after the first heart sound. In mitral valve prolapse, a mid-systolic click is heard; this is due to tense bulging of floppy mitral cusps into the left atrium.

Murmurs

Murmurs are produced by turbulence of blood flow. It depends on the anatomical abnormality, the pressure gradient along the passage, the volume of blood flow and the viscosity of blood. The anatomical abnormality can be obstruction to forward flow of blood, as in stenosed valves; regurgitation of blood through incompetent valves; and abnormal passage of blood, as in shunts.

The following points should be ascertained about murmurs:

1. Timing in the cardiac cycle
2. Location
3. Conduction
4. Intensity and any special character
5. Influence of posture and breathing

1. *Timing*

Murmurs may be systolic, diastolic, to-and-fro or continuous (**Figure 7**).

A. *Systolic murmurs* may be pansystolic, long systolic, mid-systolic or late systolic.

Pansystolic murmur starts with the first sound and merges with the second sound. Usually, it is of uniform intensity and is classically seen in organic mitral or tricuspid regurgitation and ventricular septal defect. Long systolic murmur starts with the first heart sound but falls short of

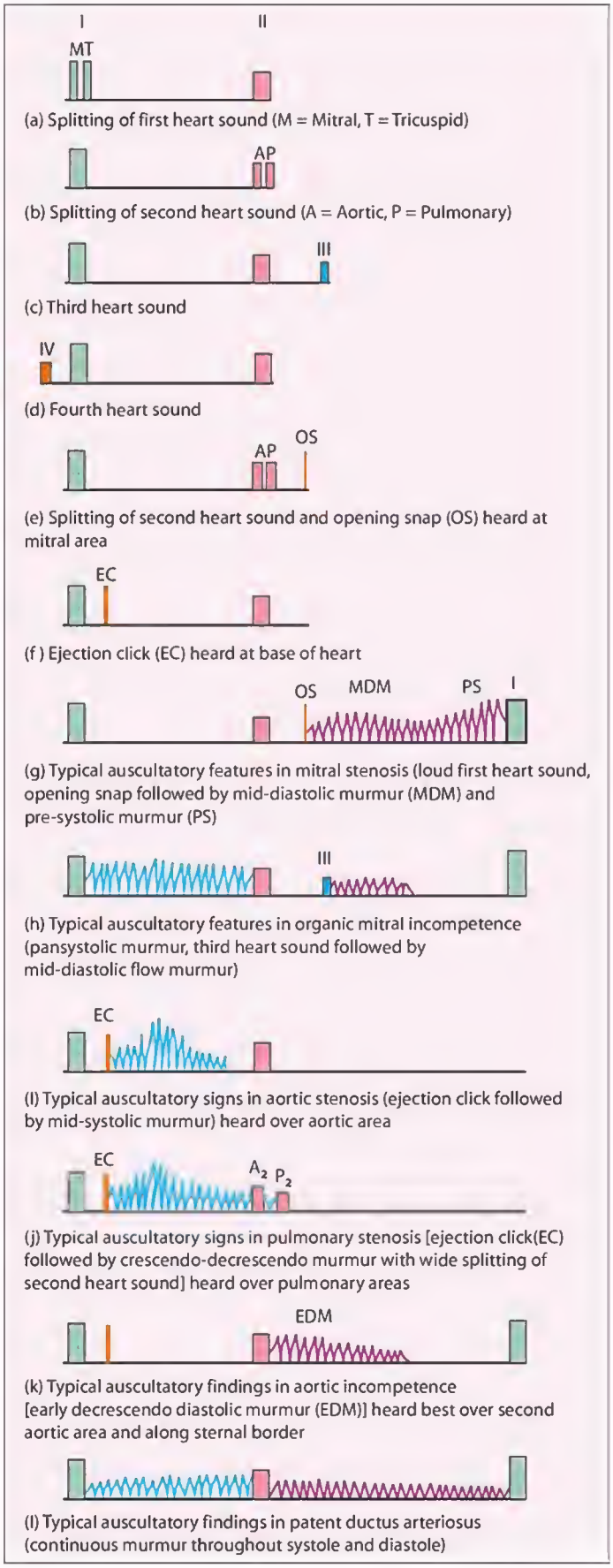


Figure 7: Heart sounds and common murmurs.

the second sound and is usually heard in functional mild mitral or tricuspid regurgitation. Mid-systolic (ejection) murmur starts after the ejection click and ends before the second heart sound. It is crescendo-decrescendo in character with maximum intensity during mid-systole. It is heard in aortic and pulmonary stenosis, systemic hypertension, atherosclerotic aortic disease and in atrial septal defect due to increased flow across the pulmonary valve. Late systolic murmur begins in mid-systole, usually preceded by a mid-systolic sound. It is usually heard in floppy mitral valve syndrome and papillary muscle dysfunction.

B. *Diastolic murmurs* may be early diastolic, mid diastolic or pre-systolic. Early diastolic murmur starts immediately after the second sound, is decrescendo in character, and is best heard at the base of the heart. It is classically seen in aortic and pulmonary regurgitation. In aortic regurgitation, it is best heard over aortic II (Erb's) area with the patient sitting and leaning forward in expiratory apnoea; it is associated with peripheral signs of large-volume pulse. In pulmonary regurgitation, the murmur is best heard over the pulmonary area during inspiration and the pulse is of small volume.

Mid diastolic murmur, seen typically in mitral and tricuspid stenosis, is a rumbling harsh murmur usually preceded by an opening snap. Mitral stenosis murmur is localised over the apex.

Carey-Coomb murmur is a short mid diastolic murmur heard in acute rheumatic fever, due to acute mitral valvulitis. The pre-systolic murmur is a crescendo murmur which ends in a loud, sharp first sound; it is caused by powerful atrial contraction forcing blood through a stenosed mitral or tricuspid valve. This murmur disappears in atrial fibrillation.

C. *To-and-fro (biphasic) murmurs* are encountered when there is a combined stenosis and regurgitation of a valve (e.g. aortic stenosis with regurgitation). To-and-fro murmurs do not cover the second heart sound.

D. *Continuous murmurs* are audible uninterrupted throughout the cardiac cycle. In continuous murmur, the blood flow is in the same direction all throughout, whereas in to-and-fro murmurs the direction reverses in diastole. Continuous murmurs are caused by flow of blood from high to low pressure areas, e.g. in patent ductus arteriosus, aortopulmonary window, rupture of aneurysm of sinus of Valsalva into the right ventricle or right atrium, arteriovenous shunts, and aorto-pulmonary collaterals (bronchial collaterals) as seen in severe tetralogy of Fallot or pulmonary atresia.

Venous hum is a soft, continuous humming sound mimicking a continuous murmur; it is caused by blood flowing through large veins.

2. *Location*

The location where the murmur is heard with maximum intensity is described. For example, murmurs of mitral stenosis and mitral incompetence are best heard over the mitral area, murmur of aortic stenosis is best heard over aortic I area, and that of aortic incompetence is best located at aortic II area.

3. *Conduction*

While a murmur of mitral stenosis is localised over the apex, the murmur of mitral incompetence is conducted towards the posterior axillary or scapular line because the direction of blood flow is from left ventricle to left atrium. The murmur of aortic stenosis is conducted to the neck vessels, and the murmur of aortic incompetence is conducted along the left sternal border towards the apex.

4. *Intensity and pitch*

Levine graded the intensity of murmurs from grades 1-6. Grade 1: very faint, just heard in quiet surroundings; 2: easily audible; 3: moderately loud but without thrill; 4: loud, with thrill, audible with full chest piece of the stethoscope; 5: very loud, with thrill, heard even with the edge of the chest piece; 6: loudest possible, with thrill, audible even with the chest piece just above the chest wall. This grading is for systolic murmurs. Diastolic murmurs are usually classified into 4 grades (from 2-5).

The pitch of a murmur reflects the pressure at which turbulence occurs. If turbulence occurs at high pressure the murmur is called high pitched, and if turbulence occurs at low pressure it is called low pitched. Small leaks produce high pitched murmurs and larger leaks produce low pitched murmurs.

5. *Influence of breathing and posture*

Mitral murmurs are best heard with the patient in the left lateral position, and aortic murmurs, with the patient sitting and leaning forward. Murmurs from the right side of the heart (pulmonary and tricuspid valve lesions) are accentuated during inspiration whereas murmurs from the left-side (aortic and mitral valve lesions) are better appreciated during expiration. With standing, most murmurs diminish except murmurs of hypertrophic obstructive cardiomyopathy (HOCM) and mitral valve prolapse (MVP) which gets louder. With squatting, most murmurs become louder but those of HOCM and MVP usually diminish.

6. *Influence of exercise*

Stenotic murmurs of mitral stenosis (MS), aortic stenosis (AS) and pulmonary stenosis (PS) become louder with both isotonic and submaximal isometric (handgrip) exercise. Murmurs of mitral regurgitation (MR), aortic regurgitation (AR) and ventricular septal defect (VSD) also increase with handgrip, but murmur of HOCM often decrease with hand grip.

7. *Influence of drugs*

Amyl nitrite inhalation decreases murmurs of MR, AR and VSD and increases murmur of AS. During the later tachycardia phase, murmurs of MS and right-sided lesions increase. Vasoconstriction by phenylephrine tends to produce opposite effects.

Functional murmurs

Organic murmurs are produced due to pathologic changes in the heart; murmurs which have no underlying anatomical abnormality are called functional or haemic murmurs.

These are mostly systolic murmurs, invariably without thrill, mainly audible at the base of the heart and are mostly found in young persons.

Prosthetic Valves Sounds

The sounds produced by prosthetic valves vary. Mechanical valves produce opening and closing clicks. Absence or diminution of click sounds raises the suspicion of malfunction of the prosthetic valve. The sounds produced by tissue prosthetic valves are more like normal heart sounds and there are no clicks.

Auscultation of Blood Vessels

A rough continuous murmur with systolic accentuation is heard over an arterio-venous fistula. In aortic insufficiency, a loud first sound or pistol-shot sound is heard over the femoral arteries. Duroziez' murmur is both systolic and diastolic and is brought about by appropriate pressure of the chest piece over the femoral artery.

Continuous arterial murmurs can be heard over the skull or eyeball in arterio-venous fistula and vascular brain tumours, over bones in Paget's disease, over the thyroid in hyperthyroidism, and over a pregnant uterus (uterine souffle). Bruits over blood vessels are due to atheromatous plaques and one should auscultate over the anterior triangle of the neck for the carotid artery, posterior triangle for the vertebral artery, infraclavicular area for the subclavian artery, and flanks or abdomen for renal artery occlusions.

Veins

A continuous humming murmur is heard over the jugular veins in hyperdynamic circulation, e.g. anaemia, hyperthyroidism. In liver cirrhosis with portal hypertension, a venous hum (Cruveilhier-Baumgarten murmur) may be heard over dilated veins connecting the caval and portal venous systems.

Friction Sounds

Friction sounds (rub) synchronous with the heart beat are diagnostic of fibrinous pericarditis. Pericardial rub is unaffected by respiration whereas pleural or pleuro-pericardial friction rubs alter with breathing.

RECOMMENDED READINGS

1. Barrett MJ, Lacey CS, Sekara AE, *et al.* Mastering cardiac murmurs: The power of repetition. *Chest* 2004;126:470.
2. March SK, Bedynek JL, Chizner MA. Teaching cardiac auscultation: effectiveness of a patient-centered teaching conference on improving cardiac auscultatory skills. *Mayo Clin Proc* 2005; 80:1443-8.
3. Pickering TG, Hall JE, Appel LJ, *et al.* Recommendations for Blood Pressure Measurement in Humans and Experimental Animals Part 1: Blood Pressure Measurement in Humans: A Statement for Professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45:142-61.
4. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels; 9th Ed. Boston, Mass: Little, Brown and Co.; 1994: pp. 253-6.

12.3 Electrocardiology

MJ Gandhi

INTRODUCTION

Before the heart contracts, an electric impulse originating in sinus node activates the heart. Electrocardiogram (ECG) is a graph obtained when the electrical potentials of an electrical field originating in the heart are recorded at the body surface. It has many limitations: it records only projections of voltage on a particular lead; it is very approximate; lead positions are not true representations of axis; it has many technical errors. Despite limitations, it has tremendous clinical utility. ECG provides information that is essential for diagnosis and therapy of many cardiac conditions. It reflects anatomic, haemodynamic, molecular, ionic and drug-induced abnormalities of the heart. It may serve as an independent marker of myocardial disease.

ACTIVATION OF HEART

The electrical impulse originates in the sinus node and activates the atria longitudinally and by contiguity. The impulse then reaches the atrioventricular (AV) node, His bundle, left and right bundle and activates the ventricles transversely from endocardial to epicardial surface. Earliest activation is septal depolarisation from left to right. This gives rise to septal Q in I, aVL, V_5 and V_6. This is followed by apical depolarisation of both RV and LV. This causes R in I, II, III. Then occurs depolarisation of entire RV and lateral wall of LV. Finally, the base of LV is activated. In entire depolarisation of ventricles LV potentials predominate over RV. The activation process will change with bundle branch blocks, and ventricular hypertrophies, presence of accessory pathway and in ventricular premature beats.

TECHNICAL ASPECTS

Electrocardiogram Paper

The ECG paper is a strip of graph paper which has vertical and horizontal lines 1 mm apart. The horizontal axis represents time, while the vertical axis denotes amplitude. There is a heavy line every 5 mm in both the planes. Thus, there are small squares, 1 mm × 1 mm and big squares, 5 mm × 5 mm.

Paper Speed

Conventional ECG is taken at a paper speed of 25 mm per second. One small square (1 mm) corresponds to 0.04 s, while a big square (5 mm) is equivalent to 0.20 s. When the ECG paper runs through 5 big squares, 1 sec recording has been taken.

Sensitivity

Voltage is measured along the vertical axis. Usually a 10 mm deflection is equivalent to 1 millivolt (mV). There is a provision to change the sensitivity in special circumstances, e.g. when ECG complexes are too small, the sensitivity can be doubled so that a 1 mV deflection is equivalent to 20 mm. When ECG complexes are too large, sensitivity may be halved so that 1 mV is equivalent to 5 mm.

Lead Systems

The following leads are taken in a conventional 12-lead ECG- (**Figure 1, Table 1**).

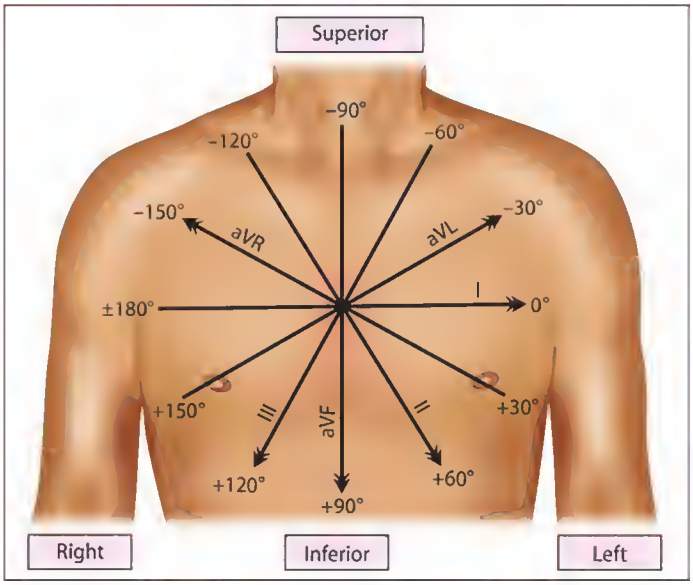


Figure 1: Leads in 12-lead ECG.

Table 1: ECG Leads

Lead	+ve input	–ve input
Bipolar limb lead		
I	LA	RA
II	LL	RA
III	LL	LA
Augmented unipolar limb leads		
aVR	RA	LA + LL
aVL	LA	RA + LL
aVF	LL	LA + RA
Praecordial leads		
V_1	Right sternal margin 4th space	Wilson central terminal (LA + RA + LL)
V_2	Left sternal margin 4th space	Do
V_3	Midway between V_2 and V_4	Do
V_4	Left midclavicular line 4th space	Do
V_5	Left ant. axillary line in same plane as V_4	Do
V_6	Left mid axillary line in same plane as V_4	Do

LA = Left arm; RA = Right arm; LL = Left leg.

Technically Good Electrocardiogram

Correct interpretation of ECG requires attention to several technical points:

With good standardisation, the corners of the signal form a right angle. When the pressure of the stylus over the ECG paper is excessive, there is over-damping which results in rounding-off of these corners. In under-damping, the calibration signal

overshoots the horizontal line. ECG complexes may become spuriously small in an over-damped tracing and small complexes like q and s waves may disappear altogether and ST depression may appear. In under-damping the complexes may become larger and small complexes like q may look significant because of artefactual increase in amplitude.

ECG should have a stable baseline. It should contain at least 3 ECG complexes in each lead. A long strip of II and V_1 should be taken if arrhythmia is suspected or present. There should be absence of alternating current interference and muscle potentials. ECG complexes should be at the centre of the ECG paper, not overshooting the margins.

DEFINITIONS

Waves (Figure 2)

The P wave is the deflection produced by atrial depolarisation. QRS complex is the deflection produced by ventricular depolarisation. Q wave is the initial negative deflection in a QRS complex. When small, it is designated 'q' but when large or pathological, it is depicted as 'Q'. R wave is the first positive deflection in the QRS complex. It is also depicted as r or R depending on its size. It may or may not be preceded by a Q wave. S wave is the first negative deflection after a positive (R) deflection. R' wave is the second positive deflection after an S wave. S' wave is the second negative deflection after an R' wave. QS complex is the term used when the entire QRS complex is negative, without any positive deflection either preceding or following it. ST and T waves are produced by ventricular repolarisation. Atrial repolarisation is represented by a wave which is not visible in the ECG as it is buried within the QRS complex. U wave is the deflection between the T wave and the ensuing P wave. Its origin is uncertain.

Intervals and Segments (Figure 2)

The RR interval is measured between two successive R waves. Either the peak of the R wave or the beginning of the QRS complex can be taken for the measurement of this interval. Ventricular rate can be calculated from the RR interval. The PP interval is the interval measured between either the peak or the beginning of two successive P waves. The PP interval is measured for calculation of the atrial rate. PR interval is measured from the beginning of the P wave to the beginning of the QRS complex. It represents the (AV) conduction time. QRS interval is the total duration of the QRS complex and is measured from the onset of Q or R wave to the J point of the complex. QT interval is measured from the beginning of the QRS complex to the end of the T wave. QT interval corresponds to the duration of electrical systole. PR segment lies between the end of the P wave and the beginning of the QRS complex. ST segment lies between the end of the QRS complex and the beginning of the T wave. The point where the QRS complex ends and ST segment begins is called the J point.

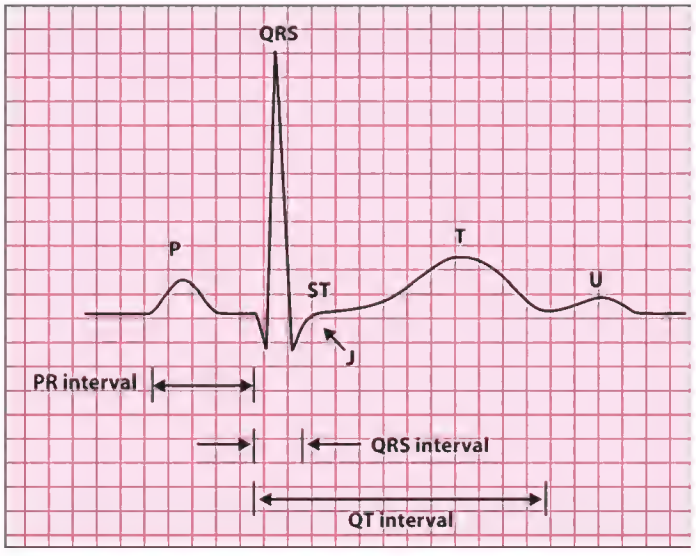


Figure 2: Waves and intervals.

NORMAL ECG

Rhythm

Normally, heart beats are regular; thus the PP and RR intervals are constant. There may be a minor variation of these intervals in normal subjects; a variation of up to 10% in adjacent cycle lengths is considered to be normal.

Rate

Comment should be made on both the atrial and ventricular rates. The atrial rate is derived from the PP interval, while the ventricular rate is derived from the RR interval. At a paper speed of 25 mm/sec the formulae are:

$$\text{Atrial rate/min} = \frac{1500}{\text{PP interval in mm}}$$

$$\text{Ventricular rate/min} = \frac{1500}{\text{RR interval in mm}}$$

Normal atrial and ventricular rates range from 60 to 100/min.

For calculation of the ventricular rate when the RR interval is irregular, as in atrial fibrillation, the number of QRS complexes are counted over 5 s in the rhythm strip and this number is multiplied by 12 to provide the number of QRS complexes in 60 s (1 min). This method enables measurement of the average ventricular rate.

Mean QRS Axis in Frontal Plane

The mean QRS vector is the approximation of all main QRS vectors due to activation of the heart in the frontal plane. It can be measured from all frontal plane leads viz. I, II, III, aVR, aVL, aVF. Attempts are also made to measure the axis in horizontal plane from praecordial leads. However, as these are unipolar leads they do not truly represent horizontal plane (HP) and hence axis in HP, thus measured, is not very reliable.

Methods

Perpendicular method

The mean QRS axis is perpendicular to lead with equiphasic or small QRS complex. For example, if the QRS is equiphasic in lead II, the QRS axis must be perpendicular to the axis of lead II.

Leads with Equiphasic QRS	QRS Axis in Frontal Plane
I (0°)	+90° or –90°
II (+60°)	–30° or +150°
III (+120°)	+30° or –150°
aVR (–150°)	+120° or –60°
aVL (–30°)	+60° or –120°
aVF (+90°)	0° or +180°

Quadrant method

QRS complexes are viewed in I and aVF. When the QRS complexes are predominantly upright (i.e. there is a dominant R in both leads), the axis is normal. If the QRS complex in I is predominantly negative (i.e. dominant S in I) while it is predominantly positive in aVF (i.e. dominant R in aVF), there is right axis deviation. If the QRS complex is predominantly positive in I but negative in aVF, left axis deviation is present. When the QRS complexes in both I and aVF are predominantly negative, the axis is indeterminate. Normal mean QRS axis in the frontal plane varies from –30° to +110°. When the axis is more than +110°, there is right axis deviation, while an axis of less than –30° represents left axis deviation.

Visual method (Table 2)

The same principles can apply to P, T and even ST segment. It makes it easy to predict ECG from QRS axis. In fact, Grant popularised ECG diagnosis by such vectorial analysis. In vectorcardiography one can measure each 0.01 s vector as there is lot of information hidden in each such vector.

Table 2: QRS in Frontal Plane (Visual Method) Predominant QRS Defection (R or S)

I	II	III	AXIS	aVL	aVR	aVF	AXIS
R	R	R	+ 30° to +90°	R			+30° to +60°
				S			+60° to 90°
S	R	R	+90° to +150°		S		+90° to +120°
					R		+120° to +150°
S	S	R	+150° to –150°			R	+150° to ±180°
						S	±180° to –150°
R	R	S	+30° to –30°			R	+30° to 0°
						S	0° to –30°
R	S	S	–30° to –90°		R		–30° to –60°
					S		–60° to –90°
S	S	S	–90° to –150°	S			–150° to –120°
				R			–90° to –120°

P Wave

Normal P wave duration does not exceed 0.10 s. Normal P waves are not more than 2.5 mm tall. P waves are normally upright in I, II, aVF and V_3 to V_6, inverted in aVR and upright, inverted or biphasic in III, aVL and V_1, V_2. P wave morphology is best studied in II and V_1.

PR Interval

Normal PR interval varies from 0.12 s to 0.20 s, i.e. 3 to 5 small squares. Normally, the PR interval should be constant though minor variations may be present.

QRS Complex

Amplitude of QRS in each limb lead (i.e. I, II, III, aVR, aVL and aVF), should be 5 mm or more. In each praecordial lead (i.e. V_1 to V_6), the QRS amplitude should be 10 mm or more. ECG is termed low voltage below these values. Normal QRS complex duration does not exceed 0.11 s (i.e. 2.75 mm) in adults. R wave is dominant in I, II, V_4 to V_6, S wave is dominant in aVR and V_1, V_2. Either R or S wave may be dominant in III, aVL, aVF and V_3 depending on QRS axis.

Q Wave

Small q waves are normally present in I, aVL, V_5, V_6. When the mean QRS axis in the frontal plane approaches +90°, small q waves may be present in II, III, aVF and V_3, V_4 also. A QS complex is commonly found in aVR. There may be deep Q waves in III alone in normal individuals; this may become less prominent on deep inspiration. Occasionally, a deep Q or QS complex is found in V_1 and even V_2. Barring III, aVR, aVL and V_1, V_2 the depth of a normal q wave is less than 25% of the height of the ensuing R wave. In aVL, the depth of a normal q wave may be up to 50% of the height of the ensuing R wave. Any Q wave with amplitude more than this is considered to be pathological. Normal q waves generally do not exceed 0.04 s (i.e. 1 mm) in duration.

ST Segment

The normal ST segment is isoelectric but ST depression < 0.5 mm in any lead is not considered to be abnormal. ST segment elevation up to 1 mm in limb leads and V_5, V_6 and 2 mm in V_1 to V_4 may be normal. The reference line for ST segment elevation is the TP segment while that for depression is the PR segment.

T Wave

Normal T waves are upright in I, II, V_4 to V_6, inverted in aVR and upright, inverted or biphasic in III, aVL, aVF and V_1 to V_3.

QT Interval

The upper limit of normal QT interval is 0.42 s in males and 0.43 s in females. QT interval should be measured in the lead where the end of the T wave is best discernible. QT interval varies with heart rate and, therefore, a correction for heart rate is done by Bazett's formula:

$$QT_C = \frac{QT\ (s)}{\sqrt{RR\ (s)}}$$

ABNORMAL ECG

Abnormal Axis Deviation

Right axis deviation may be due to right ventricular hypertrophy, left posterior hemiblock, Wolff-Parkinson-White (WPW) syndrome, technical dextrocardia and mirror image dextrocardia. Left axis deviation is commonly due to left anterior hemiblock, WPW syndrome, inferior myocardial infarction, chronic obstructive airway disease and left ventricular hypertrophy.

P Wave Abnormalities (Table 3, Figure 3)

These may be due to atrial enlargement and intra-atrial conduction abnormality. Common causes of left atrial enlargement are mitral and aortic valve disease, coronary artery disease and cardiomyopathies. Common causes of right atrial enlargement include mitral valve disease with pulmonary hypertension, cor pulmonale and acute pulmonary embolism.

Table 3: Diagnostic Criteria for LA and RA Abnormalities

LA Abnormalities	RA Abnormalities
P mitrale	P pulmonale
P Duration >120 ms in II	P amplitude >0.25 mV in II
P notching in II PR segment >1.6 mm in II	P axis >175
P terminal force in V_1 > –0.04 mm-s	Area in positive part of P in V_1 >0.06 mm-s
	qR in V_1 V_2 without infarction
	Low QRS in V_1 with three-fold or more increase in V_2

Biatrial enlargement is suggested by combined criteria.

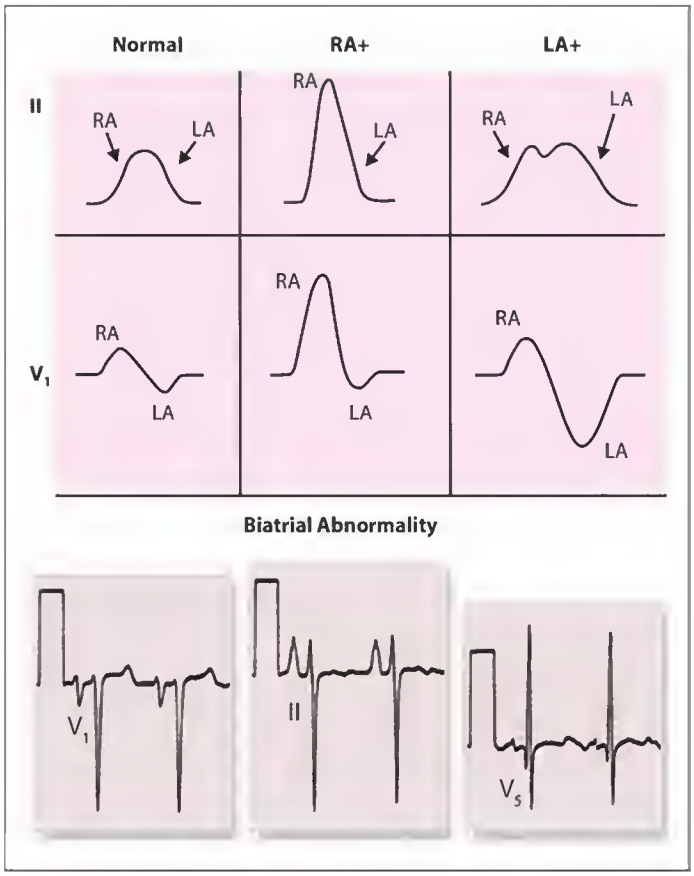


Figure 3: P wave in atrial hypertrophy.

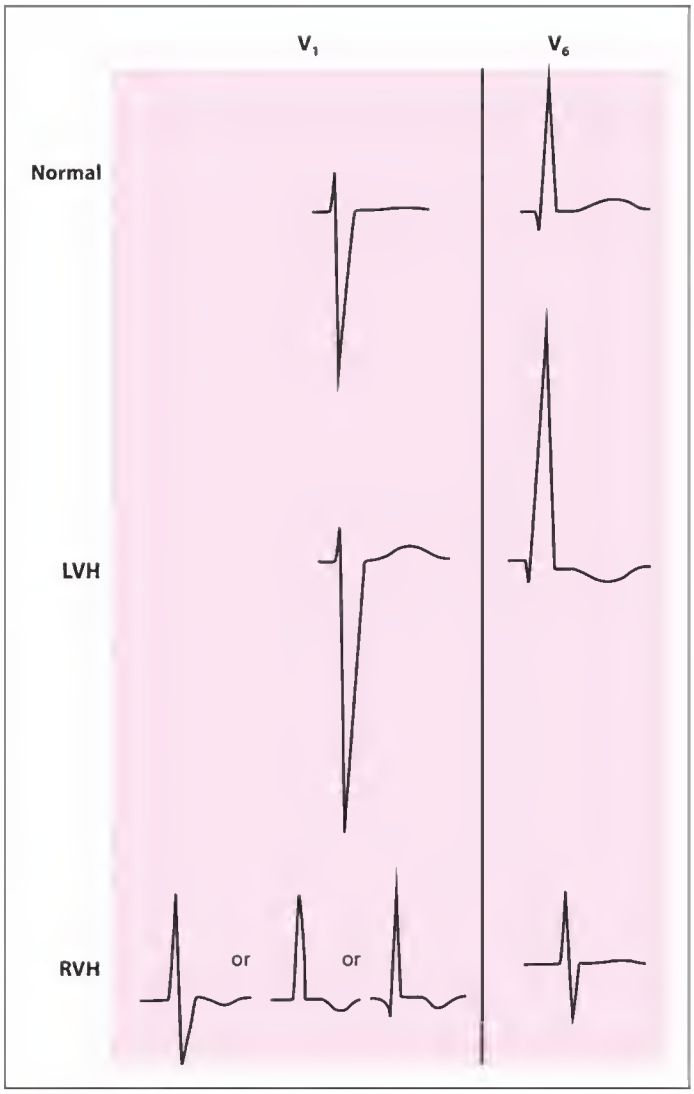


Figure 4: QRS in ventricular hypertrophy.

Abnormal PR Interval

Short PR interval is found in WPW syndrome, Lown-Ganong-Levine syndrome, nodal rhythm and atrial premature beats. Long PR interval (first degree AV block) is commonly observed in rheumatic carditis, digitalis effect and coronary artery disease.

Abnormalities of QRS Complex

Low voltage ECG, i.e. QRS amplitude of less than 5 mm in all limb leads and less than 10 mm in all chest leads, may be due to marked emphysema, myxoedema, pericardial effusion and cardiomyopathy. High amplitude is most commonly due to ventricular hypertrophy. Electrocardiographic criteria of RVH are (**Figures 4 and 5**) qR or qRS pattern in V_1, and tall R wave in V_1 R/S ratio >1, (R/S >1 is also found in true posterior myocardial infarction, WPW syndrome type A and right bundle branch block), deep S waves in V_5, V_6, rS pattern in all praecordial leads. QRS width is within normal limits. ST segment may be depressed and T wave inverted in V_1, V_2 (right ventricular strain). Right axis deviation may be present. P pulmonale is an indirect ECG sign of RVH. RVH is commonly due to mitral valve disease with pulmonary hypertension, cor pulmonale, pulmonary stenosis, tetralogy of Fallot and tricuspid regurgitation.

Left Ventricular Hypertrophy (LVH)

There are several scoring systems which have been suggested for diagnosing LVH, of which the Romhilt-Estes points scoring system is most useful (**Table 4, Figure 4**). ECG criteria for systolic (pressure) or diastolic (volume) overload are different (**Table 5**). Common causes of LVH are mitral regurgitation, aortic valve disease, systemic hypertension, coarctation of aorta and tricuspid atresia.

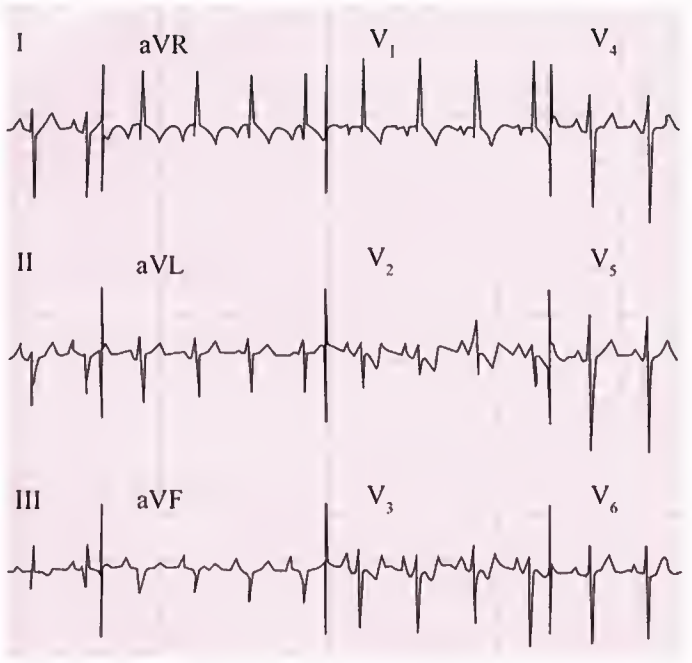


Figure 5: Right ventricular hypertrophy.

Table 4: Criteria for Left Ventricular Hypertrophy

Sokolow-Lyon Index

SV_1 + (RV_5 or RV_6) >35 mm
RaVL >11 mm

Romhilt-Estes point score system (≥5 points)	**Points**
(i) Any limb lead R or S ≥20 mm	3
SV_1 + SV_2 ≥30 mm or RV_5 + RV_6 ≥30 mm	3
(ii) ST-T changes	3
with digitalis	1
without digitalis	3
(iii) LA +	3
(iv) Left axis (≤30)	2
(v) QRS ≥90 ms	1
(vi) Intrinsicoid deflection in V_5/V_6 ≥50 ms	1

Cornell voltage criteria

SV_3 + SaVL ≥28 mm (men)
≥20 mm (women)

Table 5: ECG Criteria in LVH

	Systolic Overload	**Diastolic Overload**
Examples	Aortic stenosis, hypertension	Aortic incompetence, VSD, PDA
Septal q in V_5 to V_6	Attenuated	Prominent
Intrinsicoid deflection in V_5 to V_6	↑	Normal
ST changes in V_5, V_6, I, aVL	↓	Normal or ↑
T inversion in V_5, V_6, I, aVL	↓	Upright
QRS voltage	↑	↑

Biventricular Hypertrophy

ECG criteria of biventricular hypertrophy are definite features of LVH with right axis deviation or deep S waves in V_5, V_6 and definite features of RVH plus tall R waves in V_5, V_6 or deep Q waves in I, aVL, V_5, V_6 or large equiphasic QRS complexes in V_3, V_4 (Katz-Wachtel phenomenon).

Abnormal QRS Configuration

During sinus rhythm, the causes of abnormal QRS configuration include bundle branch block, hemiblocks, non-specific intraventricular conduction defects and pre-excitation.

Right Bundle Branch Block (Figure 6)

Causes of right bundle branch block (RBBB) include acute myocardial infarction, acute pulmonary embolism, chronic cor pulmonale and atrial septal defect. RBBB is sometimes found in healthy persons. The ECG criteria are shown in **Table 6**.

Table 6: Criteria for Right Bundle Branch Block (RBBB)

QRS > 120 ms
Broad notched R (rsr', rSR' or rSR') in V_1, V_2
Wide, deep S in V_5, V_6, and I

Left Bundle Branch Block (Table 7, Figure 6)

The common causes of left bundle branch block (LBBB) are hypertensive heart disease, dilated cardiomyopathy and acute myocardial infarction. It is most often associated with organic disease.

Pathological Q Waves

The criteria for pathological Q waves; usually present in a set of several leads, e.g. in V_1 to V_4 in anteroseptal myocardial infarction; in II, III, and aVF in inferior wall myocardial infarction (**Table 8**). Depth more than 25% of the height of the ensuing R wave in aVL, Q wave is considered to be abnormal if its amplitude is more than or equal to 50% of the height of the R wave. Deep Q waves in III may be entirely normal. In abnormal Q, the duration is more than 0.04 s. Pathological Q waves are mostly due to acute or old myocardial infarction. Rarely, pathological Q waves may be due to other causes, they are then known as 'pseudo-infarction' patterns. Deep Q waves may also be found in severe left ventricular hypertrophy but such Q waves are narrow and are not considered to be abnormal.

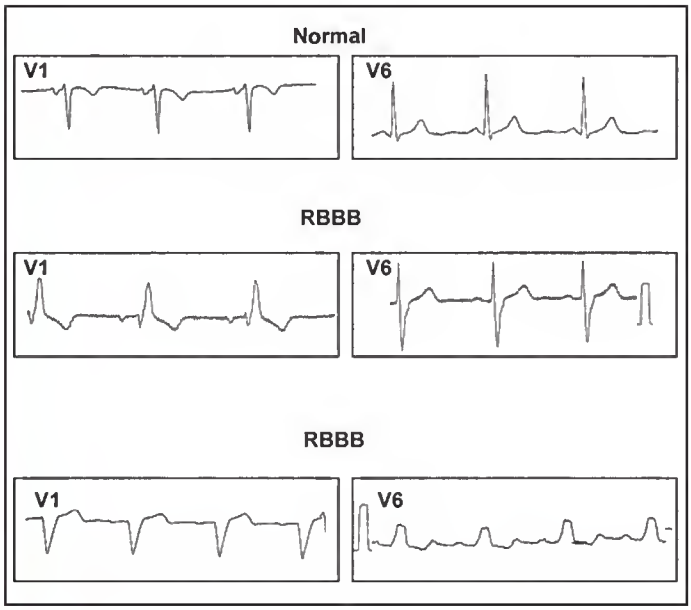


Figure 6: Lead V_1 and V_6 in Bundle Branch Blocks.

Table 7: Criteria for Left Bundle Branch Block (LBBB)

QRS ≥ 120 ms
Broad notched R in V_5 V_6 and usually in I, aVL
Small or absent initial r in V_1 V_2 with deep S
Absent septal q in left-sided leads
Intrinsicoid deflection >60 ms in V_5 V_6

Table 8: Q in Myocardial Infarction

Infarction Site	**Leads**	**Differential Diagnosis**
Inferior (diaphragmatic)	II, III, aVF	WPW (PSAP), HCM
Inferolateral	II, III, aVF, V_4 to V_6	—
Inferoposterior	II, III, aVF, V_1 (Tall R)	WPW (LT. PSAP), HCM
True posterior	V_1 (Tall R)	RVH, Atypical IRBBB, Left AP
Inferior with RV	II, III, aVF + V_{4R} to V_{6R} or V_1 to V_3	ASMI
Anteroseptal	V_1 V_2 V_3	LVH, COPD, LBBB. Chest electrode misplacement
Anterolateral	I, II, aVL, V_{4-6}	HCM, VSD
Extensive anterior	I, aVL, V_1 to V_6	—
High lateral	I, aVL	—
Anterior (apical)	V_3 to V_4	—
Posterolateral	V_{4-6}, V_1 (Tall R)	WPW (left AP)
Right ventricle	V_4R to V_6R or V_1 to V_3	ASMI

PSAP = Posteroseptal accessory pathway; AP = Accessory pathway; HCM = Hypertrophic cardiomyopathy; VSD = Ventricular septal defect; ASMI = Anteroseptal myocardial infarction.

Abnormalities of ST Segment

ST segment elevation

It is seen in acute myocardial infarction. ST segment is convex upwards. It is present over the site of infarction. It can also occur when there is transmural ischaemia, e.g. in coronary artery spasm (Prinzmetal angina) or occasionally during stress test. Occasionally, it may persist in post-myocardial infarction phase (ventricular aneurysm pattern). In acute pericarditis ST elevation is seen in all leads except aVR. ST segment is concave upwards. The above two are the commonest. But, there are other causes, viz. early repolarisation, in V_1-V_2 or V_3 in LVH/LBBB, or type IC anti-arrhythmic drugs, hyperkalaemia, hypercalcaemia, after DC-cardioversion, intracranial haemorrhage, myocarditis, trauma, tumour in LV or Brugada syndrome (RBBB with ST elevation in right praecordial leads).

ST segment depression

It is an electrocardiographic sign of myocardial ischaemia when the entire ST segment is depressed rather than the J point (QRS-ST segment junction) alone. The depression is horizontal or down-sloping. The depression exceeds 0.5 mm at a point 80 ms (2 mm) from the J point. Greater the degree of ST segment depression, more are the chances of this representing myocardial ischaemia. ST depression is however seen in many abnormalities, viz. hypertrophies, bundle branch blocks, myocarditis, cardiomyopathies, drugs, etc. They are non-specific if such changes can be mimicked by hyperventilation or standing and are also called labile ST changes.

Abnormalities of T Wave

T waves are termed tall when their height exceeds 1 mV (10 mm). Causes of tall T waves include hyperacute myocardial infarction (tall and wide T) and hyperkalaemia (tall but narrow-tented T waves).

T wave inversion is most often non-specific and transient. Causes of T wave inversion are given in **Table 9**. The most important issue in the differential diagnosis of inverted T waves is whether T wave inversion is due to myocardial ischaemia or not. The differences which may serve to separate ischaemic from non-ischaemic T waves are given in **Table 10**.

Table 9: Causes of T Wave Inversion

Physiological	Pathological
Young children (V_1 to V_4)	Ventricular hypertrophy (strain)
Young females (V_1 to V_4)	Pre-excitation syndrome
Change of posture	Bundle branch block
Deep respiration	Digitalis effect
After heavy meals	Myocardial ischaemia

Abnormal QT Interval

Prolonged QTc may be due to hereditary causes with or without deafness as a part of specific syndromes, anti-arrhythmic drugs, e.g. quinidine, procainamide, disopyramide and amiodarone, electrolyte disturbances like hypokalaemia, hypocalcaemia, liquid protein diet; during acute myocardial infarction and idiopathic. QTc prolongation may be associated with a form of polymorphous ventricular tachycardia known as 'torsades de pointes'. QTc shortening may signify hypercalcaemia.

Table 10: Ischaemic versus Non-Ischaemic T Waves

Ischaemic T Waves	Non-ischaemic T Waves
Deep	Shallow
Symmetrical	Asymmetrical
Relatively sharp and well-defined (arrow head)	Rounded and vague

Myocardial Infarction (Figure 7)

Electrocardiographic hallmarks of acute myocardial infarction are shown in **Figure 7**. The electrocardiogram also provides information about the site of infarction, its extent and stage and complications like arrhythmias and pericarditis. Depending on the location of the infarct, ECG changes of acute myocardial infarction occur in different sets of leads (**Table 8**). Persistent ST segment depression with T wave inversion signifies subendocardial or nontransmural infarction while the infarction is called transmural when new pathological Q waves appear. In resolving (recent) myocardial infarction the ST segment begins to settle down progressively till it is isoelectric. Persistent raised ST segment after 6 weeks may represent ventricular aneurysm. T wave inversion persists for a longer time but ultimately becomes upright except uncommonly when it may persist indefinitely. Reciprocal changes disappear concomitantly with ST-T changes or even earlier. Old myocardial infarction is characterised by persistent Q waves. In most instances pathological Q waves constitute the only electrocardiographic evidence of old myocardial infarction. Though pathological Q waves persist indefinitely in most cases, the size may reduce in about 20% of patients. Very rarely, Q waves may disappear altogether, especially following inferior infarction.

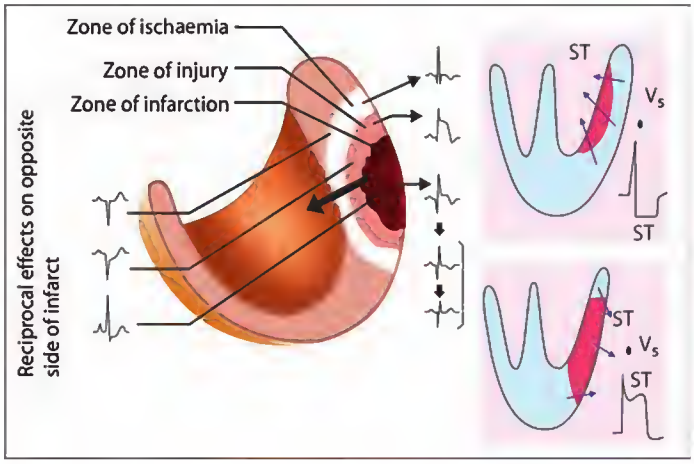


Figure 7: ECG changes in myocardial infarction.

Abnormalities of Heart Rate

Bradycardia (Figure 8)

Bradycardia is a heart rate below 60/min. This may be due to sinus bradycardia, junctional rhythm and atrio-ventricular blocks. Sinus bradycardia is recognised when a P wave precedes each QRS complex with a fixed PR interval. The ventricular rate in sinus bradycardia usually does not fall below 45/min. Causes of sinus bradycardia include athletic training, sick sinus syndrome, drugs (e.g. beta-blockers), myxoedema, uraemia, obstructive jaundice and raised intracranial pressure. In nodal rhythm, no P waves precede the QRS complexes, and the ventricular rate is generally from 45/min to 60/min (**Figure 8**).

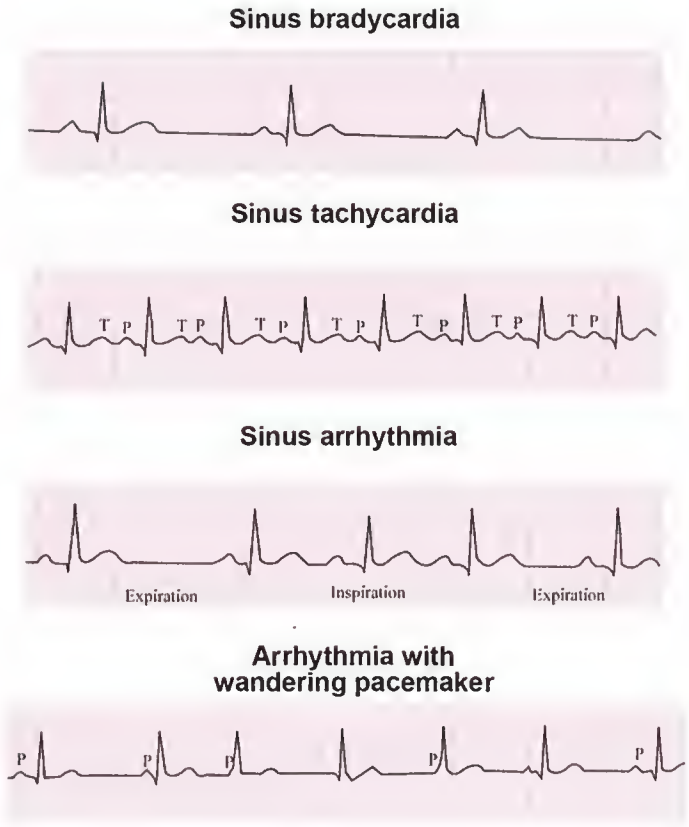


Figure 8: Abnormalities of heart rate.

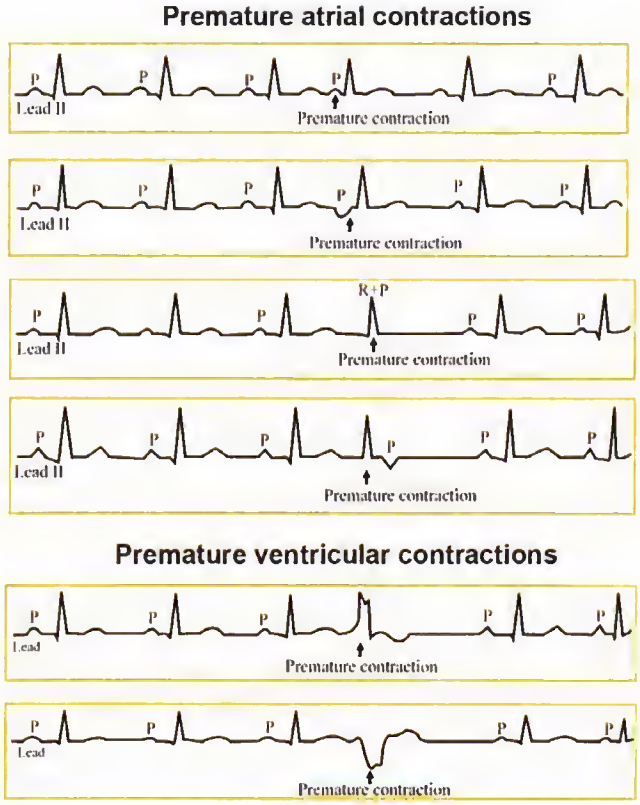


Figure 9: Ectopic beats.

Sinus tachycardia

Tachycardia is heart rate above 100/min. It is recognised by a normal P wave preceding each QRS complex. Heart rate usually does not exceed 150/min, but occasionally may be higher especially in children. Causes of sinus tachycardia include anxiety, fever, hypoxaemia, drugs, e.g. vasodilators and atropine, thyrotoxicosis, cardiac failure and acute carditis.

Ectopic beats, ectopic or re-entrant tachycardias

Atrial premature beats (Figure 9)

Atrial ectopic beats occur due to premature discharge from an ectopic atrial focus. The P wave of an atrial ectopic beat occurs before the next sinus P wave is anticipated. The configuration of the ectopic P wave is abnormal because it arises from a focus different from the sinus node. The premature, abnormal P wave of the atrial ectopic is designated P'. The compensatory pause is incomplete, i.e. the PP interval between the sinus beats which precede and follow the atrial ectopic beat is less than twice the PP interval between the two consecutive sinus beats. Atrial ectopic beats may or may not be associated with heart disease; more often they are not. Sometimes, these precede development of atrial tachycardia or atrial fibrillation. Causes of atrial ectopics are physiological like anxiety, excess tea, coffee or cola drinks and pathological as in viral infections, rheumatic heart disease, coronary artery disease, digitalis toxicity and cardiomyopathies.

Paroxysmal supraventricular tachycardia (Figure 10)

The most common form of paroxysmal supraventricular tachycardia (PSVT) is due to AV nodal re-entry with dual AV nodal pathways. Identification of P waves is difficult or impossible because atrial and ventricular depolarisations occur simultaneously. Occasionally, abnormal P waves may follow QRS complexes. The ventricular rate varies from 170 to 250/min. The rhythm is absolutely regular, i.e. the RR interval is constant. QRS morphology is usually normal. The ST segment may be depressed, and T wave may be inverted. PSVT most commonly occurs in individuals with structurally normal hearts. It is precipitated by an atrial premature beat. Occasionally PSVT occurs in association with Wolff-Parkinson-White or Lown-Ganong-Levine syndrome.

Atrial fibrillation (Figure 10)

In atrial fibrillation, the electrical activation and recovery of the atria are chaotic. Waves of depolarisation bombard the AV node at frequent (350 to 500/min) and irregular intervals with only some of them being able to pass through to the ventricles. The baseline is irregular and wavy (fibrillatory waves usually best seen in V_1). In rheumatic heart disease, the amplitude of the fibrillatory waves exceeds 0.1 mV (coarse fibrillation), while in coronary artery disease, fibrillatory waves are smaller (fine fibrillation). Occasionally the deflections are so fine that the baseline appears smooth in which case the irregular QRS complexes help to diagnose atrial fibrillation. Ventricular rate is usually 120 to 180/min in atrial fibrillation of recent onset unless the patient is already digitalised or is receiving beta-blockers or drugs like verapamil or amiodarone. The RR interval is irregularly irregular. The causes of atrial fibrillation include rheumatic heart disease, especially mitral stenosis, coronary artery disease, cardiomyopathies, thyrotoxicosis, and rarely constrictive pericarditis. Sometimes atrial fibrillation is idiopathic (lone atrial fibrillation) or occurs in chronic obstructive airway disease especially during acute respiratory infection. Transient or paroxysmal atrial fibrillation may occur following any surgery. Other causes of paroxysmal atrial

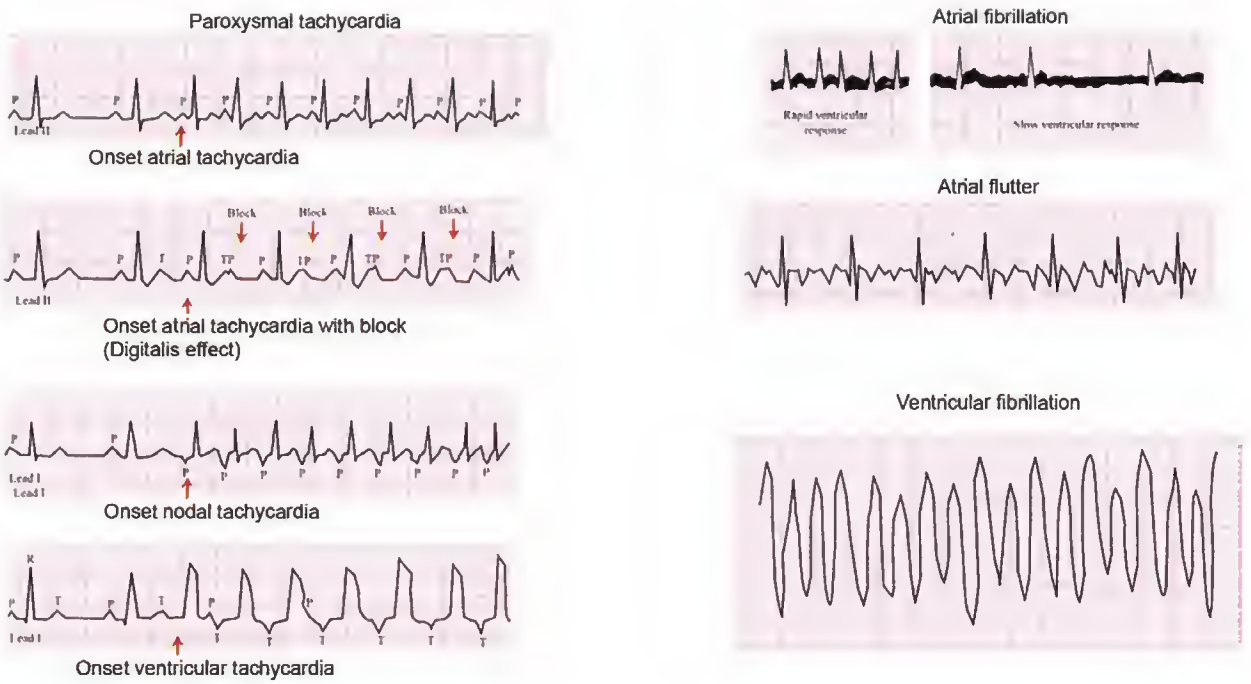


Figure 10: Atrial and ventricular tachyarrhythmias.

fibrillation include WPW syndrome, thyrotoxicosis and elderly age group.

Atrial flutter (Figure 10)

Atrial flutter (AF) is due to intra-atrial re-entry. Electrocardiographically, it is characterised by a regular, undulating baseline (flutter or F waves) resulting in a saw-tooth or corrugated appearance. There is no isoelectric line in between two P waves unlike in ectopic atrial tachycardia. Flutter waves are usually best seen in II, III, aVF and V_1. Flutter waves appear at a regular rate of 250 to 350/min. When flutter waves show some irregularity, the rhythm is designated 'flutter-fibrillation'. QRS complexes are normal and the RR interval is regular. Usually two flutter waves follow one QRS complex (2:1 AV block); however, 1:1 AV conduction may also occur. Other patterns of AV conduction like 4:1 may also occur but odd conduction ratios (e.g. 3:1) are rare. Occasionally, the AV conduction pattern is variable, giving rise to an irregular RR interval. Causes of atrial flutter are the same as for atrial fibrillation, i.e. chronic mitral valve disease, coronary artery disease and thyrotoxicosis.

Ventricular premature beats (VPBs) (Figure 9)

Ventricular premature beats (VPBs) occur due to premature discharge of a ventricular ectopic focus. There is usually no P wave preceding the QRS complex, unless the VPB is relatively late (late diastolic ventricular ectopic). The QRS complex appears earlier than anticipated, i.e. the RR interval shortens abruptly. The QRS complex is wide, bizarre and slurred or notched. When there are frequent VPBs, all may be similar in morphology (unifocal VPB) or they may show varying morphology (multifocal or multiform VPB). The ST segment is depressed and T wave inverted when the R wave is dominant in the QRS complex of the VPB. A dominant S wave is associated with the opposite pattern. A retrograde P wave may follow the QRS complex due to retrograde activation of atria across the AV node. The compensatory pause is complete, i.e. the RR interval between two sinus beats immediately preceding and following the VPB is twice the RR interval between two consecutive sinus beats. The coupling interval, i.e. the interval between the VPB and the preceding sinus beat is constant in unifocal VPBs. The coupling interval remains constant when the VPBs are multiform but is variable when these are multifocal. This is because multiform

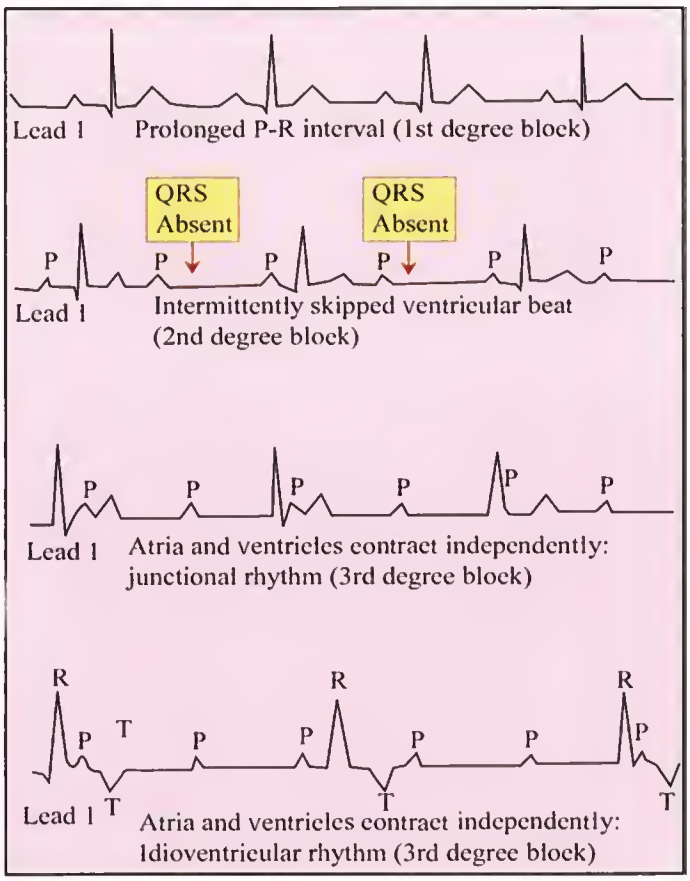


Figure 11: Atrioventricular block.

VPBs arise from the same focus though their morphology is variable while multifocal VPBs arise from different foci. The term 'ventricular bigeminy' is used when every alternate beat is a ventricular ectopic beat. It often occurs as a part of digitalis toxicity and in acute myocardial infarction. Isolated VPBs may be present in healthy individuals, especially in the elderly. Other common causes are digitalis toxicity, acute myocardial infarction, cardiomyopathies and electrolyte imbalance.

Ventricular tachycardia (Figure 10)

The diagnostic criterion of ventricular tachycardia (VT) is the occurrence of three or more successive ventricular premature contractions at a rate exceeding 100/min. Ventricular tachycardia may be non-sustained or sustained. Non-sustained tachycardia terminates spontaneously within 30 seconds while sustained ventricular tachycardia lasts for >30 seconds. Unless treated, ventricular tachycardia may degenerate into ventricular fibrillation and death. Causes of ventricular tachycardia are the same as those of VPBs. Coronary artery disease, especially acute myocardial infarction and the post-infarction period, account for a large number of cases of ventricular tachycardia. It may also occur in absence of structural heart disease when it is labelled as idiopathic ventricular tachycardia.

Ventricular fibrillation

Ventricular fibrillation (VF) is characterised by completely chaotic and irregular deflections of various height and width without any recognisable wave pattern. VF is the most common terminal event before death. Other terminal events are complete asystole, agonal rhythm (irregular ventricular complexes without any meaningful rhythm) and electromechanical dissociation (lack of mechanical contraction of myocardium despite organised electrical activity).

Atrioventricular block (Figure 11)

First degree atrioventricular block (AV block, heart block) when PR interval is >0.2 seconds. Second degree AV block is present when a QRS complex is missing following a P wave after a fixed or variable number of cardiac cycles. Second degree AV block is of two types—Mobitz type I block or Wenckebach type is characterised by a progressive prolongation of PR interval, shortening of RR intervals and dropping of a QRS complex following a number of conducted sinus beats. Mobitz type II block is characterised by a fixed PR interval without serial

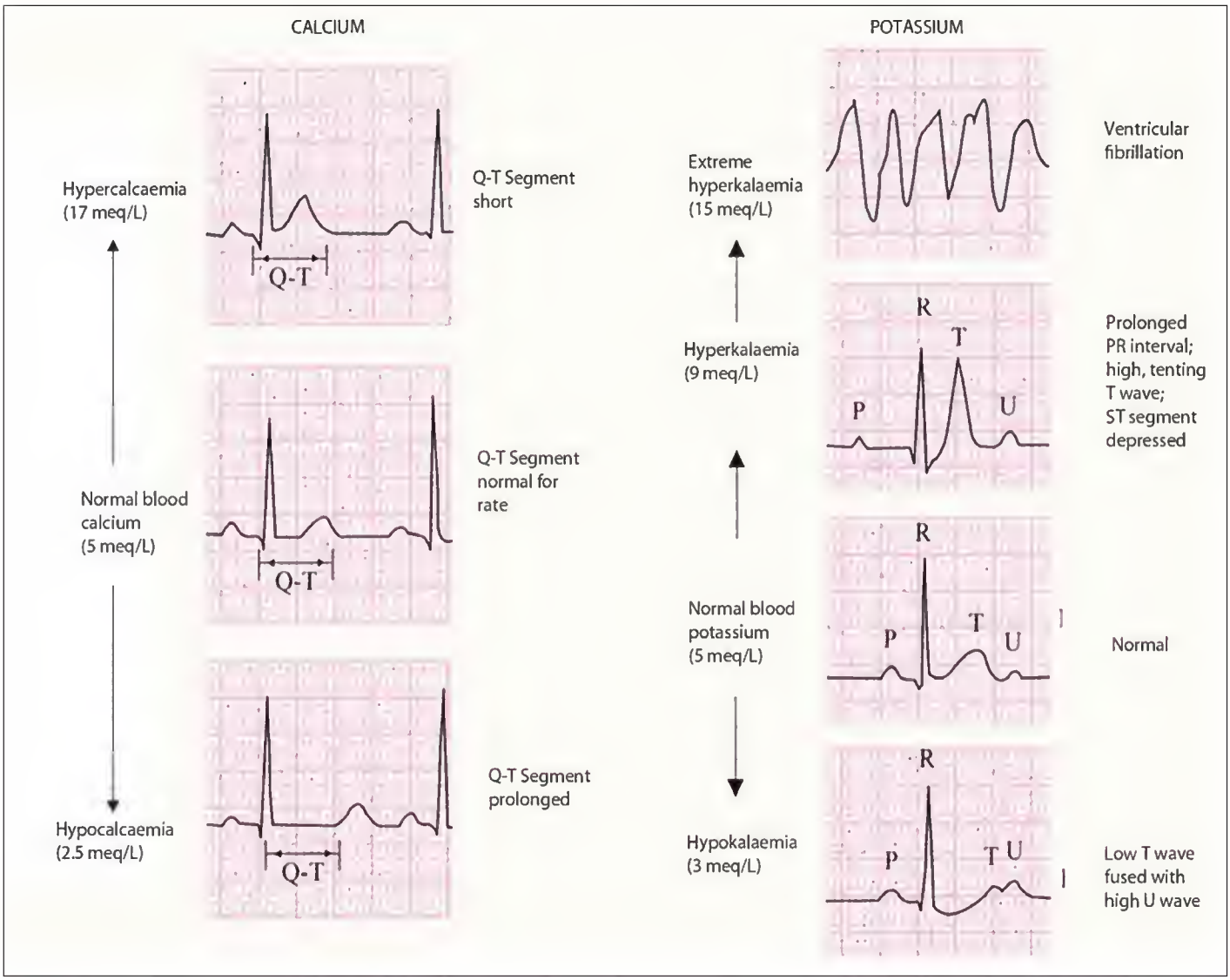


Figure 12: Effects of electrolytes on electrocardiogram.

prolongation, and intermittent, abrupt dropping of a QRS complex following a number of conducted sinus beats. The QRS complex is often wide and may exhibit either RBBB or LBBB pattern.

Mobitz type I (Wenckebach) block is generally due to failure of AV conduction at the level of the AV node. Prognostically, it is not so serious as it is unlikely to be progressive. Complete heart block either does not occur or occurs transiently following type I block. Type II block is most often due to failure of conduction below the AV nodal level, in the bundle of His or below it. It is more serious since it may progress on to an irreversible complete heart block. Common causes of second degree AV block are:- type I-acute inferior myocardial infarction, digitalis intoxication and acute carditis; type II-acute anterior myocardial infarction and degenerative disease of the conduction system. Complete heart (atrioventricular) block (CHB) is characterised by regular appearance of P waves which do not bear any relationship to the QRS complexes, i.e. the QRS complexes are dissociated from P waves. The former appear regularly at a rate of 20 to 40/min and represent discharge from the escape focus. The QRS may be normal or wide depending on the site of origin of the ventricular impulse. Failure of the escape ventricular focus to develop immediately or to remain stable after the onset of CHB, or a very slow rate, results in syncopal (Stokes–Adams) attacks due to interruption of blood supply to the brain. Recovery of the escape focus leads to consciousness within a few seconds in most cases. However, failure of recovery of the escape mechanism may result in death. Common causes of complete AV block include acute myocardial infarction (inferior and anterior), sclero-degenerative disease of the conduction system, and digitalis intoxication. Uncommonly, CHB is congenital in origin.

Electrolyte Disturbances (Figure 12)

Hypokalaemia is characterised by a prominent U wave which is generally the earliest change. Other electrocardiographic features are flattening and inversion of the T wave, ST segment depression, prolongation of PR interval and predisposition to ventricular arrhythmias. In hyperkalaemia the earliest change associated is occurrence of tall, peaked and narrow T waves. Progressive hyperkalaemia leads to a prolonged PR interval, atrial asystole, QRS widening, merging of QRS with T wave leading to sine wave configuration, and ultimately ventricular fibrillation followed by ventricular asystole.

Hypocalcaemia causes prolonged QT interval. Hypercalcaemia causes shortening of QT interval, with decreased T wave amplitude, sometimes with notching or inversion of the T wave.

RECOMMENDED READINGS

1. Castellanos A, Interian A Jr, Myerburg RJ. The resting electrocardiogram. In: Valentin Fuster, R Wayne Alexander, O'Rourke RA, *et al.* editors: *Hurst's The Heart International Edition*. New York: McGraw-Hill; 2001: pp 281-314.
2. Chug SN. *Textbook of Clinical Electrocardiography;* 1st Ed. Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2003.

12.4 Exercise Testing

Yash Pal Munjal

INTRODUCTION

Exercise testing is a non-invasive test used to evaluate the cardiovascular system's response to graded exercise under controlled conditions. Over the past eight decades it has provided useful diagnostic and prognostic information in patients of cardiopulmonary disease. With the advent of computer technology and digital imaging the various tests to assess the cardiovascular system have shown a remarkable progress and increase in their accuracy. Exercise testing has also improved in its technology, interpretation and accuracy of results. This has established 'the exercise test' as an important and useful test. This test in combination with other imaging modalities like echocardiography or radionucleotide imaging provides much more sensitivity and specificity to this test resulting in better diagnosis, better prognostication, assessment of cardiac perfusion and localisation of lesion. On the flip side the addition of these modalities significantly adds to the cost. This test has also been used to assess the athletic performance and for cardiovascular research. In association with pulmonary gas exchange measurements during exercise it provides unique and clinically relevant information about the cardiopulmonary health.

EXERCISE PHYSIOLOGY

The body adapts itself to the increasing intensity of exercise by increasing the metabolic rate. The body can increase the metabolic rate by up to 20 times the basal metabolic rate. During this adaptation the cardiac output (CO) also increases from 5 litres per minute to 25 litres to 30 litres per minute. The various adaptations mentioned above are achieved by the following haemodynamic changes:

1. Increase in heart rate
2. Increase in CO (achieved by increase in stroke volume and heart rate)
3. Increase in systolic blood pressure while the diastolic blood pressure is maintained at basal level or may show a downward trend
4. There is a fall in the total peripheral vascular resistance

To achieve the increase in the metabolic rate there is a progressive increase in the consumption of oxygen (mL/min) by various tissues. This is achieved by extracting more oxygen from the increased volume of circulating blood. Despite exercise the arteriovenous oxygen-difference is maintained within the narrow range of 15 mL/dL to 17 mL/dL. These changes in various parameters are dependent on age, gender, body mass index, type of exercise, body fitness, training and finally presence or absence of cardiovascular disease. It is evident from the above description that to meet the requirement of increased work load during exercise the total body oxygen consumption (VO_2 Max) and the oxygen consumption by the myocardium (MVO_2) increase considerably. These two parameters are distinct and their pathophysiology is at variance with one another.

The Total Body Oxygen Consumption

This is the total amount of oxygen extracted from the inspired air by the body to perform increased load of work. The CO and peripheral arteriovenous oxygen difference are the major determinants of VO_2 Max. Since the body mechanisms restrict the maximal arteriovenous oxygen (AVO) difference to a maximum of 15 mL/dL to 17 mL/dL. Thus the CO indirectly is a measure of maximal oxygen uptake (MVO_2 Max). During treadmill exercise the VO_2 Max may also be presented as the units of work load achieved. This is expressed as metabolic equivalent (MET), and it represents the oxygen consumption in litres/min. One MET is equated with the resting metabolic rate (approximately 3.5 mL of O_2/kg/min). The MET value achieved during an exercise test is presented as a multiple of the resting metabolic rate which can be measured directly by the oxygen uptake or estimated from the maximal workload achieved using equations. **Table 1** shows the level of work load achieved with various levels of exercise and its clinical significance.

Table 1: Clinically Significant Metabolic Equivalents for Maximum Exercise

1 MET	Resting
2 METs	Level walking at 3.2 kmph
4 METs	Level walking at 6.4 kmph
<5 METs	Poor prognosis, peak cost of basic activities of daily living
10 METs	Prognosis with medical therapy as good as coronary artery bypass surgery
13 METs	Excellent prognosis regardless of other exercise responses
18 METs	Athletes with high level of endurance
20 METs	Athletes at world class athletic performance

MET = Metabolic equivalent or a unit of sitting, resting oxygen uptake; 1 MET = 3.5 mL/kg/min oxygen uptake; kmph = kilometres per hour.

The Myocardial Oxygen Consumption

The myocardial oxygen consumption is the amount of oxygen utilised by the heart muscle during exercise. This is determined by various factors like left ventricular pressure and end-diastolic volume, contractile force of the heart and the heart rate. Myocardial oxygen uptake is estimated as the product of heart rate and systolic blood pressure (double product). It provides clinically useful information as angina on effort often occurs at the same myocardial oxygen demand (double product). The greater is the double product the better is the myocardial perfusion and prognosis. The double product may be low due to other limiting factors like a heavy meal, abnormal ambient temperature, organic coronary occlusion or coronary artery spasm.

The clinical and electrocardiographic (ECG) manifestations of exercise test are due to abnormalities in myocardial perfusion and function. The ECG response and angina are closely related to the increasing level of myocardial ischaemia. The other manifestations are limitation of the exercise capability, sudden spurt in systolic blood pressure or a fall in the systolic blood pressure and aberrant heart rate response to exercise. The ischaemia can also trigger cardiac rhythm disturbances and serious forms of cardiac arrhythmias may occur during exercise. These provide useful parameters to assess the myocardial ischaemia and long-term prognosis.

METHODOLOGY OF EXERCISE TESTING

There are three types of exercise modalities: (i) isotonic exercise or dynamic exercise, (ii) isometric or static exercise, and (iii) combination of the two forms of exercise.

Commonly, it is the isotonic or dynamic exercise which is used for conducting the exercise test. This can be performed on a treadmill or a bicycle ergometer. Treadmill test involves greater muscle mass and hence achieves a higher level of oxygen uptake. Based on this various dynamic protocols for conducting stress test have been enunciated. Some of them are Bruce, Naughton and Ellstead which are commonly used and, out of these, Bruce protocol is the one which is put to the maximum use. The protocol chosen for a particular patient should be such that it lasts for about 8 minutes to 12 minutes for continuous progressive exercise so that relevant information can be elucidated.

The test involves testing the heart under the stress of exercise and therefore the following prerequisites are essential:

1. The equipment must be properly calibrated and standardised.
2. A detailed history, physical examination and a pretest electrocardiogram must be done to evaluate the condition of the cardiovascular system of the patient.
3. Emergency resuscitative measures should be available at hand.
4. All due precautions must be taken before the test is performed, during the test (i.e. during the period of exercise) and after the termination of exercise.
5. All through the test the following parameters must be monitored at all times. These are electrocardiogram, blood pressure and clinical features like chest pain, dizziness, syncopal feeling or development of a third heart sound gallop or basal crepitations.
6. After the exercise has been terminated it is important to put the patient back in supine position and the monitoring should continue till all the parameters of electrocardiogram, blood pressure and heart rate have settled. But in normal individuals it must be done for at least 5 minutes post exercise.

Indications and Contraindications of Exercise Test

The indications and contraindications for stress testing are enunciated in **Tables 2 and 3** respectively.

In exercise testing, it is important to know when to stop the exercise so that no harm occurs (**Table 4**).

Table 2: Indications for Stress Testing

Evaluation of the status of coronary artery disease in patients of angina pectoris
Diagnosis of coronary artery diseases in patients with atypical chest pain or variant angina
Screening of high risk individuals, patients of diabetes or patients with two or more other coronary risk factors
Assessment of prognosis, functional capacity and evaluation of therapy
Assessment of functional capacity in patients of congestive heart failure, congenital or valvular heart disease
To evaluate patients with exercise related arrhythmias
To test the endurance capacity of athletes and those individuals who are in high risk vocations like pilots, drivers, etc.

Table 3: Contraindications to Exercise Testing

Absolute Contraindications
Unstable angina/acute myocardial infarction
Symptomatic cardiac arrhythmias with haemodynamic instability
Severe aortic disease like aortic valve stenosis and aortic dissection
Severe congestive heart failure
Recent pulmonary embolism
Test can be done with caution
Use of drugs, e.g. digitalis, β-blockers, etc.
Electrolyte imbalance
Arterial hypertension
Non-critical cardiac arrhythmias
Obstructive hypertrophic cardiomyopathy
Physical disability or unsound mind.

Table 4: Termination of Exercise Testing

Moderate to severe angina
Ataxia, dizziness
Fall in systolic blood pressure
Development of cardiac arrhythmias especially ventricular tachycardia
Significant ST segment depression (>2 mm of horizontal or down-sloping ST segment
Development of left bundle branch block or high degree of AV block
Increase in blood pressure more than 200 mm Hg
Refusal of the patient to continue exercise

Safety of Exercise Test

Exercise test is relatively a safe procedure with a high yield of diagnosis and prognosis in patients of cardiovascular disease. From a large number of series and experience of over 20 years it is estimated that there is one event per 10,000 patients. Despite the safety record of the test, it is essential to reiterate that the test must be done in the presence of a trained professional and with all resuscitative measures at hand.

INTERPRETATION OF EXERCISE TEST

It is important to interpret the exercise test in a comprehensive manner. This means that non-ECG and ECG parameters have to be taken together for interpretation. Various equations and scores have been devised based on these parameters. It is

estimated that the accuracy of stress test per se can go up to 80% with the use of these scores.

ELECTROCARDIOGRAPHIC CHANGES

Normal Electrocardiographic Changes During Exercise

The following changes in the electrocardiogram are observed while exercise in a normal adult:

(i) Increase in P wave amplitude

(ii) Shortening of PR, QRS and QT intervals with increasing heart rate

(iii) PR segment progressively becomes down-sloping in leads II, III, aVF and associated with this is the J point depression

Abnormal Response

It is predominantly the ST segment changes which are used to interpret the exercise test. The changes in ST segment can be:

(i) No change in the ST segment

(ii) Upsloping depression of ST segment

(iii) Horizontal ST segment depression

(iv) Down-sloping ST segment depression with T inversion

(v) ST segment elevation

These changes are diagrammatically presented in **Figure 1**.

ST segment depression indicates global ischaemia. The ST segment depression in inferior leads (II, III, aVF) does not predict ischaemia correctly. The ST segment depression cannot localise the site of ischaemia and the coronary artery involved. The horizontal or down-sloping ST segment depression of equal to or more than 1 mm is definite indicator of ischaemia. ST segment depression in anterior pericardium leads, i.e. V_4, V_5 and V_6, is quite important. Of all these leads, the changes in lead 5 as a single lead has maximum validity. An upsloping ST segment depression has doubtful accuracy in diagnosing ischaemia. ST segment depression 0.80 second beyond the J point of more than 1.5 mm is suggestive of ischaemia. ST segment depression seen in leads with Q wave does not carry the same importance. ST segment depression seen during the recovery phase may also indicate coronary artery diseases. ST segment elevations seen in leads without Q wave is highly suggestive of coronary artery disease and if it is associated with ST segment depression in the reciprocal leads, it indicates critical coronary lesion or a severe spasm of the coronary arteries.

ST segment depression in patients with left bundle branch block, Wolff–Parkinson–White syndrome, intraventricular conduction defects, implanted with pace makers or on drugs does not have the usual diagnostic power of ST segment depression. Some of the representative exercise tests are shown in **Figures 2 to 4**.

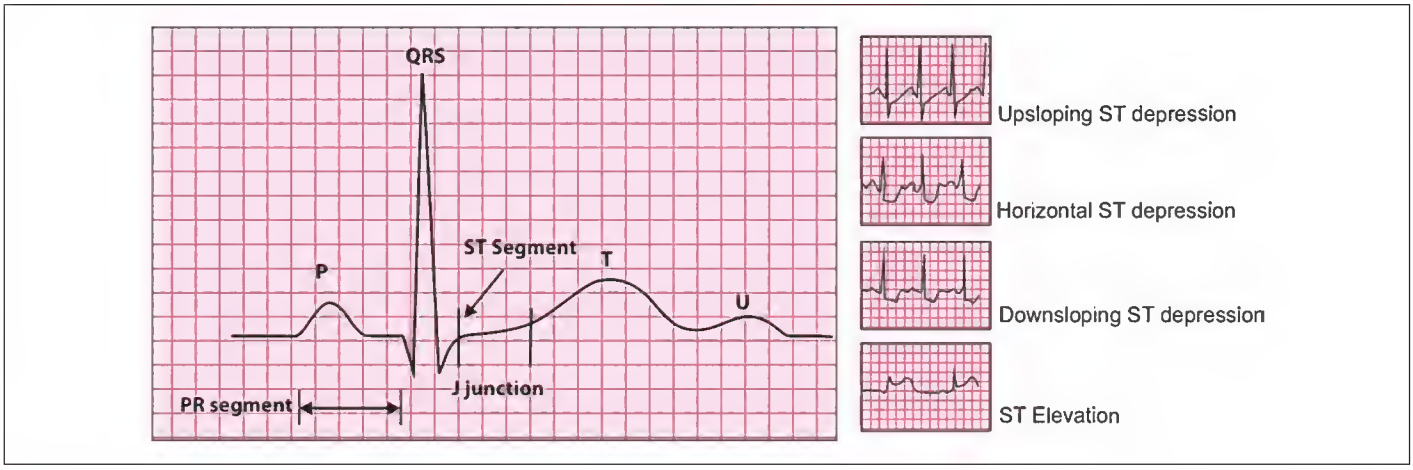


Figure 1: Electrocardiograph nomenclature.

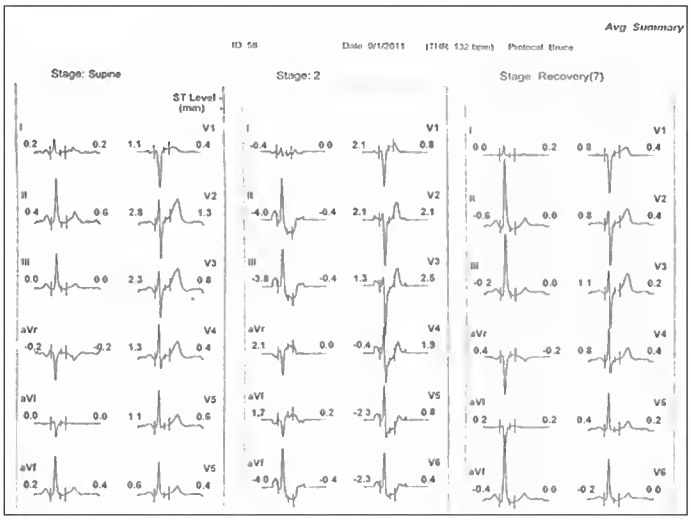


Figure 2: Exercise test showing significant horizontal ST depression.

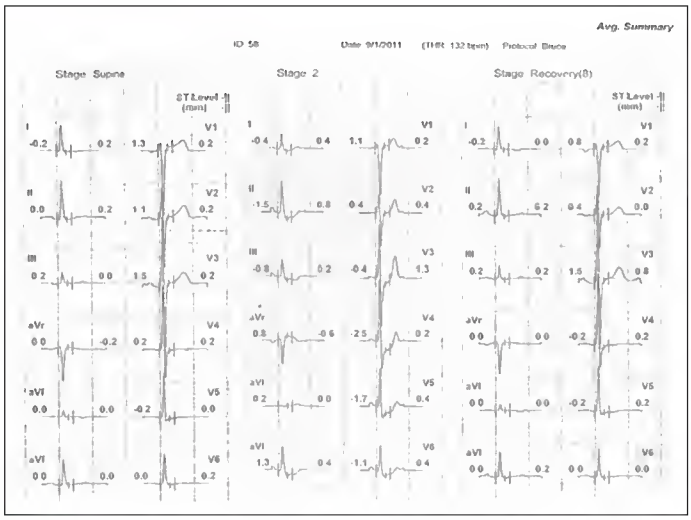


Figure 3: Exercise test showing upsloping ST depression.

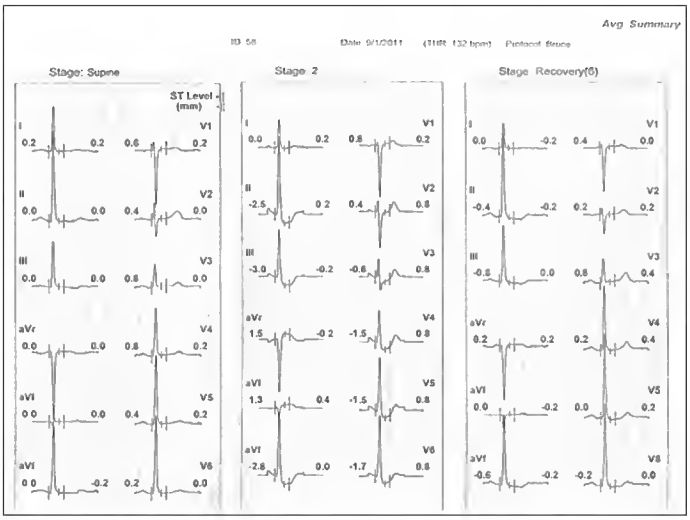


Figure 4: Exercise test showing ST-T changes and persisting in recovery.

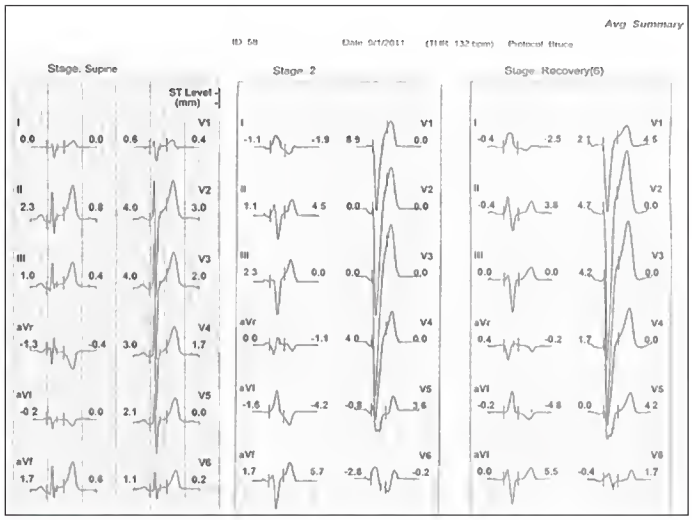


Figure 5: Exercise-induced LBBB.

Disturbances in Cardiac Rhythm

Ventricular arrhythmias in patients with known coronary artery disease or asymptomatic coronary artery disease have an increased risk of death and disability. In patients with congestive heart failure, presence of murmurs in the heart and existing ECG abnormalities at baseline, the exercise induced ventricular arrhythmias carry a grave prognosis. A sustained ventricular tachycardia with a normal baseline electrocardiogram also is associated with poor outcomes. Supraventricular tachycardias are an uncommon occurrence and do not seem important as ventricular arrhythmias. Similarly, bradyarrhythmias like development of high degree AV block are suggestive of poor myocardial function and critical coronary artery disease.

Bundle Branch Block

The development of right or left bundle branch block (LBBB) in isolation during the exercise does not indicate a bad prognosis (**Figure 5**). In case there is associated angina pectoris with development of bundle branch block then it is of grave importance.

NON-ECG PARAMETERS

Heart Rate

The heart rate increases with exercise, and inappropriate increase in the heart rate at the beginning of exercise can occur in patients predisposed to atrial fibrillation, poor effort tolerance, hypovolaemia, anaemia and in patients of left ventricular systolic dysfunction. The increase in the heart rate in response to the exercise may be blunted in patients where the sympathetic tone does not increase with the level of exercise or in sinus node dysfunction, myocardial ischaemia and patients on beta-blockers. The delay in heart rate recovery is indicative of abnormalities of vagal tone and is associated with high mortality.

Blood Pressure

As described earlier, the increasing work load of treadmill is associated with progressive increase in the systolic blood pressure while no significant change takes place in diastolic blood pressure or there may be slight fall. In patients with increased sympathetic tone, there may a sudden increase in blood pressure and an increase in blood pressure to more than 200 mm Hg systolic is an indication to stop exercise. There may be exertional hypotension (i.e. fall in blood pressure of >10 mm Hg) or the failure of the systolic blood pressure to increase beyond 120 mm Hg indicates triple vessel disease. The possibility in such patients of cardiomyopathy, hypovolaemia and left ventricular outflow obstruction has to be kept in mind and excluded.

Other Parameters

The myocardial oxygen consumption and the perfusion of the heart are measured by the double product (i.e. heart rate x blood pressure). This is also a useful predictor and a double product of more than 25,000 is desirable. It has been seen that the onset of angina most of the time takes place at the same level of double product and therefore can help in planning of exercise for patients of coronary artery disease.

The following factors, viz. duration of exercise, maximum heart rate achieved, associated ST segment changes can provide useful information about the diagnosis and prognosis.

Other Physical Parameters

The cardiac examination also has to be carried out before and during the exercise test. The development of cardiac murmurs, 3rd heart sound or evidence of left ventricular failure (development of basal crepitations) point strongly to the triple vessel disease and poor outcomes.

BENEFITS OF EXERCISE TESTING

Diagnostic Utility

An isolated stress test has a sensitivity and specificity of 68% to 77%. This is significantly lower in patients of single vessel coronary artery disease but in patients of triple vessel disease or left main disease, it may reach 80%. Use of various scores, especially like Duke Treadmill, increases the sensitivity to over 80%. The test may be false positive in women, patients on digitalis therapy, valvular heart disease, hypokalaemia and anaemia. The diagnostic utility of stress test has been established in patients with non-specific chest pain or screening of high risk cardiovascular patients. It may be used as a research tool to evaluate the effects of various forms of therapy and similarly to test patients in risky vocations like pilots, drivers, etc. The utility of stress test in assessment of

the functional status in patients of coronary artery disease, congestive heart failure, valvular heart disease is now well established and an objective assessment of improvement can be done pre- and post-therapy.

Prognosis

Stress test has been found to be quite useful to provide information on prognosis in the following clinical situations:

(i) Patients with coronary artery disease who have suffered a cardiac event or have undergone a cardiac intervention

(ii) Patients with valvular heart disease

(iii) Patients with congestive heart failure

The prognosis cannot be given in isolation but is based on the evaluation of ECG changes, changes in the heart rate, blood pressure and work load achieved. Patients who achieve a work load of less than 5 MET are associated with poor prognosis. **Table 1** gives the work load achieved, its clinical implications and prognosis. ST segment depression which is either down-sloping or horizontal and seen in more than 5 leads or ST segment depression at the beginning of exercise with a heart rate of less than 100 all carry a sinister prognosis.

CONCLUSION

Exercise stress test is the second most commonly performed test after electrocardiogram. It is a useful complimentary test to medical history and physical examination. The evidence has clearly shown that interpretation of stress test using various treadmill scores (e.g. Duke Treadmill score) improves the diagnostic and prognostic capability of the test without escalating the cost. A well-calibrated instrument and the performance of the test in an accurate manner is critical for obtaining good results. The test should only be done with clearly defined indications, and it should be avoided strictly in presence of contraindications. In this particular test, it is of vital importance that the operator should be well versed when to terminate the exercise test. The knowledge and the limitations in interpreting the test have to be understood and the result should be interpreted in a comprehensive manner using both the ECG and non-ECG criteria. The knowledge of the limitations in case of abnormal electrocardiogram at the beginning of the test has to be properly understood and rightly excluded. The use of diagnostic and prognostic scores, such as Duke Treadmill score, has increased the value of stress test very significantly.

RECOMMENDED READINGS

1. Fletcher GR, Balady GJ, Amsterdam EA, *et al*. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;104:1694-740.
2. Gibbons RJ, Balady GJ, Bricker JT, *et al*. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002;106:1883-92.

12.5 Echocardiography

Satish Kumar Parashar

INTRODUCTION

Echocardiography is the heart of clinical cardiology. In today's rapidly evolving fields of interventional cardiology, cardiac surgery, electrophysiology and clinical cardiology, echocardiography plays a major role like never before. Echo-Doppler imaging is a key component in not only establishing diagnosis, but also critical to medical and therapeutic decision-making and monitoring response to therapy. In a statement by American College of Cardiology 'Echo has been a fastest growing technique, the wealth of information which provides is unmatched, and is likely to be the stethoscope of the future'. This is because, not only it provides full anatomical and functional information, but also complete haemodynamic information. Because of its portability and providing immediate diagnosis, its role has extended to critical care areas, cardiac catheterisation and electrophysiology laboratories, operating rooms, etc. The strength of information it provides has mitigated the need of invasive studies in large number of cardiac disorders, especially valvular and congenital lesions. One of the many dramatic advances in the instrumentation is the miniaturisation of the equipment, and now palm-sized equipment is available which can be carried in the pocket during clinical rounds (**Figure 1**). Some of the other technological advancements have been transoesophageal echocardiography (TEE), 3D echocardiography, myocardial contrast echocardiography (MCE), quantitative tissue Doppler imaging (TDI), etc.

As echocardiography and Doppler is a very vast subject with its application in practically every cardiac disorder, hence due to constraint of space, some basic aspects will be discussed.



Figure 1: A small-sized hand held ultrasonic device weighing only 390 grams (*Reproduced with permission from the Editor, Indian Heart Journal*).

BASIC MODALITIES OF ECHOCARDIOGRAPHY

The basic imaging techniques, for the beginners, include conventional 2D and M-mode imaging, Doppler modalities including colour flow imaging. All these modalities rely on the presence of a special type of crystals, called piezoelectric elements, located in the transducer which is a very essential component of the equipment. These crystals vibrate by the passage of electrical current and generate ultrasound waves which are transmitted in the body. Part of the ultrasound waves are reflected back and are electronically processed in the equipment producing characteristic images. Different types of electronic transducers are available which are used for different imaging A high frequency transducer (4 to 7.5 mHz) is used for infants because they have less penetration and better resolution, because in infants and small children, the cardiac structures are closer to the chest wall. In contrast, a low frequency transducer is used in adults, because they need a deeper penetration but with lesser resolution. The current digital machines have increasingly fast processors allowing the handling of immense quantity of data.

M-Mode Echocardiography

This was the earliest form of echocardiographic examination. It provides limited information because it is virtually a single point study and does not provide information in the lateral dimension. There has been a controversy whether this modality needs to be abolished. However, it will continue to stay because in a large number of centres, it is still being used for various chamber dimensions and thickness. As will be discussed later, it still gives useful information.

2D Echocardiography

This is the starting point in any echo examination and gives a wider view of the heart. As such multiple structures can be seen in one imaging plane. Its main applicability is that it provides complete anatomical and functional information, including ejection fraction. However, it does not provide any haemodynamic information.

Standard Imaging Planes

There are a large number of imaging planes, the description of which is beyond the scope of this paper. Every plane depicts different structures and myocardial segments in a different format. However four scan planes must be used in every patient. These are: (a) Parasternal long axis view commonly referred as PLAX view (**Figure 2**); (b) Short axis view – SAX view, which is at various levels like aortic valve and great vessels mitral valve, papillary muscle, apex; (c) Various apical views like four chamber view (**Figure 3**), three chamber or long axis view, two chamber view; and (d) Subcostal view which is the best view for initiating a paediatric examination. Suprasternal, right parasternal and right supraclavicular views are taken in special situations. In any particular patient attempt should be made to obtain all views as twhese are complementary to each other. Every transducer has an index mark which is utilised for imaging the structures in a particular format, e.g. in apical four chamber view, if the index mark is pointing towards the right shoulder then the LV will be on the left-side of the screen and if it is at about 3o'clock position then it will be on right-side of the screen.

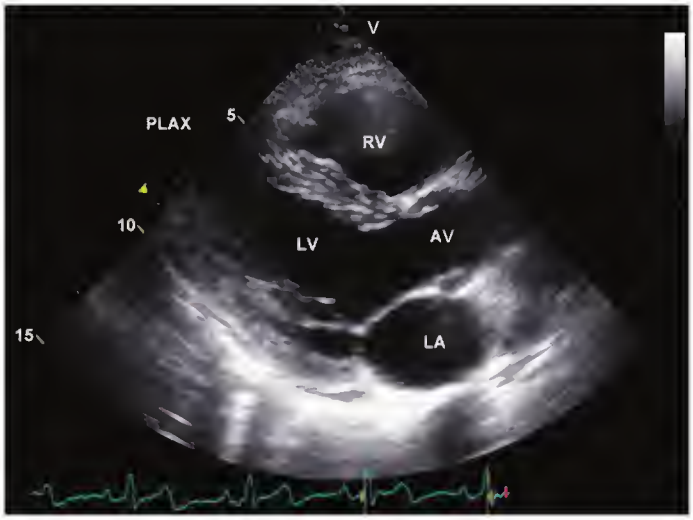


Figure 2: Systolic frame of parasternal long axis view showing opened aortic valve (AV) within the aortic root, left atrium (LA), right and left ventricles (RV, LV), closed mitral valve is between LA and LV. Interventricular septum is between RV and LV.

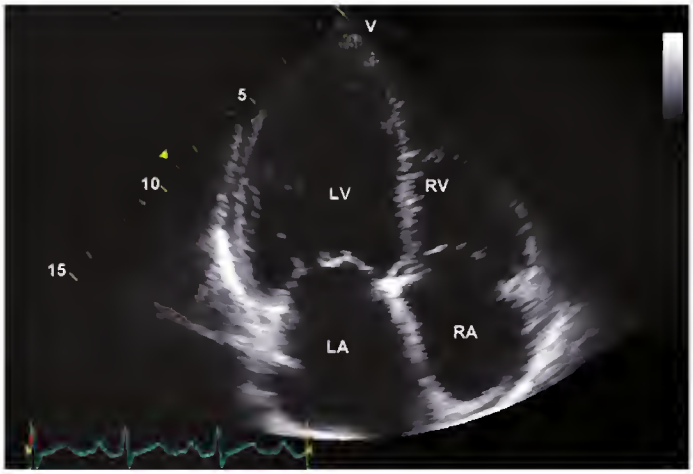


Figure 3: Apical four chamber view showing both ventricles (LV and RV) and both atria, LA (left atrium), RA (right atrium). The interatrial and interventricular septum are well seen. The mitral and tricuspid valves are between their respective atrio-ventricular chambers. The index mark is towards the right shoulder.

Doppler Echocardiography

Currently it is an integral part of any echocardiographic examination as it provides a comprehensive haemodynamic information. This is the main technique to provide accurate assessment of severity of any cardiac lesion. In Doppler, the moving red blood cells are the target from where ultrasound waves are reflected. The Doppler principle and computerised analysis of returning Doppler signals allow velocity and direction of flow to be determined. The blood flowing towards the transducer is depicted as a positive wave above the baseline and *vice versa* (**Figure 4**). Irrespective of any 2D imaging view, the transducer is always pointing downwards from the top (apex). This helps in determining whether the Doppler spectrum will be above or below the baseline. Doppler records velocity of blood flow at a particular area. This allows determination of gradients (difference of pressure between two chambers) by the well validated modified Bernoulli equation, i.e. $4 \times (\text{velocity})^2$. If the peak velocity across any valve is 4 m/s, then the peak gradient is $4 \times 4^2 = 64$ mm Hg. The mean gradient, which is an average of multiple instantaneous gradients over a cardiac cycle, is more diagnostic of severity of a lesion rather than peak gradient which is dependent on the blood flow across a structure. It is obtained by tracing the Doppler envelope (**Figure 4**). The two main Doppler modalities are: (a) pulsed Doppler which calculates low velocity flow at specific points along the jet of blood flow; and (b) continuous wave Doppler which records high velocity flows, hence is used for all diseased states like valvular lesions, shunt flows, estimation of pulmonary artery pressure, etc. One of the most important requirements of Doppler study is that best quantitative results are obtained by putting Doppler beam as parallel to the flow as possible. All quantitative parameters are under-evaluated if one is off angle to the flow. This is unlike 2D examination where best imaging is obtained if the ultrasound wave is perpendicular to the structures. This is why PLAX and SAX views are best imaged. The Doppler velocities are depicted in the vertical axis while timing is along the horizontal axis.

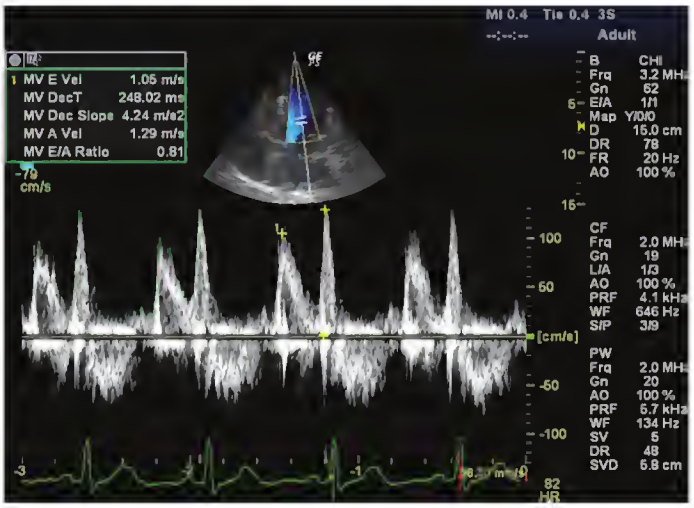


Figure 4: Doppler spectrum of mitral valve showing a positive shift above the baseline. By tracing the Doppler envelope (second from right), peak and mean gradients are obtained.

Colour Flow Mapping (CFM)

CFM is effectively an automated 2D version of Pulsed Doppler technology, in which one can visualise the actual colour coded blood flow. By convention, flow towards transducer is depicted as a red colour and flow away in blue. Normally the flow colours are smooth while in diseased flow states additional colours are added to the conventional colours known as turbulent 'mosaic pattern'. In day-to-day practice, the two main advantages of CFM are: (a) by seeing the direction of the Doppler beam can be placed parallel to the blood flow to get best quantitative results; and (b) by seeing a turbulent flow, it is immediately evident that a diseased area is being studied.

Requisites for a good echocardiographic examination:

1. A good clinical evaluation is mandatory to form a clinical impression.
2. ECG tracing must be available to know the timing sequence.
3. Patient should be as comfortable as possible.
4. The sequence of study should be 2D, CFM followed by Doppler.
5. All scan planes should be thoroughly studied.
6. All haemodynamic information should be obtained.

7. Multiple lesions can be present, so never be satisfied with detection of one lesion.
8. Determine aetiology of a particular abnormal finding, e.g. if LVH is present, explain whether it is due to aortic valve disease/cardiomyopathy/hypertension/any other lesion.

HAEMODYNAMIC INFORMATION OBTAINED FROM ECHOCARDIOGRAPHY

One of the major advantages of echocardiography is providing a haemodynamic information non-invasively. As mentioned earlier, 2D echocardiography provides a structural and functional information while Doppler gives a haemodynamic information, i.e. velocities, gradients, etc. As haemodynamics is an extensive subject hence evaluation of only right atrial (RA), and right ventricular/pulmonary artery (RV/PA) pressure will be briefly discussed.

The importance of determining RA pressure (RAP) is mainly two-fold: (a) it gives an idea of intravascular volume status and helps in management strategy; and (b) RAP is added to various right heart haemodynamic values to get a correct number. The RA pressure is mainly evaluated by inferior vena cava (IVC) diameter and its collapsibility during spontaneous respiration. In a normal individual the IVC diameter is 1.7 to 2.0 cm and there is a normal inspiratory collapse of >50%. This indicates a mean RA pressure of about 10 mm Hg. The IVC is scanned from subcostal view and measurements are made about 1 to 2 cm from IVC-RA junction with patient in supine position. The IVC collapsibility index is calculated as: IVC maximum diameter –IVC minimum diameter/IVC max × 100. A greater than 50% collapsibility indicates RAP of greater than 10 mm Hg (**Figure 5**). A dilated IVC with less than 50% collapse indicates an RAP of 15 mm Hg, while a dilated IVC and hepatic vein with no significant collapse of IVC indicates an RAP of about 20 mmHg necessitating fluid restriction and need for diuretics. On the other hand, a small IVC (<1.2 cm) with spontaneous collapse may indicate hypovolaemia requiring fluid replacement.

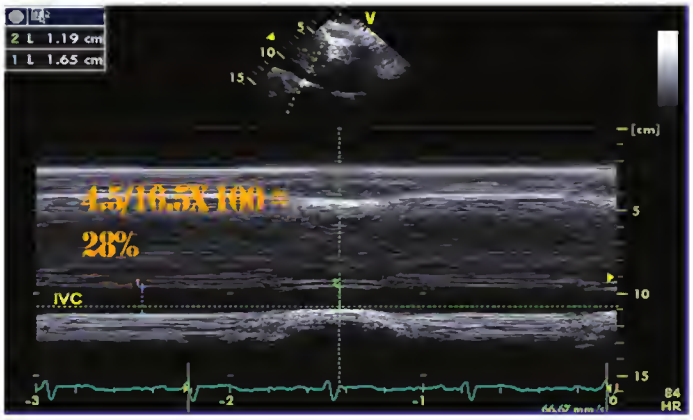


Figure 5: Decreased inspiratory collapse of inferior vena cava (IVC).

The RV and PA systolic pressures are identical in absence of any RV outflow obstruction. The quantitation is done by interrogating the jet of tricuspid regurgitation (TR). The TR occurs as a result of tricuspid annular dilatation, due to persistently increased pressure, and its peak velocity reflects pressure gradient between RV and RA. So RV/PA pressure is $4 \times V^2 + RAP$. Echocardiography underestimates PA pressure by ± 10 mm Hg because of two operator related factors: (a) underestimation of RAP; and (b) underestimation of TR jet velocity by not studying all scan planes and Doppler not being parallel to the TR jet.

COMMON CLINICAL INDICATIONS

Though the list is very exhaustive, but few clinical scenarios will be discussed as seen in day-to-day practice.

Evaluation of Cardiac Functions

Currently, the cardiac functions are classified into systolic and diastolic.

Systolic

Evaluation of systolic LV function is the most frequently asked investigation and is a very important component of cardiology practice. It forms the basis of diagnosis, prognosis and treatment of practically every cardiac disorder. Though there are a number of techniques to assess LV function like ventriculography, nuclear cardiology, cardiac MRI, cardiac CT, but echocardiography is the most practical in day-to-day practice and has a wonderful track record in assessment. The most common denominator of LV function continues to be the ejection fraction (EF) which is the stroke volume divided by end diastolic volume. The most common method for determining EF is Modified Simpsons method. It may be mentioned here that M-mode echocardiography has no role in assessing LV volumes and function. Certain factors affect the precise validity of EF like preload, afterload, contractility, heart rate, arrhythmias, poor endocardial delineation, grossly distorted left ventricle (LV), abnormal septal motion and is very operator-dependent. However, it continues to be the 'magic word' for clinicians. Though the value above 50% is considered normal but according to recommendations of American Society of Echocardiography (ASE), a value above 55% is normal, 45% to 54% is mildly abnormal, 30% to 44% moderately abnormal and below 30% severely abnormal.

To reduce the intra and inter-observer variability, other techniques are available like MCE, live 3D echocardiography, myocardial performance index, strain imaging, etc.

Diastolic dysfunction

Advanced diastolic dysfunction can lead to isolated diastolic heart failure, now referred to as heart failure with normal ejection fraction (HFNEF). In Western population it is seen in about 40% to 50% of cases. Conditions predisposing to HFNEF are hypertension with or without diabetes mellitus, coronary artery disease, cardiomyopathy, obesity, sleep apnoea syndrome, etc. Diagnosis of HFNEF is based on following criteria:

1. Presence of clinical syndrome of heart failure,
2. Presence of normal ejection fraction (>50%),
3. Presence of diastolic dysfunction,
4. E/E' (ratio of mitral Doppler E wave velocity to tissue Doppler early diastolic velocity, i.e. E' greater than 15:1 indicative of increased LV filling pressure, and
5. Usually non-dilated heart.

Echocardiography can confidently assess diastolic functions by evaluating mitral inflow Doppler, tissue Doppler, pulmonary vein, LA volume index, etc.

VALVULAR HEART DISEASE (VHD)

In view of a high incidence of rheumatic heart disease in our country, echocardiography has made a tremendous impact

in VHD. This is because of its high diagnostic capability and excellent correlation with cardiac catheterisation. As such haemodynamic studies are not required unless coronary arteries need to be evaluated. Moreover, echocardiography is very cost effective. The role of echocardiography in VHD is as follows:

1. Diagnosis
2. Assessment of severity
3. Presence of other valvular lesions, if any
4. Assessment of left ventricular functions
5. Assessment of indirect haemodynamic effects like PAH
6. Diagnosis of complications like vegetations, LA or appendage thrombus, etc.
7. Stress echocardiography in subset of patients
8. Guide to timing and type of intervention
9. Serial follow-up

To slightly elaborate few points mentioned above, echocardiography is ideal for the correct diagnosis of valvular lesions and the precise severity is assessed by Doppler, though indirect evidence is obtained by 2D echocardiography. The LV function (ejection fraction) is one of the important parameter in deciding intervention in VHD. An EF which could be normal for a normal person may be considered less for a patient with mitral regurgitation (MR), aortic stenosis (AS) or regurgitation (AR). A stress echocardiography is performed in a subset of patients, especially mitral stenosis (MS), when there is discordance between clinical symptoms and echocardiography findings, i.e. patient is dyspnoeic on mild exertion but echocardiography does not show a severe lesion. One is not clear whether dyspnoea is due to MS or other conditions like COPD, obesity, poor exercise conditioning, etc. A pre- and post-exercise study showing effect on gradients and rise of PA pressure gives a clue to diagnosis. The type of intervention depends upon various factors like the degree of calcification, status of subvalvular apparatus, leaflet mobility, thickening, degree of valvular regurgitation, etc. As such in MS, severe subvalvular thickening, calcification, large left atrial/appendage clot (**Figure 6**) or moderate mitral regurgitation favour surgical intervention.

Stenotic Lesions

All stenotic lesions, irrespective of the valve involved, are characterised by: (a) thickening/fibrosis/calcification depending upon the stage of disease; (b) doming of the cusps, when the valve is fully open, is a characteristic sign. Doming is in the direction of blood flow, i.e. convexity towards the distal chamber (**Figures 7 and 8**); (c) reduced valve mobility due to thickening or fibrosis of the cusps; (d) decreased valve orifice area; and (e) increased transvalvular gradients across the stenotic valve, depending on the degree of stenosis, as determined by Doppler.

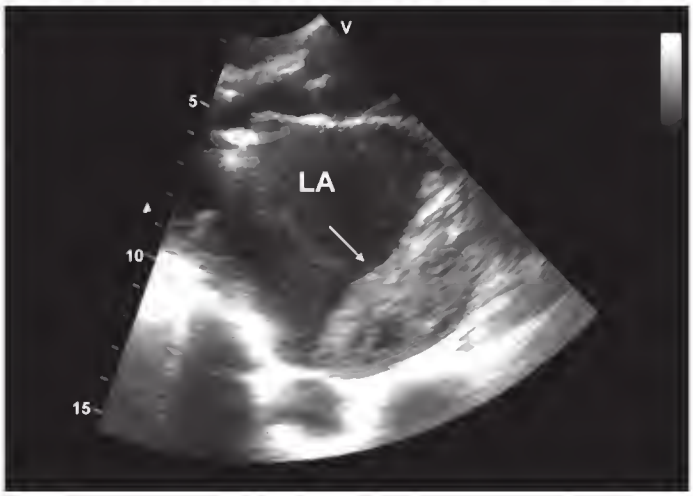


Figure 6: PLAX view showing a large thrombus (arrow) in left atrium (LA).

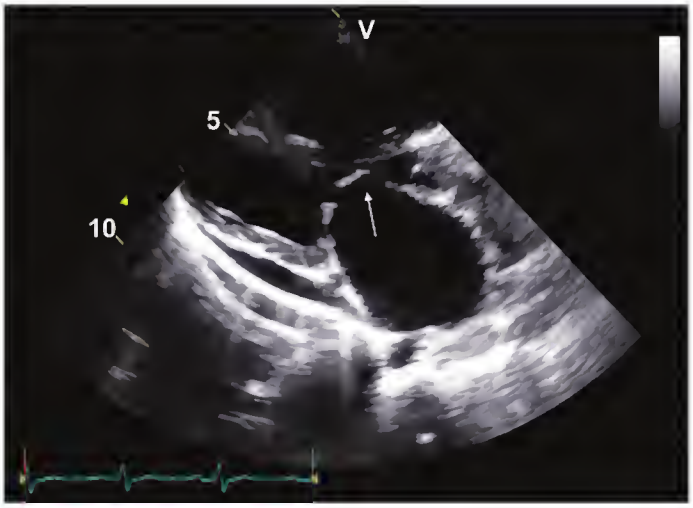


Figure 7: PLAX view in diastole showing doming of anterior mitral leaflet (arrow) with convexity towards left ventricle.

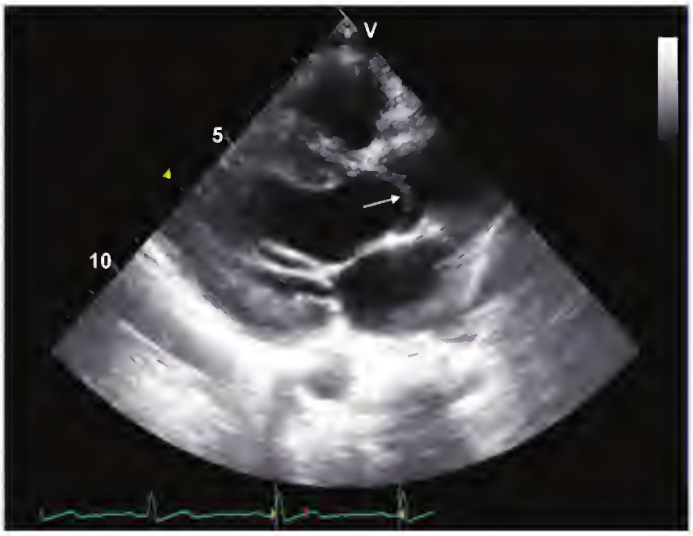


Figure 8: PLAX view in systole showing doming of aortic cusps (arrow) with convexity towards aorta.

The severity of the stenotic lesion is mainly determined by valve area and the pressure gradients, especially mean gradient across it. In MS a valve area of less than 1.0 cm^2 is indicative of severe stenosis, an area between 1.1 cm^2 and 1.5 cm^2 indicates moderate stenosis and 1.6 to 2.5 cm^2 suggests mild stenosis. The area is determined from SAX view. In case of aortic stenosis, an orifice area of less than 1.0 cm^2, in presence of normal cardiac functions, indicates severe stenosis. A mean aortic gradient of greater than 40 mm Hg, as per ASE or greater than 50 mm Hg as per European Society criteria, indicates severe stenosis.

It is imperative to scan all the valves meticulously. Concomitant tricuspid stenosis (TS) with MS is being often missed. The main cause of TS is rheumatic heart disease, but other aetiologies like tumour, vegetation, valvular damage

from catheters or pacemaker leads, etc. should not be overlooked. The normal TV velocity is 0.5 to 1.0 metres/second, and mean gradient is usually less than 2 mm Hg. TS is considered severe if mean gradient is more than 7 mm Hg, and valve area less than 1.1 cm^2.

Regurgitant Lesions

Echocardiography plays a key role in evaluation of valvular regurgitation.

The diagnosis is mainly aided by CFM which can directly visualise the jet in the receiving chamber. As regurgitant lesions produce volume overloading of the relevant chamber (LA, LV in MR and LV in AR), hence a semiquantitative idea of severity is assessed by degree of enlargement and thickening of chambers which are compensatory mechanisms. A reasonable idea of severity is assessed by Doppler and CFM. In MR an idea of severity is based on the traced area of jet, e.g. mild, moderate and severe MR are characterised by jet areas of 4.0 cm^2, up to 8 cm^2 and >8.0 cm^2 (**Figure 9**). However, there are various caveats and limitations in assessment. Vena contracta, the narrowest portion of the jet just beyond the regurgitant orifice, is a good method for assessment of severity of MR. A value more than 7 mm indicates severe MR. Similarly, in severe AR, the LV diastolic dimension is usually more than 7.5 cm, the area of LVOT occupied by AR jet is >60%, there is holodiastolic flow reversal from descending aorta as seen by pulsed Doppler and vena contracta diameter is >6.0 mm.

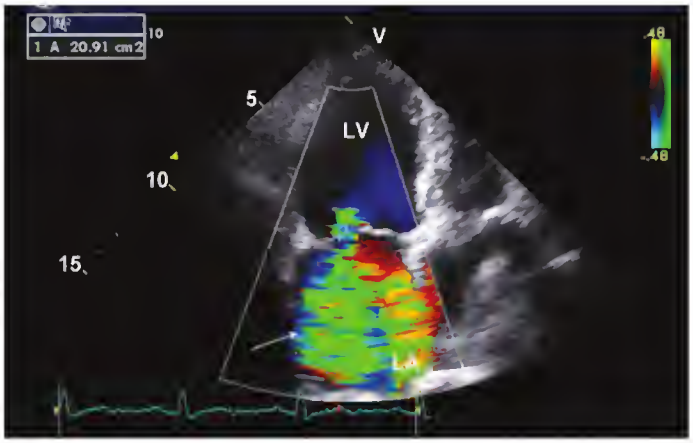


Figure 9: Apical four chamber view showing severe MR with an area of 20.9 cm^2.

LV = Left ventricle; LA = Left atrium.

Key Practical Points in Evaluation of VHD

1. A full clinical evaluation is mandatory
2. Always record heart rate, BP and cardiac rhythm as they have a bearing on severity
3. Proceed step wise from 2D echocardiography – colour flow – Doppler
4. Evaluate all scan planes to assess full anatomy and function
5. Scan all valves
6. Note any intercurrent illness which will affect the evaluation of severity by altering peak velocity
7. Match echocardiography findings with clinical findings and symptoms
8. Provide full anatomical and quantitative information including limitations of study, if any.

Prosthetic Valves

Echocardiography with Doppler is currently the modality of choice for evaluation of prosthetic valve function. The prosthetic valves are basically tissue (biological) or mechanical valves. The initial evaluation starts with clinical data followed by 2D echo for evaluation of size of cardiac chambers, LV thickness and systolic and diastolic functions. The opening and closing motion of moving parts of prostheses are visualised. The presence of abnormal echocardiography density attached to various components are seen, if present. It is advisable that magnified live images are obtained for better visualisation of leaflets and occluder mechanism. Doppler is vital for assessing valve function. It should be kept in mind that all prosthetic valves are inherent stenotic and have trivial or mild transprosthetic regurgitation. The gradients and effective orifice area across the valve are obtained. The normal and abnormal gradients depend upon the type and size of the valve.

A significantly increased gradients in a symptomatic patient points to a thrombus or pannus formation. TEE is an ideal method to look for certain complications like endocarditis, thrombosis or pannus formation. Differentiation between thrombus and pannus is important as thrombolytic therapy may be life saving in thrombus formation. Compared to pannus formation, obstruction due to thrombus is associated with a short duration of symptoms and a history of inadequate anticoagulation (INR <2.0). Thrombi are larger and have a soft ultrasound density, while pannus is a small dense mass more common in aortic position.

CONGENITAL HEART DISEASE

Over the past few decades echocardiography has become the most important technique for the diagnosis of both acyanotic and cyanotic congenital heart disease (CHD). In most of the cases a systemic and meticulously performed echocardiography gives a complete diagnosis to plan the appropriate management. Some important points in imaging an infant or neonate are as follows:

Sedation

The child should be quiet during the study. Many a times neonates and infants can be quietened by giving feed, using pacifier or keeping warm. If various methods fail, it is imperative to sedate the child as an echocardiography cannot be done in a struggling child. Sedation can be performed by oral chloral hydrate in dose of 50 to 100 mg/kg body weight with a maximum dose not exceeding 1.5 g. Alternatively, trichloryl in same dose or intranasal midazolam 0.2 to 0.5 mg/kg can be given usually up to the age of three years. It should be ensured that infant's upper clothing is removed before giving sedation.

Imaging

The aim is to image all the structures of the heart and blood vessels in a sequential and systemic, fashion by utilising all scan planes. The 2D study is followed by CFM and carefully interrogated Doppler of all valves and various other structures.

Transducer

As mentioned earlier, a high frequency transducer is preferred for infants and neonates. Sometimes, a high frequency

transducer and tachycardia gives a false impression of turbulent flow on CFM giving an appearance of 'obstruction'. Such flows should be interrogated by CW Doppler to confirm or rule out obstruction.

Cyanotic Lesions

In cyanotic lesions a right to left or bidirectional flow must be demonstrated by CFM or peripheral venous contrast echocardiography.

Peripheral Venous Contrast Echocardiography

This is a very simple but quite informative technique which can help in demonstrating a right to left intracardiac shunt in case of a cyanotic infant if CFM is inconclusive due to any technical problem. In this technique a small amount of agitated saline (3 to 5 ml of saline + about 0.5 mL of air are rapidly agitated with two syringes connected with a 3-way stop cock) is injected rapidly intravenously. As this agitated saline traverses RA and RV, these chambers get opacified. Once these microbubbles of air and saline reach the pulmonary circulation, they are destroyed as they are of a larger size than the red blood cells. Hence, in a normal situation, only right-sided chambers are opacified as these microbubbles are not able to reach the left-sided chambers (**Figure 10**).

As such an opacification of left-sided chambers implies that the contrast agent has bypassed the pulmonary circulation and opacified the left-sided chambers at any level of right to left intracardiac shunt (**Figure 11**).

As mentioned earlier, a meticulous examination obviates the need for invasive haemodynamic studies. However, it is important for the operator to have a good knowledge of basic anatomy and haemodynamics of various congenital lesions. Besides providing diagnosis, echocardiography plays a significant role in various catheter intervention procedures. **Table 1** summarises the role of echocardiography in some commonly encountered congenital cardiac defects (**Figures 11 to 17**).

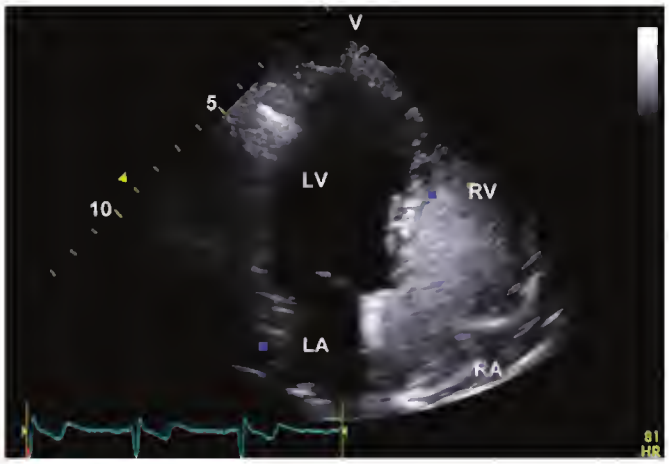


Figure 10: Normal contrast echocardiography showing opacification of only right atrium (RA) and right ventricle (RV) while LV (left ventricle) and LA (left atrium) are contrast free.

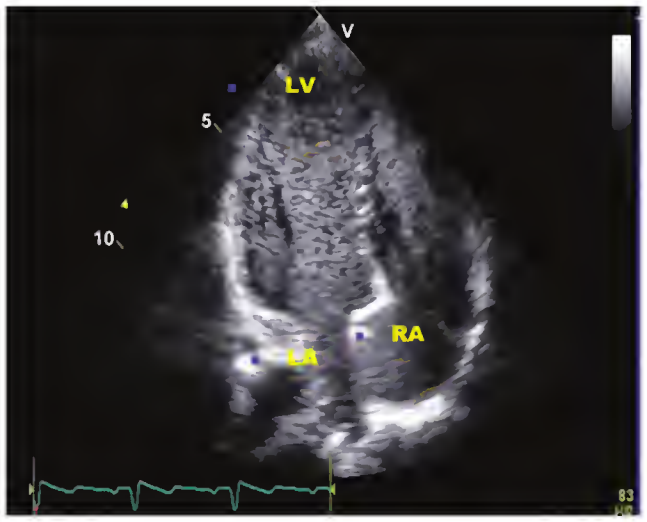


Figure 11: Contrast echocardiography in a case of secundum atrial septal defect (ASD) with saline contrast opacifying the left atrium (LA) indicating a right to left shunt at atrial level.

RA = right atrium; LV = left ventricle.

Table 1: Brief Role of Echocardiography in Some Common Congenital Cardiac Lesions

Lesion	Important Echocardiographic Features
Atrial septal defect (ASD)	Type, number and size of defects, degree of RV, RA enlargement, evaluation of PA pressure, adequacy of tissue rims around the defect, in cases of secundum ASD, for percutaneous device closure. Associated anomalies like cleft mitral valve in ostium primum defect. Sinus venosus defects can be diagnosed by transthoracic echocardiogram (TTE), though TEE is confirmatory
Ventricular septal defect (VSD)	Type, number and approximate sizing of defects, associated lesions like pulmonary stenosis, coarctation, etc. PA pressure, is it an isolated lesion or part of a complex lesion, complications like aortic regurgitation or vegetations, serial follow-up of small VSD's to see for spontaneous closure, assessment for suitability of percutaneous device closure, shunt direction of flow
Patent ductus arteriosus (PDA)	Size of the defect, direction of shunt, extent of LA and LV volume overload, pulmonary hypertension if any, suitability for percutaneous device closure, associated defects
Coarctation of aorta	Presence and site of coarctation, diameter and length of coarctation segment, gradient across the coarctation, LV functions, is there arch hypoplasia, associated anomalies like bicuspid aortic valve, left-sided obstructive lesions
Pulmonary stenosis	Site of stenosis, e.g. infundibular, valvular or supravalvular gradients across the site of stenosis, RV dysfunction if any, associated anomalies like VSD
Tetralogy of Fallot (TOF)	VSD, biventricular origin of aorta (aortic override), site and severity of RVOT obstruction which defines clinical picture and degree of cyanosis, RV hypertrophy, associated anomalies like right-sided aortic arch, concomitant ASD (pentalogy of Fallot), measurement of pulmonary annulus, pulmonary trunk
Transposition of great arteries (TGA)	Demonstrates atrio-ventricular concordance and ventriculo-arterial discordance. Origin of PA from LV and aorta from RV can be demonstrated. Associated VSD, ASD or PFO, LVOT obstruction and coronary abnormalities can be identified. Guiding catheter placement and movements during balloon atrial septostomy.

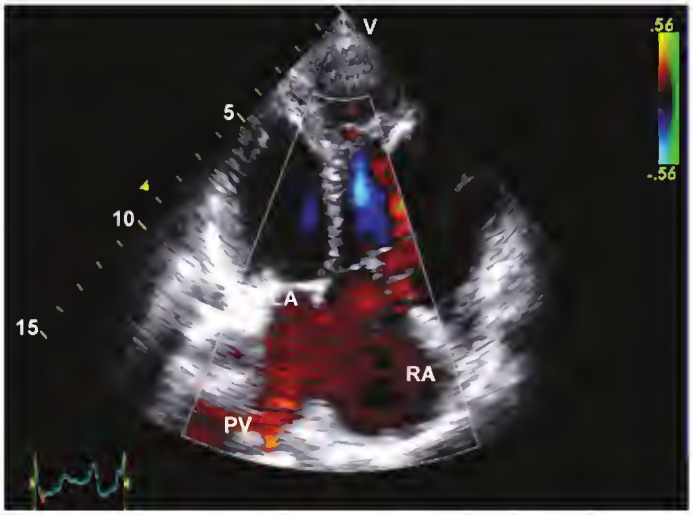


Figure 12: CFM in a case of secundum atrial septal defect with left to right shunt.

PV = Pulmonary vein; LA = Left atrium; RA = Right atrium.

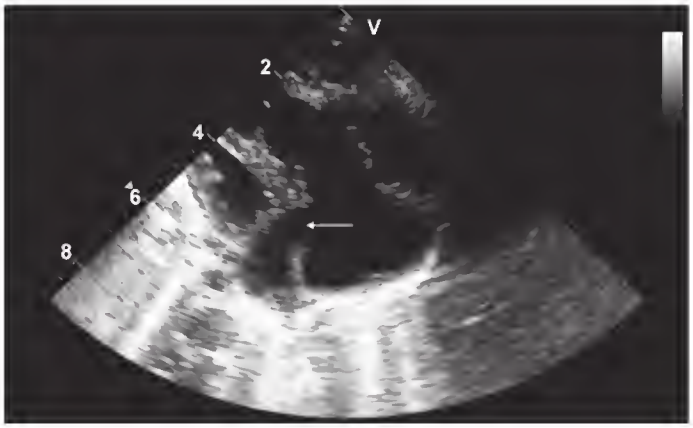


Figure 13: Apical four chamber view showing ostium primum ASD (arrow).

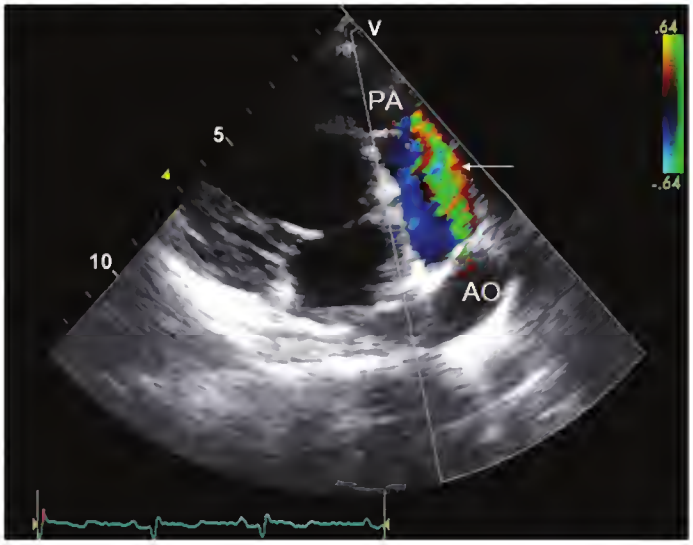


Figure 14: Short axis view showing patent ductus arteriosus (arrow) with flow from aorta (AO) to pulmonary artery (PA).

ISCHAEMIC HEART DISEASE (IHD)

In the current era of intense pharmacotherapy, thrombolytics and percutaneous coronary interventions an early diagnosis of IHD is mandatory to get maximum benefit of various interventions. Traditionally, the diagnosis of IHD is based on clinical presentation, ECG and cardiac enzymes. However, all the three have limitations

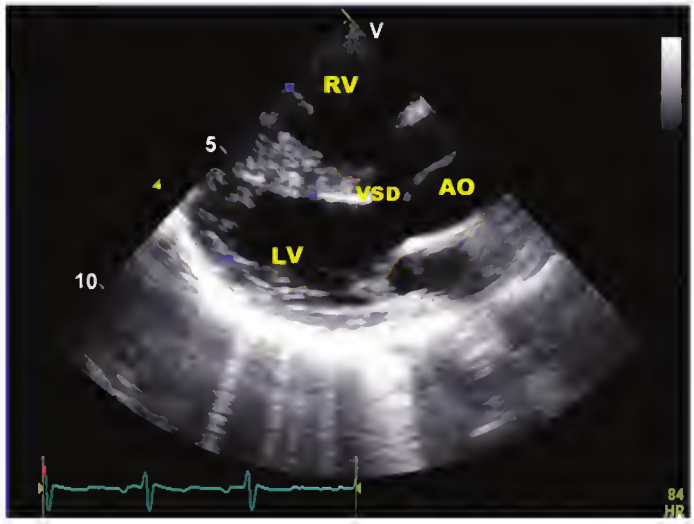


Figure 15: PLAX view in a case of teralogy of Fallot showing aortic override (AO), a large ventricular septal defect (VSD).

RV = Right ventricle; LV = Left ventricle.

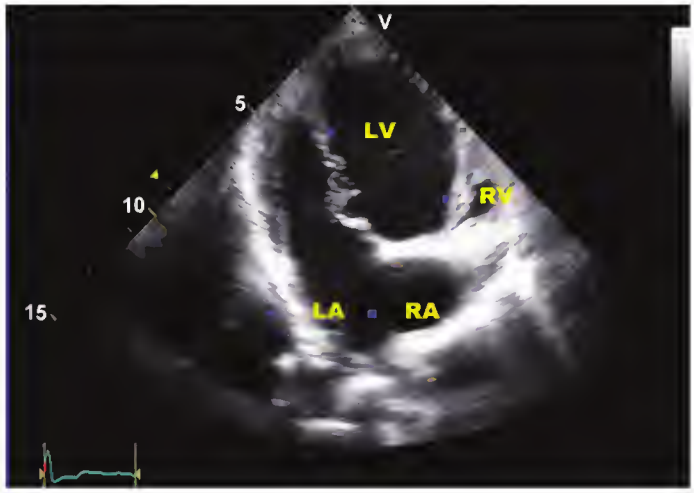


Figure16: A case of tricuspid atresia. There is atresia of tricuspid valve with a very hypoplastic right ventricle (RV), the main chamber is LV and a large ASD is present.

thereby delaying diagnosis and aggressive management. In acute myocardial infarction (AMI) echocardiography provides a correct diagnosis in about 95% of cases and hence is a life saving modality. This is because in the ischaemic cascade, in which the earliest abnormality is a perfusion defect followed by diastolic and systolic contraction abnormalities, which is then followed by chest pain, ECG changes and subsequently rise in cardiac enzymes. The earliest change of perfusion defects is diagnosed by myocardial contrast echocardiography, a technology which is still limited to few centres in India. However, the diastolic and systolic abnormalities are readily picked-up by conventional echocardiography thereby giving an immediate diagnosis. However, few practical points need to be kept in mind. What echocardiography picks-up in IHD is an ischaemia or injury at the time of study. As such echocardiography can be normal in cases of stable angina, despite having significant coronary artery disease. However, if the same patient develops spontaneous or induced angina during the study, then echocardiography will reveal regional contraction abnormalities of LV. Hence a practical dictum is that a normal echocardiography during chest pain virtually excludes IHD. Secondly, the clinician should not have a false perception that a normal resting echocardiography excludes coronary artery disease especially in both stable and unstable angina. The two most

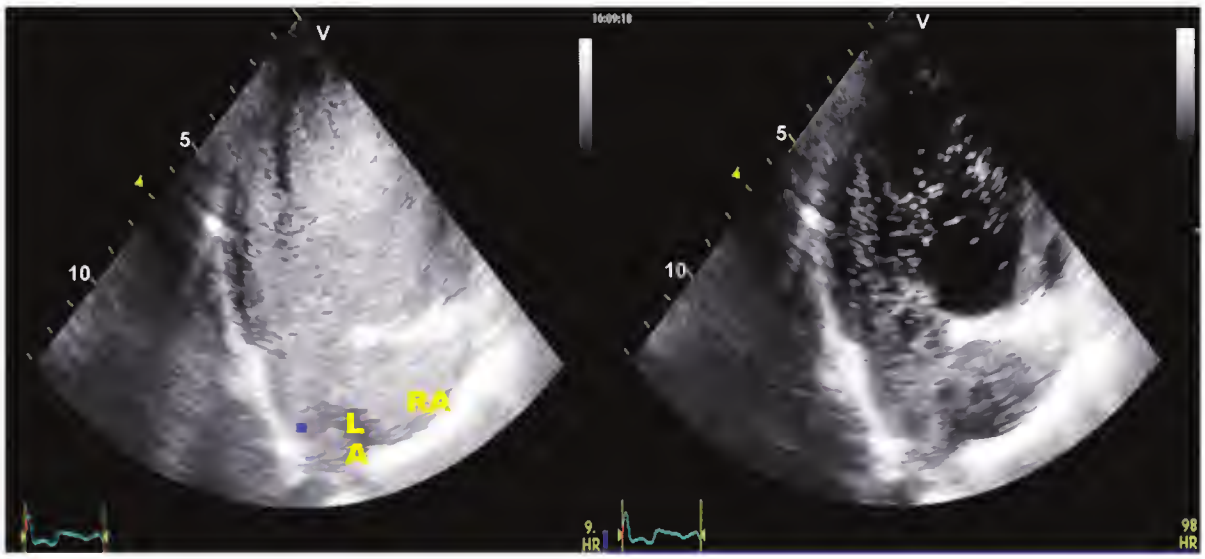


Figure 17: The patient in Figure 16 showing a large ASD, almost a common atrium, as seen on contrast echocardiography.

RA = Right atrium; LA = Left atrium.

specific diagnostic findings in AMI are: decreased systolic thickening of affected myocardial segment (a normal myocardium thickens by almost 50% during systole, while an ischaemic segment shows decreased or absent systolic thickening); and secondly, varying degrees of regional wall motion abnormalities (RWMA). The area affected is localised to the portion of myocardium perfused by the involved coronary artery. The extent of RWMA affects LV dysfunction and is one of the factors determining prognosis. The RWMA is always assessed by scanning various imaging planes. On the basis of this the myocardium is conceptually divided in 17 segments, the 17th segment being the apical cap. The role of echocardiography in IHD is summarised in **Table 2**.

Table 2: Role of Echocardiography in Ischaemic Heart Disease

Diagnosis
Diagnosis of associated cardiac defects, if any
Triage in chest pain units
Assessment of complications such as LV thrombus, acute MR, VSD, LV aneurysm, myocardial rupture, RV infarction which has a bearing on therapy
Assessment of coronary territory involved
Post-MI risk stratification/prognosis
Assessment of myocardial viability
Assessment of therapy effectiveness/change of therapy
Contribution of new technologies like MCE, tissue Doppler imaging, strain imaging, etc.

There are few situations where early echocardiography can be very informative as shown in **Table 3**.

Table 3: Early Echocardiography in Whom?

Doubt in diagnosis/early detection
Hypotension
Heart failure
Unexplained dyspnoea
Chest pain with left bundle branch block
Suspect other complications

The role of echocardiography in IHD is so important that it is recommended that every emergency room/critical care unit resident should be trained to at least recognise a RWMA.

Stress Echocardiography

This modality is being increasingly utilised in diagnosis and prognosis of IHD. This is based on the principle that in a resting state, despite significant coronary artery disease (CAD), there is no imbalance between oxygen supply and demand of the myocardium. However, if the same individual undergoes any form of exercise, the oxygen demand of myocardium is enhanced due to increased heart rate, contractility and rise in blood pressure. However, in the presence of CAD, this increased demand of oxygen cannot be met and it leads to systolic contraction abnormalities and LV dysfunction which are rapidly picked-up by echocardiography. In brief, a resting echocardiography is first performed, then the patient exercises on a treadmill till a standard end-point is reached and again an immediate post-exercise echocardiography is repeated. Instead of dynamic exercise, a pharmacological stress echocardiography with dobutamine can be performed. A normal response to exercise is hyperkinetic contractility with increasing LV ejection fraction. An abnormal response is indicated by decreased systolic thickening of affected segment, varying degrees of RWMA, paradoxical increase in LV chamber size, a decrease in ejection fraction. The accuracy for detection of CAD varies from 80% to 94% depending on the number of vessels involved.

PERICARDIAL DISORDERS

Echocardiography is one of the best non-invasive technique to diagnose pericardial disorders. Some of the indications of echocardiography are:

1. Diagnosis and semi-quantitation of pericardial effusion
2. Diagnosis of pericardial tamponade
3. Diagnosis of post-intervention or post-surgical effusion
4. Constrictive pericarditis
5. Echocardiography guided pericardiocentesis

Normally, the two layers of pericardium contain about 5 to 10 mL of fluid which acts as a buffering medium between the two layers. As the fluid accumulates, echo-wise it is seen as an echo free space between the pericardial layers (**Figure 18**). The semi-quantitation depends on the degree of echo free pericardial space and the distribution of pericardial fluid.

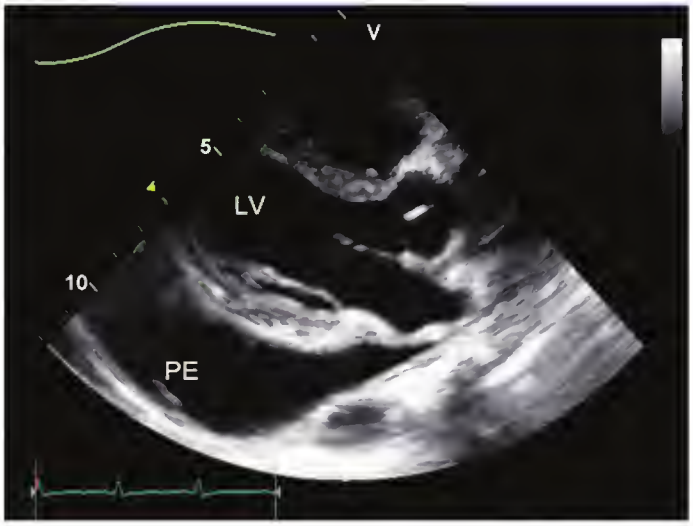


Figure 18: PLAX view showing a large posterior pericardial effusion (PE) as an echocardiogram free space between pericardial layers.

LV = Left ventricle.

An echo free space of >2.0 cm with a diffuse effusion all around the heart indicates a large effusion. The diagnosis of pericardial tamponade and constrictive pericarditis is based on 2D echocardiography features and Doppler findings, e.g. in tamponade there is pericardial effusion, diastolic RV collapse, exaggerated right atrial collapse during atrial systole due to elevated intrapericardial pressure. IVC is enlarged and shows less than 50% inspiratory collapse though it is more sensitive and less specific finding. There are several Doppler findings, but one important finding is more than 25% respiratory variation of atrioventricular valve velocities, the normal variation being less than 15%. The mitral velocity decreases during inspiration and increases following first expiratory beat.

CARDIOMYOPATHIES

The diagnosis of various forms of cardiomyopathies is based on high index of suspicion, clinical features, ECG and X-ray chest, but echocardiography plays a central role in diagnosis. Basically, the different forms of cardiomyopathy are dilated, hypertrophic (both obstructive and non-obstructive) and restrictive. However, RV cardiomyopathy, stress induced cardiomyopathy and LV non-compaction cardiomyopathy are being periodically encountered.

Dilated Cardiomyopathy (DCM)

This is basically characterised by cardiomegaly with global LV hypokinesia. There is impaired systolic and diastolic cardiac functions. Mitral regurgitation is usually present. Echocardiography also plays a role in assessing the prognosis. Some of the determining prognostic factors are: (a) degree of cardiomegaly; (b) degree of LV dysfunction; (c) extent of wall thickness of ventricles; (d) pulmonary hypertension; (e) restrictive filling pattern as assessed by mitral inflow Doppler; and (f) some tissue Doppler imaging parameters.

Hypertrophic Obstructive Cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HOCM) now referred as hypertrophic cardiomyopathy (HCM) with LVOT obstruction is a complex, genetic cardiac disorder with significant heterogeneity in clinical presentation and course. It is a common cause of sudden death in young athletes. Echocardiographically, it is characterised by asymmetrical septal hypertrophy with septal and posterior wall thickness ratio of more than 1.5:1. The septal thickness is more than 15 mm. However, the distribution and severity of hypertrophy can be variable. The LV cavity is small with normal functions. Systolic anterior motion (SAM) of anterior mitral leaflet (AML) is one of the important features of HOCM and leads to varying degree of left ventricular outflow tract (LVOT) obstruction with a gradient more than 30 mm Hg. This is because LVOT is formed by AML and interventricular septum. The degree of LVOT obstruction depends upon the duration for which IVS abuts against the septum. In the echocardiography lab, SAM and LVOT obstruction can be provoked by nitrates (**Figure 19**).

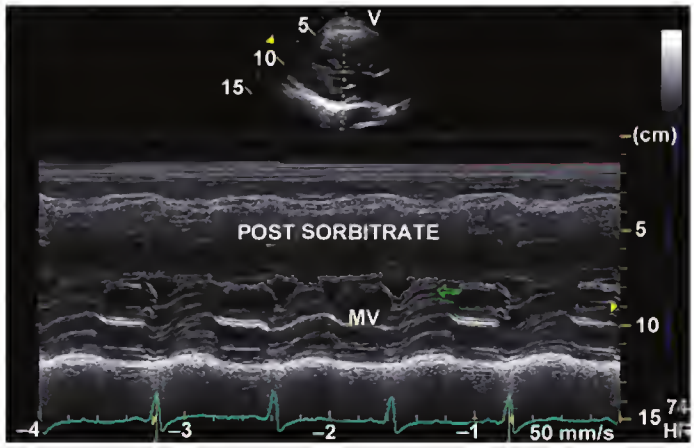


Figure 19: M-mode echocardiogram showing systolic anterior motion (arrow) of mitral valve (MV) following nitrate provocation. The whole LVOT is obliterated by the SAM abutting the interventricular septum.

INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is an infection of endocardium and intracardiac devices by infective organisms, seen macroscopically as vegetations. Early diagnosis is vital as, despite refinements in medical and surgical therapeutic approaches, the mortality is still between 25% and 30%. No single finding is diagnostic. As such a combination of high index of suspicion, clinical scenario and echocardiography are diagnostic. The role of echocardiography in IE is:

1. Identifying the underlying heart disease including intracardiac devices,
2. Diagnosis of vegetations, if present,
3. Size, mobility and location,
4. Detecting complications of vegetations,
5. Serial evaluation to assess efficacy of therapy or aetiology of worsening,
6. Prognostic stratification. Some adverse prognostic features are large (>10 mm) vegetations, hypermobile vegetations, presence of complications like abscess, leaflet rupture, extension to other areas, systemic embolism, heart failure, etc.

The echocardiography criteria of vegetations are an irregular, mobile mass attached to a free edge of leaflet or a wall. It is attached to the upstream side of the valve, e.g. ventricular side of aortic valve leaflet, atrial side of mitral and tricuspid leaflets and RV side of VSD. The motion of the vegetation is more chaotic and independent of valve motion. It is seen in multiple scan

planes (**Figure 20**). Valvular regurgitation is usually present. As vegetations once develop usually persist, unless they embolise and disappear, hence sometimes there is a difficulty in distinguishing between an active or healed vegetation. Firstly, there should be a clinical correlation as active vegetation will be associated with fever, toxaemia and other manifestations of sepsis, while old, healed vegetation may be routinely detected in virtually an asymptomatic patient. Secondly, a healing vegetations decrease in size and mobility and are more echogenic. Thirdly, a past history of IE may be available.

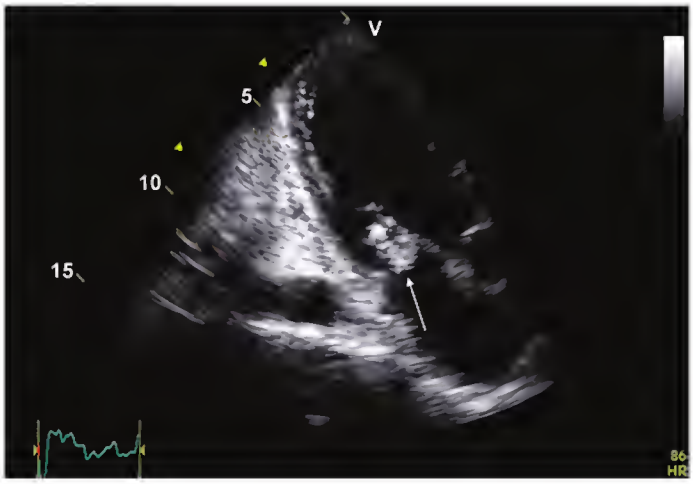


Figure 20: Vegetation seen on the atrial side of the mitral valve (arrow).

HEART FAILURE (HF)

Echocardiography is well suited to meet the growing need for non-invasive imaging of heart failure. The role of echocardiography in heart failure is: (a) diagnosis; (b) prognosis; (c) guiding therapy; and (d) monitoring follow-up.

Because HF patients often have more than one structural and/or functional abnormality contributing to their disease state, echocardiography's versatility in detecting multiple structural lesions including myocardial disorders yield obvious benefits. Assessment of LV ejection fraction is one of the primary measures. A normal EF virtually excludes an advanced myocardial disorder, i.e. systolic HF and then one looks for HFNEF. Doppler measurements provide important haemodynamic information. Some of the adverse prognostic factors in HF can be degree of LV dysfunction, LV end systolic volume of >45 ml/m^2, right ventricular functions, restrictive ventricular filling, myocardial viability, etc. Echocardiography provides important data for therapeutic decision-making like volume status of the patient by IVC parameters as described earlier, need for drugs for LV dysfunction and define candidates for implantable cardiac devices like cardiac resynchronisation therapy or implantable cardioverter defibrillator. One of the major strengths of echocardiography is repeated follow-up, especially in situations of new symptoms, clinical deterioration where it can provide the aetiology.

ROLE OF ECHOCARDIOGRAPHY BEYOND ECHOCARDIOGRAPHY LABORATORY

Since last many years the role of echocardiography has been extended much beyond the echocardiography laboratory. In many situations it has proved to be a life saving technology. Some of the areas are mentioned below:

Critical Care Units

This is the area where echocardiography is extensively employed as a bedside study. The role of echocardiography is critical in diagnosis and guiding therapy. In some areas it gives vital information whether the clinical manifestation is of cardiac or non-cardiac aetiology. Some of the common situations where echocardiography is utilised are: (a) evaluation of chest pain whether it is ischaemic or non-ischaemic; (b) unexplained hypotension/shock. Echocardiography evaluates whether it is cardiac related like acute coronary syndrome, acute valvular insufficiency, severe pulmonary hypertension, pulmonary embolism, etc. Echocardiography can also infer if it is non-cardiac like hypovolaemia, acute sepsis syndrome; (c) evaluation of dyspnoea and heart failure where echocardiography can differentiate between systolic or diastolic failure, pulmonary embolism or a pulmonary aetiology by exclusion; and (d) aetiology of worsening of clinical status in any patient which was showing improvement.

Operating Room

As a routine in large number of cardiac centres intra-operative TEE is routinely utilised especially in monitoring of valvular, congenital or other complex cardiovascular surgical procedures. Besides monitoring cardiac functions, it helps in determining the completeness and success of surgery to avoid any possible redo surgery.

Cardiac Catheterisation Laboratory

There are several non-surgical cardiovascular procedures performed in cardiac catheterisation laboratory or intensive care unit for which online echocardiography monitoring is advantageous. Some of these situations are pericardiocentesis, percutaneous valvuloplasties, closure of ASD, PDA, some VSD's, creation of an atrial septostomy in some complex cyanotic CHD. Occasionally, an emergency echocardiography may be required in catheterisation laboratory to assist in evaluating a patient who has acutely deteriorated during a procedure, to exclude any iatrogenic cardiac tamponade or to reassess intravenous function.

CONCLUSION

The progress in understanding and improvements in equipment has catapulted echocardiogram as a very important tool in diagnosis and functional assessment. The newer innovations of virtual 3D imaging, contrast echocardiography, and tissue perfusion are going to further lend greater importance to echocardiogram.

The echocardiogram helps in, valvular heart disease, congenital heart disease, diseases of myocardium and ischaemic heart disease. In valvular heart disease and congenital heart disease it has obviated the need for invasive testing to a large extent.

The addition of miniature echocardiography may obviate the use of stethoscope in clinical cardiac assessment.

RECOMMENDED READINGS

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12.6 Cardiac Imaging

Priya Jagia, Sanjiv Sharma

INTRODUCTION

Optimal interpretation of cardiac imaging studies entails a judicious synthesis of imaging evaluation with its significance within the context of clinical decision making. A basic understanding of cardiovascular haemodynamics and electrophysiology is essential for optimal interpretation of imaging information.

Plain chest X-ray is the most routinely used cost effective cardiac imaging modality. It has an advantage that it can be repeated for serial changes and has been standardised since it is the oldest and simplest available cardiac imaging modality.

Non-invasive imaging of cardiac structures is technically challenging due to a variety of reasons. Motion artefacts constitute a major limitation as these degrade the image quality. During cardiac imaging, motion artefacts are produced by cardiac pulsations, counter-clockwise cardiac rotation during different phases of cardiac cycle, diaphragmatic movement and respiratory motion. Optimal profiling of cardiac structures is also compounded by the skewed anatomy of the heart since it is tilted in all three axes and hence routine body axis views are not useful for optimal imaging in disease states. Further, there is a wide variation in the densities of surrounding tissues and these adversely influence the image quality. The haemodynamics within the heart change very rapidly during various phases of the cardiac and respiratory cycles. As a result, the window of opportunity to capture the optimal phase of physiological and biochemical events is very short and difficult to capture for desired anatomic and functional imaging. It is thus obvious that the demands on an optimal technique for cardiac imaging are tremendous. Each modality is discussed.

CHEST X-RAY IN CARDIOVASCULAR DISEASE

For accurate interpretation of chest X-rays, it is imperative to have a systematic and standardised approach, based on an assessment first of anatomy and then of physiology. Any approach must, of course, be based on an understanding of what is normal.

In the standard PA chest study, the overall heart diameter is normally less than 50% of the transverse diameter of the thorax. The heart overlies the thoracic spine, roughly three-fourths to the left of the spine and one-fourth to the right. The mediastinum is narrow superiorly and, normally, the descending aorta can be defined from the arch to the dome of the diaphragm, on the left. Below the aortic arch, the pulmonary hila are seen, slightly higher on the left than the right. On both frontal and lateral views, the ascending aorta (aortic root) is normally obscured by the main pulmonary artery and both atria.

The plain X-ray chest is usually evaluated in frontal projection (PA view) and the distance between the X-ray film and radiation source is 72 inches. It should be systematically evaluated as follows for:

- Position of the patient, fundus of the stomach, domes of the diaphragm, bony abnormalities and the tracheal shadow
- Cardiac size, contour, borders, chambers and great vessels
- Pulmonary vasculature

The proper centring should be assessed looking at distance of medial end of clavicles from midline. The stomach shadow should be seen normally to the left and the right dome is higher than the left. The trachea shadow can be seen dividing at the carina which is at the level of T4 vertebra.

Cardiac Size, Contours, Borders, Chambers and Great Vessels

Cardiac size

The plain film radiographs are still a valuable tool for identifying an enlarged heart that is abnormal. The heart size is assessed by cardiothoracic (CT) ratio which is expressed as the ratio between the maximum transverse diameter of the heart divided by the maximum transverse diameter of the thorax (**Figure 1**). The maximum transverse diameter of the heart is obtained by adding the widest distance of the right heart border from the midline and left heart border to the midline. The midline is drawn through mid point of the spine from the sternum to the diaphragm. The maximum transverse diameter of the thorax is



Figure 1: Cardiothoracic Ratio = r+l / td (where r +l = transverse diameter of the heart and td is transverse diameter of thorax. r and l are measured as the maximum distance from midline of right and left heart borders respectively).

measured as distance between inner borders of thorax obtained above the costophrenic angles. The normal average CT ratio is:

- ≤0.50 in adults
- >0.50 in children
- ≤0.60 in neonates

A normal heart may appear large because of small AP diameter due to pectus excavatum and straight back syndrome.

The heart may appear small even though it is enlarged as in downward displacement of cardiac apex in AR, because of large AP diameter in COPD (**Figure 2**), due to severe dorsal kyphosis in elderly patients or, in Addison disease and anorexia nervosa due to the absence of brown fat.



Figure 2: Chest X-ray PA view of patient with emphysema. Note the tubular appearance of heart with hyperinflated lung fields and low lying diaphragm.

In present day scenario, with use of portable X-rays AP view is done due to which CT-ratio can become abnormal. Moreover, with use of smaller films in digital X-rays the usual measurement parameters used to define cardiac chamber enlargements may not stand true.

Cardiac Contour

Any significant deviation from the normal cardiovascular contour may serve as a clue to the cardiovascular diseases (**Table 1**).

Cardiac Borders, Chambers and Great Vessels

The cardiac borders consist of right and left heart borders (**Figures 3A and B** and **Table 2**).

In frontal projection, RA forms a gentle convexity with the adjacent right middle lobe. The superior border blends above with SVC and inferior border blends below with IVC, meeting the diaphragm at a slightly acute angle. Right atrial enlargement (RAE) commonly occurs in organic tricuspid valve disease and Ebstein's anomaly. Radiographically, RAE is considered:

- When it bulges >5.5 cm to the right of the midline or
- When RA border occupies ≥3 intercostal spaces

The classic signs of right ventricular enlargement are a boot-shaped heart and filling in of the retrosternal airspace. The former is caused by transverse displacement of the apex of the right ventricle as it dilates and leads to an acute cardiophrenic angle. In adults, it is unusual for the right ventricle to dilate without left ventricular dilation, so this boot-shape is not often obvious. It is most commonly seen as an isolated finding in congenital heart disease, classically in tetralogy of Fallot (**Figure 4**). Right ventricular enlargement is often seen in mitral valve disease, secondary to pulmonary hypertension.

LA Enlargement in mitral stenosis may lead to straightening of left heart border. The straightened left heart border occurs due to dilated main pulmonary artery and bulging of the LA appendage (**Figure 5**). The enlarged LA may lead to elevation of left main bronchus, resulting in increase of carinal angle. It may cause a convex shadow of double density in the right portion of cardiac silhouette and may lead to posterior displacement of barium filled oesophagus in lateral and RAO views

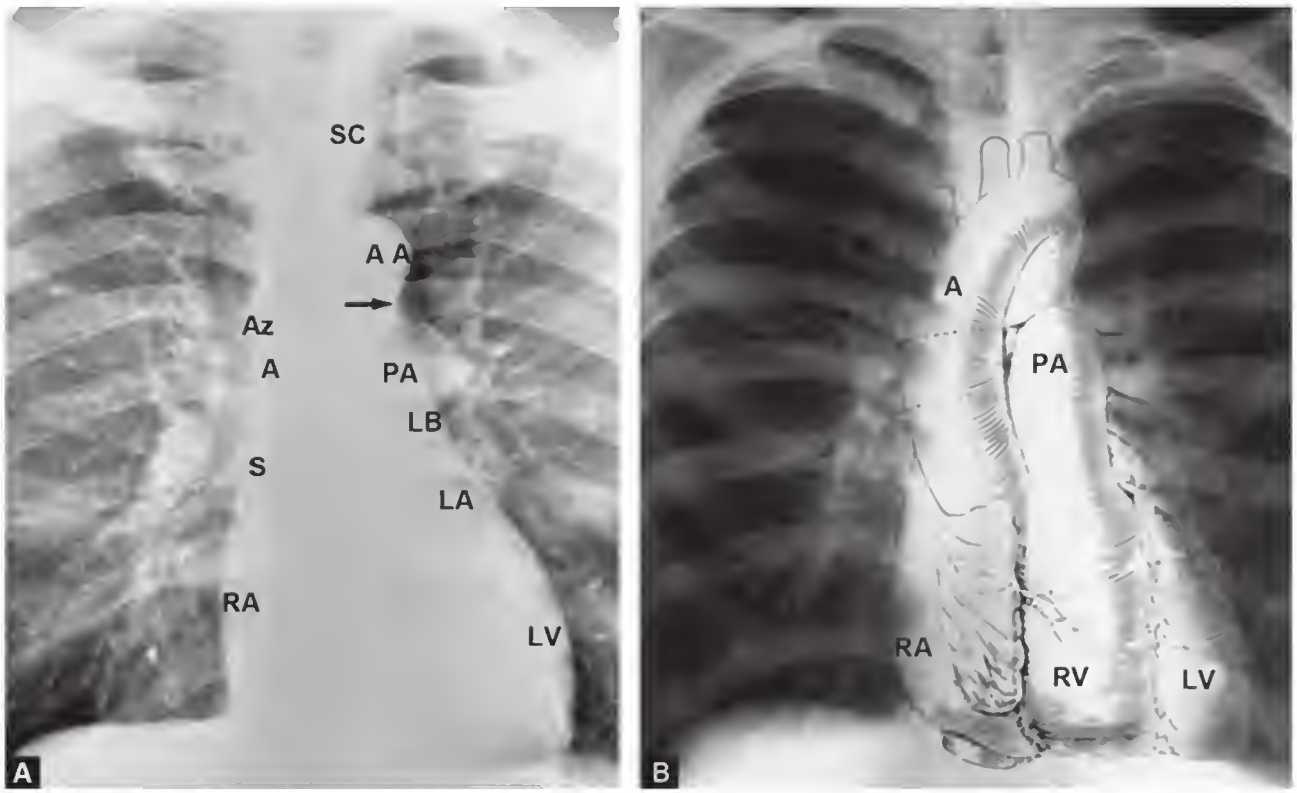
Left ventricular enlargement (e.g. in cardiomyopathies, valvular heart diseases, LV aneurysms, etc.) is characterised by a prominent, downwardly directed contour of the apex, as distinguished

Table 1: Abnormal Cardiac Contour

Features of Cardiac Contour	Causes
Mitralisation of left heart border	Mitral stenosis with pulmonary hypertension
Boot-shaped heart	Tetralogy of Fallot
Flask like or money-bag appearance with a smooth featureless cardiac border	Pericardial effusion
Triangular or a large rounded heart with a narrow pedicle	Ebstein's anomaly
Snow man or cottage loaf appearance	Total anomalous pulmonary venous connection
Egg on side appearance (mild cardiomegaly with narrow pedicle)	Transposition of great arteries
Retrosternal double density with a bulge along the cardiac border	Left ventricular aneurysm
Convex double density in the right portion of the cardiac silhouette	Enlarged left atrium

Table 2: Cardiac Borders in Chest X-ray Frontal Projection

Right Heart Border	Left Heart Border
Superior vena cava (SVC)	Aortic knuckle
Right atrium	Main pulmonary artery
	Left atrial appendage (when enlarged)
	Left ventricle



Figures 3A and B: Frontal projection of the heart and great vessels. (A) Left and right heart borders in the frontal projection. (B) Line drawing in the frontal projection demonstrates the relationship of the cardiac valves, rings, and sulci to the mediastinal borders.

A = Ascending aorta; AA = Aortic arch; Az = Azygous vein; LA = Left atrial appendage; LB = Left lower border of pulmonary artery; LV = Left ventricle; PA = Main pulmonary artery; RA = Right atrium; S = Superior vena cava; SC = Subclavian artery.

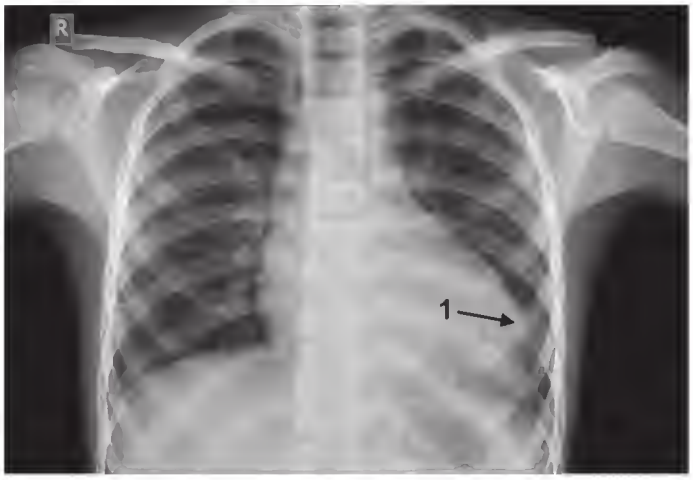


Figure 4: Chest X-ray in a patient of tetralogy of Fallot revealing boot-shaped heart, enlarged right ventricle (1) and oligaemic lung fields.

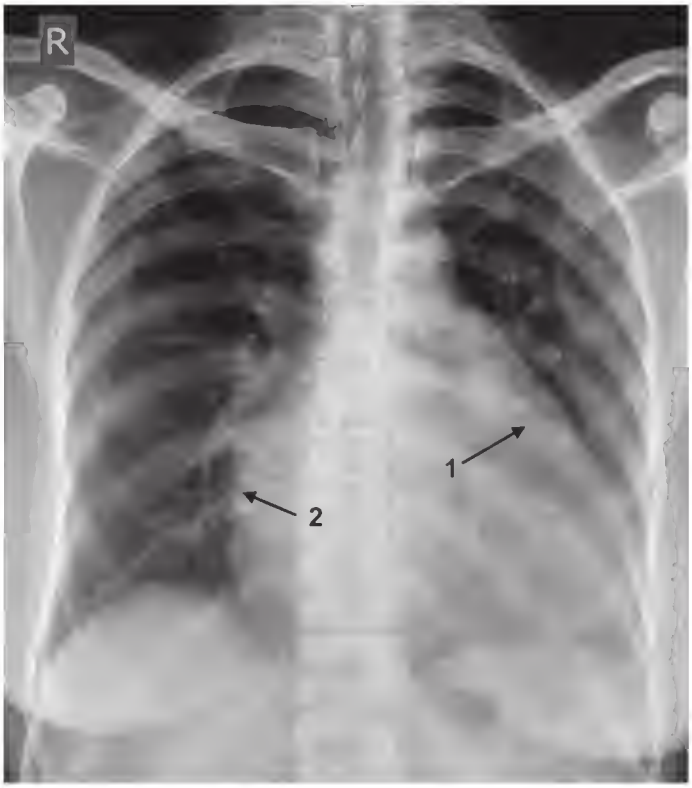


Figure 5: Chest radiograph of severe mitral stenosis. Posteroanterior view shows enlargement of the left atrium [double density shadow (1)], straightening of left heart border (2) (mitralisation) and pulmonary venous redistribution.

from the transverse displacement seen with right ventricular enlargement. Maximal left ventricular enlargement in adults occurs commonly with aortic insufficiency, often with associated aortic root dilation, whereas mitral regurgitation also manifests left atrial dilation. In contrast, aortic stenosis is characterised by left ventricular hypertrophy rather than dilation, and the left ventricle dilates only when aortic stenosis is accompanied by heart failure.

Pulmonary Vascularity

The main pulmonary artery bifurcates into left pulmonary artery (LPA) and right pulmonary artery (RPA) within the mediastinum. The LPA then courses to the left and posteriorly and hence its borders are just visible above the middle of the left hilum. The RPA, which has a horizontal course within the mediastinum, divides into lobar branches proximal to the right hilum. The

transverse diameter of right descending PA (RDPA) is 10 to 15 mm ± 1 mm in males and 9 to 14 mm ± 1 mm in females.

When pulmonary arterial flow is increased, as in patients with a high-output state (e.g. pregnancy, severe anaemia, hyperthyroidism) or left-to-right shunt, the pulmonary vessels are seen more prominently than usual in the periphery of the lung. They are uniformly enlarged and can be traced almost to the pleura, but their margins remain clear. This is typically referred as 'pulmonary plethora' due to increased pulmonary vascularity. It can be seen in acyanotic congenital heart diseases with large left to right shunts like ASD (**Figure 6**), VSD, PDA and in cyanotic patients with admixture lesions like TAPVC, truncus arteriosus, TGA with VSD, etc.

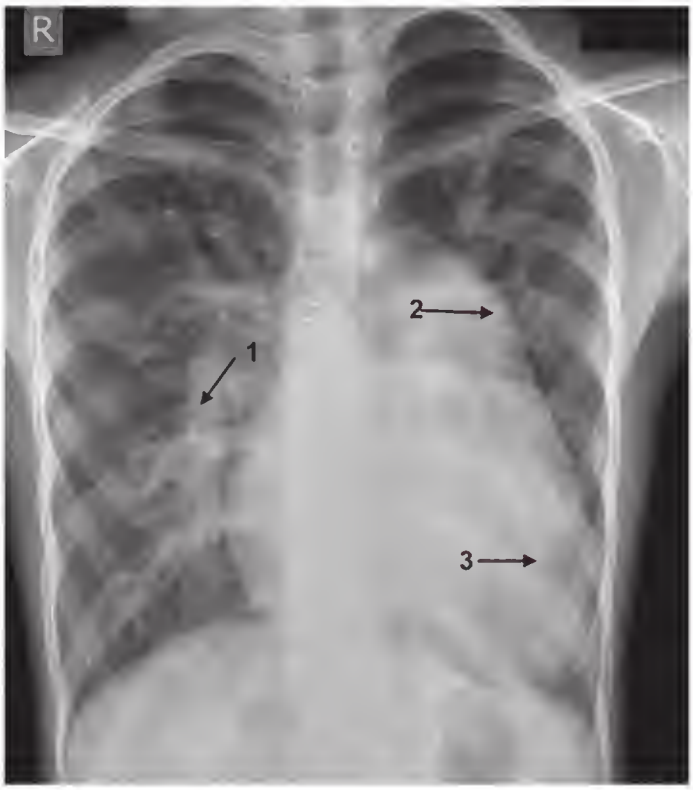


Figure 6: Chest radiograph of patient with atrial septal defect and significant left to right shunt. Marked plethora with dilated right descending (1) and main pulmonary arteries (2) with cardiomegaly (3) can be seen.

When pulmonary arterial hypertension (PAH) develops as in primary pulmonary hypertension or in Eisenmenger's syndrome, it leads to 'pulmonary oligaemia' with prominence of central pulmonary arteries like enlarged main pulmonary artery and its proximal branches. Vascular markings of outer one-third of both lung fields are not present. Pulmonary oligaemia may be seen in conditions with decreased pulmonary flow like TOF, pulmonary atresia, tricuspid atresia, TGA with PS, etc.

In patients with valvular pulmonary stenosis post-stenotic main pulmonary artery dilatation is seen with normal peripheral pulmonary vasculature.

In patients with pulmonary venous hypertension, there is a reasonably good correlation between the pulmonary vascular pattern and pulmonary capillary wedge pressure (PCWP). At a PCWP less than 8 mm Hg, the venous pattern is normal. As the PCWP increases to 10 to 12 mm Hg, there occurs redistribution of pulmonary blood flow with prominent upper lobe veins as compared to lower lobe veins called as 'cephalisation of pulmonary veins'. At pressures of 12 to 18 mm Hg, Kerley B lines appear, which are horizontal, pleuroparenchymal, peripheral linear densities. As PCWP increases acutely above 18 to 20 mm Hg pulmonary oedema occurs, with interstitial fluid present in sufficient amounts to cause a perihilar bat wing appearance.

Aorta

In PA view, the aortic arch is seen as a projection beyond the left margin of the mediastinal shadow, which is known as aortic knuckle or knob. Aortic prominence may be seen on right heart border in patients with AR with dilated aortic root or in those with aortic stenosis with post-stenotic dilatation. In elderly patients with calcified aortic valve, calcification may be visualised on aortic knuckle.

Pericardium

The pericardium is rarely distinctly definable on plain films of the chest, but there are two situations in which it can be seen: effusion and constriction. Classically, the cardiac silhouette has a 'money-bag shape' in the presence of a pericardial effusion, but such a shape is not in itself diagnostic. Pericardial calcification is most often seen in constrictive pericarditis especially of tubercular aetiology. Such calcification is usually thin and linear and follows the contour of the pericardium.

Moreover, the mechanical prosthetic valves (aortic as well as mitral) (**Figure 7**) and devices can be visualised in chest X-ray in post procedural patients.

Recent advances in both computed tomography (CT) and magnetic resonance imaging (MRI) have improved our ability to better image the cardiac anatomy and to some extent define the haemodynamic events within the heart. Comprehensive

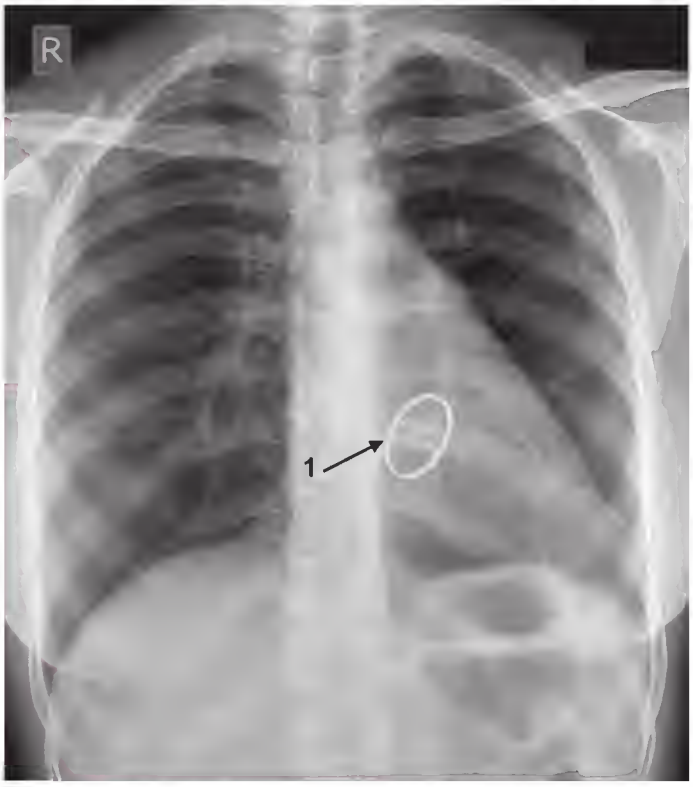


Figure 7: Chest X-ray PA view post-mechanical prosthetic mitral valve (1) replacement.

cardiac imaging includes morphological changes in structure of the heart, identification of the underlying pathoanatomy, functional and haemodynamic consequences of the insult and resultant biochemical changes. The modalities available for cardiac imaging include conventional radiology echocardiography, catheter angiography, radioisotope studies, CT and MRI. An ideal cardiac imaging modality should have very short acquisition time (to minimise motion artefact and freeze capture a biochemical event) and capability for ECG-gated orthogonal imaging to relate the morphological abnormality to a given haemodynamic and biochemical event. For optimal imaging, a large field-of-view to capture all desired structures in an image frame while retaining a high signal-to-noise ratio in the resultant image is desirable. However, at most times, these requirements are mutually contradictory. In view of the large volumes of information required, a fast processing and large storage capacity are essential requirements of an ideal imaging technique for the heart. **Table 3** below lists the diagnostic modalities excluding X-ray chest, and echocardiography useful in various disorders.

Table 3: An Overview of Suitable Techniques for Various Disease States

Congenital heart disease	For morphology – either CT or MRI. If small pulmonary arteries, CT scores over MRI because of high spatial resolution. For functional assessment, including shunt quantification in ASD, VSD, PDA and quantification of flow across shunt/graft/baffle/stenosis, MRI is advisable.
Ischaemic heart disease	For coronary artery assessment – CT angiography. Ventricular analysis and Wall motion abnormality are seen well on both CT and MRI. Perfusion studies and viability are best seen on cardiac MRI.
Cardiomyopathies (Non-ischaemic)	MRI with contrast enhancement for anatomic and functional assessment.
Cardiac masses	MRI with contrast enhancement for anatomic and functional assessment. CT is helpful in detecting calcification in mass. Rest all other features are better seen on MRI.
Pericardial diseases	MRI is more useful in depicting pericardial thickness, effusion and constriction. It helps differentiate constrictive pericarditis from restrictive cardiomyopathy. Cardiac CT shows calcification in pericardium. Pericardial thickness and constriction is also well detected on gated cardiac CT.

ASD = Atrial septal; CT = Computed tomography; MRI = Magnetic resonance imaging; PDA = Patent ductus arteriosus; VSD = Ventricular septal defects.

CARDIAC MRI

MRI offers many advantages in imaging of the heart. These include the lack of ionising radiation, orthogonal imaging capacity and superior temporal and contrast resolution as compared to CT. The relative disadvantages include lower spatial resolution, long acquisition times, inability to change orthogonal planes during post-processing and patient-specific issues such as claustrophobia, pacemaker implantation and pre-existing arrhythmias among others. Recent advances in MRI allow faster acquisition using newer sequences and have helped to obtain comprehensive morphological and functional information of the heart. Its inherent soft tissue contrast obviates the need for contrast injection for simple morphological assessment. All of the above can be obtained on an out-patient basis. Also, MRI is especially useful in post-operative settings. As a result, cardiac MRI (CMR) is fast emerging as a 'one-stop shop' for cardiac evaluation by providing virtually all the information needed for complete assessment of heart disease.

Imaging Sequences

The newer faster sequences allow acquisition of data during breath hold, thus minimising the respiratory artifacts. The sequences are ECG-gated and images are acquired mostly in end-diastole when the heart is most quiescent.

The commonly used sequences include:

1. Dark blood sequences: The flowing blood appears dark in these sequences. These include conventional spin echo, turbo or fast spin echo (TSE, FSE), HASTE, double inversion recovery FSE (Double IR-FSE). These sequences allow morphological assessment of heart and vessels without interference from bright signal from blood. These are useful for cardiac masses, myocardial and pericardial evaluation.
2. Bright blood sequences: Steady state gradient echo images show blood as bright. The sequences are balanced steady state procession sequences and have different trade names for different companies - True FISP, FIESTA, balanced FFE. These sequences are useful for cine imaging whereby images are acquired throughout the cardiac cycle. These cine images are used for functional analysis and to see any turbulent signal produced due to stenotic or regurgitant pathology.
3. Phase contrast imaging sequences: These are used for quantification of stenotic and regurgitant valvular disease, to find out Qp:Qs across a shunt and to do flow analysis across a vessel.
4. Contrast-enhanced MR sequences: These are especially useful for perfusion imaging and viability assessment. They are also indicated in evaluation of cardiac masses, cardiomyopathies and for great vessel visualisation.

Imaging Planes for the Heart

Due to skewed anatomy of the heart which is rotated along all three axes and this rotation varies from patient to patient based on the body build and girth, it is important to acquire images along the axes of 'heart' rather than along the various 'body' axes. Hence, an acquisition technique for images begins with acquiring body axis views-coronal, sagittal and axial, from which two-chamber, four-chamber, short axis, LVOT (Left ventricular outflow tract) and RVOT (Right ventricular outflow tract) views are reconstructed.

Congenital Heart Disease

MRI is useful for morphological assessment in patients with congenital heart disease (CHD). The situs, atrioventricular and ventriculoarterial communications, great vessels especially pulmonary artery size, pulmonary venous drainage, septal defects, etc. are well identified (**Figure 8**).

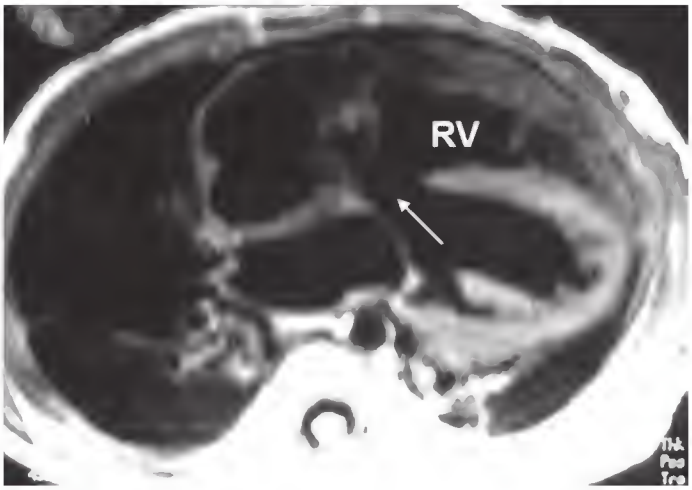


Figure 8: Four chamber T1W spin echo MR image showing perimembraneous VSD (arrow).

Functional information regarding ventricular function, Qp:Qs and quantification of regurgitant and stenotic valves can be obtained. In post-operative cases, the flow across the shunts and baffles can be quantified and gradients across narrowing determined.

For example, in a case of tetralogy of Fallot, CMR can show anatomy of pulmonary arteries, the ventricular septal defect (VSD) with degree of aortic override, pulmonary venous drainage, large aortopulmonary collaterals and ventricular morphology. Functionally, Qp:Qs across the shunt can be determined. RV functional analysis can be done. Post-operatively, flow across shunts or pulmonary regurgitation after total correction can be quantified. Residual VSDs can be picked up easily.

Valvular Heart Disease

Cine MRI in four chamber and long axis view helps pick up turbulent jets produced by the stenotic or regurgitation valvular lesions (**Figure 9**). These can then be quantified using phase contrast sequences, which help classify the severity of valvular lesion according to the flow and gradient across the valve.

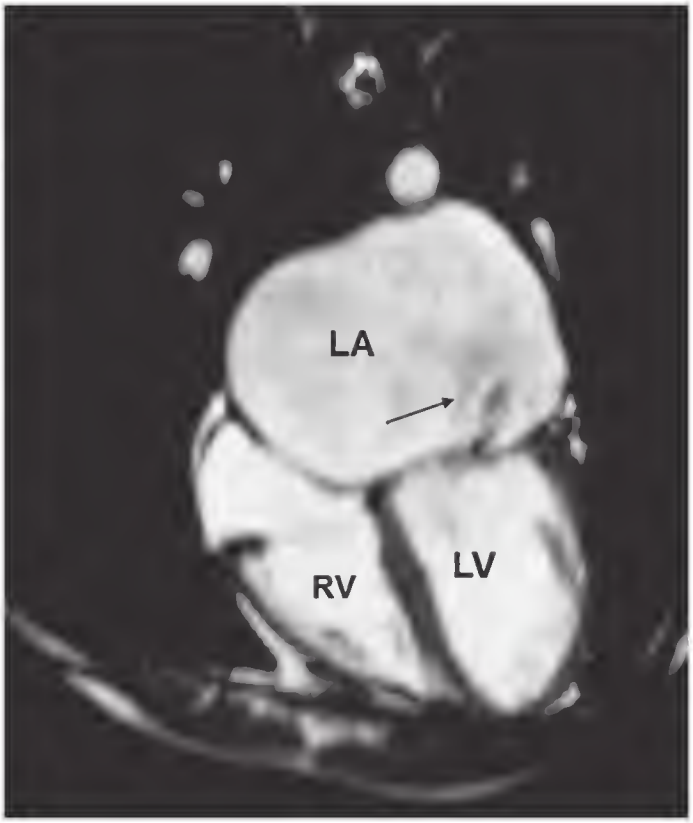


Figure 9: Four chamber bright blood TRUFISP cine MR image showing jet due to mitral regurgitation in dilated LA.

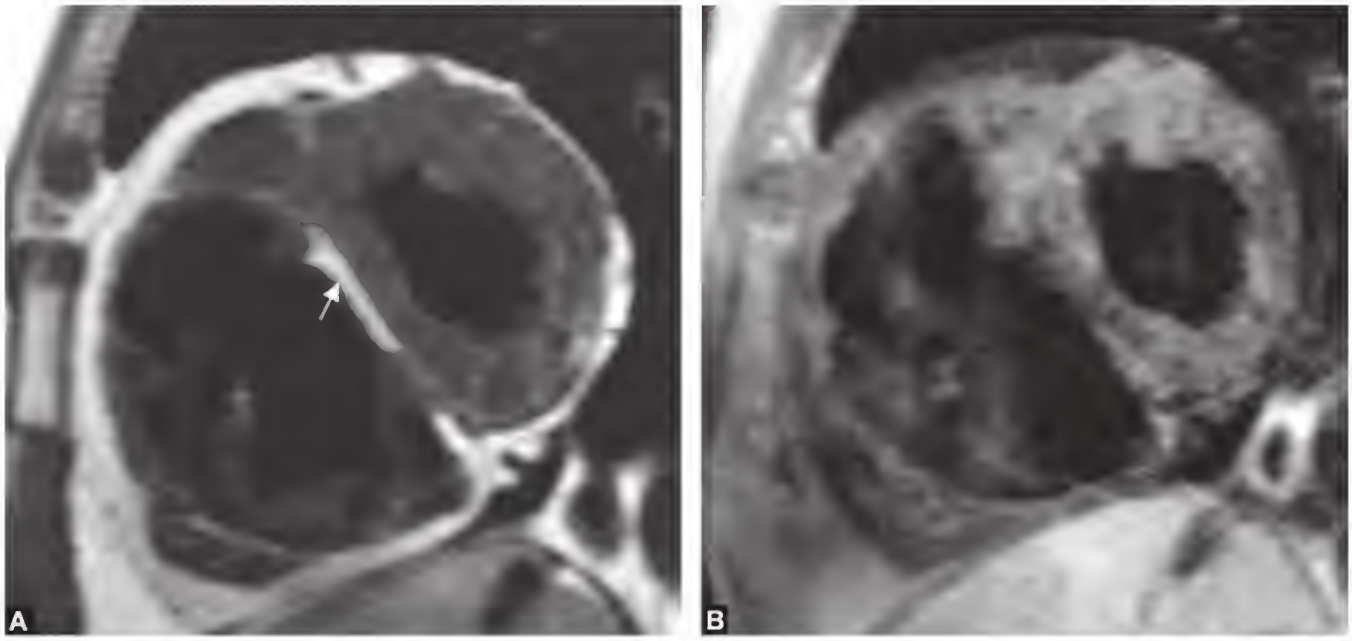
LA = Left atrium; LV = Left ventricle; RV = Right ventricle.

Planimetry for valvular area can be done to measure the stenotic valve area.

CARDIOMYOPATHIES

Arrhythmogenic Right Ventricular Dysplasia

There is fatty or fibrous infiltration of myocardium with or without thinning of myocardium (**Figures 10A and B**). There are



Figures 10A and B: MRI in arrhythmogenic right ventricular dysplasia. (A) Short axis T1W image showing bright fat infiltration (arrow) in RV side of interventricular septum; (B) Corresponding fat saturated T1W image shows bright signal of fat nulled.

associated wall motion abnormalities of RV, RV outflow tract or LV. MRI, with its inherent soft tissue contrast, is the modality of choice for diagnosing arrhythmogenic right ventricular dysplasia (ARVD). Fat is seen as bright signal on T1 and T2 weighted images and this signal disappears on fat saturation sequence. Cine images show decreased global function, regional wall motion abnormalities or aneurysms. Delayed enhancement images obtained 10 minutes after gadolinium contrast injection shows hyper-enhancement in regions of fibro-fatty replacement. This is very useful in guiding the endomyocardial biopsy.

Dilated Cardiomyopathy

MRI shows biatrial enlargement and increased size of the left and right ventricles (**Figure 11**). Mitral and tricuspid regurgitation, if present, can be well demonstrated. The pattern of enhancement in myocardium helps differentiate LV dysfunction due to dilated cardiomyopathy (DCM) or ischaemic heart disease (IHD). Majority of DCM patients do not have any late contrast enhancement. However, when present, it is in mid myocardium in non-coronary pattern which means that it does not correspond to any coronary artery territory.

Hypertrophic Cardiomyopathy

MRI is especially useful in detecting apical hypertrophy that is not well seen on echocardiography. Cine images demonstrate degree and extent of hypertrophy (**Figures 12A and B**).

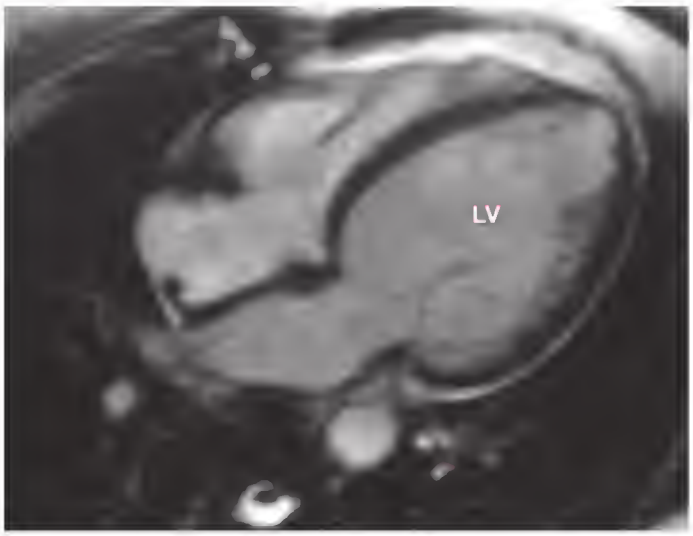
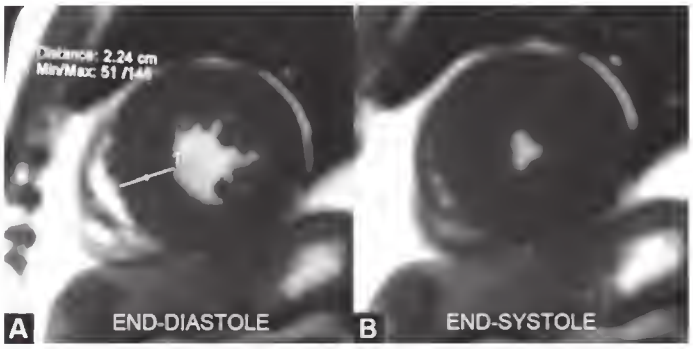


Figure 11: Four chamber bright blood MR image showing dilated left ventricle (LV) with thinned out myocardium in a patient with dilated cardiomyopathy.



Figures 12A and B: Case of hypertrophic cardiomyopathy. (A) short axis cine MR image in end-diastole showing thickened LV myocardium and (B) almost complete obliteration of LV cavity in systolic image.

End-diastolic wall thickness is measured besides quantification of cardiac function and flow dynamics of the ventricular outflow. Systolic anterior motion of mitral valve is well seen on cine MRI and the mitral regurgitation can be quantified. The total myocardial mass can be calculated and used for follow-up studies. Delayed contrast enhancement is, sometimes, seen because of fibrosis in the region of hypertrophy and such patients have higher risk of sudden cardiac death. CMR is useful for monitoring functional and anatomical outcome of surgical and pharmacological septal ablation.

Restrictive Cardiomyopathy (RCM)

There is restrictive filling and reduced diastolic volume of either or both ventricles with near normal systolic function and wall thickness.

On MRI, there is abnormal diastolic ventricular function and biatrial enlargement with normal systolic ventricular function, initially. CMR can characterise tissue, quantify myocardial mass, ventricular volumes and ejection fraction.

Common causes of restrictive cardiomyopathies include sarcoidosis, amyloidosis, haemochromatosis, storage disorders and idiopathic causes.

Amyloidosis

MRI shows thickening of left and right ventricular walls. Increased interatrial septal thickness or of posterior atrial wall greater than 6 mm is quite characteristic for amyloid infiltration. Associated pericardial and pleural effusions help differentiate amyloidosis from myocardial hypertrophy. On delayed enhancement, global subendocardial enhancement, not matching any specific coronary territory, is seen.

Sarcoidosis

CMR can help detect these cases early which is important to initiate early corticosteroid therapy that helps prevent malignant arrhythmias. Focal bright areas with low signal on T2W images suggest sarcoid granuloma. On delayed contrast images, mid wall patchy or focal enhancement is seen.

ISCHAEMIC HEART DISEASE

1. **Ventricular function:** Cardiac MRI is superior to echocardiography for assessment of ventricular function. Dynamic cine MRI images are used for volumetric analysis of ventricles and to see regional wall motion abnormalities.
2. **Myocardial perfusion (Rest and Stress):** Gadolinium contrast is injected intravenously and images are acquired during rest and after achieving pharmacological stress using intravenous adenosine in the dose of 140 µg/kg body weight for 4 to 6 minutes.

   Hibernating myocardium shows perfusion defect on stress that may not be present at rest (**Figures 13A and B**). The regional wall motion abnormality seen at rest improves after stress and there is no delayed contrast enhancement.
3. **Myocardial viability:** On delayed contrast MRI, infarcted or dead myocardium appears bright (**Figure 14**). Potential improvement after revascularisation depends on extent of infarcted wall thickness. Part of myocardium with more than 75% thickness infarcted, has poorest chances of recovery after revascularisation.



Figures 13A and B: Myocardial perfusion imaging. Short axis view showing (A) perfusion defect in inferior wall (RCA territory) on stress MR image which was not seen in (B) rest images suggesting inducible ischaemia on stress.

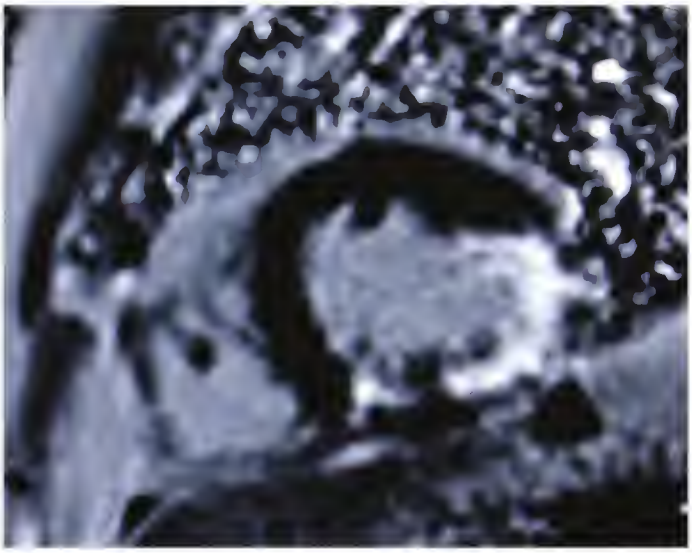


Figure 14: Delayed enhanced MRI in short axis view shows transmural infarct in the lateral wall (left circumflex artery territory).

Thus, cardiac MRI helps detect 'hibernating myocardium' and also helps in prognostication of recovery after revascularisation.

However, coronary arteries are better evaluated on CT angiography since it has a much better spatial resolution.

Pericardial Diseases

MRI is useful to differentiate constrictive pericarditis from restrictive cardiomyopathy, which is a usual diagnostic dilemma. In constrictive pericarditis, cardiac MRI shows pericardial thickness more than 4 mm. There may be associated SVC, IVC dilatation and RA enlargement. On cine MR images, abnormal diastolic septal motion ('septal bounce') is seen suggesting constrictive changes. Calcification is seen as a signal void.

Cardiac and Pericardiac Masses

Cardiac MRI is preferred for evaluation of cardiac masses since it has better soft tissue characterisation. Accurate morphological assessment, tissue characterisation, mobility of mass with cardiac cycle is well seen on MRI. Thrombus is most commonly confused as cardiac mass and it is easy to differentiate on cardiac MRI. The most common benign cardiac tumour is myxoma (**Figure 15**).

CARDIAC COMPUTED TOMOGRAPHY

With the advent of advanced multi-slice CT scanners, it has become possible to image heart with more accuracy in much shorter time. Short acquisition time (4-5 seconds vis-à-vis 45 minutes in MRI) and higher spatial resolution makes CT an investigation of choice for assessment of children with congenital heart disease.

ECG gating is done to acquire motion free images of cardiac chambers and coronary arteries. With latest multi-slice (256 and 320 slice scanners) and dual-source CT scanners available in clinical practice, it is possible to have spatial resolution less than

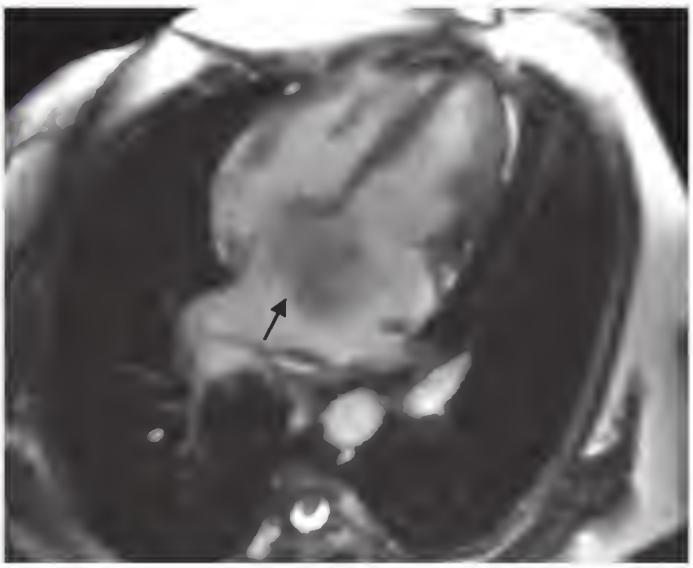


Figure 15: Bright blood MRI image in four chamber view in a case of left atrial myxoma attached to interatrial septum.

0.4 mm and gantry rotation time of 82 ms or lesser and it is no longer mandatory to reduce the heart rate. As long as it is stable, a heart rate of 90 beats per minute too can give reasonably accurate images of coronary arteries on dual source CT. Image acquisition lasts 8–10 seconds only and hence breath hold is easy.

Calcium scoring is used as screening tool in many countries in outpatient department patients. It is done by ECG-gated non-contrast single breath hold scans. A software then calculates the Agatston calcium score taking into account the area and density of calcification. A negative calcium score has a high negative predictive value for ruling out atherosclerosis and stenotic CAD. On the other hand, high calcium score indicates high probability of future hard cardiac events due to CAD. If calcium is concentrated in a single segment and overall score is more than 1,000, the interpretation of underlying coronary arteries becomes an issue and the contrast CT angiography should not be done.

CT angiogram (**Figures 16 to 19**): Sixty to eighty millilitre of non-ionic contrast is injected at the rate of 5-6 mL per second through antecubital vein. ECG-gated images are acquired in different phases of cardiac cycle and reconstructions are made from phases showing least movement.

Pooled data from multiple studies on 64 slice and dual source scanners have demonstrated high sensitivity (89%) and specificity (96%) of coronary CT angiography for evaluation of CAD. It is the modality of choice for evaluation of bypass grafts after coronary artery bypass grafting. In stented arteries, in-stent lumen can usually be well seen in stents greater than 2.5 mm but may vary with stent architecture and design.

Plaque imaging is being done with high-resolution CT angiography and Dual-energy (on Dual-source CT) to differentiate unstable versus stable plaques. Many research projects are currently going on to help identify vulnerable unstable plaque.

Functional assessment of ventricles and planimetry of the stenotic valves (**Figure 20**) can be done using cardiac CT images acquired throughout the cardiac cycle.



Figure 16: Oblique MIP CT image showing mixed plaque with calcification in mid left anterior descending artery (LAD).

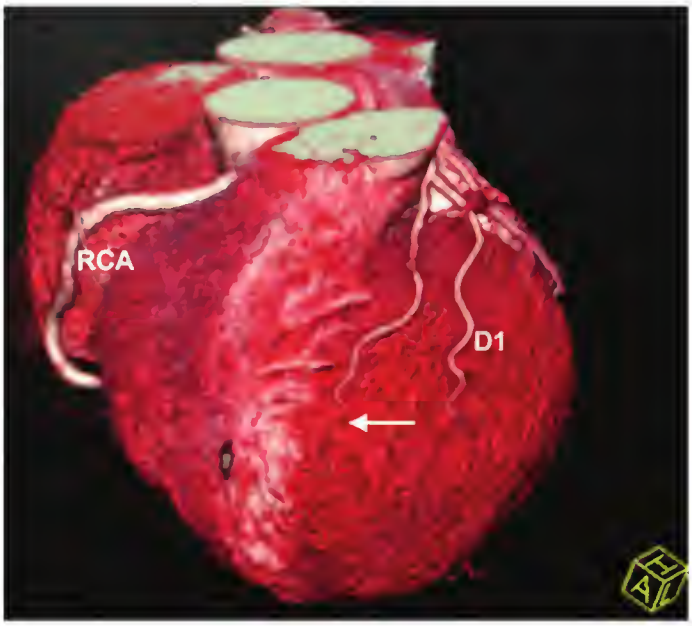


Figure 17: Volume rendered CT image showing Distal LAD Bridging (arrow).

RCA = Right coronary artery; D1 = First diagonal branch.



Figure 18: Oblique MIP-CT image showing patent stent in mid LAD.

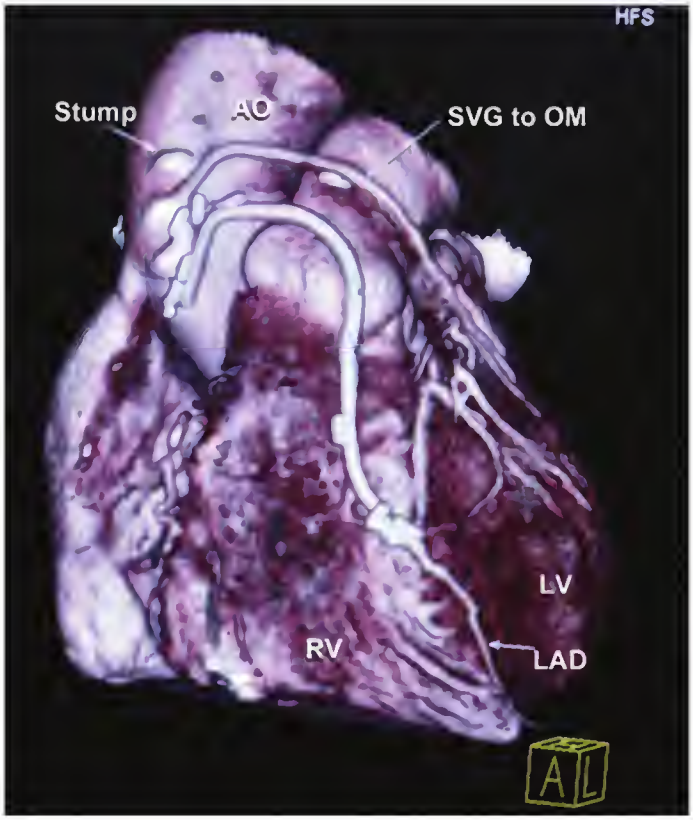


Figure 19: CT angiogram of post-operative CABG patient. Volume rendered image showing patent venous grafts to LAD and OM. A stump of occluded graft to diagonal is also seen.

AO = Aorta; LAD = Left anterior descending artery; LV = Left ventricle; OM = Obtuse marginal; RV = Right ventricle; SVG = Saphenous vein graft.

Overall, optimised cardiac imaging requires an appropriate patient selection. Both CT and MRI share advantages such as being multi-planar, out-patient based and gated acquisition among others. Factors including the speed of examination, image resolution, motion artefacts, feasibility of functional information, radiation exposure and the need for iodinated contrast influence technique selection in a given patient. Whereas claustrophobia, instability and pacemaker limit MRI; body habitus limits, pregnancy, contrast reactions limit use of CT scan. Echocardiography and SPECT may be helpful. In most clinical situations, CT and MRI are complementary in terms of the information that they can provide for optimal diagnosis, treatment planning and surveillance after treatment.

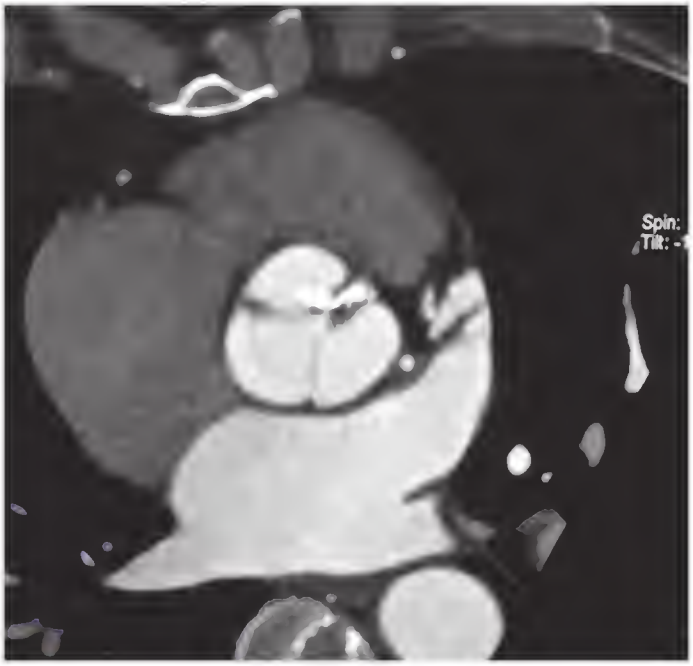


Figure 20: CT image of calcific aortic valve with thickened leaflets.

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12.7 Nuclear Cardiology

Vikram R Lele, Parag Aland

Nuclear cardiology involves use of radiopharmaceuticals to study the function of the heart (**Table 1**). Radiopharmaceuticals which have affinity for the myocardium are injected intravenously and with the help of a gamma camera, functional images of the heart are obtained. Two technologies are used: single photon emission computed tomography (SPECT) which uses single, dual or triple headed gamma cameras and isotopes of 99mTechnetium, and positron emission tomography (PET) which uses short-lived isotopes of 18F, 14O,13N, and 11C which are produced in cyclotrons and imaged with special PET cameras.

Table 1: The Scope of Nuclear Cardiology

Myocardial function
Myocardial perfusion
Myocardial metabolism
Myocardial infarction
Myocardial receptors
Atherosclerosis, apoptosis imaging
Gene therapy imaging

MYOCARDIAL FUNCTION

Nuclear medicine techniques are ideally suited for analysis of myocardial function (**Table 2**). By labelling the patient's red blood cells with radiotracer, and using ECG triggered gating, the blood pool in the heart is imaged. This study called the 'gated blood pool' (GBP) study helps to give accurate quantification of left ventricular ejection fraction (LVEF) and also the wall motion of different walls of the left and right ventricle. Analysis of the electrical conduction can also be made from special computer derived 'phase images' and asynchrony in conduction can be mapped. Diastolic function can also be quantified by analysis of the computer generated LV volume curve.

Diastolic function, estimated from the LV volume curve, gives four parameters of ventricular relaxation and filling. These are peak filling rate (PFR), time to peak filling rate (TPFR), average filling rate (AFR) and atrial contribution to LV filling.

Diastolic function abnormality occurs much earlier than systolic function abnormality in all cardiac disorders including coronary artery disease (CAD) and congestive cardiac failure. The earliest change in CAD is reduction in PFR. With exercise, the expected increment in PFR is blunted. LV function and ventricular volumes are powerful independent prognostic variables in cardiac patients. An LV end systolic volume (ESV) of < 70 mL is related to low mortality while ESV > 70 mL is related to high death rate. In aortic and mitral regurgitation, preoperative ESV > 60 mL/m^2 predicts a high-risk of peri-operative cardiac death.

Exercise induced regional wall motion abnormalities (RWMA) may appear in CAD before development of ECG abnormalities or symptoms of ischaemia. Normal subjects increase their LVEF generally by at least 5% from rest to peak exercise. Patients with significant CAD show no rise, or an actual fall compared to rest LVEF.

The 'gold standard' for LVEF measurements is MRI of the heart due to its most accurate estimation of LV volumes on which LVEF measurements are based. GBP and first-pass studies and myocardial perfusion studies are, however, reproducible, easier to perform and less expensive. GBP are used in follow-up of patients on chemotherapy for detecting early cardiotoxicity and in follow-up of cardiac transplant recipients.

MYOCARDIAL PERFUSION

Myocardial perfusion imaging (MPI) is now a well-established regularly used method in evaluation of a patient with ischaemic heart disease. The procedure involves injection of radiopharmaceutical intravenously during exercise followed by acquisition of post exercise images with a gamma camera (**Tables 3 and 4**). The patient is re-injected at rest followed by resting image acquisition. The stress and rest images are then compared. The radiopharmaceutical, usually Thallium or 99mTc methoxy isobutyl isonitrile (MIBI) is selectively picked up by the myocardium in proportion to blood flow. Areas supplied by stenosed coronary arteries do not get adequate supply of the

Table 2: The Nuclear Techniques for Evaluation of Myocardial Function

Study Name	Isotope Used	Information Obtained	Importance
Gated blood pool and first-pass studies	99mTc-pertechnetate 20 to 30 mL	Left ventricular ejection fraction (LVEF)	Robust parameter of left ventricular function. Altered in various cardiac disorders like myocardial infarction, cardiomyopathy
		Wall motion	Exercise induced wall motion abnormalities are sensitive and specific for ischaemia
		Diastolic function	Earliest to be affected in cardiac disorders
Gated myocardial perfusion scan	99mTc-MIBI/ tetrofosmin	LVEF/Wall motion, wall thickening, diastolic function, perfusion, (myocardial ischaemia, infarct)	Single test combining perfusion and function
	82Rb, $13NH_3$	Absolute quantification of myocardial blood flow, coronary flow reserve (CFR) estimation	Most accurate method for myocardial flow estimation. CFR is of great importance in management decisions

radiopharmaceutical as compared to areas supplied by normal arteries. This is seen as a 'perfusion defect'. If this defect disappears on the resting study, ischaemia is diagnosed. If the defect persists, then infarction is likely to be present.

Coronary blood flow increases several fold during exercise or following adenosine infusion, in the normal coronary vascular bed due to coronary vasodilatation in response to metabolic demand. It fails to increase appreciably in the territory of an obstructed coronary artery or arteries or in arteries with diffuse endothelial dysfunction. The ratio of resting flow to flow after maximal coronary dilatation is called the coronary flow reserve (CFR). Measurement of CFR is being increasingly recognised as vital information for making management decisions about intervention in CAD.

Table 3: Radiopharmaceuticals Used in Myocardial Perfusion Imaging

SPECT
201 Thallium
99mTc-MIBI
99mTc-Tetrofosmin
99mTc-Teboroxime
PET
82 Rubidium
13N-Ammonia

Table 4: Indications for Performing Myocardial Perfusion Imaging

1. Patients with abnormal baseline ECG (LBBB, LVH, digitalis therapy, WPW syndrome) where treadmill stress test interpretation is difficult.
2. Women: high rate of false positive stress test results.
   Patients unable to perform treadmill stress test (severe arthritis, neurological disorders, lack of motivation. Pharmacological stress test with adenosine/dobutamine can be done).
3. Asymptomatic or mildly symptomatic individuals with risk factors for ischaemic heart disease.
4. Patients with diagnosed coronary artery disease by angiography; for risk stratification and for evaluation of physiological significance of coronary stenosis.
5. Post-angioplasty for evaluation of re-stenosis.
6. Post-coronary bypass surgery for patency of grafts.
7. Post-myocardial infarction for risk stratification and viability assessment.

Based on the scan findings, the results are classified into high, intermediate and low-risk scans. Patients demonstrating 'low-risk scan' pattern can be managed medically even in presence of abnormal coronary angiograms (**Table 5**).

Patients showing 'high-risk scan' pattern should be sent for coronary angiogram (if not already performed) and for revascularisation. **Figures 1 to 3** demonstrate the low, intermediate and high-risk scan patterns. Myocardial perfusion imaging (MPI) thus performs 'gatekeeper' function in CAD management.

It has been demonstrated by large volume of data over last several years that the size and severity and reversibility of perfusion defects demonstrated on a myocardial perfusion have significant prognostic value. Small defects (low-risk scan) indicate <1% probability of cardiac events (myocardial infarct, death) in the following 2 years. Large defects (high-risk scans) indicate >8% probability of cardiac events.

Table 5: The Scan Patterns

Scan patterns
Low-risk scan
Normal perfusion, or
Small perfusion defects <10% of myocardium
Intermediate risk scan
Medium defect 10% to 20% of the myocardium, or
Small perfusion defect + LV dilatation or lung uptake of tracer
High-risk scan
Large defects >20% of myocardium, or
Medium perfusion defect + transient dilatation of LV or lung uptake of tracer

Higher the quantity of ischaemic myocardium (>12.5% of total myocardium), the better the results from interventional treatment strategies (CABG, angioplasty) rather than medical management.

Thus, MPI identifies patients who should be managed by medical versus revascularisation strategies.

PET technology allows absolute quantification of myocardial blood flow in mL/g/min and also estimates the CFR.

Coronary angiography is blind to vessels <400 microns in diameter. A significant portion of disease involves these vessels. The only way to assess these vessels is through the estimation of CFR (**Table 6**).

Table 6: The Utility of Estimating CFR

Potential clinical applications of PET MPI and CFR estimation
Impaired CFR in early coronary atherosclerosis
Hypertension
Hyperlipidaemia
Diabetes
Smoking
Impaired CFR in coronary stenosis and advanced coronary atherosclerosis
Evaluation of functional significance of coronary lesions (intermediate lesions)
Detection/delineation of multi-vessel CAD
Track disease progression/regression
Impaired CFR in non-atherosclerotic microvascular disease
Syndrome X, cardiomyopathies (HCM, DCM), hypertensive heart disease

CFR is found to be impaired in patients with hypertension, hyperlipidaemia, diabetes, and in smokers long before they develop manifest atherosclerosis and coronary disease. Corrective measures have shown normalisation or improvement in CFR.

In some patients with so called 'balanced triple vessel disease' where there is similar degree of stenosis in all three coronary arteries, a SPECT myocardial perfusion scan will look spuriously normal since the tracer will go equally badly in all stenosed territories and there will be no relative hypoperfusion in a particular territory. In this situation, an absolute quantification

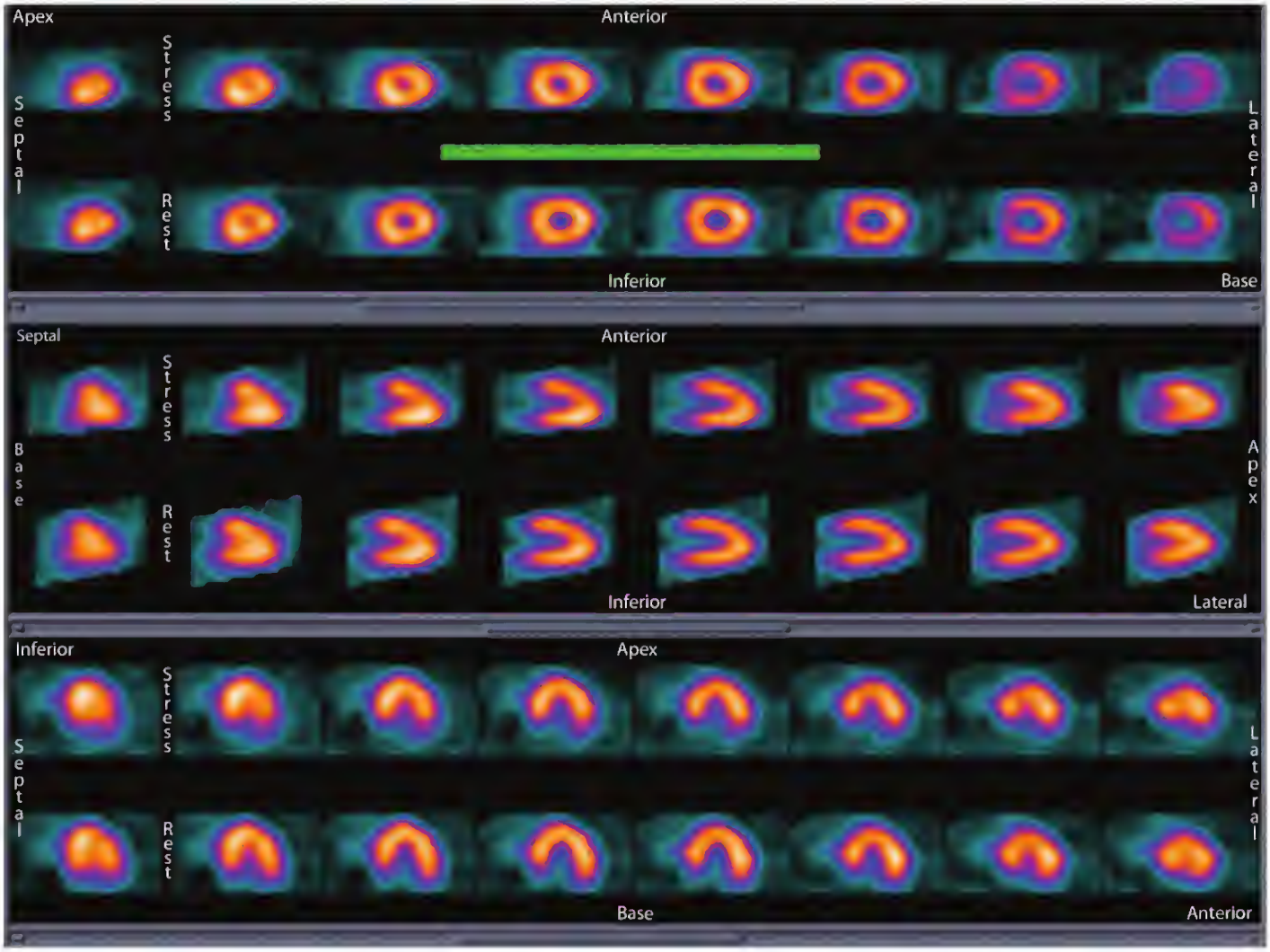


Figure 1: Shows a normal myocardial perfusion scan. Top two rows show matched short axis slices from apex to base: upper row post-stress and lower row during rest. The middle two rows show vertical long-axis slices from septum to lateral wall (upper post-stress, lower resting). The lower two rows show horizontal long axis slice from inferior to anterior wall. Note the homogenous perfusion in all areas with no perfusion defects.

of blood flow will show low values in all territories and the CFR will show low reserve.

This underscores the importance of PET scans in evaluation of MPI and CFR. Limited at the moment due to its high cost and limited availability, PET MPI and CFR will in future become the main tests in evaluation of ischaemic heart disease.

MYOCARDIAL METABOLISM

The normal myocardium predominantly uses fatty acids for its metabolic needs, to produce energy for contraction. In ischaemic conditions, the metabolism switches to the use of glucose in order to produce ATP. This is an inefficient way of producing energy, but the only way available for the myocardium in times of ischaemia.

It is possible with SPECT and PET techniques to evaluate myocardial metabolism of fatty acids as well as glucose (**Table 7**).

Evaluation of glucose metabolism has become the mainstay in detection of viable myocardium.

The switch in metabolism from fatty acids to glucose metabolism can be used to diagnose myocardial ischaemia. If a fatty acid tracer is injected during stress, ischaemic areas would show reduced uptake of fatty acid tracer. If 18F-FDG is injected during stress, ischaemic areas would show increased uptake of the glucose tracer. The normal areas would show no uptake of 18F-FDG. Stress FDG imaging is undergoing clinical studies. Hence, in patients coming to hospital with acute chest pain, a fatty acid tracer would immediately identify if there is ongoing ischaemia, showing reduced uptake of the tracer in ischaemic areas.

Table 7: Available Techniques for Imaging Myocardial Metabolism

Evaluation of myocardial metabolism with SPECT and PET
SPECT tracers
Fatty acid metabolism
123I-BMIPP, IPPA, DMIPP
PET tracers
Fatty acid metabolism
11C-Palmitate
Glucose metabolism
18F-FDG (Fluoro-deoxy-glucose)

Many times after a large myocardial infarction with a resultant low left ventricular ejection fraction, it is necessary to know if there is viable myocardium in the infarct zone. It has been conclusively shown that revascularisation provides better

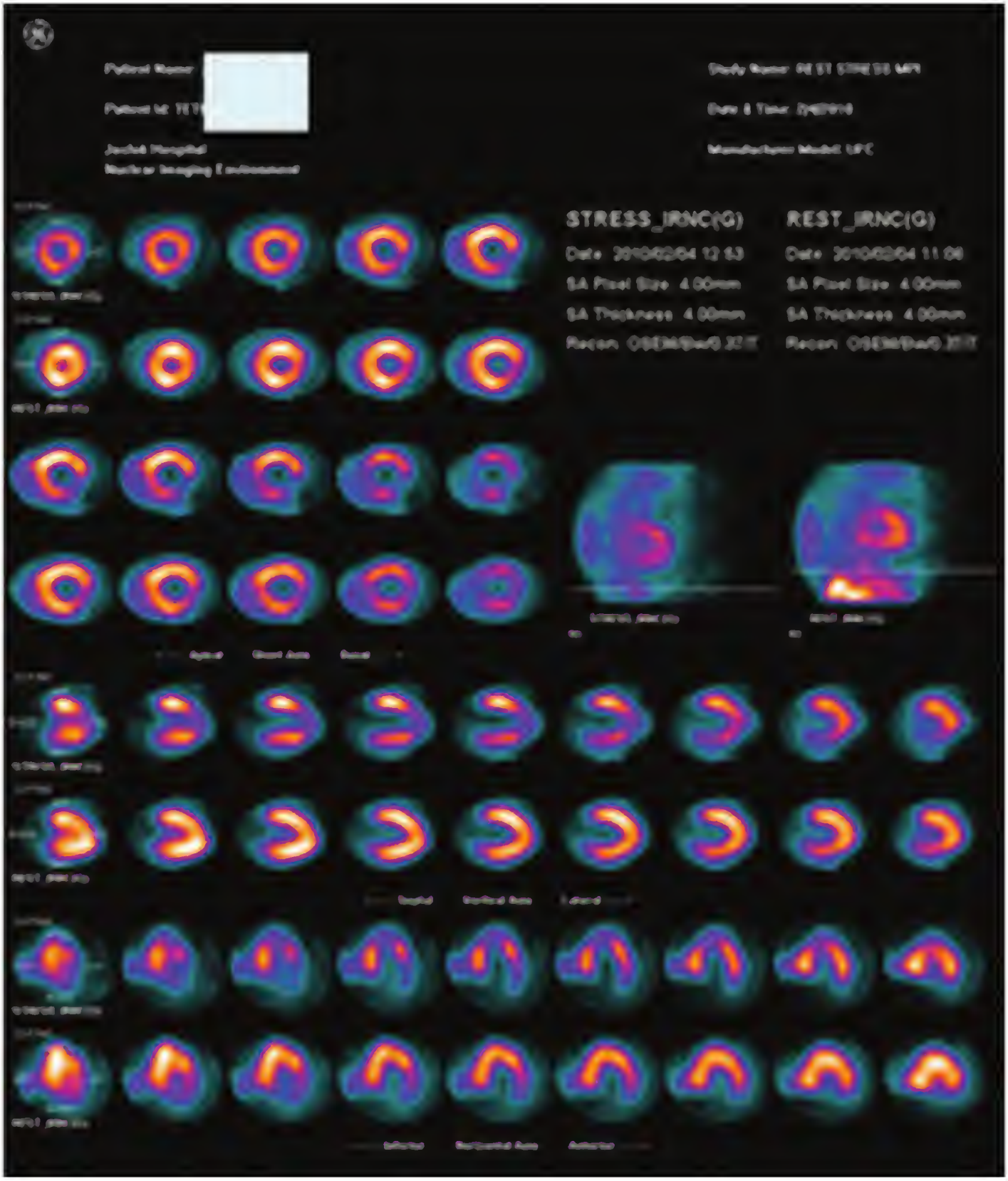


Figure 2: Shows an intermediate risk scan pattern showing medium sized perfusion defects in apex, and lateral wall.

clinical outcomes in terms of survival and symptomatic improvement in patients with viable myocardium as compared to medical therapy. Therefore, identification of viable myocardium is of great importance post myocardial infarction. Several techniques are available for this identification, namely low-dose dobutamine stress echocardiography, delayed enhanced MRI, and 18F-FDG myocardial PET. Currently, 18F-FDG PET remains the 'gold standard' for detecting myocardial viability. Viable myocytes retain capability of metabolising glucose. Dead myocytes or scar tissue cannot metabolise glucose. Hence, if a resting myocardial perfusion shows a severe perfusion defect and an FDG scan shows uptake of tracer in the same area (perfusion-metabolism mismatch), then viability is present.

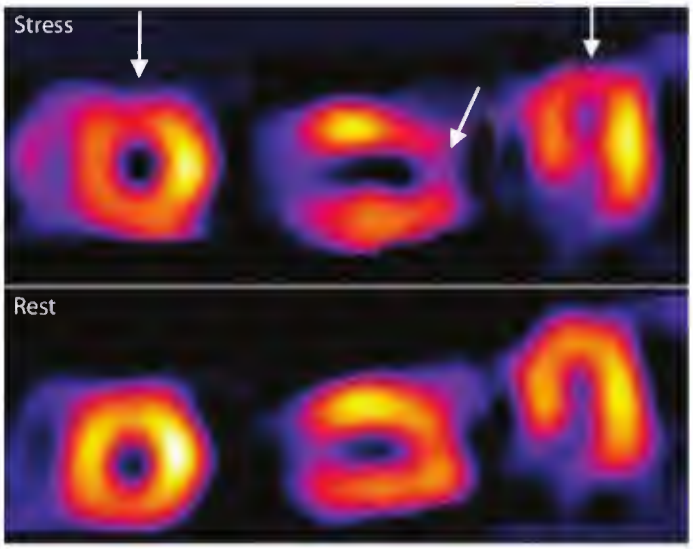


Figure 3: Shows a high-risk scan pattern with transient LV dilatation and large reversible defects in apical and anterior segments.

MYOCARDIAL INFARCTION

On standard MPI, an area of infarction is seen as a persistent perfusion defect on both the stress and rest images (fixed defect). Tracers have been developed which would be concentrated in infarcted tissue.

Glucaric acid localises in necrotic (not normal or ischaemic) tissue. Acute MI can be visualised within 1 to 2 hours of the onset of pain, in patients with or without thrombolytic therapy. Infarcts older than 2 to 3 days are not likely to show up on imaging. Tc-glucaric acid imaging will provide an important triage function in the emergency room in the evaluation of acute coronary syndromes. It will also detect peri-operative infarcts following CABG.

MYOCARDIAL RECEPTORS

Non-invasive assessment of cardiac pre-synaptic sympathetic nerve activity is possible with 123I-MIBG SPECT and 11C meta hydroxyephedrine (HED) PET. Myocardial receptor imaging has a potential diagnostic and prognostic role in patients with heart failure and cardiomyopathies. Regional uptake and washout of the radiotracer are expressed as heart to upper mediastinum (H/M) ratio in the early and late images of 123I-MIBG SPECT. A low H/M ratio strongly predicts poor outcome. Other applications include detection of diabetic autonomic neuropathy, cardiac transplant, re-innervation and re-entrant arrhythmias post-myocardial infarction.

Regional heterogeneities in β-adrenergic receptor number and reuptake occur in subjects with sudden cardiac death, and may be predictive for future events. Genetic variations in β-adrenergic receptors have major implications in terms of future development of CHF and early associated mortality. As newer third generation beta blockers like carvedilol become available, it will become increasingly important to identify markers predictive of drug efficacy for individual heart failure patients, based on sympathetic nerve imaging.

APOPTOSIS IMAGING

Pathological insults can induce apoptosis in various cardiovascular disorders, e.g. infarction and reperfusion injury, myocarditis, heart failure, heart transplant rejection. Identification of apoptosis is possible by imaging with 99mTc-annexin. The usefulness of serial imaging has been demonstrated clinically in early detection of cardiac transplant rejection by positive scans. Upon immunosuppressive therapy with cyclosporine the scans become negative within two days.

ATHEROSCLEROSIS AND GENE THERAPY IMAGING

For ensuring success of gene and cell based therapies, it is of prime importance to develop technology for non-invasive monitoring of the location and duration of gene expression, distribution and targeting of therapeutically engineered cells and vector particles *in vivo*. A number of advances have been achieved in high resolution, *in vivo* imaging methods, such as bioluminescence imaging, MRI, PET and various fluorescence imaging techniques, including fluorescence-mediated tomography (FMT) and near infrared fluorescence (NIRF) reflectance imaging.

Identifying patients at high-risk for an acute cardiovascular event such as myocardial infarction or stroke and assessing the total atherosclerotic burden are clinically important. Currently available imaging modalities can delineate vascular wall anatomy and, with novel probes, target biologic processes important in plaque evolution and plaque stability.

CONCLUSION

Nuclear cardiology has established itself as a very important diagnostic tool in the management of heart disease. By its unique ability to study physiological processes and their alteration in health and disease, it provides important diagnostic and prognostic information vital for making appropriate management decisions. Information from anatomical modalities should be combined with physiological information from nuclear cardiology techniques for full understanding of disease pathophysiology and appropriate management.

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12.8 Cardiac Catheterisation and Angiocardiography

Lekha Adik Pathak, NO Bansal

INTRODUCTION

The introduction of cardiac catheterisation ushered in the era of modern cardiology with marked improvement in the diagnostic capabilities of cardiac ailments and followed in turn, with the key-hole approach to treatment of a large majority of the cardiac patients since the 1980s. Even today angiography is considered 'gold standard' in the diagnosis of coronary artery disease (CAD).

HISTORY

Cardiac catheterisation opened the way for the study of anatomy and physiology of heart. The development of cardiac catheterisation has had profound impact on the diagnosis and treatment of CAD and congenital and valvular heart diseases. The noted 19th century French physiologist Claude Bernard catheterised and measured pressure in the various cardiac chambers and great vessels of the animal heart. The first catheterisation of the living human heart was performed by a young surgeon, Werner Forssmann (on himself) in 1929 in Eberswald, Germany. Cardiac catheterisation paved the way for coronary arteriography. The first coronary angiogram was performed by F. Mason Bones on October 30, 1958; since then it has revolutionised our understanding and treatment of CAD. The coronary angiogram not only provided objective evidence to support or refute the clinical diagnosis of angina pectoris but, more importantly, led to first studies of the natural history of patients with CAD. The coronary angiogram provided the road map necessary for the successful development of coronary angioplasty. On 16 September 1977, Andreas Gruentzig performed the first coronary angioplasty in an awake human, a 37-year-old insurance salesperson with proximal LAD lesion and thus described a new way of achieving coronary revascularisation by the endovascular dilation of an obstructing lesion, that he referred to as percutaneous transluminal coronary angioplasty (PTCA).

CARDIAC CATHETERISATION PROCEDURE

Cardiac catheterisation procedure involves:

1. Pressure measurements: To calculate pressure, gradients and valve areas.
2. Oximetry data: To measure oxygen saturation and for calculation and directions of shunts.
3. Contrast injections for opacification of cardiac chambers and coronary angiograms.

Indications

The decision to perform cardiac catheterisation must be based on a careful balance of the risk of procedure against the anticipated benefit to the patient. Indications of cardiac catheterisation are enumerated in **Table 1**.

Contraindications

There is no absolute contraindication to cardiac catheterisation. Relative contraindications are given in **Table 2**.

Technique

Cardiac catheterisation is performed in adults and older children under light sedation and local anaesthesia with xylocaine. However, in smaller children and infants, general anaesthesia is required. The portals of entry commonly employed are as under:

Table 1: Indications of Cardiac Catheterisation

Diagnostic	
	To define cardiovascular anatomy in patients with congenital or acquired heart diseases
	To define coronary artery anatomy
	To assess ventricular function
	To determine intracardiac/intravascular pressures and measure flow (cardiac output) for calculation of physiological parameters
	To determine transvalvular gradients across cardiac valves and to quantify valvular regurgitation when there is disparity between clinical and echocardiographic findings
	For electrophysiologic (EP) studies to localise the site of heart block and the nature and pathway of cardiac arrhythmias
	To perform endomyocardial biopsies
Therapeutic	
	Percutaneous coronary interventions (PCI)
	Valvular dilations such as balloon mitral valvuloplasty (BMV), balloon pulmonary valvuloplasty (BPV), balloon aortic valvuloplasty
	Device closure of atrial septal defects (ASD), ventricular septal defects (VSD), patent ductus arteriosus (PDA) and other uncommon congenital defects such as coiling or device closure of ruptured sinus of Valsalva aneurysm (RSOV), and coiling of coronary artery fistulas
	Balloon atrial septostomy as in patients with transposition of great arteries (TGA)
	Radiofrequency ablation (RFA) of foci of cardiac arrhythmias and pathways of aberrant conduction
	Local thrombolysis in patients with pulmonary artery embolism
	Alcohol septal ablation in HOCM

Table 2: Relative Contraindications of Cardiac Catheterisation

Uncontrolled ventricular irritability (increased risk of ventricular tachycardia/fibrillation)
Digitalis toxicity
Electrolyte imbalance (e.g. uncontrolled hypokalaemia)
Uncorrected hypertension
Concurrent febrile illness
Decompensated heart failure
Severe renal insufficiency, unless dialysis is planned
Severe allergy to radiographic contrast agent
Prothrombin time >18 or INR >2 or bleeding diathesis

Femoral route

The femoral artery and vein are the most commonly used vessels for cardiac catheterisation. It is important to puncture these vessels at correct level, i.e. 1 cm to 2 cm below the inguinal ligament (and not the inguinal skin crease) which runs from the

anterior superior iliac spine to pubic tubercle. Though earlier puncture was done using Seldinger technique with a Seldinger needle, nowadays most of the cardiac catheterisation laboratories use a single wall puncture needle. Once the needle is in the vessel, it is stabilised with the left hand and a guide wire (0.035 or 0.038 inch) with J tip is inserted via the needle into the vessels, while making sure that there is no resistance felt during its advancement. The needle is then removed and a skin nick (if not already done) is made. An appropriate sized sheath is then threaded over the guide immediately after sheath insertion. The catheters are then guided under fluoroscopic control to appropriate site, through the sheath (**Figure 1**).

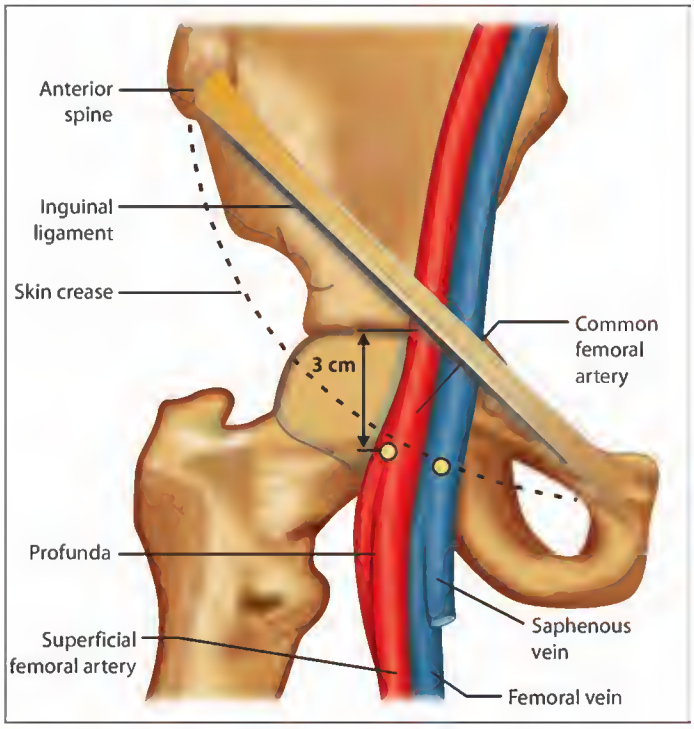


Figure 1: Regional anatomy relevant to percutaneous femoral arterial and venous catheterisation. Schematic diagram showing the right femoral artery and vein coursing underneath the inguinal ligament, which runs from the anterior superior iliac spine to the pubic tubercle. The arterial skin nick should be placed approximately 1 cm to 3 cm below the ligament and directly over the femoral arterial pulsation, and the venous skin nick should be placed at the same level but approximately one finger-breadth more medially. Although this level corresponds roughly to the skin crease in most patients, the anatomical localisation relative to the inguinal ligament provides a more constant landmark.

Radial artery route

This approach is especially useful for those with peripheral arterial disease and morbid obesity. The preferred site of puncture is approximately 1 cm to 2 cm proximal to the radial styloid. Radial artery cannulation is done using a micropuncture needle (21 gauge). Using the technique as described above, an appropriate sized sheath (5 or 6 F) is inserted into the vessel. Anticoagulation (usually, heparin) and cocktail of vasodilators (NTG 100 mg to 200 mg, verapamil 1.25 mg to 2.5 mg) is administered immediately after sheath insertion. As the risk of post-procedural radial artery occlusion is up to 3%, palmar arch patency must be assessed prior to the procedure. This is done by Allen's test. Both the radial and ulnar arteries are compressed while the patient is asked to make and open fist 3 to 4 times. Ulnar artery compression is then removed and the time taken for the palm to get flushed is noted. Absent or delayed flushing suggests inadequate palmar arch blood flow. A modification of Allen's test (first developed by Hovagim and validated by Gerard Barbeau) can also be done. This method involves placing a pulse oximeter probe on the thumb while compressing the radial artery. Adequacy of palmar arch blood flow is confirmed by the presence of an arterial waveform (even if with reduced amplitude or delayed appearance) and oxygen saturation of >90%. The patency of radial and ulnar arteries is best confirmed by Doppler study. The major advantages of radial artery approach are faster time to ambulation and rare access site bleeding complications. Limitations include smaller artery size and inability to take venous access.

Other sites

Brachial artery can be approached over the antecubital fossa by both percutaneous technique and surgical cut-down. Axillary artery can be entered over the head of humerus. In the new born, umbilical artery can be used for catheterisation.

GENERAL PRINCIPLES

Figure 2 outlines the hardware and machine used for cardiac catheterisation.

Certain general principles should be followed during cardiac catheterisation. Haemodynamic measurements should precede angiographic studies, so that the pressure and flow measurements are made as close as possible to the basal state. Measurements of pressure and cardiac output should be made as simultaneously as possible. Cardiac output can also be measured using thermodilution techniques.

Limit total contrast volume for the study (in paediatric patients, this should not exceed >5 mL/kg). Currently, most contrast media used are non-ionic with low osmolality. Nowadays, 10% to 30% of coronary angiograms and angioplasties are done via radial route and it is increasing still further in view of great patient comfort and less bleeding. The blood samples need to be acquired with the patient breathing (or being ventilated with) air or a gas mixture containing no more than a maximum of 30% oxygen.

INTERPRETING TRACINGS

Atrial Tracings

Atrial tracings have three positive waves namely 'a', 'c' and 'v' and two descents namely 'x' and 'y'. The 'c' wave is often missing. Left atrium (LA) tracings differ from those of right atrium (RA) in the form that 'v' wave is taller than 'a' wave in the former (**Figure 3**) Also pressures are generally higher in the LA tracing. Tall 'a' waves in the RA tracing suggest tricuspid stenosis (TS), pulmonary stenosis (PS), and significant pulmonary hypertension (PH). Tall 'a' waves in the LA tracing suggest mitral stenosis (MS) and left ventricular hypertrophy (LVH) due to any cause. In atrial fibrillation (AF), 'a' wave is absent. Tall 'v' waves in the RA tracing suggest tricuspid regurgitation (TR) and in the LA suggest mitral regurgitation (MR). A well marked 'y' descent rules out significant stenosis of the respective AV valve. In cardiac tamponade, the 'x' descent is present but 'y' descent is absent. A rapid 'x' and 'y' descent (M or W sign) is seen in constrictive pericarditis.

Ventricular Tracings

Left ventricular end-diastolic pressure (LVEDP) is somewhat higher than right ventricular end-diastolic pressure (RVEDP) reflecting the greater stiffness of LV. High right ventricular systolic pressure (RVSP) is seen in PS and PH due to any cause. Raised

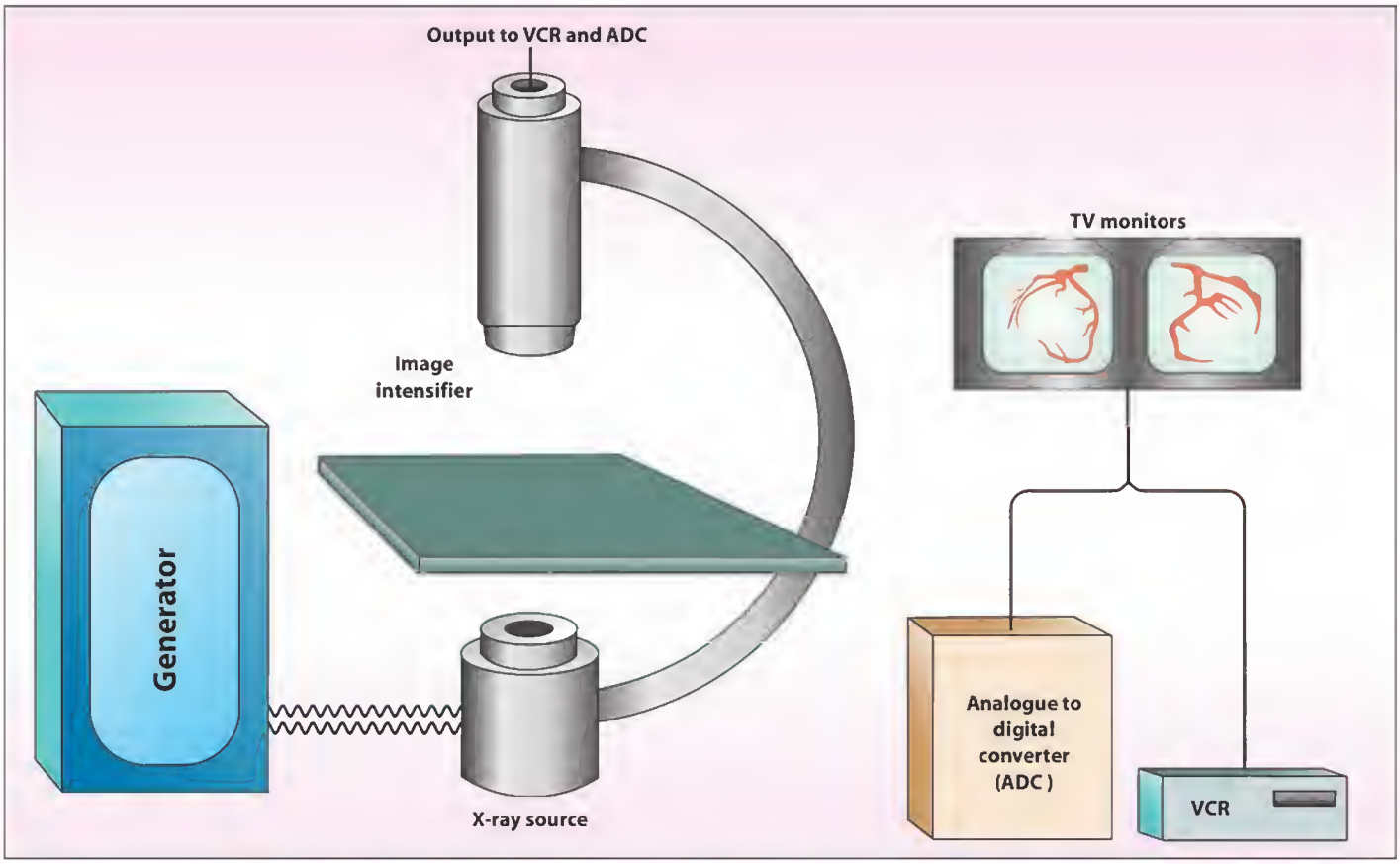


Figure 2: Cineangiography equipment. The major components include a generator, X-ray tube, image intensifier attached to a positioner such as a C-arm, optical system, video camera, videocassette recorder (VCR), analog to digital converter (ADC), and television monitors. The X-ray tube is the source of the X-ray beam, which passes superiorly through the patient.

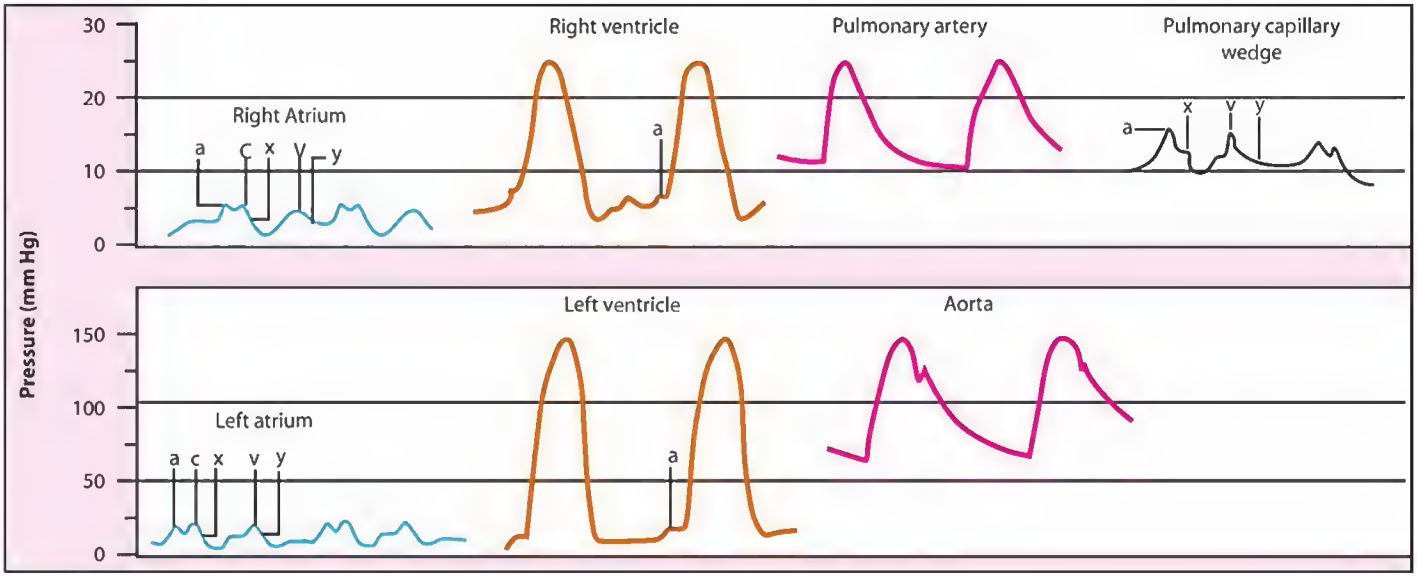


Figure 3: Normal right- and left-heart pressures recorded from fluid-filled catheter systems in a human.

left ventricular systolic pressure (LVSP) is seen in systemic hypertension and left ventricular outflow tract obstruction (LVOTO) due to any cause (aortic stenosis, hypertrophic obstructive cardiomyopathy). Higher ventricular end-diastolic pressures reflect ventricular dysfunction or restrictive physiology.

Arterial Tracings

In severe aortic regurgitation (AR), the arterial pulse pressure is wide with a high systolic pressure and lower diastolic pressure. With significant aortic stenosis (AS), there is decapitation of systolic pressure. Similar changes are seen in respective pulmonary artery tracings in those with PR or PS. Pulmonary arterial wedge pressure obtained by wedging the right heart catheter far out into a pulmonary artery branch reflects the LA pressure in individuals without any vascular lung disease or pulmonary venous obstruction. It is, thus, a measure of LV diastolic pressure in those with normal functioning mitral valve.

Pressure recordings provide an important clue to the presence of valvular stenosis. With significant stenosis of semilunar valves, a systolic pressure gradient is present between the respective great artery and the ventricular chamber (**Figure 4**). Stenosis across the AV valves results in pressure gradients in diastole between the respective atrial and ventricular chamber. (**Table 3** gives normal pressure values of chambers and across valves).

Table 3: Haemodynamic Data

Chamber	Normal Values
RA pressure	Mean 1 to 5 mm Hg
RV systolic pressure (RVSP)	15 to 30 mm Hg
RV end diastolic pressure (RVEDP)	1 to 7 mm Hg
PA systolic pressure (PASP)	15 to 30 mm Hg
PA diastolic pressure (PADP)	4 to 12 mm Hg
PA mean	9 to 19 mm Hg
PCWP	Mean 4 to 12 mm Hg
LA pressure	Mean 2 to 12 mm Hg
LV systolic pressure (LVSP)	90 to 140 mm Hg
LV end diastolic pressure (LVEDP)	5 to 12 mm Hg
Aorta systolic pressure	90 to 140 mm Hg
Aorta diastolic pressure	60 to 90 mm Hg
Mean aortic pressure (MAP)	70 to 105 mm Hg
Systemic vascular resistance	1170 ± 270 dynes sec/cm^{-5}
Pulmonary vascular resistance	67 ± 30 dynes sec/cm^{-5}
Oxygen consumption	125 mL/m^2
AV oxygen difference	30 to 50 mL/L
Cardiac output	4 to 8 L/min

Valve Area

Calculation of valve area is based on the hydraulic formula usually referred to as the 'Gorlin formula'. The calculation depends on obtaining estimates for valve flow in mL/s during the time that the valve is open.

Normal mitral valve area in adults is 4 to 5 cm^2. When it is less than 1 cm^2, it becomes critical MS. In adults, the normal aortic valve area is 3 to 4 cm^2 and critical AS is said to be present when valve area is less than 0.8 cm^2.

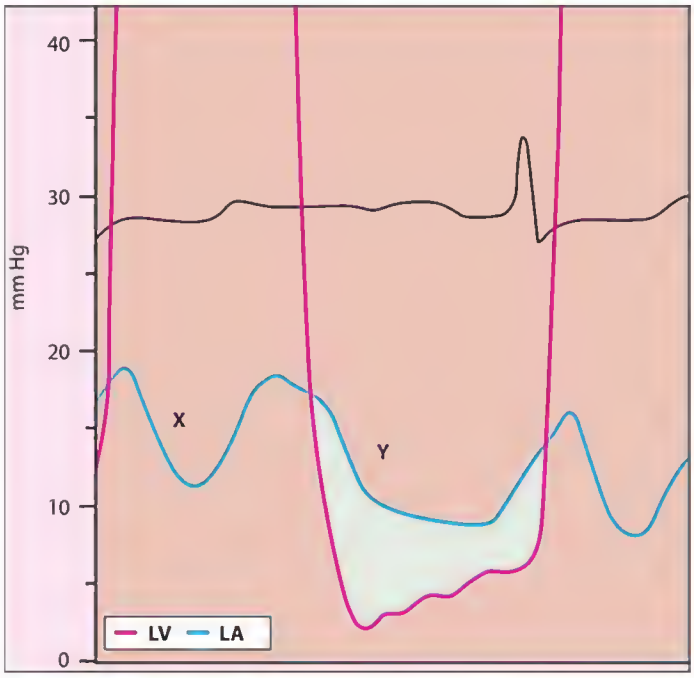


Figure 4: Pressure gradient in a patient with mitral stenosis. The pressure in the left atrium (LA) exceeds the pressure in the left ventricle (LV) during diastole, producing a diastolic pressure gradient (green shaded area).

Shunt Detection

Cardiac catheterisation data are also used to detect, localise and quantify left to right shunt or right to left shunts. For example, a step-up in oxygen saturation from 65% in the RA to 80% in pulmonary artery is indicative of large left to right shunt that may be due to ventricular septal defect. Pulmonary to systemic flow ratio (Qp:Qs) can be calculated as it provides a simple and reliable estimate of the extent to which pulmonary flow is increased or reduced and provides a useful insight into the severity of the haemodynamic disturbance in most cases. It is also very simple to perform, employing the oxygen saturation data. The formula is:

$$Qp:Qs = \frac{Sat\ AO - Sat\ MV}{Sat\ PV - Sat\ PA}$$

where Sat AO is aortic saturation, Sat MV is mixed venous saturation; Sat PV is pulmonary vein saturation, and Sat PA is pulmonary artery saturation.

Calculation of pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) is very important in cases of shunts to decide further treatment options.

ANGIOGRAPHY (CONTRAST INJECTION)

The goal of coronary angiogram is to examine the entire coronary anatomy including the native vessels and bypass grafts, if any. The coronary artery can be delineated by opacifying it with contrast material which is injected via a catheter that is engaged to the respective coronary artery sinus. Images of the coronary artery are recorded by filming with digital cineangiography systems at 10 to 30 frames/s. Each coronary artery is visualised in several views and analysed for the anatomy, number and severity of stenosis (commonly expressed as % stenosis relative to normal segment) (**Figures 5 to 7**).

VENTRICULOGRAM

A ventriculogram can be performed by rapid injection of radio-opaque contrast agent into the chamber to be assessed. A power injector injects the contrast agent at a pre-selected flow rate, volume and pressure. The catheter used is usually an end-hole catheter with multiple side-holes (pigtail catheter) as it can

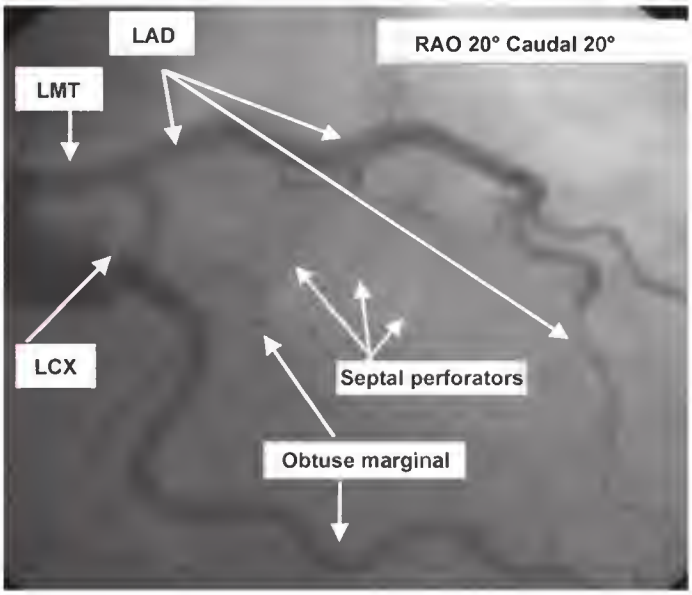


Figure 5: Left coronary angiogram in right anterior oblique (RAO) caudal view, showing left main trunk (LMT), left anterior descending (LAD) and left circumflex arteries (LCX) and their branches.

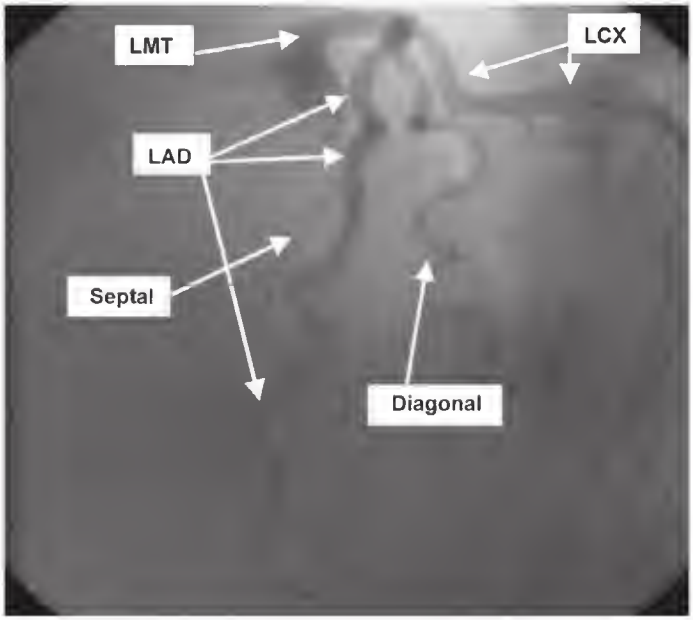


Figure 6: Left coronary angiogram in left anterior oblique (LAO) cranial view.

LMT = Left main trunk; LAD = Left anterior descending; LCX = Left circumflex artery.

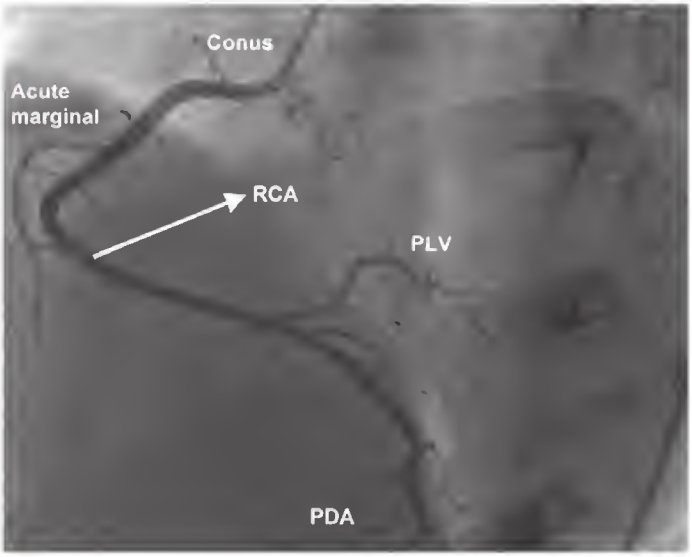


Figure 7: Right coronary angiogram in right anterior oblique (RAO) view, showing right ventricular, posterior left ventricular (PLV) and posterior descending (PDA) branches.

RCA = Right coronary artery.

rapidly deliver a bolus of the contrast agent without recoil. Ventricular wall contraction can be visually assessed by ventriculogram. Regional abnormalities of wall motion include diminished inward motion of myocardial segment (hypokinesia), absence of movement of myocardial segment (akinesia) and paradoxical systolic expansion of regional myocardial segment (dyskinesis). Also ventricular end-diastolic pressures can be determined. Ventricular systolic function can also be assessed by calculating ejection fraction, dp/dt or stroke work.

Besides aortography may be performed when indicated (as in quantification of aortic regurgitation, identification of aortic aneurysm and/or aortic dissection) to define the size of aortic root and thoracic aorta.

Various procedures, like balloon valvuloplasties of AV valves can be easily done, by percutaneous route, with the help of contrast ventriculograms (**Figure 8**).



Figure 8: Balloon mitral valvuloplasty showing the inflated Inoue balloon across the mitral valve.

COMPLICATIONS

Serious complications of cardiac catheterisation include death, myocardial infarction (MI), or stroke. Their incidence is < 1%. The risk of vascular injury requiring transfusion or surgical repair is <2%. Perforation of heart or great vessels may occur, especially when using the trans-septal technique. Vasovagal reactions are common and respond well to atropine. Major arrhythmias occur in 1% patients and include ventricular tachycardia/fibrillation and bradyarrhythmias. Because cardiac catheterisation is inherently a sterile procedure, infection is extremely unusual. Iodinated contrast agents may trigger allergic reactions. At least 5% of patients experience a transient rise in serum creatinine (contrast induced nephropathy) following coronary angiography; however, nowadays non-ionic low osmolar contrast agents are widely used which have significantly lower incidence (1%) of allergic reaction. Hypotension and heart failure may occur sometimes especially in those with extensive CAD or depressed LV function.

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12.9 Pharmacotherapy of Cardiovascular Disorders

J C Mohan, Vipul Mohan

INTRODUCTION

It is well known that cardiovascular diseases are the number one cause of mortality in the world. Cardiovascular pharmacotherapy has been a tremendous success story. Underlying this success has been knowledge of the neuro-endocrine signal transduction pathways, receptors, enzymes, cytokines and ion channels involved in pathogenesis of disease process.

MANAGEMENT OF ANGINA AND MYOCARDIAL ISCHAEMIA

Angina results from an imbalance between myocardial perfusion and myocardial metabolic demands. Heart rate (HR) reduction can alter both elements of this imbalance beneficially. The resulting increase in diastolic filling time should improve myocardial perfusion; myocardial oxygen demand varies directly with HR. It is essentially due to demand-supply mismatch of oxygen at mitochondrial level. There is, however, a weak relationship between severity of pain and degree of oxygen deprivation in the heart muscles.

About five million patients in India use anti-anginal drugs. Anti-anginal efficacy is documented by improved exercise tolerance, reduction in angina attack rate and short-acting nitrate use, and anti-ischaemic efficacy by reduction in exercise-induced electrocardiogram (ECG) ST-segment depression.

Pharmacological Approach in Ischaemia/Angina

Pharmacological treatment of angina encompasses both the prevention of the complications of coronary atherosclerosis and the relief of symptoms. Progress of atherosclerosis can be retarded by statins, anti-RAAS agents and blood pressure lowering drugs. Modes of relief of ischaemia are shown in **Table 1**.

Table 1: Modes of Relief of Ischaemia

Reduce energy expenditure (mainstay)
Increase oxygen delivery (increase myocardial blood flow)
Increase oxygen efficiency (complimentary)
Combined

Drugs which reduce myocardial contractility, HR and/or systolic blood pressure are the mainstay of anti-anginal therapy (**Table 2**). These include beta-adrenergic receptor blockers, calciumchannel blockers and direct sinus node inhibitors.

Nitrates

Sublingual nitrates work rapidly, i.e. within minutes, and the effect lasts for about 30 to 45 minutes. Profound relief of symptoms is the result of venodilatation, after-load reduction and coronary dilatation. Many nitrate delivery systems have been developed for chronic prophylactic use (**Table 3**). It has become clear, however, that patients can develop at least partial tolerance to this therapy. The use of nitrate-free interval between dosing is an effective means of overcoming the development of tolerance; although in some cases, a rebound of symptoms may occur at this time. Eccentric dosing of oral nitrates is a recognised way of reducing nitrate tolerance. This can be obviated by the concomitant use of another class of anti-anginal agents. Nitrates do not influence morbidity or mortality.

Table 2: Major Classes of Anti-anginal Drugs

Organic nitrates (reduce pre-load and increase coronary blood flow)
Pure negative chronotropic agents (direct sinus node inhibitors, like ivabradine, cilobradine, etc.)
Negative chronotropic and negative inotropic agents (beta-adrenergic receptor blockers and phenylalkylamine and benzothiazepine calcium channel blockers, like verapamil, diltiazem, etc.)
Vasodilatory non-chronotropic calcium channel blockers (nifedipine, nitrendipine, amlodipine, etc.)
Delayed sodium current (phase I sodium channel blockers) modifiers, like ranolazine
Nitric oxide donors, like nicorandil and nebivolol
Metabolic modulators (trimetazidine, perhexiline maleate, diacetoacetate, etc.)

Table 3: Different Types of Nitrates

Short-acting nitrates: Nitroglycerine, amyl nitrate
Intermediate-acting nitrates: Isosorbide dinitrate
Long-acting nitrates: Isosorbide mononitrate

Calcium antagonists

Calcium antagonists cause coronary and peripheral vasodilation. Furthermore, smooth muscle relaxation and reduction of after-load together with the negative inotropic effects of some of the agents will reduce myocardial oxygen consumption. While various formulations of the two prototype papaverine-like and benzothiazepine-like calcium antagonists, verapamil and diltiazem are widely available, most current development involves analogues of the nifedipine-like dihydropyridine class. The calcium antagonists are a structurally heterogeneous group of compounds with important differences in pharmacological action.

Verapamil slows conduction through the atrioventricular node and has important negative inotropic effects as well as causing smooth muscle relaxation which leads to an increase in coronary blood flow and a reduction in after-load. The dihydropyridines, such as nifedipine and amlodipine, also cause smooth muscle relaxation but have no effect on cardiac pacemaker tissue which may result in a reflex increase in the HR. In common with other calcium antagonists, these drugs have negative inotropic effects, which are, however, less marked than those of verapamil. The effect of diltiazem is

similar to those of verapamil though it has a less potent effect of left ventricular function.

Beta-adrenergic receptor blockers

Catecholamines stimulate largely type 1 beta-receptors present in myocardium. Although this activation of beta-1 receptors provides inotropy, chronotropy and lusitropy which is extremely useful in acute situations, chronic overstimulation creates a state of energy starvation, calcium overload, mechanical inefficiency, hypertrophy, inhibition of repair, extracellular matrix synthesis, state of inflammation and hypokalaemia and aggravates angina and ischaemia (**Table 4**). Beta-receptor antagonists counteract these deleterious effects by occupying the receptors and displacing catecholamines.

Table 4: Mechanisms of Anti-Ischaemic Action of Beta-Blockers

Reduced energy expenditure by slowing the heart rate
Reduced energy expenditure by negative inotropy
Improved myocardial flow by prolonging diastolic filling period
Improvement in mechanoenergetics
Reverse remodelling of the dysfunctional ventricular myocardium

Usually, beta-adrenergic receptor blocking agents are used orally for chronic prophylaxis and can be administered once or twice a day in progressively increasing doses till resting heart rate reaches about 60 beats per minute or adverse effects appear. Usual doses of atenolol (100 mg per day), metoprolol (200 mg per day), bisoprolol (10 mg per day), nebivolol (5 to 10 mg per day), carvedilol (50 mg per day) are sufficient for this purpose. Intravenous propranolol, atenolol and metoprolol have been used during rest angina, especially when associated with tachycardia (**Figure 1**).

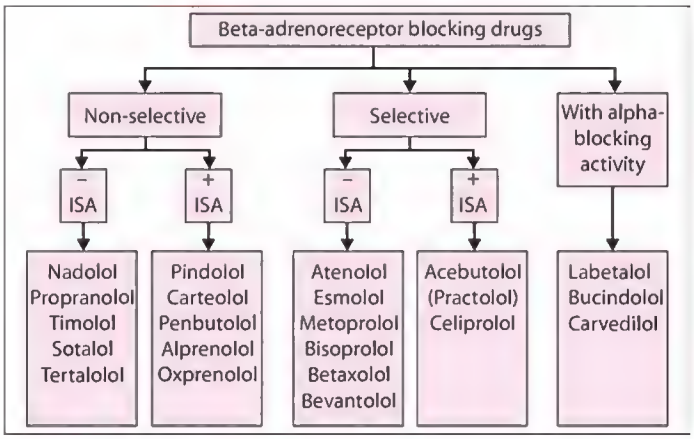


Figure 1: Classification of beta-adrenoreceptor blockers on the basis of cardio-selectivity and intrinsic sympathomimetic activity (ISA).

Metabolic modulators

Metabolic modulators are the agents that may reduce symptoms without affecting haemodynamics, inotropy and/or chronotropy. Glucose oxidation is the key step to be influenced in a metabolic approach to the treatment of ischaemia/reperfusion diseases, such as angina. Free fatty acids are the main fuel for the healthy heart, with a lesser contribution from the oxidation of glucose and lactate. Myocardial ischaemia alters fuel metabolism, causing an accelerated rate of glucose conversion to lactate and a switch from lactate uptake by the heart to lactate production. Metabolic modulators produce a switch in substrate utilisation by the heart. Glucose is 16% more oxygen efficient, and hence, switching from free fatty acids to glucose will relieve ischaemia in a strained heart.

Most commonly used metabolic modulator as an anti-ischaemic agent is trimetazidine in a maximum dose of 60 mg per day. It is the mitochondrial enzyme long-chain 3-ketoacyl coenzyme A thiolase, inhibition of which triggers a balancing increase in pyruvate oxidation and reduces the accumulation of lactate.

MANAGEMENT OF ACUTE CORONARY SYNDROME

Besides the usual measures like bed rest, hospitalisation, oxygen therapy, pain relief and use of above-mentioned anti-ischaemic drugs, it needs to be stratified into a risk category based upon well-established scoring systems and algorithms. High-risk patients need a combination of pharmacotherapy with catheter-based interventions while non-high-risk patients are usually managed conservatively with potent anti-platelet and anti-thrombotic drugs along with plaque stabilisers, like statins and anti-RAAS agents. Drug therapy for acute coronary syndrome is summarised in **Table 5**.

Table 5: Drug Therapy for Acute Coronary Syndrome

Dual oral anti-platelet therapy
Anti-thrombotic therapy
Thrombolytic therapy for ST-elevation myocardial infarction
Anti-ischaemic therapy with emphasis on beta-blockers, calcium channel blocking agents and nitroglycerine
Plaque stabilising therapy like statins in high doses and beta-receptor blocking agents
Anti-RAAS agents after stabilisation
Potent intravenous anti-platelet agents for catheter-based interventions

Aspirin has been thoroughly evaluated as an anti-platelet drug and was found to prevent vascular death by approximately 15% and non-fatal vascular events by about 30% in a meta-analysis of more than 100 randomised trials in high-risk patients. The best characterised mechanism of action of the drug is related to its capacity to inactivate permanently the COX activity of prostaglandin H-synthase-1 and -2 (also referred to as COX-1 and COX-2). The saturability of the anti-platelet effect of aspirin at low doses, the lack of dose-response relationship in clinical studies evaluating its anti-thrombotic effects, and the dose dependence of its side effects all support the use of as low a dose of aspirin as has been found to be effective in the treatment of various thromboembolic disorders.

Dual anti-platelet therapy has become the standard of care for all cases of acute coronary syndrome because of their synergistic and additive benefits. Initially, it was used to be aspirin (75 to 300 mg per day) along with ticlopidine but now it is aspirin with clopidogrel (75 to 150 mg per day). Newer drugs like prasugrel and ticagrelor may replace clopidogrel in near future at least in high-risk cases. **Table 6** shows the anti-platelet drug therapy currently being used in patients with acute coronary syndrome.

Dual anti-platelet treatment is required for at least one year after an episode of acute coronary syndrome or percutaneous coronary intervention. Selected cases may, however, require longer treatment. Subsequent to one year, aspirin alone or clopidogrel alone in aspirin-intolerant patients is sufficient.

Table 6: Anti-Platelet Drugs

Cyclooxygenase-1 inhibitors	
	Aspirin
Adenosine diphosphate receptor inhibitors	
	Clopidogrel
	Elinogrel
	Prasugrel
	Ticlopidine
	Ticagrelor
	Cangrelor (both oral and intravenous)
Phosphodiesterase inhibitors	
	Cilostazol
Glycoprotein IIB/IIIA inhibitors (intravenous use only)	
	Abciximab
	Eptifibatide
	Tirofiban
	Defibrotide
Adenosine reuptake inhibitors	
	Dipyridamole

Glycoprotein IIB/IIIA Inhibitors

Platelet membrane glycoprotein (GP) IIb/IIIa receptors constitute the final common pathway of platelet aggregation, the integrin GPIIb/IIIa antagonists prevent cross-linking of platelets. The inhibitors of GP-IIb/IIIa include monoclonal antibodies against the receptor (Abciximab), naturally occurring Arg-Gly-Asp sequence (RGD) containing peptides isolated from snake venoms, synthetic RGD- or Lys-Gly-Asp sequence (KGD) containing peptides, and peptidomimetic and non-peptide RGD mimetics (eptifibatide and tirofiban) that compete with fibrinogen, von Willebrand factor, and/or perhaps other ligands for occupancy of the platelet receptors.

Anti-thrombotic Agents

Anti-thrombotic agents includes only those drugs which affect the coagulation cascade are described in **Table 7**.

Table 7: Anti-Thrombotic Agents Used in Acute Coronary Syndrome

Non-selective indirect thrombin Inhibitors	
	Unfractionated heparin
	Low-molecular weight heparins
Direct thrombin inhibitors	
	Hirudin
	Bivalirudin
	Argatroban
	Dabigatran
	Ximelagatran
Selective factor Xa inhibitors	
	Fondaparinux
	Rivaroxaban
	Apixaban

Unfractionated heparin is still the most commonly used anti-thrombotic agent with a bolus dose of 50 to 100 units/kg of weight followed by 10 to 15 units/kg per hour infusion for at least 48 hours and may be even longer.

Unfractionated heparin preparations contain molecules of widely varying sizes (3,000-30,000 Daltons; mean 15,000 Daltons), but anticoagulant activity is limited to the relatively small proportion of molecules (approximately 30%) whose structures include the pentasaccharide sequence. This active fraction of heparin preparations is non-selective in its ability to enhance anti-thrombin III-mediated inhibition of both thrombin and factor Xa, demonstrating equipotent activities in anti-factor IIa (thrombin)-specific and anti-factor Xa-specific assays.

Heparin is heavily sulphated, causing it to bind non-specifically to various plasma and cellular proteins. This contributes to heparin's unfavourable pharmacokinetic properties, including a complex clearance mechanism and a relatively short, dose-dependent half-life. It also leads to reduced bioavailability and consequently, an unpredictable anticoagulant response in different individuals, which requires frequent laboratory monitoring of activated partial thromboplastin time to ensure adequate anticoagulation without enhanced bleeding risk. Heparin's high degree of non-specific binding is directly responsible for a number of undesirable complications that represent major drawbacks to unfractionated heparin therapy; these complications include changes in platelet function that contribute to bleeding complications, heparin resistance, osteoporotic changes, and most important, heparin-induced thrombocytopaenia.

Low molecular weight heparin preparation

Short chains containing the pentasaccharide sequence predominate, but longer chains that contain the pentasaccharide sequence as well as thrombin-binding structures are included in all low molecular weight heparin (LMWH) preparations to varying degrees. Thus, LMWH that shares the same mechanism of anti-thrombin III-mediated inhibition as unfractionated heparin, targets factor Xa preferentially but also exerts some anti-factor IIa activity, based on the degree to which longer chains are present in different commercial LMWH preparations.

As a therapeutic agent, LMWH is rapidly absorbed into plasma and has a longer half-life relative to that of unfractionated heparin. The higher bioavailability of LMWH compared with that of unfractionated heparin leads to a more predictable dose response and, therefore, a reduced need for routine laboratory monitoring of haemostatic variables; this renders LMWH relatively easy to use in clinical practice. Dalteparin, enoxaparin, tinzaparin, nadroparin, reviparin and certoparin are approved for use.

Advantages of LMWH are subcutaneous twice daily administration, no monitoring and somewhat better efficacy. Usually, enoxaparin or dalteparin are used for 5 to 7 days. Classic indications are conservative management of acute coronary syndrome, following thrombolysis and in a few selected cases after catheter-based interventions.

Thrombolytic Agents

Thrombolytic agents are used in patients with ST-elevation myocardial infarction (MI) (other indications being submassive pulmonary embolism, prosthetic valve thrombosis, selected cases of thrombotic stroke, proximal deep vein thrombosis, etc.). Time to reperfusion remains a key modifiable determinant of mortality in ST-elevation MI. Despite many years of medical advances, the time from symptom onset until the start of pharmacological reperfusion treatment remains largely unchanged, with a median of approximately 2.5 to 3 hours.

Thrombolytic drugs dissolve blood clots by activating plasminogen, which forms a cleaved product called plasmin. Plasmin is a proteolytic enzyme that is capable of breaking cross-links between fibrin molecules, that provide the structural

integrity of blood clots. Due to these actions, thrombolytic drugs are also called 'plasminogen activators' and 'fibrinolytic drugs'.

Streptokinase (1.5 M units over one hour) and urokinase are inexpensive and used as infusion. Alteplase is used as bolus followed by short infusion (100 mg dose). Reteplase (5 units double bolus) and tenecteplase (50 to 60 mg rapid bolus) can be given as bolus and hence are of great use in pre-hospital thrombolysis. Their efficacy is similar to or better than alteplase. Thrombolysis is always followed by 5 to 7 days of anti-thrombotic therapy to prevent rebound thrombosis.

MANAGEMENT OF SYSTEMIC ARTERIAL HYPERTENSION

See the chapter on Essential Hypertension

MANAGEMENT OF HEART FAILURE

Over the last 20 years, enormous progress has been made in the pharmacotherapy of chronic heart failure. Large, randomised, control trials of inhibition of the renin-angiotensin-aldosterone system and sympathetic nervous system have led to substantial improvements in both morbidity and mortality.

The primary goal of drug therapy in heart failure (HF) is to improve cardiac function and to reduce the clinical symptoms associated with HF (e.g. oedema, shortness of breath, exercise intolerance). Improving cardiac function along with reducing blood volume can dramatically improve the clinical symptoms. The treatment of HF caused by systolic dysfunction follows clear clinical guidelines based upon numerous clinical trials. Diastolic dysfunction, however, is more difficult to treat and there is no clear consensus regarding the best therapeutic options other than targeting clinical symptoms related to fluid retention. In addition, drugs that can adversely affect patients with HF due to systolic dysfunction should be avoided or withdrawn. These include non-steroidal anti-inflammatory drugs, most anti-arrhythmic drugs, and the non-dihydropyridine calcium channel blockers (i.e. diltiazem and verapamil). Drug therapy for systolic HF is grouped in four categories as shown **Table 8**.

Diuretics, especially loop diuretics, are the most efficacious in relieving clinical symptoms of shortness of breath and signs of peripheral oedema. The diuretic-induced reductions in ventricular filling pressures and ventricular cavity size, decreases in mitral regurgitation and resulting increases in forward cardiac output, all may be favourable in HF. Digoxin reduces hospitalisations for HF in patients with sinus rhythm. It maintains a role in those with advanced chronic HF and atrial fibrillation, where rate control may improve symptoms.

Angiotensin-converting enzyme (ACE)-inhibitors are an important component of standard HF therapy (Class I) in patients with current or prior symptoms of HF and depressed left ventricular systolic function. The mechanism of action consists of improvement in left ventricular geometry, ejection fraction and filling pressures. Randomised trials have shown that ACE-inhibitor therapy leads to symptomatic improvement, reduced hospitalisation and enhanced survival in patients with HF and systolic dysfunction. Angiotensin receptor blockers provide a unique pharmacological mechanism for inhibiting the RAS and these are mostly used in ACE-I intolerant patients.

Although seemingly paradoxical, beta-receptor blocking drugs have been able to reduce HF mortality by about 35% in various randomised trials. The strategy for administering all β-blocking agents in the setting of chronic heart failure is to start at extremely low doses and increase the dose gradually. The pharmacological half-lives of metoprolol tartrate, carvedilol, and bucindolol dictate twice-daily dosing, whereas bisoprolol and metoprolol succinate CR can be given once daily.

Aldosterone antagonists like spironolactone and eplerenone have been used in HF with impressive mortality benefits.

MANAGEMENT OF CARDIAC ARRHYTHMIAS

There are four main classes in the Vaughan-Williams classification of anti-arrhythmic agents as described here:

Table 8: Drugs for the Prevention and Treatment for Chronic Heart Failure

Drug	Initial Daily Dose(s)	Maximum Total Daily Dosage
Angiotensin-converting enzyme inhibitor		
Captopril	6.25 mg three times	50 mg three times
Enalapril	2.5 mg two times	10 mg two times
Lisinopril	2.5-5.0 mg once	20-35 mg once
Ramipril	1.25-2.5 mg two times	2.5-5 mg two times
Perindopril	2 mg once	8-16 mg once
Fosinopril	5-10 mg once	40 mg once
Angiotensin-receptor blocker		
Trandolapril	0.5 mg once	4 mg once
Valsartan	40 mg two times	160 mg two times
Candesartan	4 mg once	32 mg once
Losartan	12.5 mg once	50 mg once
Beta-receptor blocker		
Carvedilol	3.125 mg two times	25 mg two times (50 mg two times if more than 85 kg)
Bisoprolol	1.25 mg two times	10 mg once
Metoprolol succinate CR/XL	12.5-25 mg once	200 mg once
Spironolactone	12.5-25 mg once	25-50 mg once
Eplerenone	25 mg once	50 mg once
Combination of hydralazine-isosorbide dinitrate	10-25 mg/10 mg three times	75 mg/40 mg three times
Fixed dose of hydralazine-isosorbide dinitrate	37.5 mg/20 mg (one tablet) 3 times	75 mg/40 mg (two tablets) 3 times
Digoxin	0.125 mg once	0.375 mg once

Class I Agents

The class I anti-arrhythmic agents interfere with the sodium (Na^+) channel. These are grouped by what effect they have on the Na^+ channel and what effect they have on cardiac action potentials.

These agents are also called membrane stabilising agents. The 'stabilising' is the word used to describe the decrease of excitogenicity of the plasma membrane which is brought about by these agents (Also noteworthy is that a few class II agents like propranolol also have a membrane stabilising effect).

Class I agents are divided into three groups (1a, 1b and 1c) based upon their effect on the length of the action potential.

1. 1a lengthens the action potential (right shift), e.g. quinidine, procainamide, disopyramide.
2. 1b shortens the action potential (left shift), e.g. lignocaine, bretylium, mexiletine.
3. 1c does not significantly affect the action potential (no shift), e.g. flecainide, encainide, ajmaline, propafenone.

Class II Agents

Class II agents are conventional beta-blockers. They act by blocking the effects of catecholamines at the β_1-adrenergic receptors, thereby decreasing sympathetic activity on the heart. These agents are particularly useful in the treatment of supraventricular tachycardias. They decrease conduction through the AV node. Class II agents include atenolol, esmolol, propranolol and metoprolol.

Class III Agents

Class III agents predominantly block the potassium (K^+) channels, thereby prolonging repolarisation. Since these agents do not affect the Na^+ channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias. Typical examples are amiodarone, sotalol, dofetilide and dronedarone.

Class IV Agents

Class IV agents are slow calcium channel blockers. These decrease conduction through the AV node and shorten phase two (the plateau) of the cardiac action potential. Thus, these reduce the contractility of the heart, so may be inappropriate in HF. However, in contrast to beta-blockers, these allow the body to retain adrenergic control of HR and contractility. Class IV agents include verapamil and diltiazem.

Others

These include the following:

1. Digoxin decreases conduction of electrical impulses through the AV node and increases vagal activity via its central action on the central nervous system.
2. Adenosine
3. Magnesium sulphate has been used for *torsades de pointes*.

MANAGEMENT OF PULMONARY HYPERTENSION

The drugs used for the management of pulmonary hypertension are:

1. Calcium channel blockers (only in patients with demonstrable vaso-reactivity)
2. PDE-5 inhibitors (sildenafil, tadalafil)
3. Endothelin receptor antagonists (bosentan, ambrisentan, sitaxentan)
4. Prostaglandins (iloprost, epoprostenol, treprostinil)
5. Oral anticoagulants

MANAGEMENT OF CARDIOGENIC SHOCK

Circulatory shock is a life-threatening emergency that results in death in approximately half of all patients.

Intravenous vasopressors provide inotropic support increasing perfusion of the ischaemic myocardium and all body tissues. However, extreme heart rates should be avoided because they may increase myocardial oxygen consumption, increase infarct size, and further impair the pumping ability of the heart. No particular vasopressor has been shown to be superior to another except recent data which suggest some superiority of norepinephrine over dopamine. Carefully chosen combinations of vasopressors may be useful.

Dopamine may provide vasopressor support. With higher doses, it has the disadvantage of increasing the HR and myocardial oxygen consumption. Intravenous (IV) continuous infusion of 5 to 20 mcg/kg per minute; increase by 1 to 4 mcg/kg per minute q 10 to 30 minutes to optimal response (>50% of patients have satisfactory responses with doses <20 mcg/kg per minute).

Dobutamine, inamrinone (formerly amrinone), or milrinone may provide inotropic support. In addition to their positive inotropic effects, inamrinone and milrinone have a beneficial vasodilator effect, which reduces pre-load and after-load. Some of these drugs are described below:

Milrinone: Loading dose, 50 mcg/kg IV over 10 min; continuous infusion: 0.375 to 0.75 mcg/kg per minute IV.

Norepinephrine: Norepinephrine infusion must be considered in refractory cardiogenic shock, though it significantly increases after-load but is less arrhythmogenic (Dosage: 0.5 to 1 mcg/min IV infusion initially, titrated to effect; not to exceed 30 mcg/minute).

Levosimendan: Levosimendan, though not approved for use in the USA, can be considered in conjunction with vasopressors. It should be used with caution as it can cause hypotension. When used with vasopressors, levosimendan may improve haemodynamics and improve coronary blood flow. However, there are no trials with this drug in patients with cardiogenic shock.

In summary, these are exciting times for cardiovascular pharmacotherapy. Novel molecules are being developed. Older drugs are undergoing reappraisal. Polypharmacy-based one type of system is being challenged. Combination therapy and fixed-drug combinations are gaining ground. Targets for drugs are being redefined. It would not be long before many of today's dogma shall become obsolete.

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12.10 Heart Failure

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INTRODUCTION

Heart failure (HF) is defined as the inability of the heart to pump blood forward at a rate sufficient to meet the metabolic demands of the body, or the ability to do so only if the cardiac filling pressures are abnormally high. It most commonly results from myocardial or extra-myocardial abnormalities which interfere with normal left ventricular function. It may result from a sudden overwhelming cardiac load, as with an acute hypertensive crisis, or a chronic cardiac stressor such as systemic hypertension. Chronic HF that results predominantly from an abnormality of ventricular emptying, due to impaired contractility or excessive afterload, is often termed systolic HF. Heart failure that results from an abnormality of ventricular filling was previously referred to as diastolic HF. Heart failure with preserved ejection fraction is now the preferred term, as the physiologic abnormalities in this condition are not solely restricted to either diastole or systole. HF may be the final and most severe manifestation of nearly every form of cardiac disease including coronary atherosclerosis, valvular disease, hypertension, congenital heart disease and the cardiomyopathies. The mortality rate in patients with HF has remained unacceptably high despite improvements in therapy, making early detection of susceptible persons, who would benefit from preventive measures imperative.

PATHOPHYSIOLOGY

The heart normally accepts blood at low filling pressures during diastole and then propels it forward at higher pressures in systole. In a healthy individual, the cardiac output is matched to the body's total metabolic need through adjustments in heart rate and ventricular stroke volume. Stroke volume is a function of ventricular preload, afterload and contractility. Within a physiologic range, ventricular output increases in relation to the preload or stretch on the myocardial fibres before contraction. The ventricular wall stress that develops during systolic ejection, or afterload, reflects the resistance the ventricle must overcome to empty its contents. This pressure determines the end-systolic volume of the left ventricle independent of the preload. Myocardial contractility accounts for changes in the force of contraction independent of the preload and afterload, and can be augmented by increasing the cycling rate of actin-myosin cross-bridge formation in the cardiac myocyte. Heart failure aetiologies can be grouped into those with impaired contractility, increased afterload or impaired ventricular filling.

Systolic HF results from diminished capacity of the affected ventricle to eject blood because of impaired myocardial contractility or excessive afterload. Loss of contractility may result from destruction of myocytes, abnormal myocyte function or fibrosis. Conditions associated with impaired contractility include dilated cardiomyopathy, chronic volume overload due to valvular insufficiency and myocardial ischaemia or infarction. Pressure overload impairs ventricular ejection by significantly increasing resistance to flow. These conditions result in a reduced stroke volume as systolic emptying ceases at a higher end-systolic volume than normal. When normal pulmonary venous return is added to the increased end-systolic volume that has remained in the ventricle because of incomplete emptying, the diastolic chamber volume increases resulting in a higher than normal end-diastolic volume and pressure. Conditions resulting in excessive afterload include uncontrolled systemic hypertension and aortic stenosis. Although an increase in preload induces a compensatory rise in stroke volume via Frank-Starling mechanism, impaired contractility or increased afterload cause the end-diastolic volume to remain elevated. During diastole, the persistently elevated left ventricular pressure is transmitted to the left atrium through the open mitral valve and to the pulmonary veins and capillaries. An elevated pulmonary capillary hydrostatic pressure results in transudation of fluid into the pulmonary interstitium and symptoms of pulmonary congestion.

Heart failure with preserved ejection fraction results from impaired ventricular filling resultant from mechanical obstruction or impaired diastolic relaxation. Left ventricular hypertrophy, hypertrophic cardiomyopathy, restrictive cardiomyopathy and myocardial ischaemia result in reduced chamber compliance and diastolic dysfunction. Mitral stenosis and pericardial constriction obstruct normal ventricular filling necessitating elevated diastolic pressures. Filling of the ventricle occurs at higher than normal pressures and is transmitted retrograde to the pulmonary and systemic veins.

Isolated right ventricular failure is less common and usually reflects increased right ventricular afterload due to disease of the lung parenchyma or pulmonary vasculature. When the right ventricle fails, the elevated diastolic pressure is transmitted retrograde to the right atrium with subsequent congestion of the systemic veins. The most common cause is actually left-sided HF, where elevated pulmonary vascular pressures resultant from left ventricular dysfunction lead to excessive right ventricular afterload.

NEUROHORMONAL MODEL FOR HEART FAILURE

Clinicians have used a variety of increasingly complex model systems to describe the syndrome of HF. It was initially viewed as a problem of excessive salt and water retention caused by renal blood flow abnormalities. Later, haemodynamic studies revealed that HF is associated with a reduced cardiac output and excessive peripheral vasoconstriction. Although the cardiorenal and cardiocirculatory models for HF explain the excessive salt and water retention that patients experience and provide a rational basis for the therapeutic use of diuretics, inotropes and vasodilators, neither of these models explain the relentless disease progression that occurs in this syndrome. It is increasingly apparent that HF can no longer be described in

simple haemodynamic terms. Some experts suggest that HF should be viewed as a neurohormonal model, in which it progresses as a result of the overexpression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation.

Heart failure is a progressive disorder that is initiated after an index event either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or alternatively disrupts the ability of the myocardium to generate a force, thereby preventing the heart from contracting normally. The index event may have an abrupt onset, as in the case of a myocardial infarction; it may have a gradual or insidious onset, as in the case of haemodynamic pressure or volume overloading; or it may be hereditary, as in the case of the genetic cardiomyopathies. In most instances, patients will remain asymptomatic or minimally symptomatic for a prolonged period. This is likely due to a number of compensatory mechanisms which become activated in the setting of cardiac injury and appear to modulate left ventricular (LV) function within a physiological range such that the functional capacity of the patient is preserved or only minimally depressed.

The principal neurohormonal systems involved in the response to HF are the sympathetic nervous system, the renin-angiotensin-aldosterone system, anti-diuretic hormone, endothelin, natriuretic peptides and nitric oxide. Neurohormonal activation is acutely beneficial in patients with HF since the elevations of cardiac contractility, vascular resistance and renal sodium retention tend to restore the cardiac output and tissue perfusion towards normal. The deleterious effects, however, predominate over the long-term leading to pulmonary and peripheral oedema, increased afterload, pathologic myocardial remodelling and more rapid progression of myocardial dysfunction. The major pathophysiologic process in the progression of HF appears to be cardiac remodelling, often referred to as progressive chamber enlargement over time and obligatory reduction in ejection fraction. The ability of ACE inhibitors and beta-blockers to improve survival and slow progression of this disease in clinical trials is compatible with this hypothesis. Clinical studies have additionally shown that other medical and device therapies have favourable effects on cardiac remodelling, resulting in stabilisation or reversal of LV chamber mass and dilation. Although the precise cellular and molecular mechanisms that are responsible for this "reverse remodelling" are not fully known, recent studies have demonstrated that improvement in ventricular function is associated with favourable changes in myocardial gene expression.

EPIDEMIOLOGY

The magnitude of HF is difficult to assess with precision since reliable, population-based estimates of its prevalence, incidence and prognosis are lacking. Large differences exist among studies in their definition of the condition and the methods used to establish its presence. HF affects nearly twenty-three million people worldwide. There is an increase in prevalence due to ageing of the population and improved survival of patients due to modern therapeutic interventions. The worldwide prevalence and incidence rates of HF are approaching epidemic proportions, as evidenced by the relentless increase in the number of hospitalisations, the growing number of HF-attributable deaths and the spiralling costs associated with the care of HF patients.

The prevalence of HF increases exponentially with age. Data suggest the lifetime risk in the United States of developing HF is 20%. Investigations using echocardiography estimate that only 50% of patients with LV dysfunction are symptomatic. Half of the patients who develop HF have a normal or preserved LV ejection fraction. The Framingham Heart Study estimated the prevalence of symptomatic HF in the United States as 0.8% and 6.6% in the sixth and ninth decades of life.

The population-attributable risk for HF was prospectively estimated to be 62%, 17%, 10%, 8%, 3%, and 2% for coronary artery disease, cigarette smoking, hypertension, obesity, diabetes mellitus and valvular heart disease respectively, in the US. Ischaemic cardiomyopathy is the most common cause of systolic HF in the western world, whereas hypertension and valvular heart disease have become less common due to improvements in detection and therapy. The exact cause cannot be determined in 20% to 30% of cases and is, therefore, classified as idiopathic. Ageing, female gender, hypertension, diabetes mellitus, LV hypertrophy, coronary artery disease and infiltrative cardiomyopathies are associated with diastolic dysfunction.

The prevalence or risk of developing HF in emerging nations is less defined due to a lack of population-based studies. Hypertension has the greatest impact on the development of this syndrome and is estimated to account for 39% of events in men and 59% in women. A recent study at an urban African hospital demonstrated that 88% of *de novo* presentations for HF were attributed to uncontrolled hypertension, idiopathic dilated cardiomyopathy or right-sided heart failure. Valvular heart disease only accounts for 7% to 8% of cases. Pathologies associated with a high cardiac output, such as anaemia, are seldom responsible for the development of HF in a normal heart. However, in the presence of underlying structural heart disease, the additional work required in high output conditions may contribute to overt congestive failure. Rheumatic heart disease remains a major cause of HF in Africa and Asia. Chagas disease is still an important aetiology in South America. As developing nations undergo socio-economic development, the epidemiology of HF is becoming similar to that of Western Europe and North America.

CLINICAL MANIFESTATIONS

Heart failure is a bedside diagnosis that is defined by clinical assessment. The clinical manifestations result from impaired forward cardiac output and/or elevated venous pressures and relate to which of the ventricles has failed. The cardinal symptoms of chronic LV failure are dyspnoea, exercise intolerance and fatigue. Elevated pulmonary venous pressures cause transudation of fluid into the lung parenchyma, increasing work of breathing due to reduced pulmonary compliance, increased airway resistance and stimulation of juxtacapillary receptors. Accumulation of lactic acid due to low cardiac output may contribute to this sensation.

As HF advances, dyspnoea occurs with progressively less strenuous activity and ultimately is present even at rest. The New York Heart Association (NYHA) functional classification, although somewhat vague, remains the most commonly used standard to describe severity of signs and symptoms. Additional common symptoms related to left ventricular congestion include orthopnoea, nocturnal cough and paroxysmal

nocturnal dyspnoea. Orthopnoea is the sensation of laboured breathing while lying flat and is relieved by sitting upright. Orthopnoea and nocturnal cough result from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressures. Paroxysmal nocturnal dyspnoea is severe, sudden nocturnal breathlessness which occurs hours after going to bed. It results from gradual reabsorption of lower extremity interstitial oedema into the circulation with subsequent intravascular volume expansion and increased venous return to the heart and lungs. Common symptoms related to chronic right ventricular congestion include abdominal discomfort, anorexia, nausea, peripheral oedema and weight gain. Elevated systemic venous pressures result in abdominal discomfort due to hepatic engorgement and capsular distention. Anorexia and nausea may result from oedema within the gastrointestinal tract. Weight gain and peripheral oedema result from the accumulation of interstitial oedema within the dependent portions of the body. Common symptoms related to low cardiac output include fatigue, weakness, dulled mental status and nocturia. These result from impaired skeletal muscle, cerebral and renal perfusion.

The physical signs of HF depend on the severity and chronicity of the condition and again can be divided into those due to left or right cardiac dysfunction. Common signs of left-sided HF include pulmonary rales, wheezing, increased intensity of S2, S3 or S4 gallop and a mitral regurgitation murmur. Pulmonary rales result from the popping open of small airways which had been closed off by oedema fluid before inspiration, while 'cardiac asthma' results from compression of larger airways. An early diastolic sound, or S3, signifies increased left ventricular end-diastolic pressure in patients with decreased left ventricular function. A late diastolic sound, or S4, may result from forceful atrial contraction into a stiffened LV. Left ventricular dilation can result in incomplete closure of the mitral valve during systole and functional mitral regurgitation. Common signs of right-sided HF include distention of the jugular veins, hepatic enlargement, dependent oedema, right ventricular heave or gallop and tricuspid regurgitation murmur. Signs of impaired peripheral perfusion, cardiac cachexia, diaphoresis, tachycardia, tachypnoea and narrow pulse pressures are often signs of advanced disease.

PROGNOSIS

Morbidity and mortality after the onset of symptomatic HF are extremely high despite improvements in therapy. This is a progressive condition, beginning with predisposing factors and leading to the development and worsening of clinical illness. The latest American College of Cardiology and American Heart Association (ACC/AHA) guidelines have classified HF using a new staging system that emphasizes the evolution and progression across a continuum. Stage A patients are at high-risk for developing heart failure without structural heart disease. Stage B patients have structural heart disease but have not yet developed symptoms of HF (post-myocardial infarction, hypertension, valvular disease or asymptomatic LV dysfunction). Stage C patients had past or current symptoms of HF associated with underlying structural heart disease. Stage D patients have end-stage disease requiring specialised advanced therapy. It is important to note that a patient classified as Stage B has a better prognosis than one with Stage C NYHA class I symptoms.

A major challenge in the management of HF is the accurate identification of those patients who have a poor prognosis and would, therefore, be most likely to benefit from intensive medical therapy. Although multiple variables have been identified as predictors of survival within a large population, their ability to predict survival in individual patients is limited. Many factors affect patient outcomes including co-morbid medical conditions, psycho-social factors and intensity of medical care. The most frequently predictors of adverse outcome directly or indirectly reflect the severity of cardiac dysfunction. Prospective studies have demonstrated a one-year mortality of 5% for patients in NYHA functional class I, 15% in classes II-III and 64% in class IV. Exercise variables such as maximal oxygen consumption and six-minute walk testing provide the most objective assessment of functional capacity in patients with heart failure and are an important component in the evaluation of patients for advanced heart failure therapies.

Need for hospitalization is an important marker for poor prognosis. In-hospital, 30-day and one-year mortality after index hospitalisation are estimated to be 6%, 11% and 30% in the US. Additional univariate predictors of survival in systolic HF include signs of congestion or reduced tissue perfusion on physical examination; severe LV systolic dysfunction; concomitant diastolic dysfunction or right ventricular dysfunction with associated pulmonary hypertension; attenuated response to diuretics or lack of haemodynamic improvement with therapy; echocardiographic evidence of left ventricular remodelling; ventricular dyssynchrony resulting from conduction system defect; severe ventricular ectopy after exercise; evidence of neurohormonal activation including hyponatraemia, elevated brain natriuretic peptide (BNP), reduced heart rate variability and sinus tachycardia; ischaemic cardiomyopathy; concomitant paroxysmal atrial fibrillation, sleep-disordered breathing, renal insufficiency or anaemia; elevated serum troponin or markers of inflammation; low serum cholesterol or weight loss.

The prognosis in HF patients with preserved ejection fraction is less well-defined. Although once thought to be better than those with systolic dysfunction, recent evidence suggests similar mortality rates. The two main causes of death in patients with HF are sudden death due to arrhythmias and progressive pump failure. It has been postulated that progressive pump failure, sudden death due to arrhythmia and sudden death during episodes of clinical worsening each account for one-third of cardiovascular mortality in this population.

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12.11 Heart Failure Management

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Therapy for heart failure (HF) is divided into 2 distinct clinical scenarios and approaches: acute decompensated HF and, chronic stable HF (**Table 1**). The goals of therapy are different: in decompensated HF it is to stabilise the patient, improve organ perfusion and filling pressures; in chronic stable HF, the aim is to extend survival, good quality of life and delay disease progression. Approach therapy for patients with chronic HF is based on their stage classification. Diuretics, vasodilators and positive inotropic agents are used to improve symptoms. Neurohormonal inhibitors are used to reduce mortality and delay disease progression.

Table 1: Treatment of Heart Failure

Decompensated Heart Failure	Chronic Stable Heart Failure
Diuretics	**Diuretics**
Loop diuretics (IV)	Loop diuretics (po)
Thiazides (IV)	Thiazides (po)
Vasodilators	antagonists
Nitrovasodilators (IV)	**Vasodilators**
Direct acting nitrates (po)	Nitrovasodilators (po)
Calcium channel blockers (IV; in the setting of angina or hypertension)	Direct acting nitrates (po)
Natriuretic peptides (nesiritide)	**Positive inotropic agents**
Positive inotropic agents	Digitalis
Beta-adrenergic receptor agonists	**Neurohormonal inhibitors**
Phosphodiesterase inhibitors	Angiotensin converting enzyme inhibitors
Phosphodiesterase inhibitors with calcium sensitizer action	Angiotensin receptor blockers
	Beta-adrenergic blockers

NON-PHARMACOLOGICAL THERAPIES

These therapies apply to patients with decompensated and chronic HF, at all stages.

Diet

1. Dietary instruction regarding sodium intake is one of the cornerstones of HF treatment. It plays a very important role in the prevention of acute recurrent events.
2. Sodium restriction (2 to 3 g daily) is recommended for all patients, regardless of their left ventricular ejection fraction (LVEF). Further restriction (<2 g daily) is recommended for those with moderate to severe HF.
3. Fluid intake less than 2 litre daily is recommended for patients with serum sodium less than 130 mEq/L and patients with volume retention.
4. Prealbumin and caloric evaluation is recommended for patients with cardiac cachexia and unintentional weight loss.

Other Therapies

1. Continuous positive airway pressure if there is a diagnosis of sleep apnoea has been shown to improve symptoms of dyspnoea.
2. Oxygen supplementation is seldom needed in HF patients. If oxygen saturation is low, evaluation for pulmonary disease or residual pulmonary oedema is recommended.
3. Treatment of depression with appropriate therapy is very important. Selective serotonin re-uptake inhibitors (SSRIs) are preferred.

Routine Healthcare

1. Limit daily consumption of alcohol to less than 2 drinks in men and less than 1 drink in women. In patients with alcoholic cardiomyopathy, total abstinence is recommended.
2. Pneumococcal and influenza vaccinations are indicated.
3. Endocarditis prophylaxis is not recommended based on the diagnosis of HF alone.
4. Nonsteroidal anti-inflammatory drugs are not recommended due to associated fluid, salt retention and acute renal failure.
5. Exercise training, with the goal of 30 minutes of moderate exercise activity at least five times per week.

PHARMACOLOGICAL THERAPIES

Two classes of agents have become the cornerstone of therapy to delay or halt progression of cardiac dysfunction and improve mortality: angiotensin converting enzyme (ACE) inhibitors and beta-blockers.

ACE-Inhibitors

They block the renin-angiotensin-aldosterone system (RAAS) and should be used in all patients with HF and LVEF less than 40%. They block the conversion of angiotensin I into angiotenin II, as well as degradation of bradykinin. Kinins are responsible for the cough and angioedema present in 5% of patients. There has been evidence of 'angiotensin II escape', however this has not been translated into clinical trials and ACE inhibitor remain the prefer red medication, over angiotensin receptor blockers (ARBs).

Foetal angiotensin I receptors are growth stimulators, therefore should not be used in pregnant patients. They have an anti-adrenergic effect secondary to decrease in norepinephrine production. Finally, angiotensin II produces efferent arteriolar vasoconstriction to improve glomerular filtration rate (GFR) and after decrease in production of angiotensin II, renal function could worsen.

ACE inhibitors have been shown in double-blind, placebo-controlled trials to produce clinical benefit, increase LVEF and improve survival. Should be started at the lowest dose and titrated as tolerated to doses used in clinical trials (**Table 2**), during concomitant uptitration of beta-blockers. Patients should not receive an ACE inhibitor if they have experienced life-threatening side effects (angioedema or anuric renal failure).

They should be used with extreme caution if the patient is hypotensive, have bilateral renal artery stenosis, potassium greater than 5.5 meq/L, or creatinine greater than 3 mg/dL. Renal function and potassium should be checked within 1 to 2 weeks.

Table 2: Medication Dosage in Chronic HF

Medication	Usual Dosage	Target Doses in HF
Loop diuretics		
Frusemide	10 to 360 mg/day	
Bumetanide	0.5 to 20 mg/day	
Torsemide	2.5 to 200 mg/day	
Thiazide diuretics		
Chlorothiazide	50 to 100 mg/day	
Hydrochlorothiazide	25 to 50 mg/day	
Chlorthalidone	25 to 100 mg/day	
Metolazone	5 to 10 mg/day	
K^+ sparing diuretics		
Eplerenone	25 to 50 mg/day	50 mg/day
Spironolactone	12.5 to 25 mg/day	25 mg/day
ACE-inhibitors		
Captopril		50 mg tid
Enalapril		10 mg bid
Lisinopril		20 mg qd
Ramipril		10 mg qd
Trandolapril		4 mg qd
Fosinopril		80 mg qd
Quinapril		80 mg qd
Angiotensin receptor blockers		
Candasartan		32 mg qd
Losartan		150 mg qd
Valsartan		160 mg bid
Beta-blockers		
Bisoprolol		10 mg qd
Carvedilol		25 mg bid
Metoprolol succinate (XL)		200 mg qd
Other vasodilators		
Fixed dose of Hydralazine/nitrates		75 mg hydralazine + 40 mg isosorbide dinitrate, tid
Hydralazine		75 mg qid
Isosorbide dinitrate		40 mg qid

Alternative for ACE-inhibitors

Angiotensin receptor blockers (ARBs) are recommended for those patients intolerant to ACE inhibitors. Both drugs have similar effect on renal function, potassium and blood pressure. Angioedema has been reported very infrequently with ARBs and patients that experience that side effect with ACE inhibitors, should have a trial with ARBs. If a patient is intolerant to ACE inhibitors and ARB, then the combination of hydralazine/nitrates could be used. There is no evidence to support the routine use of ARBs in combination with ACE inhibitors.

Beta-Blockers

Beta-blockers interfere with the actions of the sympathetic nervous system and have been shown to be effective in clinical trials in reducing morbidity and mortality. Only metoprolol succinate, bisoprolol and carvedilol are approved in HF therapy. They are recommended for all HF patients with reduced LVEF, with or without previous myocardial infarction. It can also be used in patients with recent decompensation of HF, after optimization of volume status and successful discontinuation of IV diuretics/inotropes. If possible, beta-blockers should be initiated in the hospital setting to evaluate tolerability. These are indicated even in patients with diabetes mellitus, peripheral vascular disease and/or asthma and chronic obstructive lung disease. It should be used with caution if recurrent hypoglycaemic episodes or resting limb ischaemia is present. These are contraindicated in active bronchospasm. Beta-blockers should be initiated at low doses and titrated up to optimal doses every 2 weeks (**Table 2**). Beta-blockers should be continued in patients experiencing a symptomatic exacerbation, unless they develop cardiogenic shock or refractory volume overload.

Diuretics

These drugs improve congestion, dyspnoea and retard adverse remodelling in the ventricle due to reduced wall stress. Diuretics do not improve survival, except for aldosterone antagonists, and should not be used as monotherapy.

Diuretics are prescribed for patients with previous or current fluid retention. Intravenous formulations should be used if significant volume overload. In patients with difficult to treat HF, combination of diuretics acting by different mechanisms often works synergistically. Non-steroidal anti-inflammatory drugs can inhibit the natriuretic effect of many diuretics and produce renal failure.

Loop diuretics

This class of diuretics includes: furosemide, bumetanide, torsenide, ethacrynic acid and piretanide. The most commonly used is furosemide. Its half-life is 1.5 hours and total duration of action 4 to 6 hours. The effect can be as fast as 10 minutes if given intravenously. Acutely (within minutes), they not only produce venodilation and decrease wedge pressure, but also cause neurohormonal activation. Side-effects include hypochloraemic metabolic alkalosis, hypokalaemia, hyponatraemia, hypocalcaemia, increased uric acid and higher risk of gout.

Loop diuretics are the preferred therapy in HF, because of better fluid clearance (20% to 25% increase in sodium excretion compared to 5% to 10% seen with thiazides) and effectiveness despite renal insufficiency. The optimal doses are detailed in **Table 2**. Importantly, loop diuretics can induce a sulfa-like toxicity in those patients with a sulfa allergy (skin photosensitivity, blood dyscrasias, hepatitis, pancreatitis, interstitial nephritis and pneumonitis).

Thiazide diuretics

This class of diuretics includes chlorthalidone, hydrochlorothiazide and metolazone. The total duration of action is 16 to 24 hours. Side effects include hypokalaemia, hyponatraemia, mild metabolic alkalosis, hypercalcaemia and increase in uric acid and higher risk of gout. Metolazone is the only thiazide effective in patients with renal failure.

Thiazide diuretics are the preferred therapy in hypertension, because these are effective for almost 24 hours. High doses of thiazide diuretics (50 to 200 mg daily) will be more helpful in the treatment of HF and volume overload, however they produce more metabolic adverse effects like hyperglycaemia, high triglycerides and low-density lipoproteins (LDL).

These effects are rarely seen with low-dose (12.5 mg or 25 mg daily).

K^+ sparing diuretics

This includes triamterene, amiloride and mineralocorticoid receptor antagonists (spironolactone and eplerenone). The main side effects is hyperkalaemia. These are weak diuretics because in HF, the sodium retention occurs before the collecting ducts and they not effective in achieving a negative sodium balance if used alone. Spironolactone produces gynaecomastia, impotence and menstrual irregularities in up to 10% of patients. These effects have not been observed with eplerenone because these are more selective. These diuretics are contraindicated if creatinine greater than 2.5 mg/dL, GFR less than 30 mL/min or potassium greater than 5.0 mEq/L.

Vasodilators

Systemic vascular resistance (SVR) is increased in HF as a result of neurohormonal activation. Vasodilators increase cardiac output and blood flow to organs (**Table 3**). Vasodilators are more important in the treatment of acute decompensated HF and only hydralazine/nitrates combinations have been approved for chronic HF therapy. Importantly, pure vasodilators (without a neurohormonal effect) have not demonstrated a reduction in mortality and, in fact, powerful vasodilators, like the prostacyclin epoprostenol, increase mortality in HF.

Nitrovasodilators

Nitroglycerin: These are powerful venodilators, mainly in epicardial coronary flow (used in acute coronary syndromes). No effect on mortality. In acute decompensated HF, they lower filling pressures and increase cardiac output. The main limitation is the development of tolerance after 24 hours. Hydralazine can attenuate nitrate tolerance.

Nitroprusside: It has a very quick onset of action and, therefore, preferred in decompensated HF. Complications include cyanide toxicity and coronary steal. It should be used only for a short period of time.

Table 3: Vasodilators

Medication	Site of Action: Vein	Site of Action: Arteriolar
Nitrates	+++	+
Hydralazine	+	+++
CCBs	+	+++
Minoxidil	++	+++
Prostacyclins	+++	++
Nesiritide	+++	+
ACE inhibitor, ARB	++	+

Nesiritide

It is a vasodilator and has a direct natriuretic effect on the kidneys. Nesiritide is less arrhythmogenic than dobutamine. Titration or boluses are no longer recommended because of potential hypotension and acute renal failure.

Positive Inotropic Agents

Digoxin

Weak positive inotrope used to improve symptoms in patients LVEF ≤ 40% and recurrent admissions for HF exacerbation, despite optimal therapy. Digoxin does not improve mortality or is beneficial if preserved LVEF. The usual dose is 0.125 mg daily with a goal level less than 1.0 ng/mL. The narrow safety profile and significant drug interactions are the main reasons why digoxin is utilized rarely. Side effects include cardiac arrhythmias, heart block, gastrointestinal symptoms, neurological complaints (visual disturbances, disorientation and confusion). Digoxin toxicity could be precipitated by hypokalaemia, hypomagnesaemia, renal failure or hypothyroidism.

Beta-adrenergic agonists

These have a positive inotropic and chronotropic effect (**Table 4**). They have a short half-life (minutes) and that is one of their advantages over phosphodiesterase (PDE) inhibitors. Dobutamine is preferred over dopamine for most patients with decompensated HF who have not responded well to intravenous diuretics. The limitations of dobutamine are: (1) It does not work as well if patient has desensitisation of beta-receptors as happens with end-stage HF; (2) It cannot be effectively used with high levels of beta-blockers; (3) It only modestly reduces elevated pulmonary arterial pressure and pulmonary vascular resistance (PVR). Epinephrine is a vasodilator and vasoconstrictor, utilised in cases of concomitant septic and cardiogenic shock. Norepinephrine is a powerful vasoconstrictor not recommended in HF.

Phosphodiesterase inhibitors (Milrinone)

They are good inotropes without the associated chronotropic effect. Their vasodilator properties are both a strength and weakness of this medication. These work particularly well in patients with secondary pulmonary hypertension due to HF. Problems by its use are: (1) hypotension; (2) prolonged half-life and (3) 80% of the medication is renally excreted and should be used with caution in patients of renal failure, (for detail therapy see chapter pharmacotheraphy of cardiovascular disorders).

Table 4: Adrenergic Agonists.

Medication	β1 affinity	β2 affinity	α affinity
Dobutamine	+++++	+++	+
Dopamine	+++++	+++	+++++
Epinephrine	++++	++++	++++++
Norepinephrine	++++	+++	++++
Isoproterenol	++++	++++	0
Phenylephrine	0	0	++++++

ACUTE DECOMPENSATED HEART FAILURE

In acute HF, the aim of therapy is to provide immediate symptomatic relief of pulmonary oedema and rescue patients from imminent cardiorespiratory collapse by optimising the haemodynamic status. The emphasis is on agents given intravenously (**Table 1**). The hallmark of therapy is intravenous loop diuretics. If the patient exhibits signs of normal cardiac output, nitrates or nesiritide could be used to assist with vasodilation. If there is low cardiac output and end-organ damage, inotropic agents could be used, however, there is no evidence that these give long-term benefit, and in fact, could cause more harm and increase mortality. Reduction of hospitalisations for acute HF is important to reduce morbidity and mortality.

CHRONIC HEART FAILURE: THERAPIES BY HEART FAILURE STAGE

The objectives of therapy are: (1) to prevent progressive damage to the myocardium (prevention); (2) to prevent or reverse further enlargement of the heart (reverse remodeling); (3) to improve the quality of life by relief of symptoms; and (4) to prolong life. While the era of device therapy for HF is currently expanding at a tremendous rate, the clinician should be aware of the importance of achieving specific pharmacologic goals in their HF patients. The pathophysiology of symptoms in chronic HF is not well understood, but in contrast to acute HF is not directly related to high left atrial pressure.

Stage A—Preventive Therapy

Recognition that many risk factors can be modified and that treating HF is difficult and costly has focused attention on preventive strategies for HF. Treatment of systemic hypertension, with or without hypertrophy, reduces the development of HF. Myocardial infarction confers an 8- to 10-fold increased risk for subsequent HF. Early identification and treatment of risk factors is the most significant step in limiting the public health impact of HF. See previous chapter for more details as well as **Tables 5 and 6**. Routine evaluation of B-type natriuretic peptide (BNP) for asymptomatic patient evaluation is not recommended. ACE-inhibitors are recommended for prevention of HF in patients at risk.

Table 5: Indications to Suspect Heart Failure (Perform History and Physical)

Conditions	Test findings
Hypertension	Arrythmias
Diabetes mellitus	Abnormal ECG (LBBB, LVH, Q waves)
Elevated BMI	Cardiomegaly in chest X-ray
Coronary artery disease	
Atherosclerotic disease (peripheral vascular disease or cerebrovascular disease)	
Valvular heart disease	
First degree relative with HF	
Cardiac toxins exposure	
Obstructive sleep apnoea	

Table 6: Indications to Assess Cardiac Structure by Echocardiogram

Coronary artery disease
Valvular heart disease
First degree relative with HF
Supraventricular tachycardia: Atrial fibrillation or flutter
Abnormal ECG (LVH, LBBB, Q waves)
Ventricular tachycardia or fibrillation
Cardiomegaly on chest X-ray

Stage B

These patients will have cardiac structural changes but have not developed HF symptoms yet. It is important to determine the aetiology of HF, with particular attention to reversible causes including coronary ischaemia. Coronary angiography should be considered when pre-test probability is high. Laboratory testing for unusual aetiologies of HF is recommended if no cause is identified. Endomyocardial biopsy is only recommended in cases of rapidly progressive clinical HF with severe heart block or arrhythmias. Also important is to identify any exacerbating factors for HF, co-morbidities that could influence therapy and barriers to adherence. Treatment recommendations include smoking cessation, optimal blood pressure control, avoiding deconditioning and alcohol abstinence if previous history of excessive alcohol intake is present. Pharmacological therapies for asymptomatic patients with LVEF less than 40% include: ACE-inhibitors and beta-blockers.

Stage C

This category includes patients with structural changes that have developed symptoms. All recommendations for Stage B HF patients apply to patients with symptoms. The New York Heart Association (NYHA) functional classification, determines the pharmacological and device therapy in HF patients. The degree of volume excess is a key consideration in the treatment of HF. ACE-inhibitors and beta-blockers are recommended for all patients, aldosterone antagonist and digoxin should be reserved for those with NYHA class III-IV.

The utilisation of implantable cardioverter defibrillatory (ICD) for primary prevention of sudden cardiac death in HF patients improves survival significantly. The recommendations for ICD are: (1) patients with LVEF ≤ 35% and NYHA class II-III symptoms (ischaemic and non-ischaemic cardiomyopathies); (2) patients undergoing cardiac resynchronisation therapy (CRT) implantation; (3) survivors of cardiac arrest from ventricular fibrillation or haemodynamically unstable ventricular tachycardia that is not due to a reversible aetiology like acute myocardial infarction. If there is severe refractory HF and the life expectancy is less than 1 year, an ICD is not recommended.

Biventricular pacing seeks to improve and synchronize ventricular contraction, which results in less mitral regurgitation and increase diastolic filling time. Cardiac resynchronization therapy is indicated in: (1) patient with LVEF ≤35%, QRS ≥120 ms plus NYHA class III symptoms despite optimal medical therapy; (2) selected ambulatory NYHA IV patients in sinus rhythm, with LV dysfunction and QRS ≥120 ms; (3) may be considered in patients with NYHA class I or II symptoms, LV dysfunction and QRS ≥150 ms; and 4) may be considered in patients with LV dysfunction in whom frequent chronic pacing is expected (i.e. complete heart block).

Stage D

While there has been a significant positive impact on HF outcomes with the advent of new pharmacologic approaches to treatment, the disease remains burdensome. End-stage HF patients have poor quality of life, frequent hospitalisations, and higher mortality, despite optimal medical management. They also produce major economic stress on the healthcare system. The possibility of salvage by medical therapy at this stage is remote.

The goals of therapy differ from those in stages A, B and C and will include palliation of symptoms and hospice, reducing rates of hospitalisations, and in subjects that are eligible, cardiac transplantation and/or left ventricular assist devices (LVADs). In patients with recurrent admissions, inotropic therapy should be considered as a bridge to transplantation/LVAD or as part of the hospice period. The indications for transplantation are listed on **Table 7**.

Table 7: Indications for Heart Transplantation or LVAD Evaluation

Absolute indications

- For haemodynamic compromise due to HF
  - Refractory cardiogenic shock
  - Inotrope dependent
- Peak VO_2 <10 mg/kg/min with achievement of ventilator threshold
- Severe symptoms of ischaemia and refractory angina, not amenable to revascularisation
- Recurrent symptomatic ventricular arrythmia

Relative indications

- Peak VO_2 11 to 14 mg/kg/min (or 55% predicted) and major limitation in performance of daily activities
- Recurrent instability of fluid balance/renal function not due to patient non-compliance with medical regimen

Not appropriate indications

- Low left ventricular ejection fraction
- Functional class III or IV heart failure
- Peak VO_2 >15 mg/kg/min (and >55% predicted) and no other indications

Heart failure has worse prognosis than many cancers and premature death from progressive acute decompensated HF or sudden cardiac death is common. Hospice services should be implemented after the patient has been evaluated at a specialised centre and determination that LVAD or transplantation is ill-advised. It is important to allow adequate time (weeks to months) for medications and other therapies to exert a beneficial effect before considering these advance therapies.

RECOMMENDED READINGS

1. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2010; 16: e1-e194.
2. Jessup M, Abraham WT, Casey DE, *et al.* 2009 Focused Update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults. *Circulation* 2009; 119: 1977-2016.
3. Opie LH, Gersh BJ. Drugs for the heart. Elsevier Saunders 2005.
4. Zipes DP, Libby P, Bonow RO, *et al.* Braunwald's Heart Disease: A textbook of cardiovascular medicine. Elsevier Saunders 2005.

12.12 Acute Rheumatic Fever

R Krishna Kumar

INTRODUCTION

Acute rheumatic fever (RF) is an immune-mediated non-suppurative consequence of pharyngitis due to group-A beta-haemolytic *Streptococcus* (GABHS). The morbidity resulting from an episode can be considerable and rarely, an episode of RF may result in death. However, the major concern relating to RF is often not the episode itself but the long-term consequences of damage to heart valves, rheumatic heart disease (RHD) that often results from recurrence of RF. For this reason, RF and RHD are often clubbed together in discussions on epidemiology. RF-RHD continues to be a major public health problem in many parts of India. The impact of the disease through disability, premature deaths and economic losses is substantial at all levels. It is important for physicians to be thoroughly familiar with the diagnosis and management of RF as well as preventive strategies both for the individual as well as for the population.

In the past four to five decades, there have been modest advances in our understanding of the disease process. There have been minor changes in the diagnostic criteria and management practices for RF have also largely remained unchanged for the last 20 to 30 years. However, there have been important changes in the epidemiology both in India and the rest of the world. There appears to have been a sharp decline in RF and RHD in parts of India that have shown improving indices of human development. Physicians living in these parts of India need to be mindful of the prospect of over-diagnosis of RF. For most of India, however, the disease is still quite common and it is important to not miss the initial episode of RF because secondary penicillin prophylaxis still remains the most effective way of preventing RHD.

In this chapter, the existing information on aetiopathogenesis, diagnosis and management of RF will be summarised. There will be additional emphasis on the epidemiology of the disease and an effort will be made to focus on data from India over the last several years.

EPIDEMIOLOGY

There is an undeniable relationship between the incidence of RF and of living standards. A sharp decline in RF and RHD occurred in industrialised nations all over the world with improving living standards and with introduction of penicillin. Industrialised nations now have an average annual RF incidence of less than 0.5 per 100,000 and RHD prevalence of less than 0.05 per 1,000. Improved living standards translate into reduction in overcrowding, better access to healthcare and more widespread use of antibiotics, all of which allow prompt treatment of streptococcal infections and help abort epidemics. However, the small but significant resurgence of the RF in parts of the US during the mid-eighties suggested that additional factors also contribute to occurrence of RF, albeit in a small way. Selected populations in Australia, New Zealand and the Pacific islands also appear to have a very high occurrence of RF and RHD that is perhaps in part explained by a genetic predisposition.

A number of studies have attempted to document RF incidence and RHD prevalence in India. School surveys are traditionally considered useful for this purpose because the denominator is clear. However, school surveys will miss older patients with RHD. In areas where RF and RHD are on the decline most patients with RHD tend to be older. Population-based registries have the potential to capture all age groups but are heavily dependent on referral mechanisms. Hospital-based statistics have serious limitations because only the most seriously affected are represented.

It is important to recognise, however, that data from these highly selected regions are not representative of the country as a whole. The parts of the country with the highest prevalence today are also those regions with the poorest healthcare infrastructure. Most comparative studies have reported a substantially higher prevalence in rural regions. Because of serious limitations in the healthcare delivery systems, the magnitude of the problem remains unrecognised in many poorly-served regions. Very few systematic surveys are available from rural populations with a poor healthcare infrastructure, urban slums and tribal colonies. Given the extraordinary variations in indices of human development across the country and even within regions, it is difficult to make generalisations for the entire country. **Table 1** summarises the results of selected studies from India over the last 50 years.

Table 1: Rheumatic Fever/Rheumatic Heart Disease Status in India

Authors	Place	Year	Age (yrs)	Population Studied	RHD Prevalence (per 1000)	RF Incidence (per 1000/yr)
Padmavati	Delhi (urban)	1984-94	5 to 10	40,000	3·90	0·38
Lalchandani *et al*	Kanpur	2000	7 to 15	3,963	4·54	0·75
Jose *et al*	Vellore	2001-02	5 to 18	2,29,829	0.68*	—
Soman *et al***	Ernakulam	2002-04	5 to 16	25,033	0.12*	0.08

RHD = Rheumatic heart disease; RF = Rheumatic fever.
** These studies used strict diagnastic criteria (echacardiagram canfirmatian af diagnasis).*
*** Unpublished data af the Jaivigyan ICMR rheumatic fever and rheumatic heart disease in Ernakulam district.*

AETIOLOGY

Rheumatic fever is an excellent example of a condition where all three components of the classic epidemiologic triad: agent, host and environment interact to result in the development of the disease.

The Agent

The role of preceding group-A beta-haemolytic streptococcal pharyngeal infection in the development of RF was suspected and firmly proven in the early 1930s and this association remains undisputed to this day. The clearest evidence of causality was provided by the demonstration of efficacy of penicillin prophylaxis dramatically reducing recurrences of RF. Further, mass penicillin prophylaxis terminated epidemics of RF in closed populations and in civilian populations as well. Streptococcal pharyngeal infections also result from other streptococci (groups B, C, G and F), but these do not result in RF.

Notwithstanding the clear demonstration of the association between GABHS and RF some aspects of this association that are unclear. The occurrence of group-A beta-haemolytic streptococcal pharyngeal infection has remained unchanged in various parts of the world including developed nations. Yet in most of these nations RF fever has declined substantially. Certain aspects of the association between GABHS and RF have been defined:

Epidemics of streptococcal infection are far more likely to cause RF than endemic streptococcal infections. The frequently quoted figure of 3% for epidemics and 0.3% for endemic infections are derived from studies in the 1950s on adult military recruits and civilian medical practice respectively. The risk of RF increases dramatically in recurrent attacks of GABHS infections in children and adults with a previous episode of RF.

The intensity of antigenic stimulus as suggested by the anti streptolysin-O (ASO) antibody titres correlate with attack rates of RF.

There is a carrier state for GABHS infections. This refers to the isolation of GABHS from asymptomatic patients. This does not translate into a risk of development of RF and does not require treatment.

The molecular basis of rheumatogenic potential of GABHS is unclear. There is also no clear relationship between specific serotypes and the propensity to produce RF. The virulence of streptococcus is closely linked to its rheumatogenic potential. The M protein is responsible for the ability of GABHS to resist phagocytosis. However, there appears to be no consistent relation between specific M protein serotypes and the incidence of RF after GABHS infection.

Host Factors

The first attack of RF typically occurs between 5 and 15 years with a peak at 8 years. Attacks are uncommon below 5 years and rare below 3 years. Virulent GABHS epidemics can result in RF occurring for the first time in young adults. There are anecdotal reports of initial attacks in the fourth or fifth decades.

While both sexes are equally predisposed to develop RF, chorea is strikingly uncommon in post-pubertal males. Interestingly, selected large community surveys from India on RHD have shown a striking female preponderance.

Genetically-programmed determinants of host susceptibility to RF have been studied extensively. These determinants include a variety of genes in the HLA-DR loci and B-cell alloantigens. Loose associations have been identified for different racial-ethnic groups. The available information seems to indicate that heredity plays a small role, if at all, in the development of RF.

Environmental Factors

Trends in RF and RHD over the last one-and-a-half centuries, in both the developed and developing countries, all point towards environmental factors such as poor living conditions, overcrowding and access to healthcare as the most significant determinants of disease distribution. Indeed, global, and to a substantial extent regional, distributions of RF and RHD are still largely influenced by socio-economic indices. Parts of India that have good human development indices (HDI), such as Kerala, have a much lower incidence of RF when compared to parts of India with low HDI, such as Chhattisgarh or Orissa. It is generally believed that crowded living conditions, with close interpersonal contacts, contribute to the rapid spread and persistence of virulent streptococcal strains. However, population density does not correlate well with RF incidence. Variations within India are best explained by education and access to health care including perhaps antibiotic usage. Seasonal variations in the incidence of RF (i.e. high incidences in early autumn, late winter and early spring) closely mimic variations in streptococcal infections in temperate climates. Such variations are not significant in the tropics.

PATHOGENESIS AND PATHOLOGY

The fact that RF represents an immunologic consequence of GABHS infection is largely uncontested. However, significant gaps remain in our understanding of many of the specific pathways involved. This together with the absence of a reliable and consistently reproducible animal model has come in the way of developing a suitable vaccine for the disease.

Pathology of Rheumatic Carditis

All components of the cardiac tissue are affected. Acute pericarditis occurs in 18% of cases and results in adhesions because of its fibrinous nature. Small-to-moderate effusions are also common. However, large effusions and tamponade is distinctly rare. Pericarditis is self-limiting and does not result in constriction unlike tuberculous or pyogenic pericarditis. Acute endocardial and valvular inflammation is characterised by tiny vegetations that neither embolise nor are infected.

Valvular involvement alone has long-term consequences. The valve heals with fibrosis and results in incompetence or stenosis. Not uncommonly, during acute RF one or more chordae of the mitral valve may rupture resulting in a flail leaflet and severe mitral regurgitation. Myocardial involvement is typically confined to the interstitium and does not result in myocardial damage or dysfunction.

The histological hallmark of rheumatic carditis is the Aschoff body. This is a granulomatous lesion, less than 1 mm in size, found in the endocardium, subendocardium and in the perivascular regions of the interstitium. It consists of a central area of fibrinoid necrosis surrounded by cardiac histiocytes (Aschoff cells or Anitschkow myocytes).

Pathology of Arthritis and Chorea

Synovial thickening and fibrinous exudates without any pannus formation are typical of rheumatic arthritis. Joint lesions heal

without any permanent damage. The pathologic basis of chorea is unclear. A variety of changes have been described in the cortex, cerebellum and basal ganglia (especially the caudate nucleus). The specificity of these changes is not established.

Pathogenesis of Rheumatic Heart Disease following Rheumatic Fever

Among the tissues affected during an episode of RF, only heart valves suffer permanent damage. All other affected tissues typically heal with no residual sequelae. Thus, pericarditis resolves completely without constriction, chorea resolves without long-term neurologic consequences and arthritis does not leave behind any disability. The reasons why heart valves are permanently damaged by one or more episodes of RF have not been fully understood. The following hypothesis appears most plausible.

Histopathological findings indicate widespread vascular disease throughout the body during an acute episode of RF. The immunological findings suggest that RF predominantly damages the vascular endothelium and mesothelium. The adjacent subendothelial and submesothelial tissues are affected to a very limited depth. Despite the diffuse collagen – vascular involvement, one of the mysteries of the pathology, of RF is the remarkable tendency for the disease to heal rather than to scar the tissues it affects, with the exception of cardiac valves. The damaged endothelium gets replaced by a new endothelium within days after injury without significant scarring. The valves are structurally unfortunate in having a small core of connective tissue covered by two layers of endothelium.

It is likely that the endothelium suffers initial damage due to a humoral immune response, the damage resulting in VCAM-1 being expressed on the endothelium. This is followed by activation of cellular immune response. As a result, CD4+, CD8+, T lymphocytes and macrophages get attached to the valvar endothelium and migrate to the connective tissue core. This sets up an inflammatory response. The inflammation is accompanied by neovascularisation of the valve substance. The endothelium of the newly formed vessels may serve as a substrate for additional inflammation and perhaps setup a vicious cycle of inflammation, neovascularisation and further damage resulting eventually in a permanently scarred valve.

DIAGNOSIS AND CLINICAL MANIFESTATIONS OF ACUTE RHEUMATIC FEVER

Jones Criteria

Duckett Jones introduced specific criteria in 1944 as a set of clinical guidelines for the diagnosis of rheumatic fever (RF) and carditis. The clinical features of RF were divided into major and minor categories, based on the prevalence and specificity of manifestations. The criteria needed to be sensitive enough to limit under-diagnosis and specific enough to limit over-diagnosis. Over the years, there have been modifications and revisions proposed by the American Heart Association (AHA) to improve the specificity of these criteria largely dictated by the declining incidence of RF in industrialised nations. In 1988 and subsequently in 2002-2003, WHO introduced specific modifications to the Jones criteria to allow wider application in today's developing world.

For the diagnosis of a primary episode of RF, it is recommended that the major and minor clinical manifestations of RF, the laboratory manifestations, and evidence of a preceding streptococcal infection should all continue according to the 1988 WHO recommendations. In the context of a preceding streptococcal infection, two major manifestations, or a combination of one major and two minor manifestations, provide reasonable evidence for a diagnosis of RF. The WHO has continued to maintain that a diagnosis of a recurrence of RF in a patient with established RHD should be permitted on the basis of two minor manifestations plus evidence of a recent streptococcal infection.

INDIVIDUAL MANIFESTATIONS OF RHEUMATIC FEVER

Major Manifestations

Carditis

Valvulitis is always seen in patients with carditis and is often clinically evident. Rheumatic pericarditis and myocarditis do not occur without accompanying valvulitis.

The initial symptom of carditis is often the pain of pericarditis or symptoms of heart failure typically manifesting about 2 to 3 weeks after the onset of RF. Symptoms may be subtle in children with nausea and vomiting resulting from gastric congestion, right upper quadrant pain because of hepatic capsule distension or non-productive cough from pulmonary congestion. Carditis may be present particularly with insidious onset in young children under the age of 6 years. This is identified as a separate category (insidious or chronic carditis) and is typically not accompanied by arthritis.

Signs and symptoms of carditis can be classified depending on the pathology.

Pericarditis

Pericarditis results in chest pain and is identified through auscultation of a friction rub. This may or may not be accompanied by a small pericardial effusion that is identified by echocardiography. In presence of mitral and/or aortic valve lesions, a pericardial friction rub strongly suggests acute RF. Pericarditis is equally diagnostic in primary episode or a recurrence of RF.

Myocarditis

Left ventricular function is rarely affected in acute rheumatic fever and heart failure is almost always the result of acute valvular regurgitation. Disproportionate tachycardia and a soft first heart sound are accompanying features of rheumatic carditis.

Endocarditis/Valvulitis

For patients who do not have a history of RHD, the presence of apical holosystolic murmur of mitral regurgitation (with or without apical mid-diastolic murmur, Carey Coomb's) or basal early diastolic murmur strongly supports the diagnosis of acute RF. For patients with previous RHD, a definite change in the character of any of the murmurs or the appearance of a new significant murmur suggests the presence of carditis. Mitral regurgitation may disappear (58% to 74%) in time but aortic involvement is usually permanent.

Arthritis

Arthritis is the most frequent major manifestation of RF, occurring in up to 75% of patients in the first attack of RF. It

occurs early in the course of the disease, as the presenting complaint. Arthritis is often the only major manifestation in adolescents as well as in adults. The articular manifestations in RF typically present as migratory polyarthritis, most often in the larger joints (commonly in the knees and ankles); the wrists, elbows, shoulders and hips are less frequently involved; and the small joints of the hands, feet, cervical and thoracic or lumbar spine are rarely affected. Inflamed joints are characteristically warm, red and swollen, and an aspirated sample of synovial fluid may reveal a high average leucocyte count. Tenderness in rheumatic arthritis may be out of proportion to the objective findings and severe enough to result in excruciating pain on touch. The term 'migratory' reflects the sequential involvement of joints with each completing a cycle of inflammation and resolution, so that some joint inflammation may be resolving while others are beginning. Many cases of rheumatic arthritis do not conform to this characteristic description. Monoarthritis may occur, for example, typically when anti-inflammatory therapy is initiated before RF is fully expressed. Frequently, several joints may be affected simultaneously, or the arthritis may be additive rather than migratory. Inflammation in a particular joint usually resolves within two weeks and the entire bout of polyarthritis in about a month if untreated.

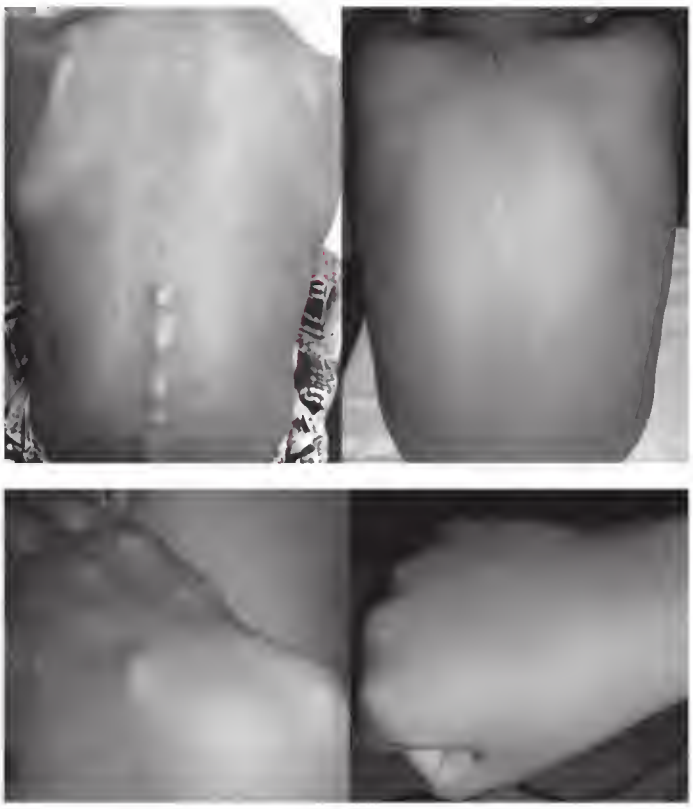
Chorea

Sydenham's chorea occurs in fewer than 10% patients with rheumatic fever.

Chorea occurs primarily in children and is rare after the age of 20 years. It occurs primarily in females and almost never occurs in postpubertal males. Sydenham's chorea is characterised by emotional lability, uncoordinated movements, and muscular weakness. The onset may often be difficult to determine, as initially the child may become fretful, irritable, inattentive to schoolwork, fidgety or even severely disturbed. Physical incoordination soon becomes apparent, perhaps manifested as clumsiness and a tendency to drop objects, which progresses to spasmodic, uncoordinated movements. On physical examination, the movements are abrupt and erratic. All muscle groups may be affected, but erratic movements of the hands, feet and face are most evident. Facial movements include grimaces, grins and frowns. When the tongue is protruded, it resembles a 'bag of worms' and speech is jerky and staccato. Handwriting becomes illegible and the patient may stumble when attempting to walk. When the hands are extended, the dorsum assumes a 'spoon' or 'dish' configuration due to flexion of the wrist and hyperextension of the metacarpophalangeal joints. When raising the hands above the head, the patient may pronate one or both hands ('pronator sign'). Patients with chorea are unable to sustain a titanic contraction; therefore, when asked to grip the examiner's hand, their irregular, repetitive squeezes have been termed 'milkmaid grip'. Although the choreiform movements are usually bilateral, they may be unilateral (hemichorea). The choreiform movements disappear during sleep, decrease with rest and sedation, and can be briefly suppressed by volition. They may be accentuated by asking the patient to perform several voluntary movements at once. Neither sensory deficits nor pyramidal tract involvement are present. The latent period between the onset of the initiating streptococcal infection and the onset of Sydenham's chorea may be as long as several months. There is no definitive laboratory test for establishing a diagnosis of Sydenham's chorea, and the diagnosis is largely clinical.

Subcutaneous Nodules and Erythema Marginatum

Subcutaneous nodules and erythema marginatum are rare; usually, present in fewer than 10% of cases. Because the skin over them is not inflamed, they may easily be missed if not carefully sought on physical examination. Subcutaneous nodules are found over extensor surfaces of joints, are seen most often in patients with long-standing rheumatic heart disease and are rare in patients experiencing an initial attack. They are invariably associated with carditis and typically occur six weeks after the initial attack (**Figure 1**).



During acute rheumatic fever 6 weeks later

Figure 1: Subcutaneous nodules in rheumatic fever: These pictures have been obtained from an 8-year-old boy who had characteristic subcutaneous nodules in a number of locations including the back and dorsum of the hand as shown in the figure. Six weeks after presentation, following administration of anti-inflammatory medications that included a course of steroids, the nodules disappeared completely.

Erythema marginatum is an extremely uncommon manifestation. It is a macular eruption with rounded borders – usually concentrated on the trunk with serpiginous margins. It is only noticeable in fair-skinned individuals and tends to be very evanescent.

Minor Criteria

The minor criteria are non-specific and may be present in many clinical conditions. Fever occurs in almost all rheumatic attacks at the onset, usually ranging from 101°F to 104°F (38.4°C to 40.0°C). Diurnal variations are common, but there is no characteristic fever pattern. Arthralgia without objective findings is common in RF. The pain usually involves large joints, may be mild or incapacitating and may be present for days to

weeks, often varying in severity. Abdominal pain and epistaxis may occur in only about 5% of patients with RF.

Interpretation of Jones Criteria

To fulfil the Jones criteria, two major criteria, or one major criterion and two minor criteria, plus evidence of an antecedent streptococcal infection (see below) are required. The latter may be provided by recovery of the organism on culture or by evidence of an immune response to one of the commonly measured group A streptococcal antigens (e.g. antistreptolysin O, antideoxyribonuclease B, and anti-hyaluronidase). Insidious or chronic carditis and chorea can occur several weeks after GABHS infection, and therefore, do not require the essential criteria of evidence of streptococcal infection for the diagnosis of RF.

Interpretation of Laboratory Data

Antistreptolysin O test

Although widely used, ASO test has important limitations that need to be understood. ASO is positive in 85% of RF patients. The antibody levels in the normal population are influenced by several variables such as age, geographic location, socio-economic status, season of the year and genetic factors. Attempts to define normal values in Indian children indicate considerable variability. Several normal children had strikingly high titres.

In the absence of normative data for a given geographic region, ASO in excess of 240 for adults and 320 for children are considered to be abnormal. However, ASO titres have to be interpreted with caution in patients with suspected RF. Mere elevation of ASO in the presence of non-specific symptoms should not be labelled as RF. Penicillin prophylaxis should not be initiated on this basis. If necessary, a repeat titre should be obtained after a week. ASO antibodies appear after 7 to 10 days, peak at 2 to 3 weeks following GABHS infection and drop steadily thereafter.

Other streptococcal antibody tests

Other antibodies to extra-cellular streptococcal antigens (AntiDNAse B, antihyaluronidase, antistreptokinase and antistreptococcal esterase) can be used to improve sensitivity. If some of these tests are combined with ASO, the overall sensitivity can be improved to more than 95%. However, these tests are not generally available, particularly in smaller clinics in the developing world.

Throat culture

Throat swabs should be obtained carefully and inoculated within 5 hours of being obtained or should be transferred using appropriate transport methods. Throat swab culture does not differentiate between carrier and an active infection. Delays in obtaining throat swabs are common in the field setting and many patients receive antibiotics before samples can be obtained.

Rapid antigen detection

Rapid detection of streptococcal antigens from throat swabs using latex agglutination or enzyme immunoassay is a practical alternative to the throat swab. It has a sensitivity of 60% to 90% and a specificity of 95%.

Acute phase reactants

Both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are widely available. Unlike ESR, CRP levels are not increased in presence of anaemia and not diminished in the presence of heart failure.

Electrocardiogram

Prolonged PR interval is accepted as a minor criterion and is not a sign of carditis. Accelerated junctional rhythm is well described in children. Higher grades of heart block (2nd degree or complete heart block) have also been described.

The WHO 2002-2003 criteria for the diagnosis of RF are shown in **Table 2**.

Role of Echocardiography for the Diagnosis of Rheumatic Fever

According to the WHO recommendations, clinical examination remains the basis of diagnosis of RF and carditis, and the role of echocardiography should be considered supportive. However, an echo-Doppler examination should be performed if the facilities are available. Echocardiography offers several clues to support the diagnosis of rheumatic fever (**Table 3**). Echocardiogram has several additional benefits in guiding appropriate therapy and in prognostication. However, strict echocardiographic criteria should be used to diagnose valve regurgitation. It is important not to label small colour Doppler jets of physiologic mitral regurgitation as significant. If mild mitral regurgitation is identified in absence of a murmur, the features suggestive of RF is a discrete posteriorly directed jet that often reaches the left atrial wall.

MANAGEMENT

The management algorithm for rheumatic fever is shown in **Figure 2**.

General Measures

Hospitalisation is recommended for confirmation of diagnosis, treatment initiation, patient and family education. A throat culture should be obtained; blood should be drawn for ASO, ESR, CRP and blood culture (if infective endocarditis needs to be ruled-out). A chest X-ray and an echocardiogram should also be done. Rest is recommended for 4 weeks for patients with carditis.

Eradication of Pharyngeal Streptococcal Infection

Eradication of the pharyngeal streptococcal infection is mandatory to limit repetitive exposure to streptococcal antigens. A single dose of benzathine penicillin (1.2 million units) is ideal. Alternatives include penicillin V (250 mg qid for 10 days) or erythromycin (250 mg qid for 10 days) for those with penicillin allergy.

Suppression of the Inflammation

Anti-inflammatory treatment with salicylates or steroids does not appear to influence the long-term outcome of RF or progression of heart valve lesions. Salicylates or steroids should be initiated only after a diagnosis of RF is confirmed. Aspirin, 100 mg/kg/day divided into 4 to 5 doses, is generally adequate for achieving a clinical response. The optimal aspirin dose should ensure an adequate response but avoid toxicity. After 2 weeks, the dose can be decreased to 60 to 70 mg/kg per day

Table 2: 2002-2003 WHO Criteria for the Diagnosis of Rheumatic Fever and Rheumatic Heart Disease (Based on the Revised Jones Criteria)

Major manifestations	Two major or one major and two minor manifestations plus evidence of a preceding group A streptococcal infection
Minor manifestations	Two major or one major and two minor manifestations plus evidence of a preceding group A streptococcal infection
Supporting evidence of a preceding streptococcal infection within the last 45 days	Two minor manifestations plus evidence of a preceding group A streptococcal infection
	Other major manifestations or evidence of group A streptococcal infection not required
	Patients do not require any other criteria to be present for the first time with patient diagnosed as having rheumatic heart mitral stenosis or mixed mitral valve disease and/or aortic valve disease
Primary episode of RF	Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules
Recurrent attack of RF in a patient without established rheumatic heart disease Recurrent attack of RF in a patient with established rheumatic heart disease	Clinical: fever, polyarthralgia Laboratory: elevated acute phase reactants (erythrocyte sedimentation rate or leucocyte count)
Rheumatic chorea, insidious onset rheumatic carditis	Electrocardiogram: prolonged P-R interval
Chronic valve lesions of RHD	Elevated or rising antistreptolysin-O or other streptococcal antibody, or a positive throat culture, or rapid antigen test for group A streptococci, or recent scarlet fever

1. *Patients may present with polyarthritis (or with only polyarthralgia or monoarthritis) and with several (3 or more) other minor manifestations, together with evidence of recent group A streptococcal infection. Some of these cases may later turn out to be rheumatic fever. It is prudent to consider them as cases of 'probable rheumatic fever' (once other diagnoses are excluded) and advise regular secondary prophylaxis. Such patients require close follow up and regular examination of the heart.*
2. *This cautious approach is particularly suitable for patients in vulnerable age groups in high incidence settings.*
3. *Infective endocarditis should be excluded.*
4. *Some patients with recurrent attacks may not fulfil these criteria.*
5. *Congenital heart disease should be excluded.*

Table 3: Echocardiographic Findings Suggestive of Rheumatic Fever

Structure	Modality	Findings
Mitral valve	Two-dimensional imaging	Thickened leaflets Limited mobility of posterior mitral leaflet Nodules on leaflet margins (25%) Flail anterior or posterior (rare) leaflet Evidence of chronic RHD Thickened chordal apparatus Varying degrees of stenosis Limited mobility of AML
	Colour Doppler	Posteriorly directed jet of mitral regurgitation
Aortic valve	2D colour Doppler	Thick leaflet margins Varying grades of aortic regurgitation Evidence of RHD Aortic stenosis Reduced leaflet mobility
Tricuspid valve	2D and colour Doppler	Rarely affected in the initial episode; chronic RHD is associated with organic tricuspid valve involvement in up to 30% with leaflet thickening, and varying degrees of TR; tricuspid stenosis is relatively uncommon but well-described
Atria	M-mode and 2D	Left atrial enlargement is an inevitable consequence of significant mitral regurgitation
Ventricles	M-mode and 2D	Left ventricle enlargement is a result of mitral regurgitation. LV function tends to be well-preserved except in the presence of acute severe MR. LV dysfunction is, therefore, rare in the absence of significant MR.

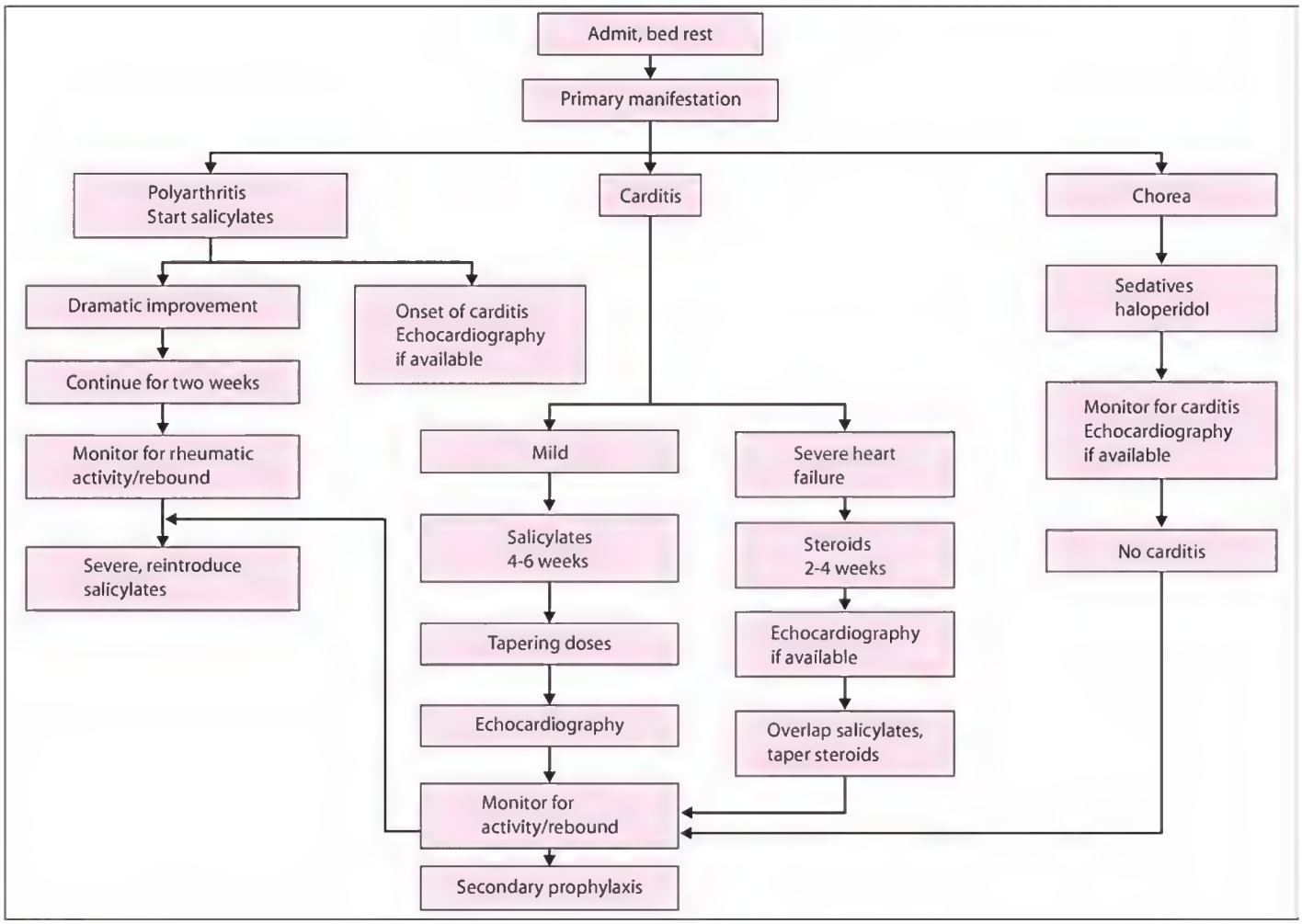


Figure 2: Algorithm for management of acute rheumatic fever.

for an additional 3 to 6 weeks. Any other non-steroidal anti-inflammatory drug (NSAID) can be used as an alternative for those allergic to aspirin.

Patients with carditis and heart failure should receive steroids to facilitate early recovery. Steroids rapidly relieve symptoms and shorten duration of hospitalisation. Steroids are also advisable in patients who do not respond to salicylates and who continue to worsen and develop heart failure despite anti-inflammatory therapy. Prednisone (1 to 2 mg/kg-day, to a maximum of 80 mg/day given once daily, or in divided doses) is usually the drug of choice. In life-threatening circumstances, therapy may be initiated with intravenous methylprednisolone. After 2 to 3 weeks of therapy, the dosage may be decreased by 25% each week. While reducing the steroid dosage, a period of overlap with aspirin is recommended to prevent rebound. Duration of treatment is dictated by the clinical recovery. Typically 4 to 6 weeks of total treatment is advisable. However, prolonged treatment is sometimes necessary for the small proportion of patients (5%).

Management of Heart Failure

Although heart failure in RF generally responds to bed rest and steroids, diuretics, angiotensin converting enzyme inhibitors and digoxin are often initiated early. This allows greater patient comfort and may help shorten the duration of hospitalisation. The role of ACE inhibitors in acute mitral or aortic valve regurgitation is controversial.

Management of Chorea

Chorea has traditionally been considered to be a self-limiting benign disease, requiring no therapy. However, there are recent reports that a protracted course can lead to disability and/or social isolation. The signs and symptoms of chorea do not respond well to anti-inflammatory agents or steroids. Supportive measures such as rest in a quiet room together with medications such as haloperidol, diazepam, and carbamazepine have all been reported to be effective. Pimozide is a new drug that is believed to be effective in rheumatic chorea.

Role of Surgery in Refractory Heart Failure

Under exceptional circumstances, valve replacement operation may be advised to help manage refractory heart failure from severe mitral (or rarely aortic) valve leakage. Typically, the valve leaflets are flail. Mitral valve repair can be considered for patients after the acute inflammation subsides because of the possibility of recurrence of mitral regurgitation from ongoing inflammation. Exceptionally, valve repair has been undertaken during the acute phase.

NATURAL HISTORY OF VALVE LESIONS

Mitral regurgitation associated with acute RF has a tendency to decline over the next several weeks or months once the acute inflammation subsides. Rarely, it may disappear altogether. There are also instances where stenosis develops with time.

PREVENTION

Primary Prevention

This refers to prevention of occurrence of RF for the first time following an episode of streptococcal sore throat infection. The antibiotic regimens are essentially identical listed for eliminating *Streptococci* from the throat during an acute episode of RF.

Secondary Prophylaxis (Prevention of Recurrences of RF)

One of the most important aspects of management of acute RF is the prevention of its recurrence through continuous antibiotic prophylaxis regimes. **Table 4** lists prophylactic regimes recommended by WHO.

Duration of secondary prophylaxis

The following WHO recommendations are widely accepted:

Patient without proven carditis

For 5 years after the last attack, or until 18 years of age (whichever is longer).

Patient with carditis mild mitral regurgitation or healed carditis

For 10 years after the last attack, or at least until 25 years of age (whichever is longer).

Patients with established rheumatic heart valve disease or following valve surgery or balloon mitral valvotomy

Life-long prophylaxis is usually recommended. However, some cardiologists do recommend discontinuation of prophylaxis after the age of 40 years because the likelihood of recurrence of RF beyond this age is considered minimal.

Table 4: Secondary Prophylaxis Following an Episode of Rheumatic Fever

Antibiotic	Mode of Administration	Dose
Benzathine penicillin	Single intramuscular injection every 3 to 4 weeks*	12,00,000 units for patients ≥30 kg; 600,000 units for patients <30 kg**
Penicillin V	Oral	250 mg twice daily
Sulphonamide (sulphadiazine, sulphadoxine, sulphisoxazole)	Oral	1 gm daily for patients ≥30 kg and 500 mg daily for patients <30 kg
Erythromycin (for those allergic to penicillin)	Oral	250 mg twice daily

** 3 weekly injections are recommended for RF prophylaxis in high prevalence regions.*
***For patients <30 kg in high prevalence regions, 600,000 units can be administered every 2 weeks.*

RECOMMENDED READINGS

1. Narula J, Reddy KS, Tandon R, *et al.* Rheumatic fever. In: Narula J, Reddy KS, Tandon R, *et al. American Registry of Pathology.* Washington DC: 1999; pp 41-68.
2. Padmavati S. Rheumatic fever and rheumatic heart disease in India at the turn of the century. *Indian Heart J* 2001; 53: 35-7.
3. Rheumatic fever and rheumatic heart disease. Report of a WHO Study Group. World Health Organization, Geneva, 2004 (Technical Report Series No. 923).

12.13 Valvular Heart Disease (I)

CN Manjunath

Rheumatic heart disease (RHD) constitutes the most common form of valvular heart disease in India. The reported prevalence of RHD is 1.0 to 5.4 per 1,000 school children in our country. Only 50% of patients with established RHD give a past history of rheumatic fever. This may be attributed to subclinical carditis or the difficulty encountered in diagnosis.

Rheumatic valvulitis most commonly affects the mitral valve (70% to 75%) followed by combined mitral and aortic involvement (20% to 25%), with isolated aortic disease being uncommon (5% to 8%). Though pathological involvement of tricuspid valve is seen in 30% to 50% of patients, clinical manifestations are rare. The mitral valve is most commonly affected in RHD because it withstands a high left ventricular (LV) pressure of about 120 mm Hg during systole (aortic valve is subjected to about 80 mm Hg during diastole).

MITRAL STENOSIS

Mitral stenosis (MS) is a condition characterised by structural abnormality of the mitral valve apparatus that results in obstruction to left ventricular inflow. The most common cause of MS is rheumatic carditis. Other causes are extremely uncommon and include congenital MS, mitral annular calcification (MAC), carcinoid syndrome, mucopolysaccharidosis, Fabry's disease, Whipple's disease, amyloidosis and methysergide therapy.

Isolated MS occurs in 25% of all RHD patients and about 40% have combined MS and mitral regurgitation (MR). The female to male ratio is 2:1.

Pathology

The mitral valve apparatus is composed of the annulus, anterior and posterior mitral leaflets which are attached to the anterolateral and posteromedial papillary muscles via the chordae tendinae (about 120 in number). The normal mitral valve orifice area is 4-6 cm^2. The mechanism by which the initial episode of rheumatic fever progresses onto MS, has been explained by two theories, namely the smoldering process of rheumatic carditis and 'Selzer and Cohn' hypothesis. According to this hypothesis, the initial mitral valvulitis leads to abnormal flow patterns across the mitral leaflets that promote thickening, fibrosis and calcification of leaflets. The thickened leaflets fuse along their edges, i.e. commissures, resulting in a stenosed mitral valve which has a 'Fish mouth' or 'Buttonhole' appearance. This commissural fusion may be associated with cuspal or chordal fusion or both. The severity of MS is determined by several parameters as enumerated in **Table 1**.

Pathophysiology

In normal individuals, the mean pressure in the left atrium (LA) is 2 to 12 mm Hg, whereas the LV end-diastolic pressure ranges from 5 to 12 mm Hg. During diastole, the mitral valve opens and blood flows from LA to LV and no pressure gradient exists across the mitral valve. When the mitral valve orifice area (MVOA) is reduced to < 2.0 cm^2, the LA pressure has to increase to propel the blood from LA to LV. In severe MS, the mean LA pressure may become as high as 25 mm Hg to maintain antegrade flow across the mitral valve. This diastolic transmitral pressure gradient is the haemodynamic hallmark of MS. During tachycardia, the diastolic phase shortens and the time available for blood flow from LA to LV is reduced. In such situations, the LA pressure raises abruptly and dramatically to maintain adequate transmitral blood flow. The elevated LA pressure is transmitted backwards into the pulmonary veins resulting in pulmonary venous hypertension which causes dyspnoea. When the mean LA pressure exceeds 25 mm Hg pulmonary oedema occurs. Hence conditions that cause tachycardia like exercise, anaemia, fever, pregnancy and atrial fibrillation worsen the symptoms of MS. On the other hand, treatment with beta-blocker lowers the heart rate and increases the diastolic filling period and produces symptomatic relief.

Table 1: Assessment of Severity of Mitral Stenosis

	MVOA (cm^2)	Mean Gradient (mm Hg)	PASP (mm Hg)
Mild MS	>1.5 to 2.0	<5	<30
Moderate MS	1.0 to 1.5	5 to 10	30 to 50
Severe MS	<1.0 to 0.5	10 to 20	>50
Critical MS	<0.5	>20	

MVOA = Mitral valve orifice area; PASP = Pulmonary artery systolic pressure.

Long standing MS eventually leads to pulmonary arterial hypertension (PH), the mechanism of which is explained by Jordan's hypothesis. According to this hypothesis, when the pulmonary venous pressure increases, fluid passes into alveolar walls and promotes thickening and fibrosis of the wall resulting in hypoxaemia. This hypoxaemia is sensed by chemoreceptors that lead to reflex pulmonary arterial vasoconstriction. This triad of passive pressure transmission, reflex vasoconstriction and obliterative changes in the vascular bed causes PH. When pulmonary artery pressure exceeds 60 mm Hg, right ventricular (RV) dysfunction with tricuspid regurgitation (TR) occurs. When PH is severe, the chance of developing pulmonary oedema decreases and symptoms of right heart failure dominates the clinical picture.

LA enlargement is a consequence of MS and fibrosis of atrial wall due to rheumatic carditis. The disorganisation of atrial muscle bundles coupled with in homogenous refractory periods culminates in atrial fibrillation (AF). Initially, AF tends to be paroxysmal and later on becomes permanent. Incidence of AF in symptomatic MS is 30% to 40%.

Clinical Features

The age of presentation of MS in Western countries is third or fourth decade. We, in India, often seen them in second decade.

Those presenting in teens are called as juvenile mitral stenosis. The most common symptom of MS is exertional dyspnoea. It is accompanied with history of orthopnoea and paroxysmal nocturnal dyspnoea (PND) which distinguish dyspnoea to be due to pulmonary venous hypertension (PVH). Patients have history of dyspnoea, orthopnoea, PND for a long duration. Second important symptom is haemoptysis. It can occur due to various causes as shown in **Table 2**.

Table 2: Causes of Haemoptysis in Mitral Stenosis

Pulmonary apoplexy (rupture of thin walled bronchial veins)
Acute pulmonary oedema
Pulmonary infarction
Winter bronchitis
Pulmonary haemosiderosis

History of palpitations is prominent in these patients specially when they develop atrial fibrillation (AF). Patients symptoms worsen after the onset of AF. They also complain of fatigue due to low cardiac output at this stage. Pedal oedema occurs later when right heart failure sets in and patients have pain in right hypochondrium due to hepatomegaly. Hoarseness of voice (Ortner's syndrome or cardiovocal syndrome) can occur due to compression of left recurrent laryngeal nerve by dilated LA or pulmonary artery. Chest pain is a rare symptom and can occur due to pulmonary hypertension, RV ischaemia or associated coronary artery disease.

The clinical findings in MS are characterised by mitral facies - pinkish purple patches on cheeks (due to low cardiac output and peripheral vasoconstriction). Patients are often weak and cachexic. The pulse is of normal volume and regular in sinus rhythm. It is irregular when AF occurs. Absent peripheral pulse denotes possible embolic occlusion. The blood pressure is normal. In AF, average of three values of BP should be taken. The JVP shows prominent 'a' wave in sinus rhythm. 'a' wave is absent in AF.

On cardiac examination, the apical impulse is normal in position and tapping (due to loud S1) in character. Apex displaced down and out (LV apex) denotes associated MR or AR. In gross, RV enlargement apex is shifted out but not downward. The left parasternal impulse heave his present due to RVH. In second space, P2 is palpable and PA pulsations can be felt denoting pulmonary artery hypertension. On auscultation, the first heart sound is loud S1 in sinus rhythm. LA pressure is high and this causes mitral leaflets to be well recessed into LV cavity. With onset of systole, the LV pressure rises rapidly and the valve closes with wide closing excursion causing loud S1. S1 is varying in intensity in AF. A soft S1 denotes calcific MS or associated MR or AR. The second heart sound is normally split and loud P2 denotes PH. An opening snap (OS) is snappy, high frequency sound heard 40 to 120 ms after S2. During early diastole, the high LA pressure causes rapid, excursion of anterior mitral leaflet to fully open position. The tensing of leaflets in this open position causes OS. Absent OS denotes calcific or fibrosed non pliable MS. The murmur due to diastolic flow cross stenosed mitral valve is a mid diastolic murmur (MDM). It is a rough, rumbling, low-pitched murmur best appreciated at apex in expiration, with bell of stethoscope with patient in left lateral position. The MDM is accentuated by exercise, coughing, squatting, amyl nitrite inhalation and decreased by strain phase of Valsalva manoeuvre.

A presystolic murmur (accentuation of MDM) occurs due to LA contraction which increases flow in presystolic phase augmenting MDM in sinus rhythm. It is absent in AF although it can occur in AF during beats with short cycle length (Crile's hypothesis). The other causes of MDM at apex are a Carey Comb murmur (acute rheumatic fever valvulitis), Austin Flint murmur in aortic regurgitation and MDM due to left atrial myxoma. The other murmur often heard is a pansystolic murmur of TR that increases in intensity with inspiration and is best heard in the lower left sternal border.

Two factors help in assessing severity of MS, clinically. The shorter the A2-OS interval more severe is the stenosis. The duration of MDM is directly proportional to severity of MS. A MDM that occupies the entire diastole denotes severe stenosis. The pliability of the valve is assessed by the intensity and sharpness of S1 and presence of OS.

Complications and Natural History

The complication unrelated to severity of stenosis includes AF, embolism and infective endocarditis. Incidence of systemic embolism is 20% and risk factors include age, size of LA and AF. Other complication includes pulmonary hypertension and heart failure.

The time interval from rheumatic fever to development of MS is 15 to 20 years. It further takes 5 to 10 years to progress from NYHA class II to III or IV. In India, the latent period is short and severe symptomatic stenosis occurs as early as 6 to 12 years of age. MS occurring before 18 years is termed as juvenile MS. The MVOA decreases by 0.09 cm^2/year. Five-year survival rate is 64% in NYHA class III patient and only 15% in class IV.

Investigations

ECG and radiographic findings are shown in **Tables 3 and 4**.

Table 3: ECG Findings

ECG shows evidence of LA enlargement in the form of bifid 'P' waves in lead II and 'P' terminal force in V1 >0.04 mms (Morris index)
Rhythm may be sinus or atrial fibrillation
An R/S ratio >1 in V1 denotes right ventricular hypertrophy (RVH)
When QRS axis is >60°, MVOA is usually <1.3 cm^2 and extreme right axis denotes severe PH

Table 4: Radiological Abnormalities

LA enlargement: Double density, splaying of carina, straightening of left heart border
Pulmonary venous hypertension
Grade 1 – Prominent upper lobe veins
Grade 2 – Kerley B, A and C lines
Grade 3 – Bat wing appearance of pulmonary oedema
Pulmonary arterial hypertension: Dilated PA (>17 mm in men, >16 mm in women)
Pulmonary haemosiderosis
Cardiomegaly suggests associated MR or AR or tricuspid disease

Echocardiography

Echocardiography is the investigation of choice to diagnose MS. The salient findings are described in **Table 5**. Out of 98,302 echocardiogram done between 1st January, 2009 and 31st December 2009 at Sri Jayadeva Institute of Cardiovascular

Sciences and Research, Bangalore, 8.6% (8,512) were diagnosed with RHD. Of these, 8,512 echocardiograms predominant MS constituted 55%, predominant MR 22% and combined MS and MR about 18%.

Table 5: Echocardiographic Findings in MS

Diastolic doming of mitral valve with thickened leaflets and commissural fusion, resulting in fish mouth appearance
Reduced EF slope
Determine severity of MS by:
MVOA by planimetry and pressure half time
Mean gradient by pulsed wave Doppler across mitral valve
Calculation of PA pressure by TR jet gradient
Calcification, submitral fusion
LA enlargement (Manjunath *et al*)
Site and size of LA clot can be assessed
Assess other valvular lesion and ventricular function
Assess suitability for balloon mitral valvotomy (BMV) using Wilkin's score or Cormier classification

Treatment

Medical

Penicillin prophylaxis is indicated in all rheumatic MS patients atleast up to 40 years. Asymptomatic patients with mild to moderate MS require only regular follow-up. But symptomatic patients require the following:

1. Diuretics to reduce pulmonary venous hypertension. Frusemide (20 to 40 mg) in combination with spironolactone (25 to 50 mg) is the preferred combination.
2. Beta-blocker in low dose is indicated even in sinus rhythm, as it prevents tachycardia and hence sudden surge in LA pressure and provides symptomatic relief. Digoxin has no role in MS in sinus rhythm.
3. Oral anticoagulation in presence of AF.
4. Patients should avoid sport activities and heavy exertion.

Restoration to sinus rhythm is possible in patients with AF, only when LA size is <5.5 cms. Patient should be optimally anticoagulated for a period of 4 weeks and clot should be ruled-out before cardioversion. All AF patients require rate control with beta-blockers, calcium channel blockers and digoxin. The target heart rate is 60 to 80 beats/min at rest and <100 beats/min with mild exercise. Anticoagulation to achieve an INR of 2.0 to 3.0 is warranted.

Balloon mitral valvotomy

Balloon mitral valvotomy (BMV) in the procedure of choice when indicated. The indications are as under. BMV is indicated in patients with suitable valve morphology, when they are: (i) symptomatic (NYHA class II, III or IV) with moderate to severe MS; (ii) asymptomatic with severe MS with PA pressure > 50 mmHg at rest or > 60 mm Hg on exercise or new onset AF; (iii) MR less than moderate; and (iv) absence of LA thrombus

Mitral stenosis in pregnancy shows worsening of symptoms specially in second trimester due to fluid overload. These patients may need semi-urgent corrective BMV during pregnancy. Mitral restenosis occurs often (~60% to 70%) after 8 to 12 years. These patients require repeat procedures like BMV, CMV or valve replacement.

BMV is contraindicated in patients with (i) bicommisural calcification; (ii) densely calcified valve; (iii) more than moderate MR; (iv) specific types of LA clot; and (v) lack of expertise.

Complications of BMV include MR (15%, of which 2% require emergency surgery), cardiac tamponade (1% to 3%), stroke (1%) and residual ASD (5%). The overall mortality is about (0.5% to 1%). Data from national interventional council registry shows that in the year 2006; total of 7,221 BMVs were performed in India with a procedural success of 96%.

Mitral valve replacement

Mitral valve replacement is indicated in:

1. Symptomatic (NYHA class III or IV) patients with moderate to severe MS when BMV is contraindicated
2. Symptomatic (NYHA class I or II) with severe MS when PA pressure is > 60 mmHg if BMV is contraindicated
3. Other value requiring surgery.

Open mitral valvotomy is currently done only when the chest is opened for some other surgery, presence of left atrial clot or in Lutembacher's syndrome. Closed mitral valvotomy (CMV) was performed earlier. This has been replaced now with BMV.

MITRAL REGURGITATION

RHD is the commonest cause of mitral regurgitation (MR). Incidence of isolated rheumatic MR is 10%. MR may be acute or chronic based on the mode of onset.

Chronic Mitral Regurgitation

The aetiopathogenesis of chronic MR is listed in **Table 6**.

Table 6: Aetiopathogenesis of Chronic MR

RHD: Fibrosis, shortening and retraction of leaflets and subvalvular structures leads to non-coaptaton of leaflets
MVP: Redundant leaflets with interchordal hooding
Degenerative: Calcification causes loss of sphincteric action of annulus
DCM: Annular dilation
HCM: SAM of mitral valve and intrinsic abnormalities of valve
Connective tissue disorders: Valvulitis and vegetation
Congenital: Cleft AML in AV canal defect

DCM = Diloted cordiomyopathy; HCM = Hypertrophic cordiomyopothy; SAM = Systolic onterior motion.

Mitral regurgitation may be primary (valve disease) or secondary (functional). Secondary MR occurs in dilated cardiomyopathy or ischaemic heart disease.

Mitral valve prolapse (floppy mitral valve) is one of the more common causes of mild mitral regurgitation often seen in young women. It may be associated with Marfan's syndrome or connective tissue disorders. It may present with some benign arrhythmias (VPC's), atypical chest pain or small increased risk of stroke. It is characterised by mid systolic click and late systolic murmur. In some patients, chordal rupture can occur resulting in severe MR. These patients benefit from β-blockers.

Pathophysiology

During systole, the LV end-diastolic volume is ejected into aorta and LA. In chronic MR, LA is compliant; hence it accommodates the regurgitant volume without increase in LA pressure. As the

LA receives blood from both pulmonary veins and LV during systole, there is volume overload of LA. This increased volume of blood in LA is emptied into LV resulting in LV volume overload. As LV volume increases, LV dilation occurs. This, in turn, leads to mitral annular dilation and worsening of MR. Thus, a vicious cycle is established wherein 'MR begets MR'.

The increased LV preload (increased volume of blood from LA) and reduced afterload (decreased forward flow into aorta) coupled with eccentric hypertrophy of LV leads to supranormal ejection fraction (EF) (>60%) and normal cardiac output is maintained. This constitutes the compensated phase and patient may be asymptomatic for many years despite severe MR. Even a fall in EF to low normal levels (50% to 60%) denotes onset of LV dysfunction. This constitutes the decompensated phase and leads to progressive LV dysfunction and heart failure.

Giant LA (>65 mm) is a feature of chronic MR and it predisposes to AF. LA thrombus is less likely as compared to MS. Other complications of MR include infective endocarditis (IE), pulmonary arterial hypertension and heart failure.

Clinical Features

The predominant symptom of MR is chronic fatigue due to low cardiac output. Palpitations may be due to LV volume overload or AF. Unlike MS, dyspnoea is a late symptom of MR and denotes LV dysfunction, pulmonary hypertension or noncompliant LA.

The clinical findings are: the pulse is usually normal but may show a pseudo collapsing character (due to LV volume overload, increased volume of blood is pumped rapidly into aorta, giving a rapid upstroke to the pulse). It is generally regular since AF is less common in MR than in MS although these patients have larger LA. The blood pressure is usually normal. The JVP is unremarkable. On cardiac examination, the apical impulse is hyperdynamic and is shifted downwards and laterally. The parasternal impulse shows rocking motion of the precordium (LA enlargement causes late systolic pulsation in lower left sternal border). On palpation, LV apex and S3 may be there. Features of PAH are late and less prominent than in MS. On auscultation, S1 is soft (reduced leaflet excursion due to abnormal leaflets) and S2 widely split (due to early occurrence of A2, as LV systole is completed earlier). S3 is audible due to increased flow rate across mitral valve (denotes severe MR). A pansystolic, blowing, high-pitched murmur of uniform intensity is best heard at the apex and radiates to axilla (radiates to sternum if MR is due to posterior leaflet abnormality). The murmur does not vary in intensity following an ectopic beat because regurgitant volume is unchanged due to reduced regurgitant orifice area and increased regurgitant fraction. This helps in differentiating from aortic stenosis (AS) murmur. In dynamic auscultation, squatting and handgrip increase intensity of murmur and standing, Valsalva, exercise and amyl nitrite decrease the intensity of murmur. In some cases with severe MR, a soft MDM may be heard due to early rapid filling.

Clinically MR is considered severe, when:

1. Apex is hyperdynamic and shifted down and out
2. Presence of S3
3. Flow MDM at apex
4. Wide split S2

Intensity of PSM is not related to severity of MR.

Natural History

Mild-to-moderate MR remain asymptomatic for several years. Asymptomatic severe MR invariably progresses to symptoms or LV dysfunction within 10 years. The 5 and 10 year survival of symptomatic, severe MR is 30% and 10% respectively, without intervention. Annual mortality is about 6.3%.

Investigations

Electrocardiography and radiographic findings of MR are indicated in **Tables 7 and 8**.

Table 7: ECG Findings of MR

Normal
LA enlargement
Atrial fibrillation (AF)
LV hypertrophy (LVH) with volume overload pattern
Q waves in V5, V6

Table 8: CXR in MR

Cardiomegaly of LV type
LA enlargement (can be aneurysmal)
Evidence of pulmonary venous hypertension is rare. However, with onset of LV dysfunction, it is evident.

Echocardiography

Echocardiography is the investigation of choice to diagnose, assess severity and determine treatment options. Findings in MR are described in **Table 9**.

Table 9: Echocardiography in MR

Dilated LA and LV
Assess mitral apparatus for cause of MR
MR is severe when:
MR jet area to LA area >50%
Dense spectral pattern on Doppler
Vena contracta >6 mm
Large PISA (Proximal isovelocity surface area)
Systolic flow reversal in pulmonary vein
Assess PA pressure and ventricular function
EF <60% denotes LV dysfunction

Treatment

Medical

Penicillin prophylaxis is indicated up to 40 years of age. Infective endocarditis prophylaxis is not required. Asymptomatic patient with MR requires only regular follow-up. But symptomatic patient requires the following:

1. Diuretics, if pulmonary venous hypertension is present.
2. ACE-inhibitors are indicated, when EF is <60%.
3. AF requires cardioversion or rate control and anticoagulation.

Medical management has very little to offer for MR patients and surgery is the treatment of choice when warranted.

Surgery

Mitral valve repair is preferred over mitral valve replacement (MVR) when feasible. MVR is possible in: MVP MR, ischaemic MR, annular dilation, chordal rupture, leaflet perforation, and children with pliable valves. Rheumatic MR usually requires MVR rather than repair.

Indications of MVR/repair

1. NYHA class II, III or IV symptoms with severe MR
2. Asymptomatic patient with severe MR, when:
   - EF <60%
   - LV end systolic dimension >40 mm
   - PASP >50 at rest or >60 mm Hg on exercise
   - New onset AF

Two types of valves are used for replacement. Metallic valves and bioprosthetic valves. Metallic valves (bi-leaflet, e.g. St. Jude valve) require anticoagulation for lifelong, to keep INR between 2.5 and 3.0. These have longer life. The bioprosthetic valve do not require anticoagulation, however, these valves show dehiscence after 8 to 10 years. Choice of valve depends on age, education level and choice of patient.

MVR is not indicated in severe symptomatic MR when EF <30%, as the perioperative mortality exceeds conservative management.

Percutaneous mitral valve repair (PMVR) using MitraClip is a promising therapy for select subset of MR.

Acute Mitral Regurgitation

Acute MR is a cardiac emergency. The causes of acute MR are listed in **Table 10**.

Table 10: Aetiology of Acute MR

Acute coronary syndrome (papillary muscle dysfunction/rupture)
Infective endocarditis
Acute rheumatic carditis
Post-BMV
Trauma
Prosthetic valve dysfunction
Chordal rupture

Ischaemia of papillary muscles can cause acute MR. The anterolateral papillary muscle has dual blood supply from diagonal and obtuse marginal coronary branches and is less prone for ischaemia. The posteromedial papillary muscle is supplied only by PDA branch and is prone for ischaemia.

In acute MR, the LA is small, noncompliant and is unable to accommodate the regurgitant blood. So the LA pressure rises sharply and abruptly, resulting in acute pulmonary oedema and even cardiogenic shock. Most common symptom of acute MR is sudden onset of breathlessness. Unlike chronic MR, apical impulse is normal in character and the systolic MR murmur is shorter and ends well before A2. Normal LA and LV dimensions with severe MR on Doppler echocardiography suggest the diagnosis of acute MR.

Haemodynamic stabilisation is achieved with nitroprusside, inotropic support and intra-aortic balloon pump. Emergency mitral valve repair or replacement is the treatment of choice.

TRICUSPID STENOSIS

Tricuspid stenosis (TS) always occurs along with rheumatic MS. Rare cause of TS includes carcinod syndrome, IE, tumour and endomyocardial fibrosis. Clinically significant TS occur only in 5% of patients. Pathology of the valve is similar to MS except that calcification is uncommon. Presence of transtricuspid mean diastolic pressure gradient is the haemodynamic hallmark of TS.

Organic tricuspid valve disease should be suspected when right heart symptoms and signs dominate the clinical picture. Most common symptom of TS is fatigue due to reduced cardiac output. Symptoms of MS like dyspnoea and orthopnoea are characteristically absent. Gross ascites and pedal oedema are invariably present. JVP reveals prominent 'a' waves and slow 'y' descent. Absent parasternal heave with presystolic pulsatile, tender hepatomegaly suggests RV inflow obstruction. In addition to the auscultatory findings of mitral valve disease, an opening snap and a crescendo-decrescendo mid-diastolic murmur at lower left sternal border, which increases on inspiration, are present.

ECG and radiograph reveal RA enlargement. Radiographic findings of pulmonary venous hypertension are rare. The echocardiograph shows diastolic doming of tricuspid valve. A mean tricuspid gradient of >2 mm Hg confirms the diagnosis of TS and a gradient >5 mm Hg denotes severe TS.

Judicious use of two or more diuretics that have different mechanism of action with intensive salt restriction is required to treat the pedal oedema and ascites. Percutaneous transvenous tricuspid commisurotomy can be done where feasible. Alternatively, open valvotomy can be done at the time of surgery for the other valvular lesions. Rarely, valve replacement with bioprosthetic valve may be required for optimal outcomes.

TRICUSPID REGURGITATION

Tricuspid regurgitation (TR) may be classified as: primary TR – intrinsic abnormality of valve, and secondary TR – dilation of RV and tricuspid annulus causes TR.

Secondary or functional TR is the most common type and is usually due to left heart disease. Most common cause of primary TR is RHD. Other causes include IE, carcinoid syndrome, Ebstein's anomaly, tricuspid valve prolapse or drugs. *Staphylococcus aureus* endocarditis and IE in intravenous drug abusers are notorious for developing TR.

Clinically, patients present with fatigue, ascites and pedal oedema. JVP is elevated with prominent 'C-V' waves. Tender systolic pulsations of liver may be appreciated. In secondary TR, a PSM that increases in intensity with inspiration is heard in lower left sternal border, whereas, in organic TR, the murmur is low in intensity and occupies only first half of systole. Other corroborative evidence of pulmonary hypertension like parasternal heave, loud P2, pulmonary ejection systolic murmur, ejection click or Graham Steell murmur may be present in secondary TR.

ECG shows RA enlargement. Radiograph shows RV type of cardiomegaly with gross RA enlargement. Echocardiography is useful to assess the severity and aetiology of TR. If the pulmonary artery systolic pressure exceeds 55 mm Hg, then TR is likely to be secondary.

Aggressive diuretic therapy is needed to reduce oedema. Secondary TR requires appropriate treatment for underlying disease. If the tricuspid annulus exceeds 21 mm/m^2, then tricuspid annuloplasty (Ring or De Vegas annuloplasty) is a must

to relieve symptoms and this can be done during surgery for other valves.

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12.14 Valvular Heart Disease (II)

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AORTIC STENOSIS

Aetiology

The three common causes of aortic stenosis (AS) are congenital, rheumatic and degenerative. It is seen in patients who are 35 years or older and results from calcification of a congenital or rheumatic valve or of a normal valve that has undergone 'degenerative' changes. Rare causes of AS include obstructive infective vegetations, homozygous type II hyperlipoproteinaemia, Paget's disease of bone, rheumatoid disease, ochronosis, and irradiation.

Pathophysiology

AS can be mild, moderate or severe depending on the constriction and calcification of aortic valve. This causes pressure overload on the left ventricle leading to concentric LV hypertrophy, keeping the cardiac output in the normal range (**Table 1**).

Table 1: Severity of Aortic Stenosis According to Valve Area and Consequent Gradient Across Valve and Echo Doppler Jet Velocity

	Valve Area (cm^2)	Gradient (mm Hg)	Doppler Jet Velocity (m/sec)
Mild	>1.5	<25	<3
Moderate	1 to 1.5	25 to 40	3 to 4
Severe	<1.0	>40	>4

As the severity of AS increases, cardiac output remains within the normal range at rest but fails to increase in proportion to the amount of exercise performed or does not increase at all. Eventually left ventricular failure occurs giving rise to pulmonary hypertension and right-sided heart failure (**Figure 1**).

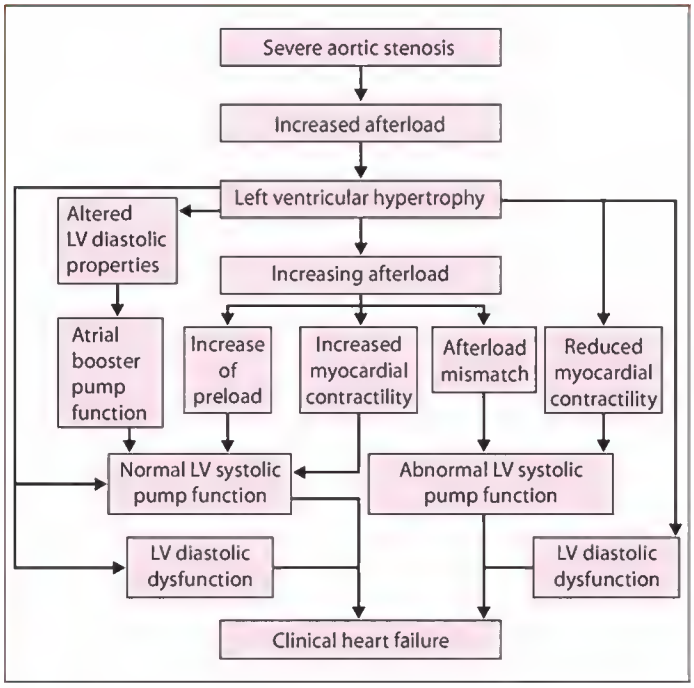


Figure 1: Pathophysiology of aortic stenosis.

Clinical Features

History

Most patients with valvular AS are asymptomatic. The symptoms of AS are angina pectoris, syncope, exertional presyncope, dyspnoea (on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, pulmonary oedema), and the symptoms of heart failure. Sudden cardiac death is stated to occur in 5% of patients with AS. It occurs only in those with severe valve stenosis. Typical angina pectoris occurs with or without associated CAD. Exertional syncope occurring on effort is caused by either systemic vasodilatation in the presence of a fixed or inadequate cardiac output, an arrhythmia, or both. Dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, and pulmonary oedema result from varying degrees of pulmonary venous hypertension. Systemic venous congestion is rather a late phenomenon with enlargement of the liver and peripheral oedema results from increased systemic venous pressure and salt and water retention. There is an increased incidence of gastrointestinal arteriovenous malformations, also known as Heyde syndrome. As a result, these patients are susceptible to gastrointestinal haemorrhage and anaemia. Bleeding can be caused by an acquired defect in the structure of von Willebrand factor. Calcific systemic embolism may occur.

Physical examination

The arterial pulse is slow rising and late peaking (parvus et tardus). A systolic thrill may be felt in the carotid arteries. The jugular venous pulse and the heart size are normal in absence of heart failure. The cardiac impulse is heaving and sustained in character with the presence of palpable S4. The S2 may be single since A2 and P2 are superimposed or A2 is absent or soft. It may be paradoxically split because of late A2. A systolic ejection sound is often present in young patients with valvular AS and patients with bicuspid AV.

An aortic systolic thrill is often present at the base of the heart. The turbulent flow across stenotic aortic valve causes a mid-systolic ejection murmur that peaks late in systole. In older patients, the systolic ejection murmur may be heard only at the apex of the heart (Gallavardin phenomenon). The intensity of the systolic murmur varies from beat to beat. This characteristic is helpful in differentiating AS from MR, in which the murmur is usually unaffected. The murmur of valvular AS is augmented by squatting, which increases stroke volume. It is reduced in intensity during the strain of the Valsalva manoeuvre and when standing.

Severe AS is indicated by slow rising pulse, presence of S4, paradoxical splitting of S2 and late peaking systolic ejection murmur. In the presence of heart failure, the jugular venous

pressure is often increased, the LV is dilated, a third heart sound is present, and the systolic murmur may be very soft or absent. Physical findings are summarised according to severity in **Table 2**.

Table 2: Physical Findings with Varying Severity of Aortic Valve Stenosis

	Mild AS	Moderate AS	Severe AS + Normal LV Function	Severe AS + LV Dysfunction	Severe AS + Heart Failure[a]
Arterial pulse	Normal	Slowly rising	*Parvus et tardus*	*Parvus et tardus*	Small volume
Jugular venous pulse	Normal	Normal	Normal	Normal	±
Carotid thrill	±	±	±	±	±
Cardiac impulse	Normal	Heaving	Heaving, sustained palpable 'a' wave	Heaving	Heaving or reduced
Precordial thrill	±	±	Usually ++	±	–
Auscultation					
S4	–	±	+	+	–
S3	–	–	–	±	+
ESS	+	±	–	–	–
Peak of ESM	Early systole	Mid systole	Late systole	Late to midsystole, soft	Mid systole, soft or absent
S2	Normal	Normal or single	Single or paradoxical	Single	Single

Investigations

The ECG, chest radiograph and echocardiography are baseline investigations required before these patients management plan can be made. The salient features of these investigations in aortic stenosis are shown in **Tables 3 to 5**.

Table 3: ECG Findings

Left ventricular hypertrophy with or without secondary ST-T wave changes. (Pressure overload pattern – ST depression and T wave inversion in lateral leads)

LA enlargement/hypertrophy

Sometimes shows conduction delay, left bundle branch block.

Heart blocks (calcification) can occur rarely

Atrial fibrillation indicates associated mitral disease or heart failure

Table 4: Radiological Abnormalities

Normal sized heart

Dilated proximal ascending aorta (post-stenotic dilation)

Calcification of aortic valve (better seen on fluoroscopy). Calcification does not mean severe AS

Late stages heart size large with pulmonary venous hypertension

Table 5: Echocardiography

Valve thickening and doming on 2D and gradient across valve on CW Doppler

All severe AS in adults will be calcified

Allows definition of valve anatomy, cause of AS, calcification and assessment of severity of AS

Left ventricular hypertrophy, systolic functions (ejection fraction) can be evaluated

Assessment of aortic root dilatation and associated mitral valve disease

Chest X-ray

Cardiac catheterisation and angiography

The main indication for cardiac catheterisation and angiography is to look for associated CAD in these patients before surgery. Otherwise, the lesion can be assessed and followed-up with echocardiography. The gradient on cardiac catheterisation is seen by measuring simultaneous LV and ascending aortic pressures. Cardiac output can be measured by either the Fick principle or the indicator dilution technique.

Natural History

The natural history of AS in the adult consists of a prolonged latent period. Once moderate stenosis is present (jet velocity >3 m/s), the average rate of progression is an increase in jet velocity of 0.3 m/s per year, an increase in mean pressure gradient of 7 mm Hg per year, and a decrease in valve area of 0.1 cm^2 per year. Eventually, symptoms of angina, syncope, or heart failure develop and the outlook changes dramatically. After the onset of symptoms, average survival is 2 to 3 years, with a high-risk of sudden death.

Management

Medical treatment

Patients with severe AS should be cautioned to avoid vigorous athletic and physical activity. Exercise stress testing should be absolutely avoided in symptomatic patients. Symptomatic patients with severe AS are usually operative candidates because medical therapy has little to offer. However, medical therapy may be necessary in patients who are considered to be inoperable (usually because of comorbid conditions that preclude surgery). Diuretics must be used with caution because hypovolaemia may reduce the elevated LV end-diastolic pressure, lower cardiac output, and produce orthostatic hypotension. ACE inhibitors should be used with caution but are beneficial in treating patients with symptomatic LV systolic dysfunction who are not candidates for surgery. Beta-adrenergic blockers can depress myocardial function and induce LV failure and should be avoided in patients with AS. AF should be treated promptly (**Table 6**).

Surgical treatment

Children: In the adolescent or young adult with severe congenital AS, balloon aortic valvotomy is recommended in all symptomatic patients and in asymptomatic patients with a transvalvular gradient greater than 60 mm Hg or in those with ECG showing ST changes at rest or with exercise. The same indications are appropriate for surgical intervention, although balloon valvotomy is probably preferable at experienced centres.

Adults: Aortic valve replacement (AVR) is the treatment of choice for patients of severe AS. AVR is indicated for symptomatic patients with severe AS, patients with severe AS undergoing coronary artery bypass graft surgery (CABG), patients with severe AS undergoing surgery on the aorta or other heart valves, and patients with severe AS and LV systolic dysfunction (ejection fraction less than 0.50).

Table 6: Medical Treatment of Patients with Aortic Valve Stenosis

Antibiotic prophylaxis
Infective endocarditis
Recurrent rheumatic carditis
Restriction of activities
Severe exercise
Competitive sports
Arrhythmias
Prevent and/or control
Restore sinus rhythm, if possible
Cardiac medications (only if essential)
Avoid negative inotropic and proarrhythmic agents if possible
Diuretics – use cautiously
Arteriolar and venodilators – use cautiously
Follow-up of asymptomatic patients
Mild aortic stenosis: every 2 to 5 years
Moderate aortic stenosis: every 6 to 12 months
Develop symptoms: immediate

AORTIC REGURGITATION

Aetiology

Aortic regurgitation (AR) can result from disease of the aortic valve (aortic cusp) and due to dilatation of aortic root. Physical findings can help differentiate between these although echocardiography is required for this. Generally, AR is chronic in most conditions. However, acute AR can be seen in infective endocarditis, aortic dissection and during acute rheumatic fever (Table 7).

Table 7: Aetiology of Chronic Aortic Valve Regurgitation

Aortic root dilatation
Hypertension with aortic root dilatation, atherosclerosis
Various forms of aortitis and arteritis, e.g. giant cell arteritis and Takayasu disease, syphilis
Connective tissue disease, e.g. Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome
Autoimmune diseases, e.g. ankylosing spondylitis, rheumatoid arthritis, and systemic lupus erythematosus
Congenital lesions, e.g. supravalvular or discrete subvalvular aortic stenosis, ventricular septal defect, and aneurysm of the sinus of Valsalva
Aortic valve diseases
Congenital bicuspid valve
Rheumatic heart disease
Previous infective endocarditis

Pathophysiology

Acute AR results in severe volume overload of left ventricle with resultant pulmonary congestion as LV chamber is small and LV and LA pressures are increased markedly. There is a fall in cardiac output due to decrease in stroke volume.

In contrast, in cases of chronic aortic regurgitation eccentric cardiac hypertrophy with the increased preload allows a large increase in LV end-diastolic volume. The large total stroke volume allows forward stroke volume to be normal despite a large regurgitant volume. The large total stroke volume along with the wide pulse pressure produces most of the physical signs of aortic regurgitation. The combined pressure and volume overload stimulates the development of both concentric and eccentric hypertrophy. After many years, LV dysfunction eventually develops, with further LV dilation, elevation of LV filling pressure, decreased EF, and reduced total and forward stroke volume.

Natural History

The rate of progression to symptoms and/or LV systolic dysfunction is about 4.3% per year in asymptomatic patients of severe AR. Sudden death occurs at the rate of less than 0.2% per year in this subgroup of patients. The average rate of symptom onset in patients with depressed LV function is greater than 25% per year. Mortality rates of greater than 10% per year have been reported in patients with angina pectoris and greater than 20% per year in those with heart failure.

Clinical Features

History

Patients with aortic regurgitation in the chronic compensated phase are often entirely asymptomatic. As LV decompensation proceeds, symptoms of dyspnoea, palpitations, orthopnoea, and in advanced cases, paroxysmal nocturnal dyspnoea and peripheral oedema occur. Nocturnal angina occurs due to bradycardia and increased AR with reduced aortic diastolic pressure leading to diminished coronary perfusion.

Physical examination

In patients with chronic, severe AR, the head frequently bobs with each heartbeat (de Musset sign), and the pulses are of the 'water-hammer' or collapsing type with abrupt distention and quick collapse (Corrigan pulse). A bisferiens pulse may be present and is more readily recognised in the brachial and femoral arteries than in the carotid arteries. Traube sign (also known as 'pistol shot sounds') refers to booming systolic and diastolic sounds heard over the femoral artery; Müller sign consists of systolic pulsations of the uvula; and Duroziez sign consists of a systolic murmur heard over the femoral artery when it is compressed proximally and a diastolic murmur when it is compressed distally. Capillary pulsations (i.e. Quincke sign) can be detected by pressing a glass slide on the patient's lip, by transmitting a light through the patient's fingertips, or by exerting gentle pressure on the tip of a fingernail.

Systolic arterial pressure is elevated, and diastolic pressure is abnormally low. Hill sign refers to popliteal cuff systolic pressure exceeding brachial cuff pressure by more than 60 mm Hg. Korotkoff sounds often persist to zero even though intraarterial pressure rarely falls below 30 mm Hg. The point of change in Korotkoff sounds (i.e. the muffling of these sounds in phase IV) correlates with the diastolic pressure.

The apical impulse is diffuse and hyperdynamic and is displaced laterally and inferiorly. The augmented stroke volume may create a systolic thrill at the base of the heart or suprasternal notch, and over the carotid arteries. The PR interval may be prolonged, causing a soft S1. A2 may be normal or accentuated when AR is due to disease of the aortic root but is soft or absent when the valve is causing AR. P2 may be obscured by the early diastolic murmur. Thus, S2 may be absent or single or exhibit narrow or paradoxical splitting. A systolic ejection sound, presumably related to abrupt distention of the aorta by the augmented stroke volume, is frequently audible. S3 gallop correlates with an increased LV end-diastolic volume. Its development may be a sign of impaired LV function, which is useful in identifying patients with severe AR who are candidates for surgical treatment.

The aortic regurgitant murmur, the principal physical finding of AR, is one of high frequency that begins immediately after A2. The murmur is heard best with the diaphragm of the stethoscope while the patient is sitting up and leaning forward, with the breath held in deep exhalation. The severity of AR correlates better with the duration than with the intensity of the murmur. When the murmur is musical ('cooing dove' murmur), it usually signifies eversion or perforation of an aortic cusp. In patients with severe AR and LV decompensation, equilibration of aortic and LV pressures in late diastole abolishes the late diastolic component of the regurgitant murmur. When regurgitation is caused by primary valvular disease, the diastolic murmur is heard best along the left sternal border in the 3rd and 4th intercostal spaces. However, when it is caused mainly by dilation of the ascending aorta, the murmur is often more readily audible along the right sternal border. Many patients with chronic AR have a harsh systolic outflow murmur caused by the increased total LV stroke volume and ejection rate. A mid-diastolic and late diastolic apical rumble, the Austin Flint murmur, is common in severe AR and may occur in the presence of a normal mitral valve. This murmur appears to be created by rapid antegrade flow across a mitral orifice that is narrowed by the rapidly rising LV diastolic pressure caused by severe aortic reflux impinging on the anterior leaflet of the mitral valve. The Austin Flint murmur may be difficult to differentiate from that caused by mitral stenosis (MS), but the presence of an opening snap and a loud S1 in MS and the absence of these findings in AR are helpful clues. As the LV end-diastolic pressure rises, the Austin Flint murmur commences and terminates earlier.

The diastolic murmur of AR may be accentuated when the patient sits up and leans forward or by interventions that raise the arterial pressure, such as squatting or isometric exercise. The intensity of the murmur is reduced by interventions that lower the systolic pressure, such as inhalation of amyl nitrite or the strain of the Valsalva manoeuvre. The Austin Flint murmur, like the murmur of AR, is augmented by isometric exercise and administration of vasopressors and is reduced by amyl nitrite inhalation.

In sharp contrast to the patients with chronic AR patients with acute, severe AR appear gravely ill, with tachycardia, severe peripheral vasoconstriction and cyanosis, and sometimes with pulmonary congestion and oedema. The peripheral signs of AR are often not impressive and certainly not as dramatic as in patients with chronic AR. The normal or only slightly widened pulse pressure may lead to serious underestimation of the severity of the valvular lesion. The LV impulse is normal. S1 may be soft or absent because of premature closure of the mitral valve. Closure of the mitral valve may be incomplete, and diastolic MR may occur. Evidence of pulmonary hypertension, with an accentuated P2, S3, and S4, is frequently present.

The early diastolic murmur of acute AR is lower pitched and shorter than that of chronic AR. The Austin Flint murmur is often present, but is brief and ceases when LV pressure exceeds left atrial pressure in diastole. With premature diastolic closure of the mitral valve, the presystolic portion of the Austin Flint murmur is eliminated (**Table 8**).

Table 8: Physical Findings with Varying Severity of Chronic Aortic Valve Regurgitation

	Mild AR	Moderate AR	Severe AR	Severe AR + Left Ventricular Systolic Dysfunction	Severe AR + Heart Failure + Left Ventricular Systolic Dysfunction
Arterial pulse	Normal	Corrigan + to ++	Corrigan +++	Corrigan ++	Corrigan +
Arterial pressure					
Systolic	Normal	Increased + to ++	Increased +++	Increased ++	Normal +
Diastolic	Normal	Decreased + to ++	Decreased +++ to ++++	Decreased ++ to +++	Decreased +
Pulse pressure	Often normal	Increased + to ++	Increased +++ to ++++	Increased ++ to +++	Increased +
Cardiac impulse	Often normal	Hyperdynamic	Very hyperdynamic visible ± chest may rock	Hyperdynamic	May be hypodynamic
Precordial thrill					
Systolic	–	±	±	±	–
Diastolic	–	–	±	±	–
Auscultation					
S4	–	–	–	–	–
S1	Normal	Often soft	Soft	Soft	Soft
S2	Normal	Normal or single	Often single	Often single	Often single
S3	–	+	++ to +++	+++	+++
ESM	±	+	+ to ++	+ to ++	+
AoDM	+	++	+++ to ++++	++ to +++	+ to ++
Austin Flint murmur	–	–	±	–	–

Investigations

ECG, chest radiograph and echocardiography are baseline investigations (**Tables 9 to 11**). These reveal features of LV dilatation and volume overload which are the hallmark of chronic aortic regurgitation.

Table 9: ECG Findings

Left axis deviation with left ventricular hypertrophy of volume overload, pattern (prominent Q waves in leads I, aVL, and V3 through V6)

Tall and upright T-waves. Later on inverted T-wave, with ST-segment depressions

Intraventricular conduction defects occur late in the course and are usually associated with LV dysfunction

Table 10: Radiological Abnormalities

Marked enlargement of cardiac shadow

Calcification of the aortic valve uncommon

Dilation of the ascending aorta (more than in AS)

Severe aneurysmal dilation of the aorta suggests aortic root disease (Marfan syndrome, cystic medial necrosis, or annuloaortic ectasia)

Linear calcifications in the wall of the ascending aorta – syphilitic aortitis

Acute AR: less cardiac dilatation and more pulmonary venous hypertension

Table 11: Echocardiography

Transthoracic echocardiography: measurement of LV end-diastolic and end-systolic dimensions and volumes, ejection fraction, and mass. Serial measurements for follow-up

High-frequency fluttering of the anterior leaflet of the mitral valve during diastole

Doppler echocardiography and colour flow Doppler imaging are the most sensitive and accurate non-invasive techniques in the diagnosis and evaluation of AR

AR can be quantified into mild, moderate, and severe AR on above basis

LV size and ejection fraction are normal

Cardiac catheterisation and angiography

Cardiac catheterisation is undertaken when the severity of AR is not clear on non-invasive evaluation. The indications for selective coronary angiography are the same as for aortic stenosis.

Management

Medical treatment

Majority of patients with AR are not candidates for prophylaxis. Patients with mild or moderate AR should be followed clinically and by echocardiography. Asymptomatic patients with chronic, severe AR and normal LV function should be examined at intervals of approximately 6 months. Patients with AR who have limitations of cardiac reserve and/or evidence of declining LV function should avoid heavy exertion. Systemic arterial diastolic hypertension should be treated because it increases the regurgitant flow; vasodilating agents such as nifedipine or ACE-inhibitors are preferred and beta-blocking agents should be used with great caution. AF and bradyarrhythmias are poorly tolerated and should be prevented, if possible.

Vasodilator therapy

There is considerable uncertainty regarding vasodilator therapy. Short-term studies spanning 6 months to 2 years have demonstrated beneficial haemodynamic effects of oral hydralazine, nifedipine, felodipine, and ACE-inhibitors. But, in view of conflicting data, definitive recommendations regarding the indications for long-acting nifedipine or ACE-inhibitors are not possible.

Surgery: Indications

AVR is the treatment of choice in symptomatic patients. Chronic medical therapy may be necessary in some patients who refuse surgery or are considered to be inoperable because of co-morbid conditions. These patients should receive an aggressive heart failure regimen with ACE-inhibitors (and perhaps nitrates), digoxin, diuretics, and salt restriction, but beta-blockers should be avoided. In patients who are candidates for surgery but who have severely decompensated LV function, vasodilator therapy may be particularly helpful in stabilising patients while preparing for operation. Such patients also respond, at least temporarily, to treatment with digitalis glycosides, salt restriction, and diuretics.

AVR is indicated for following patients with AR:

1. Symptomatic patients with severe AR.
2. Asymptomatic patients with chronic severe AR and LV systolic dysfunction (ejection fraction 0.50 or less) at rest.
3. Patients with chronic severe AR while undergoing CABG or surgery on the aorta or other heart valves.
4. Asymptomatic patients with severe AR with normal LV systolic function (ejection fraction greater than 0.50) but with severe LV dilatation (end-diastolic dimension greater than 75 mm Hg or end-systolic dimension greater than 55 mm Hg).

PULMONARY VALVE DISEASE: VALVULAR PULMONIC STENOSIS

Aetiology

Diseases of pulmonary valve (PV) are more often congenital in origin. There are 3 morphological types of congenital pulmonary stenosis (PS): (i) typical dome-shaped PV; (ii) dysplastic PV; and (iii) unicuspid or bicuspid PV.

Pulmonary valve disease as an acquired condition in the adult is extremely rare and may be seen in rheumatic fever, bacterial endocarditis, carcinoid heart disease, etc.

Pathophysiology

PS increases RV afterload and causes right ventricular hypertrophy. Right ventricular hypertrophy under usual circumstances maintains normal pulmonary blood flow. When the normal output is not maintained, right ventricular failure ensues. This occurs in two instances: in neonates with critical PS and in patients with severe PS later in childhood or adulthood. With increased right ventricular systolic pressure, RV compliance decreases and resulting increased right atrial pressure may cause right to left shunt through patent foramen ovale.

Natural History

Adult patients with mild valvular PS do not progress. Moderate PS can progress in 20% of unoperated patients and may require intervention. Patients with severe PS will have had balloon or surgical valvotomy to survive to adult life. Long-term survival in patients with repaired pulmonary valve stenosis is similar to that of the general population, with excellent to good functional class at long-term follow-up in most patients.

Clinical Features

History

Many patients with PS are asymptomatic when first seen. With severe PS, RV hypertrophy develops, and symptoms of dyspnoea, fatigue, chest pain, palpitations, presyncope, and decreased exercise tolerance may occur. If the right atrial (RA) pressure increases, features of right heart failure are present and the opening of a patent foramen ovale may occur along with cyanosis.

Physical examination

Most adult patients with PV or other RVOT obstructive lesions are normal in appearance, although certain phenotypical syndromes occur that include valvular, branch, or peripheral PS. These include the rubella syndrome, Noonan syndrome (60% have a dysplastic valve), Alagille syndrome, Williams syndrome and Keutel syndrome.

Physical examination may reveal a prominent jugular A wave, a right ventricular lift, and possibly a thrill in the 2nd left intercostal space. Auscultation reveals a normal S1, a single or split S2 with a diminished P2 (unless the obstruction is supravalvular, in which case the intensity of the P2 is normal or increased), and a systolic ejection murmur best heard in the 2nd left intercostal space. When the pulmonary valve is thin and pliable, a systolic ejection click will be heard which decreases on inspiration. As the severity of the pulmonary stenosis progresses, the interval between S1 and the systolic ejection click becomes shorter, S2 becomes widely split, P2 diminishes or disappears, and the systolic ejection murmur lengthens and peaks later in systole, often extending beyond A2. An ejection click seldom occurs with dysplastic pulmonary stenosis. Signs of right heart failure are present in advanced stages (**Table 12**).

Investigations

Electrocardiogram

With pulmonary valve stenosis, the electrocardiogram reflects the haemodynamic severity of the lesion. With severe pulmonary stenosis, the electrocardiogram shows right axis deviation and right ventricular hypertrophy with a qR wave in the V_1 lead. With moderately severe pulmonary stenosis, there is an rSR' in the V_1 lead. With severe right ventricular hypertrophy, peaked P waves in the II, III, and aVF leads reflect right atrial abnormality.

Chest radiograph

With severe pulmonary stenosis, right ventricular hypertrophy is manifested by lifting of the apex off the left hemidiaphragm and filling in of the retrosternal space in the lateral chest radiograph. The heart size on chest radiograph is usually normal unless there is RV failure or an associated cardiac lesion. Dilatation of the main and left pulmonary artery is common in doming but not in dysplastic PS or in subpulmonic stenosis. Calcification may be seen in older patients. The RA and RV may be enlarged if there is RV decompensation.

Echocardiography

The echocardiogram is generally definitive. A Doppler gradient is evident, the valve mobility can be assessed along with subpulmonic or supravalvular stenosis, the size and function of the RV can be determined and any vegetation on pulmonary valve can be assessed. Continuous, pulsed, and colour-flow Doppler confirm any pulmonary regurgitation, tricuspid regurgitation, or right-to-left shunting. Saline microcavitations can also confirm a right-to-left shunt. When the PS is severe, interventricular septal flattening may occur. In patients with a dysplastic valve, the valve is thickened and immobile, and there is lack of a dilated pulmonary main trunk. With carcinoid involvement of the pulmonary valve, thickening and lack of flexibility can be seen.

Table 12: Parameters for Severity of Pulmonary Stenosis

Haemodynamic Evaluation: Degree of Obstruction	Haemodynamic Evaluation: Peak Systolic Doppler Gradient (mm Hg)	Haemodynamic Evaluation: RV Systolic Pressure (mm Hg)	Physical Examination
Trivial	<25	<50	—
Mild	25 to 49	50 to 74	**Jugular venous pressure:** Normal except mildly increased 'a' wave **RV palpation:** No RV lift **Auscultation:** Ejection sound present (decreases with inspiration: systolic ejection murmur increases with inspiration and ends in midsystole) generally grade 3/6 or less
Moderate	50 to 79	75 to 100	**Jugular venous pressure:** Elevated; 'c-v' wave if present
Severe	>80	>100	Increased 'a' wave **RV palpation:** RV lift; generally no impulse over PA; thrill may be present **Auscultation:** No ejection sound; prolonged RV outflow tract systolic ejection murmur with no P2 or wide split of second sound if P2 present; murmur often 3-6/6 in intensity; right-sided S4

Cardiac catheterisation and angiography

Cardiac catheterisation is rarely necessary for diagnosis. Gradients above, at, and below the PV should be obtained. A peak RV systolic value of <35 mm Hg and a systolic PV gradient of <10 mm Hg are the upper limits of normal. RV function can be assessed, and shunting through any patent foramen ovale can be defined. RV angiography helps to define contractile function, the presence of infundibular obstruction, and the mobility of the PV. Pulmonary angiography assesses the degree of PR and any stenotic lesions in the main, branch, or peripheral pulmonary arteries.

Management

No intervention is required in mild PS. With severe PS, right ventricular failure most commonly occurs after the fourth decade of life. With severe pulmonary valve stenosis, surgical repair in the past has given good long-term results. At present, balloon valvotomy is the treatment of choice, even in the adult with congenital pulmonary valve stenosis. Immediate and intermediate results are similar to those of surgery. Following are the recommendations regarding percutaneous or surgical intervention in patients with valvular pulmonary stenosis:

1. Balloon valvotomy is recommended for asymptomatic patients with a domed pulmonary valve and a peak gradient greater than 60 mm Hg or a mean gradient greater than 40 mm Hg (in association with less than moderate pulmonic valve regurgitation).
2. Balloon valvotomy is recommended for symptomatic patients with a domed pulmonary valve and a peak gradient greater than 50 mm Hg or a mean gradient greater than 30 mm Hg (in association with less than moderate pulmonic regurgitation).
3. Surgical therapy is recommended for patients with severe PS and an associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular PS, or supravalvular PS.

PULMONARY REGURGITATION

Aetiology

By far, the most common cause of pulmonic regurgitation (PR) is dilation of the valve ring secondary to pulmonary hypertension (of any aetiology) or to dilation of the pulmonary artery, either idiopathic or consequent to a connective tissue disorder such as the Marfan's syndrome. The second most common cause of PR is infective endocarditis. Less frequently, PR is iatrogenic and is induced at the time of surgical treatment of congenital PS or tetralogy of Fallot. Less common causes include trauma, carcinoid syndrome, rheumatic involvement, injury produced by a pulmonary artery flow-directed catheter, syphilis, and chest trauma.

Pathophysiology

In pulmonary valve regurgitation, there is a volume overload of the right ventricle, resulting in dilatation of the right ventricle and, eventually, eccentric right ventricular hypertrophy. With the increased right ventricular stroke volume, there is dilatation of the proximal pulmonary arteries. In the absence of pulmonary hypertension, even severe volume overload of the right ventricle is well-tolerated for many years; however, the prognosis is not entirely benign, because right ventricular dysfunction and right heart failure can occur.

With pulmonary hypertension, the patient has right ventricular hypertrophy, and pulmonary regurgitation occurs with dilatation of the pulmonary valve annulus. The degree of pulmonary regurgitation is usually not severe and is rarely haemodynamically significant. Right ventricular dilatation and dysfunction leading to right ventricular failure are more frequent in these patients as a result of the right ventricular systolic overload rather than as a result of the pulmonary regurgitation.

Clinical Features

History

Patients with pulmonary hypertension have symptoms related to the cause of the pulmonary hypertension. Patients with PR owing to endocarditis have symptoms related to the infection such as fever, left heart failure if the mitral or aortic valve is infected, or septic pulmonary emboli with an infected tricuspid valve. When the patient has PR due to carcinoid tumour, the symptoms are dominated by those seen with metastatic carcinoid tumour.

Isolated PR causes RV volume overload and may be tolerated for many years without difficulty unless it complicates, or is complicated by, pulmonary hypertension.

Physical examination

The physical findings in isolated PR are those of a prominent right ventricular anterior precordial lift, frequently with a lift in the second left interspace that is caused by the dilated pulmonary artery. There is also a diastolic murmur along the left sternal border in the second and third interspaces. With isolated pulmonary valve regurgitation, this murmur starts 0.04 to 0.06 seconds after the aortic second sound and is characteristically short and low-pitched.

If pulmonary hypertension is present, the second heart sound is single and accentuated, and the diastolic murmur starts with P2 and is high-pitched and decrescendo in character. This is called the Graham-Steell murmur.

If the pulmonary regurgitant volume is large, an early peaking systolic ejection murmur ending before the second heart sound may be heard and can be grade 3 to 4/6 in loudness.

Investigation

Electrocardiogram

In the absence of pulmonary hypertension, PR often results in an ECG that reflects RV diastolic overload, i.e. an rSr (or rsR) configuration in the right precordial leads. PR secondary to pulmonary hypertension is usually associated with ECG evidence of RV hypertrophy.

Chest radiograph

Both the pulmonary artery and the right ventricle are usually enlarged, but these signs are nonspecific.

Echocardiography

Two-dimensional echocardiography shows RV dilation and in patients with pulmonary hypertension, RV hypertrophy as well. RV function can be evaluated. Abnormal motion of the septum

characteristic of volume overload of the right ventricle in diastole and/or septal flutter may be evident. The motion of the pulmonic valve may point to the cause of the PR. Doppler echocardiography is extremely accurate in detecting PR and in helping to estimate its severity.

Management

PR alone is seldom severe enough to require specific treatment. Treatment of the primary condition, such as infective endocarditis, or the lesion responsible for the pulmonary hypertension, such as surgery for mitral valvular disease, often ameliorates the PR. Surgical treatment directed specifically at the pulmonic valve, such as patients with severe PR caused by surgical correction of tetralogy of Fallot, is required only occasionally because of intractable right heart failure. Under such circumstances, valve replacement may be carried out, preferably with a porcine bioprosthesis or a pulmonary allograft.

MULTIVALVULAR DISEASE

Multivalvular involvement is caused frequently by rheumatic fever, myxomatous heart disease, Marfan's syndrome and other connective tissue disorders. Degenerative calcification of the aortic valve may be associated with degenerative mitral annular calcification and cause AS and MR. Different pathological conditions may affect two valves in the same patient, such as infective endocarditis on the aortic valve causing AR and ischaemia causing MR.

In patients with multivalvular disease, the clinical manifestations depend on the relative severities of each of the lesions. Usually, the proximal lesion tends to mask the distal lesion.

It is important to recognise multivalvular involvement preoperatively because failure to correct all significant valvular disease at the time of operation increases mortality considerably. In patients with multivalvular disease, the relative severity of each lesion may be difficult to estimate by clinical examination and noninvasive techniques because one lesion may mask the manifestations of the other. For this reason, patients suspected of having multivalvular involvement and who are being considered for surgical treatment should undergo careful clinical evaluation and both full Doppler echocardiographic evaluation and right- and left-cardiac catheterisation and angiography.

Mitral Stenosis and Aortic Regurgitation

Approximately 10% of patients with mitral stenosis (MS) have severe rheumatic AR. In keeping with the general observation that a proximal lesion may mask a distal lesion, significant AR may be missed in patients with severe MS. On the other hand, MS may be missed or, conversely, may be falsely diagnosed on clinical examination of patients with obvious AR. An accentuated S1 and an opening snap in a patient with AR should suggest the possibility of mitral valvular disease. However, an Austin Flint murmur is often inappropriately considered to be the diastolic rumbling murmur of MS. These two murmurs may be distinguished at the bedside by means of amyl nitrite inhalation, which diminishes the Austin Flint murmur but augments the murmur of MS; isometric handgrip and squatting augment both the diastolic murmur of AR and the Austin Flint murmur. Echocardiography, particularly pulsed Doppler echocardiography, is of decisive value in detecting MS and MR.

Since double-valve replacement is associated with increased short-term and long-term risk, balloon mitral valvotomy can be the first procedure. If this causes LV dilation, AVR can follow. Alternatively, open mitral valvotomy and AVR can be performed at the same time.

Aortic Stenosis and Mitral Stenosis

This combination is most commonly caused by rheumatic heart disease. The murmur of MS may not be easily discerned in presence of severe aortic valve stenosis. The loud systolic murmur of AS is also heard at the apex and hypertrophied left ventricle may mask the diastolic rumble of MS. Similarly, the low cardiac output resulting from severe MS may result in underestimation of the severity of AS as the resulting gradient is low. The echocardiogram exhibits pathology in both valves, and the severity of MS based on pressure half time is unaffected by AS. The peak and mean gradients are underestimated because of reduced cardiac output.

Percutaneous balloon valvotomy for MS may result in increased cardiac output and acute LV failure may develop when the severity of AS has not been recognised. The appropriate treatment consists of aortic valve replacement and mitral valve repair or replacement.

Aortic Stenosis and Mitral Regurgitation

This combination of lesions is usually caused by rheumatic heart disease. The combination of severe AS and mitral regurgitation (MR) is a hazardous one. AS augments the volume of MR flow, whereas the presence of MR diminishes the ventricular pre-load necessary for maintenance of the LV stroke volume in patients with AS. The result is a reduced forward cardiac output and marked left atrial and pulmonary venous hypertension. The development of AF (due to left atrial enlargement) has an adverse haemodynamic effect in the presence of AS. The physical findings may be confusing. In patients with severe AS and MR, both valves must usually be treated surgically by AVR and, if possible, by MV repair or MVR.

Aortic Regurgitation and Mitral Regurgitation

This relatively frequent combination of lesions may be caused by rheumatic heart disease, myxomatous degeneration, or by dilation of both annuli in patients with connective tissue disorders. The left ventricle is usually greatly dilated. The clinical features of AR usually predominate. When both valvular leaks are severe, this combination of lesions is poorly tolerated. The normal mitral valve ordinarily serves as a 'backup' to the aortic valve, and premature (diastolic) closure of the mitral valve limits the volume of reflux that occurs in patients with acute AR. With severe combined regurgitant lesions, regardless of the cause of the mitral lesion, blood may reflux from the aorta through both chambers of the left-side of the heart into the pulmonary veins. Physical and laboratory examinations usually show evidence of both lesions. An S3 and a brisk arterial pulse are frequently present. The relative severity of each lesion can be assessed best by Doppler echocardiography and contrast angiography. This combination of lesions leads to severe LV dilation.

MR that occurs in patients with AR secondary to LV dilation often regresses following AVR alone. If severe, the MR may be

corrected by annuloplasty at the time of AVR. An intrinsically normal mitral valve that is regurgitant because of a dilated annulus should not be replaced.

Mitral Stenosis and Tricuspid Regurgitation

If pulmonary hypertension is severe and the tricuspid valve anatomy is not grossly distorted, improvement in tricuspid regurgitation (TR) can be expected after correction of MS. On the other hand, if there is severe rheumatic deformity of the tricuspid valve, dilatation of the tricuspid annulus, or severe TR, competence is likely to be restored only by surgery.

If the mitral valve anatomy is favourable for percutaneous balloon valvotomy and there is concomitant pulmonary hypertension, valvotomy should be performed regardless of symptom status. After successful mitral valvotomy, pulmonary hypertension and TR almost always diminish.

If mitral valve surgery is performed, concomitant tricuspid annuloplasty should be considered, especially if there are preoperative signs or symptoms of right-sided heart failure, rather than risking severe persistent TR, which may necessitate a second operation. Annuloplasty of the tricuspid valve based on tricuspid dilatation (tricuspid annulus diameter >35 mm) improves functional status independent of degree of TR.

Triple-Valve Disease

Haemodynamically significant disease involving the mitral, aortic and tricuspid valves is uncommon. Patients with trivalvular disease may present in advanced heart failure with marked cardiomegaly, and surgical correction of all three valvular lesions is imperative. However, triple-valve replacement is a long and complex operation. It should be avoided, if possible. In many patients with trivalvular disease, it is possible to replace the aortic valve, repair the mitral valve, and perform a tricuspid annuloplasty or valvuloplasty.

When multiple prosthetic valves must be inserted, it is logical to select either two bioprostheses or two mechanical prostheses for the left side of the heart. If the patient is to be exposed to the hazards of anticoagulants for one mechanical prosthesis, it seems unreasonable to add the potential risks of early failure of a bioprosthesis. However, if two mechanical prostheses are selected for the left side of the heart, the use of a bioprosthesis in the tricuspid position is suggested.

RECOMMENDED READINGS

1. Bonow RO, *et al*. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008; 52: e1-142.
2. Coats L, Bonhoeffer P. New percutaneous treatments for valve disease. *Heart* 2007; 93: 639-44.
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12.15 Infective Endocarditis

Shyam S Kothari

Infective endocarditis (IE), an endovascular microbiological infection of cardiovascular structures, remains a serious illness. The various considerations in the diagnosis and management of IE provide such a challenge that it can be said that 'know IE and you know medicine.' In this chapter, salient aspects of IE are recapitulated with an emphasis on Indian experience.

EPIDEMIOLOGY

Despite several advances in the field of medicine, the incidence of IE has not reduced significantly over last 50 years, but the pattern of the disease has changed. IE occurs in 1-6/100,000 patient years in the Western world. There are no systematic population based data from India, but the incidence may be higher due to large number of rheumatic heart disease (RHD) and untreated congenital heart disease (CHD) patients in India. Hospital-based studies show a higher, prevalence of underlying RHD, lower pick up of vegetations and blood cultures and greater mortality in the Indian series as compared to the western data. These trends are shown in **Table 1**.

IE is uncommon in infants and children and the incidence increases with age. Males outnumber females (M:F = 1.7:1 in general, but up to 7:1 in patients above 70 years of age in some series). About 75% of episodes occur in diseased native valves, whereas infection on a normal native valve is increasingly seen as nosocomial infection in immunocompromised, elderly, diabetics, and in intravenous drug users. The relative proportions of valves involved in IE is interesting and possibly result from the difference in the pressure gradients across the valves. In an autopsy series of 1,024 patients in the pre-antibiotic era, the proportions of involved valves were mitral valve in 86 %, aortic 55%, tricuspid valve 19% and pulmonary valve in 1.1%. Nowadays higher proportion of aortic valve involvement may be seen in elderly and tricuspid valve in drug addicts. The different underlying lesions have different risks of being affected by IE, perhaps depending on the strength of the abnormal haemodynamic jets. For example, IE is very uncommon in atrial septal defect where the blood flows from left to right atrium with low pressure difference compared to ventricular septal defects with high pressure gradients between the ventricles. It is also uncommon in patients with Eisenmenger's syndrome where the difference in pressures between the chambers is abolished and there are no high velocity jets. Further, in mitral valve lesions also, IE is uncommon in patients of mitral stenosis compared to patients with mitral regurgitations. The general risks are shown in **Table 2**.

It is clinically useful to consider IE (1) in terms of the tempo of the disease (acute or subacute); (2) in terms of the valve involved (diseased native, normal native or prosthetic valve); and (3) in terms of the causative organism (common organism like *Streptococcus viridans*, or virulent like methicilin resistant *Staphylococcus aureus* or fungi, or unknown organisms). The major differences between acute and sub acute bacterial

Table 1: A Comparison of Indian and Western Series of Infective Endocarditis

Characteristics	Indian Series		Western Series	
	Choudhury, *et al*	Garg, *et al*	Meta-analysis	EHS
Duration	1981–91	1992–2001	1993–2003	April–July
Episodes	190	198	3,784	159
Age (years)	25±1.2	27.6±12.7	36-69	56±17
Identifiable preceding event (portal of entry) (%)	15	16.6	NA	41-48
Predisposing condition RHD (%)	42	46.9	NA	NA
CHD (%)	33	28.6	NA	NA
PVE (%)	1	10.4	7-25	26
IV drug abuse	0.5	0	15	NA
Echocardiogram positive (%)	64	89.9	NA	82
Blood culture positive (%)	47	67.7	90	86
Surgery for IE (%) in-hospital	1	23	25-40	52
Mortality (%)	25	21	16	12.6

EHS = European heart survey; RHD = Rheumatic heart disease; CHD = Congenital heart disease; PVE = Prosthetic valve endocarditis; IV = Intravenous; IE = Infective endocarditis.

Table 2: Risk of IE in Various Cardiac Lesions

High Risk	Moderate Risk	Low Risk
Prosthetic heart valves	Mitral valve prolapse with MR	Mitral valve prolapse without MR
Previous IE	Degenerative valvular disease in elderly patients	Isolated ASD
Tetralogy of Fallot	Tricuspid regurgitation	Cardiac pacemaker
Especially with BT shunt	Pure mitral stenosis	Prior CABG
PDA	Tricuspid stenosis	Prior Kawasaki's disease
Aortic regurgitation	Pulmonary stenosis	Rheumatic fever without valvular dysfunction
Mitral regurgitation	Hypertrophic obstructive cardiomyopathy	
Mitral stenosis with regurgitation		
VSD		
Coarctation of aorta		

endocarditis are shown in **Table 3**. These considerations influence the treatment and prognosis. Thus, subacute IE caused by *Streptococcus viridans* in a RHD patient is viewed differently from staphylococcal endocarditis on a native mitral valve in a patient on maintenance haemodialysis.

Table 3: Salient Features of Acute and Sub-acute Bacterial Endocarditis (Significant Overlap is Seen)

	Acute	Sub-acute
Onset (from bacteraemia)	Within 2 weeks	Within 2 months
Progression	Days to weeks	Weeks to months
Organism	Virulent (i.e. *Staphylococcus aureus*)	Less virulent (i.e. *Streptococcus viridans*)
Structural heart disease	Absent	Present

PATHOGENESIS

The hallmark of IE is the presence of vegetation in the endocardium of the heart. Normal endocardium is resistant to infection, but a traumatised endocardial surface is exposed to platelets and fibrin. Local trauma from an abnormal blood jet or systemic factors may result in unhealthy endocardium. A coagulum of platelet and fibrin is formed on the endocardial surface resulting in non-bacterial thrombotic endocarditis (NBTE). Any subsequent bacteraemia may colonise such vegetation. The vegetation are avascular and the fibrin layer possibly provide a barrier from leucocytes, thus bacteria rapidly grow within these vegetations. Early treatment may eradicate infection from vegetation but after 3 days it is not possible to get rid of the bacteria from vegetations due to high density and other dynamics of bacterial growth, thus underlying the need for long-term bactericidal antibiotics therapy for IE. The micro-organisms grow within vegetation and shed bacteria in circulation frequently; some of the colonies become metabolically inactive and hence difficult to eradicate. The infection can spread locally, or systemically.

The vegetation may occur at the valves, on mural endocardium (e.g. in front of the VSD jet), in aorta (beyond coarctation site), in pulmonary arteries (at the ductus arteriosus insertion site) or in aneurysms. In the valves typically, vegetation occur on the atrial surface in mitral valve in a patient with mitral regurgitation and ventricular surface of aortic valves in patients with aortic regurgitation respectively. These observations are consistent with Rod Board's hypothesis of bacterial colonisation resulting from venturi effects of jet lesions. In Libman-Sacks endocarditis, and in marantic IE, the vegetation occur at the ventricular surface of MR, on chordae tendineae, etc. In a patient of aortic regurgitation due to IE, mitral valve may become infected and the vegetation are seen at the chordae where the jet of aortic regurgitation strikes the mitral valve (**Figure 1**). The vegetation of IE may grow from few millimetres to as large as few centimetres and may obstruct the valve. These may regress with treatment or may disappear due to embolisation. Increasing size of vegetation during treatment usually, but not always, indicate persistent infection and treatment failure. Large vegetations are seen in fungal endocarditis, and also with Gram-negative IE but size of vegetation is not a reliable criterion for the diagnosis of the organism. The clinical features of the disease result from infection, local destruction in the heart, embolism, and immune activation.

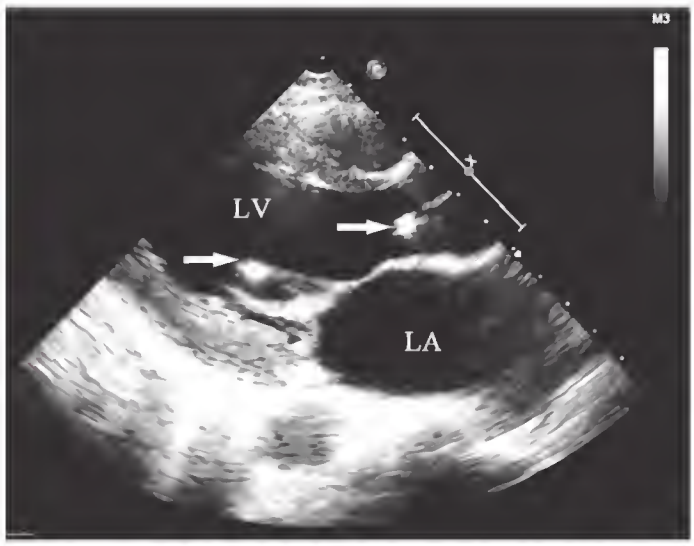


Figure 1: Echocardiogram (parasternal long axis view) showing vegetations on aortic and mitral valves (arrows).

LA = Left atrium; LV = Left ventricle.

THE ORGANISMS

It is good to remember that while many micro-organisms may cause IE, most episodes are caused by only a few bacterial species of streptococci and staphylococci. The organism causing IE have certain peculiarities, viz. ability to adhere to the endothelial surface, or the ability to penetrate normal endothelial barrier. It is hypothesised that factors such as fibronectin binding proteins on *S. aureus*, clumping factors or glucans on *S. viridans* are important in this regard. Despite frequent occurrence of Gram-negative bacteraemia, organisms such as Klebsiella, or Salmonella rarely cause IE. Generally speaking, nearly 75% to 80% of the episodes are caused by streptococcal and staphylococcus sp., 5% Gram-negative bacilli (of HACEK groups mainly, and Pseudomonas), 5% fungi, and rest by other uncommon organisms including coxiella, legionella, anaerobes (<1%), and others. The other organism must be considered in the clinical context. For example, fungal IE in patients who have received broad spectrum antibiotics for long time for some systemic infection, Brucella or Q fever in a dairy worker or a veterinarian who has chronic IE with large vegetations and negative blood cultures. Bartonella in a HIV positive homeless destitute, but such association or background is not enough to establish the diagnosis. A brief discussion about the common organisms is in order.

Streptococci

Streptococcus viridans species (*S. mitis*, *S. salivarius*, *S. sanguinis*) is a normal commensal organism of the oropharynx and still remains the commonest cause of native valve IE in the average community setting. Most *Streptococcus viridans* are penicillin sensitive although some strains may require higher minimum inhibitory concentration (MIC). Some strains of streptococci (e.g. abiotrophia) are fastidious and require special culture medium and also higher MIC for cure.

Streptococcus bovis has emerged as a common cause of IE in elderly. Isolation of this organism in blood culture in a patient mandates the evaluation of gastrointestinal tract for colonic cancer or polyps.

Streptococcus faecalis (enterococci) is a commensal of genitourinary tract and is an uncommon cause of community acquired IE. The microbe has a high order of resistance to antibiotics. It causes a recalcitrant form of IE needs special considerations for treatment. Occasionally, it can cause acute form of IE.

B streptococcus may cause IE in neonates or in the post-partum setting. β haemolytic streptococci, the cause of acute rheumatic fever, causes a destructive IE but is a very rare occurrence.

Staphylococci

Staphylococcus aureus has been increasingly seen now and has become the commonest cause of IE in some series. Typically, it causes acute IE with local destruction, CNS embolism and metastatic septic foci. *S. epidermidis*, a coagulase negative *Staphylococcus* is a normal commensal of skin flora and is the commonest cause of early prosthetic valve IE . It may also cause destructive IE. *S. lugdunensis*, another coagulase negative *Staphylococcus* has emerged as cause of destructive IE. *S. aureus* can also cause subacute IE.

Other Organisms

Gram-negative organism of HACEK group cause IE in <5% cases. (HACEK include *Haemophilus, Actinobacter, Cardiobacter, Eikenella, Kingella). Pseudomonas aeruginosa* rarely cause IE, but may be an important cause in drug addicts, in HIV positives, and in nosocomially acquired IE. Fungi are dreaded cause of IE (*candida* or aspergillosis) and typically occur in a settings for fungal sepsis like post-operative prosthetic valve IE. Anaerobes cause <1% IE. Other interesting causes of IE include brucella, chlamydia, psittacosis, legionella, mycobacterium, tropheryma whippelei, bartonella, etc.

CLINICAL FEATURES

IE has protean manifestations and is not uncommon for patients to remain undiagnosed for months as PUO. With the advent of echocardiography, the diagnosis is facilitated very significantly, still patients may present to neurology, nephrology or haematology departments with different complaints. The clinical manifestation of IE can be grouped into four headings:

1. **Constitutional Features**

   Anorexia, fatigue, night sweats and feeling unwell are universal. Weight loss can be quite significant and is attributed to cytokine activation. Aches, pains, arthralgia and backache are common and may be the presenting features confusing the primary diagnosis.

   Fever is almost always present in IE, and has no typical pattern. Recurrent chills at onset favours a bacteraemic illness, though frank rigors are uncommon. The usual temperature varies from 100 °F to 103 °F, but hectic fever with rigors may be seen in acute IE. Fever is sometimes not reported by the patient and may not be conspicuous in nearly 5% of patients such as frail elderly, renal failure, due to prior antibiotic use or in immunosuppressed patients.

2. **Cardiac Involvement**

   A heart murmur is present in the majority of patients, but may be faint or absent in right-sided endocarditis. The patient may have a murmur from a previous lesion and change in murmur may not be appreciable. Changing murmurs or new murmur may occur with valve destruction, chordal rupture, paravalvular leaks or fistulae formation. Local invasion and destruction occur rapidly in acute IE but may occur with all IE, albeit, slowly and uncommonly with usual *Streptococcus viridans* IE. *Staphylococcus aureus, S. lugdunensis*, beta-haemolytic streptococci and pseudomonas cause rapidly destructive IE. Extension beyond valve ring resulting in annular abscess, myocardial abscesses, pericardial extension and tamponade or coronary artery embolism may all lead to worsening cardiac status, but the valve lesions are the most significant amongst all of these as the cause of heart failure. Mechanical complication may occur even after bacteriological cure of IE. Congestive heart failure is the commonest cause of death from IE.

3. **Embolism**

   Embolisms to organs is often clinically silent, although detected in autopsy in 60%. Any organ may be involved by embolism of the vegetations from IE, but brain, spleen, kidneys, bowels, limbs, or lungs (in right-side IE) predominate. Embolism occurs in nearly 50% of patients with IE and is the presenting feature in many patients because it often occurs early in the disease. The incidence of embolism is high in the first 2 weeks of illness and falls rapidly with treatment even though it may occur after full treatment in some patients. It occurs at a rate of 12 per 1,000 patient days in the initial 2 weeks, but decrease to 1.2 per 1,000 patient days after 2 weeks of treatment. It is difficult to predict embolism. Various features such as size, shape, mobility, location of vegetations, causative organism and other characteristics of patients have been studied to predict embolisation. Vegetations more than 10 mm, vegetations on anterior mitral leaflet (which moves twice during diastole), and that caused by *S. aureus*, fungi, or Gram-negative bacilli are more likely to embolise. Mobility of vegetation is difficult to quantify and some studies suggest that mobility is only a matter of size of vegetation and not independent predictor of embolism. Increasing size of vegetation during treatment is associated with higher risks of embolism. In one study, presence of anti-phospholipid antibodies predicted embolism, but in general, predicting embolisation in an individual patient is not possible.

   Embolism occurs at branch point of arteries. In CNS, 90% of embolism occurs in middle cerebral artery territory leading to serious neurological deficits. Embolism to splenic artery is common but clinically may not be apparent or may cause splenic infarct. Pain in left hypochondrium referred to left shoulder in a patient of IE is suggestive of splenic infarct. Similarly, renal infarct may cause loin pain, hypertension, and haematuria. Mesenteric ischaemia, and limb threatening ischaemia may also occur with embolism. Bacteria or fungi can be grown from materials recovered at surgery. Embolism of IE is not influenced by anticoagulant or antiplatelet treatment. Right-sided IE is regularly accompanied by pulmonary embolism leading to lung infiltrate, consolidation, infarct, abscess or pulmonary artery pseudoaneurysms. Mycotic aneurysms result from embolisation to vasa vasorum of the vessels and subsequent weakness of the wall or from direct arterial wall

infection. These are most commonly seen in the brain and may result in catastrophic haemorrhage. Mycotic aneurysm are more common with *S. viridans* than staphylococcal IE.

4. **Immunological Manifestation**

IE results in intense humoral and cellular immune stimulation. Peripheral stigmata of IE are supposed to result from immune complex deposition although septic embolism may account for some of these.

Osler's Nodes

Typically, 2 to 15 mm pea-shaped, painful reddish nodules in the pulp of fingers and toes are seen in classical IE. These are uncommonly seen in acute IE, and possibly result from vasculitis. Sometimes, bacteria have been recovered from these lesions. Similar lesions may occur in gonococcal infection, haemolytic anaemia, SLE, marantic endocarditis, and in extremities with cannulated infected arterial lines. Lesions are transient, multiple and do not ulcerate.

Janeway's Lesion

Flat macular erythematous non-painful lesion in palms and soles, often seen in acute *Staphylococcus* IE. Bacteria may be isolated from these.

Petechiae and Purpura

Petechiae are common, may occur in crops, seen after few weeks of infection and usually identified in sublingual, subconjunctival areas, but can occur anywhere in the skin. They represent vasculitis, thrombocytopaenia, or sepsis. Streaky lines in nails are not characteristic of IE and may occur from trauma or other causes in many hospitalised patients.

Roth's Spots

Retinal haemorrhages with white centres are Roth's spots. These lesions are seen in number of conditions and represent capillary haemorrhages, not bacterial infection. These are also seen in anaemia, leukaemia, vasculitis, diabetes, carbon monoxide poisoning and rarely in HIV. These lesions undergo changes quickly.

INVESTIGATIONS

Haematological

Normocytic normochromic anaemia of chronic disease is the rule in IE. Leucocytosis is not common and normal counts are seen in 70% to 80%. Acute IE (staphylococcal and others), and fungal infection cause leucocytosis. Shift to left and toxic granulations may occur. ESR is very useful, though non-specific test, and should not be omitted. Mean ESR in IE is in the range of 50 to 60 mm in first hour. (High ESR as minor criteria is >30 mm in patients less than 60 years, and >50 for older patients). CRP (>100 mg/L) is faster to resolve than ESR. A very high ESR helps in narrowing differential diagnosis in patient of PUO.

Other haematological tests are sometimes useful. Rheumatoid factor is positive in half of the cases, specially with longer clinical course. Circulating immune complex are seen in majority of patients but have no major additional value. Cryoglobulinaemia may occur. Non-specific elevation of gamma globulin is common. Serum complement is reduced in patients with glomerulonephritis and IE. Anti-streptolysin O (ASLO) is not elevated (except in the rare β haemolytic streptococcal IE). Elevated procalcitonin is seen with sepsis, more so in staphylococcal sepsis. Serum ferritin, acute phase reactant may be elevated early in the course, but in chronic phase it is more often elevated in malignancy and Still's disease.

Urine

Microscopic haematuria is common. Gross haematuria suggests renal infarct. Proteinuria, casts may occur in patients with glomerulonephritis. Rapidly progressive crescentic glomerulonephritis sometimes occurs in IE and it resolves with antibiotics treatment, and/or with plasmapheresis.

Blood Culture

Blood culture must be carefully obtained with antiseptic precautions. It is recommended to take three sets of cultures (at least 1 hour apart), and from two separate venipunctures, (10 mL blood in adults) in each bottle is required, in sicker patients, empirical treatment may be started after taking culture; but in stable patients who have received prior antibiotics waiting for 48 hours before taking cultures should be practised. Addition of polysulphonates or resins to culture bottles may be helpful. Better culture medium like BACTEC improve the positivity rates and yield results early but are not widely available. If there is no growth after 5 to 7 days and IE is suspected, subcultures on special media should be done. But chances of contaminant growth also increase after 5 to 6 days. Fastidious organisms like nutritional variant *S. viridans*, or HACEK organisms need special culture media techniques.

Help of microbiologist should be sought early in the disease and since each laboratory may have local protocols, this should be discussed. Acridine dye test is sometimes useful in identifying organism even with obviously negative cultures.

Isolation of a microbe typically known to cause IE is highly likely to be the significant, but sometimes it is difficult to distinguish contaminant from the culprit, or simple bacteraemia from IE. Staphylococcal bacteraemia is associated with IE in nearly a quarter but enterococcal bacteraemia have IE in only 10% of patients. Community acquired bacteraemia, persistent bacteraemia in the absence of obvious focus favour the diagnosis of IE. Diphtheroids, acinetobacter are common commensals and contaminants but isolation from multiple cultures may be significant. Polymicrobial IE is uncommon except in drug addicts.

Several bacteria do not grow in the culture medium and serological tests or histological confirmation is required for the diagnosis. Example includes Brucella, Q fever, bartonella, legionella. More recently PCR techniques are utilised for the diagnosis of some of these, and in future wider availability of PCR probes for usual IE will make the diagnosis quick for routine cases as well. Identification of bacterial 16SrRNA and specific DNA after amplification can identify responsible agent from tissues obtained at operation in culture negative cases. However, PCR may remain positive in treated old IE as well. Similarly, histological demonstration of micro-organism from valves, sometimes, may represent dead bacteria.

Antibiotic sensitivity of the organism is a vital information for selection of antibiotics, though sometimes *in vivo* sensitivity may be different. Finding the minimum inhibitory concentration (MIC) to antibiotic like penicillin is useful in the treatment of IE, but is not widely practised.

ECHOCARDIOGRAPHY

Echocardiography is the cornerstone of the diagnosis of IE and has revolutionised the management of IE. Presence of vegetations, new onset valve regurgitation, annular abscess or valve dehiscence are diagnostic of IE. Of these, vegetations are most important. Typical vegetation of IE is seen as oscillating mass few mm to cm(s) in size attached to valve or mural endocardium having an independent mobility. Vegetations more than 2 mm are identifiable by echo-cardiogram, but the identification of vegetation is dependent on the experience of operator. Vegetations may be confused with some normal tissues like Chiari malformations in right atrium, parts of normal chordae, surgical stitch. Vegetations may also occur in other disease like marantic and Libman-Sacks endocarditis or anti-phospholipid antibody syndrome and in acute rheumatic fever. Sometimes, the vegetations may be too small or sessile, or represent previous treated IE. Further, up to 20% patients may have limited echocardiographic windows. Thus, possibilities of misdiagnosis and missed diagnosis of IE remain even with echocardiography. In general, transthoracic echocardiography has a sensitivity of 65% to 70% for the diagnosis of IE. Transoesophageal echo-cardiography (TEE) is preferred in doubtful cases, in poor echo-cardiographic window, or prosthetic valve IE, and for monitoring the complications of IE.

Echocardiography is required to monitor the course of the illness and is extremely useful for therapeutic decisions as it also gives haemodynamic information and idea about therapeutic response. Severity of regurgitation, ventricular function, extension of infection, and size of vegetation are easily evaluated by echocardiogram repeatedly. With effective treatment, vegetation size generally decreases. Increase in size of vegetation is a risk marker for embolism or poor prognosis. Echocardiography should not be done as a screening test for patients with fever in whom IE is not likely.

DIAGNOSIS

The diagnosis of IE is a clinical diagnosis. Although modified Duke's criteria (**Tables 4A and 4B**) are widely recognised as important in the diagnosis of IE, it cannot be overemphasised that the comprehensive picture of the patient should be taken into account. Bacteraemia with typical organisms known to cause IE and vegetations on echocardiogram combined make the diagnosis of IE definite. These are considered major criteria for the diagnosis in Duke's criteria. In the absence of one of these major criteria, minor criteria need to be looked into. Since, we have large number of culture negative cases, the modified Dukes criteria that involve the minor criteria are important for us. As such, performance of Dukes scheme has not been rigorously evaluated in Indian setting, but the basic principles are useful for uniformity. The diagnosis of IE is considered rejected if alternative diagnosis is firmly established or if fever disappears before 4 days of treatment without recurrence. The differential diagnosis of PUO is long, but tuberculosis, autoimmune diseases, malignancy like lymphoma pose major problems.

Practically, the most difficult differential diagnosis in a known RHD patient involve the consideration of rheumatic activity versus IE as both can cause fever, raised ESR, arthralgia, worsening failure and even vegetations. In rheumatic fever, the symmetrical small vegetations are different, ASO is raised, nodules may be present, and fever is not long-lasting. However, a careful appraisal of entire clinical picture is always required.

Table 4A: Original Duke Criteria for the Diagnosis and Classification of Infective Endocarditis

Major Criteria	Minor Criteria	Diagnosis
Positive blood culture Typical organism in >2 blood cultures in the absence of a primary focus (*Staphylococcus aureus*, enterococci, *Streptococcus viridans*, *Streptococcus bovis*, HACEK) Persistently positive blood culture drawn more than 12 hour apart or all ¾ drawn at least 1 hour apart between first and last **Evidence of endocardial involvement** Positive echocardiogram (TEE) Oscillating intracardiac mass on valve, implanted material or supporting structures in path of regurgitant jets Abscess New partial dehiscence of prosthetic valve New valvular regurgitation	Predisposition Heart condition Drug abuse Fever >38°C Vascular phenomena Major arterial emboli Janeway's lesions Septic pulmonary infarcts Immunologic phenomena Osler's nodes Roth's spots Rheumatoid factor Glomerulonephritis Microbiologic evidence Positive blood culture Positive serologic finding Echocardiographic evidence consistent with infective endocarditis but not meeting the major criteria	Definite 2 Major 1 Major and 3 minor 5 Minor Pathologic/histologic findings Possible Findings fell short of the definite but not rejected categories Rejected Alternate diagnosis Resolution of the infection with antibiotic therapy for less than 4 days No pathologic evidence after antibiotic therapy

Table 4B: Suggested Modifications of Duke's Criteria

Major criteria: consider the following as major criteria

Staphylococcal bacteraemia (irrespective of community or nosocomially acquired, or with or without a focus)

Positive serology for coxiella, chlamydia, bartonella

Positive molecular diagnosis for specific gene targets of bacteria and fungi

Minor criteria: add the following as minor criteria

Raised CRP (>100 mg/L),

Raised ESR (>30 for <60 yrs, and >50 for older)

Newly diagnosed clubbing

Splinter haemorrhages

Microscopic haematuria

Splenomegaly

Petechiae, or purpura

Delete the following from minor criteria

Echocardiogram consistent with IE but not meeting major criteria

Diagnosis

Possible IE can be diagnosed either with one major and one minor, or three minor criteria alone

TREATMENT

The treatment of IE entails long course of bactericidal antibiotics intravenously, monitoring for response, decision for surgical treatment if required, attention to portal of entry if possible, and ancillary measures for patients well-being including anticipatory guidance for preventing recurrence. Recommended antibiotic treatment charts are available in all standard texts, the principles of drug therapy are summarised.

1. Therapy has to be of sufficient dose and duration to eradicate bacteria, prevent mortality, and relapse. Usually 4 weeks therapy is required. All patients should be hospitalised for at least 2 weeks initially.
2. Longer-term treatment (6 to 8 weeks) is recommended if the symptoms have been present for >3 months, if IE is complicated by embolism, poor response, likely resistant bacteria, atypical organisms, or for prosthetic valve endocarditis (8 weeks).
3. In penicillin sensitive organism, penicillin is better than vancomycin. The dose of penicillin to be used in a patient (12-24 million units in 4-6 divided doses) depends on the available or perceived sensitivity of the organism, or clinical IE.
4. Intermittent bolus or continuous infusion are probably equally effective, boluses are usually preferred. Attention to planning of veins to be used, changing intravenous lines 48 hourly, use of central lines and aseptic precautions are customary details.
5. Therapy for staphylococcal sp. is based on methicillin sensitivity and not coagulase status. Almost all *Staphylococcus* are penicillin resistant, methicillin sensitive strain respond better to methicillin congeners.
6. Rifampicin is utilised in patients with prosthetic valves, or foreign materials and staphylococcal IE.
7. Fluoroquinolones can be substituted for *Staphylococcus* resistant to aminoglycosides as additional therapy.
8. Aminoglycosides are added carefully and therapy is only for few days in *Staphylococcus*, or for 2 weeks. In some organism, 4 weeks duration is required with careful attention to renal and vestibular functions.
9. Enterococci do not respond to methicillin, cephalosporin and often have resistance to aminoglycosides as well. Combination therapy is preferred.
10. Linezolid, daptomycin are increasingly used for vancomycin resistant enterococci or *Staphylococcus aureus*, and others.
11. A consultation from infectious disease specialist should be obtained in difficult circumstances.
12. Culture negative endocarditis can be treated with vancomycin, ceftriaxone and gentamicin pending further insight into the possible organism (some prefer only vancomycin and gentamicin).
13. Ideally trough drug levels should be measured, but is not possible in most circumstances.
14. Surgery should be considered early, rather than late, in some situations.

Treatment of common organisms is shown in the **Table 5**. Therapy of atypical organisms need special considerations and consultations with infectious disease specialists. Therapy for brucella include doxycycline with streptomycin, (with or without rifampicin), and in children trimethoprim-sulphamethoxazole and rifampicin, Q fever needs doxycycline with hydroxychloroquine (possibly with fluoroquinolones), bartonella can be treated with amoxicillin with gentamicin or tetracyclines/macrolides antibiotics. These are not detailed here.

Surgery for Infective Endocarditis

Surgical treatment during IE may be required because of (1) severe congestive heart failure from mechanical complications, (2) uncontrolled infection, and (3) repeated embolism. While complications of surgery is higher during IE than without IE, but the mortality without surgery in such patients is very high and surgery is preferred and should be done early without waiting for infection to subside. Although, mortality despite operation in these circumstances may be as high as 20% to 40%, mortality without operation is in the range of 60% to 90%. The chances of postoperative IE in the replaced valves are not higher than 2% to 3%. Early prosthetic valve endocarditis, paravalvular leak, annular abscesses, fungal endocarditis, persistent fever >2 weeks despite antibiotics in the absence of other causes, and embolisms are typical indications for consideration of operative treatment.

Various types of operative procedures may be required. Thorough debridement, patch repairs, vegetectomy and valve repair may be done, usually valve replacement is needed. The choice of valve is individual preference and outcomes are not different between mechanical or biological valves. Some may prefer homografts. If the patient has suffered a CNS event, it is better to postpone surgery, if possible. Open heart surgery should be postponed by 3 to 4 weeks after a haemorrhage in the brain and at least a few days to weeks after an infarct because of the use of anticoagulation during open heart surgery and the risks of adverse neurological outcomes.

Anticoagulation in Infective Endocarditis

Anticoagulation increase the chances of CNS bleed and should be avoided. In a patient with mechanical prosthetic valve, careful titration of minimal possible anticoagulation should be used. It is preferable to stop oral anticoagulant and rely on heparin for the duration of therapy.

Table 5: Treatment of Infective Endocarditis (Common Organisms)

Microorganism	Antibiotics	Dose (Per Day)	Duration
Streptococcus viridans	Penicillin G	12 to 24 MU/6 doses[1]	4 weeks[2]
Streptococcus bovis	Amoxicillin or	100 to 200 mg/kg	4 weeks[2]
	Ceftriaxone	2g in (100 mg/Kg) single dose	4 weeks[2]
	If penicillin allergy-vancomycin	30 mg/kg in 2 doses	4 weeks[2]
Enterococcus	Amoxicillin or ampicillin with	200 mg/kg in 4 to 6 dosage	4 to 6 weeks
	gentamicin	3 mg/kg in 2 to 3 doses	
	If penicillin allergic vancomycin with gentamicin[3]	30 mg/kg in 2 to 3 doses	
Staphylococcus	Flucloxacillin or oxacillin	12 g/d in 4 to 6 doses	4 to 6 weeks
	If penicillin – allergic vancomycin	30 mg/kg in 2 doses	4 to 6 weeks
	Optional gentamicin	3 mg/kg	5 days
Prosthetic valve IE	Vancomycin with	30 mg/kg in 2 dose	≥ 6 weeks
Or MRSA	rifampicin with	1,200 mg in 2 dose	≥ 6 weeks
	gentamicin	3 mg/kg in 2 dose	2 weeks
Fungal endocarditis	Amphotericin	1 to 1.5 mg/kg[4]	6 to 8 week or more
	Flucytosine	100 to 150 mg/kg in 4 doses	
	or fluconazole (second line only)	600 to 800 mg or 10 to 12 mg/kg	
		oral or IV in 2 doses	
Culture negative	Vancomycin with	30 mg/kg in 2 dose	4 to 6 weeks
	Gentamicin and	3 mg/kg in 2 dose	
	Ceftrioxone[5]	2 g in single dose	
IE HACEK	Ceftriaxone or	2g single dose	4 to 6 weeks
	Ampicillin-sulbactam	12 gm (2 g Ampicillin and 1 g Sulbactam)	
	If allergic, ciprofloxacillin	in 4 doses or 300 mg/kg ampicillin 6 hourly,	
		800 mg IV or 1,000 mg oral in 2 doses	

1 = Dose of penicillin depends on the MIC for the orgonism, in the absence of that doto, empiricolly decided; 2 = The durotion of theropy should be 6 weeks if the symptoms hove losted for more thon 3 months. For uncomplicated and responsive endocorditis, some authors hove reported cure with 2 weeks therapy of ceftrioxone; 3 = for uncommon voncomycin resistont or multidrug resistont enterococci, Linezolid 600 mg IV or orol BD hos been used; 4 = Amphotericin has to be built up slowly to this dose after initiol test dosages, lipid soluble formulations may be better toleroted. Newer ontifungals like caspofungin and newer ozoles are being tried; 5 = Treatment of culture negative endocorditis varies with the clinical background. Some outhors recommend adding ceftriaxone to cover Grom-negative organisms.

Monitoring During Therapy

Monitoring the patient during long course of treatment is vitally important. Most patients start showing clinical improvement and become afebrile within a week. Some may respond slowly. The diagnosis is doubted if the patient becomes afebrile in less than 4 days of therapy. Appetite, body weight, sense of well being should be evaluated routinely and thorough physical examination daily is mandatory. Echocardiography should be repeated weekly. Blood cultures, haemogram, ESR, chest radiographs, renal parameters, are monitored frequently. Recurrence of fever after initial response may occur (**Table 6**) due to several reasons. Drug fever may occur without rash and

Table 6: Fever During the Treatment

Cause	Indicators	Treatment
Uncontrolled infection	Continuing ill-health, metastatic foci, extension of infection in heart	Review choice or dosages of antibiotics
Annular abscess	Conduction disturbance on ECG, pericarditis suggest the diagnosis, often missed, TEE useful	Consider change in antibiotics, surgery
Organ infarcts	Renal, pulmonary or spleen, may become infected Splenic common, ultrasound/CT required	Splenic abscess may need precutaneous drainage or splenectomy
Mycotic aneurysms	Common in CNS, may cause cerebral haemorrhage, not routinely searched	Aneurysm can decrease with antibiotics, surgery may be required
Thrombophlebitis	Minor phlebitis more often incriminated as cause than actual, may miss more serious cause	Change IV lines frequently, if peripheral
Drug fever	Common with penicillin after 3rd week, rash, eosinophilia may not be present Patient appear less toxic despite high fever	Require to change antibiotics, total duration of treatment should count
Super infection	May be nosocomial fungal or Gram-negative infection Reflects poor hospital practices, broad index of suspicious required	Addition of appropriate therapy required
Immunologic phenomenon	For example, a patient with glomerulonephritis, or immune mediated phenomena in otherwise responding patient	Glomerulonephritis may remit after surgical removal of infection
Wrong diagnosis or double disease	SLE, lymphoma, tuberculosis may masquerade, double disease diagnosis is against the law parsimony (i.e. diagnose one condition in a patient), but very rarely does occur	Treat according to the diagnosis

can be high grade. Other investigations like abdominal ultrasound and CT are utilised as required. Splenic infarct or abscess can be diagnosed with both. Mycotic aneurysms are not routinely searched in the absence of symptoms. MR angiography can detect CNS aneurysms if suspected.

SPECIAL SITUATIONS

Prosthetic Valve Endocarditis

IE in patients with prosthetic valve occurs nearly in 1% in the first year and 0.5% per year afterwards. Early prosthetic valve endocarditis (PVE) occurring within 2 months of operation results from contamination in the operative or post-operative period and carry very high mortality. Organisms like coagulase negative *Staphylococcus* or *S. aureus*, *Pseudomonas*, *Candida* predominate. Some authors consider early PVE till 1 year period. Surgical treatment is the rule for early PVE and antibiotics are required for 6 to 8 weeks. IE later is due to the usual organisms but carries a higher-risk. PVE is essentially an annular infection, and therefore, chances of annular abscess are higher.

Culture Negative Endocarditis

Culture negative endocarditis, although thought of as a group, actually encompass different entities. Culture could be negative because of (1) prior antibiotic therapy in otherwise a usual endocarditis, the commonest cause, (2) poor culture techniques, inadequate sample, media, transport, etc., (3) fastidious organisms needing special media like abiotrophia, HACEK, etc., and (4) organism that do not grow in blood culture like aspergillus, tropheryma whipplei, coxiella. The approach to these groups should be different. As discussed above, serological tests are useful in the diagnosis of brucella, Q fever, etc., and PCR is being utilised for many bacteria and improves the positive yield. In the absence of any clinical clues, suggested broad-spectrum cover include vancomycin with gentamicin and ampicillin or ceftriaxone.

Infective Endocarditis in Children

IE is uncommon before 2 years of age, except as nosocomial infection in neonates in presence of intravenous cannula and central lines. *Staphylococcus aureus* and candida dominate. Tricuspid valve endocarditis may present with unexplained dyspnoea due to unanticipated pulmonary embolism. Most other IE in children occur in the presence of a CHD or RHD. IE in the VSD or tetralogy of Fallot patients occurs as right-sided endocarditis (**Figures 2 and 3**). Systemic embolism does not occur unless there is a right to left shunt or IE occur in the left-sided structures also. Pulmonary complications like infiltrate, infarct, abscess, pulmonary artery pseudo-aneurysm occur. Response to therapy can be satisfactory. Surgery might have to be resorted to in the presence of active infection in unsatisfactory responders. Ligation of ductus arteriosus is frequently followed by response to therapy in patients with ductus arteriosus and pulmonary valve endocarditis.

Infective Endocarditis in Drug Addicts

IE in drug addicts usually affects normal tricuspid valve, but may also occur on aortic, and mitral valves. Right-sided IE responds well to therapy. Some may have HIV, but IE in them also responds well, unless CD4 counts drop low. Polymicrobial IE or IE due to unusual organisms like bartonella may occur. Addicts using pentazocine have high chances of pseudomonas, and heroine addicts injecting brown heroine in lemon juice frequently have candida.

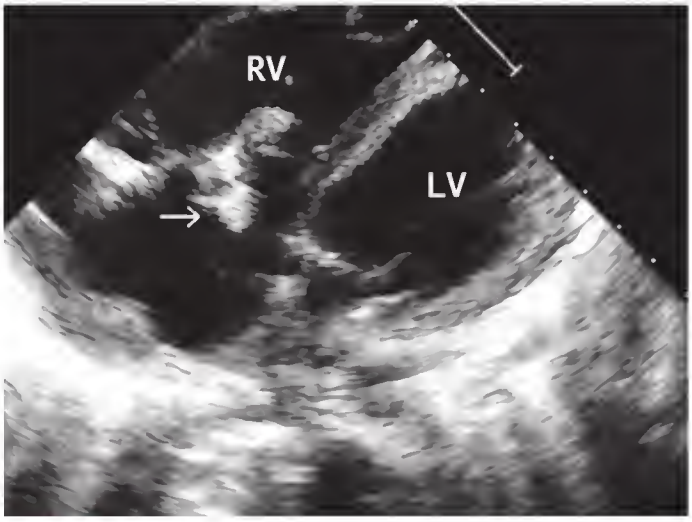


Figure 2: Echocardiogram in four chamber view showing vegetations (arrow) on tricuspid valve in a patient of small ventricle septal defect (not seen).

LV = Left ventricle; RV = Right ventricle



Figure 3: Chest radiograph of a patient of tetralogy of Fallot having right-sided infective endocarditis. Note the shadow in right lower chest from a pulmonary infarct.

In Elderly

IE in elderly is increasingly seen and is more common in males. The underlying predisposing lesion often is mitral valve prolapse with mitral regurgitation or degenerative valvular aortic stenosis. Co-morbidities decide the clinical course. Drug therapy will need extra care and dose adjustments with attention to renal and hepatic functions.

MORTALITY

Without treatment IE is invariably fatal. Rare case reports of recovery in the pre-antibiotic era may be misdiagnosis. Antibiotics reduced the mortality but IE has a mortality of 20%

Table 7: Prevention of Infective Endocarditis

Underlying Lesions	Procedures	Antibiotics
Rheumatic heart disease Prosthetic valves Previous infective endocarditis Congenital heart disease Unrepaired cyanotic CHD including palliative shunts and conduits Within 6 months of repair, devices Residual lesions near patches, or prosthesis Valve disease after cardiac transplant	Dental procedure Involving periapical region of teeth or perforation of the oral mucosa or gingival tissues Respiratory procedures Respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy, (none for bronchoscopy) Skin and soft tissue Surgical procedure that involves infected skin, skin structure, or musculoskeletal tissue Genitourinary or Gastrointestinal procedures None	Oral amoxicillin 2 g (50 mg/kg), or Intravenous/intramuscularly ampicillin 2 g, cefazolin, ceftriaxone 1 g (50 mg/kg) In allergic to penicillin: Oral cephalexin 2 g (50 mg/kg), or azithromycin/clarithromycin 500 mg (15 mg/kg), or intravenous clindamycin 600 mg

to 40% even in current era. Further reduction in mortality is expected with more frequent surgical treatment. Mortality rates depend on several factors, but large size vegetations, heart failure portends poorer prognosis. Some subsets have particularly high mortality. Prosthetic valve IE has a mortality of 30% to 55% with surgery and 60% to 90% without surgery. The mortality in fungal IE is 60% to 90% despite treatment. With concerted efforts, protocol driven management and teamwork of cardiologist, microbiologists, surgeons and infectious disease specialist, the mortality of *Streptococcus viridans* IE can be as low as 7% to 10%, but enterococci and *Staphylococcus* mortality remains about 10% and 10% to 20% respectively. Right sided IE in drug addicts have a better response and lower mortality.

PREVENTION

In experimental settings, antibiotics administration before inoculating bacteria prevented colonisation and IE, and hence for years, elaborate recommendations were made for drugs to be given before procedures expected to cause bacteraemia. With time, it became clear that bacteraemia occur in daily living activities (like brushing, chewing, etc.) far more frequently than procedure induced, and that very few episodes of IE, if at all, could be prevented by such administration as previously advised. Further, costs and adverse effects of antibiotics use (including development of resistance) are not negligible. Therefore, it is prudent to advise all patients on maintaining good oral health and routine dental visits. Such is not the routine in India, but that can help reducing IE burden more than any antibiotic prophylaxis. Antibiotics before procedures are recommended only to patients in whom risks of occurrence and consequences of IE (if it occurs) are considered high (**Table 7**). No IE prophylaxis is recommended for gastrointestinal or genitourinary procedures in the American Heart Association recommendations. Dental procedures which may cause gum bleeding or apical tissue handling would cause bacteraemia are specified. Only single dose 2 gm amoxicillin is recommended where required.

There have been no new data about RHD, and these patients could have poor oral hygiene. Individual judgement should still be used in advising prophylaxis. No prophylaxis is required for vaginal delivery, tattooing, ear piercing, or TEE.

CONCLUSIONS

The following parameters recapitulate important aspects of management of infective endocarditis.

Do's and Don'ts of Infective Endocarditis

1. Prevent IE by anticipatory guidance on oral hygiene in RHD, CHD and other at risk patients.
2. Think of IE in all susceptible patients with fever, anaemia, weight loss, or heart failure.
3. Do not rely overly on any test including echocardiogram as false positive and false negatives are not uncommon.
4. Think of plausible portal of entry/organism before deciding on therapy.
5. Do not jump to the latest antibiotics, nor slavishly follow the regimens, think critically.
6. Monitor trends carefully, anticipate the complications but do not change antibiotics frequently with any minor alterations including 1 to 2 days fever.
7. Keep the surgeon in the loop for decision regarding early surgery, if required.
8. Prevent recurrence, relapse by appropriate advice and management.

RECOMMENDED READINGS

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12.16 Atherosclerosis

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INTRODUCTION

Atherosclerosis is multi-focal, multi-factorial smouldering inflammatory disease that affects the intima of medium sized and large arteries, resulting in intimal thickening that may lead to luminal narrowing and inadequate blood supply. Atherosclerosis derives its name from the Greek word 'adhere'—means gruel or porridge, and 'sclerosis' means hardening, i.e. hardening of gruel-like material inside the blood vessels.

According to the original concept, atherosclerosis was thought to be just a bland proliferative process. The advent of cell biology era of atherosclerosis modified the earlier view and implicated inflammatory mechanism in disease development. According to that concept, endothelial denudation resulted in platelet aggregation and release of platelet-derived growth factor (PDGF) which led to the proliferation of smooth muscle cells in the arterial intima. Current evidence integrates inflammation as a key regulatory process with multiple other risk factors in atherosclerosis.

PATHOGENESIS

Early Atherosclerotic Lesions

The earliest lesions of atherosclerosis, i.e. fatty streaks, are present in the aorta from early childhood and may even begin to develop early in foetal life. They are highly cellular inflammatory lesions consisting of macrophage foam cells (intracellular lipid) and T-lymphocytes (immune reaction). Fatty streaks do not protrude into the lumen and hence are not symptomatic. Fatty streaks develop under an intact but activated, dysfunctioning endothelium particularly atherosclerosis prone areas with pre-existing intimal thickening. Hypercholesterolaemia is associated with increased endothelial permeability, increased transcytosis and intimal retention of lipoproteins and endothelial activation with focal expression of vascular cell adhesion molecule 1 (VCAM-1) leading to monocyte and T-lymphocyte adhesion. It is thought that inflammatory cells are recruited by adhesion molecules and chemokines such as monocyte chemoattractant protein-1 (M-CSF) and activated in the intima by factors such as oxidised lipids and cytokines. Within the intima, the monocyte-derived macrophages engulf the blood derived low-density lipoprotein (LDL), possibly through their scavenger receptors after oxidative modification and become lipid-filled foam cells. These inflammatory cells constitute the major part of the early fatty streak lesions (**Figure 1**).

Fate of Fatty Streaks

Fatty streaks can progress to more advanced lesions because they occur at the same anatomic sites. A smaller fraction of fatty streaks appears to progress to more advanced symptomatic lesions.

Advanced Atherosclerotic Lesions

When lipids begin to accumulate, extracellular atherogenesis has passed beyond the fatty streak stage. Two different processes

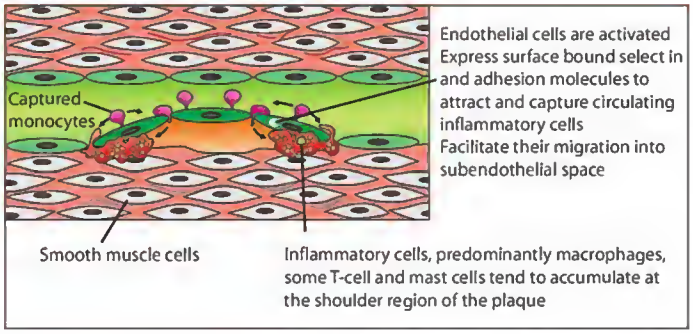


Figure 1: Formation of fatty streak.
Source: Weissberg, Heart 2000;83:247-52.

are responsible for the extracellular accumulation of lipids. Blood-derived atherogenic lipoprotein particles may be trapped directly within the proteoglycan-rich extracellular matrix and/or lipid may be released from the macrophage foam cells after their death by apoptosis. Within a lipid-rich core, erythrocytes and their lipid-rich membranes may contribute to the expansion of the core (plaque rupture and haemorrhage).

There is accumulation of smooth muscle cells which gives rise to a heterogeneous spectrum of plaques ranging from fibro-fatty plaques (abundant smooth muscle cells) to thin-cap fibroatheroma (scanty smooth muscle cells with rich lipid core). With the passage of time endothelial denudation takes place and adherent platelets can be seen over mature plaques. Growth factors released from the adherent platelets and micro thrombi may stimulate the smooth muscle cells within the plaque to produce more connective tissue matrix.

Neovascularisation

Neovascularisation is frequently present at the base of advanced atherosclerotic plaques and is thought to be derived from vasa vasorum derived new vessels. Vasa vasorum developing from the adventitial layer of vessel wall also serve the purpose of transit of leukocytes and other growth factors inside the plaque.

Vulnerable Plaque and Plaque Instability

Pathological studies indicate that certain plaques are more prone to develop acute myocardial infarction (MI) than others. These are called vulnerable plaques, i.e. plaques which are at high risk of for disruption or thrombosis leading to symptomatic cascade of acute coronary events. Vulnerable plaques are characterised by the following:

- A thin fibrous cap (thin cap fibroatheroma or TCFA),
- A large lipid pool of cholesterol esters,
- Heightened inflammation,
- Positive remodelling of the vessel (outward expansion of the opposite wall of the vessel), and
- Extensive neovascularisation.

Vulnerable plaque ruptures due to uneven thinning of the fibrous cap. Rupture usually occurs often at the shoulders of the lesion where macrophages enter, accumulate and are activated. Degradation of the fibrous cap results from elaboration of matrix metalloproteinases such as collagenases, elastases and stromelysins. The metalloproteinases are stimulated by activated T-cells which promote plaque instability and rupture (**Figure 2**).

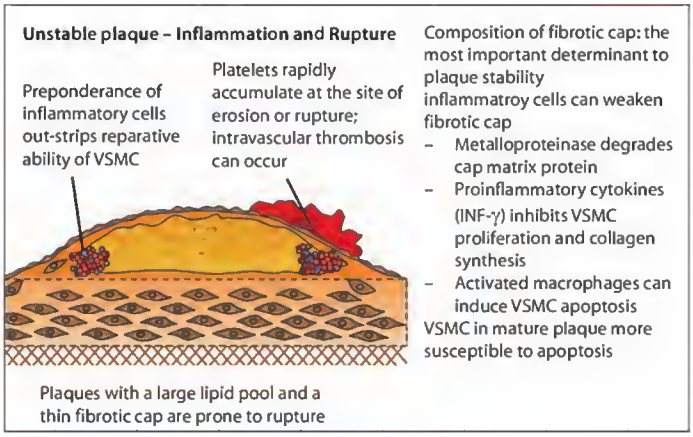


Figure 2: Vulnerable (instable) plaque formation.

VSMC = Vascular smooth muscle cell; INF-γ= Interferon-gamma.
Source: Weissberg, Heart 2000; 83: 247-52.

Role of Innate and Adaptive Immunity

Innate immunity is the primitive arm of inflammation and constitutes immune response that is elicited without 'education' of the immune system. This response is very rapid and combats perceived foreign invaders. Natural antibodies, certain complement proteins and families of cell surface receptors recognise microbial products and provide primordial host defence responses. These receptors include scavenger receptors which cause uptake of modified lipoproteins, and are toll-like receptors (TLR) that recognise microbial structures and products. These receptors trigger a complex intracellular signalling cascade that stimulates the production of pro-inflammatory cytokines and other inflammatory mediators. The cellular recruitment seen very early in atherosclerosis is an example of innate immunity. The mononuclear phagocytes get attached to activated endothelial cells by leucocyte adhesion molecules. Maturation of monocytes into macrophages, their multiplication and production of mediators ensues. Recent evidence suggests that mononuclear recruitment is a continuous process which is also seen in established lesions and could be a therapeutic target for targeting monocytes for treatment. In the presence of hyperlipidaemia, there is an enrichment of proinflammatory subset of monocytes. Apart from monocytes, there is now firm evidence that mast cells release vasoactive small molecules such as histamine and leukotrienes, serine proteinases and heparin — a cofactor in growth factor action and angiogenesis. Certain pharmacological agents can modulate mast cell function and this can have therapeutic implications. There are links between lipoproteins and innate immunity. Modified lipoproteins such as oxidised lipoproteins and oxidised phospholipids may drive inflammation. A lipoprotein-associated phospholipase-A2 (Lp-PLA2) currently targeted in clinical trials may generate proinflammatory derivatives of oxidatively modified lipoproteins (apolipoproteins).

Recent data suggest that CIII, a constituent of certain triglyceride-rich lipoproteins incites inflammation by binding to TLR2. The activation of platelets results in secretions of proinflammatory cytokines such as CD40-ligand and also myeloid-related protein (MRP) 8/14. The MRP serves as a biomarker for adverse cardiovascular events and can promote endothelial cell apoptosis, a process thought to be vital in plaque thrombosis.

Adaptive immunity requires antigen presenting cells, such as dendritic cells. The dendritic cells populate atherosclerotic plaques and present antigens to T-lymphocytes, thus forming the key limb of adaptive immunity. These antigens in relation to atherosclerosis are heat shock proteins (HSP), components of plasma proteins and some microbial structures. T-cells proliferate and produce cytokines that amplify inflammation. There are several types of T-cells. Helper T-cells (Th1) response appears to aggravate atherosclerosis as it amplifies proinflammatory pathway by gamma interferon production. The Th2 cells produce cytokines that modulate inflammation. These cytokines such as interleukin (IL)-4 can promote humoral immunity. Regulatory T-cells can, however, dampen atherosclerotic response. There is also a role of CD8 marker T-cells or cytotoxic T-cells or CD8 cells. CD8 T-cells are capable of killing smooth muscle cells and macrophages and cause lesion growth and complications.

Humoral immunity is mediated by B-lymphocytes. B-lymphocytes secrete antibodies which attenuate rather than aggravate atherosclerosis. Splenectomy aggravates athero-sclerosis by eliminating some population of B-cells. Humoral immunity against oxidised LDL might protect against atherosclerosis and may be a potential target of vaccine therapy.

RISK FACTORS FOR ATHEROSCLEROSIS

Classic risk factors of atherosclerosis are also known as traditional risk factors. These risk factors can predict atherosclerotic coronary events to a certain extent. The NCEP ATP- III is based on traditional (old) risk factors of age, sex, total cholesterol, HDL cholesterol, systolic BP and smoking. In a more recent scoring system (PROCAM), eight risk variables are identified: age, LDL cholesterol, diabetes, smoking, HDL cholesterol, triglycerides (TG), systolic BP, family history of premature coronary artery disease. **Table 1** presents risk factors for atherosclerosis.

Hypertension

Hypertension is considered to be one of the traditional risk factors of atherosclerosis. Concentrations of angiotensin-II, the principal product of renin-angiotensin system are often elevated in patients with hypertension. Angiotensin-II is a potent vasoconstrictor. In addition to cause hypertension, it can contribute to atherogenesis by stimulating the growth of smooth muscle cells. Angiotensin binds to specific receptors in smooth muscle cells resulting in activation of phospholipase C, which can lead to increase in intracellular calcium and smooth muscle contractions, increased protein synthesis and smooth muscle hypertrophy. It also increases smooth muscle lipooxygenase activity which can increase inflammation and oxidation of LDL. Hypertension also has proinflammatory actions such as increasing the formation of hydrogen peroxides and free radicals such as superoxide anions and hydroxyl radicals in plasma. These substances reduce the formation of nitric oxide (NO) by endothelium, increase leucocyte adhesion and increase peripheral resistance.

Table 1: Old, Old/New, and New Risk Factors for Atherosclerosis

Old	Old/New	New
Sex (men > women)	High-normal blood pressure	Apolipoprotein B; Apolipoprotein A-1
Age	Metabolic syndrome	Triglycerides; triglyceride-rich lipoprotein remnants
Family history of premature cardiovascular disease	Diabetes mellitus; impaired glucose tolerance; impaired fasting glucose	Small, dense LDL; oxidised LDL; antibodies against oxidised LDL
Total cholesterol; LDL cholesterol; HDL cholesterol (negative risk factor)		Lipoprotein(a)
Hypertension		Homocysteine
Smoking		High-sensitivity C-reactive protein
Overweight/obesity		

LDL = Low-density lipoprotein; HDL = High-density lipoprotein.

Smoking

Smoking increases the risk of atherosclerosis by several mechanisms. Cigarette smoking is associated with increased levels of lipoproteins and the effects of oxidants in cigarette smoke renders LDL more susceptible to peroxidative modification by cellular elements such as macrophages and vascular smooth muscle cells. The inflammatory cells recruited in the atherosclerotic plaques are increased in smokers. Nicotine activates the complement system as well, which causes increased inflammation in the vessel wall. Certain chemicals in tobacco smoke tend to activate factor XII and favour thrombus formation. The risk associated with smoking diminishes slowly after smoking cessation and equals to non-smokers after 3 years of cessation.

Diabetes Mellitus

In the first 20 years of the Framingham Heart Study, the incidence of cardiovascular disease among men with diabetes mellitus was twice than that among men without diabetes. Among women with diabetes, the incidence of cardiovascular disease was three times than that among women without diabetes. Microalbuminuria and silent myocardial ischaemia at baseline has predictive value for future coronary heart disease (CHD) in asymptomatic patients with type II diabetes. Subjects with impaired glucose tolerance and those with insulin resistance are more likely to have subclinical atherosclerosis (Framingham Offspring Study) and it is no wonder that NCEP considers diabetes as a CHD risk equivalent. Type II diabetes is associated with insulin resistance. Insulin resistance reduces the ability of adipose tissue to clear/store circulating lipids, in part because of reduced lipoprotein lipase activity. This results in paradoxical elevation in serum TG and free fatty acids (FFA). There is also elevation in the apoB due to increased lipogenesis by the liver. Insulin resistance is characterised by the formation of more atherogenic (small dense) LDL. It can also stimulate inflammation. The secretion of proinflammatory mediators initiated by systemic insulin resistance stimulates several intracellular cascades of nuclear factor kappa beta pathway.

Metabolic Syndrome

Metabolic syndrome encompasses a range of cardiovascular risk factors such as elevated TG (> 150 mg/dL), low HDL cholesterol (men < 40 mg/dL; women < 50 mg/dL), impaired fasting glucose (≥ 110 mg/dL), high blood pressure (≥ 130/85 mm Hg) and increased waist circumference (men > 90 cm, women > 80 cm in Asians) is believed to increase the risk for CHD at any level of LDL cholesterol. Further, the presence of metabolic syndrome has a greater impact on the incidence of CHD in women than men. Leptin is a protein that plays a role in fat metabolism and closely correlates with insulin resistance and is an independent risk factor for CHD.

Lipid Risk Factors

Triglycerides and triglyceride-rich remnant lipoproteins

Though there was some initial debate on the role of hypertriglyceridaemia as an independent CHD risk factor, data from the PROCAM study showed a significant relation between hypertriglyceridaemia and CHD risk independent of LDL cholesterol and/or HDL cholesterol. Triglyceride-rich lipoproteins comprise a great variety of nascent and metabolically modified lipoprotein particles. The capacity to enter the subintimal area of the vasculature is inversely related to the size of the lipid particles. Whereas chylomicrons and large very low-density lipoprotein (VLDL) particles are unable to pass through the endothelial layers, smaller VLDL, IDL and LDL particles can enter the suboptimal space. In the Framingham Offspring Study, both remnant lipoprotein (RLP)-cholesterol and RLP-TG were significantly increased in diabetic men and women compared to non-diabetes. Remnant lipoproteins were independent risk factors for atherosclerosis. Lipoprotein (a) [Lp (a)] is formed by joining a lipoprotein that is structurally similar to LDL in protein and lipid composition to a carbohydrate-rich hydrophilic protein Apo (a). The Lp (a) particles contain Apo (a) and Apo (B) in a 1:1 molar ratio. Most of the data on Lp (a) comes from retrospective studies. Prospective studies, however, have mixed results. However, plasma Lp (a) is indeed an independent risk factor for CHD in both men and women. The Lp (a) levels above 33 mg/dL and high LDL cholesterol (>163 mg/dL was associated with increased cardiovascular risk compared with Lp (a) levels below 33 mg/dL.

Homocysteine

Homocysteine is formed during demethylation of methionine, whereas its degradation takes place via remethylation and/or trans-sulphuration). Impaired homocysteine metabolism has been implicated as a risk factor in atherosclerosis, cerebrovascular disease and peripheral vascular disease. Hyperhomocysteinaemia results from genetic cause (enzyme deficiencies), vitamin deficiency (folic acid, B12, B6), use of certain medications and impaired renal function. Direct relations between homocysteine, cigarette smoking, diabetes, obesity and hypertension have been suggested. The exact mechanism by which hyperhomocysteinaemia may translate into increased CHD and/or thrombotic risk remains speculative. Both direct toxic effects on endothelial cells, in part due to oxidative stress as well as more indirect mechanisms have been postulated. However, treating hyerhomocysteinaemia with vitamins has not shown to be beneficial in large studies both in terms of stroke and cardiovascular event reduction.

Thrombogenic/Haemostatic Factors

Elevated plasma fibrinogen and factor VII are potential risk factors for CHD. Other thrombogenic/haemostatic factors that have been investigated in their potential role in atherogenesis and/or thrombosis include von Willebrand factor and plasminogen activator inhibitor-1.

High-Sensitivity C-Reactive Protein and Other Inflammatory Markers

Since atherosclerosis represents a chronic inflammatory state, inflammatory parameters (e.g. IL-6, tumour necrosis factor-alpha) have predictive value for future cardiovascular events. Data shows that CRP has additive value for predicting CHD risk on top of traditional risk factors. hs-CRP is associated with subclinical pericardial coronary calcification in men and women and is significantly elevated in patients suddenly dying of severe coronary artery disease. Elevated hs-CRP constitutes an independent predictor of advanced plaques in dyslipidaemic subjects and early onset carotid atherosclerosis with increased intima-media thickness and elevated serum levels of inflammatory markers. Matrix-metalloproteinase 9 concentration has been identified as a novel predictor of cardiovascular mortality in patients with coronary artery disease. Elevated IL-10 has a more favourable prognosis in patients with acute coronary syndrome (ACS) and elevated CRP levels.

Though there is no definite hard evidence of a causal relation between infection and atherosclerosis, studies are accumulating that indicate a possible role of infection. Viral agents such as cytomegalovirus (CMV), enterovirus, influenza virus, human parvovirus B19, herpes simplex viruses and bacterial agents such as *Chlamydia* have been studied extensively. Other potential agents such as *Helicobacter pylori* and periodontitis have been implicated. In a recent meta-analysis, it has been shown that influenza vaccination in patients with CHD can lower the risk of acute myocardial infarction.

Periodontitis is associated with atherosclerotic cardiovascular disease, though direct causal relation is not yet established. The incidence of atherosclerotic cardiovascular events increase in patients with chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and psoriasis.

Biomarkers such as hs-CRP, IL- 6, IL- 8, soluble CD40 ligand are all markers of widespread inflammatory process in the vessel wall and can be identified by laboratory assays to detect subclinical atherosclerosis. There was an association between CRP and carotid atherosclerosis as assessed by ultrasono-graphy among 3,173 men and women enrolled in the Framingham Offspring Study. Overall, they found that increasing levels of CRP were predictive of carotid artery disease. Elevated levels of CRP may reflect the presence of vulnerable plaque that is at high-risk of rupture, as opposed to solely reflecting the burden of atherosclerosis. Emerging data, however, suggest that CRP may be a mediator as well as marker of atherosclerosis. CRP induces expression of cellular adhesion molecules, IL-6 and endothelin-1 by endothelial cells. Recently, interest has focused on the measurement of a circulating soluble form CD40 L (sCD40) for risk stratification of patients with or at risk of developing coronary artery disease. However, in a large multiethnic population-based sample, sCD40L was not associated with most atherosclerotic risk factors or subclinical atherosclerosis.

Technology has now made it possible to image atherosclerosis and the day is not far when it will be routinely used in identifying vulnerable plaques which are prone to rupture. It is yet unproven that therapies directed at sealing such plaques are beneficial. Techniques to image "vulnerable" plaque is given in **Table 2**.

Table 2: Techniques to Image "Vulnerable Plaque"

Angioscopy
Intravascular ultrasound
Palpography
Virtual histology
Near-infrared/Raman spectroscopy
Ocular coherence tomography/ocular frequency domain imaging
Thermography
Vasa vasorum imaging
Magnetic resonance imaging (invasive and non-invasive)
Positron emission tomography/computed tomography
Molecular imaging

TREATMENT/PREVENTION

Systemic pharmacotherapy is the cornerstone of plaque stabilisation, with reductions in lipid content, inflammation and vasa vasorum neovascularisation. Statin therapy in high-dose has been documented to be beneficial in atherosclerotic plaque regression. In the A study to evaluate the effect of Ultrasound rosuvastatin an Intravascular derived coronary Atheroma Burden trial, rosuvastatin 40 mg per day led to an absolute regression in atheroma volume. Increasing HDL levels have been found to be antiatherogenic. However, even with the best combination consisting of high dose statins, ACE-inhibitors and aspirin, there is still a 22% recurrent coronary event rate in 2 years. Regional therapy such as photodynamic therapy and cryotherapy as intravascular treatment of coronary segments may be beneficial in near future. Plaque sealing with balloon expandable stents may tackle the vulnerable plaque.

Vaccine development for atherosclerosis

Historically, vaccines have been proven to be safe and efficient for protection against infectious diseases. Several antigen targets have been proposed for vaccine design, implementation and efficacy for atherosclerosis. Ideal vaccines for atherosclerosis should provide protective immunity against infection-derived pro-atherogenic antigens and also immune tolerance for auto-immunogenic selfantigens. LDL was the earliest target for vaccine therapy as it is a major mediator of atherosclerosis. Studies focusing on a knockdown of Ox-LDL showed a decrease in atherosclerotic lesion size. Immunisation with phosphatidylcholine (PC) containing *Streptococcus pneumoniae* generated vaccine which showed reduced atherosclerosis. However, the major problem with Ox-LDL is the chance of cross-reactivity. For greater OX-LDL specificity, more recent studies have targeted ApoB-100 peptide fragments. Studies to target the potential antigenicity of heat shock protein (HSP) mycobacterial HSP 65 elicit a pro-atherogenic response. Immunisation of patients with HSP 70 also showed decreased atherosclerosis. Following the idea that molecular mimicry is the mechanism responsible for cross-reactivity with foreign HSP, vaccination against infectious agents like influenza virus has been examined in the context of atherosclerosis. Vaccines

against more risk factors and proteins like nicotine, angiotensin-1, gherkin and periodontitis have also been examined with some interesting results. Thus, vaccine development for atherosclerosis is already underway and showing promising results.

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12.17 Ischaemic Heart Disease

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Ischaemic heart disease (IHD) is characterised by myocardial impairment due to imbalance between coronary blood flow and myocardial requirement. The commonest cause of IHD is atherosclerotic coronary artery disease (CAD). Non-atherosclerotic causes of myocardial ischaemia are rare and include coronary spasm (Prinzmetal's angina), coronary artery embolism, coronary arteritis (polyarteritis nodosa, Takayasu's disease, systemic lupus erythematosus), cocaine abuse or spontaneous dissection of coronary arteries.

CORONARY CIRCULATION

The left main and right coronary arteries arise from the left and right coronary sinuses of the aortic root, distal to the aortic valve. Within 2.5 cm of its origin, the left main coronary artery divides into the left anterior descending artery (LAD), which runs in the anterior interventricular groove, and the left circumflex artery (LCX), which runs in the atrioventricular groove. The LAD gives branches to supply the anterior part of the septum (septal perforators) and the anterior, lateral and apical walls of the left ventricle (diagonals). The LCX gives obtuse marginal branches that supply the lateral, posterior and inferior segments of the left ventricular (LV).

The right coronary artery (RCA), runs in the right atrio-ventricular groove, giving acute marginal branches that supply the RA, RV and inferoposterior aspects of the LV. The posterior descending artery runs in the posterior interventricular groove and supplies the inferior part of the interventricular septum. It arises from the RCA in approximately 85% of people (dominant right system) and from the LCX in the remainder (dominant left system). The coronary anatomy varies greatly from person to person and there are many normal variants.

The RCA supplies the sino-atrial (SA) node in about 60% of individuals and in the remaining 40% SA node is supplied by LCX. The AV node is supplied by a small AV nodal artery which arises from the dominant coronary artery (RCA in 85%) (**Figure 1**). Proximal occlusion of the RCA, therefore, often results in sinus bradycardia and may also cause AV nodal block. Abrupt occlusions in the RCA, due to coronary thrombosis, result in infarction of the inferior part of the LV and often the RV. Abrupt occlusion of the LAD leads to anterior wall or anteroseptal myocardial infarction (MI). LCX causes infarction in the anterolateral territory of the LV. Acute occlusion of the left main coronary artery is usually fatal.

PHYSIOLOGY

The myocardium relies almost exclusively on oxidative metabolism for its energy needs. Even at rest the transmyocardial oxygen extraction is near maximal with a coronary venous O_2 saturation that is lowest in the body (25% to 35%). Any increase in myocardial O_2 demand can only be met by proportional increase in myocardial blood flow, chiefly mediated by reduction in coronary arteriolar resistance. The left coronary artery fills only in diastole while the RCA shows both systolic and diastolic coronary flow.

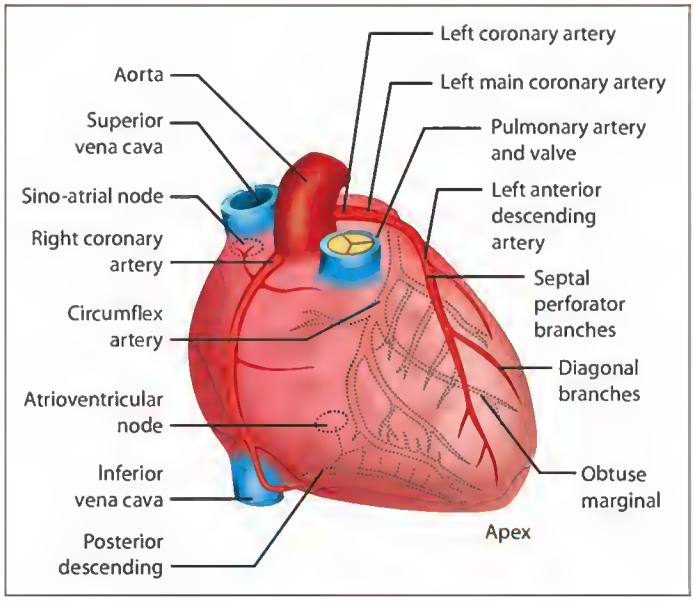


Figure 1: The coronary arteries of the heart. Diagram of the anterior view.

MAGNITUDE OF THE PROBLEM

Cardiovascular disease accounts for approximately 12 million deaths annually and is the commonest cause of death globally. Previously considered a disease of the affluent, the past three decades have seen considerable decline in the incidence and prevalence of atherosclerotic CAD in the industrialised western world; whereas at the same time, this problem is assuming epidemic proportions in the developing world. Asian Indians, whether living in their own country or elsewhere, have much higher incidence of CAD as compared to all other ethnic groups.

While the incidence of coronary artery disease has reduced by 50% in the west, in India it has doubled in the last 25 years. The prevalence of coronary artery disease in the years 1960, 1980, 1990 and 2000 progressively increased (2%, 4% to 6%, 9.5% and 10% to 15% respectively). In the rural India, the CAD prevalence increased two-fold from 2% to 4%. In urban India, the increase was three-fold from 3.45% to 9.45%. In 1990, 25% deaths in India were attributable to cardiovascular disease compared to 9% due to diarrhoeal disease, 12% due to respiratory infections and 5% due to tuberculosis.

RISK FACTORS

The National Heart Lung and Blood Institute of USA initiated the Framingham Heart Study in 1949 and by 1961, the concept of risk factors for CHD was established with hypertension and hypercholesterolaemia being identified for intervention.

The classically defined eight risk factors for CAD are hypertension, dyslipidaemia, diabetes, physical in activity and sedentary lifestyle, central obesity, stress and type A personality, family history of CAD and smoking. Of these, smoking, diabetes, hypertension and family history of premature CAD are particularly important. **Table 1** enlists the modifiable and non-modifiable risk factors for CAD.

Table 1: Risk Factors for Clinical Atherosclerosis

Non-Modifiable	Modifiable
Age	Dyslipidaemia
Male gender	Hypertension
Family history of CHD	Diabetes
Presence of CHD	Abdominal obesity
Menopause	Smoking
Physical inactivity	Diet

Asian Indians have the highest ethnic risk of CAD despite lower rates of smoking, hypertension, obesity and higher vegetarianism. The insulin resistance syndrome (metabolic syndrome X), lipoprotein(a), atherogenic dyslipidaemic phenotype and some newer emerging risk factors [homocysteine, tissue plasminogen activaetor (tPA), plasminogen activator inhibitor (PAI-1), fibrinogen, infections and inflammation] may be more relevant as underlying genetic susceptibility associated with a modest abnormality in lipid and lifestyle factors makes CAD assume an aggressive course in Asian Indians. Important risk factors in Asian Indians have been listed in **Table 2**. The INTERHEART study (2004) on 25,000 myocardial infarction patients confirmed nine risk factors attributing to CAD—ApoB/ApoA-1, smoking, diabetes, hypertension, abdominal obesity, psychosocial, fruits and vegetable intake, exercise and alcohol. Of these ApoB/ApoA-1 and smoking were especially associated with increased incidence of myocardial infarction in younger patients.

Table 2: Coronary Risk Factors for Asian Indians

Fixed
- Male age >35 years
- Female age >45 years
- Family history of premature CAD (at age <55 years)

Modifiable: Non-lipid
- Hypertension
- Cigarette smoking/tobacco abuse
- Diabetes mellitus/insulin resistance syndrome
- Apple obesity or body mass index >23
- Homocysteine >10 mmol/L
- High PAI – 1

Modifiable: Lipid
- Total cholesterol >150 mg/dL
- Triglycerides >150 mg/dL
- LDL cholesterol >100 mg/dL
- ApoA lipoproteins <100 mg/dL
- HDL <40 mg/dL males, <50 mg/dL females

Modifiable: Lipoprotein ratios
- TC/HDLc >4.5
- LDLc/HDLc >3.5
- ApoA/ApoB <1.2

SPECTRUM OF MYOCARDIAL ISCHAEMIA

The ischaemic heart disease can present as stable effort angina, unstable angina, non-Q wave MI, Q wave MI, heart failure and sudden cardiac death (**Table 3**). The understanding of the conversion of a stable atherosclerotic lesion to a plaque rupture with thrombosis has provoked a unifying hypothesis for the aetiology of acute coronary syndromes.

Table 3: Nomenclature of Myocardial Ischaemia

Old	Present
Asymptomatic	Asymptomatic
Stable effort angina	Stable effort angina
Unstable angina	Acute coronary syndromes, unstable angina without necrosis
Non-Q wave MI	Non-ST elevation MI (NSTEMI) (evidence of myocardial necrosis)
Q wave MI	ST elevation MI (STEMI)
Sudden death	Sudden death
Silent ischaemia	Ischaemic cardiomyopathy

CLINICAL PRESENTATION

Symptoms

The typical clinical presentation of angina refers to poorly localised retrosternal discomfort with radiation to neck, shoulders, arms, jaws, epigastrium or back; usually, not above the jaw and not below the umbilicus. Angina is typically triggered by physical activity, emotional stress, exposure to cold, consuming a heavy meal or smoking.

Pain is poorly localised, vague chest discomfort which may be described as squeezing, burning, tightness, choking, heaviness, hot or cold sensation, dyspnoea, fatigue, weakness, lightheadedness, nausea, diaphoresis, altered sensorium and syncope. These symptoms have been called angina equivalents.

Pain lasts for 2 to 8 minutes. Ischaemia seldom lasts more than 30 minutes without causing acute myocardial infarction (AMI). Pain is relieved with rest or sublingual nitroglycerine in 2 to 5 minutes.

It is less likely to be angina if it is localised (finger pointing), less than 30 s, or more than 30 min without AMI, exclusively at rest (except unstable/Prinzmetal), pricking or jabbing and changing sites of pain (**Figure 2**).

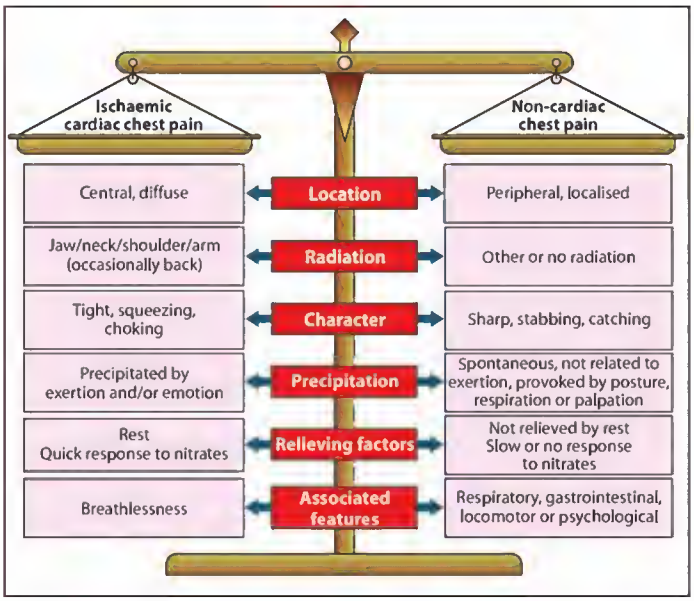


Figure 2: Identifying ischaemic versus non-cardiac chest pain.

The location of pain and its relation with exertion are two important factors in patient's history for determination of cause of chest pain. In presence of both factors (diffuse retrosternal pain and aggravation with exertion; relief on rest), chest pain is likely to be due to underlying CAD in 90% of patients. In presence either of one factor (atypical chest pain), underlying CAD is likely in 50% of patients. If both the factors are absent, the cause of pain is most likely non-cardiac.

A few patients have walk-through angina (pain gets relieved while the patient continues to walk). Decubitus angina is believed to be caused by blood volume shifts towards the lungs, resulting in rise in LV end-diastolic pressure. Nocturnal angina may be associated with nightmares.

Prinzmetal's angina attributable to intense coronary vasospasm was described first in 1959 by Prinzmetal with a consistent yet atypical pattern of angina at rest (non-threshold angina) precipitated by cold, emotional stress and smoking which was associated with ST-segment elevation. Paradoxic responses consistent with endothelial dysfunction have been described. Intense vasospasm is also seen in subjects who abuse cocaine and amphetamine. Provocative testing by inducing hyperventilation or administering intracoronary acetylcholine or ergonovine typically precipitate an attack of variant angina associated with focal spasm.

Grading of angina is based on NYHA classification, specific activity scale index and Duke activity status index. **Table 4** lists the conditions to be considered in differential diagnosis of coronary pain.

DIAGNOSTIC TESTING

For a patient with stable CAD, investigations are aimed at excluding non-cardiac cause of chest pain, assessment of risk factors for modification, risk stratification, stress testing to evaluate inducible ischaemia, LV function assessment, assessment for silent myocardial ischaemia and assessment of coronary anatomy where indicated.

Risk Factors

The patient should be evaluated for presence of underlying diabetes mellitus (Fasting and post-prandial blood sugar levels, HbA1C), dyslipidaemia (raised total cholesterol, LDL-C, VLDL-C, triglycerides, ApoB and reduced HDL-C). The presence of markers like hs-CRP, lipoprotein (a), homocysteine, tPA, PAI-I, fibrinogen, etc. can be indicators of underlying atherosclerosis.

Baseline Electrocardiogram

This is likely to be normal in over 90% cases and only helps to recognise LVH, bundle branch block, old MI or pre-excitation. A normal ECG does not exclude ischaemia as being a cardiac cause.

Stress Testing

Exercise is a common physiological stress used to elicit cardiovascular abnormalities not present at rest and to determine the adequacy of cardiac function. As exercise progresses, in individuals with underlying CAD, there occurs a mismatch between oxygen supply and demand which may manifest with electrocardiographic, regional wall motion or myocardial perfusion abnormalities. The commonly used exercise stress tests to diagnose underlying CAD are—treadmill stress test, dobutamine stress echocardiography and stress perfusion imagining.

Treadmill stress test

Treadmill stress test remains a cornerstone of cardiovascular evaluation. It is a simple, safe and cost-effective test in the diagnosis of coronary artery disease. The average present

Table 4: Common Causes of Chest Pain Mimicking Chronic Stable Angina

System	Syndrome	Clinical Description	Key Distinguishing Features
Cardiac	Angina	Retrosternal chest pressure, burning, or heaviness; radiating occasionally to neck, jaw, epigastrium, shoulders, or left arm	Precipitated by exercise, cold weather, or emotional stress; duration < 2 to10 minutes
Oesophageal	Acid peptic disease, gastro-oesophageal reflux	History of retrosternal burning, bloating sensation and reflux (linked angina)	Association with meals and posture, may be relieved by S/L nitrates
Musculoskeletal	Costochondritis	Sudden onset of intense fleeting pain	May be reproduced by pressure over affected joint; occasional patients have swelling and inflammation over costochondral joint
	Cervical disc disease	Sudden onset of fleeting pain	May be reproduced with movement of neck
	Trauma or strain	Constant pain	Reproduced by palpation or movement of chest wall or arms
Infections	Herpes zoster	Prolonged burning pain in dermatomal distribution	Vesicular rash, dermatomal distribution
Psychological	Panic disorder	Chest tightness or aching, often accompanied by dyspnoea and lasting 30 minutes or more, unrelated to exertion or movement	Patient may have other evidence of emotional disorder

Physical Findings

The physical finding may reveal risk factors of CAD. These include elevated BP, corneal arcus, xanthelasma, retinal arteriolar changes, diagonal earlobe crease, etc. The cardiovascular system (CVS) examination is normal (except for audible S4) in most individuals with stable angina. The presence of systolic murmur may suggest underlying aortic stenosis, mitral valve prolapse (MVP) or hypertrophic obstructive cardiomyopathy (HOCM) as cause of angina.

sensitivity and specificity of exercise testing in diagnosing coronary artery disease in 68% and 77%. In single vessel disease, the sensitivity ranges from 25% to 71% while that for left main and triple vessel disease is 86%. The results are less specific with more false positive outcomes in patients with marked resting ST-segment depression, digitalis effect, valvular heart disease, hypokalaemia and young female subjects with non specific T wave changes. Stress echocardiography and thallium stress testing increase the diagnostic yield especially in the above subsets.

Prognostic yield of exercise testing results should not be considered in isolation. Exercise parameters associated with adverse prognosis include duration of symptom limiting exercise, more than 5 METs, exercise-induced ST-elevation, sustained ventricular tachycardia, down-sloping ST-segment depression involving more than 5 leads and 5 minutes into recovery. On the other hand, excellent exercise tolerance more than 10 METs generally indicates good prognosis regardless of anatomical disease.

Stress perfusion imaging and myocardial cellular metabolism assessment

See chapter 7 of this section.

Echocardiography and stress echocardiography in CAD

Use of ultrasound for analysing the structure and function of the heart provides useful non-invasive information in the overall assessment of a patient of CAD. Global LV systolic function frequently guides the choice of therapy. Segmental wall motion abnormalities are useful and specific. These wall motion abnormalities can be segmentally scored. Various complications of CAD such as dyssynergic areas, aneurysm, intramural clot, free wall rupture, pseudoaneurysm formation, pericardial effusion, mitral filling patterns, assessment of aetiology and severity of mitral regurgitation, assessment of tricuspid regurgitation, deduction of PA pressure and LVEDP can be performed. Myocardial viability assessment can be performed using dobutamine stress echocardiography in patients with CAD and LV dysfunction. Stunned myocardium is a transient myocardial dysfunction that occurs after an acute episode of ischaemia and may occur despite the restoration of normal blood flow. This may last several days to weeks. Contrast echocardiography and cardiac MRI are techniques that reliably identify 'stunned myocardium'. Impaired regional myocardial energy production, calcium overload, free radical injury and ischaemic damage to extra-cellular matrix may be underlying mechanisms for stunning.

Hibernating myocardium refers to persistently dysfunctional myocardial segments in chronic low flow state who have potential for recovery of function with restoration of flow. Positron emission tomography comparing a perfusion tracer rubidium and metabolism tracer, flurodeoxy glucose (FDG), cardiac MRI and dobutamine stress echocardiography are techniques developed to identify hibernating myocardium. Dobutamine stress echocardio-graphy has been found to be the best predictor of improvement following revascularisation ('contractile reserve') although cardiac MRI may be more specific for diagnosis of viability.

Dobutamine echocardiography is an established technique for the identification of hibernating myocardium. A segmental comparison of systolic thickening before and after administration of dobutamine is performed using recorded images. Low-dose dobutamine inducing increased systolic thickening at low dose that deteriorates at high dose ('biphasic response') is most specific for predicting response to revascularisation. The greater the number of viable segments, the greater is the chance of survival after revascularisation.

There are thus several techniques for identification of viability. PET is the 'gold standard' but dobutamine echocardiography may be the most specific for prediction of improvement following revascularisation. However, cardiac MRI probably identifies scar tissue the best with excellent reproducibility and will probably be used more extensively to make decisions about intervention in the future.

Ambulatory Electrocardiographic Monitoring

Silent myocardial ischaemia is defined as documented episodes of ischaemia not associated with any typical or atypical symptoms that occur among patients with obstructive coronary artery disease. Holter monitoring is required to identify these clinically asymptomatic events. The asymptomatic MI and ischaemic episodes are common in diabetics.

Coronary Angiography

The coronary arteries can be visualised by either invasive or computed tomography (CT) coronary angiography. While CT coronary angiography presently cannot be considered a routine replacement for invasive coronary angiography, clinical application, especially to rule-out coronary stenoses in patients who do not have a high pretest likelihood of disease, is conceivable.

The major epicardial branches and their second- and third-order branches can be visualised using coronary arteriography. CAD is considered to be significant when more than 70% stenosis of arterial diameter is seen in one or more of these vessels or more than 50% of left main coronary artery is involved. Stenoses of less than 50% has major prognostic implications because these lesions most commonly lead to plaque rupture and acute MI. Subcritical stenoses of less than 50% are best characterised as non-obstructive CAD; obstructive CAD is classified as one-, two- or three-vessel disease.

Cardiac Biomarkers

See chapter 18 and 19 of this section.

Multislice CT Coronary Angiogram

CT scan in CAD has multiple potential uses: assessment of ventricular function, visualisation of coronary arteries and evaluation of coronary artery calcification. Coronary calcium is a surrogate marker for coronary atherosclerotic plaque but only non-linear correlations exist between amount of coronary calcium and angiographic severity of CAD. Therefore, the detection of even large amounts of coronary calcium does not imply the presence of significant stenosis, but the complete absence of coronary calcium rules out significant CAD. Thus, multislice CT, in experienced hands is a modality that can rule-out significant CAD in low-risk population non-invasively. Applications beyond this are still subject to validation but the non-invasive nature of this investigation makes it an attractive application for intense scrutiny.

THERAPY OF CORONARY ARTERY DISEASE

Goals of treatment are to improve quality of life, reduce incidence of unstable angina and MI, decrease frequency and severity of anginal episodes and to improve the longevity. The modalities of treatment are risk factor modification, lifestyle modification, pharmacological measures and revascularisation shown in **Table 5** and **Figure 3**.

Table 5: Methods of Treatment of CAD

- Lifestyle modification
- Pharmacologic
  - Anti-platelets
  - Lipid lowering agents
  - Nitrates
  - Beta-blockers
  - Calcium channel blockers
- Adjunctive treatments
  - Metabolic modulation: Trimetazidine
  - LV Dysfunction
    - ACE-inhibitors
    - Aldosterone antagonists
  - Gene therapy
  - Stem cell therapy
- Percutaneous coronary intervention
- Surgical revascularisation

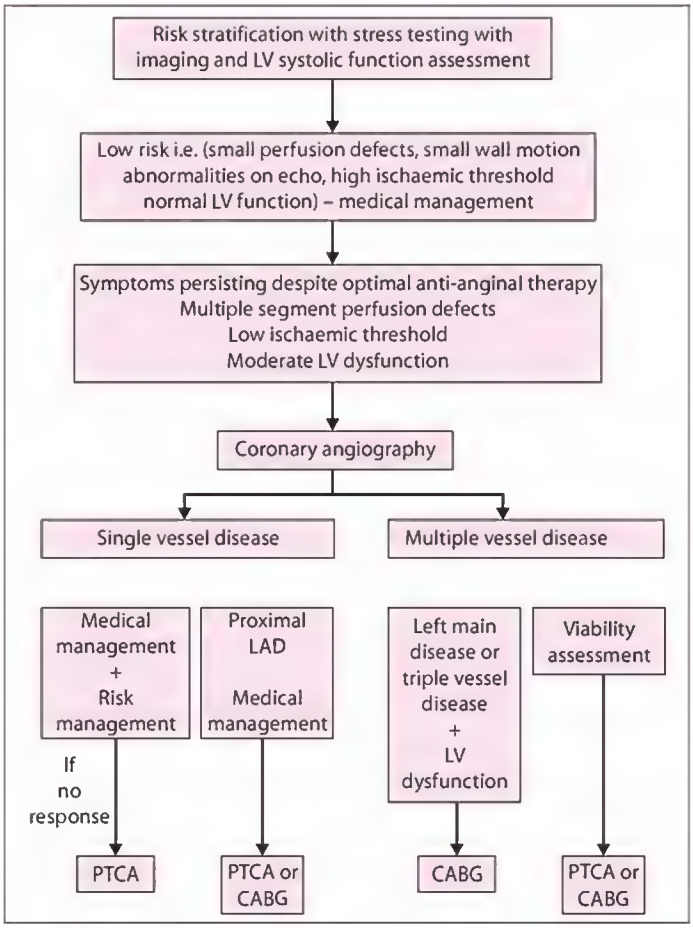


Figure 3: Approach for management of patient with stable angina.

CABG= Coronary artery bypass grafting; PTCA= Percutaneous transluminal coronary angioplasty.

Risk Factor Modification

Control of hypertension

Patients of angina and hypertension benefit with control of BP to less than 140/90 mm Hg (more aggressive reduction in diabetics). A meta-analysis of nine major trials of antihypertensive treatment of elderly patients showed 12% reduction in all-cause mortality, 25% reduction in CAD mortality and 30% reduction in stroke mortality. The totality of available data suggests that BP control favourably influences outcome. There is a debate about the best agent for BP control in uncomplicated hypertension, but beta-blockers have a definite role in symptomatic CAD. ACE-inhibitors and calcium channel blockers can be used in patients with CAD for effective BP control.

Diabetes mellitus and insulin resistance

Strict control of diabetes has beneficial effects in reducing the incidence of microvascular complications such as retinopathy and renal disease. The effect on macrovascular complications is less established. Diabetes is considered a CAD equivalent and patients should be started on treatment for secondary prevention of CAD. Diabetes accelerates atherosclerotic process and leads to more severe, extensive diffuse disease with higher left main disease and less collaterals. The major risk factors are amplified in diabetics with diabetic dyslipidaemia (high TG and small dense LDL and low HDL), increased prevalence of hypertension and insulin resistance syndrome. Efforts to target all risk factors among diabetics must be undertaken with exercise, control of body weight and blood sugar, smoking cessation, lipid lowering and aggressive control of blood pressure.

Dyslipidaemia

Dyslipidaemia, especially hypercholesterolaemia, elevated LDL and decreased HDL levels are strongly associated with increased risk for CAD. 1% reduction in cholesterol causes a 2% to 3% reduction in CHD risk. NCEP ATP-III guidelines recommend different therapeutic targets depending on a patient's overall risk. Patients with existing CHD (or a CHD risk equivalent, such as diabetes or peripheral vascular disease) are at the highest risk for a cardiovascular event and thus have the lowest LDL target (less than 100 mg/dL), with the option of setting the goal at less than 70 mg/dL for those who have had a recent acute coronary event or who have CVD combined with either diabetes or severe or poorly controlled risk factors.

Lipoprotein(a) is an LDL-like particle with apolipoprotein(a) attached to apolipoprotein B. A large body of literature links Lp(a) to CAD especially among Asian Indians. Cardiovascular risk appears to increase incrementally with Lp(a) but more with Lp(a) greater than 30 mg/dL.

Lifestyle Modification

Smoking cessation, a healthy diet and regular exercise, maintaining ideal body weight, improving fitness levels can only be achieved by lifestyle modification, dietary advice and counselling. These may forestall the need for pharmacologic measures to reduce coronary risk.

Cigarette smoking may be the single-most preventable cause of death and its cessation reduces risk of CAD mortality by 50% in 1 year. After 10 years, the coronary mortality risk is reduced to that of non-smokers. Exposure to second-hand smoke increase risk to death due to CAD by 30%. Cigarette smoking activates platelets, increase circulating fibrinogen, increases heart rate and blood pressure.

Exercise

Exercise conditions the skeletal muscles, which decreases oxygen consumption for the same workload. It also lowers heart rate for any level of exertion. It is recommended that aerobic isotonic exercises with a goal of 85% age predicted maximal heart rate for 20 to 30 minutes be achieved 3 to 4 times a week for secondary prevention.

Diet

Vegetarian diets with less than 10% fat and no dairy products have been shown to be beneficial. It is recommended to limit saturated fat intake to less than 7% of calories, keep trans fatty acids as low as possible and use dietary adjuncts to improve the likelihood of attaining LDL-C goals like dietary fibre, dietary plant stanol/sterol esters, etc.

Obesity

Obesity especially central obesity is associated with increased risk of developing CAD. Obese patients have higher all cause mortality rates and are more likely to be diabetic. Hence, regular exercise is recommended in obese patients for adequate weight loss and risk reduction.

Stress and type A personality

In patients with stress and type A personality, biofeedback relaxation techniques and yoga can help modify anger, hostility and stress.

Pharmacological Measures

Patients with chronic stable angina need to be treated with anti-anginal medications. The three conventional anti-anginal class of drugs are nitrates, beta-blockers and calcium channel blockers. Beta-blockers are the preferred agents and should be used in all unless contraindicated. Target resting heart rate of 60 and post-activity heart rate of less than 100 is to be achieved with adequate beta-blocker doses. Cardioselective agents like metoprolol and bisoprolol are preferred. Nitrates—short-acting (isosorbide dinitrate) and long-acting are used 3 times and 2 times a day, respectively. Nitrates are good agents for acute relief of angina for which amyl nitrate and isosorbide dinitrate are used. In patients with class III and IV angina, polytherapy with all three class of agents is used. All these patients need to be on aspirin. Statins (simvastatin, atorvastatin, rosuvastatin, etc.) should be used to achieve LDL goals of less than 70 mg/dL. ACE-inhibitors (preferably ramipril) retard the progress of atherosclerosis in patients with CAD and have mortality reducing effects as documented in HOPE study.

Revascularisation

The modalities available for revascularisation in patients with CAD are coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA). The option of treatment strategy is based on risk stratification with stress testing and LV systolic function assessment. Low-risk patients (small perfusion defects, small wall motion abnormalities on echo, high ischaemic threshold, normal LV function) can be managed medically. Persistence of symptoms despite optimal anti-anginal therapy, presence of multiple segment perfusion defects, low ischaemic threshold and moderate LV dysfunction warrant coronary angiography (CAG). In patients with single vessel disease, medical management can be the treatment option in low-risk patients. In case of persistent symptoms and high-risk patients (e.g. proximal LAD involvement), double vessel disease, PTCA is recommended. Surgical revascularisation is the treatment of choice for significant left main disease and triple vessel disease with diminished LV function. Registry based data suggests that multivessel stenting may be as efficacious in the short term as CABG. Diabetics often have small-sized vessels with diffuse disease and are poor candidates for PCI-based therapies. In insulin-requiring diabetics, CABG is definitely better. The grafts used in CABG patients include venous (reversed saphenous vein grafts harvested from legs) and arterial grafts [left internal mammary artery (LIMA) and radial artery grafts]. The arterial grafts (LIMA) have better patency and long-term outcomes (especially in diabetics).

Acute complications of PTCA include death (<1.0%), periprocedural MI (0.4%), abrupt closures due to dissections and thrombus, etc. A 15% to 20% restenosis rate has been reported with the bare metal stents. The advent of DES has reduced restenosis rates to 8% to 12%. However, subacute and late stent thrombosis have emerged as a small but definite risk in patients who undergo intervention with a DES.

Percutaneous intervention and medical therapy should be viewed as complimentary rather than opposing strategies. While PTCA improves coronary blood flow considerably more than lipid lowering, its effects are restricted to the target vessel and need to be followed with lipid lowering and medical management.

Compared to medical treatment CABG improves survival among high-risk patients with stable angina such as left main disease, three vessel disease with impaired LV function and two vessel disease including proximal LAD stenosis associated with LV dysfunction. The greater use of arterial conduits, minimal access surgery and surgery without cardio-pulmonary bypass has improved surgical results.

Newer Approaches

Therapy with direct infusion of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been shown to increase collaterals flow. Approaches using gene therapy to overexpress endogenous growth factors to improve development of collaterals have been proposed. However, initial optimism was not supported by trial-based evidence.

Stem cell therapy has been used in all situations in CAD and currently is under intense scrutiny in the immediate post-MI situation. There are conflicting data in this situation and the verdict is still not out. Currently, stem cell therapy is only being used in clinical trial situations.

CORONARY ARTERY DISEASE IN WOMEN

Women with CAD may present differently than men, have different pathophysiologies and risk profiles and are often significantly older and thus often have poorer outcomes. Plaque compositions are different (more cellular and fibrous), more endothelial dysfunction, more plaque erosion compared to rupture and more thrombogenesis (higher fibrinogen). They also have worse outcomes after CABG (more LVH, smaller coronary size). Women also have higher incidence of microvascular angina, vasospastic angina and abnormal coronary vasodilator reserve. However, they also have a higher incidence of atypical chest pain, a fact that often complicates evaluation of chest pain in women. Non-invasive diagnostic testing is more often false-positive in women and mortality after MI is worse in women after 60 years as compared to men. Diabetes eliminates the 'female advantage' of women. Obesity and fat distribution appear to be more independent risk factors than in men. The premenopausal female has a relative protection against CAD and a multitude of observational studies have suggested that oestrogen replacement therapy reduces risk. The recently reported heart and oestrogen/progestin replacement study (HERS) showed no reduction in recurrent coronary events in the active treatment arm in postmenopausal female survivors of AMI.

CONCLUSION

In summary, the treatment of coronary artery disease is continuously evolving. Current treatment involves constant risk stratification, modification of risk factors, optimising anti-platelet therapy, controlling blood pressure and blood sugar, symptomatic relief and revascularisation. Prevention of CAD should be an important part of health education as it may be the most cost-effective measure towards reducing the disease burden of this modern epidemic.

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12.18 Acute Coronary Syndrome

Gurpreet Singh Wander, Naveen Kumar Gupta

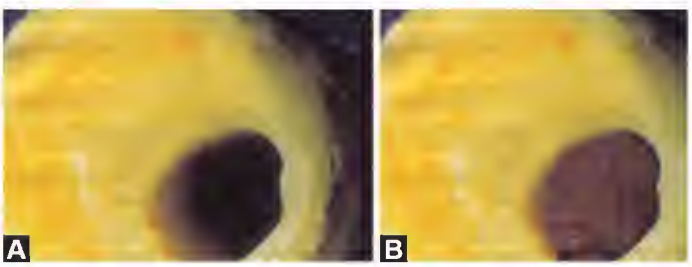
The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischaemia and covers the spectrum of clinical conditions ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). Unstable angina was the term used earlier and now NSTEMI is used more commonly. The present chapter deals with UA and NSTEMI which are closely related conditions but they differ in severity. STEMI (acute myocardial infarction) is discussed in next chapter.

EPIDEMIOLOGY

According to OASIS registry, Indian patients are 7 to 8 years younger than Western patients with mean age of 57 years as against 65 years in Western population. Also, our patients are more often diabetic. A large registry – CREATE registry was done in 2008, involving 20,000 patients admitted in multiple centres in India. Thirty three per cent of these patients were less than 50 years of age. Patients of NSTEMI/STEMI reached hospital later as compared to the Western patients. In young patients coming from poorer socio-economic strata, smoking was the risk factor in 50% of the patients. In older individuals from rich areas, diabetes and hypertension were more important risk factors. The mortality rate of NSTEMI in CREATE registry was 4% which is 1% more than in Western registries.

PATHOPHYSIOLOGY

Atherosclerosis is the ongoing process of plaque formation that involves primarily the intima of large and medium-sized arteries; the condition progresses overtime, before manifesting itself as an ACS. The pathogenesis of ACS involves an interplay among the endothelium, the inflammatory cells, and the thrombogenicity of the blood. After plaque rupture (or endothelial erosion), the subendothelial matrix (which is rich in tissue factor, a potent procoagulant) is exposed to the circulating blood; this exposure leads to platelet adhesion followed by platelet activation and aggregation and the subsequent formation of a thrombus (**Figure 1**). Two types of thrombi can form: a platelet-rich clot (a *white clot*) that forms in areas of high shear stress and partially occludes the artery, or a fibrin-rich clot *(a red clot)* that is the result of an activated coagulation cascade and decreased flow in the artery. Red clots are frequently superimposed on white clots, and cause total occlusion resulting in STEMI. When occlusion is subtotal, UA/NSTEMI are usually the result (**Figure 2**).



Figures 1A and B: (A) Atheromatous plaque; (B) Ruptured plaque with thrombus.

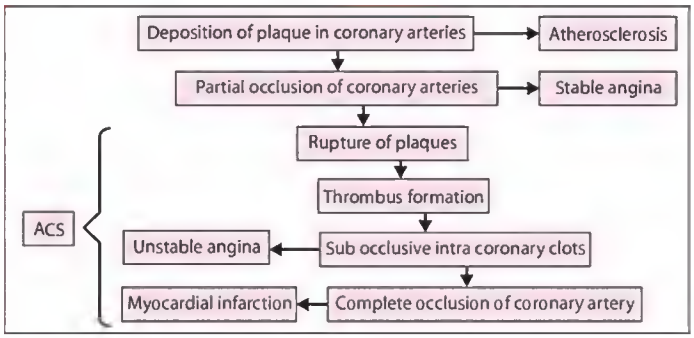


Figure 2: The spectrum of acute coronary syndromes.

The high-risk or vulnerable plaques are characterised by a large lipid core, thin fibrous caps, a high density of macrophages and T lymphocytes, a relative paucity of smooth muscle cells, locally increased expression of matrix metalloproteinases that degrade collagen, eccentric outward remodelling, and increases in plaque neovascularity and intraplaque haemorrhage. Inflammation, an important determinant of the 'vulnerability' of plaques, is related to an increase in the activity of macrophages at the site of plaque. Seventy per cent of lesions on coronary angiography that cause ACS are less than 50 per cent stenosis of arterial diameter. So most ACS episodes are due to rupture of non-obstructive plaques. The plaque usually ruptures at shoulder point.

CLINICAL FEATURES

History

ACS occurs more commonly in males. As compared to stable angina, the discomfort associated with UA is more severe, occurs at rest, lasts longer and is usually described as frank pain (**Figure 3**). It is located in the substernal region (sometimes,

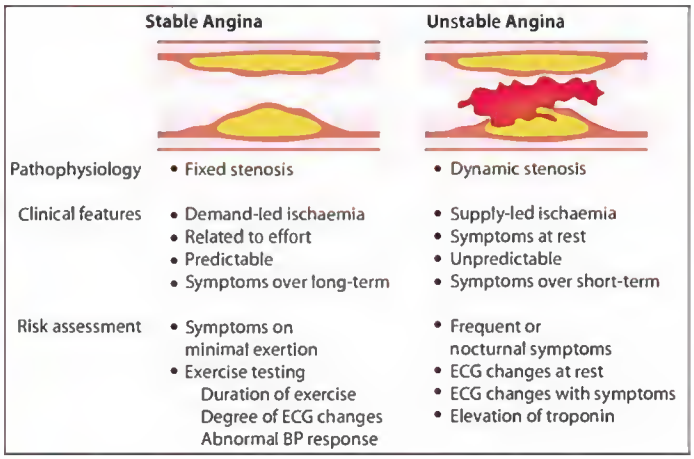


Figure 3: Clinical features and risk assessment of patients with stable or unstable angina.

the epigastric area), radiates to the neck, jaw, left shoulder, and left arm. The discomfort is often accompanied by burping and eructations and is at time mistaken as 'gas' by the patients. Some patients may present with symptoms other than chest discomfort; such 'angina equivalents' symptoms include dyspnaea (most common), nausea and vomiting, diaphoresis, and unexplained fatigue. Atypical presentations are more common among women, elderly people and in diabetics. Rarely, syncope may be the presenting symptom of ACS. Besides characteristics of pain other factors that help to identify pain of CAD are older age, male sex, a history of CAD and number of traditional risk factors present.

Unstable angina was sub classified by Dr. Eugene Braunwald as class I, II, III according to severity and prognostic significance. It is also sub classified as A,B, C according to clinical circumstances (**Table 1**).

A diagnosis of NSTEMI can be made when the ischaemia is sufficiently severe to cause myocardial damage that results in the release of a biomarker of myocardial necrosis into the circulation (cardiac-specific troponins T or I, or muscle and brain fraction of creatine kinase [CK-MB]).

Table 1: Braunwald Clinical Classification of Unstable Angina

	Secondary UA (A)	Primary UA (B)	Post-MI Angina (C)
New onset angina (I)	I A	I B	I C
Angina at rest not within preceding 48 hours (II)	II A	II B	II C
Angina at rest within 48 hours (III)	III A	III B-T Positive III B-T Negative	III C

Arrow indicates that with increasing severity prognosis worsens.

Clinical Examination

The cardiovascular examination is mostly normal. The findings that indicate a large area of ischaemia and high-risk include diaphoresis; pale, cool skin; sinus tachycardia; a third or fourth heart sound; basilar rales; and hypotension. The physical examination may also provide clues that can help in determining the differential diagnosis. For example, unequal pulses or a murmur of aortic regurgitation indicates possible aortic dissection, whereas a pericardial friction rub suggests acute pericarditis.

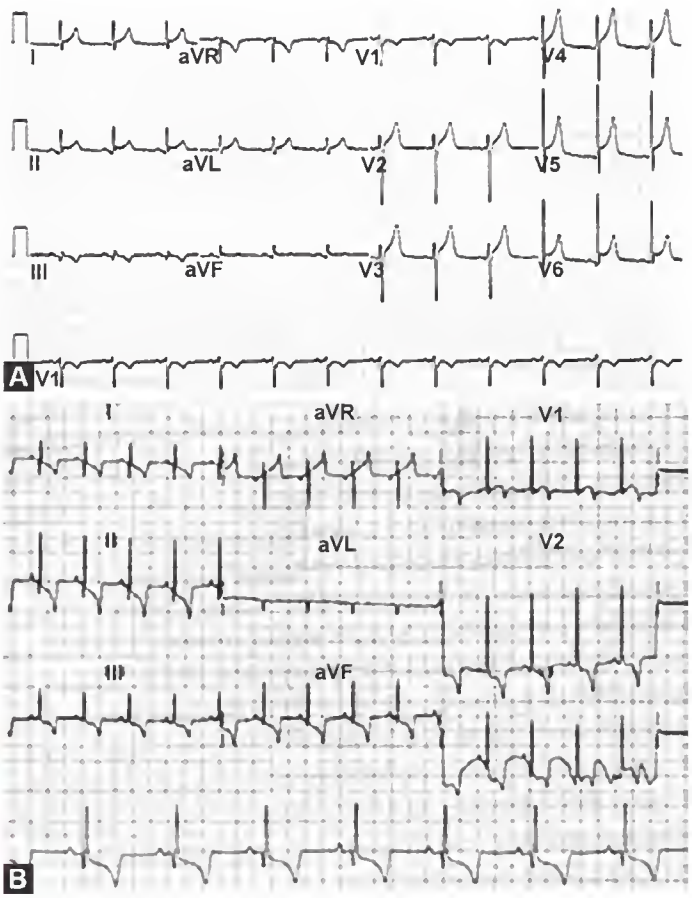
INVESTIGATIONS

Electrocardiography

Findings on ECG associated with UA include ST-segment depression, transient ST-segment elevation, T-wave inversion, or some combination of these changes. Depending on the severity of the clinical presentation, these findings are present in 30% to 50% of the patients. New ST-segment deviation, even of only 0.05 mV, is an important and specific measure of ischaemia and prognosis. T wave inversion is sensitive for ischaemia but is less specific. Patients with no ECG changes are at a lower risk of complications than those with ECG changes. Myocardial ischaemia is dynamic and patients hospitalised for UA/NSTEMI should undergo serial ECG tracings or continuous ST segment monitoring (**Figure 4**).

Cardiac Biomarkers

Markers of myocardial necrosis should be measured in all patients of acute coronary syndromes and include CK-MB and troponin-T/troponin-I. They are used for the diagnosis of NSTEMI and for prognostication. Troponins are more sensitive and specific than any other biomarker. Both qualitative as well as quantitative measurements are available. There is a direct relationship between the degree of troponin elevation and mortality. Patients with elevated Troponin levels have 25% risk of death or MI at 6 months as compared to less than 5% risk in patients with normal Troponin levels. Troponins are not released before 4 to 5 hours of symptoms, so these should be measured after 4 to 5 hours of symptom onset and if results are negative, these are measured after 8 to 12 hours of symptom onset. Troponins remain elevated up to 10 to 14 days of symptom onset. Levels of CK-MB start increasing after 10 to 12 hours of symptom onset and remain elevated for 24 to 36 hours. It is rapid, cost- efficient and detects early reinfarction but lacks specificity in setting of skeletal muscle disease or injury, including surgery.



Figures 4A and B: Electrocardiographic changes in ACS. (A) Normal or non-diagnostic ECG; (B) ST depression or dynamic T wave inversions.

Other Laboratory Tests

A chest X-ray is usually obtained at the time of admission. A full lipid profile should be obtained within 24 hours of the onset of ACS. Elevated CRP levels relate to an increased risk of mortality. B-type natriuretic peptide (BNP) provides useful prognostic information across the entire spectrum of patients with ACS as a marker of heart failure which may be associated in some high-risk patients.

Echocardiography

Echocardiography is the rapid bed side tool for assessment of regional wall motion abnormalities (RWMA), LV functions and mitral regurgitation. It also helps to rule out conditions like aortic

stenosis (AS), hypertrophic obstructive cardiomyopathy (HOCM) and mitral valve prolapse (MVP) which may have similar presentations.

Risk Stratification

Patients of ACS have variable prognosis. At one end of spectrum are young patients with new onset angina, no ECG changes, non-elevated biomarkers and no haemodynamic instability. These patients are managed pharmacologically and they should undergo non-invasive testing (TMT, stress echocardiography) after 10 days of symptom onset. At the other end are patients with history of recurrent/rest angina, fresh ECG changes, elevated biomarkers and, haemodynamically unstable patients who need early invasive treatment strategy in the form of PCI.

Patients with ACS are risk stratified on the basis of certain criteria, to assess which of them would benefit from early invasive therapy (percutaneous coronary intervention) and who will be managed conservatively (**Table 2**). Many risk profile models like TIMI (**Table 3**), GRACE have been proposed for triage assessment. The TIMI risk score is determined by seven variables, each of which is assigned one point. Patients with scores of five or more have been shown to have a higher risk of adverse events and a higher mortality and these patients should be considered for early coronary angiography and revascularisation.

Forty per cent of rich and 8.5% of the poor patients had coronary angiography done in the CREATE registry. So besides above listed factors, socio-economic status also effects the decision for invasive strategy.

Table 2: Selection of Initial Treatment Strategy: Invasive versus Conservative

Invasive	Recurrent angina or ischaemia at rest or with low-level activities despite intensive medical therapy
	Elevated cardiac biomarkers (TnT or TnI)
	New or presumably new ST-segment depression
	Signs or symptoms of HF or new or worsening mitral regurgitation
	High-risk findings from non-invasive testing
	Haemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 month
	Prior CABG
	High-risk score (e.g. TIMI, GRACE)
	Reduced left ventricular function (LVEF < 40%)
Conservative	Low-risk score (e.g. TIMI, GRACE)
	Patient or physician preference in the absence of high-risk features

CABG = Coronary artery bypass grafting; GRACE = Global registry of acute coronary events; HF = Heart failure; LVEF = Left ventricular ejection fraction; PCI = Percutaneous coronary intervention; TIMI = Thrombolysis in myocardial infarction; TnI = Troponin I; TnT = Troponin T.

Coronary Angiography

Coronary angiography is done in all patients who are stratified as high-risk by risk profile models as described above. Angiography is the key in diagnosing the extent, location and severity of lesions and in planning revascularisation [percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)]. More than 80% patients with UA/NSTEMI show significant coronary lesions on coronary angiography.

Table 3: The TIMI Risk Score

TIMI Risk Score (No. of Risk Factors)*	Risk of Death, MI, or Urgent Revascularisation (%)
0 or 1	~ 5%
2	~ 10%
3	~ 15%
4	~ 20%
5	~ 25%
6	~ 40%

** Risk factors include: Age ≥ 65 years; ≥ 3 CAD risk factors; Known CAD (>50% stenosis); Prior aspirin therapy; ≥ 2 anginal episodes in last 24 hours; ST deviation ≥ 0.5 mm; Elevated Troponins.*

MANAGEMENT

The principles of management are general measures, pharmacological therapy and revascularisation.

General Measures

Patients with definite ACS are admitted to the hospital for further treatment. Admission to the coronary care unit (CCU) is recommended if there is an evidence of active, ongoing ischaemia or haemodynamic or electrical instability. The other measures include bed rest till patient is pain free for at least 24 hours, mild sedation, quiet environment, morphine or pethidine if pain is not substantially relieved by nitrates and beta-blockers and stool softeners to avoid straining.

Pharmacological Therapy

In general, all patients should receive dual anti-platelet agent therapy (aspirin and clopidogrel), antithrombotic therapy (unfractionated heparin or low molecular weight heparin), beta-blockers, statins and ACE-inhibitors.

Dual anti-platelet therapy includes aspirin and clopidogrel. Aspirin blocks the synthesis of thromboxane A2 by irreversibly inhibiting cyclooxygenase 1, thereby diminishing platelet aggregation. Randomised trials demonstrate that, compared with placebo, aspirin reduces the risk of death or MI by more than 50% for patients presenting with UA/NSTEMI.

Clopidogrel is a thienopyridine derivative that blocks the P2Y12 adenosine diphosphate (ADP) receptor on platelets. This action decreases platelet activation and aggregation, increases bleeding time, and reduces blood viscosity. Therapy with clopidogrel and aspirin is recommended for essentially all patients with UA/NSTEMI.

The platelet GP IIb/IIIa inhibitors are potent and specific inhibitors of platelet aggregation. They act by interrupting the final common pathway of fibrinogen-mediated cross-linkage of platelets. Several large trials involving patients with UA/NSTEMI have shown that the GP IIb/IIIa inhibitors are of substantial benefit for patients at high-risk, those undergoing PCI, or both. Three agents are currently available for use: abciximab, eptifibatide, and tirofiban. The main risk associated with GP IIb/IIIa inhibitors is an increased rate of haemorrhage, usually at the site of vascular intervention.

Low molecular weight heparins (LMWH) have several advantages over conventional heparins, including ease of administration (twice a day), a lower rate of thrombocytopaenia, more bioavailability, and less binding to plasma proteins, a factor that renders monitoring the level of anticoagulation unnecessary.

The factor Xa inhibitor fondaparinux is equivalent for efficacy compared with enoxaparin with a lower risk of major bleeding and have the better benefit risk ratio besides once daily dosing.

Direct thrombin inhibitors have several potential advantages over indirect thrombin inhibitors (such as UFH or LMWH): do not require a cofactor such as anti-thrombin for their action and directly inhibit clot-bound thrombin, no interaction with plasma proteins and no thrombocytopaenia. Bivalirudin is used for the treatment of patients with UA/NSTEMI selected for an early invasive strategy.

Nitrates act as vasodilator, thereby reducing myocardial oxygen demand via venodilatation and enhance myocardial oxygen delivery by dilating large coronary arteries and improving collateral flow to ischaemic areas. Nitrates relieve chest pain but do not reduce mortality in ACS.

Beta-blockers can be used IV initially, if there is ongoing ischaemia and pain, followed by oral therapy. Beta-blockers inhibit β-1 adrenergic receptors in the myocardium and decrease myocardial contractility and heart rate, thereby reducing myocardial oxygen demand. They reduce the incidence of subsequent MI, recurrent ischaemia, or both.

Calcium channel blockers are used in patients with resistant ischaemia despite beta-blocker therapy and in those with contraindications to beta-blockers. Calcium channel blockers inhibit the contraction of both the myocardium (thereby reducing myocardial oxygen demand) and the vascular smooth muscle (thereby causing coronary vasodilatation and improving myocardial blood flow). These agents should not be administered to patients with severe LV dysfunction or pulmonary oedema.

In the absence of contraindications, lipid-lowering therapy with statins should be initiated for all patients with UA/NSTEMI, regardless of baseline LDL cholesterol levels.

Revascularisation

Revascularisation consists of measures to open the culprit vessel/(s) to improve the perfusion to the ischaemic myocardium, after identification of the location and extent of the lesions on coronary angiography (CAG). It can be done by percutaneous coronary intervention (PCI), i.e. percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG).

The choice of the revascularisation procedure depends on several factors, including the patient's age, clinical status, location and extent of lesions and especially, in the Indian setting—financial status. In CREATE registry, 6.7% of the patients of NSTEMI get PCI as compared to 30% patients in Western registries. This major difference is due to cost factor. In general, patients with significant triple vessel disease, left main coronary artery lesions and with lesions that are anatomically difficult to stent, are candidates for CABG.

In the field of PCI, many advances have been made. Earlier, it involved simple balloon dilatation of lesions (with consequent high restenosis rates). With the availability of bare metal stents (BMS), restenosis rates were significantly reduced across the coronary lesions. The development of special stents coated with drugs like sirolimus and paclitaxel [drug-eluting stents(DES)], further reduced restenosis rates to single digit percentages. These drugs have an anti-mitotic effect, whereby they inhibit neointimal proliferation, which is considered the major mechanism of in stent restenosis. To prevent the rate of progression of late restenosis, newer polymer free stents are under investigation.

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12.19 Acute Myocardial Infarction

Gurpreet Singh Wander, Naved Aslam

Acute myocardial infarction (AMI) is a clinical syndrome that results from occlusion of a coronary artery with resultant death of cardiac myocytes in the region supplied by that artery. When these patients present in emergency, they have ST elevation in ECG and so are referred as ST elevation myocardial infarction (STEMI). Depending on the distribution of the affected coronary artery, AMI can produce a wide range of clinical sequelae, varying from a small, clinical silent region of necrosis to a large area of infarcted tissue resulting in cardiogenic shock and death.

AMI is the leading cause of death in the developed and developing countries, including India. The true incidence of AMI is difficult to judge because of varied reporting pattern. Moreover, up to 1/3rd cases die at home before they reach hospital or are examined by qualified practitioner. The risk of having an AMI increases with age, male gender, smoking, dyslipidaemia, diabetes, hypertension, abdominal obesity, a lack of physical activity, low daily fruit and vegetable consumption and psychosocial factors. As much as 90% of risk of AMI has been attributed to these modifiable risk factors in the INTERHEART study.

PATHOPHYSIOLOGY

AMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery (vascular injury) previously affected by atherosclerosis. As discussed in previous chapter, acute coronary syndrome occurs due to rupture of atheromatous plaque and subsequent formation of thrombus over it. STEMI and AMI occur when this thrombus causes complete occlusion of coronary artery, thus resulting in myocardial necrosis. Myocardial necrosis starts early within 15 to 20 minutes of occlusion and is complete by 6 to 9 hours depending on collateral circulation and recanalisation. It is for this reason that first 6 hours are most risky (time for primary ventricular fibrillation) and also any reperfusion therapy has to be done within this period. The central area of myocardial necrosis is surrounded by area of myocardial injury which is surrounded by area of myocardial ischaemia. Initially, inflammatory cells reach the site of myocardial necrosis and endocardium becomes eroded. Over period of 2 to 6 weeks, scarring occurs and results in myocardial scars which subsequently, remodels over months in the form of dilatation of infarcted segment and latera also of the non-infarcted segment in case the size of infarct is large.

In rare cases, AMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities and coronary spasm. The amount of myocardial damage caused by coronary occlusion depends on the territory supplied by the affected vessel, the duration of coronary occlusion, the quantity of blood supplied by collateral vessels to the affected tissue, the demand for oxygen of the myocardium whose blood supply has been suddenly limited, native factors that can produce early spontaneous lysis of the occlusive thrombus, and the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

CLINICAL PRESENTATION

A precipitating factor is present before AMI in ~15% cases, such as vigorous physical exercise, emotional stress, or a medical or surgical illness. Circadian and seasonal variations have been reported with increased incidence in the morning within a few hours of awakening and during winter months.

The most common presentation for AMI is abrupt onset chest, neck or jaw discomfort, which is usually described as pressure, burning or squeezing in character. Pain in AMI is usually very severe, persistent and is relieved only with opiates. The pain of AMI may radiate up to the jaw and to the umbilicus. AMI can be the first presentation of CAD or it can occur in a patient with known angina pectoris. Symptoms typically last more than 20 minutes. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom. In about quarter of patients, the infarction may not be recognised because of atypical symptoms. About 20% patients have silent infarction, usually in diabetics and elderly.

Physical Findings

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and cold extremities occurs commonly. Usually, patients have sinus tachycardia due to pain and anxiety. Patients are often tachypnoeic. About one-fourth of patients with anterior infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and up to one-half with inferior infarction show evidence of parasympathetic hyperactivity (bradycardia and/or hypotension). The jugular venous pulse should be carefully examined, its elevation in the setting of inferior myocardial infarction (MI) without left heart failure suggests right ventricular myocardial infarction (MI). Detection of right ventricular MI is vital because it portends a much worse prognosis than isolated inferior MI and the management strategy is different than isolated inferior MI.

The praecordium is usually quiet, and the apical impulse may be difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop in the periapical area within the first days of the illness and then may resolve. Other physical signs of ventricular dysfunction include fourth and third heart sounds. A transient mid-systolic or late systolic apical systolic murmur due to dysfunction of the mitral valve apparatus may be present. A pericardial friction rub is heard in many patients with transmural AMI at some time in the course of the disease, if they are examined frequently. The carotid pulse is often decreased in volume, reflecting reduced stroke volume.

Temperature elevations up to 38°C may be observed during the first week after AMI.

DIFFERENTIAL DIAGNOSIS

The pain of AMI can simulate pain from acute pericarditis, pulmonary embolism, acute aortic dissection, costochondritis, and oesophageal rupture, café coronary. Pain of aortic dissection radiates to back and can be suspected in presence of unequal peripheral pulses. Acute pericarditic pain increases with inspiration.

Laboratory Findings

Myocardial infarction progresses through the following temporal stages: acute (first few hours to seven days), healing (7 days to 30 days), and healed (>29 days). When evaluating the results of diagnostic tests for AMI, the temporal phase of the infarction must be considered. The laboratory tests of value in confirming the diagnosis may be divided into four groups: (1) ECG, (2) serum cardiac biomarkers, (3) cardiac imaging, and (4) coronary angiography.

Electrocardiogram

During the initial stage, total occlusion of an epicardial coronary artery produces ST segment elevation. Most patients initially presenting with ST segment elevation ultimately evolve Q waves on the ECG. The most rapid and helpful test in assessing patient with suspected AMI is the 12-lead, ECG. It should be performed as soon as possible, after the patient's arrival in the emergency, since the presence or absence of ST elevation determines the preferred management strategy. Tall T wave and ST elevation is first sign and occur within minutes. ST elevation changes from concave upwards to coving (convex upwards) within few hours and is then accompanied with T wave inversion. Q waves are formed in 6 to 12 hours. The central area of necrosis is represented by Q waves, surrounding area of injury by ST segment changes and outer area of ischaemia by T wave changes. The Q wave persists for whole life. ST and T wave changes revert to normal by 6 weeks to 3 months. For a diagnosis of ST elevation MI (AMI), ST elevation must be present in at least two contiguous leads. For anterior MI, the precordial (V_1 to V_6) leads demonstrate ST elevation and if there is lateral wall involvement, lead I and aVL may also show ST elevation. In inferior MI leads II-III and aVF are affected (**Figures 1 to 3**). In addition to standard ECG leads, right ventricular leads should be recorded in all patients with inferior MI. In posterior MI, usually due to circumflex artery occlusion, changes seen on a standard ECG may be reciprocal ST depression and R waves

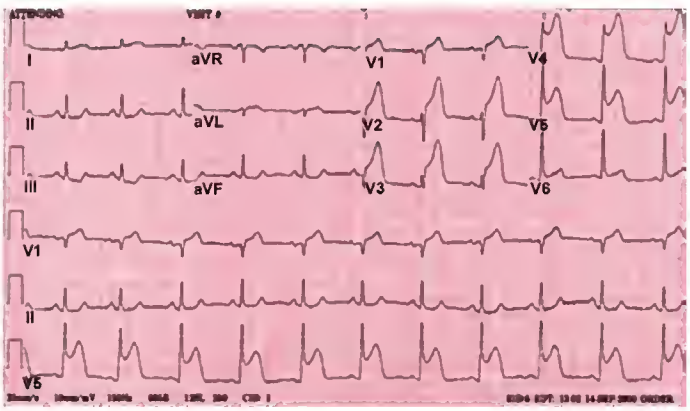


Figure 1: Anterior wall myocardial infarction.

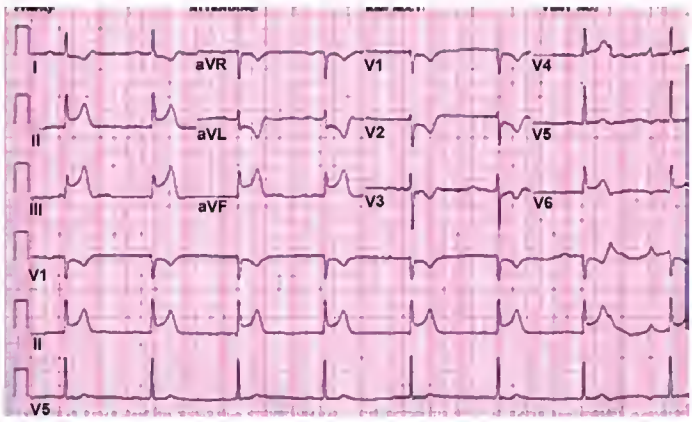


Figure 2: Inferior wall myocardial infarction.

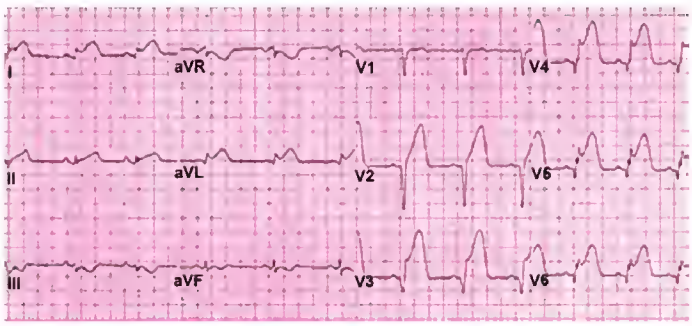


Figure 3: Anterolateral wall myocardial infarction.

(reciprocal of Q waves) in the anterior leads. The ECG pattern should prompt the use of posterior ECG leads V_7 to V_9 which may show ST elevation. Sometimes determining whether ECG changes are new or old may be difficult, serial ECGs are necessary to diagnose dynamic changes.

Cardiac Biomarkers

Cardiac biomarkers become detectable in the peripheral blood once the capacity of the cardiac lymphatics to clear the interstitium of the infarct zone is exceeded and spill over into the venous circulation occurs. CPK-MB is used most commonly. Myoglobin is the first to rise but since it is non specific, it is not used clinically. Troponins are also useful. The use of these markers is shown in **Tables 1 and 2**.

The *nonspecific reaction* to myocardial injury is associated with polymorphonuclear leucocytosis, which appears within a few hours after the onset of pain and persists for 3 to 7 days; the white blood cell count often reaches levels of 12,000/mL to 15,000/mL. The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

Cardiac Imaging

Abnormalities of wall motion on two-dimensional echocardiography are almost universally present. Early detection of the presence or absence of wall motion abnormalities by bedside echocardiography can aid in management decisions. Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of AMI.

Table 1: Various Cardiac Markers in AMI

	CK-MB	Myoglobin	Cardiac Troponins
Description	High energy transfer cytoplasmic protein	O_2 binding haem protein, rapidly released myocyte injury	Regulatory proteins for calcium – dependent interactions between actin and myosin
Origin	Cardiac and skeletal muscle	Cardiac and skeletal muscle	Cardiac muscle
Release kinetics peak rise	2 to 3 hours; sensitivity 94% at 8 hours and <50% at 2 hours	1.5 to 2 hours	3 to 4 hours
Return to normal	24 to 48 hours	8 to 12 hours	10 to 14 days
Advantages	Able to detect early reinfarction	Marker to detect very early MI	More sensitive and specific than CK-MB best marker for MI with skeletal muscle injury, small MI or late MI (>2 to 3 days)
Disadvantages	Low sensitivity for detection of very early (<6 hr) MI small MI; false positive with skeletal muscle trauma, CPR, cardioversion, cardiac surgery	Low sensitivity for detection of late MI with skeletal muscle trauma, CPR and renal failure	Low sensitivity for detection of early (<6 hr) MI or late reinfarction

Table 2: Use of Serum Cardiac Markers in Relation to Time

Subset	Total CK	CK-MB	Myoglobin	Cardiac Troponins
MI < 4 hours	–	–	+	–
MI 4 to 12 hours	+	+	+	+
MI >2 to 10 days	–	–	–	≥
Early reinfarction	+	+	≥	–
Small MI	–	–	–	+
MI after operation of trauma	–	≥	–	+

+ Useful, ≥ some volue, – not useful.

Myocardial perfusion imaging can be useful in some cases with doubtful diagnosis.

Coronary Angiography

Coronary angiography is done either at admission prior to primary PCI or pre discharge for assessment of disease. In a conservative approach, patients of MI are subjected to non-invasive stress evaluation (TMT, stress echocardiography, myocardial perfusion imaging) and those with inducible ischaemia are taken-up for coronary angiography while those with no inducible ischaemia are treated medically.

INITIAL MANAGEMENT

Pre-Hospital Care

The prognosis in AMI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical complications ('pump failure'). Most out-of-hospital deaths from AMI are due to the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 hours of the onset of symptoms, and of these, over half occur in the first hour. Therefore, the major elements of pre-hospital care of patients with suspected AMI include:

1. Recognition of symptoms and seeking of medical attention.
2. Emergency medical team for resuscitative manoeuvres and defibrillation.
3. Transportation to hospital for managing arrhythmias and providing advanced cardiac life support.
4. Reperfusion therapy.

The biggest delay usually occurs not during transportation to the hospital but rather between the onset of pain and the patient's decision to call for help which can be best reduced by health care professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention.

Management in the Emergency Department

Many aspects of the treatment of AMI are initiated in the Emergency Department and then continued during the in-hospital phase of management.

Aspirin is essential in the management of patients with suspected AMI. Rapid inhibition of cyclooxygenase-1 in platelets followed by a reduction of thromboxane A_2 levels is achieved by buccal absorption of a chewed 160 to 325 milligram tablet in the emergency department. Six hundred mg of loading dose of clopidogrel followed by 60 mg once daily should be given to all patients of AMI (dual anti-platelet therapy).

When hypoxaemia is present, oxygen should be administered by nasal prongs or face mask (2 to 4 L/min) for the first 6 to 12 hours after infarction; the patient should then be reassessed to determine if there is a continued need for such treatment.

Sublingual nitroglycerin can be given safely to most patients with AMI. Up to three doses of 0.4 mg should be administered at about 5-minute intervals. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (< 90 mm Hg) or in whom there is clinical suspicion of right ventricular infarction (inferior infarction on ECG, elevated jugular venous pressure, clear lungs, and hypotension).

Morphine is a very effective analgesic for the pain associated with AMI. Morphine is routinely administered by repetitive (every 15 min) intravenous injection of small doses (2 to 4 mg) rather than by the subcutaneous administration of a larger quantity, because absorption may be unpredictable by the latter route.

MANAGEMENT STRATEGIES

The primary tool for screening patients and making triage decisions is the initial 12-lead ECG. When ST-segment elevation of at least 2 mm in two contiguous precordial leads and 1 mm in two adjacent limb leads is present, a patient should be considered a candidate for reperfusion therapy.

Reperfusion, either pharmacologically (by fibrinolysis) or by PCI, accelerates the opening of infarct-related arteries in those patients. Timely restoration of flow in the epicardial infarct–related artery, combined with improved perfusion of the downstream zone of infarcted myocardium, results in a limitation of infarct size.

Pharmacologic or Mechanical Reperfusion

Although primary PCI is considered the reperfusion strategy of choice, it is clear that this advantage is time dependent and limited to specific patient populations. Most patients in India are given thrombolytic therapy due to cost factor and also since cardiac catheterisation lab facilities are not available widely. In the CREATE registry almost ~8% patients of AMI get primary PCI in our country for this reason. In 2008, 55% of the patients of AMI got thrombolysed as against 30% in 1990s since patients are now reaching hospitals early.

Fibrinolytic therapy of STEMI significantly improves mortality rates; treatment within six hours of the onset of symptoms leads to a reduction in mortality between 26 and 65 per 1,000 patients treated which has been extensively documented.

Fibrinolytic agents

The fibrinolytic agents differ in several properties, as summarised in the text and **Table 3**.

Streptokinase: Streptokinase (SK) is a bacterial protein with half-life of 23 minutes. SK is antigenic, has less fibrin specificity, and causes systemic lytic effects in clinical doses. It is least expensive of fibrinolytics and still widely used globally. SK is administered by short-term (1 hour) infusions. This is the agent of choice of our country.

Tissue-type Plasminogen Activator (tPA): Tissue-type plasminogen activator (tPA) is the major intrinsic (physiologic) plasminogen activator. The short half-life has necessitated bolus/infusion regimens (over 1 to 3 hours). tPA is given as 15 mg bolus, then 0.75 mg/kg over 30 min (maximum 50 mg), then 0.50 mg/kg over 60 min (maximum 35 mg).

Reteplase: It is a non-glycosylated, single chain deletion variant of human tPA. It is given in two bolus injections 30 minutes apart.

Tenecteplase: Tenecteplase (TNK) is a triple mutant and is given as single bolus dose (30 to 50 mg) over 1 to 2 minutes. The ease of administration of TNK, together with its reduced transfusion requirements, has led to its general acceptance and favoured status. Lower rates of dosing errors with bolus fibrinolytics such as TNK also contribute to superior clinical outcomes. TNK is dosed by weight (supplied in 5 mg/mL vials): 60 kg = 6 mL; 61–70 kg = 7 mL; 71–80 Kg = 8 mL; 81–90 kg = 9 mL; 90 kg = 10 mL.

The absolute and relative contraindications to fibrinolytic therapy are summarised in **Table 4**.

Primary angioplasty

Primary percutaneous coronary intervention (PCI) has been very successful in accomplishing mechanical reperfusion of the coronary artery in patients presenting with AMI (**Figures 4A to C**).

Mechanical reperfusion has the potential to overcome many of the limitations of fibrinolytics. The overall risk of intracranial bleeding is significantly lower with PCI. There is a significant superiority of primary PCI, especially among patients in which it was logistically feasible to accomplish reperfusion within 90 minutes of presentation. Primary PCI is preferred modality of reperfusion over fibrinolytic therapy. However, this is available to small percentage of patients in India and also in Western world: 10% and 35% respectively.

When performing primary PCI for patients presenting with STEMI, coronary stents, either Bare metal stent (BMS) or Drug eluting stent (DES), should be used whenever technically feasible. Significant clot burden may complicate acute STEMI, management.

Bypass surgery may be required owing to anatomic considerations, such as left main disease or coronary disease not suitable for immediate PCI, or mechanical complications from the MI such as acute severe mitral regurgitation, ventricular septal defect or a failed PCI.

Table 3: Comparison of Fibrinolytic Agents Approved by the US FDA for Intravenous Use

	SK (Streptokinase)	tPA (Alteplase)	tPA (Reteplase)	TNK (Tenecteplase)
Dose	1.5 million units (MU) in 30 to 60 min	100 mg in 90 min	10 u + 10 u 30 min apart	30 to 50 mg Over 5 seconds
Circulating half life (min)	20	6	18	20
Antigenic	Yes	No	No	No
Allergic reactions	Yes	No	No	No
Systemic fibrinogen depletion	Severe	Mild moderate	Moderate	Minimal
Intracerebral haemorrhage	0.4%	0.7%	0.8%	0.7%
Patency (TIMI-2/3) rate, 90 min	51%	73% to 85%	83%	77% to 88%
Lives saved per 100 treated	3	4	4	4

Based on the finding from the GUSTO trial that tPA saves 1 more additional life per 100 treated than dose SK.

Adjuvant therapy

All patients should be treated with ASA and a thienopyridine (currently clopidogrel) as soon as possible following diagnosis. The choice of anticoagulant therapy, in part, is dictated by the method of reperfusion undertaken. Following fibrinolytic therapy, both fondaparinux and LWWHs improve clinical outcomes compared with UFH. Direct thrombin inhibitors (Bivalirudin) appear to be a reasonable alternative to UFH, and preferred in settings of thrombocytopaenia or prior heparin-induced thrombocytopaenia.

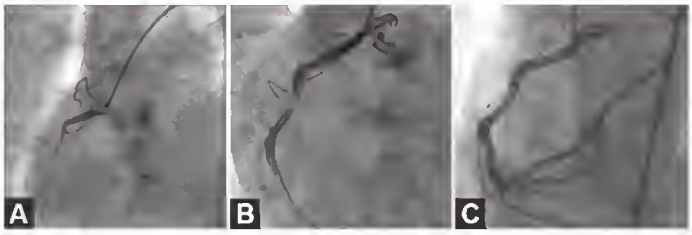
Table 4: Contraindications and Cautions for Fibrinolysis in STEMI

Absolute contraindications

- Any prior ICH
- Known structural cerebral vascular lesion (e.g. arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3 months

Relative contraindications

- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP greater than 180 mm Hg or DBP greater than 110 mm Hg)
- History of prior ischaemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (greater than 10 minutes) CPR or major surgery less than 3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Non-compressible vascular punctures
- For streptokinase: prior exposure (more than 5 days ago) or prior allergic reaction
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding



Figures 4A to C: Primary angioplasty of right coronary artery (RCA). (A) Coronary angogram showing RCA filled with thrombus. (B) Partial flow in RCA after thrombus aspiration. (C) TIMI grade III flow after stenting.

In patients undergoing primary PCI, UFH has traditionally been administered, based primarily on theoretical grounds and the experience of experts. There is evidence that the addition of a GP IIb/IIIa receptor antagonist improves outcomes (abciximab, eptifibatide, tirofiban). There is now evidence from a single, moderately sized trial that bivalirudin is as efficacious as the combination of UFH plus a GP IIb/IIIa receptor antagonist.

Bleeding complications in patients with AMI remain relatively common and may be as important to long-term outcome as ischaemic events.

COMPLICATIONS

Complications following AMI are enumerated below.

1. Arrhythmias
2. Heart failure
3. Cardiogenic shock
4. Sudden death
5. Reinfarction, extension and expansion of infarction
6. Infarction of papillary muscle of mitral valve – mitral regurgitation (MR)
7. Rupture of interventricular septum leading to ventricular septal defect (VSD)
8. Thrombus in LV causing peripheral embolism
9. Cardiac rupture
10. Deep vein thrombosis in legs causing pulmonary embolism
11. Pericarditis during massive infarction
12. Aneurysm of ventricle with thrombosis and thrombo-embolic phenomenon
13. Dressler's syndrome (post-myocardial infarction syndrome)

Arrhythmias

Various types of arrhythmias that can follow AMI are listed in **Table 5**.

Table 5: Important Arrhythmias in Acute Myocardial Infarction

Ventricular premature beats
Ventricular tachycardia
Ventricular fibrillation
Accelerated idioventricular rhythm
Atrial premature beats
Atrial tachycardia
Atrial fibrillation

Premature ventricular complexes are the commonest and can be forerunners of lethal ventricular arrhythmia viz ventricular tachycardia or fibrillation. Ventricular fibrillation is the major cause of death in those who die before receiving medical attention.

Bradyarrhythmias and conduction disturbances may also occur in the form of sinus node dysfunction, AV nodal block or distal conduction disturbances (bundle branch block or complete heart block). *The details of arrhythmias are outlined in the respective chapter on Tachyarrhythmias and Bradyarrhythmias Chapters 23 and 24 of section 12.*

Heart Failure

The extent of LV dysfunction is a strong predictor of short- and long-term prognosis after MI. The Killip and Kimball classification stratifies MI patients from low to very high risk based upon clinical signs of heart failure (**Table 6**). It remains a reasonably accurate predictor of short-term survival.

Table 6: Killip and Kimball Classification

Class	Clinical Features	Mortality
Killip I	MI with no HF	6%
Killip II	MI with mild HF (basal rales)	17%
Killip III	MI with severe HF (rales ≥50% of lung fields)	38%
Killip IV	Cardiogenic shock	81%

The presence of clinical signs of left ventricular failure is a strong indicator of a poor long-term prognosis. It is manifested by

breathlessness, cough, haemoptysis, perspiration, S3, S4 gallop and pulmonary rales in some, the symptoms may be minor in others. Measurements of left ventricular function and diastolic volume predict short-term and long-term prognosis after STEMI.

Severe forms of LV failure need haemodynamic monitoring with a balloon-tipped, flow-guided Swan-Ganz catheter placed in the pulmonary artery. Cardiac output is estimated by thermodilution technique. In the absence of mitral valve disease, pulmonary artery diastolic pressure reflects LV filling pressure (normal value 0 to 14 mm Hg) and is high in LV failure. An arterial line to monitor systemic blood pressure is also required. Medical management involves intravenous nitroglycerine infusion. If low, then the infusion of vasopressor like dopamine can be started along with nitroglycerine. Recently eplerenone, aldosterone inhibitor in doses of 25 to 50 mg is used to treat LVF in AMI.

Intra-aortic balloon counterpulsation can be a life-saving measure. The balloon is placed in the aorta distal to the left subclavian artery. It is inflated during diastole, thus improving the flow of blood into the coronaries, and deflated in systole thereby reducing ventricular after load.

ACE-inhibitors unequivocally reduce mortality overall, and the benefit appears to be greatest among patients with depressed LV function, overt heart failure or anterior infarction.

The initiation of ACE-inhibitor therapy early in the course of infarction results in greater improvement in ejection fraction.

All patients with post-MI LV dysfunction should be administered ACE-inhibitors unless contraindicated or not tolerated.

Cardiogenic Shock

Cardiogenic shock is a syndrome characterised by hypotension and peripheral hypoperfusion, usually accompanied by high LV filling pressures. The common clinical manifestations of these haemodynamic derangements include mental obtundation or confusion, cold and clammy skin, and oliguria or anuria. Cardiogenic shock is the most common cause of in-hospital mortality after MI. When cardiogenic shock is not secondary to a correctable cause such as arrhythmia, bradycardia, hypovolaemia or mechanical defect, short-term mortality is 80%.

Inotropic drugs (dopamine, dobutamine, epinephrine, norepinephrine) have been subjected to detailed study and widespread use in cardiogenic shock, but no benefit on mortality has been demonstrated.

One important cause of hypotension which responds to treatment is hypovolaemia. This may be caused by vomiting, diuretics or inadequate fluid intake and is treated by adequate fluid replacement. The pulmonary end-diastolic pressure (PAEDP) must be kept around 15 to 18 mm Hg since the infarcted ventricle needs a higher filling pressure to maintain its cardiac output. If PAEDP is low, colloids must be infused to increase it until the cardiac output is maximised. Raising it beyond 20 mm Hg will aggravate pulmonary oedema.

An aggressive approach with reperfusion therapy and intra aortic balloon pulsation treatment of patients in cardiogenic shock due to predominant LV failure is associated with lower in-hospital mortality rates than standard medical therapy.

Fibrinolysis could be considered for the patient with cardiogenic shock if access to PCI is not readily available.

Reinfarction, Extension and Expansion of Infarction

In STEMI treated with fibrinolysis, reinfarction can occur in 4% to 8% of the patients. The reinfarction rate is significantly lower when primary percutaneous coronary intervention (PCI) is the initial treatment.

Acute Mitral Regurgitation

Mitral regurgitation (MR) complicating acute myocardial infarction (**Figure 5**) ranges from mild papillary muscle dysfunction (no haemodynamic compromise) to severe form (ruptured papillary muscle) leading to heart failure or cardiogenic shock and is more common in females with inferior posterior infarction.

The diagnosis is made clinically with pansystolic murmur, maximal at the apex, and radiation to the axilla. Echocardiographic examination is invaluable in confirming the diagnosis. The persistence of cardiogenic shock or severe failure with preserved LV function usually indicates that an important mechanical complication is present.

Ventricular Septal Rupture

Rupture of the interventricular septum occurs in approximately 2% of the female patients with large anterior wall MI (**Figure 6**). Early diagnosis may offer some hope of early repair. Most

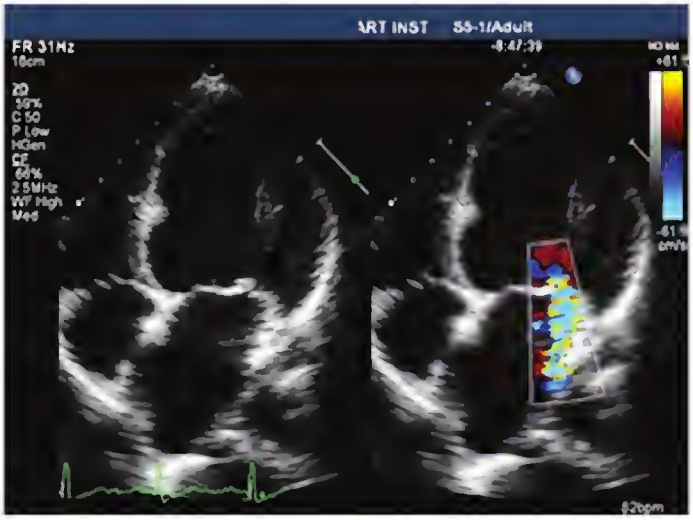


Figure 5: Colour Doppler showing lateral jet of acute mitral regurgitation due to papillary muscle dysfunction.

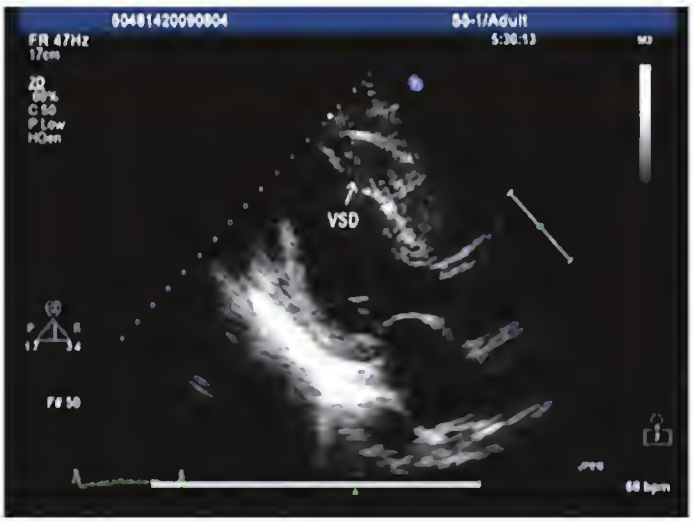


Figure 6: Echocardiogram showing rupture of septum.

patients with septal rupture develop signs of acute right- and left-sided heart failure and a loud pan systolic murmur at the left sternal border along with systolic thrill. Echocardiography with Doppler colour flow mapping localises the defect accurately.

Early closure is now recognised to yield better results. Although early surgical intervention may increase operative mortality, overall mortality is reduced. Transcathethter closure is a feasible alternative to surgical closure of post-MI septal rupture.

Cardiac Thromboembolism

The risk of thromboembolism (**Figure 7**) is more in patients with large anterior infarctions and patients with atrial fibrillation. Emboli are more common within the first few months after infarction than later, and with large, irregular shaped thrombi, particularly those with frond-like appendages.

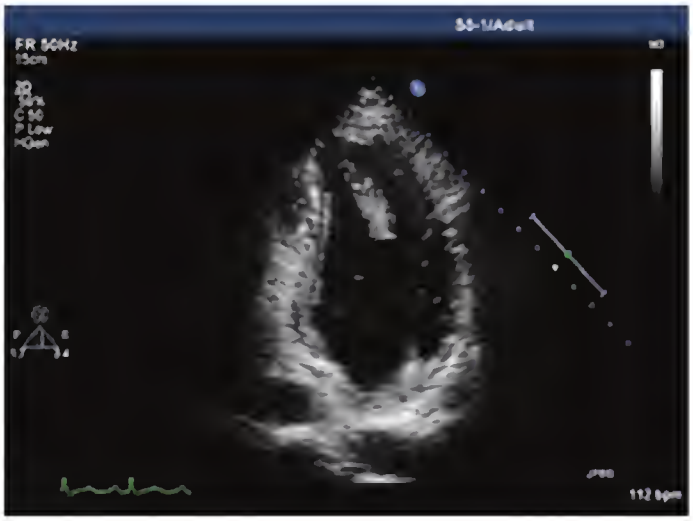


Figure 7: Echocardiogram showing apical aneurysm with formation of thrombus.

Anticoagulation with heparin followed by Warfarin for six months has been shown to reduce the incidence of thromboembolism in patients with documented intra cavitary thrombus.

Free Wall Rupture

Rupture of the free wall of the left ventricle is an almost uniformly fatal, commonly under recognised complication. It occurs most frequently in elderly women with large anterior wall MI who have been given late fibrinolytic therapy. The usual presentation is sudden collapse associated electrical mechanical dissociation, and failure to respond to cardio pulmonary resuscitation. Urgent echocardiography is invaluable in the assessment of a patient who develops the above clinical features.

Pericarditis

Pericarditis occurs in approximately 25% of patients with Q wave infarctions within the first week. A pericardial friction rub may be present with or without symptoms. High-dose aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to treat the symptoms of post-infarction pericarditis.

A pericardial effusion can be detected by echocardiography in some of these patients. Cardiac tamponade is a rare complication of fibrinolytic therapy for acute MI.

Left Ventricular Aneurysm (Figure 7)

Left ventricular aneurysms develop most commonly after large transmural anterior MIs. A ventricular aneurysm can often be palpated as a dyskinetic region adjacent to the apical impulse. A third heart sound and signs of heart failure may also be detected. It is recognised by persistent ST elevation in the ECG and dyskinesia seen on echocardiography and radionuclide or contrast ventriculography. It may result in persistent LV failure, arrhythmias and systemic embolism.

A pseudoaneurysm is a rare complication of MI that develops when a myocardial rupture is sealed off by surrounding adherent pericardium. The aneurysmal sac may progressively enlarge but maintains a narrow neck, in contrast to a true ventricular aneurysm. Differentiation of left ventricular pseudoaneurysm from true aneurysms is made with echocardiography or magnetic resonance imaging.

Surgery should be considered in all patients with LV pseudo-aneurysms.

Dressler's Syndrome

A form of post infarction pericarditis, occurring 7 days to 6 weeks after the acute event characterised by prolonged or recurrent pleuritic chest pain, a pericardial friction rub, fever, pulmonary infiltrates or a small pulmonary effusion, and an increased sedimentation rate. The incidence has reduced after the introduction of reperfusion into clinical practice.

Non-steroidal anti-inflammatory drugs and steroids may be required for control of Dressler's syndrome.

Right Ventricular Infarction and Failure

Right ventricular (RV) infarction typically occurs in association with inferior or posterior MI. Patients with RV infarction complicating inferior MI have three times the risk of death of patients without RV infarction.

The clinical features of RV infarction complicating inferior MI include hypotension, jugular venous distension on inspiration (Kussmaul's sign) and clear lung fields, ST elevation of more than 1 mm in V4R.

Echocardiography commonly reveals wall motion abnormalities of the right ventricle and interventricular septum.

Early reperfusion may improve the prognosis in patients who have primary PCI for treatment of their cardiogenic shock, those with right ventricular infarction fared better than patients with cardiogenic shock due to left ventricular infarction.

Volume loading can normalise blood pressure and increase cardiac output. It is the vital step in management of patients with right ventricular MI.

Use of inotropic agents and maintenance of atrioventricular synchrony with atrioventricular pacing is often critical to the maintenance of a satisfactory cardiac output. Successful reperfusion with fibrinolysis or PCI appears to reduce the incidence of RV infarction and is associated with dramatic recovery of right ventricular function and reduced mortality.

Psychosocial Complications

An estimated 20% to 50% of post-infarction patients have high levels of psychosocial stress, including anxiety, depression, denial, hostility, and social isolation and have a significantly adverse effect on outcome.

Cardiac rehabilitation programmes provide psychologic and social support to patients after MI, in addition to education about risk factors and their modification.

POST-MYOCARDIAL INFARCTION MANAGEMENT (TABLE 7)

Most patients after MI, if they can afford, should have coronary angiography done before discharge. Those with left main and triple vessel disease with LV dysfunction and or proximal LAD disease need coronary artery bypass graft (CABG). Those with single vessel disease with significant viable myocardium need PCI. Others can be managed medically with statins, aspirin, beta-blockers and ACE-inhibitors. Revascularihsation of infarcted territory has not been shown to be useful.

Table 7: Late Management of MI

Risk stratification and further investigation

Life style modification

- Cessation of smoking
- Diet (weight control, lipid lowering)
- Regular exercise

Secondary prevention drug therapy

- Anti-platelet therapy (aspirin and/or clopidogrel)
- Additional therapy for control of diabetes and hypertension
- β-blocker
- Aldosterone receptor antagonist
- ACE-inhibitor/ARB
- Statin

Rehabilitation devices

- Implantable cardiac defibrillator (high-risk patients)

PROGNOSIS

In almost 25% of all cases of MI, death occurs within a few minutes without medical care, half the deaths occur within 24 hours of the onset of symptoms and about 40% of all affected patients die within the first month. A 30 days survival is of more than 85% of patients who are admitted in hospital. Early death is usually due to an arrhythmia and is independent of the extent of MI. Late outcomes are determined by extent of myocardial damage; AV block and ventricular arrhythmias. Old age, depression and social isolation are also associated with a higher mortality. Of those who survive an acute attack, more than 80% live for a further year, about 75% for 5 years, 50% for 10 years and 25% for 20 years.

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12.20 Hypertension

M Paul Anand

INTRODUCTION AND EPIDEMIOLOGY

Hypertension is a very strong risk factor for cardiovascular diseases (CVDs). It is estimated that it increases the risk at least two-fold for CVDs including coronary artery disease (CAD), congestive heart failure (CHF)/stroke (ischaemic and haemorrhagic), renal failure and peripheral arterial disease. Usually other risk factors like diabetes are also commonly associated with hypertension.

Hypertension is present globally but its prevalence varies amongst countries and sub populations. The prevalence of diabetes increases with growing age and it is estimated that starting from around 15% to 20% in the early age it increases to 75% to 80% in individuals above 70 years of age.

There are no well-coordinated national surveys of the prevalence of hypertension available from the Indian subcontinent. Several regional small surveys in the last two decades with varying protocols have reported a prevalence which varies from 6.15% to 36.36% in men and 2% to 39.4% in women in urban areas and from 3% to 36% in men and 5.80% to 37.2% in women in rural areas.

More recent surveys in urban population have reported higher prevalence. All these surveys with one exception were based on a casual reading taken only on one occasion.

In the survey in Mumbai, diagnosis of hypertension [systolic blood pressure (SBP) 140 mm Hg and/or diastolic blood pressure (DBP) 90 mm Hg] was based on the average of 3 initial readings and confirmed on 2 subsequent occasions in those found to have high blood pressure on the first visit. The overall prevalence based on readings at the time of the first visit was 34.12% and the prevalence based on the average of three readings on the third occasion was 26.9%.

DETERMINANTS

A strong familial and genetic predisposition exists and a number of modifiable predisposing factors have been identified.

Role of Genetics

Epidemiological studies suggest that 20% to 60% of essential hypertension is inherited and the remainder is acquired or environmental.

Age and Sex

Almost all surveys show that blood pressure (BP) rises with age in both men and women. In adult women, BP is lower than in men of comparable age, but the rise is more steep thereafter and around middle-age BP is about the same; in later life it is higher in women.

Weight Gain

Increased weight appears to be a major controllable risk factor for new onset of hypertension. The Framingham Study showed approximately 1 mm Hg rise of SBP for every 1.25 Kg of weight gain. Abdominal obesity as evidenced by waist circumference of 80 cm in women and 90 cm in men has also been found to be associated with the risk for hypertension. Abdominal obesity may well be the most dangerous. It appears that 70% of hypertension in men and 60% in women could be attributed to abdominal obesity.

Salt Intake

Several communities whose intake of sodium chloride is 3 g or less per day have low average BP. The Intersalt Study of 10,079 men and women from 32 countries projected that a 100 mmol/day lower sodium intake over a lifetime would result in a 9 mm Hg smaller rise in SBP from 25 to 55 years age. The Intersalt Study demonstrated a clear relationship between the salt intake and the level of BP among communities.

Alcohol Intake

Excessive alcohol intake is an important risk factor for hypertension. Excess consumption accounts for 5% to 30% of all hypertension. Several studies including the Intersalt Study have shown a strong and independent positive relationship between alcohol intake and increase in BP.

Physical Activity

Sedentary individuals have a 20% to 50% increased risk of developing hypertension. Observational and experimental studies have revealed the role of physical inactivity and its association with high BP.

Smoking

Tobacco smoking has been reported to cause acute rise of BP, whether prolonged smoking leads to sustained hypertension has not been established.

DEFINITION OF HYPERTENSION

There is a continuous relationship between the level of BP and the risk of its complications. All definitions of hypertension, including those issued by Joint National Committee (JNC) in prevention, detection, evaluation and treatment of high blood pressure (seventh report) (JNC-7) and World Health Organization (WHO)/International society of hypertension (ISH) are arbitrary.

At present, hypertension in adults aged 18 years and older who are not acutely ill, is defined as "SBP of 140 mm Hg or greater and/or DBP of 90 mm Hg or greater or any level of BP in patients taking antihypertensive medication". BP is classified into various stages as shown in **Table 1**.

Table 1: Classification of Blood Pressure for Adults Aged 18 Years or Older*

	(JNC VI Category)		(JNC VII Category)	
Category	**Systolic (mm Hg)**		**Diastolic (mm Hg)**	
Optimal	<120	And	<80	Normal
Normal	120 to 129	Or	80 to 84	Prehypertension
High normal	130 to 139	Or	85 to 89	
Hypertension**	140	Or	90	Hypertension
Stage 1	140 to 159	Or	90 to 99	Stage 1
Stage 2	160 to 179	Or	100 to 109	Stage 2
Stage 3	180	Or	110	

** Not taking antihypertensive drugs and not acutely ill. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 160 to 192 mm Hg should be classified as Stage 2 hypertension, and 174/120 mm Hg should be classified as Stage 3 hypertension.*

*** Based on the average of two or more readings taken at each of two or more visits after an intial screening.*

JNC = Joint national committee; SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

PRE-HYPERTENSION

The designation pre-hypertension is intended to identify those individuals in whom early intervention by adoption of healthy lifestyle could reduce BP, decreasing the rate of progression of BP to hypertensive levels with age, or prevent hypertension entirely. Individuals who are pre-hypertensive are not candidates for drug therapy on the basis of their level of BP and should firmly and unambiguously be advised to practice lifestyle modification in order to reduce their risk of developing hypertension in the future. Moreover, individuals with pre-hypertension who also have diabetes or kidney disease should be considered for appropriate drug therapy if a trial of lifestyle medication fails to reduce their BP to 130/80 mm Hg or less.

Apart from being at twice the risk of developing hypertension, compared to persons with normotension, the total morbidity, mortality and economic loss caused by cardiovascular events amongst high normal blood pressure (pre-hypertension) population far exceeds that caused by hypertensive population. The new name suggests that it is urgent for the person so diagnosed to invest time and effort to implement lifestyle changes.

SYSTOLIC BLOOD PRESSURE

In persons older than 50 years, SBP of more than 140 mm Hg is much more important cardiovascular disease (CVD) risk factor than DBP.

A large body of epidemiologic data indicates that SBP is far more important than DBP as a determinant of cardiovascular risk, except in younger age groups. Epidemiologically, systolic hypertension is the most common form of hypertension and far easier to measure correctly.

The National Health and Nutrition Examination Survey (NHANES) has shown that Isolated systolic hypertension (ISH) (SBP 140 mm Hg with DBP 90 mm Hg) was present in 65% of all hypertensives 60 years age in both men and women. Recent data from Framingham Study has further reinforced the prognostic significance of raised SBP. The importance of SBP in risk prediction has been convincingly shown in 12 years data from 316,000 men screened from the multiple risk factors intervention trial (MRFIT) study.

ISOLATED SYSTOLIC HYPERTENSION

Isolated systolic hypertension (ISH) is defined as SBP of 140 mm Hg or greater and DBP below 90 mm Hg and staged appropriately (e.g. 170/82 mm Hg is defined as Stage 2 ISH). ISH is present in two-thirds of all hypertensives 60 years of age.

In older patients aged 60 years and above, in diabetic subjects and patients on antihypertensive medication, the BP should be measured in supine, sitting and in standing positions to detect postural hypotension.

If atrial fibrillation is present, additional readings may be required to estimate the average SBP and DBP.

In young obese persons with hypertension, high BP should be measured with an appropriately large cuff.

HOME MEASUREMENT

Home measurement has the advantage that it distinguishes sustained hypertension from "white-coat hypertension", a condition noted in patients whose BP is elevated in the physician's clinic but normal at other times. There is no universally agreed upper limit of normal home BP, but readings of 135/85 mm Hg or greater should be considered elevated.

AMBULATORY BLOOD PRESSURE MEASUREMENT

Twenty-four hour ambulatory BP measurements have shown marked fluctuations of BP in the same individual. A close correlation has been demonstrated between ambulatory BP levels and the extent of target organ damage.

Ambulatory BP measurements has been found to be useful to identify white coat hypertension, evaluate drug-resistant hypertension, episodic hypertension, hypotensive episodes while on medication and to evaluate antihypertensive drugs. One of the recommended definitions of normal BP and hypertension using ambulatory BP measurements is given in **Table 2**.

Table 2: Blood Pressure Thresholds (mm Hg) for Definition of Hypertension with Different Types of Measurement

	SBP (mm Hg)	DBP (mm Hg)
Office or Clinic	140	90
Ambulatory BP measurement (24-hour average)	125	80

COMPLICATIONS OF HYPERTENSION

Hypertension is a major risk factor for the development of CVD. Its impact for stroke and end-stage renal failure is greatest. Hypertensives when compared to normotensive, develop twice as much coronary heart disease (CHD), four times as much congestive heart failure (CHF) and seven times as much stroke. While there is no critical level, the risk of CVD rises progressively with the level of SBP and DBP.

Cardiovascular risks in hypertensives are also markedly affected by other co-existing risk factors.

PATHOPHYSIOLOGY OF HYPERTENSION

BP is defined as the product of cardiac output and peripheral resistance. Hypertension is, therefore, said to be caused by increased cardiac output and/or increased peripheral resistance.

Each of these primary factors is determined by a complex series of interactions (**Figure 1**). Increased cardiac output, though involved in the initiation of hypertension, does not persists. The typical haemodynamic finding in established hypertension is an elevated peripheral resistance and normal cardiac output. What causes the resistance to go up is not fully understood.

It is also suspected that heredity plays a role as a background to most of these abnormalities, especially along with varying contributions of three environmental factors—sodium, stress and obesity.

Factors Involved in Increased Cardiac Output

Increased circulating fluid volume

Excess sodium intake can cause hypertension by increasing fluid volume and preload, thus, increasing cardiac output, as well as by its effects on vascular reactivity and contractility. Many studies, such as the Intersalt Study, have verified the ability of dietary salt to elevate BP in some populations (salt-sensitive), but not in all individuals. Sodium sensitivity of some individuals may play a pivotal role. Some investigators have also identified a sodium pump inhibitor as being responsible for volume expansion in hypertension.

Renal sodium retention

Excessive sodium retention by the kidney has also been proposed as an important factor. One reason for this could be decreased filtration surface area (FSA) due to decreased nephron number or FSA per glomerulus.

Resetting of pressure-natriuresis

A resetting of the pressure-natriuresis relationship wherein a rise in SBP evokes further sodium retention has been proposed as a possible renal mechanism.

Renin-angiotensin system

The renin-angiotensin system (RAS) plays an important role in salt and water homeostasis and BP control (**Figure 2**).

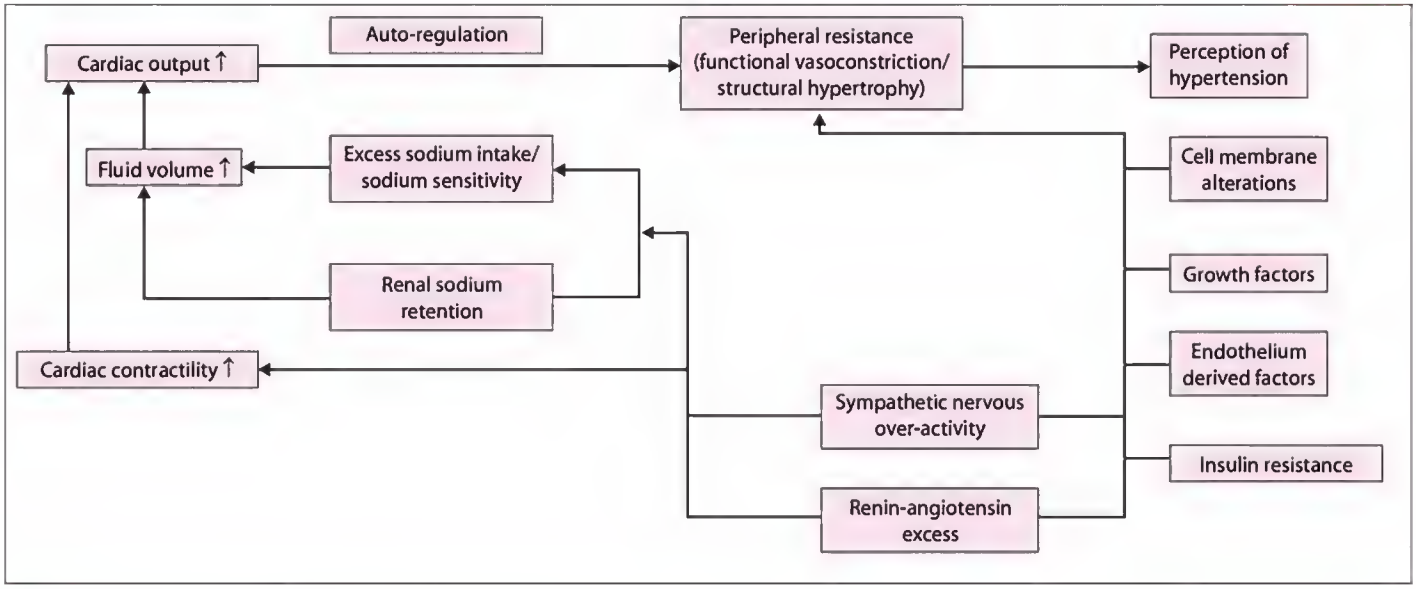


Figure 1: Factors involved in the pathogenesis of hypertension.

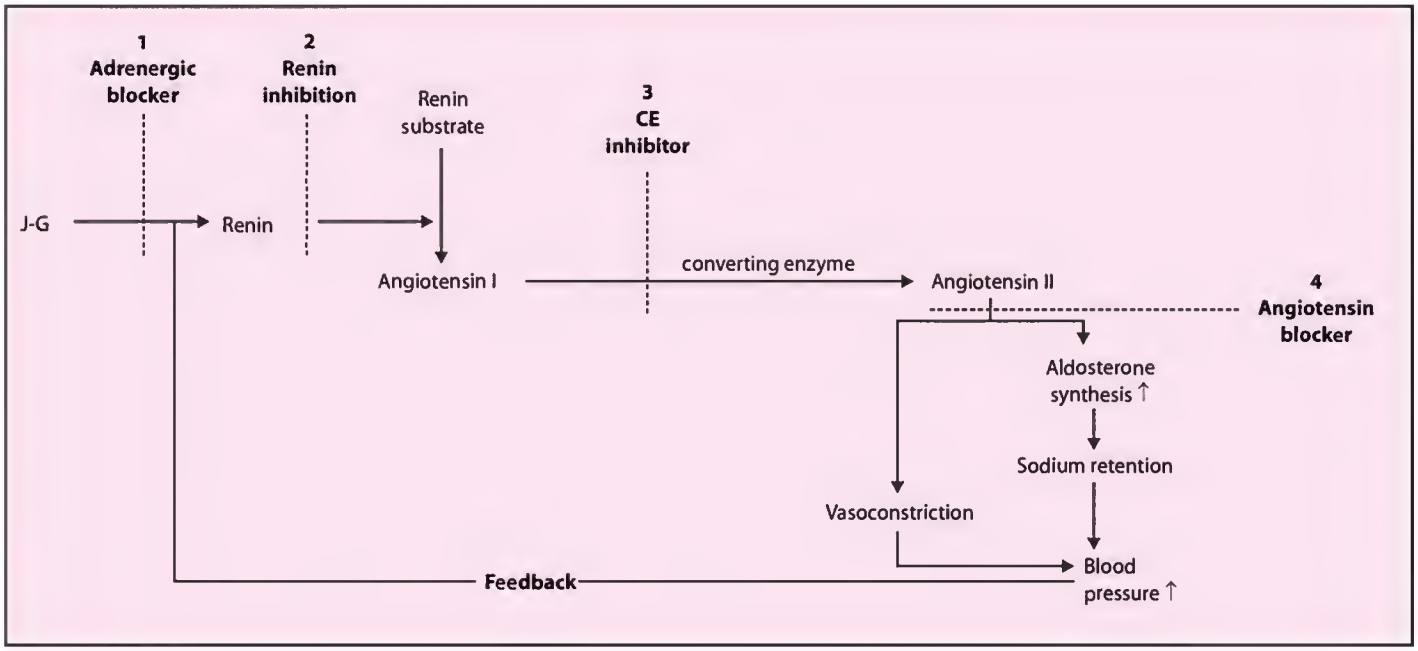


Figure 2: Role of renin-angiotensin system in the pathogenesis of hypertension. Note the effect of drugs at various steps in the pathway.

Inappropriate release of renin culminating in the formation of angiotensin II (which causes vasoconstriction) is also a possible mechanism for hypertension.

Sympathetic nervous over-activity

The sympathetic nervous system (SNS) directly or indirectly dictates the state of cardiac output and systemic vascular resistance. Thus, excessive activity of SNS may increase the BP. Sympathetic over-activity may also augment renin release.

Increased peripheral resistance

The final common feature of established hypertension is a raised peripheral resistance, that can be associated with both functional constriction and structural vascular remodelling and hypertrophy. Direct mediation and interaction of numerous factors such as increased intracellular calcium, growth factors such as angiotensin II and insulin like growth factor, endothelium-derived relaxing factor (EDRF), prostaglandins and endothelin may also be involved.

EVALUATION

Evaluation of patients with documented hypertension has three objectives. These are to identify known causes of high BP, to assess the presence or absence of target organ damage and to identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment.

Data for evaluation acquired through medical history, physical examination, laboratory tests and other special diagnostic procedures.

MEDICAL HISTORY

Hypertension is largely asymptomatic and is often diagnosed on routine examination. Early morning headache, often localised to the occipital region as a symptom is usually a feature of severe hypertension. Other symptoms, though uncommon, may be dizziness, fatigue and palpitation. In addition, symptoms related to organ damage involving the heart, brain, kidneys and eyes may be present in severe hypertension.

Medical history should include the following: (a) duration and level of elevated BP, symptoms of CAD, heart failure, cerebrovascular disease, peripheral vascular disease and renal disease; (b) symptoms of diabetes mellitus, dyslipidaemia, gout, sexual dysfunction or other co-morbid conditions; (c) family history of high BP, premature CAD, stroke, dyslipidaemia and diabetes; (d) symptoms suggesting secondary causes of hypertension (see chapter on secondary hypertension); (e) history of smoking or tobacco use, physical activity, dietary assessment including intake of sodium, alcohol, saturated fat and caffeine; (f) history of use of all prescribed and over-the-counter medications which may raise BP or interfere with the effectiveness of antihypertensive drugs; (g) history of oral contraceptive use and hypertension during pregnancy; (h) history of previous antihypertensive therapy, including adverse effects experienced, if any; and (i) psychosocial and environmental factors.

PHYSICAL EXAMINATION

In uncomplicated mild to moderate hypertension, physical examination other than raised BP may be normal. The signs, when present, are those of target organ damage or those of the underlying cause of secondary hypertension.

The initial physical examination should include the following: (a) record three BP readings separated by 2 minutes each, with the patient in either supine or sitting position and after standing for at least 2 minutes; (b) record height, weight and waist-hip ratio; (c) examine the pulse and the extremities for delayed or absent femoral and peripheral arterial pulsations, bruits and pedal oedema; (d) look for arcus senilis, xanthelesma and xanthomas; (e) examine the heart for evidence of LVH, CAD, CHF and record rate and rhythm; (f) neurological examination for evidence of past or ongoing cerebrovascular disease; (g) examine the optic fundus to detect hypertensive retinopathy (**Table 3**); (h) examine the lungs for rales and rhonchi; (i) examine the abdomen for bruits, enlarged kidneys, masses, and abnormal aortic pulsation.

Table 3: Keith and Wagner's Grading of Hypertensive Retinopathy

Grade 1	Thickening and tortuosity of arteries showing 'silver wire' appearance
Grade 2	Grade 1 changes plus arteriovenous nipping
Grade 3	Grade 2 changes plus flame-shaped (superficial) haemorrhages and cotton wool exudates
Grade 4	Grade 3 changes plus papilloedema

LABORATORY INVESTIGATIONS

Important laboratory investigations to be carried out in a hypertensive patient are given in **Table 4**.

Table 4: Laboratory Investigations

For most hypertensive patients

- Urine for protein, glucose and microscopic (red blood cells/ other sediments)
- Haemoglobin, fasting blood glucose, serum creatinine, potassium and total cholesterol
- Electrocardiogram

Additional investigations when cost is not a constraint

- Lipid profile, uric acid
- Chest radiography
- Echocardiogram

Tests for secondary hypertension

(see chapter 22 Secondary hypertension in this section)

FACTORS INFLUENCING RISK AND RISK STRATIFICATION

Before initiating therapy, patient's overall risk should be assessed taking into consideration presence of additional risk factors, extent of target organ damage and other associated clinical conditions (**Table 5**).

Prognosis of these patients, choice of drugs and need for urgency of therapy will be dependent on the overall risk stratification (**Table 6**).

MANAGEMENT OF HYPERTENSION

Goals of Therapy

The primary goal of therapy of hypertension is effective control of BP to prevent, reverse or delay the progression of complications, and thus, reduce the overall risk of an individual without affecting the quality of life.

Table 5: Factors Influencing Risk

Risk Factors for Cardiovascular Disease	Target Organ Damage	Associated Clinical Conditions
Age >55 years	Left ventricular hypertrophy detected by electrocardiogram and/or echocardiography	Cerebrovascular Disease
Male sex	Microalbuminuria/proteinuria and/or elevation of serum creatinine (1.2 to 2.0 mg/dL)	Ischaemic stroke
Post-menopausal women	Ultrasound or radiological evidence of atherosclerotic plaques in the carotids	Cerebral haemorrhage
Smoking and tobacco use	Generalised or focal narrowing of retinal arteries	Transient ischaemic attack
Diabetes mellitus		Heart Disease
Family history of premature CAD (Men <55 years, Women <65 years)		Myocardial infarction
Increased waist-hip ratio		Angina
High LDL or total cholesterol, low HDL cholesterol and high triglycerides		Coronary revascularisation
		Congestive heart failure
		Renal Disease
		Diabetic nephropathy
		Renal failure (serum creatinine 2.0 mg/dL)
		Vascular Disease
		Symptomatic arterial disease including non-specific aortoarteritis
		Dissecting aneurysm
		Advanced Hypertensive Retinopathy
		Haemorrhages or exudates
		Papilloedema

Table 6: Risk Stratification

Other Risk Factors and Disease History	Blood Pressure (mm Hg)		
	Stage 1 SBP 140 to 159 or DBP 90 to 99	**Stage 2 SBP 160 to 179 or DBP 100 to 109**	**Stage 3 (Severe Hypertension) SBP ≥180 or DBP ≥110**
No other risk factors	Low risk	Medium risk	High risk
1 to 2 risk factors*	Medium risk	Medium risk	Very high risk
3 or more risk factors or Target organ damage* and/or diabetes	High risk	High risk	Very high risk
Associated clinical conditions**	Very high risk	Very high risk	Very high risk

Risk strata (typical 10-year risk of stroke or myocardial infarction): Low risk < 15%, Medium risk 15% to 20%, High risk 20% to 30%, Very high risk > 30%
SBP = Systolic blood pressure; DBP = Diastolic blood pressure.
** See Table 5; ** See Table 7*

Antihypertensive therapy should achieve and maintain SBP below 140 mm Hg and DBP below 90 mm Hg and lower if tolerated, while controlling other modifiable risk factors.

The ultimate public health goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity or mortality. Since most individuals with hypertension, especially those >50 years age, will reach the DBP goal once the SBP goal is achieved, therefore, the primary focus should be of attaining the SBP goal. Treating SBP and DBP to targets that are <140/90 mm Hg is associated with a decrease in CVD complications. In patients with hypertension and diabetes or renal disease, the BP goal is <130/80 mm Hg. Gradual reduction of BP to the optimal level over a period of 2 to 6 months is prudent therapeutic goal except in stage 3 hypertension.

Threshold of Therapy and Level of Control

Among diabetic patients participating in the hypertension optimal treatment (HOT) study, there was a significantly lower risk of CAD in patients with the lowest target DBP of <80 mm Hg.

The United Kingdom Prospective Diabetes Study (UKPDS) showed that a tight control of BP (average achieved 144/82 mm Hg) in diabetic patients conferred a substantial reduction in the risk of CAD compared to a less tight control of BP (average achieved 154/87 mm Hg).

In view of the above studies, it would seem desirable to achieve optimal or normal BP in young, middle-aged and (below 130/80 mm Hg) in diabetic patients and those with renal disease, at least high normal BP in elderly patients (below 140/90 mm Hg).

MANAGEMENT STRATEGY

Having assessed the patient and determined the overall risk profile management of hypertension should proceed as follows: In low risk patients, institute lifestyle modifications

Table 7: Lifestyle Interventions for Blood Pressure Reduction

Intervention	Recommendation	Expected Systolic Blood Pressure Reduction (Range)
Weight reduction	Maintain ideal body mass index below 23 kg/m^2	5 to 20 mm Hg per 10 kg weight loss
DASH diet	Consume diet rich in fruits, vegetables, low-fat dairy products with reduced content of saturated and total fat	8 to 14 mm Hg
Dietary sodium restriction	Reduce dietary sodium intake to <100 mmol/day (<2.4 g sodium or <6 g sodium chloride)	2 to 8 mm Hg
Physical activity	Engage in regular aerobic physical activity, for example, brisk walking for at least 30 minutes most days	4 to 9 mm Hg
Alcohol moderation	Men 60 mL per day, twice a week Women 30 mL per day, twice a week Abstinence is preferred	2 to 4 mm Hg
Tobacco	Total abstinence	Smoking or consumption of tobacco in any form is the single most powerful modifiable lifestyle factor for the prevention of major cardiovascular and non-cardiovascular disease in hypertensives

and observe BP for a period of three months before deciding whether to initiate drug therapy or not (**Table 7**).

In high risk group, use lifestyle modification therapy with drug therapy forthwith.

In medium risk patients, institute lifestyle modifications and monitor BP on a monthly basis. If after a period of three months, BP remains above 140/90 mmHg then initiate drug therapy. In high and very high risk groups, initiate immediate drug treatment for hypertension and other risk factors. The primary concern should be to lower SBP as recent evidence suggests that the level of SBP control correlates better with reduction of mortality than the level of DBP control.

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12.21 Management of Hypertension

Sandhya Kamath

INTRODUCTION

The management of hypertension is a multifaceted blood pressure (BP) exercise. The goal is optimum control so that complications can be prevented.

APPROACH TO THE PATIENT

The first step is to confirm the diagnosis of hypertension by accurate measurement of BP. A detailed history and physical examination should be done to screen for other cardiovascular disease risk factors, secondary causes of hypertension, consequences of hypertension, associated co-morbidities, assess lifestyle and determine what should be the ideal treatment.

History

Most people with primary hypertension do not have any obvious symptoms. The more common symptoms can be: Chronic headache that lasts for days rather than hours frequently present in the occipital area, dizziness or vertigo, blurry vision, double vision, increased sleepiness, nausea, shortness of breath, palpitations, fatigue, general tiredness, flushed face, epistaxis, a strong need to urinate often (especially during the night), tinnitus and many other non-specific symptoms.

Physical Examination

BP should be measured in both arms in sitting, standing and supine position to evaluate for postural hypotension; and at least once in both lower extremities in young hypertensives to rule out aortoarteritis. Heart rate and rhythm should be recorded. Irregularly, irregular pulse suggests atrial fibrillation which is very common in hypertension. Height, weight, waist-to-hip ratio should be measured and body mass index (BMI) calculated. Examine the neck for thyromegaly. Palpation of the blood vessel wall for stiffness, and bruit in the carotids will identify atherosclerotic disease. Cardiovascular system examination may reveal the apex beat to be displaced downward and outward depicting left ventricular hypertrophy. Loud S_2 due to closure of aortic valve and S_4 gallop (attributed to noncompliant left ventricle and diastolic dysfunction) may be heard. Evaluate for signs of congestive heart failure. Auscultate for an abdominal bruit that may be heard in the lower epigastrium on either side of the midline as a sign of renovascular hypertension. An enlarged, palpable kidney is most probably due to polycystic kidney. A thorough neurologic examination including fundoscopy should be performed. Fundus examination has to be done and it may show changes which are shown in **Table 1**. These changes reflect the duration of hypertension roughly.

One should look out for features of secondary hypertension in the history and physical examination.

Table 1: Keith-Wagener-Barker Classification

I	Sclerosis of arterioles—focal, diffuse constriction, copper wire and silver wire arteriolar reflex
II	AV crossing changes
III	Flame shaped haemorrhages, cotton wool spots, retinal oedema, retinal microaneurysms
IV	Grade III changes with papilledoema with or without macular star

Laboratory Investigations

Basic laboratory tests for initial evaluation are enumerated in **Table 2**.

Table 2: Laboratory Investigations

Complete blood count, ESR and haematocrit
Routine urine examination
Albuminuria—for renal involvement
Microscopic haematuria—malignant hypertension
BUN and serum creatinine
Serum potassium, sodium for adrenal involvement and as baseline prior to institution of treatment
Blood sugar, and lipidogram (total cholesterol, triglycerides) for co-morbid conditions
ECG, 2D-echocardiogram for diastolic dysfunction
Abdominal ultrasonography for kidney size, vascular anomalies.

MEASUREMENT OF BLOOD PRESSURE

Various devices for the measurement of BP and their relative merits have already been discussed in the earlier chapter.

MANAGEMENT

The management of hypertension, especially the primary hypertension comprises of two major aspects: (i) lifestyle modification; and (ii) pharmacotherapy of hypertension.

Lifestyle Modifications

These are presented in brief in **Table 3**. In addition the behavioural theory and discussed.

Behavioural techniques, meditation and yoga

Transcendental meditation and yoga are also widely believed to reduce BP. However, larger and more random controlled trials are needed to confirm benefits of these practices.

Antihypertensive Agents

Principles of treatment

The BP remains poorly controlled in many of the patients. The most important reason is lack of awareness about the condition and its ensuing complications. Asymptomatic nature of the condition results in poor compliance; and last but not the least

side effects of antihypertensive agents like weakness, sleepiness, forgetfulness and impotence cause the patients to avoid the drugs. But this can be overcome by prescribing newer agents that have fewer side effects.

Before initiating therapy, additional risk factors, extent of target organ damage and other associated conditions should be assessed (**Table 4**). The prognosis, choice and urgency of therapy will depend on the overall risk stratification (**Table 5**). The algorithm for the management of hypertension in general is depicted in **Figure 1**.

Significance of Systolic and Diastolic Blood Pressure and Pulse Pressure

In the past, recommendations for the treatment were based on diastolic blood pressure (DBP). Today systolic blood pressure (SBP) has assumed prominence. Joint National Committee on prevention, detection, evaluation and treatment of high BP (JNC-7) has stated that SBP is a much more important cardiovascular risk factor than DBP in those older than 50 years. A wide pulse pressure largely reflects a high SBP, and may be the most accurate predictor of all.

Table 3: Lifestyle Modifications for Blood Pressure Reduction

Intervention	Recommendation	Expected BP Reduction
Weight reduction	Maintain body mass index <23 kg/m^2	10 mm Hg/10 kg weight loss
Diet	Rich in fruits, vegetables, low-fat dairy products, and Less of saturated and total fat	8 to 14 mm Hg
Dietary sodium restriction	Reduce dietary sodium intake to <2.4 g sodium or < 6 g NaCl	2 to 8 mm Hg
Physical activity	Regular aerobic physical activity, e.g. brisk walking for at least 30 min most days	4 to 9 mm Hg
Alcohol moderation	Men <60 mL per day. Women <30 mL per day. Abstinence is preferred	2 to 4 mm Hg
Tobacco	Total abstinence	—

Source: Adapted from Indian Hypertension Guidelines – II. As minimum number of times as feasible.

Table 4: Factors Influencing Risk of Cardiovascular Diseases

Risk Factors for Coronary Artery Disease	Target Organ Damage	Associated Clinical Conditions
Age >55 years Male sex Post-menopausal women Smoking and tobacco use Diabetes mellitus Family history of premature CAD (Male <55 years) (Female <65 years) Increased waist-hip ratio, High LDL or total cholesterol, low HDL cholesterol and high triglycerides High sensitivity C-reactive protein and homocysteine levels might evolve as markers for high risk of vascular damage Estimated GFR <60 mL/min	Left ventricular hypertrophy detected by electrocardiogram and/or echocardiography Microalbuminuria/proteinuria and/or elevation of serum creatinine (1.2 to 2.0 mg/dL) Urinary albumin creatinine ratio Ultrasound or radiological evidence of atherosclerotic plaques in the carotids Hypertensive retinopathy	Cerebrovascular disease Ischaemic stroke Cerebral haemorrhage Transient ischaemic attack Heart disease Myocardial infarction Angina Coronary revascularisation Congestive heart failure Renal disease Diabetic nephropathy Renal failure (serum creatinine >2.0 mg/dL) Vascular disease Peripheral arterial disease including non-specific aorto-arteritis Aortic dissection Advanced hypertensive retinopathy Haemorrhages or exudates Papilloedema

CAD=Coronary artery disease; GFR= Glomerular filtration rate; LDL=Low density lipoprotein; HDL=High density lipoprotein.
Source: Adapted from Indian Hypertension Guidelines – II.

Table 5: Risk Stratification of Patients with Hypertension

Stage	Other History	Blood Pressure (mm Hg)		
		Stage 1 SBP 140 to 159 or DBP 90 to 99	Stage 2 SBP 160 to 179 or DBP 100 to 109	Stage 3 SBP >180 or DBP >110
I	No other risk factors	Low risk	Medium risk	High risk
II	1-2 risk factors	Medium risk	Medium risk	Very high risk
III	>3 or more risk factors/TOD/diabetes	High risk	High risk	Very high risk
IV	ACC	Very high risk	Very high risk	Very high risk

SBP=Systolic blood pressure; DBP=Diastolic blood pressure; TOD=Target organ damage; ACC=Associated clinical conditions.
Source: Adapted from Indian Hypertension Guidelines – II.

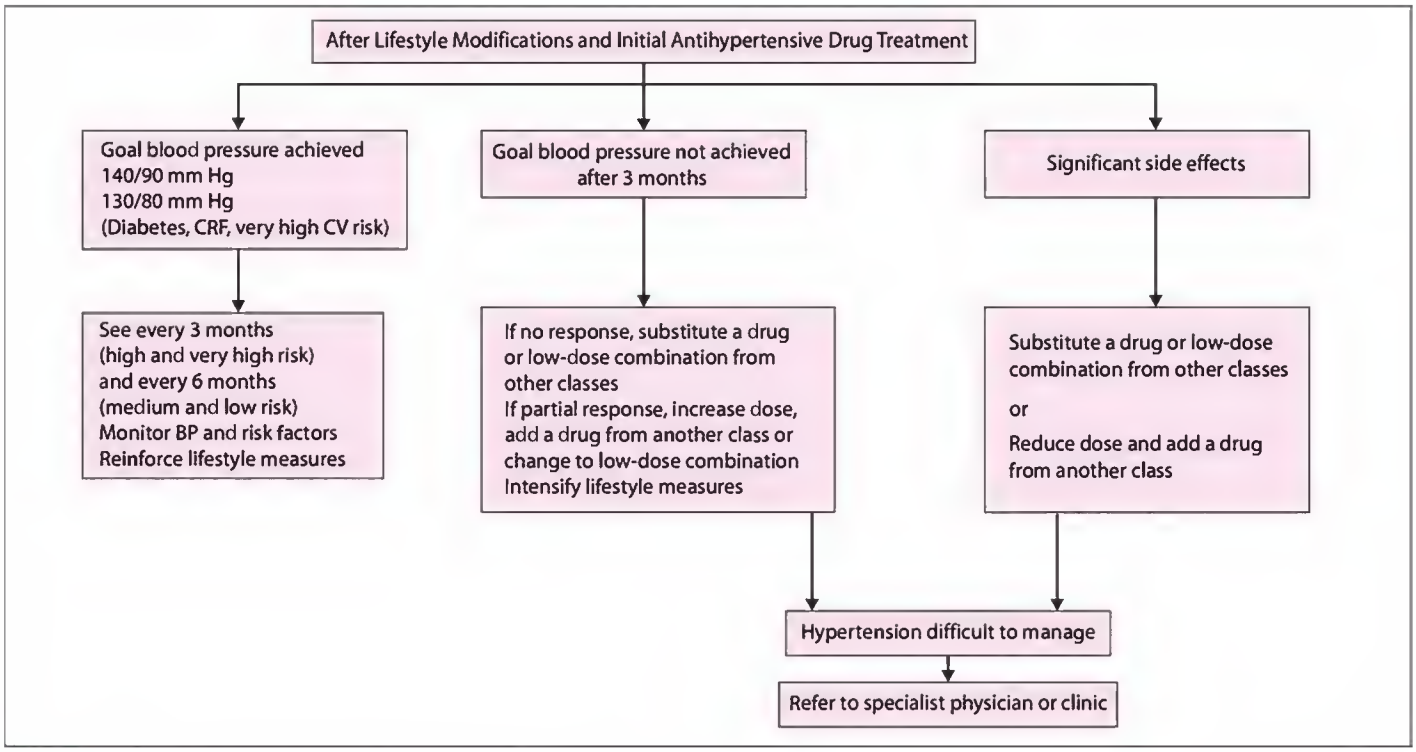


Figure 1: Algorithm for the management of hypertension.

Blood Pressure Level

It is desirable to achieve optimal or normal BP in young and middle aged patients with uncomplicated hypertension. Antihypertensive therapy should achieve and maintain SBP below 140 mm Hg and DBP below 90 mm Hg or lower if possible; simultaneously controlling other modifiable risk factors. The goal BP in diabetic patients should be below 130/80 mm Hg, in those with stroke should be below 130/85 mm Hg and at least high normal (below 140/90 mm Hg) in the elderly.

Choice of antihypertensive agents and their dosage are given in **Tables 6 and 7**. It is cautioned that there can be interactions between antihypertensive agents and other concomitant medications (**Table 8**).

Table 6: Guidelines for Selecting the Most Appropriate Antihypertensive Drugs

Class of Drugs	Definite Indications	Possible Indications	Definite Contraindications	Relative Contraindications
Diuretics	Heart failure Elderly patients Systolic hypertension	Diabetes	Gout	Dyslipidaemia
Beta-blockers	Angina Post-myocardial infarction Tachyarrhythmia Heart failure	Pregnancy Diabetes	Asthma and chronic pulmonary disease Heart block	Dyslipidaemia Peripheral vascular disease
Calcium channel blockers	Angina Elderly Systolic hypertension Diabetes	Peripheral vascular disease Cerebrovascular accident (CVA)	Heart block	Congestive heart failure
Angiotensin converting enzyme (ACE)-inhibitors	Heart failure Left ventricular dysfunction Post-myocardial infarction Significant proteinuria Diabetes	CVA	Pregnancy and lactation Bilateral renal artery stenosis Hyperkalaemia	Moderate renal failure (creatinine levels >3 mg/dL)
Angiotensin II receptor blockers (ARBs)	ACE-inhibitor induced cough or intolerant to ACE-inhibitor	Heart failure CVA	Pregnancy and lactation Bilateral renal artery stenosis Hyperkalaemia	Moderate renal failure (creatinine levels >3 mg/dL)
Alpha-blockers	Prostatic hypertrophy	Glucose intolerance Dyslipidaemia	—	Orthostatic hypotension Congestive heart failure

CVA = Cerebrovascular accident.
Source: Adapted from Indian Hypertension Guidelines – II.

The issue of which drug is the best choice for initial therapy and which is the ideal combination are still debated. JNC VII has advocated a low-dose thiazide diuretic for initial therapy. European Hypertension Society guidelines has recommended that whatever class of antihypertensive seems most appropriate should be used. World Health Organization (WHO) guidelines state that a diuretic is preferred, but any class of antihypertensives may be used. Thus, two of the three major guidelines have given preference to low-dose diuretics as initiating agents in uncomplicated patients. However, because of their metabolic complications these are not very popular. Diuretics combine well with most of the antihypertensives.

Table 7: Commonly Used Antihypertensive Drugs and Their Dosage

Class	Drug	Dosage (mg/day)
Diuretics	Hydrochlorothiazide	6.25 to 25
	Chlorthalidone	12.5 to 25
	Indapamide	1.5 to 2.5
	Amiloride	5 to 10
	Triamterene	50 to 100
	Spironolactone	25 to 50
Beta-blockers	Atenolol	25 to 100
	Metoprolol	25 to 100
	Bisoprolol	2.5 to 10
	Nebivolol	2.5 to 5
Calcium channel blockers (CCBs)	Amlodipine	2.5 to 10
	Diltiazem	90 to 360
	Verapamil	80 to 240
ACE-inhibitors	Enalapril	2.5 to 20
	Lisinopril	2.5 to 20
	Ramipril	1.25 to 10
	Perindopril	2 to 8
	Quinapril	10 to 80
Angiotensin II receptor blockers (ARBs)	Losartan	50 to 100
	Candesartan	8 to 32
	Valsartan	40 to 160
	Irbesartan	150 to 300
	Telmisartan	40 to 160
Alpha-blockers	Prazosin	2.5 to 10
	Doxazosin	1 to 4
Centrally acting drugs	Clonidine	0.1 to 0.3
	Methyldopa	500 to 1500

Source: Adapted from Indian Hypertension Guidelines – II.

Table 8: Drug Interactions

NSAIDs including COX-2 inhibitors decrease efficacy of diuretics, beta-blockers and ACE-inhibitors
Concomitant use of beta-blockers and non-dihydropyridine CCBs can result in heart blocks
Combined use of ACE-inhibitors and potassium sparing diuretics may result in hyperkalaemia
Cyclosporine levels are increased with diltiazem and verapamil
Concomitant use of tricyclic antidepressants with methyldopa is to be avoided

Source: Adapted from Indian Hypertension Guidelines – II.

Diuretics

Diuretics are basically divided into four groups: (i) Thiazide diuretics, (ii) loop diuretics, (iii) aldosterone antagonists and (iv) other potassium sparing diuretics.

Diuretics are recommended as first-line agents in the treatment of hypertension. Their advantage is that these are more effective in reducing cardiovascular mortality, coronary heart disease (CHD), cardiac failure, stroke and overall mortality than other agents. These are inexpensive and combine well with most of the other antihypertensive agents like beta-blockers, angiotensin converting enzyme (ACE)-inhibitors and, angiotensin II receptor blockers (ARBs). However, because of inherent natriuretic property of dihydropyridine calcium channel blockers, this combination is less effective. Low-dose diuretics remain the preferred initial treatment in the elderly and obese hypertensives.

It should be emphasised that diuretics should be prescribed in low dosage equivalent to 12.5 mg of hydrochlorothiazide. High doses of diuretics give rise to metabolic side effects like dyslipidaemia, hyperglycaemia, hyperuricaemia, hypokalaemia and hypomagnesaemia. This is the reason why death due to coronary artery disease (CAD) has not decreased as much as expected. Quality of life is disturbed as impotence is a frequent side effect. Another disadvantage is that the antihypertensive response to diuretics is not immediate, but takes at least two weeks to manifest.

Beta-blockers

The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension. This conclusion is based on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on CHD when compared to placebo or no treatment. These have multiple adverse effects like increased risk of diabetes mellitus due to loss of insulin sensitivity, rise in plasma triglycerides and lowering of HDL, increase in body weight, easy fatigability and reduced exercise tolerance. Indications for the use of beta-blockers in the treatment of hypertension are enumerated in **Table 6**.

The ideal beta-blocker for treatment of hypertension would be one that is long-acting, cardioselective, lipid neutral, glucose neutral and with vasodilating effects. Vasodilator beta-blockers labetalol, carvedilol and nebivolol cause less metabolic side effects and should be used instead of metoprolol or atenolol. However, there are no good outcome data for their use in hypertension without concomitant indications.

Calcium channel blockers

Calcium channel blockers (CCBs) are divided into two groups: dihydropyridine (DHPs—nifedipine, amlodipine, nicardipine, lacidipine) and non-dihydropyridine (verapamil, diltiazem). They reduce the BP primarily by reducing the peripheral vascular resistance (PVR) aided by an initial natriuretic effect. Due to the reduction in PVR, CCBs especially the DHPs cause reflex stimulation of the adrenergic system and tachycardia. Hence, these should be used with caution in patients with CAD especially the short-acting ones. Non-DHPs tend to decrease catecholamine levels. Several studies have shown that CCBs are safe and effective and particularly useful to prevent stroke.

CCBs seem to be particularly suitable for elderly hypertensive patients since these agents do not cause salt and fluid retention, postural hypotension, sedation, depression, or biochemical abnormalities. Moreover, their use is compatible with several common diseases of old age, such as diabetes, obstructive lung disease, and peripheral vascular disease. CCBs should be used as initial monotherapy for hypertension in angina pectoris (non-DHPs), Raynaud's phenomenon and supraventricular tachycardia (non-DHPs). Because of their favourable metabolic profile, CCBs are recommended in diabetes mellitus and dyslipidaemias. Patients on CCBs do not require regular blood chemistry checks.

Potential side effects from taking a CCBs include oedema of lower extremities, headache, light-headedness, dry mouth, skin rash, fatigue, nausea, constipation, gastro-oesophageal reflux disease (GERD).

ACE-inhibitors

The commonly used ACE-inhibitor are listed in **Table 7** along with their dosages. The various ACE-inhibitor have few practical differences except for duration of action. ACE-inhibitor block the conversion of angiotensin I to angiotensin II. Therefore, these lower arteriolar resistance and increase venous capacity; increase cardiac output and cardiac index, stroke work and volume, lower renovascular resistance, and lead to increased natriuresis.

ACE-inhibitor preferentially relax the renal efferent arterioles, thereby reduce intraglomerular pressure, and may cause a rise in serum creatinine. The commonest adverse effect of ACE-inhibitor is intractable cough; others being hypotension, hyperkalaemia, headache, dizziness, fatigue, nausea and angioedema. There is also some evidence to suggest that ACE-inhibitor might increase inflammation-related pain. Contraindications to ACE-inhibition are bilateral renal artery stenosis and pregnancy. Caution should be used when using ACE-inhibitor in patients with serum creatinine >2 mg% and they should be avoided when serum creatinine is >3 mg%.

ACE-inhibitor can be used as monotherapy in mild or moderate hypertension. They form effective combinations with diuretics and CCBs. Moderate salt restriction is essential for optimal effect. They are preferentially used in diabetic hypertensive patients, for cardioprotection post-myocardial infarction and in hypertension with heart failure. These are also known to reduce proteinuria especially in diabetics. Contrary to earlier belief, they are well-accepted in the elderly. These offer vascular protection in diabetics and in renal disease.

Angiotensin-II receptor blockers (ARBs)

ARBs are the fastest growing class of antihypertensive drugs. These are virtually free from side effects.

Angiotensin II receptor antagonists are primarily used for the treatment of hypertension where the patient is intolerant of ACE-inhibitor therapy. These do not inhibit the breakdown of bradykinin or other kinins, and are thus, only rarely associated with the persistent dry cough and/or angioedema that limit ACE-inhibitor therapy. More recently, these have been used for the treatment of heart failure in patients intolerant of ACE-inhibitor therapy, particularly candesartan. These show benefit in hypertensive patients with type II diabetes, and may delay the progression of diabetic nephropathy. The angiotensin II receptor blockers have differing potencies in relation to BP control, with statistically differing BP effects at the maximal doses.

ARBs block the renin-angiotensin system as do ACE-inhibitor, with much the same effects but at greater cost. Thus, it is preferable to use ACE-inhibitor and ARB should be substituted only if ACE-inhibitor intolerance develops.

Alpha-adrenergic blockers

Prazosin, terazosin and doxazosin are the common α-blockers available. They are free from metabolic or lipid side effects, but postural hypotension, dizziness, diarrhoea, tachycardia and fluid retention can be troublesome.

Today, α-blockers are used in patients with features of metabolic syndrome or in men with benign prostatic hypertrophy in whom they provide symptomatic relief. These combine well with other drugs and when used as third-line of therapy provide the required lowering of BP in patients who had not fully responded to full doses of initial two drugs.

Phenoxybenzamine and phentolamine are combined α1 and α2 blockers used in pheochromocytoma. Labetalol and carvedilol also have limited α-blocking activity.

Renin inhibitors

Aliskiren is the agent belonging to this group which is the only new class introduced in the past decade. It provides dose-dependent and sustained 24-hour efficacy, the magnitude of this effect is similar to other classes of drugs when the maximum recommended dose is used (300 mg). Aliskiren adds to the antihypertensive effect of an ARB or concomitant diuretic.

Direct vasodilators

Hydralazine is infrequently used today because it has no effect on regression of left ventricular hypertrophy, and patients taking hydralazine may develop lupus-like syndrome. The use of minoxidil is limited due to its sodium-retaining properties and development of hirsutism.

Centrally acting agents

Alpha-methyldopa still remains the drug of choice in hypertension in pregnancy. Clonidine and guanethidine are not used because of their unfavourable side effect profile.

METABOLIC ABNORMALITIES IN ASSOCIATION WITH HYPERTENSION

The dysmetabolic syndrome of insulin resistance is the common denominator of the complex inter-relation between hypertension, obesity and maturity-onset diabetes. High-doses of diuretics and beta-blockers worsen insulin resistance with risk of overt diabetes and/or lipid abnormalities. Other classes of antihypertensive agents such as ACE-inhibitor, ARBs or alpha-blockers improve insulin sensitivity, and CCBs are neutral. Hence, these classes become the logical first-line antihypertensives for patients with any component of the dysmetabolic syndrome.

HYPERTENSION WITH SPECIAL SITUATIONS

Dyslipidaemias

A statin should be concomitantly administered in patients with hypertension and dyslipidaemia because of the significant cardioprotection and stroke prevention that has been shown by the ASCOT-LLA study. Antihypertensive drugs that can be

used are CCBs, ACE-inhibitor, ARBs and α-blockers. Alpha-blockers are clearly known to improve lipid profile.

Obesity

The characteristics of obesity-related hypertension are increased plasma volume, high cardiac output, and low peripheral vascular resistance. The basic mechanisms include salt and water reabsorption, insulin resistance and increased sympathetic outflow. Weight loss should be advocated very strictly. Low-dose diuretic, ACE-inhibitor and/or ARB is advocated. Beta-blockers should be avoided.

Angina

CCBs (verapamil) and α-blockers are effective anti-anginal and antihypertensives as well. ACE-Is, ARBs and diuretics help indirectly by regression of LVH and/or reduction in BP.

POST-INFARCT HYPERTENSIVE PATIENTS

Beta-blockers, ACE-inhibitor or ARBs are in any case indicated in the post-infarct state and should handle the hypertension as well. Lowering of BP too rapidly may cause sympathetic activation and reflex tachycardia and should be avoided. Hypertension in patients with acute coronary syndrome should be treated aggressively. The target BP should be 130-140/90-95 mm Hg.

HYPERTENSION IN THE ELDERLY

Treatment of hypertension in the elderly definitely protects against the development of stroke. Systolic rather than diastolic hypertension is seen in this age group. SBP should be brought down to at least 140 mm Hg. DBP may also come down. But caution should be exerted to see that it is not lowered below 80 mm Hg in order to avoid coronary hypoperfusion. Also, postural hypotension should be watched for and taken care of immediately. Lifestyle modifications are important for the management of hypertension in the elderly.

Low-dose diuretics are the preferred agents. Dihydropyridine calcium channel blockers are able to reduce morbidity and mortality in the elderly. ACE-inhibitor and ARBs are also used. Beta-blockers are to be avoided. Combination therapy is required in nearly two-thirds of patients.

DIABETIC HYPERTENSIVES

Hypertension is present in nearly 50% of type I diabetics secondary to renal damage and 80% of type II diabetics as a component of metabolic syndrome. The BP goals are stricter than non-diabetics. JNC VII has recommended a goal BP of 130/80 mm Hg. The choice is ACE-inhibitor or ARB. A low-dose diuretic may be used. CCBs can be the third drug. Alpha-blockers are metabolically neutral are also appropriate.

Lifestyle modifications have to be aggressive. Tight control of diabetes, effective BP control and low protein diet improve overall outcome.

HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is diagnosed when the DBP is more than 85 mm Hg. The diagnosis requires two consecutive measurements of BP. DBP more than 110 mm Hg requires urgent attention.

Hypertension in pregnancy can be divided as: (i) pre-eclampsia, (ii) chronic hypertension in pregnancy, (iii) pre-eclampsia superimposed on chronic hypertension in pregnancy, and (iv) gestational hypertension.

The drug of choice for hypertension in pregnancy is alpha-methyldopa. CCBs and labetalol can also be used. ACE-inhibitor, ACE-II receptor blockers are contraindicated. Use of low-dose diuretics is discouraged because pre-eclampsia is a volume-depleted state. Intravenous labetalol and hydralazine are effective agents in emergency situations. Intravenous magnesium sulphate is the drug of choice for prevention and treatment of seizures, and can lower the BP to some extent. In some instances, antihypertensive drugs fail to lower the BP and the only means of controlling BP is to induce delivery.

HYPERTENSION IN SOME SPECIAL SITUATIONS

Cerebrovascular Accidents

In ischaemic stroke, the BP should not be reduced to less than 160/100 mm Hg. This should be done gradually and carefully monitored over 24 to 48 hours. In acute intracerebral haemorrhage, the BP should be maintained below 180 mm Hg and 105 mm Hg respectively.

Renal Disease

The BP goal should be less than 120/80 mm Hg. All patients with microalbuminuria, irrespective of the presence of hypertension need to be treated with antihypertensives in order to retard the progression of renal disease. Low-dose diuretics, CCBs, beta-blockers and alpha-methyldopa can be used in patients with renal disease. ACE-inhibitor and ARBs have shown favourable effects on progression of renal disease, especially in diabetics. However, these should not be used in patients with serum creatinine of ≥ 3 mg/dL. Salt restriction and protein restriction form an integral part of dietary recommendations.

Chronic Obstructive Airway Disease

Long-acting CCBs are safe and effective drugs. Low-dose diuretics may be used. ACE-I, ARBs, beta-blockers, alpha-beta blockers are not recommended.

RESISTANT HYPERTENSION

Resistant hypertension is defined as blood pressure that remains elevated above treatment goals despite administration of an optimal three-drug regimen that includes a diuretic. High BP that is under control, but requires four or more medications to treat it, is also considered resistant to treatment.

It is emphasised that measurement of BP should be accurate before labelling a patient as having resistant hypertension. Proper BP measurement technique must be used, the size of the BP cuff should be accurate and the BP readings must be recorded on two separate occasions.

Causes of resistant hypertension are enumerated in **Table 9**.

Table 9: Causes of Resistant Hypertension

Noncompliance with treatment
Lifestyle factors: obesity, excess salt intake, heavy alcohol consumption
Secondary hypertension
Fluid retention: usually expansion from kidney failure
Medications: corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, sympathomimetic agents present in nasal drops

Management

Resistant hypertension requires special consideration in terms of evaluation and treatment. Confirming resistance is the first step in evaluating difficult-to-treat high BP. Successful treatment of resistant hypertension requires consideration of lifestyle factors that contribute to treatment resistance, diagnosing and treating secondary causes of high BP and using multiple-drug treatments effectively. Uncontrolled hypertension is not the same as resistant hypertension. Uncontrolled BP can be caused by poor medication adherence and/or an inadequate treatment regimen. Additionally, it is important to make sure that what appears to be resistant hypertension is actually not 'pseudohypertension' or 'white coat hypertension'.

Combine agents with different mechanisms of action. A triple drug regimen of an ACE-inhibitor or ARB, CCBs and a thiazide diuretic is effective and generally well-tolerated. Some patients may benefit from adding mineralocorticoid receptor antagonist (MRA) to their treatment regimens. Combinations of three or more drugs must be tailored to the individual.

Dose Timing

Taking at least one antihypertensive medicine at bedtime had better BP control, in particular, lowering night-time BP.

Adherence

Steps should be taken to help patients take medications regularly and properly. Prescriptions should be simplified as much as possible by using long-acting combination drugs and once-daily dosing. More frequent clinic visits and home BP monitoring will generally help patients adhere to their treatment routine. Though an expensive and labour-intense option, a team approach to treatment including nurse case managers, pharmacists and nutritionists can improve treatment results.

HYPERTENSIVE EMERGENCIES

It is the clinical state of the patient, the degree of and/or progression of target organ damage that defines a hypertensive emergency and not the absolute level of BP.

Hypertensive emergencies are severe elevations in BP, often higher than 220/140 mm Hg, complicated by clinical evidence of progressive target organ dysfunction. These patients require immediate admission and BP reduction (not necessarily to normal ranges) to prevent or limit further target organ damage, e.g. hypertensive encephalopathy, intracranial haemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary oedema, dissecting aneurysm of aorta, acute renal failure, eclampsia of pregnancy. Immediate admission to a monitored unit and parenteral antihypertensive therapy are indicated.

Severe hypertension (urgencies) are marked elevations of BP, usually higher than 180/110 mm Hg. Evidence of target organ damage may be often present, but non-progressive. Manifesting symptoms may include headache, shortness of breath, and pedal oedema. Management in the emergency department with oral agents is sufficient. Follow-up within 24 to 72 hours is recommended. In many cases patients present with BP higher than 180/110 mm Hg, without clinical symptoms and have no clinical evidence of target organ damage. They may be initiated on a two-drug regimen if previously untreated, or an existing treatment regimen may be modified. Emotional distress or non-adherence to prior treatment may be the cause. These patients do not require BP reduction to normal and, after brief observation in the emergency room, can be discharged, with follow-up scheduled within 3 to 7 days.

Drugs used in hypertensive emergencies are enlisted in **Tables 10 and 11**.

Table 10: Preferred Drugs for Select Hypertensive Emergencies

Emergency	Drugs of Choice	Target Blood Pressure
Aortic dissection	Nitroprusside + esmolol	110 to 120 mm Hg SBP as soon as possible
AMI, ischaemia	Nitroglycerin, nitroprusside, nicardipine	Secondary to ischaemia relief
Pulmonary oedema	Nitroprusside, nitroglycerin, labetalol	Improve symptoms 10% to 15% in 1 to 2 hrs
Renal emergencies	Fenoldopam, nitroprusside, labetalol	Target BP 20% to 25% in 2 to 3 hrs
Catecholamine excess	Phentolamine, labetalol	Control paroxysms 10% to 15% in 1 to 2 hrs
Hypertensive encephalopathy	Nitroprusside	20% to 25% in 2 to 3 hrs
Subarachnoid haemorrhage	Nitroprusside, nimodipine, nicardipine	20% to 25% in 2 to 3 hrs
Ischaemic stroke	Nitroprusside (controversial), nicardipine	0% to 20% in 6 to 12 hrs

Table 11: Oral Agents for the Treatment of Hypertensive Urgencies

Agent	Dosage	Onset/Duration of Action	Precautions
Captopril	25 mg PO; repeat as needed; SL, 25 mg	15 to 30 min/ 6 to 8 hrs SL 10 to 20 min/ 2 to 6 hrs	Hypotension, renal failure, bilateral renal artery stenosis
Clonidine	0.1 to 0.2 mg PO, repeat hourly as required to total dosage of 0.6 mg	30 to 60 min/ 8 to 16 hrs	Hypotension, drowsiness, dry mouth
Labetalol	200 to 400 mg PO; repeat every 2 to 3 hrs	1 to 2 hrs/ 2 to 12 hrs	Bronchoconstriction, heart block, orthostatic hypotension
Amlodipine	2.5 to 5 mg	1 to 2 hrs/ 12 to 18 hrs	Tachycardia, hypotension

PO = Per orally; SL = Sublingual.

CONCLUSIONS

Management of hypertension includes not just the control of BP, but also other risk factors and associated conditions with special attention on prevention of target organ damage. A wide variety of agents are available. Diuretics are preferred agents. But there are compelling indications in special disease situations. It is essential to achieve 'goal' BP, in order to retard the development of TOD.

RECOMMENDED READINGS

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12.22 Secondary Hypertension

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INTRODUCTION

India has a very high prevalence of hypertension which is more in the urban population (20%) than in the rural population (10%). It is estimated that there are 89 million hypertensive people in India and about 180 million can be put under the category of pre-hypertension as per the prevailing criteria of Joint National Committee (JNC) VII definition.

In this large pool of hypertensive population, 93% to 95% comprise of primary hypertension where no definitive cause is discernible. However, 5% to 7% of individuals suffer from secondary hypertension and these patients are amenable to therapy (medical or surgical) depending on the aetiological factors. In the early stages of secondary hypertension if corrective treatment is effectively done, then hypertension can be practically cured or alleviated very significantly.

DEFINITION

Secondary hypertension is usually caused by treatable underlying pathology and it constitutes approximately around 5% to 7% of the total hypertensive population. Amongst the various causative factors, renal hypertension is responsible for the largest proportion followed by the endocrinal hypertension and hypertension due to use of oral contraceptives. A very small proportion is caused by vascular, immunological and neurological abnormalities (**Table 1**).

Table 1: Important Causes of Secondary Hypertension

Primary/Essential Hypertension	93% to 95%
Secondary Hypertension	5% to 7%
Renal causes	3% to 5%
Parenchymal	2% to 3%
Renovascular	1% to 2%
Endocrine causes	0.3% to 1.0%
Phaeochromocytoma	<0.1%
Primary aldosteronism	0.3%
Cushing's syndrome	<0.1%
Other endocrinopathies	
Thyroid disorders	0.5%
Parathyroid disorders	
Pituitary disorders	
Oral contraceptives/drugs	0.5%
Miscellaneous	0.5%

DIAGNOSIS

The importance of early diagnosis has already been emphasised. This will help in effective early intervention so that the disease may be cured even before target organ damage takes place and may provide a long lasting relief to the patient. To diagnose secondary hypertension, basic principles are the same as in any other patient of hypertension. A detailed history, examination and common laboratory tests are to be carried out. The history and the investigations may raise the suspicion of secondary hypertension. Some of the important clinical features include hypertension starting at extreme of ages, in younger age or elderly people above the age of 50 years. The other indicators are refractory hypertension which is difficult to manage and in endocrinal causes of hypertension the bio-chemical abnormalities may be seen. Coarctation of aorta should be suspected in cases with radio-femoral delay. Renal bruits may be heard in renal artery stenosis while episodic accelerated hypertension with neurofibromatosis may point to phaeochromocytoma. The other specific investigations in various categories of secondary hypertension are listed in **Table 2**.

IMPORTANT CAUSES OF SECONDARY HYPERTENSION

Renal Hypertension

Reno-parenchymal causes

This is one of the most common causes of secondary hypertension accounting for 2% to 5% of the hypertensive population. Diabetes, interstitial tubular disease, glomerular disease, polycystic kidney disease (PKD), analgesic and gouty nephropathy are some of the important causes.

The other causes which are renal-mediated are post-renal transplant patients as well as drug-induced due to cyclosporine, steroids, and sustained use of erythropoietin. In most of these patients, the pathophysiological features are expansion of the body fluid, sodium retention and inappropriate activation of the renin angiotensin aldosterone system (RAAS). The salient features of parenchymal hypertension are given below.

Hypertension occurs early in parenchymal and PKD while interstitial renal disorders cause hypertension in terminal stages. Hypertension further aggravates the deterioration of renal function and nephropathy. Treatment of early hypertension is essential for prevention of cardiovascular disease as well as kidney dysfunction. The rise in glomerular capillary pressure in glomerulonephritis and diabetic nephropathy leads to excessive protein loss and therefore aggressive management of hypertension is mandatory.

The protein excretion in interstitial kidney disease, pyelonephritis, PKD and hypertensive nephrosclerosis is minimal. However, if protein loss becomes excessive, aggressive management of hypertension is required. The commonly used drugs are calcium channel blocking agents and other conventional drugs. Angiotensin converting enzyme (ACE)-inhibitors should preferably be avoided in patients with high creatinine values.

Renovascular hypertension

The pathophysiology of renovascular disease resulting in hypertension is depicted in **Figure 1** and the various causes of renal artery stenosis are tabulated in **Table 3**.

Table 2: Clinical Features and Laboratory Investigations in Secondary Hypertension

Clinical and Laboratory Parameters	Suspected Disorder	Further Diagnostic Studies
Systolic/diastolic bruit heard in renal area	Renovascular disease	Ultrasound Doppler imaging, MR angiography, captopril radioisotopic renography, renal arteriography
Mass in renal region, loin pain, colic, stones, haematuria	Nephrolithiasis, UTI, polycystic kidney disease	Ultrasound - KUB, intravenous urography, contrast CT urography
Renal insufficiency, atherosclerotic cardiovascular disease, oedema, elevated blood urea nitrogen and creatinine levels, proteinuria	Renal parenchymal disease	Creatinine clearance, renal ultrasonography
Paroxysmal or persistent hypertension, headache, diaphoresis, tachycardia, palpitations, neurofibromatosis, *café-au-lait* spot (skin)	Pheochromocytoma	Increased urinary catecholamine metabolites (vinyl mandelic acid, metanephrines, normeta-nephrines), plasma free metanephrines
Hypernatraemia, hypokalaemia muscles weakness	Hyperaldosteronism	Ratio of plasma aldosterone to plasma renin activity, CT of adrenal glands
Weight gain, fatigue, weakness, hirsutism, amenorrhoea, moon facies, buffalo hump, purple striae, truncal obesity, hypokalaemia	Cushing's syndrome	Dexamethasone suppression test
Headache, fatigue, visual problems, enlargement of hands, feet, tongue, coarse features	Acromegaly	Growth hormone levels, CECT brain
Heat intolerance, weight loss, tachycardia, palpitations, systolic hypertension, exoph-thalmos tremor, sweating, etc.	Hyperthyroidism	Thyroid profile
Fatigue, weight loss, hair loss, swelling, diastolic hypertension, muscle weakness	Hypothyroidism	Thyroid profile
Kidney stones, osteoporosis, depression, lethargy, muscle weakness	Hyperparathyroidism	Serum calcium, parathyroid hormone levels
Snoring, day-time somnolence, obesity	Obstructive sleep apnoea	Sleep study
Weak pulses, decreased or delayed femoral pulse of low amplitude, pulsations in neck, bruit over inter-scapular region, abnormal chest radiograph	Coarctation of aorta, aorto-arteritis	Doppler or CT imaging of aorta-angiography
High salt intake, excessive alcohol intake, obesity	Dietary effects	Detailed history, alcoholic intake and calculate salt intake
Polycythaemia in COPD, erythropoietin use in renal disease	Side effects of erythropoietin	Trial of drug if possible

MR = Magnetic resonance; KUB = Kidney, ureter, and bladder; CT = Computed tomography; CECT = Contrast enhanced computed tomography; COPD = Chronic obstructive pulmonary disease.

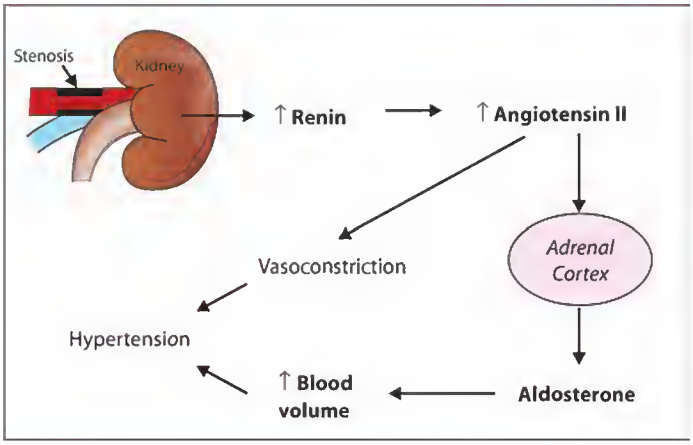


Figure 1: Renovascular hypertension and role of renin angiotensin aldosterone system.

Table 3: Causative Factors for Renal Artery Stenosis

Atherosclerosis	Vasculitis
Fibromuscular dysplasia	Renal artery embolism
Aorto-arteritis	Radiation arteritis

A number of lesions develop in renal arteries which cause hypertension, the most frequent being atherosclerosis. Others include fibromuscular dysplasia which has distinct arteriographic features. The choice of treatment depends on the type and severity of lesion.

Diagnosis

Most patients present in a way similar to essential hypertension. Certain clinical features may point to renovascular hypertension. These include abdominal bruit, drug-resistant hypertension, sudden onset pulmonary oedema, worsening renal function with use of ACE-inhibitors and sudden development of hypertension in the elderly.

Duplex ultrasound screening with colour Doppler flow studies of renal arteries has great potential for diagnosis of occlusive renal arterial disease with high sensitivity and specificity for detecting stenosis in more than 90% cases. Digital subtraction renal arteriography allows direct visualisation of the site and extent of renal artery stenosis. Though this is an invasive procedure and requires the use of contrast agent, it provides highly accurate information. Magnetic resonance angiography

is now often used as a non-invasive alternative. It is one of the definitive diagnostic procedures.

Management

Renal angioplasty and stenting are now the treatment of choice for renal artery stenosis. Anatomic quantification and functional significance of the lesion must be established first. Balloon dilatation alone is not sufficient as the lesion particularly in atherosclerosis is mostly ostial and re-stenosis is common. Therefore, stenting is advocated in most cases. It relieves ischaemia to the kidney and even if it does not normalise the blood pressure (BP), it will allow an easier control of BP. It will also contribute to long-term preservation of renal function. Renal stenting is particularly useful when the lesion is severe but renal function is still relatively well-preserved. When the kidney function has severely deteriorated, renal angioplasty often does not help. The drug therapy is an important factor in the treatment. Any drug other than the ACE-inhibitor can be initiated for control of hypertension. More than one drug may also be used, if necessary.

ENDOCRINAL CAUSES OF SECONDARY HYPERTENSION

Hyperaldosteronism

This endocrinal disorder causes hypertension due to excessive sodium retention, volume expansion and increased peripheral resistance. It can be either primary or secondary. The most common cause of secondary hyperaldosteronism is hyperreninism secondary to renal artery stenosis. The prevalence of primary hyperaldosteronism varies from 0.05% to 2% of the hypertensive population. Aldosterone producing adenoma is usually unilateral and is the most common cause of primary hyperaldosteronism in adults. It is found most commonly in patients of 20 to 50 years of age. Primary hyper aldosteronism presents with hypertension and hypokalaemia. In primary hyperaldosteronism, about 5% to 15% of patients may have normal serum potassium levels.

Idiopathic hyperaldosteronism (IHA) is the second most common cause of primary aldosteronism in adults but it is the most common cause in children. The bilateral adrenal hyperplasia associated with idiopathic hyperaldosteronism is thought to be due to an extra-adrenal stimulus.

Diagnosis

The diagnosis of hyperaldosteronism is made by the measurement of plasma aldosterone and plasma renin activity taking the blood samples in the morning after 15 minutes of rest. Tests that may help to identify the presence of autonomous hypersecretion of aldosterone are the fludrocortisone suppression test, saline loading tests and captopril suppression test.

A computed tomography or magnetic resonance image may identify the presence of an adenoma. An assessment of plasma aldosterone before (supine) and after 2 to 4 hours of upright posture may also be helpful.

Management

The control of BP with antihypertensive agents, correction of hypokalaemia and surgical removal of adenoma are the mainstay of treatment. Removal of an adrenal adenoma cures hypokalaemia within two weeks in all cases but hypertension only in about 70% of cases. Spironolactone is the drug of choice for primary hyperaldosteronism in small dose, e.g. 12.5 mg to 25 mg per day to start with. However, a higher dose of 200 mg to 400 mg per day may be required. Spironolactone can cause impotence, decreased libido, menstrual irregularities and gynaecomastia. Amiloride (10 to 40 mg per day) is the drug of choice for sexually active men. Amiloride blocks sodium channels at the distal renal tubules thus increasing sodium and chloride excretion and decreasing potassium excretion. Side effects include headache, fatigue, impotence, increased uric acid levels, and gastrointestinal complaints. If a second antihypertensive agent is needed, calcium channel blockers and ACE-inhibitors can be added.

Cushing's Syndrome

It occurs due to glucocorticoid excess and the patients have moon facies, truncal obesity, abdominal striae, hirsutism, hyperglycaemia, weak bones, cataracts, muscle weakness and hypertension. Hypertension is present in 80% of patients with Cushing's syndrome which is due to the sodium retaining effects of glucocorticoids and increased production of mineralocorticoids. Other contributory factors are increased production of renin substrate or steroid-induced change in vascular reactivity. Hypertension is common and severe with adrenal malignancy as compared to Cushing's disease. Bilateral adrenalectomy virtually cures all patients with Cushing's disease but it will also require permanent steroid replacement therapy for life. For pituitary adenomas, selective excision of the adenoma is warranted. Post-surgery radiotherapy may be needed to reduce the incidence of relapse.

Phaeochromocytoma

These are catecholamine secreting tumours, most commonly seen in the age group of 30 to 50 years. Up to 80% to 90% of pheochromocytoma are found in one or both adrenal glands. Most patients with pheochromocytoma have headache, sweating or palpitations. Hypertension may be sustained or paroxysmal. A clinical syndrome of baroreflex failure may be confused with pheochromocytoma which occurs from denervation of carotid baroreceptor following carotid body tumour resection, carotid artery surgery, neck irradiation or trauma. In this condition, the patient has labile hypertension with phases of acute severe rise of BP. Pheochromocytomas can be surgically excised. However, it is appropriate that preoperatively a stable alpha-adrenergic blockage is achieved and once this is established, beta-blockers can be added to the treatment as these can help to prevent catecholamine-induced arrhythmias. If the tumour is inoperable, radiation therapy is the most effective treatment modality with β-blockade use. These tumours can be successfully removed surgically in 90% of cases.

Hyperthyroidism

It induces systemic vasoconstriction, an increase in blood volume and increased cardiac activity all of which can lead to hypertension.

Hypothyroidism

Hashimoto's disease is one of the major causes of hypothyroidism. However, it is rarely diagnosed due to hypertension with non-specific symptoms such as malaise,

goitre and hypercholesterolaemia. Treatment of hyperthyroidism (carbimazole, surgical excision or radioablation) is useful. Hypertension can then be easily controlled but use of β-blockers may also be useful. It is not very clear why some patients with hypothyroidism develop hypertension. It may be related to decreased tissue metabolism reducing the release of vasodilator metabolites, thereby producing vasoconstriction, increased systemic vascular resistance and decreased cardiac output.

Other Endocrinal Causes of Hypertension

Acromegaly

Acromegaly is caused by growth hormone producing pituitary adenoma and hypertension is noted in about 40% of patients.

Primary hyperparathyroidism

It is caused by parathyroid adenoma or hyperplasia. Hypertension manifests in about 20% of patients with primary hyperparathroidism.

VASCULAR DISORDERS

Coarctation of Aorta

It is an easily diagnosed congenital defect that leads to hypertension. Absent or weak femoral arterial pulse gives clue to the diagnosis. It can be confirmed by echocardiography, MR angiography or conventional angiography. Early diagnosis and operative treatment before the age of 5 years is essential. Choice of treatment of coarctation is mostly by surgical correction. Balloon angioplasty and stent implantation is also practiced.

Aorto-arteritis

It is a fairly common cause of hypertension in India amongst the younger population. Various regions of the aorta, great vessels and renal arteries are involved resulting in hypertension. Its pathogenesis is uncertain and most likely immune-mediated. Diagnosis is clinically suspected due to absent or unequal peripheral pulsations with thoracic or abdominal bruits. It can be confirmed by MR angiography or digital angiography. Treatment includes immunosuppressive therapy, angioplasty and surgery.

Arteritis Syndrome

Arteritis syndrome involving the renal arteries can cause alternative obstruction and dilatation of renal vessels and this can start from aorta and its major branches. Hypertension is seen in 40% of the patients. The causation of hypertension is multifactorial.

Other Forms of Angiitis

These include polyarteritis nodosa and progressive systemic sclerosis (PSS). All these conditions are autoimmune disorders. Polyarteritis nodosa is complicated by hypertension in about 30% of patients which can progress to renal failure. While PSS presents with malignant hypertension and renal crisis, aggressive and rapid control of BP is the key for preventing kidney damage.

SLEEP APNOEA

It is a disorder in which breathing halts briefly but repeatedly during sleep. Most people with sleep apnoea snore and are overweight. Whether overweight or not, even mild sleep apnoea is associated with high BP. The mechanism of hypertension may be related to sympathetic activation and hormonal changes associated with repeated periods of apnoea-induced hypoxia, hypercapnea and stress associated with the loss of sleep. Sleeping with a nasal continuous positive airway pressure (CPAP) device is the treatment of choice. As the sleep apnoea improves, BP tends to improve as well.

Various drugs that can cause hypertension are listed in **Table 4**.

Table 4: Hypertension Caused by Drugs

Drug Class	Drug Examples
Immunosuppressive agents	Cyclosporine, tacrolimus, corticosteroids
Nonsteroidal anti-inflammatory drugs	Ibuprofen, naproxen, piroxicam
COX-2 inhibitors	Celecoxib, rofecoxib, valdecoxib
Oestrogens	Oestrogen oral contraceptives*
Anti-obesity	Sibutramine, phentermine
Stimulants	Nicotine, amphetamines
Mineralocorticoids	Fludrocortisone
Anti-Parkinsonian	Bromocriptine
MAO inhibitors	Phenelzine
Anabolic steroids	Testosterone
Sympathomimetics	Pseudoephedrine

** Oral contraceptives are one of the common causes of drug-induced hypertension.*

Erythropoietin

The underlying mechanisms in drug-induced hypertension include sympathetically-mediated vasoconstriction, direct pressor effect, stimulation of endogenous vasoactive substances, e.g. endothelin, increase in blood viscosity, salt and water retention, stimulation of renin angiotensin-aldosterone system and interference of central BP regulation.

DISEASES OF BRAIN AND CENTRAL NERVOUS SYSTEM

Hypertension may be observed in cerebrovascular accidents like cerebral haemorrhage, cerebral infarction and chronic subdural haematoma. Hypertension may also been seen due to symptomatic activities in patients with head injury, brain tumours and encephalitis. Release of intracranial pressure offers relief in some of these patients.

CONCLUSIONS

Secondary hypertension has varied and multiple causes but renal and vascular causes account for a large proportion of patients with secondary hypertension. The success of management lies in early diagnosis and effective management.

RECOMMENDED READINGS

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12.23 Bradyarrhythmias

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DEFINITION

Bradyarrhythmias are a group of rhythm disorders manifested by a ventricular rate in adults less than 60 beats per minute (bpm) under basal/awake conditions. The prevalence of bradyarrhythmias is more in elderly patients. It is a frequent finding in clinical practice, and its presentation may range from an incidental finding in asymptomatic patients to life-threatening atrioventricular (AV) block.

AETIOPATHOGENESIS

Automaticity or intrinsic impulse formation is the property of every cardiac cell. The sino-atrial (SA) node, as the primary cardiac pacemaker with the highest frequency in impulse formation, maintains the heart rate in response to the metabolic requirements and alterations of the autonomic nervous system. The conduction system of the heart comprising of the SA node, AV node and the His-Purkinje system is responsible for the synchronous conduction of the impulses from the atria to the ventricles.

Bradyarrhythmias occur due to:

1. abnormalities in impulse generation at sinus node (sinus node dysfunction),
2. abnormalities in conduction of impulse (disturbances in atrioventricular conduction system), and
3. a combination of abnormalities in impulse generation and conduction.

SINUS NODE DYSFUNCTION

Sinus node dysfunction is a clinical syndrome, encompassing a wide range of electrophysiological abnormalities, in combination with other clinical manifestations. This is also called 'Sick Sinus Syndrome'. These are due to abnormalities in the automaticity of sinus node cells or transmission of the sinus impulse into atria or increased susceptibility for atrial tachyarrhythmias. Causes of sinus node dysfunction are given in **Table 1**.

Table 1: Causes of Sinus Node Dysfunction

Idiopathic	
Drug induced	
	Anti-arrhythmic drugs, especially beta-blockers, sotalol and amiodarone
	Antipsychotic agents such as lithium, phenothiazines, amitriptyline
	Digitalis
Heart/Systemic disease	
	Acute inferior wall MI
	Hypothyroidism, hypothermia, hyperkalaemia and hypoxia
	Infiltrative disorders such as amyloidosis and sarcoidosis
Autonomically mediated	
	Vasovagal syncope
	Carotid sinus hypersensitivity

Clinical Features

In the early stages, most patients are asymptomatic. The typical symptoms of sinus node dysfunction due to inadequate cardiac output are:

Syncope or near-syncope, dizziness, palpitations, and decreased exercise capacity or fatigue.

The diagnosis of sinus node dysfunction is done by a 12-lead electrocardiogram (ECG) recordings, routine telemetric monitoring in the hospital or 24 hours ambulatory Holter recordings and exercise testing to judge the chronotropic response.

Autonomic testing such as carotid sinus massage, head-up tilt testing and Valsalva manoeuvres also help in establishing the diagnosis. Invasive electrophysiology studies are nearly obsolete for diagnosing sinus node dysfunction (SND).

The various bradyarrhythmias due to SND are:

Sinus Bradycardia

Sinus bradycardia is conventionally defined as sinus rate less than 60 bpm in adults during the wakeful state. However, in fit populations with a higher vagal tone, the normal waking sinus rate can go down to even 50 bpm (**Figure 1**). Sinus bradycardia is often a benign arrhythmia. Association of clinical symptoms is, therefore, essential in evaluating sinus bradycardia as being physiological or indicative of a pathological state.

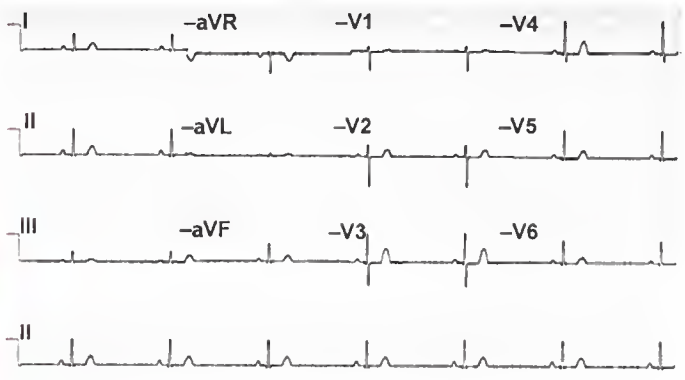


Figure 1: Sinus bradycardia.

Sinus Pause and Sinus Arrest

Sinus pause or sinus arrest is the failure of atrial activation, due to the inability of the sinus node to form impulses. A sinus pause is characterised by the absence of P-waves for a duration of more than 1.5 s. The pause is not an exact multiple of the preceding PP intervals (**Figure 2**). A sinus arrest is a more severe form where the delay is more than 3 (**Figure 3**).

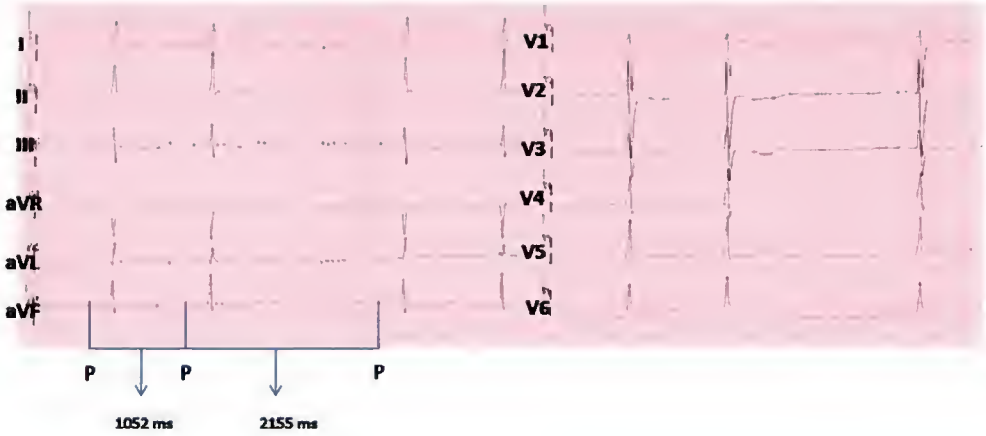


Figure 2: Sinus pause.

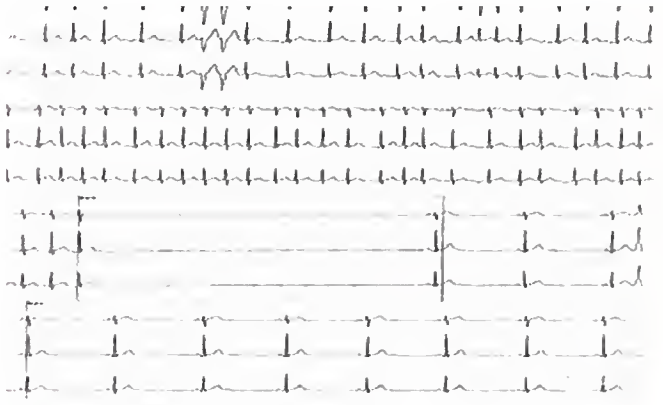


Figure 3: Sinus arrest following termination of atrial fibrillation.

Sino-atrial Exit Block

Sino-atrial exit block is the failure in conduction of sinus impulse into atria. Sino-atrial exit block can be graded into 3 degrees: *first degree, second degree and third degree.*

In a 12-lead surface ECG, SA block is manifest only as a second-degree or third-degree SA block. Electro-cardiographically, SA block is characterised by the absence of normal P waves and the duration of pause recognisable as an exact multiple of the preceding PP interval, unlike sinus pause/arrest.

First-degree SA block

The time for propagation of the sinus impulse into the atria is significantly prolonged. This cannot be identified clinically or electrocardiographically.

Second-degree SA block

Second-degree SA block can be further classified as:

Mobitz type I SA (Wenckebach) block

It is characterised electrocardiographically by progressive lengthening of SA conduction, until no P-wave appears for one beat and the sequence begins again. There is group beating, with gradually shortening PP intervals, followed by a pause which is less than twice the shortest cycle.

Mobitz type II SA block

It is characterised electrocardiographically by fixed PP interval, before and after the pause with the pause being a multiple of the PP interval. Type II SA block is named as 2:1, 3:1 block, etc. according to the ratio of the PP interval with the pause (**Figure 4**).

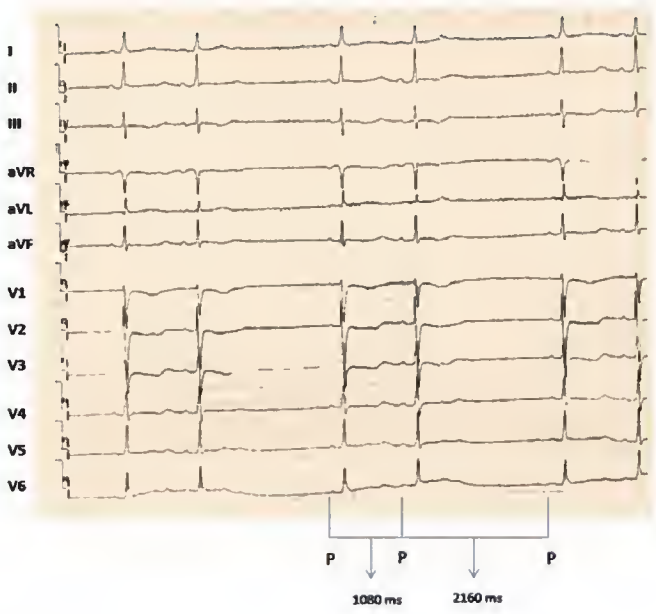


Figure 4: 2:1 Sino-atrial block.

Third-degree or complete SA block

It is manifest as absence of P-waves, with long pauses resulting in ectopic atrial or ventricular rhythms. Complete SA block cannot be differentiated from sinus arrest on a surface ECG.

DISORDERS OF ATRIOVENTRICULAR CONDUCTION

Conduction blocks in the AV conduction system can occur in the AV junction or at different levels in the His-Purkinje system. The blocks in the His-Purkinje system such as bundle branch blocks or intraventricular conduction defects do not necessarily show bradycardia.

AV Block

AV block (erroneously called as heart block) is the failure in regular conduction of the impulse from atria to the ventricle at the AV junction. The diagnosis of the AV block can be done adequately from the ECG from the PR interval, QRS duration and ventricular rates on the surface ECG.

AV block can be also graded into 3 degrees: *first degree, second degree and third degree.*

Causes of AV Block

Causes of AV block are given in **Table 2**.

Table 2: Causes of AV Block

Physiologic
- Athletes
- Sleep

Drug-induced
- Digitalis, verapamil, beta-blockers, amiodarone, etc.

Vagally mediated
- Carotid sinus hypersensitivity
- Neurocardiogenic syncope

Heart/Systemic disease
- Lenegre's disease: sclero-degenerative
- Lev's disease: fibrocalcific
- Myocardial infarction
- Congenital complete AV block
- Viral myocarditis
- Hyperkalaemia
- Traumatic—after surgery or radiofrequency ablation close to the AV node

First-degree AV block

The time for conduction of impulse from the atria to the ventricles is significantly prolonged in first-degree AV block. An ECG with a paper speed of 25 mm/s will show the prolongation of the PR interval by more than 200 ms (**Figure 5**).

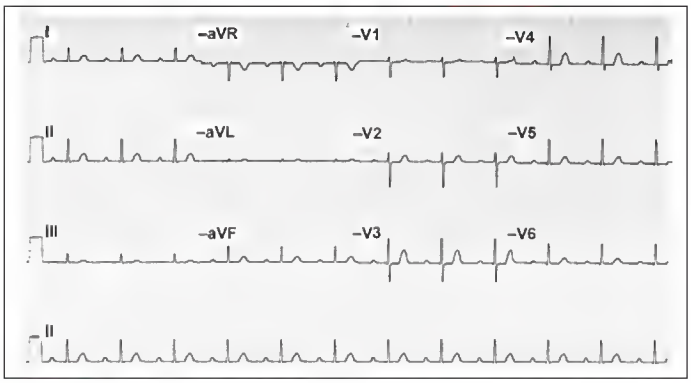


Figure 5: First-degree AV block (PR interval is 260 ms).

Second-degree AV block

Second-degree AV block is further divided into:

Mobitz type I (Wenckebach phenomenon)

It is characterised in an electrocardiogram by a sequence which begins with a normal or prolonged PR interval, and with each successful beat the PR interval lengthens until block of the impulse occurs and a beat is dropped. The R-R interval shortens typically. This type of block invariably is at the level of the AV node (**Figure 6**).

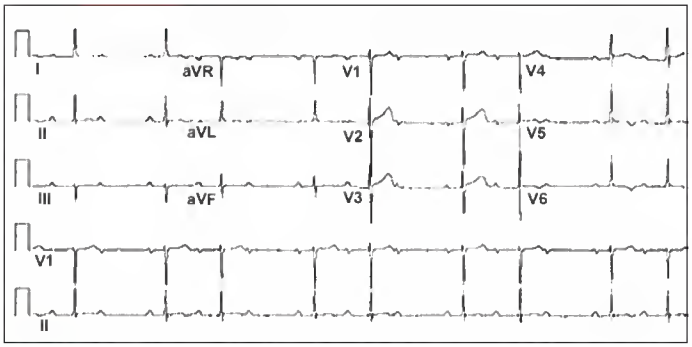


Figure 6: Second-degree AV block Mobitz 1 (AV Wenckebach).

Mobitz type II

It is characterised in an electrocardiogram by a PR interval which is prolonged but constant, but some P waves are not conducted (**Figure 7**).

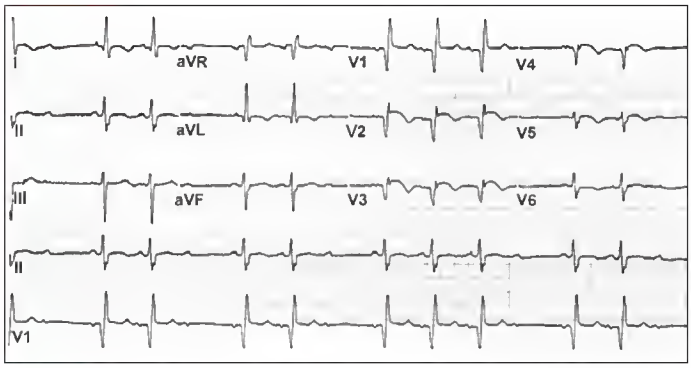


Figure 7: Second-degree AV block Mobitz 2 – RBBB. The ECG also shows an evolved anterior wall myocardial infarction with left-axis deviation.

2:1 AV block

In case of only 2:1 AV block, it is not possible to classify it as type 1 or type 2; hence a separate category of 2:1 AV block in our classification (**Figures 8A and B**).

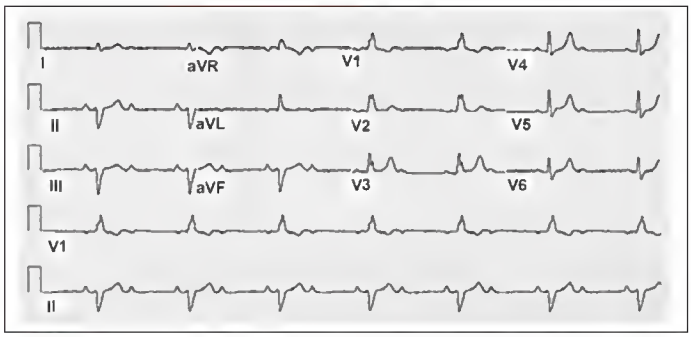


Figure 8A: 2:1 AV block. There is also RBBB and LAFB.



Figure 8B: 2:1 AV block-narrow QRS. The PR interval is also prolonged.

Third-degree or complete AV block

It results in the complete interruption of conduction from the atria to the ventricle. In an ECG, it is characterised by the failure of all P waves to conduct to the ventricle. There is consequently an escape rhythm from a subsidiary pacemaker in the AV junction at heart rates lower than the typical sinus rate for the subject. The QRS complexes are normal or near normal in shape if the subsidiary pacemaker

is situated in the lower AV node (**Figure 9A**) and wide (**Figure 9B**) if the ectopic pacemaker is situated peripherally in the ventricular musculature.

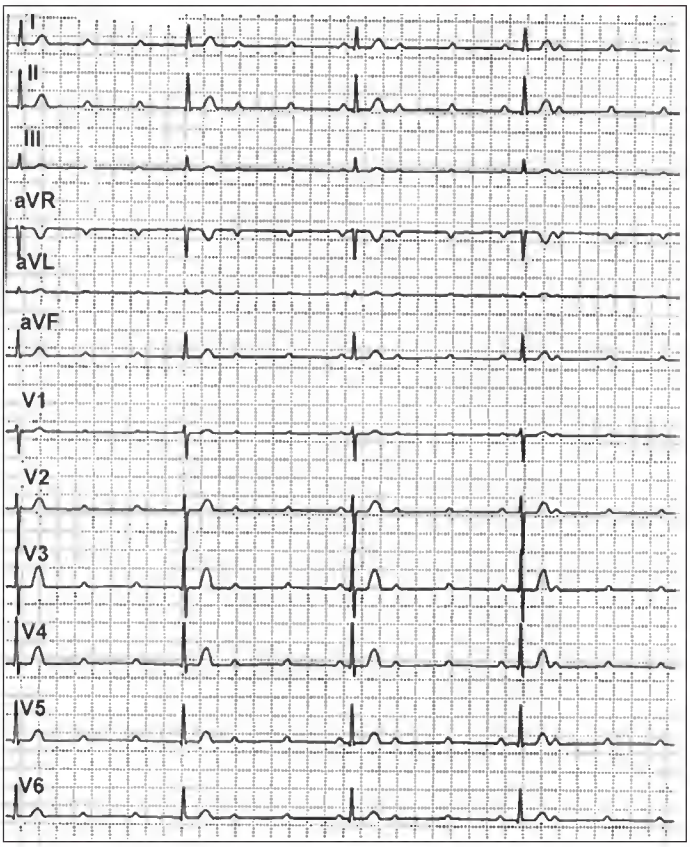


Figure 9A: Complete AV block. Narrow QRS escape rhythm.

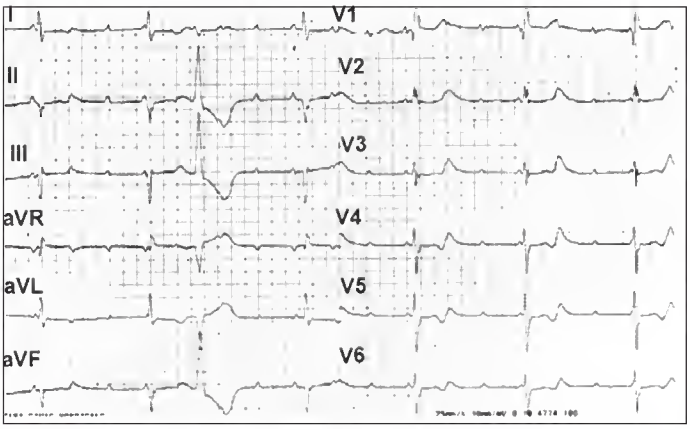


Figure 9B: Complete AV block. Wide QRS escape rhythm. One premature ventricular complex is also seen.

A narrow (normal) QRS escape rhythm is generally more stable, while a wide QRS escape rhythm carries a grave prognosis.

High-grade AV block

When 2 or more consecutive sinus P waves are blocked, it is termed as high-grade AV block.

Paroxysmal AV block

Sudden episodes of high-grade AV block when there is otherwise normal conduction is termed as paroxysmal AV block (**Figure 10**).

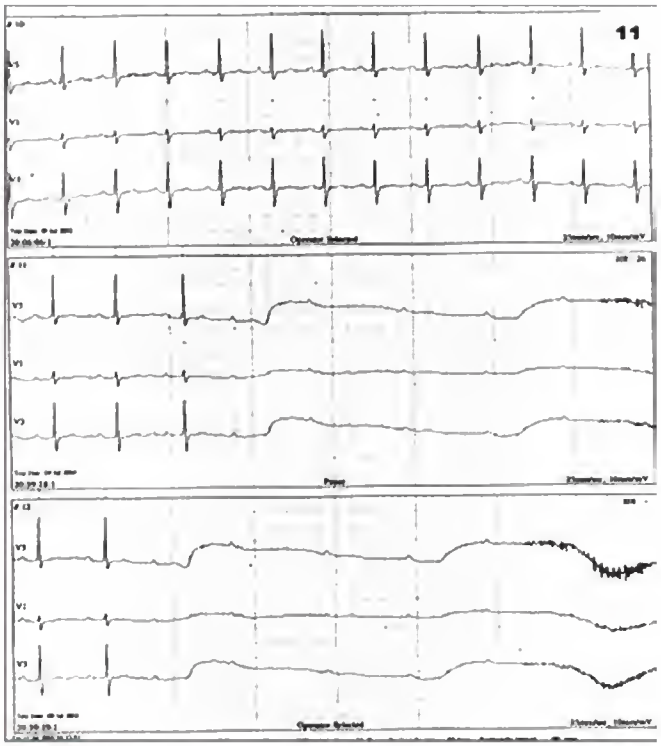


Figure 10: 24-hour Holter showing paroxysmal AV block. Likely to be vagally-mediated since there is sinus slowing along with asystole.

AV Dissociation

This is a descriptive term for a phenomenon and not a disease entity by itself. Hence, AV dissociation is not synonymous with AV block. AV dissociation connotes that the atria and ventricles are activated by separate pacemakers. This is seen in complete AV block, many cases of ventricular tachycardias, and severe sinus bradycardia (isorhythmic AV dissociation) (**Figure 11**).

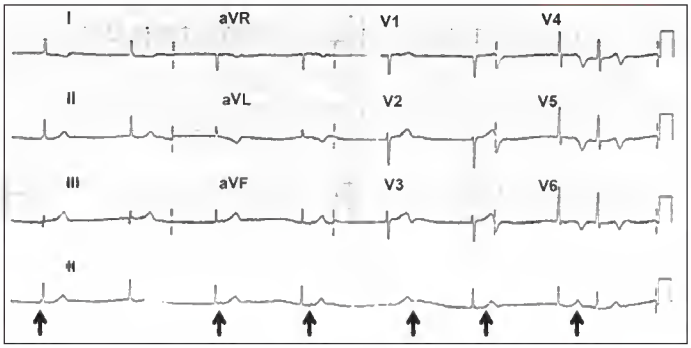


Figure 11: Isorhythmic AV dissociation. Sinus bradycardia; competing junctional escape rhythm. The sinus P is occasionally conducted. Arrows denote sinus P waves.

TREATMENT

Bradycardia is a common finding in general practice, and the clinical presentation may range from an incidental finding in asymptomatic patients to life-threatening heart block.

For the management of patients with bradycardia, it is crucial that the symptoms be recognised as related to a low ventricular rate. The suspicion of bradycardia in the differential diagnosis of haemodynamically compromised patients must usually be followed by immediate ECG recording and interpretation. A careful clinical evaluation is necessary and should include history taking, physical examination and

laboratory studies including tests of thyroid function as well as continuous 24-hour ECG recording. Identification of treatable, reversible causes of the bradycardia is the key for successful management. There is no reliable long-term medication for increasing the sinus rate.

Management of Sinus Node Dysfunction (SND)

In patients with known causes for sinus node dysfunction (SND), treatment should be directed towards the underlying aetiology. Theophylline and beta-agonists have been used to treat bradycardia symptomatically, but it does not prevent syncope. Permanent pacing is considered essential in all symptomatic cases of sinus node dysfunction. Atrial-based pacing is the ideal option for patients with significantly symptomatic sinus node dysfunction (**Figure 12**).

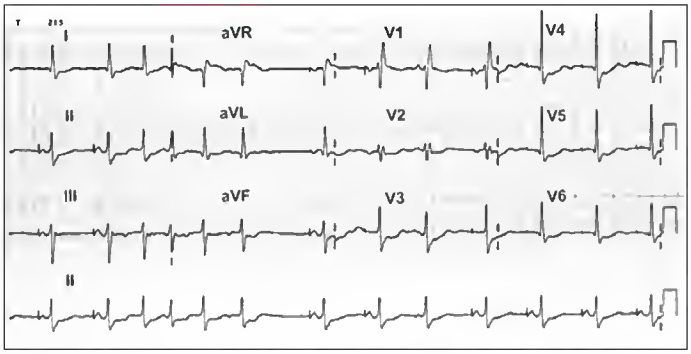


Figure 12: Atrial (AAI) pacing.

Management of Atrioventricular Conduction Disturbances

The prognosis and management of AV block depends on the level of AV block and its association with symptoms. Identification of the cause for AV conductional disturbances is important in recognising them as transient or irreversible. Drug-induced AV block can be resolved by withdrawing the causative drugs. Permanent pacing must be considered if the drugs are essential for treatment of other medical conditions. Temporary pacing is indicated in AV blocks due to conditions such as digitalis toxicity, hyperkalaemia or acute myocardial infarction till the resolution of the block. In all other cases, permanent pacing is indicated. An AV sequential pacemaker is preferable for AV block (**Figure 13**).

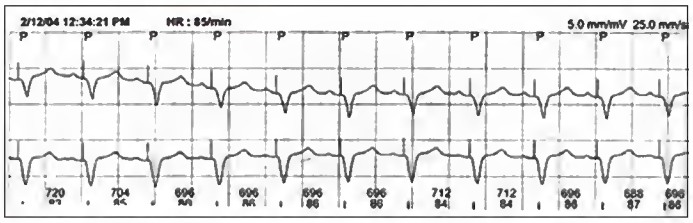


Figure 13: AV sequential pacing (atrial sensed, ventricle paced).

RECOMMENDED READINGS

1. Epstein AE, DiMarco JP, Ellenbogen KA, *et al.* ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008; 117: e350-408.
2. Fuster V, O'Rourke RA, Walsh R, *et al. Hurst's The Heart*; 12th Ed. New York: McGraw Hill Company; 2008.
3. Gupta AK, Maheshwari A, Lokhandwala Y. Evaluation of syncope: an overview. *Indian Pacing Electrophysiol J* 2001; 1: 12-22.
4. Panicker GK, Lokhandwala Y, Desai B. Choosing pacemakers appropriately. *Heart Asia* 2009; 1: 26-30.

12.24 Tachyarrhythmias

Amit Vora

INTRODUCTION

The origin and spread of cardiac electric activity is the function of specialised cells forming the natural pacemaker sites and conduction system within the cardiac muscle. Normally, the electrical impulse is generated at the sinus node at a rate ranging from 60 to 100 per minute and propagates to activate both atria and further reach the ventricles via the atrioventricular (AV) node and His-Purkinje system. By convention any heart rate beyond 100 per minute would be defined as tachycardia. Tachycardia can be classified as shown in **Figure 1**.

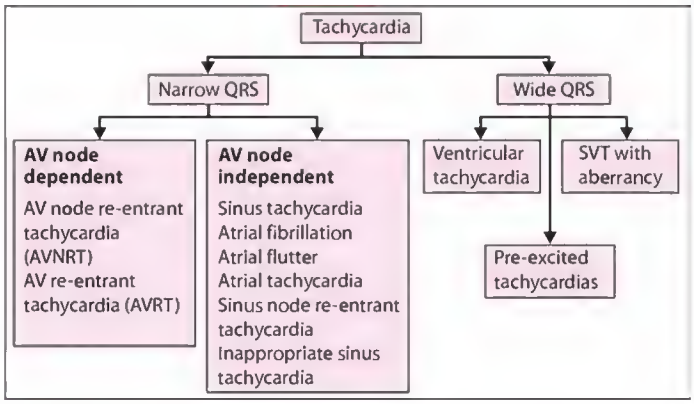


Figure 1: Classification of tachyarrhythmias.

MECHANISMS OF TACHYARRHYTHMIAS

Disorders of Impulse Formation

Automaticity

Under certain conditions like ischaemia and electrolyte imbalance, the resting membrane potential of cardiac muscle cells may become less negative. This can give rise to automaticity, i.e. spontaneous phase IV depolarisations. This has been implicated in certain arrhythmias like some types of atrial tachycardia (e.g. digitalis-induced), and accelerated junctional rhythm.

Triggered activity

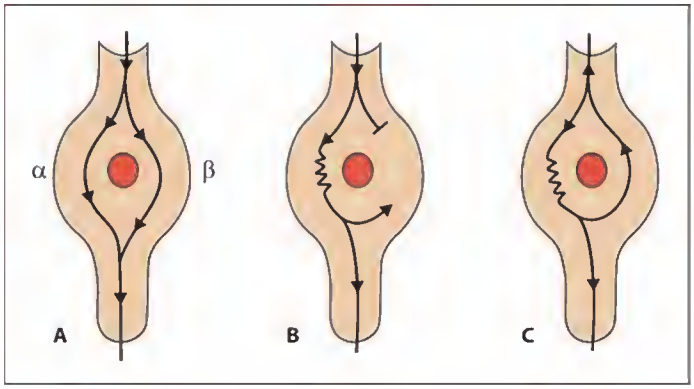
Triggered activity is initiated by after-depolarisations, which are oscillations in the membrane potential initiated by the preceding action potential. These may be early after-depolarisations, i.e. occurring in phase 2 or 3 of the action potential, or delayed after-depolarisations, i.e. occurring after repolarisation is complete. Early after-depolarisations have been implicated in tachycardias in congenital and acquired forms of the long QT syndrome. Delayed after-depolarisations are implicated in some digitalis-induced arrhythmias, right ventricular outflow tract tachycardia related to exercise, etc.

Disorders of Impulse Conduction

Re-entry

Under specific circumstances, the cardiac impulse may detour from its destined path and return to a previously depolarised area to re-excite it (re-enter) if it has recovered excitability. If this sequence is repetitive, a tachycardia may then result.

Re-entry requires the presence of two conducting pathways, with slow conduction in one pathway and a unidirectional block in the other, as shown in the **Figure 2**.



Figures 2A to C: (A) The electrical impulse travels through two pathways, i.e. α and β. These meet at a common exit point. (B) Since the two pathways have different refractory periods, an extra stimulus is blocked in β pathway but can conduct slowly over α pathway, and' re-enter' the β pathway retrograde. (C) This results in sustained circus movement. Tachycardia.

SUPRAVENTRICULAR TACHYCARDIA

Sinus Tachycardia

The common causes are fever, anxiety, hypovolaemia, hyperthyroidism, infection and pulmonary thromboembolism. Upright P waves in the electrocardiography (ECG) leads II, III, aVF; inverted P in aVF and transition from biphasic to upright waveform in the precordial leads help to distinguish from atrial tachycardias. Carotid sinus massage to slow the sinus rate may help to distinguish the P wave morphology. Sinus tachycardia is a marker of underlying pathophysiologic state and by itself does not warrant any treatment.

Unusually, there is persistent 'inappropriate' sinus tachycardia in the absence of any underlying cause. Paroxysmal onset of rapid sinus rates could be sinus node re-entrant tachycardia. Reassurance and beta-blockers are generally effective and only rarely does one resort to radiofrequency (RF) ablation with only a modest success.

Atrial Tachycardia

The ectopic P wave in atrial tachycardia (AT) most often precedes the QRS complex (**Figure 3**) and its morphology can suggest the site of origin of the tachycardia. Atrial tachycardia could be paroxysmal, the most common type recognised by its sudden onset and offset. The rare type is incessant or permanent. The mechanism for paroxysmal atrial tachycardia can be re-entry or triggered activity and in case of more gradual onset and offset, abnormal automaticity. While can arise from any site, there are certain common sites of origin. These are the right

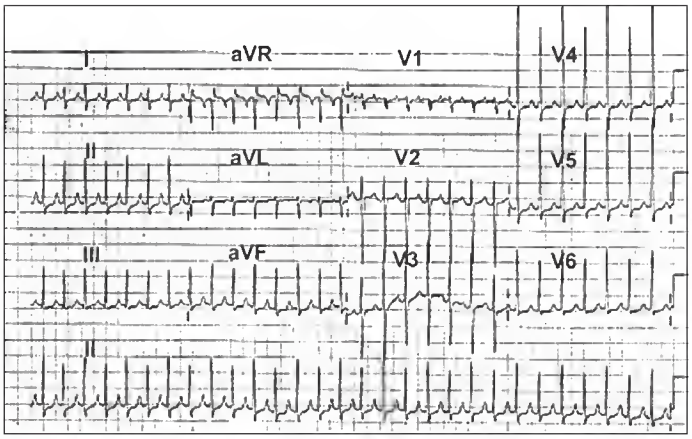


Figure 3: Atrial tachycardia. The dented T wave suggests ectopic P wave fused with it.

atrial appendage, crista terminalis, area around the coronary sinus ostium and area around the pulmonary vein orifices. In the presence of valvular disease and enlarged atria, multiple sites of origin may be present.

Incessant atrial tachycardia is a serious arrhythmia as it can result in left ventricular dysfunction, described as 'tachycardiomyopathy'. This ventricular dilatation and dysfunction is entirely reversible if sinus rhythm is restored. Amiodarone, propafenone, flecainide and quinidine are the drugs that act on the atrium and help terminate as well as prevent atrial tachycardia. For drug-resistant atrial tachycardia, ventricular rate can be controlled by drugs that depress AV nodal conduction, viz. verapamil, diltiazem, beta-blockers and digoxin. The preferred therapy for sustained or recurrent atrial tachycardia is RF ablation with a success rate of 90%. This procedure eliminates the site of origin and achieves permanent cure.

Atrial Flutter

The underlying mechanism is a macro-re-entrant circuit within the atrium. There are many varieties of atrial flutter; Type 1 or common or typical type is identified by inverted flutter waves in the inferior leads with characteristic 'saw-tooth' appearance (**Figure 4**). In these patients, there is abnormal slow conduction of electrical impulse in the isthmus region (area between the tricuspid annulus, inferior vena cava and coronary sinus). This leads to macro-re-entrant circuit within the right atrium in a counter-clockwise direction, i.e. superiorly along the septum and

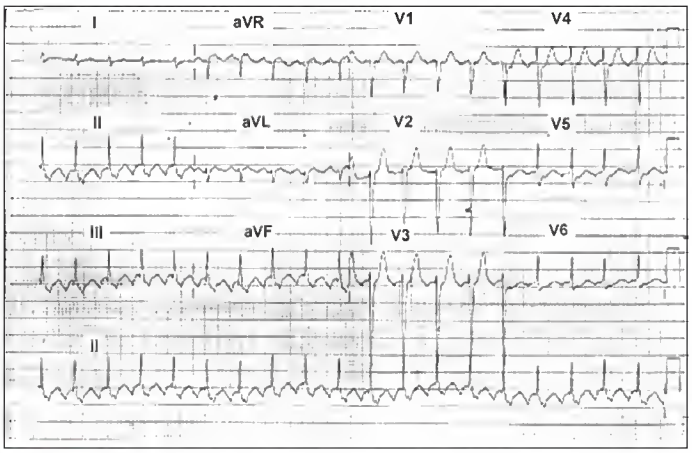


Figure 4: Typical atrial flutter with 2:1 AV conduction. Note the classic saw-tooth pattern of the flutter waves.

downwards from the sino-atrial node region along the crista towards the isthmus. Type 2 or atypical atrial flutter is due to a reverse circuit, i.e. clockwise with positive flutter waves in inferior leads. Left atrial flutter, often seen with mitral valve disease is rapid and atypical in its morphologic characteristics. The ventricular rate during atrial flutter is usually slower than the atrial rate, due to physiologic block of some of the atrial impulses in the AV node. The drug treatment is similar to that of AT. Electrical cardioversion with 100 to 200 J may be necessary in patients with haemodynamic compromise or uncontrolled rapid ventricular rates. Both the typical and atypical right atrial flutter can be cured by RF ablation along the isthmus. The left atrial flutter or multiple re-entrant circuits are less amenable to RF ablation.

Atrial Fibrillation

Multiple, simultaneous re-entrant circuits and rotor waves in both atria are responsible for initiating and sustaining atrial fibrillation (AF). The common causes are valvular heart disease, corpulmonale, cardiomyopathy, hyperthyroidism and atrial septal defect. Occasionally, lone AF is seen without any obvious cause. The atria are activated 400 to 500 times a minute. The fibrillatory waves may be fine or coarse on the ECG (**Figure 5**). Like atrial flutter, the ventricular rate in AF depends upon the AV nodal conduction. The pulse is irregular in rhythm and volume. Currently, AF is classified as new onset, paroxysmal (spontaneously terminating), persistent (can be terminated pharmacologically or by cardioversion) and permanent (cannot be terminated).

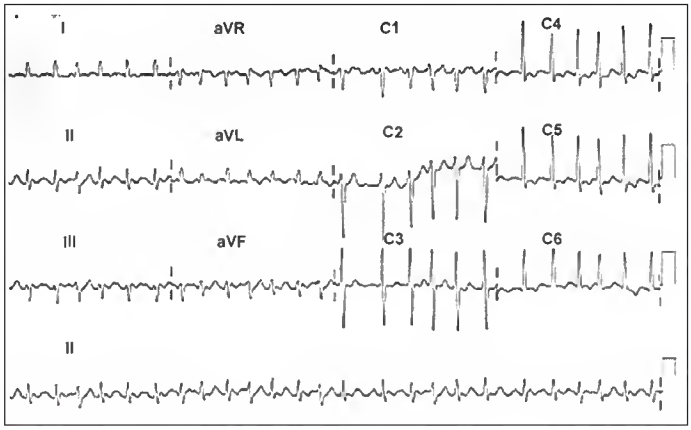


Figure 5: Atrial fibrillation with rapid ventricular rate.

The pharmacologic treatment involves ventricular rate control or restoring and maintaining sinus rhythm. Rate control approach is reasonable for first episode of AF, left atrial size greater than 6 cm, advanced age, pulmonary/thyroid disease and haemodynamically unrelieved valvular heart disease.

Importantly, the underlying cardiac or pulmonary cause needs to be tackled. A combination of amiodarone/sotalol and electrical cardioversion (200 to 360 J) is often effective. Rarely, drug-resistant AF with rapid ventricular rate resulting in tachycardiomyopathy can be effectively treated by RF ablation of the AV node and a permanent pacemaker implantation to provide a steady, controlled ventricular rate. Surgical maze procedure especially for patients undergoing valve surgery can be attempted to restore sinus rhythm. RF ablation as a cure in patients with paroxysmal AF and no structural heart disease has become a possibility in experienced centres.

Various patients with AF require anticoagulation according to their risk profile (**Table 1**).

Table 1: Guidelines for Anticoagulation in Patients with Atrial Fibrillation

Risk	Risk Factors	Anticoagulation
High risk	Prior stroke, TIA, embolism Rheumatic valvular heart disease Prosthetic valve	Definitely indicated if any of the risk factors are present
Moderate risk	Age >75 years Hypertension Diabetes mellitus LVEF ≥ 35%	Indicated if more than one risk factor are present
Low risk	Age 65-75 years Female gender Coronary artery disease Thyrotoxicosis	Not indicated

TIA = Transient ischaemic attack; LVEF= Left ventricular ejection fraction.

Atrioventricular Nodal Re-Entrant Tachycardia

This is the commonest type of paroxysmal supraventricular tachycardia (SVT). The age of onset is usually between 30 and 50 years and it is more common in women. The basis for this arrhythmia is dual pathways around the AV node, referred as slow and fast pathways. In these patients, an APB can activate the re-entrant circuit producing the typical slow-fast AV nodal re-entrant tachycardia (AVNRT) (**Figure 6**). Due to simultaneous activation of the atria and ventricles during AVNRT, the right atrial contraction produces back pressure on the jugular veins, described as the frog sign. Acute termination may be spontaneous or by vagal manoeuvres like carotid sinus massage, but often intravenous medication (diltiazem, verapamil or adenosine) is needed. For recurrent episodes the preferred drugs are verapamil, diltiazem or beta-blockers. However, the treatment of choice is RF ablation. The slow pathway is selectively ablated leaving the normal fast pathway conduction intact. With RF ablation, 99% of patients with AVNRT can be permanently and safely cured.

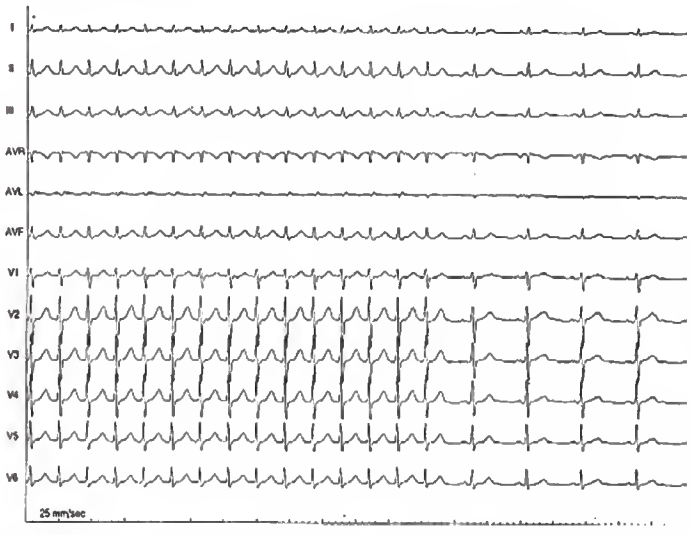


Figure 6: A 12-lead ECG of AVNRT. The P wave is buried within the QRS and only distorting the terminal portion as suggested by a pseudo S wave in inferior leads and pseudo R in lead V_1.

Atrioventricular Re-Entrant Tachycardia

AV re-entrant tachycardia (AVRT) is mediated by an accessory pathway which joins the atrium and ventricle (other than the AVN) and is a breach in continuity of the fibrous ring of the AV annulus. This has been described as the Kent bundle and responsible for the Wolff-Parkinson-White (WPW) syndrome and AVRT.

Accessory pathways are present in 0.2% of people. It is estimated that 50% of these people will experience tachycardia at some stage in life, generally starting in the second or third decade. This amounts to approximately 2 million patients in India. These accessory pathways may manifest in the ECG if they are capable of conducting antegrade. Such overt pathways lead to WPW syndrome. Majority of these pathways are 'concealed', since they can conduct only retrograde (from ventricle to atrium) and hence cannot be diagnosed from the sinus rhythm ECG. In either case, these pathways can give rise to macro-re-entrant tachycardias. Most of these tachycardias are 'orthodromic', the impulse going down the AV node and up the accessory pathway. The ECG at such time would show a narrow QRS tachycardia (**Figure 7**). The accessory pathways may conduct antegrade during tachycardia resulting in a wide QRS (pre-excited) tachycardia. This is described as anti-dromic tachycardia. AF in these patients can potentially be lethal as the ventricular rate can be faster than 300 per minute leading to ventricular fibrillation. Orthodromic tachycardias can be terminated similar to AVNRT. For pre-excited tachycardias, intravenous flecainide, amiodarone or electrical cardioversion are the alternatives. RF ablation is again the preferred choice as the success rate is as high as 98%. It is almost a mandatory recommendation for patients presenting with AF and rapid conduction over the accessory pathway.

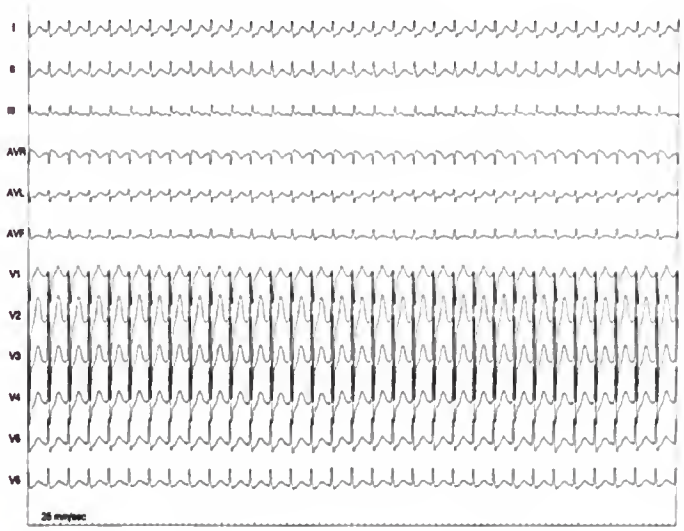


Figure 7: Narrow QRS, regular tachycardia. RP shorter than PR with ST depression in leads I and aVL and discordant ST deviation in leads aVL and aVR suggestive of orthodromic AVRT.

Various form of paroxysmal SVTs can be differentiated depending upon the RP interval and concordance of ST segment, as summarised in **Figure 8**.

Usually, SVT presents on ECG as a narrow QRS tachycardia. Occasionally, there is a wide QRS tachycardia due to bundle branch block during SVT. This can be differentiated from VT as shown subsequently (**Table 2**).

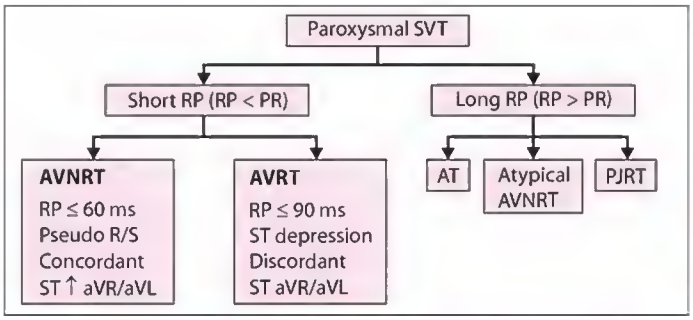


Figure 8: ECG identification of types of paroxysmal supraventricular tachycardia.

Table 2: VT *versus* SVT with Aberrancy

Ventricular tachycardia	SVT with Aberrancy
VA dissociation and fusion – present 50%	Typical bundle branch block pattern
Prolonged intrinsicoid deflection	Concordance of QRS axis and BBB morphology
Discordance between QRS axis and BBB morphology (LBBB with RAD)	
Known structural heart disease	

Simple clinical tools like carotid sinus massage can help in diagnosis of tachycardia as shown in **Table 3**.

Table 3: Effect of Carotid Sinus Massage on Tachycardia

Tachycardia	Effect
Paroxysmal supraventricular tachycardia—AVNRT or AVRT	Termination of tachycardia
AT/A flutter/A fibrillation	AV block; arrhythmia continues, more P'/F/f waves than QRS
Ventricular tachycardia	Tachycardia continues, VA block
Pre-excited tachycardia	Termination

Summary of management of paroxysmal supraventricular tachycardia is given in **Table 4**.

Table 4: Management of Paroxysmal Supraventricular tachycardia

Acute termination
- Vagal manoeuvres
- Intravenous Adenosine: 6 to 12 mg or 0.1 to 0.3 mg/kg (rapid bolus)
- Intravenous Verapamil/diltiazem: 5 to 15 mg or 0.1 to 0.2 mg/kg (over 1 to 2 min)

Long-term treatment
- Verapamil
- Beta-blockers
- Flecainide/Propafenone

Permanent cure
- Radiofrequency ablation

VENTRICULAR TACHYARRHYTHMIAS

Vast majority (90%) of the wide QRS tachycardia are ventricular tachycardia (VT). Identifying VT as either being mono-morphic or polymorphic is crucial to determine the prognosis and treatment. From a clinician's view-point, the next important step in VT management is to identify the underlying structural/electrical heart disease as shown in **Table 5**.

Monomorphic VT

This is usually regular with the rate varying from 150 min to 300/min (**Figure 9**). The QRS morphology is similar from complex to complex in a given lead in monomorphic VT. Constant variation in morphology of QRS is described as polymorphic. The monomorphic nature must be characterised on a 12-lead ECG, since on a single monitor lead a polymorphic VT may falsely appear monomorphic.

Table 5: Ventricular Arrhythmias: Clinical Scenario

Structural heart disease
- Ischaemic heart disease
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Arrhythmogenic right ventricular cardiomyopathy

Idiopathic VT (in normal heart)
- Right ventricular outflow tract VT
- Fascicular VT
- Others

Primarily electrical disease
- Long QT and torsades
- Brugada syndrome
- Idiopathic VF

Specific VT
- Bundle branch re-entrant VT
- Bi-directional VT

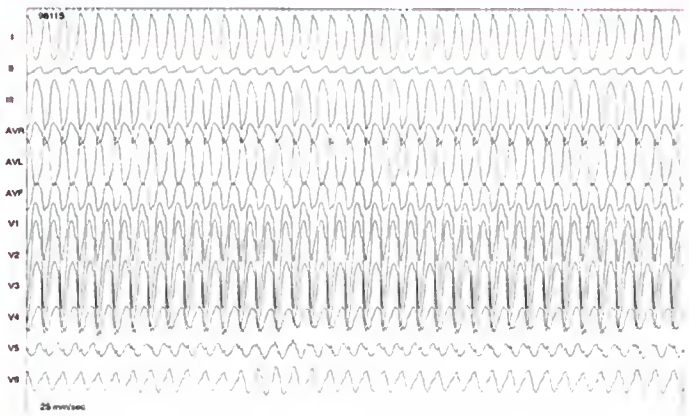


Figure 9: Rapid, monomorphic ventricular tachycardia.

Infarct Scar

This is the commonest setting of monomorphic VT. Re-entry circuits form in the islands of viable myocardium embedded in fibrous tissue. Commonly, such VT is seen to start a few months to years after a myocardial infarction (MI). The patient may be very stable during VT or there may be haemodynamic collapse, depending on the underlying ventricular function. Rarely is acute ischaemia a precipitating factor. Emergency management requires intravenous procainamide or amiodarone, since lignocaine is effective in less than 30% of these patients. If haemodynamically unstable, electrical cardioversion with 100-360 J is advisable. Implantable cardioverter defibrillator (ICD) is the treatment of choice in patients with past ischaemic heart disease and VT. ICD is the device like pacemakers implanted subcutaneously under the clavicle with electrodes in the right atrium and ventricle. The device detects VT/VF and delivers either overdrive pacing or shock and restores sinus rhythm (**Figure 10**). Beta-blockers often in combination with amiodarone are used when ICD is not feasible. Alternatively, sotalol can be tried.

Cardiomyopathy

Both dilated cardiomyopathy as well as hypertrophic cardiomyopathy may cause monomorphic VT. Re-entry or

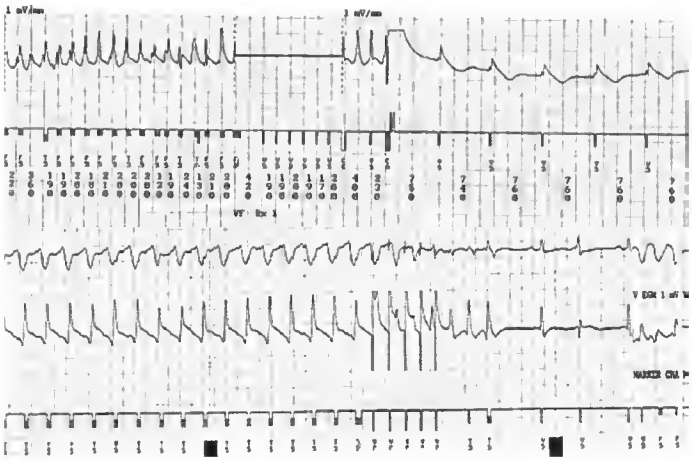


Figure 10: Electrograms from the implantable cardioverter defibrillator. Top panel shows detection of VF and successful treatment with shock. Bottom panel shows successful overdrive pacing to terminate VT.

automaticity around areas of fibrosis is the usual cause. The management is essentially similar to that for infarct scar VT.

Treatment Plan for Sustained Monomorphic Ventricular Tachyarrhythmias

Anti-arrhythmic drugs:-

Intravenous procainamide 10 to 14 mg/kg bolus (< 50 mg/min) and 1 to 4 mg/min as maintenance;

Intravenous amiodarone 150 mg over 10 minutes, 1 mg/min for 6 hours and then 0.5 mg/min over 18 hours

Over-drive pacing

Electric cardioversion

Arrhythmogenic Right Ventricular Cardiomyopathy

Young adults presenting with VT showing a left bundle branch block like morphology. It is often misdiagnosed as idiopathic VT. In 30% of cases, it is familial. The ECG in sinus rhythm is usually abnormal, showing T inversions and sometimes the classical epsilon wave in lead V_1 (**Figure 11**). The right ventricular disease may be subtle and hence missed at echocardiography. A signal averaged ECG helps in identifying abnormal late potentials and magnetic resonance imaging is often diagnostic with right ventricular wall thinning and fatty replacement of myocardium. Treatment options are sotalol, amiodarone, beta-blockers and

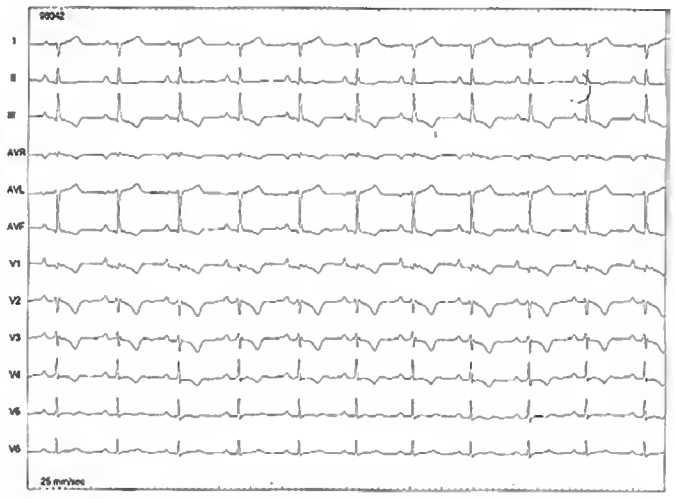


Figure 11: Twelve-lead ECG of a patient with ARVC, showing classic epsilon waves in lead V1 and T wave inversion in precordial leads.

verapamil. With life-threatening VT, an implantable defibrillator is advisable.

Idiopathic Ventricular Tachycardia

Often VT is seen in healthy young adults who have no structural heart disease. Two patterns are common, one arising from the right ventricular outflow tract and the other from the left ventricular posterior fascicle. The right ventricular outflow tract VT shows a LBBB-like morphology and a vertical QRS axis and is either repetitive, ill-sustained or could be sustained (**Figure 12**). It is exercise-induced and responds well to beta-blockers. The idiopathic left VT shows a RBBB-like morphology with left or north-west QRS axis deviation (**Figure 13**). It is relatively narrow as it arises from the left posterior fascicle. Acute termination with adenosine or verapamil is possible. Hence, idiopathic left VT is often misdiagnosed as SVT. Both the idiopathic VTs have a natural history very similar to SVTs (benign outcome) and can be permanently cured by RF ablation. There are many other locations of idiopathic VT now described, especially the left ventricular outflow tract VT.

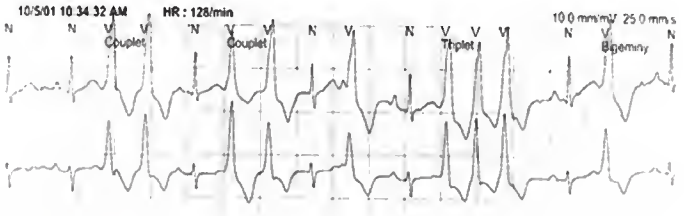


Figure 12: Right ventricular outflow tract (RVOT) VT. Holter strip show repetitive form and the bottom 12-lead ECG show sustained VT.

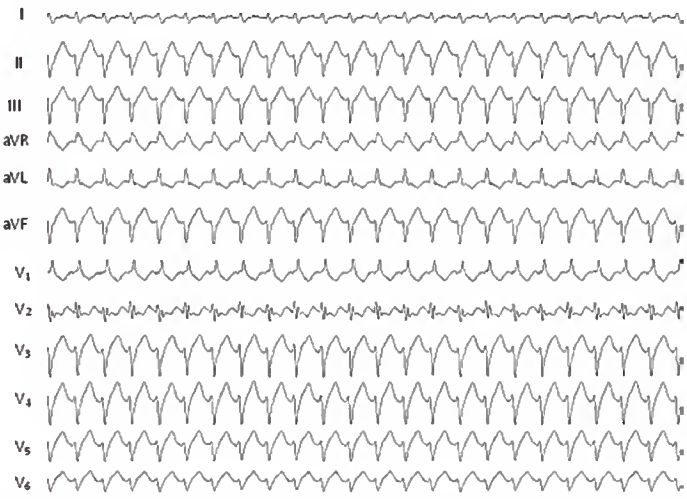


Figure 13: Twelve-lead ECG of idiopathic left ventricular tachycardia (ILVT). Note the relatively narrow QRS with RBBB-like morphology and left-axis deviation.

Polymorphic VT

This is a life-threatening arrhythmia since it can degenerate into ventricular fibrillation (VF). The underlying abnormalities include long QT syndrome and acute ischaemia.

Long QT Syndrome

This could be either congenital or acquired. The congenital long QT syndrome is a genetic defect, whereas, the acquired form is due to hypokalaemia or potassium channel blocking cardiac or non-cardiac drugs. The characteristic arrhythmia, *torsades de pointes* (**Figure 14**) is triggered by a VPB which occurs while

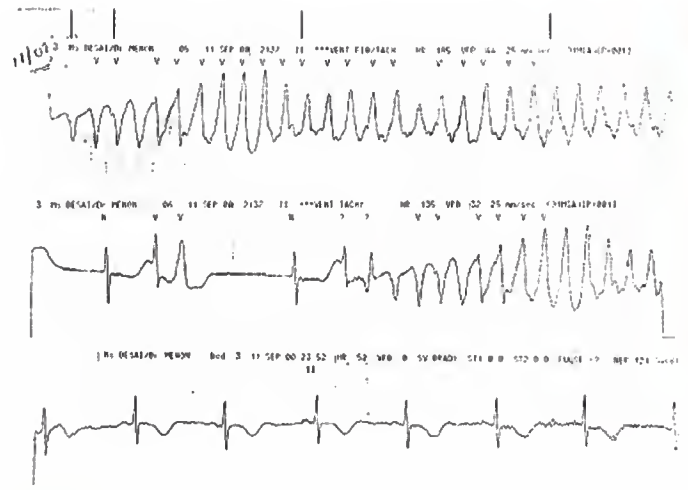


Figure 14: Torsades de pointes. Polymorphic VT in a patient with acquired long QT.

the ventricles are still depolarising. The torsades is often self-terminating, but is fatal in the event it is sustained. The commonest presentation is unexplained syncope and the ECG must be carefully assessed for QT prolongation. Beta-blockers with pacemaker are the treatment of choice for the congenital long QT syndrome. Left cervical stellate ganglionectomy and ICD implantation are other options for the resistant variety. Removal of the offending agent and correcting electrolyte imbalance is the mainstay for the acquired long QT variety. Intravenous lignocaine, phenytoin and isoprenaline are known to shorten the QT and may be useful.

Acute ischaemia

Unstable angina or MI can be complicated by polymorphic VT. Acute termination can be achieved with defibrillation (300-360 J) or intravenous lignocaine 2 mg/kg. Further management entails aggressive efforts to alleviate ischaemia. Acute coronary syndrome can often precipitate an electrical storm defined as two or more sustained VT requiring electric cardioversion within 24 hours. The principles of managing electrical storm are outlined in **Table 6**.

VENTRICULAR FIBRILLATION

The commonest setting for ventricular fibrillation (VF) is MI and structural heart disease with left ventricular systolic dysfunction. In acute MI the VF occurrence is classified as primary and secondary.

Table 6: Principles of Managing Electrical Storm

Anti-ischaemic measures
NTG, heparin, thrombolysis, revascularisation
Anti-adrenergic drugs
Heavy sedation
Beta-blockers
Anti-arrhythmic drugs
Lignocaine—no role as primary prophylaxis
Beta-blockers
Adjuvants
Intravenous magnesium
Electrical cardioversion

Primary ventricular fibrillation

It occurs within the first 24 hours of MI. Severe electrical instability triggered by ischaemia is the mechanism. If terminated by prompt defibrillation, the long-term prognosis is similar to that of uncomplicated infarction. Unless further arrhythmias occur, anti-arrhythmic drugs (except beta-blockers) are not necessary.

Secondary ventricular fibrillation

This is seen after established infarction, usually after 24 hours. Patients who develop secondary VF usually have large infarction with severe left ventricular dysfunction. Therefore, the prognosis is grim. If defibrillation is successful, lignocaine or amiodarone are advisable. Urgent efforts to stabilise and improve the ventricular function are warranted.

The last decade has seen the potential of the life-saving ICD therapy. It is now established to be beneficial in all patients with VT and abnormal hearts. Its role has been suggested for primary prophylaxis in high-risk individuals, i.e. post-MI, ejection fraction less than 0.30, wide QRS (> 120 ms), NYHA II, non-sustained VT, T wave alternant or abnormal heart rate variability and electrophysiology study inducing sustained VT. Radiofrequency ablation is used only as a salvage procedure when there are recurrent VTs requiring multiple ICD shocks.

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12.25 Sudden Cardiac Death

Ashish K Thakur

DEFINITION

Sudden cardiac death (SCD) and sudden cardiac arrest (SCA) refer to a catastrophic symptom complex due to sudden cessation of cardiac output and haemodynamic collapse leading to death or non-fatal outcomes. Over the years, SCD has been traditionally used as the term encompassing all forms of this syndrome but successful resuscitation or spontaneous reversion to a cardiac rhythm compatible with circulation and life would now be classified as SCD survivor or SCA rather than SCD. The 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) defines SCA as 'sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation'. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal.

EPIDEMIOLOGY

Over million people die every year of SCD across the world. Accurate data for SCD as a cause of death are difficult to obtain, and are certainly unavailable from Indian subcontinent. However, data from United States suggests up to 15 % of total deaths annually could actually be due to SCD. SCD is twice as more common in men than women and its incidence of SCD rises with age, coronary artery disease (CAD), ventricular dysfunction and structural heart disease. Majority (up to two-thirds) of SCD/SCA occurs in the setting of CAD where it may be the initial mode of presentation in about 20% patients. About half of all mortality in acute myocardial infarction could be due to SCD, occurring before hospital admission. Various forms of structural heart diseases are known to increase SCD risk and some continue to be identified.

AETIOPATHOGENESIS

The most common mechanism of SCD is haemodynamic collapse due to ventricular fibrillation (VF) (**Figure 1**) or sustained ventricular tachycardia (VT) (**Figure 2**). The initial symptoms leading up to the event are generally very infrequent or inconspicuous, unless in the setting of acute coronary syndrome (ACS) with typical cardiac sounding chest pain. The cardiac arrest leads to quick unconsciousness and collapse due to cerebral hypoperfusion, respiratory arrest and depending on the specific

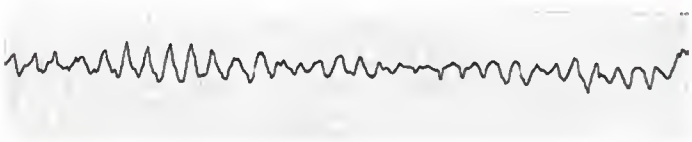


Figure 1: ECG strip showing ventricular fibrillation.

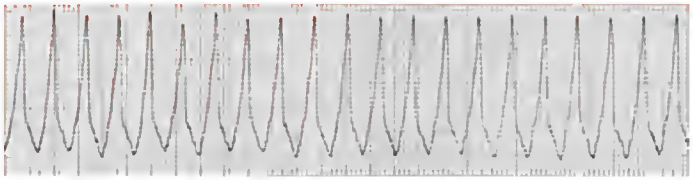


Figure 2: ECG strip showing ventricular tachycardia.

clinical scenario, death might follow if resuscitation is not successful or is not attempted or unavailable. As mentioned, CAD causes up to two-thirds of SCD which occurs most commonly in the setting of ACS than stable angina patients. Various causes of SCD are listed in **Table 1**. A minority (about 10%) of SCD is caused by dilated cardiomyopathy and heart failure (ventricular dysfunction), hypertrophic cardiomyopathy and other structural heart abnormalities. Arrhythmogenic right ventricular dysplasia (ARVD) is a condition associated with fibrosis of the right ventricle best diagnosed by cardiac MRI and is now an established cause of SCD.

Table 1: Causes of Sudden Cardiac Death (SCD)/Sudden Cardiac Arrest (SCA)

SCD with coronary disease
Acute coronary syndromes
Stable angina
Coronary embolism
Non-atherogenic CAD (arteritis, dissection, congenital coronary anomalies and coronary spasm)
SCD with structurally abnormal heart
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Valvular heart disease (mitral valve prolapse)
Congenital heart disease
Arrhythmogenic right ventricular dysplasia (ARVD)
Myocarditis
Cardiac tamponade
Cardiac rupture
Aortic dissection
SCD with no structural heart disease
Prolonged QT syndrome
Brugada syndrome
WPW (pre-excitation) syndrome
Catecholaminergic VT/VF
Familial SCD
Chest wall trauma (commotio cordis)
Non-cardiac causes of SCD
Pulmonary embolism
Central airway obstruction
Haemorrhagic stroke
Drowning

SCD can also occur in a structurally normal heart in about 10% cases, especially in young individuals, mainly due to genetic or acquired predisposition to electrophysiological abnormalities causing life-threatening ventricular arrhythmias. Prolonged QT

syndrome is well known to predispose to life-threatening ventricular arrhythmias (*torsades de pointes*). A minority of ventricular pre-excitation (WPW syndrome) patients could have VF due to antegrade conduction via the accessory pathway if they went into atrial fibrillation.

Brugada syndrome is known to significantly increase the risk of SCD. This condition is diagnosed by typical ECG findings (right bundle branch block and ST elevation in right precordial leads) and electrophysiological testing. Some rather fascinating and recently identified conditions with high SCD risk include catecholaminergic VT/VF (heightened sympathetic surge leading to arrhythmias). Evidence also suggests that the whole symptom complex of SCD is actually a very complex process, often triggered by various factors like stress, plaque rupture causing ACS, electrolyte abnormalities (low potassium/magnesium) and some pro-arrhythmic drugs. Identifying otherwise healthy individuals at high-risk for SCD may be very difficult. In general, traditional cardiovascular risk factors also tend to enhance the SCD risk. In addition, family history of SCD is a very important risk marker, increasing it by twice at most. Non-cardiac conditions presenting as SCD include pulmonary embolism, aspiration, drowning and other major respiratory emergencies.

PROGNOSIS

It is important to discuss this at this stage before dealing with the management aspects of this SCD/SCA. Being a life-threatening emergency, it occurs mostly out-of-hospital and is not witnessed. The risk of recurrence may be as high as 50% in 12 months time. The response time to effective resuscitation largely determines the clinical outcomes. Understandably the prognosis is much better for in-hospital SCD. It may sometimes be quite difficult to establish whether it is true SCD or 'non-cardiac SCD'.

Current evidence in the published literature indicates that about 25% to 40% of witnessed VF is likely to survive until hospital discharge. This is better if the underlying cardiac rhythm is VT, where survival may be up to 65% to 70%. However, only about 30% of the out-of-hospital SCD have successful resuscitation and eventually just about 10% survive to discharge. Many of these patients have significant neurological problems due to anoxic brain injury. The poor outcomes for out-of-hospital SCD can be predicted from factors like advanced age, prolonged resuscitation, haemodynamic support, heart failure, renal impairment, and persistent neurological dysfunction. Interestingly, majority of in-hospital deaths for SCD survivors are due to non-cardiac causes like pneumonia, sepsis, multi-organ failure and neurological problems.

MANAGEMENT

As mentioned before, the outcome following SCD depends upon numerous factors including the underlying rhythm and the rapidity of resuscitation. Management of a SCD scenario initially comprises of aggressive resuscitation as per protocols and, if successful, to find and treat any reversible factors, like coronary disease amenable to revascularisation by angioplasty or bypass surgery. This should be followed by strategies for secondary prevention (re-occurrence of SCD event). On the contrary, primary prevention strategy is to be adopted for people with high risk of SCD.

Commonly performed cardiac tests in SCD survivors include echocardiogram and coronary angiogram. Cardiac MRI and electrophysiological testing are further and highly valuable tools to rule out any structural heart disease and abnormal electrical pathways, respectively.

SECONDARY PREVENTION

Device therapy with implantable cardioverter defibrillator (ICD) is the treatment of choice for majority of SCD survivors after careful consideration. Various criteria and guidance have been proposed, and the 2006 UK National Institute of Clinical Excellence (NICE) for the use of ICD for secondary prevention is summarised in **Table 2**. It is very important to remember that the ICD itself just treats the dysrhythmia rather than preventing it. Further, some of these difficult clinical scenarios may need electrophysiological testing with a view towards ablative therapy. Patients with propensity for recurrent arrhythmias also require 'top up' medical therapy with beta-blockers or class III anti-arrhythmic agents (e.g. amiodarone). The drugs are much less efficacious and should be considered only for their adjunctive role or where ICD implantation is deemed inappropriate (much reduced life expectancy otherwise, terminal cancer, significant co-morbidities).

PRIMARY PREVENTION

This is a very interesting area due to various subsets of patients/people who may be classified as being at high-risk of having SCD Primary prevention is aimed at preventing the occurrence of first SCD event in high-risk patients. This includes careful and thorough assessment, which comprises of detailed cardiac evaluation to exclude any structural heart disease, patient and family screening where necessary and tests like echocardiogram, coronary angiogram, cardiac MRI and electrophysiological testing. Genetic tests may also be necessary to identify patients carrying the high-risk genes and they could be offered prophylactic treatment. The three most important groups for primary prevention include at-risk post-myocardial infarction patients, high-risk cardiomyopathy (including hypertrophic cardiomyopathy), and patients with Brugada syndrome, Long QT syndrome, Pre-excitation (WPW syndrome) and familial SCD. These patients, after careful assessment, should receive an ICD. The 2006 UK-NICE guidance for ICD for primary prevention of SCD is listed in **Table 3**. Adjunctive medical therapy may be necessary, as explained before.

Table 2: 2006 UK National Institute of Clinical Excellence Guidance for Implantable Cardioverter Defibrillators (ICDs) for Secondary Prevention (Defined as the Prevention of an Additional Life-Threatening Event in Survivors of Sudden Cardiac Events or in Patients with Recurrent Unstable Rhythms)

Patients who present, in the absence of a treatable cause, with one of the following:

a. Having survived a cardiac arrest due to either VT or VF.
b. Spontaneous sustained VT causing syncope or significant haemodynamic compromise.
c. Sustained VT without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF of less than 35%) (no worse than class III of the New York Heart Association functional classification of heart failure).

Table 3: 2006 UK National Institute of Clinical Excellence Guidance for Implantable Cardioverter Defibrillators (ICDs) for Primary Prevention (Defined as Prevention of a First Life-Threatening Arrhythmic Event)

Patients who have:

1. A history of previous (more than 4 weeks) myocardial infarction (MI) and:
   either
   left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure)
   and
   non-sustained VT on Holter (24-hour ECG) monitoring
   and
   inducible VT on electrophysiological (EP) testing
   or
   left ventricular dysfunction with an LVEF of less than 30% (no worse than class III of the New York Heart Association functional classification of heart failure)
   and
   QRS duration of equal to or more than 120 milliseconds
2. A familial cardiac condition with a high-risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular-dysplasia (ARVD), or have undergone surgical repair of congenital heart disease.

In patients with previous MI, the highest risk patients are the ones with significantly impaired ventricular systolic function with or without ventricular ectopy. The heart failure patients may or may not have ischaemic heart disease, and a subset of them benefit from prophylactic ICD implantation. A lot of these patients now receive combined device therapy comprising of cardiac re-synchronisation (for heart failure) and ICD (for SCD prevention), which is called CRT-D. In addition to device therapy, conventional secondary prevention treatment with beta-blockers and ACE-inhibitors or angiotensin receptor blockers also reduce the SCD incidence, especially in post-MI patients.

COMMUNITY

There may be many patients at high-risk of SCD but how to identify them? This issue is difficult and currently just a 'tip of the iceberg', with only a handful being diagnosed and treated successfully. With its proven benefits, many countries are putting in a lot of efforts into primary prevention of SCD and the need to identify the high-risk patient is vital to this. The various ways to do this in the community include assessment of family history, vague symptoms (many have dizzy spells, unexplained collapses), ECG screening, etc. The role of general practitioners is invaluable to suspect and refer these cases to tertiary centres. Many cases require genetic screening and there are now established clinical genetics services in many countries. Information about familial conditions predisposing to SCD is widely available on the internet, including support groups for patients and families, who need on-going counselling and specialist input.

CONCLUSIONS

SCD is often a fatal clinical condition with a dramatic presentation, often associated with CRD. Many conditions with structural heart disease predispose to SCD. There are now many known conditions with normal structural heart and high-risk for SCD/SCA due to electrical abnormalities. Over the years, the prognosis for in-hospital SCD has improved but it still remains very poor for out of hospital events. Advances in diagnostic technologies like electrophysiology, cardiac MRI and genetic testing have helped to find out the susceptible patients. Treatment of SCD is mainly based on device therapy with ICD for secondary/primary prevention along with adjunctive drug and/or electrophysiological options where necessary.

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12.26 Congenital Heart Disease

Sunita Maheshwari

The estimated incidence of congenital heart disease (CHD) is 1%, i.e. 1 out of 100 children have some form of CHD, either major or minor. In India, it is possible that the incidence may be higher due to deficiency of folic acid, consanguinity, etc. Pre-conceptual folic acid (i.e. taken 3 months before pregnancy) has been documented to reduce the incidence of heart disease, so all women planning a pregnancy should be advised to start folic acid.

The majority of congenital heart diseases (CHDs) occur as isolated defects and are not associated with other diseases. However, these can also be a part of various genetic and chromosomal syndromes such as Down's syndrome (AV canal), Turner's syndrome (coarctation), Marfan's syndrome (aortic root dilation, mitral valve prolapse), Noonan's syndrome (pulmonary stenosis), and DiGeorge's syndrome (tetralogy of Fallot and other conotruncal anomalies).

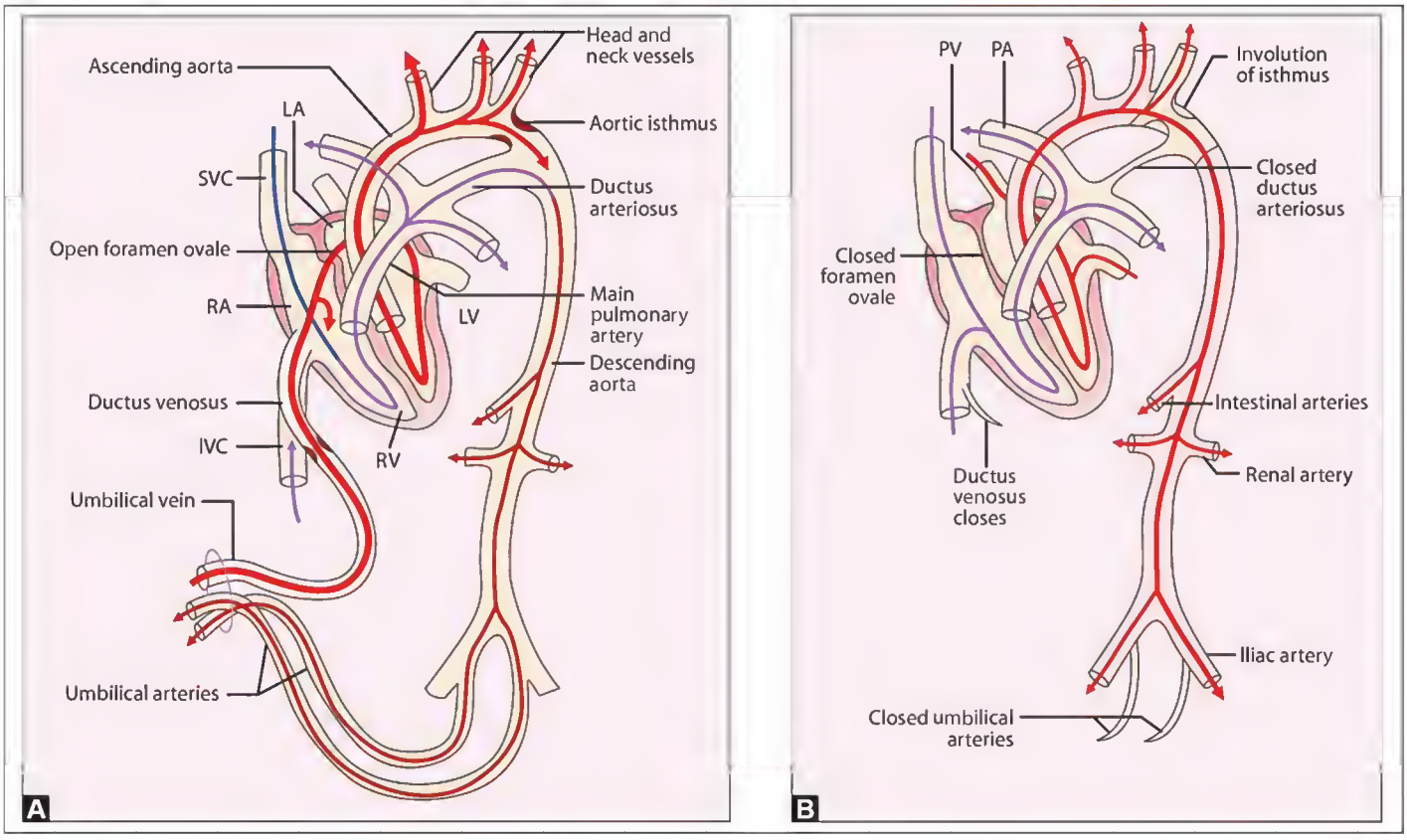
No known cause can be identified for most congenital heart defects. Drugs such as retinoic acid for acne, alcohol, and infections (such as rubella) during pregnancy can contribute to some congenital heart problems.

The clinical diagnosis of cardiac lesions in children requires not just clinical skills but a high index of suspicion and a systematic diagnostic approach.

As several lesions are now detected early, the main questions are whether to intervene or not and if yes, then when? This chapter will focus on some key issues, e.g. operability and clinical diagnosis with emphasis on some of the major lesions.

THE FOETAL CIRCULATION

Understanding the foetal circulation helps clarify how some forms of CHD occur (**Figures 1A and B**). The foetus has only a



Figures 1A and B: Changes in the circulation at birth. (A) In the foetus, oxygenated blood comes through the umbilical vein where it enters the inferior vena cava (IVC) via the ductus venosus (red). The oxygenated blood streams from the right atrium (RA) through the open foramen ovale to the left atrium (LA) and via the left ventricle (LV) into the aorta. Venous blood from the superior vena cava (SVC) (blue) crosses under the main blood stream into the RA and then, partly mixed with oxygenated blood (purple), into the right ventricle (RV) and pulmonary artery (PA). The pulmonary vasculature (PV) has a high resistance and so little blood passes to the lungs; most blood passes through the ductus arteriosus to the descending aorta. The aortic isthmus is a constriction in the aorta that lies in the aortic arch before the junction with the ductus arteriosus and limits the flow of oxygen-rich blood to the descending aorta. This configuration means that less oxygen-rich blood is supplied to organ systems that take up their function mainly after birth, e.g. the kidneys and intestinal tract. (B) At birth, the lungs expand with air and PV resistance falls, so that blood now flows to the lungs and back to the LA. The left atrial pressure rises above right atrial pressure and the flap valve of the foramen ovale closes. The umbilical arteries and the ductus venosus close. In the next few days, the ductus arteriosus closes under the influence of hormonal changes (particularly prostaglandins) and the aortic isthmus expands.

small flow of blood through the lungs, as it does not breathe in utero. The foetal circulation allows oxygenated blood from the placenta to pass directly to the left-side of the heart through the foramen ovale without having to flow through the lungs.

Congenital defects may arise if the changes from foetal circulation to the extra uterine circulation are not properly completed. Atrial septal defects (ASDs) occur at the site of the foramen ovale. A patent ductus arteriosus may remain if it fails to close after birth. Failure of the aorta to develop at the point of the aortic isthmus and where the ductus arteriosus attaches can lead to narrowing or coarctation of the aorta (COA).

In foetal development, the heart develops as a single tube which folds back on itself and then divides into two separate circulations. Failure of septation can lead to some forms of ASDs and ventricular septal defects (VSDs). Failure of alignment of the great vessels with the ventricles contributes to transposition of the great arteries, tetralogy of Fallot and truncus arteriosus.

ACYANOTIC HEART DISEASES

Atrial Septal Defect

Atrial septal defect (ASD) is one of the most common congenital heart defect and occurs twice as frequently in females. Frequently missed in childhood, this lesion causes problems of pulmonary hypertension (PH) after adulthood is reached. ASD, typically, is symptomatic in childhood poor weight gain, frequent respiratory infections and rarely congestive heart failure (CHF) have been ascribed to it. In general, however if a child is in cardiac failure and the diagnosis is an ASD, a detailed evaluation for some other anomaly (e.g. partial or total anomalous pulmonary venous return), mitral involvement valve should be performed.

Types of atrial septal defect

Four types of ASDs or interatrial communications exist: ostium primum, ostium secundum, sinus venosus and coronary sinus defects (**Figures 2A and B**). Most are ostium secundum defects involving the fossa ovalis that in utero was the foramen ovale. Ostium primum defects result from a defect in atrioventricular septum and are associated with cleft mitral valve.

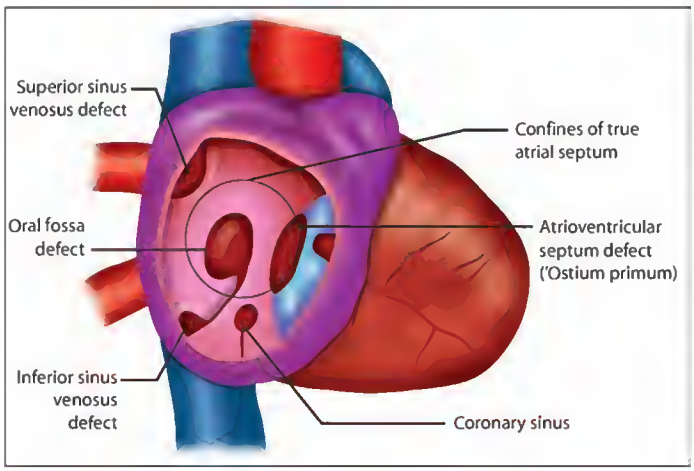


Figure 2A: Various types of atrial septal defects.

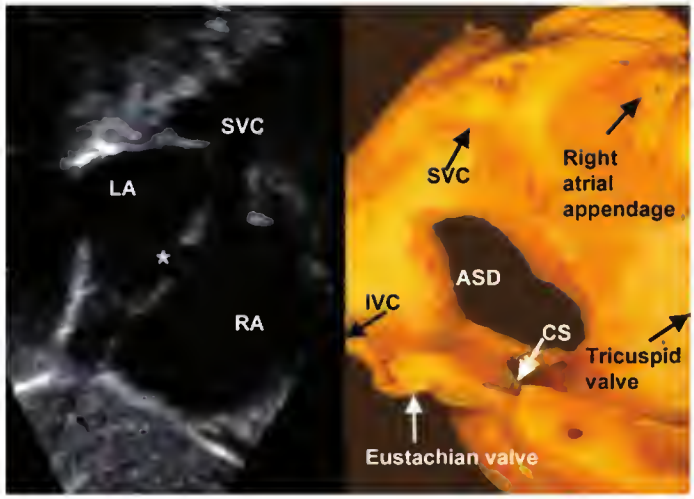


Figure 2B: Morphology of atrial septal defect (ASD).

ASD = Atrial septal defect; S = Coronory sinus; IVC = Inferior vena cava; SVC = Superior vena cava; RA = Rightatrium; LA = Left atrium.

Clinical evaluation

A wide split second heart sound is present. The ECG invariably shows some variant of the rsR' pattern in lead V1, consistent with right ventricular volume overload. In sinus venosus defects, a superior P wave axis occurs. Echocardiography-transthoracic or in doubtful cases, transoesophageal echo, can confirm the diagnosis (**Figure 3**). It demonstrates the location of the ASD-primum, secundum or sinus venosus as well as right heart volume overload and a non-invasive assessment of pulmonary artery pressure (PAP).

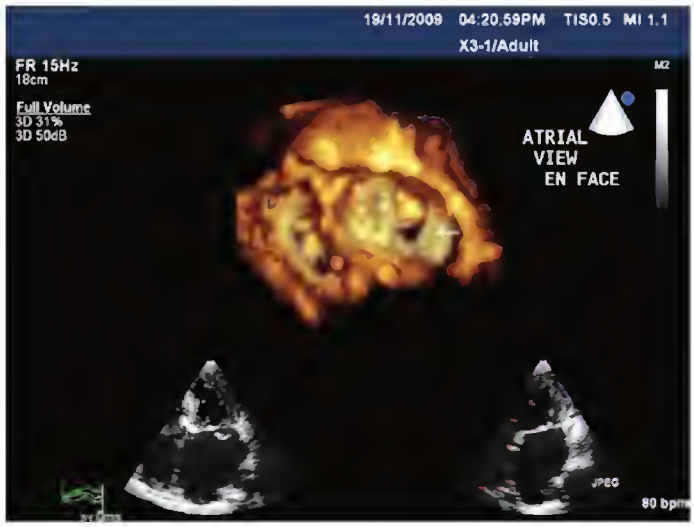


Figure 3: A three-dimensional echocardiographic en face view of atrial septal defect.

Management

As a result of increased flow into the pulmonary circulation, there is right ventricular volume load and a gradual increase in pulmonary vascular damage and resistance, which typically occurs in the 2nd and 3rd decade of life. Although the right ventricular volume overload is well-tolerated for many years there is eventual RV failure. Additionally, PH has been noted in 13% of Indian patients less than 10 years of age. Based on this data, and to avoid the deleterious effect of longer periods of RV volume overload, the optimal age for closure of ASD is around 4 to 5 years of age.

ASD can either be closed surgically by an open-heart procedure or non-surgically in the cardiac catheterisation laboratory using devices. An ostium secundum ASD with septal rim on either side is amenable to device closure (**Figure 4**). However, at present, sinus venosus and ostium primum defects need

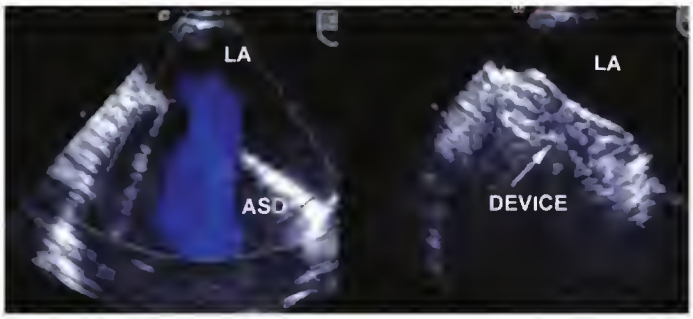


Figure 4: The left image is a transoesophageal echocardiogram of ostium secundum ASD with colour flow before device closure, whereas the right-side shows post-release of an Amplatzer device.

surgery. Now-a-days, minimal access surgery to avoid a long thoracotomy scar can also be performed via a short sternal incision or a lateral thoracotomy.

Ventricular Septal Defects

VSDs are among the commonest cardiac lesions in children. In the classification by Soto *et al*, the ventricular septum is considered to have four components: an inlet septum separating the tricuspid and mitral valves; a trabecular septum, which extends from the attachments of the tricuspid leaflets outward to the apex; the smooth-walled outlet or infundibular septum; and the membranous septum (**Figures 5A and B**). Physiologically, these are classified as large (PAP equals left ventricular pressure), moderate (PAP < LV pressure) and small (normal pulmonary artery pressures). Symptoms and natural history, to a large extent, depend on the pulmonary vascular resistance (PVR).

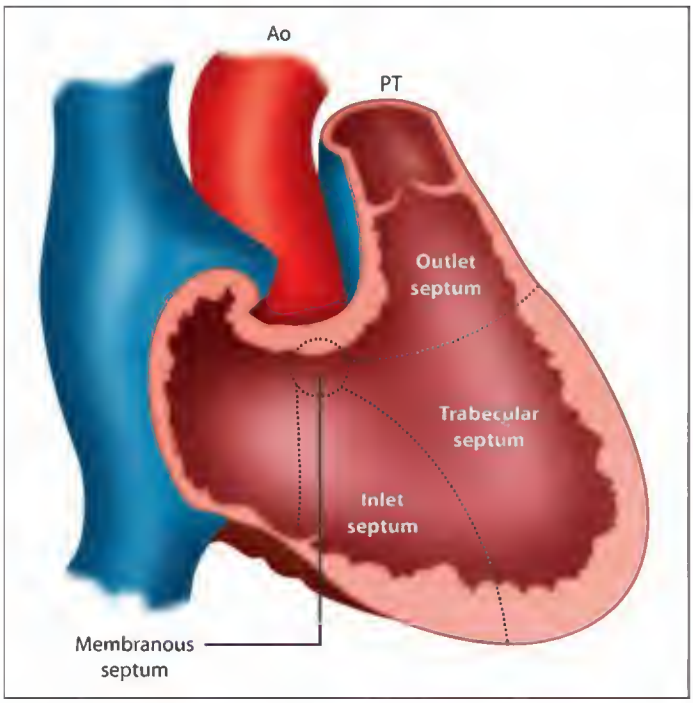


Figure 5A: Four components of the ventricular septum.

Ao = Aorta; PT=Pulmonary trunk.

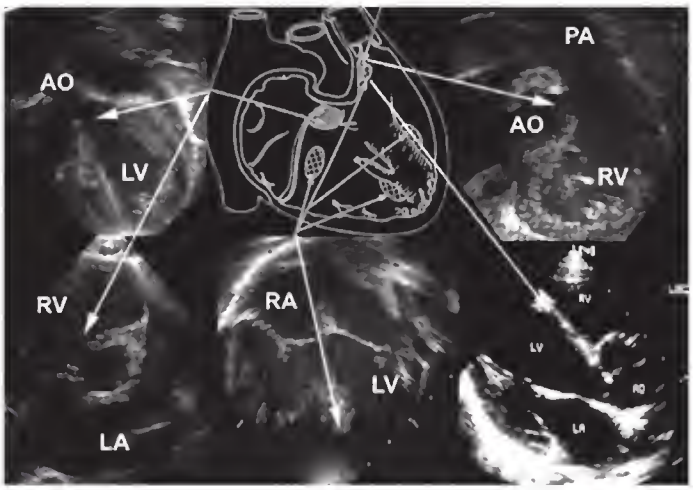


Figure 5B: Montage of the different types of ventricular septal defects. The central diagram outlines the location of the various types of defects as seen from the right ventricle. The two left images show a perimembranous ventricular septal defect. The bottom middle echocardiogram is a muscular apical defect. The upper right image is a right anterior oblique view in a doubly committed ventricular septal defect. The lower right is a short-axis view showing an outlet ventricular septal defect with prolapse of the right coronary cusp.

AO=Aorta; LV=Left ventricle; PA=Pulmonary artery; RA=Right atrium; RV=Right ventricle.

Congenital VSD occurs as a result of incomplete separation of ventricles. Embryologically, the interventricular septum has a membranous and a muscular portion, and the latter is further divided into inflow, trabecular and outflow portions. Most congenital defects are perimembranous, i.e. at junction of membranous and muscular portion.

Large VSD, severe pulmonary hypertension and low PVR

These VSDs, initially present with tachypnoea, sweating due to increased sympathetic activity, poor feeding, and failure to thrive in an infant. On examination, there is evidence of over circulation and pulmonary hypertension: respiratory distress, an active praecordium, a short systolic ejection murmur, a loud second heart sound, a mid diastolic rumble from increased flow across the mitral valve, hepatomegaly and radiographic evidence of cardiomegaly and plethora. A moderate VSD (**Figure 6**) showing turbulence while a large VSD (**Figure 7**) showing no turbulence.

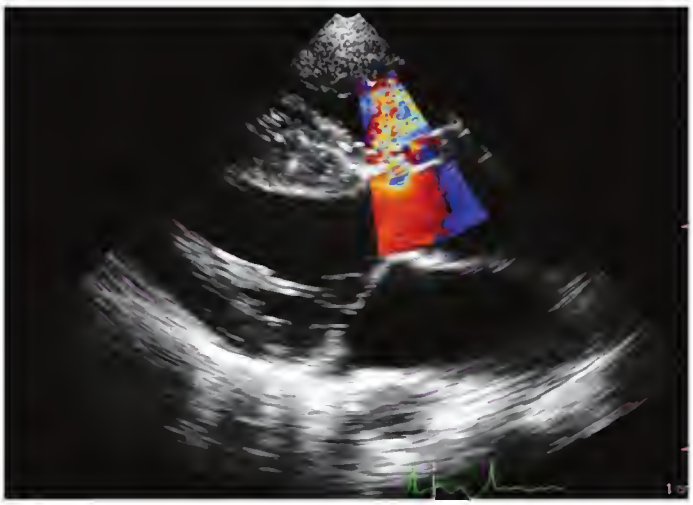


Figure 6: Parasternal long axis view demonstrating turbulence through perimembranous VSD.

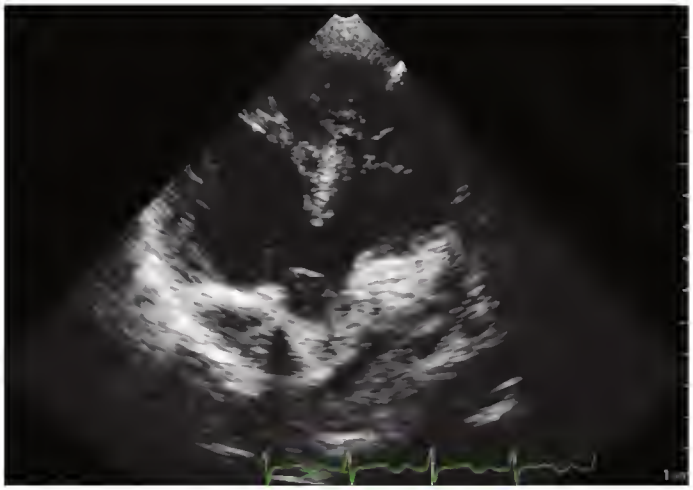


Figure 7: Four-chamber view demonstrating large inlet VSD.

Large VSD, severe pulmonary hypertension and high PVR

Once the pulmonary resistance increases, the pulmonary blood flow reduces and the symptoms regress. At this point, as there is no evidence of CHF, caretakers feel reassured. This is the danger period as intervention gets delayed. Once the pulmonary resistance becomes higher than the systemic resistance, the flow across the VSD changes from right to left leading to cyanosis. On examination, the praecordium is typically quiet with no significant murmurs (as the LV and RV pressures are equal in large VSDs, there are typically no murmurs across a large VSD; as the pulmonary flow decreases, the pulmonary ejection murmur also disappears), a banging S2 and radiographic evidence of a normal sized heart with distal pruning. Once Eisenmenger syndrome develops, it is too late for intervention.

When an infant is seen with a large VSD, there is a chance that it will get smaller with time, but studies differ in respect to probability. A patient with a large VSD seen at 1 month has an 80% chance of closing; whereas a 6-month-old with a large defect has less than a 50% chance of spontaneous closure.

Management

Infants with large VSD typically develop signs of CHF at 6 to 8 weeks of life when the pulmonary vascular resistance is low and the physiological anaemia is at its *nadir*. Therapy includes digoxin, diuretics, and after-load reducing agents. Additionally, treating anaemia is helpful as anaemia can aggravate the failure. If there is heart failure in spite of medications and/or failure to thrive, early surgical closure at 3 to 4 months of life is warranted. If a baby is doing well but has a large VSD, this defect should still be closed early, i.e. by 5 to 6 months, as an occasional patient will develop irreversible PH by 6 to 12 months of age.

Moderate VSD

This is a pressure restrictive defect and the PAPs are protected. Therefore, there is no risk of developing Eisenmenger syndrome.

If there is moderate cardiomegaly and plethora, and the child is otherwise asymptomatic, one can watch for 2 to 4 years. If the VSD does not get smaller, surgical closure is advised to prevent the long-term problems of LV dysfunction secondary to volume over load.

Small VSD

Less than 10 years of age: The consensus is to leave it alone and follow-up for any development of aortic regurgitation (AR).

More than 10 years of age: The issue of surgically closing small holes at this age is controversial. Advocates of closure quote the risk of endocarditis. Conservatives use the argument that it still may close, the only ill effect is endocarditis, which is treatable, and why take the small but present risk of surgery. Most cardiologists would agree that the risk of open-heart surgery is greater than the risk of endocarditis, so leave well enough alone.

The only exception to this is in the presence of aortic regurgitation (AR). In about 5% of VSD, and especially in the supracristal variety, the aortic valve cusp prolapses into the VSD as a result of a Venturi effect resulting in AR. Once this occurs, it is progressive over the following 5 to 10 years. Therefore, the development of AR detected either by echo or by finding a new diastolic murmur on examination is an indication for closure of a small VSD. The indication and timing of VSD closure are summarised in **Table 1**.

Table 1: Timing of Closure of Ventricular Septal Defects

The timing of closure of VSDs is dependent on the size and the symptoms of the defect
Large VSD
Persistent CHF, failure to thrive – close by 3 to 4 months of age
No CHF but pulmonary artery hypertension (PAH): surgery by 5 to 6 months
Moderate VSD
Wait until age 2 to 4 years, earlier, if failure to thrive
Small VSD
If aortic regurgitation develops or previous episode of endocarditis, early surgery is warranted

Patent Ductus Arteriosus

Clinical evaluation

The clinical presentation of a patent ductus arteriosus (PDA), like other left to right shunts, depends on its size and the pulmonary vascular resistance (PVR). In large PDA, the presentation is similar to a large VSD with signs of over-circulation, absence of a significant murmur, a loud S2 and radiographic evidence of cardiomegaly and plethora. Bounding pulses are a clue to a large PDA or aorto-pulmonary window (APW) being the cause of the heart failure. The ECG demonstrating a large continuous flow into the pulmonary artery from the aorta clinches the diagnosis (**Figure 8**). Patients

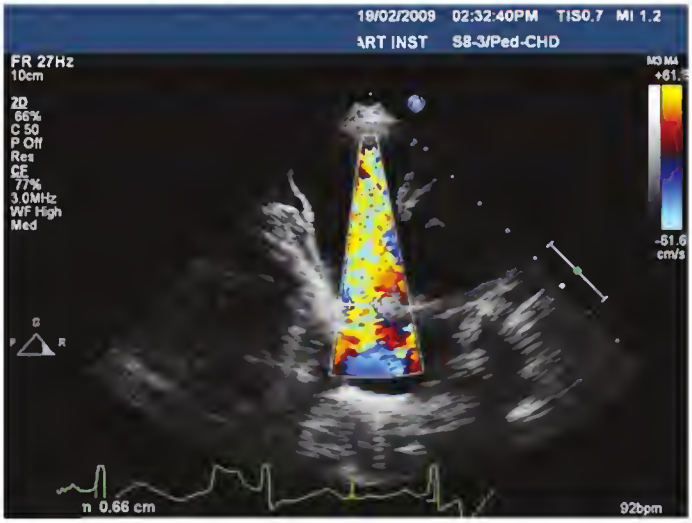


Figure 8: Ductal view on transthoracic echocardiography demonstrating patent ductus arteriosus.

with smaller PDA have the classic continuous Gibson's machinery murmur heard best at the infraclavicular area or the left upper sternal border. As the aortic pressure is higher than the PAP in both systole and diastole this results in a continuous murmur. Patients with large PDA with substantial PH may develop differential cyanosis (pink fingers, blue toes). Continuous murmur will be absent in these cases.

Management

With small PDA, the main risk is endarteritis. However, with larger ducts, there can be a significant volume load on the left heart. For both these reasons, PDA need to be closed. Closure of small PDA is done to prevent subacute bacterial endocarditis (SBE).

If the clinical examination suggests a PDA but there is no evidence on the echocardiogram, one needs to keep in mind the diagnosis of APW. This is a connection between the aorta and the main pulmonary artery and leads to pulmonary over-circulation and hypertension and clinical findings similar to a large VSD or PDA.

The methods used for closure of a PDA include surgical ligation or division via a lateral thoracotomy or non-surgical closure via the deployment of coils or devices across the PDA.

Coarctation of the Aorta

Coarctation of the Aorta (CoA), a narrowing of the arch, occurs in 6% to 8% of patients with CHD. Untreated, coarctation has a poor natural history. In Campbell's classic study, the mean age of death was 34 years. The most common causes of death were heart failure (26%), aortic rupture (21%), endocarditis (18%), and intracranial haemorrhage (12%). Early therapy has several advantages, one being the lower incidence of chronic hypertension. The prevalence of hypertension was 6% in patients who underwent coarctation repair at less than 5 years of age, compared to 30% to 50% in those whose coarctation was repaired at an older age. For all these reasons, early diagnosis and therapy is imperative.

Clinical evaluation

The clinical presentation of CoA is variable. In newborns, the patent ductus arteriosus supports the distal circulation. The RV pumps to the descending aorta via the PDA. As a result, neonates present with signs of right heart failure. Once the PDA closes, the baby has no flow to the lower body and goes into shock.

In older children, the diagnosis may be more subtle – intermittent claudication, upper limb hypertension or the finding of diminished femoral pulses. The best way to never miss a coarctation is to palpate the femoral or dorsalis pedis pulse at every visit.

The ECG may show left ventricular hypertrophy and the radiography can demonstrate the classic rib notching (from development of collaterals) in older children. Echocardiography is diagnostic and demonstrates the narrowing of the arch and the pressure gradient across the CoA (**Figure 9**).

Management

Once diagnosed, CoA is treated either surgically or non-surgically. In newborns and young infants, surgery is the best option as the recurrence rate with angioplasty is high. In older infants and children, balloon angioplasty can be performed with a high success rate and reasonable degree of safety. In older children with near adult sized aortas, the availability of stents has increased

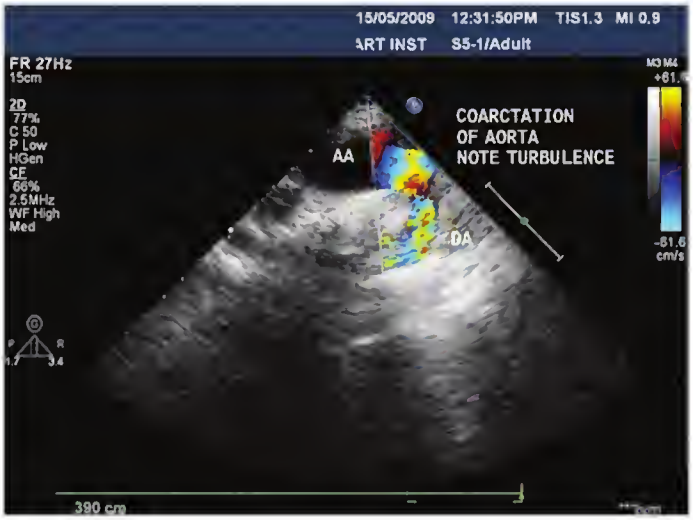


Figure 9: Echocardiography demonstrating the narrowing of the arch and the pressure gradient across the CoA.

the success rate of non-surgical procedures. (Stents are made of stainless steel and can be deployed at the site of coarctation to permanently relieve the obstruction.)

Congenital aortic stenosis and pulmonary stenosis have been discussed in the chapter of Valvular Heart Disease (Chapter 14 of this section).

CYANOTIC HEART DISEASE

Tetralogy of Fallot

In cyanotic heart disease, by far, tetralogy of Fallot (TOF) remains the most common diagnosis. TOF was described over 100 years ago by a French physician, Etienne-Louis Arthur Fallot as a condition consisting of pulmonary arterial stenosis, an interventricular septal communication, deviation of aorta to the right, and concentric hypertrophy of the RV. This lesion still bears his name (**Figure 10**).

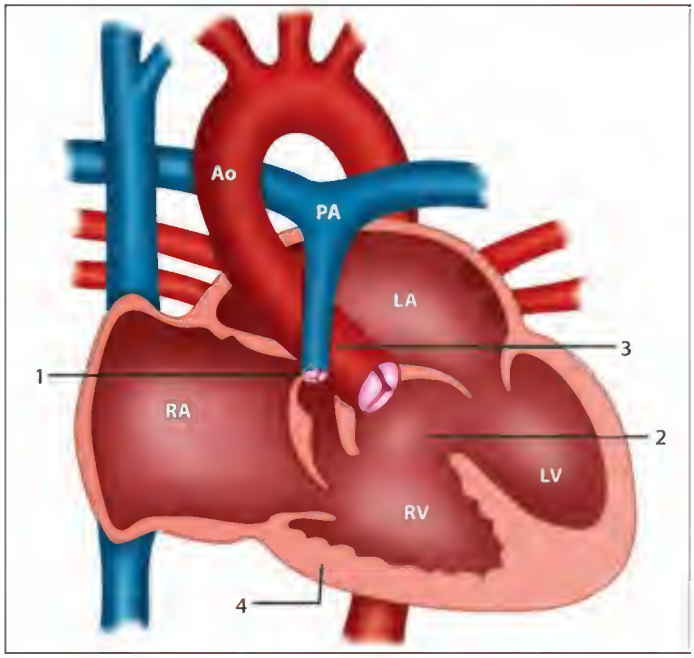


Figure 10: Diagrammatic representation of tetralogy of Fallot.

1=Pulmonary stenosis; 2=Ventricular septal defect; 3=Overriding aorta; 4=Right ventricle hypertrophy.

Ao = Aorta; LA = Left atrium; LV = Left ventricle; PA = Pulmonary artery; RA = Right atrium; RV = Right ventricle.

Clinical Evaluation

The main symptom of cyanosis is related to the degree of pulmonary stenosis; the more the stenosis the more the right to left shunt, the less the pulmonary blood flow and the more the cyanosis. Hypoxic spells occur in infancy, typically in the early mornings and are characterised by tachypnoea, increasing cyanosis and at times, syncope.

Physical examination varies from no murmur during a spell to a systolic ejection murmur to continuous murmurs due to collaterals. The classical ECG findings are right axis deviation and RVH with a radiography demonstrating low pulmonary blood flow and the 'boot shaped' heart. Cardiac catheterisation is no longer routinely indicated. Cardiac computed tomography (CT) or catheterisation is performed if there is a question regarding distal pulmonary arteries or coronary arteries.

Management

Medical management is limited to treating spells, preventing dehydration and fever which can precipitate spells, treating iron deficiency and advising endocarditis prophylaxis. Beta-blockers are used as a bridge to delay surgical intervention.

When to surgically intervene in TOF has always been a contentious issue. In our country, the approach has been to do a complete correction (i.e. closing the VSD and opening the RVOT with or without a transannular patch) by the age of 6 to 18 months, depending on the centre. Waiting until '10 kg' is no longer required and surgical repair can be done as early as is indicated, for instance in the United States – total TOF correction is done soon after birth. In patients with small pulmonary arteries or with a coronary artery crossing the right ventricular outflow tract, a Blalock Taussig (BT shunt) can be performed as a first stage.

Transposition Complexes

The key anatomical feature that characterises this group of diagnoses is ventriculoarterial discordance. This is most commonly seen in the context of AV concordance, also known as complete transposition or d-TGA (dextro-TGA). Congenitally corrected TGA or l-TGA (levo-TGA) is combination of ventriculoarterial discordance with AV discordance (**Figure 11**).

Transposition of the Great Arteries (d-TGA)

In d-TGA, the right ventricle gives rise to the aorta and the LV to the pulmonary artery. This leads to deoxygenated blood going to the body and oxygenated blood returning to the lungs. If there is inadequate mixing (i.e. via an ASD, VSD, PDA), the baby presents with increasing cyanosis leading to acidosis and, eventually, death.

Clinical evaluation

Classically it presents in male children with cyanosis, a single second heart sound and no murmur. The radiograph may show the 'egg on side' appearance, and the diagnosis is confirmed on echocardiography wherein the LV gives rise to the PA and the RV connects to the aorta.

Management

Cardiac catheterisation is no longer indicated unless a balloon atrial septostomy needs to be performed to increase mixing. A non-invasive alternative is prostaglandin (PGE1) which can help open the PDA and help with mixing, thus alleviating cyanosis. The dose needs to be titrated and reduced if hypotension or apnoea occurs.

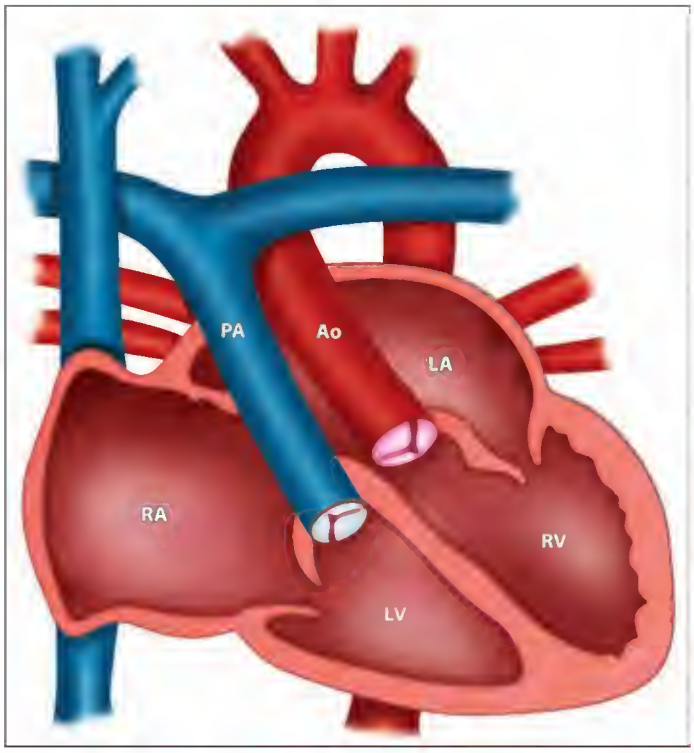


Figure 11: Diagrammatic representation of congenitally corrected transposition of the great arteries.

Ao = Aorta; LA = Left atrium; LV = Left ventricle; PA = Pulmonary artery; RA = Right atrium; RV = Right ventricle.

The ideal operation is an arterial switch operation where the RV is connected back to the PA and the LV is connected back to the aorta leading to a 'normal heart'. Early diagnosis and treatment of d-TGA is essential for the following reason: The LV pumps to the pulmonary artery which is a low pressure artery. Within 4 weeks, the LV undergoes 'disuse atrophy' and it regresses. At this point if an arterial switch is done then the LV is unable to generate enough pressure to pump to the body and it fails. Thus, an arterial switch should ideally be done in the first 4 weeks of life.

Total Anomalous Pulmonary Venous Connection (TAPVC)

Instead of the pulmonary veins connecting normally to the LA, they connect to the RA. An obligatory ASD then allows right to left shunting to maintain left heart output.

Clinical evaluation

Any obstruction along the pathway leads to significant cyanosis, acidosis, low cardiac output, pulmonary venous congestion, a small heart on radiograph and eventual early death. In non-obstructed TAPVC, the presentation is similar to an ASD with a systolic ejection murmur and a widely split S2. Clinically, one can differentiate between the two with an oxygen saturation probe which will reveal a lower oxygen saturation in TAPVC.

Management

Echocardiography is diagnostic and early surgical correction is indicated; this is one of the true paediatric cardiac surgical emergencies.

Truncus Arteriosus

In this lesion, the pulmonary arteries arise from the ascending aorta and typically are at high pressure. This is one of the causes of babies presenting with heart failure and cyanosis, other lesions being single ventricle, TGA-VSD, TAPVC, etc.

Clinical evaluation

These babies are present with CHF and bounding pulses (due to rapid run off into the pulmonary arteries). On examination, these may have a high-pitched early diastolic murmur from truncal regurgitation, in addition to the single S2 and systolic murmurs.

Management

The only remedy is surgical correction where the pulmonary arteries (PA) are connected back to the RV with or without a homograft. Re-operation may be needed in 2 instances: (1) if a homograft is placed, which the baby outgrows with growth thus requiring a new, larger homograft, and (2) pulmonary valve replacement, in some cases. Families need to be counselled that re-operation may be needed over time.

Tricuspid Atresia and Other Forms of Single Ventricle

Babies with single ventricle can present in two ways: (1) with cyanosis if pulmonary stenosis is the main issue and (2) heart failure and pulmonary overflow if there is no pulmonary stenosis. In single ventricle situations, the fundamental issue is that one chamber is doing the work of two chambers. The goal, therefore, of treatment is to connect the superior vena caval blood (Glenn shunt) to the pulmonary arteries to reduce the load on the single ventricle. In order to do this, the PAP must be low. So, in babies with pulmonary stenosis, a Glenn shunt can be done by 6 to 9 months of age. In babies with high flow situations, CHF and high PAP, a pulmonary artery banding needs to be done at 1 month in order to reduce PA pressure to a level where a Glenn shunt can be done later. The Fontan operation, wherein the inferior vena cava is connected to the pulmonary artery, relieves cyanosis completely but it has its own long-term issues. Its routine use, therefore, has been called into question. In single ventricle situations, prognosis is variable but not as dismal as previously thought.

Ebstein's Anomaly

Ebstein's anomaly refers to a downward displacement of tricuspid valve tissue into the RV. Thus, a portion of the RV acts like the atrium. This atrialised RV contracts poorly and interferes with right ventricular filling.

Dyspnoea, fatigue and palpitation are the usual symptoms. Cyanosis is present due to right to left shunt at the atrial level. A systolic murmur of tricuspid regurgitation is heard at the lower left sternal border. The first and second heart sounds are widely split and third and fourth heart sounds may be heard. Thus, multiple scratchy quality heart sounds is an important feature of Ebstein's anomaly.

Box-like globular cardiac configuration is seen on chest radiography which closely resembles a large pericardial effusion. ECG shows tall and peaked P waves. The diagnosis is confirmed by echocardiography (**Figure 12**).

Patients who are symptomatic should undergo a tricuspid valve repair in which marsupialisation of the atrialised RV is undertaken with realignment of the tricuspid cusps to the tricuspid annulus. This procedure is preferred over operations in which the tricuspid valve is replaced with a prosthetic valve.

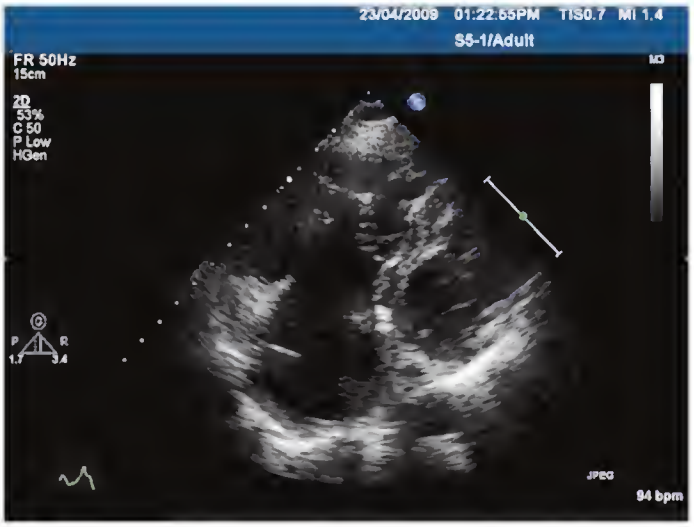


Figure 12: Chamber view demonstrating apical displacement of septal leaflet of tricuspid valve in Ebstein's anomaly.

IMAGING IN CONGENITAL HEART DISEASE

When it comes to the preferred choice of imaging for CHD in children, echocardiography has no match. Optimum windows, zero radiation and easy availability of the expertise make echocardiography, 'the investigation of choice'. However, CT is an extremely helpful complementary imaging modality in the evaluation of CHD. Poor acoustic windows and poor depiction of extracardiac vascular structures are the major limitations of echocardiography, both of which can be successfully overcome with the use of cross-sectional CT imaging. Short acquisition times and, thereby, decreased requirement for sedation leads to CT definitely scoring over magnetic resonance imaging (MRI) in children.

Cardiac CT and MRI are being increasingly utilised to assess pulmonary artery anatomy (e.g. in TOF), arch anomalies (e.g. complex coarctations, interrupted aortic arch), pulmonary veins (e.g. TAPVC where pulmonary venous drainage is unclear), vascular rings and slings, etc.

ASSESSING OPERABILITY IN CHD

The issue of operability arises often for clinicians involved in the care of children with heart disease. In infants less than 6 months of age one can generally make an assumption that the children are operable as irreversible pulmonary vascular obstructive disease (PVOD) is unusual at that age. In older infants, and particularly in older children or adults, the question of how much and how reversible the PVOD is often arises.

A key concept is that in all large left to right (L-R) post-tricuspid shunts (i.e. VSD, PDA, atrioventricular canal (AV canal), APW, etc.) the systemic, i.e. aortic pressure is directly transmitted to the pulmonary artery. Therefore, in large shunts there is severe pulmonary artery hypertension (PAH) right at birth. As time progresses, the high flow and high pressure cause an elevation in pulmonary vascular resistance (PVR). It is this change in PVR that determines symptoms and operability.

For a variable period of time after PVR starts to increase, changes in lung vasculature may still be reversible following correction of the defect, i.e. the patient may still be operable. However, once irreversible PVOD is established, closure of the defect may

actually worsen the natural history and hasten mortality as a result of right heart failure.

Fundamental Concept

If the PVR is low, the shunt will be L-R and the patient will exhibit signs of pulmonary overcirculation. A patient with low PVR is always operable.

If the PVR is high, the shunt will become R-L and there will be signs of cyanosis without overcirculation. A patient with high PVR may be inoperable.

Using this concept one can come to a conclusion of operability looking for features of pulmonary overcirculation. A child with low PVR, i.e. who is operable has the following clinical features (**Table 2**).

Table 2: Clinical Features Favouring Surgery Based on Pulmonary Vascular Resistance

Symptoms of heart failure, e.g. failure to thrive, sweating, etc.
Tachycardia
Tachypnoea
An active hyperdynamic praecordium
A loud P2 along with a systolic ejection murmur of high flow (across the pulmonary valve in a VSD and across the aortic valve in a PDA/APW)
Potentially a mid diastolic rumble related to increased flow across the mitral valve
Evidence of LV volume load on ECG
Cardiomegaly and pulmonary plethora on CXR
An echo showing primarily a left to right shunt and a dilated LA/LV. In aorto-pulmonary window, reversal of flow in the aortic arch/descending aorta is a powerful predictor of operability as it suggests that the PVR is lower than the systemic vascular resistance (SVR)

On the other hand, a patient who is inoperable will have no clinical features of pulmonary over-circulation (**Table 3**).

Borderline Operability

In certain situations the clinical features are borderline. A patient with a quiet praecordium, no flow murmur, an oxygen saturation of 90% but mild cardiomegaly on CXR and equal sized ventricles with a bidirectional shunt on echo poses an operability diagnostic dilemma and a therapeutic challenge. In such cases,

Table 3: Criteria Showing High Pulmonary Vascular Resistance and Inoperable Defects

A quiet praecordium
Absence of a systolic ejection flow murmur in the presence of a loud banging P2
Evidence of cyanosis or an oxygen saturation less than 85% to 90%. (In a PDA the lower limb saturation would be measured)
Right ventricular hypertrophy on ECG
Absence of cardiomegaly or plethora on CXR with peripheral pruning
Primarily right to left shunting on the echo with right heart dilation

a cardiac catheterisation may add value in terms of a decision. Traditionally, a calculated PVR of less than 8 RU with oxygen/nitric oxide or other pulmonary vasodilators is considered evidence of operability. Although 100% oxygen has been conventionally used to assess the degree of 'reversibility', the role of oxygen in outcome prediction remains questionable. A recent multicentre haemodynamic study of patients with CHD and PH concluded that the reliability of pre-operative haemodynamic cath lab evaluation of operability was limited despite the use of vasodilators.

In a large PDA balloon occlusion of the duct can be performed. The demonstration of a substantial fall, especially of the PA diastolic pressure, suggests operability. However 100% correlation between this and operability has not been noted in all studies.

In conclusion, CHD is a diverse group of lesions with varying presentations. Early and accurate diagnosis along with timely intervention is the key to long-term good outcomes.

RECOMMENDED READINGS

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2. Malcolm S Thaler. *The Only Ekg Book You'll Ever Need;* 2nd Ed. Lippincott; 1995.
3. *Moss and Adams heart disease in infants, children and adolescents;* 5th Ed. Williams and Wilkins; 1995.
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12.27 Heart in Systemic Diseases

Aspi R Billimoria

The heart is involved in many systemic disorders. In most of these conditions, other manifestations like joint involvement or CNS affection may predominate and the cardiac involvement is often considered as a 'complication'. In a few patients, especially those with thyroid disease, cardiac manifestations may be the presenting complaints and may even precede other systemic manifestations.

HEART IN ENDOCRINE DISORDERS

Thyroid Disorders

Both thyroxine (T_4) and triiodothyronine (T_3) have a direct stimulatory effect on the myocardium.

Hyperthyroidism

Excess thyroid hormone has a direct effect on the heart but many of the clinical manifestations are due to increased beta-adrenergic stimulation. The increased basal metabolism leads to increased oxygen demand, resulting in tachycardia and increased cardiac output. The positive inotropic action of the hormone increases the force of contraction which, if untreated, results in high-output failure.

Signs and symptoms

Apart from signs of hyperthyroidism like ocular signs and goitre, the patient may complain of palpitations, dyspnoea or angina. The pulse is rapid and of high volume (due to the high-output state) and may be irregular if atrial fibrillation is present. Systolic hypertension is invariably present. A loud first heart sound and a third heart sound may be present with a systolic murmur in the left parasternal region. The hyperdynamic heart may cause rubbing of the normal pericardium against the pleura, resulting in a scratchy sound, the Means-Lerman scratch. In advanced untreated cases, there may be signs of cardiac failure.

Investigations

The commonest electrocardiographic changes are sinus tachycardia or atrial fibrillation (which may be at first paroxysmal and then permanent). The P wave may be notched and the PR interval may be prolonged. About 15% of patients have a right bundle branch block.

Treatment

Cardiac manifestations generally do not respond to conventional cardiac drugs without specific anti-thyroid treatment. Beta-blockers are useful as they slow the heart rate and suppress beta-adrenergic activity. Digitalis and diuretics are useful in treating cardiac failure.

Hypothyroidism

The heart becomes pale and flabby and dilates. Histopathology reveals swelling of the myofibrils, loss of striations and interstitial fibrosis. There is increased capillary fragility which leads to leakage of fluids into the interstitial spaces, resulting in pericardial effusion.

Signs and symptoms

There is bradycardia and the pulse is of low volume. The blood pressure is usually low but in a few cases there may be hypertension. The heart size is enlarged and the heart sounds may sound distant. A pericardial rub may be heard. Severe cardiac failure may be present. A few patients may complain of angina or suffer myocardial infarction due to secondary hyperlipidaemia.

Investigations

The electrocardiogram characteristically reveals sinus bradycardia, low voltage and flat T-waves. The QT interval may be prolonged. Changes of pericardial effusion may be seen. Chest X-ray reveals an enlarged heart and signs of pericardial effusion. Pericardial effusion can be confirmed by echo-cardiogram.

Treatment

The cardiac manifestations do not respond to conventional therapy unless hormone replacement therapy is instituted. It is advisable to start with a low dose of thyroid hormone in elderly patients and those with angina, as tachycardia may exacerbate myocardial ischaemia.

Adrenal Disorders

Hyperaldosteronism

Hypersecretion of aldosterone results in hypertension, hypokalaemia and metabolic acidosis. The diagnosis is suspected when the patient has diastolic hypertension and low serum potassium. Treatment is aimed at removal of the mineralocorticoid-producing tumour but in patients who are at poor risk for surgery, spironolactone in high doses (up to 200 mg/day) may be given.

Cushing's syndrome

The cardiac manifestations are usually those of hypertension and ischaemic heart disease due to hyperlipidaemia. The treatment is that of the primary disease.

Adrenal insufficiency

Decreased secretion of glucocorticoids results in marked hypotension which worsens on standing. The electrocardiogram reveals sinus bradycardia, flat or inverted T-waves and generalised low voltage. The treatment is by replacement therapy with corticosteroids.

Phaeochromocytoma

This is a catecholamine-producing tumour which causes severe adrenergic stimulation, resulting in hypertension and tachycardia. The catecholamine release and its manifestations are usually episodic, though, hypertension may be permanent

in a few cases. The heart may develop a cardiomyopathy-like picture in chronic cases.

Electrocardiography reveals left ventricular hypertrophy, T-wave inversion, sinus tachycardia and occasionally, paroxysmal atrial tachycardia.

The adrenergic activity should be blocked initially with alpha-adrenergic blockers like phenoxybenzamine or prazosin. Later on, beta-blockers or calcium-channel blockers may be added. Treatment is by surgical excision of the tumour.

Pituitary Gland Disorders

Acromegaly

The cardiovascular manifestations include hypertension, ischaemic heart disease and congestive heart failure. The heart size is markedly enlarged, out of proportion to the rest of the splanchnomegaly. The hypertension responds well to conventional therapy.

HEART IN ANAEMIA

Chronic severe anaemia (haematocrit < 25%) leads to a high-output state. Since the oxygen-carrying capacity of the RBCs is reduced, accumulation of metabolites occurs in the tissues and causes peripheral vasodilatation leading to reflex tachycardia and hyperkinetic circulatory state. Chronic anaemia leads to work hypertrophy of the heart and finally to its dilatation and cardiac failure.

Signs and Symptoms

The commonest symptoms are fatigue, dyspnoea on exertion, anginal pains and swelling of the ankles.

Physical examination reveals tachycardia and collapsing pulse, and pistol-shot sound and Duroziez's murmur may be audible over the femoral artery. The heart may be clinically enlarged and the apex beat hyperdynamic. There may be loud heart sounds and a systolic 'haemic' murmur at either the base or the apex of the heart. Mid-diastolic murmurs across the mitral and tricuspid valves may be heard and are due to increased flow. If the ventricles dilate, murmurs of tricuspid and mitral regurgitation may be heard. Dilatation of the great vessels may cause murmurs of aortic and pulmonary regurgitation. There may be signs of congestive cardiac failure.

Investigations

Electrocardiogram reveals tachycardia and flattened or inverted T waves. X-ray chest may show a normal or dilated heart. The haemogram reveals the underlying anaemia.

Treatment

The treatment is that of anaemia and, if possible, it's underlying cause. Severe anaemia may require blood transfusions. Transfusion of whole blood may overload the circulation; in these cases packed cells may be transfused after intravenous frusemide injection. Digoxin is not useful in treating cardiac failure due to anaemia, though diuretics may help in reducing the oedema.

HEART IN MALNUTRITION AND VITAMIN DEFICIENCY

Protein-Calorie Malnutrition

This is seen mainly in children either as marasmus or kwashiorkor and is due to deficiency of protein intake. Kwashiorkor may also be seen in adults. The heart becomes thin-walled and flabby and there is atrophy of the muscle fibres. Clinically, the patient has hypotension, low pulse pressure and low cardiac output. Generalised signs of malnutrition are seen.

Beriberi

Beriberi is due to thiamine (vitamin B1) deficiency and is either of the dry or wet variety. The heart is involved in wet beriberi. It may occur due to deficient intake in patients eating polished rice, or in alcoholics and in diabetes. It may also form part of generalised hypovitaminosis.

Thiamine helps in the oxidation of pyruvic acid to lactic acid and deficiency leads to pyruvate and lactate accumulation. This results in peripheral vasodilatation and reflex tachycardia, a hyperkinetic circulatory state. Renal retention of sodium and water leads to increased blood volume. Chronic beriberi may result in congestive cardiac failure.

Signs and symptoms

The patient complains of severe dyspnoea on exertion and swelling of the legs, along with the classical signs of dermatitis and peripheral neuropathy. On examination, there is tachycardia, wide pulse pressure and signs of cardiac failure, with pericardial or pleural effusion. Auscultation may reveal a third heart sound and apical systolic murmur.

Investigations

Electrocardiogram shows sinus tachycardia, low-voltage QRS complex and T-waves, and prolongation of the QT interval. Chest X-ray will show an enlarged cardiac shadow and signs of pericardial or pleural effusion.

Diagnosis

The diagnosis is made clinically by the presence of hyperkinetic circulatory state, skin changes and peripheral neuropathy. Laboratory analysis will reveal increased blood pyruvate and lactate levels.

Treatment

Patients do not respond well to conventional cardiac therapy. Thiamine given in doses of 100 mg daily, either intravenous or intramuscular, brings about dramatic improvement in a few days. Concurrent treatment with digoxin, diuretics and a low-sodium diet is also advisable.

HEART IN COLLAGEN DISEASES

Systemic Lupus Erythematosus

The heart is involved in 50% to 60% of cases of SLE. There are three modes of involvement.

Pericarditis is the commonest lesion. Exudative pericardial effusion occasionally may cause cardiac tamponade. Rarely there may be constrictive pericarditis.

Endocarditis takes the form of Libman-Sacks verrucous vegetations, which are formed of degenerated valve tissue and may be as large as 3 mm. Usually, they do not cause any valvular malfunction.

Myocarditis is present on histopathology at autopsy which reveals fibrinoid necrosis and changes of angiopathy.

Polyarteritis Nodosa

This disease is characterised by necrotising inflammation of the blood vessels, also involving those of the heart. The coronary arteries are involved and angina pectoris and myocardial infarction may result. Hypertension, due to renal artery involvement, is very common and may lead to congestive heart failure. Atrial flutter and fibrillation are also observed in some cases.

Scleroderma

This disease is characterised by vasculitis, but the process is slow and results in scarring and fibrosis, leading to obliteration of small vessel lumen. Obliteration of pulmonary vessels leads to the development of pulmonary hypertension. Coronary artery involvement is common and leads to precipitation of anginal attacks and myocardial infarction. Myocardial involvement due to fibrosis results in congestive cardiac failure. Atrio-ventricular conduction defects are also observed, as is pericarditis. Cardiac dilatation may produce regurgitation murmurs.

Rheumatoid Arthritis

All the cardiac tissues are involved. Valvular involvement is due to rheumatoid granulomas, and the commonest valves affected are the aortic and the mitral, with regurgitation as the end result. Myocarditis, due to granulomas, may precipitate left ventricular failure. Pericarditis resembling tuberculosis is quite common and may occur in as many as 50% of cases. About 20% of the cases may have coronary arteritis.

Reiter's Disease

The heart is involved usually only in the acute stages of the disease when pericarditis and atrio-ventricular conduction defects may occur. Auscultation may reveal apical systolic murmur and occasionally aortic and mitral regurgitation.

SYPHILITIC HEART DISEASE

Syphilitic Aortitis and Aortic Regurgitation

Syphilis most commonly involves the ascending aorta, probably because it has a richer lymphatic supply. Fibrous tissue replaces normal aortic wall tissue, leading to weakening of the walls and aneurysm formation. The aneurysm is usually fusiform in shape. The aorta assumes a 'tree bark' appearance due to wrinkling of the intima. If the infection and inflammation extend into the root of the aorta, it may cause dilatation of the aortic annulus and result in aortic regurgitation. The latter is characterised by a loud second sound ('*bruit de tambour*') and an early diastolic regurgitation murmur which is better heard on the right sternal border, owing to the dilated aorta. The EDM of rheumatic aortic regurgitation is better heard in the left third intercostal space (Erb's area).

Coronary Ostial Narrowing

This results in angina pectoris. However, it differs from the angina caused by atherosclerosis in the following manner: attacks come on at rest, anginal pain lasts for a longer period of time, and angina is not relieved by sublingual nitrates.

Syphilitic Myocarditis

This is not commonly seen now. Gumma formation was common in earlier times and resulted in atrio-ventricular conduction blocks.

Treatment

All patients with cardiovascular syphilis should be given antibiotic therapy to check further progress of the disease. Surgery is indicated for aneurysm and aortic regurgitation. Coronary ostial narrowing may be treated by endarterectomy or bypass grafting.

HYPERKINETIC CIRCULATORY STATES

Hyperkinetic circulatory states comprise conditions where the resting cardiac output is increased to more than 6 litres/minute. The principal contributing factor is lowered peripheral vascular resistance (afterload) leading to increased venous return. This may be the result of peripheral vasodilatation or of peripheral shunting as in arteriovenous fistulae. The cardiac output rises due to an increase in heart rate, stroke volume or both. Usually, the patients cope with the problem well and do not develop cardiac failure. However, in patients in whom the problem develops acutely, cardiac failure may result. Causes of hyperkinetic circulatory states are given in **Table 1**.

Table 1: Causes of Hyperkinetic Circulatory States

- **Physiological**
  - After a hot bath
  - Vigorous exercise
  - Pregnancy
- **Pathological**
  - Chronic high-output states
    - Thyrotoxicosis
    - Chronic severe anaemia
    - Beriberi
    - High fever
    - Paget's disease of bones
    - Systemic arteriovenous fistulae
    - Hyperkinetic heart syndrome
    - Hepatic diseases
  - Acute high-output states
    - Severe anaemia and thyrotoxicosis that worsen suddenly
    - Acquired arteriovenous fistulae

Paget's Disease of Bones

This is characterised by a process of rapid bone formation and resorption at various sites, with increased vascularity of the affected bones. However, this is not the cause of the high-output state, which is believed to be due to increased blood flow in the cutaneous vessels overlying the affected bones, in order to dissipate the heat produced because of increased metabolism of the bones.

There are no specific findings in the cardiovascular system. Metastatic calcification of the valve rings and conduction tissues may occur, resulting in atrioventricular blocks. There is no specific treatment for the high-output state, except that for Paget's disease itself.

Arteriovenous Fistulae

They produce high-output states only if they are large in size. Clinical findings reveal a high-volume pulse and mild tachycardia. Pressure over the fistula may slow the heart rate (Nicaladoni-Branham's sign). If the fistula is superficial, the skin over it may be warmer and auscultation usually reveals a 'machinery' murmur. Auscultation of the heart may reveal third and fourth heart sounds. These fistulae may be congenital or acquired.

Congenital fistulae may be single or multiple and may vary in size from that of a strawberry birthmark to huge, ugly swellings

that disfigure the limbs. They are more common in the lower limbs. The affected limb may be swollen and enlarged. Hereditary haemorrhagic telangiectasia is a congenital condition in which arteriovenous fistulae may occur. These often involve the liver and lungs. The liver may be enlarged and palpable and a bruit may be heard over it.

Acquired fistulae usually occur after gunshot and stab wounds and are commonly found in the thighs. Due to the increased blood flow, the affected limb increases in size. Other types of acquired fistulae are shunts that are surgically made for haemodialysis, those occurring in Wilms' tumour and, rarely, by rupture of an aortic aneurysm into the inferior vena cava.

Diagnosis

The skin changes over the fistula, the enlarged limb and the continuous murmur are pathognomonic. The electrocardiogram may be either normal or may reveal mild left ventricular enlargement. Chest roentgenograms reveal either a normal sized or a slightly enlarged heart. To localise the site of the fistula, angiograms may be necessary.

Treatment

Small fistulae may be left alone, especially if they do not cause cosmetic embarrassment. Surgical excision yields excellent results; this may, however, not be possible in all patients, especially those having multiple or very large fistulae.

Hyperkinetic Heart Syndrome

This syndrome usually occurs in young men; they have a high-output state without any detectable cause. They complain of palpitations and atypical chest pain. Examination shows a high pulse pressures and third and fourth heart sounds; in some patients, systolic murmurs are heard. The exact cause of the syndrome is not known.

Treatment with beta-adrenoreceptor blockers yields excellent results.

Hepatic Diseases

Hepatocellular failure leads to vasodilatation resulting in high-output states. There may also be arterio-venous fistulae in the lungs. The exact cause is not known. These may be due to hypoxia or diminished deactivation of vasodilator substances and oestrogens in the liver.

RECOMMENDED READINGS

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12.28 Disorders of the Myocardium

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Disorders of the myocardium are an important and heterogeneous group of diseases. The term 'cardiomyopathy' was first used in 1957 and is defined by World Health Organization as 'a disease of the myocardium associated with cardiac dysfunction'. Various classifications for cardiomyopathies have been proposed. American Heart Association has divided cardiomyopathies into 2 groups: primary cardiomyopathies (solely or predominantly confined to heart muscle); and secondary cardiomyopathies (pathological myocardial involvement as part of generalised systemic disorders) (**Figure 1**).

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM), the most common form of cardiomyopathy, is characterised by ventricular dilatation and impaired contraction of left or both ventricles leading to systolic dysfunction. It is more common in males and between the ages of 20 and 50 years. The 5-year survival after diagnosis is 50%.

Aetiology

Dilated cardiomyopathy can occur in an idiopathic form or secondary to other cardiac or systemic diseases (**Table 1**). Idiopathic form may represent sequelae of remote episodes of viral myocarditis. Autoimmunity has also been implicated as the underlying mechanism in idiopathic DCM. About 25% to 35% of cases of DCM are familial. A large number of genes have been implicated. Modes of inheritance include autosomal dominant (AD) with incomplete penetrance, autosomal recessive (AR) and X-linked.

Clinical Presentation

Clinical picture is dominated by symptoms of left ventricular failure. Some patients remain asymptomatic for years. Others present with symptoms of fatigue and weakness due to diminished cardiac output. Elevated left ventricular (LV) filling pressures result in symptoms of exertional dyspnoea, paroxysmal nocturnal dyspnoea and orthopnoea. Clinical course is punctuated by thromboembolism and atrial or ventricular arrhythmias. Chest pain may result from underlying coronary artery disease (CAD) or pulmonary embolism. Features of right heart failure may develop in late stages of the disease.

Physical findings include tachycardia, low arterial pressure and cool extremities secondary to low cardiac output. Jugular venous pressure (JVP) may be elevated with prominent 'a' and 'v' waves. Dependent oedema, ascites and hepatomegaly indicate right heart involvement. Cardiovascular examination reveals marked cardiomegaly with palpable third heart sound. Auscultatory findings include soft S1, prominent S3 and pansystolic murmurs of mitral and tricuspid regurgitation.

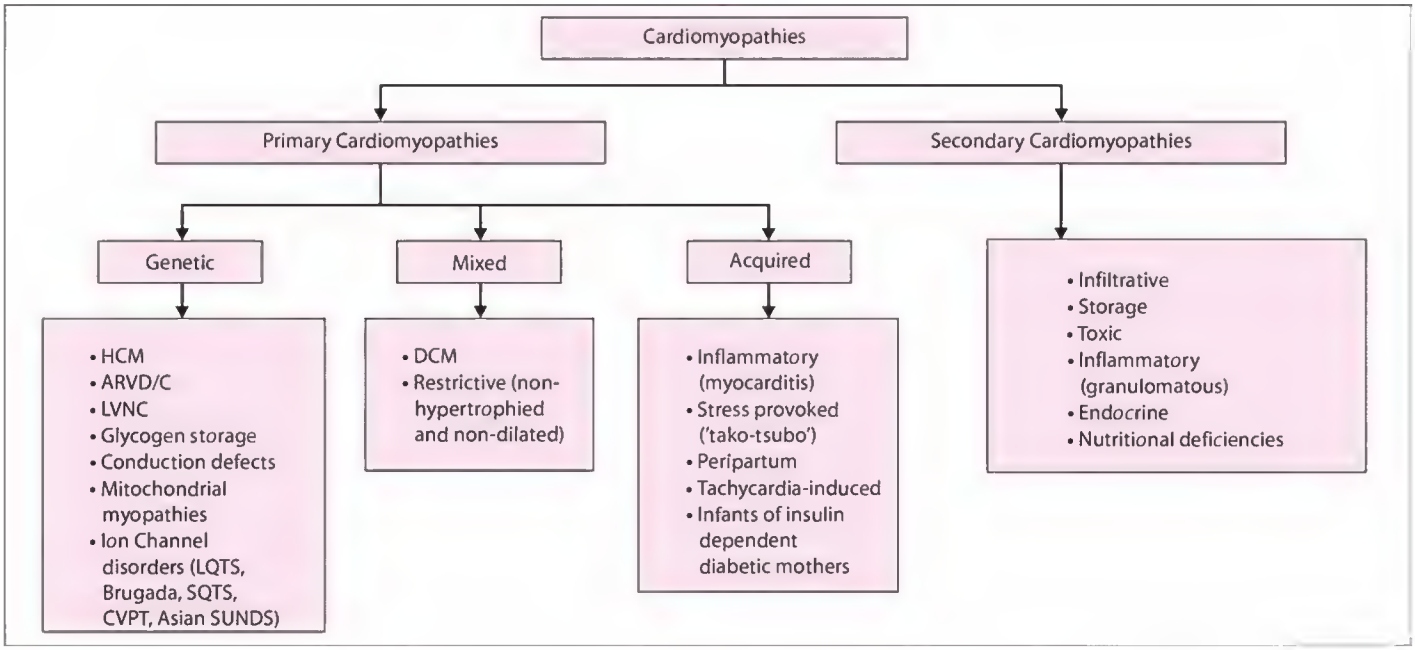


Figure 1: American Heart Association (AHA) classification of cardiomyopathies.

HCM = Hypertrophic cordiomyopothy; DCM = Diloted cardiomyopothy; ARVD/C = Arrhythmogenic right ventriculor dysplosio/cardiomyopothy; LVNC = Left ventriculor noncompoction; LQTS = Long-QT syndrome; SQTS = Short-QT syndrome; CVPT = Catecholominergic polymorphic ventriculor tochycordia; SUNDS = Sudden unexploined nocturnol deoth syndrome.

Pulmonary venous congestion produces tachypnoea and rales over bilateral basal lung fields.

Table 1: Secondary Causes of Dilated Cardiomyopathy

Endocrine disorders	
	Cushing's disease
	Diabetes mellitus
	Growth hormone abnormalities
	Hypothyroidism/hyperthyroidism
	Phaeochromocytoma
Nutritional deficiencies	
	Carnitine
	Selenium
	Thiamine
Metabolic disturbances	
	Hypocalcaemia
	Hypophosphataemia
	Uraemia
Toxins	
	Ethanol
	Antiretroviral agents
	Chemotherapeutic agents: Anthracyclines
	Radiation
	Cocaine
	Phenothiazines
	Heavy metals: cobalt, lead, mercury

Investigations

Electrocardiographic findings are non-specific. They include isolated T-wave changes, septal Q-waves, prolonged atrioventricular conduction, bundle branch blocks, and atrial or ventricular arrhythmias. Echocardiography is the main stay of diagnosis and reveals dilatation of left ventricle and other chambers with globally diminished systolic function (**Figure 2**). It may identify mural thrombi, quantify mitral and tricuspid regurgitation and assess severity of pulmonary hypertension. Echocardiography excludes secondary causes like valvular heart disease. Thallium myocardial perfusion imaging or coronary angiography is required to definitely exclude CAD. Endomyocardial biopsy (EMB) is done in selected cases to rule out myocarditis, infiltrative disorders like amyloidosis, sarcoidosis, haemochromatosis and storage disorders. Detection of viral antigen in EMB specimen may help to plan anti-viral therapy.

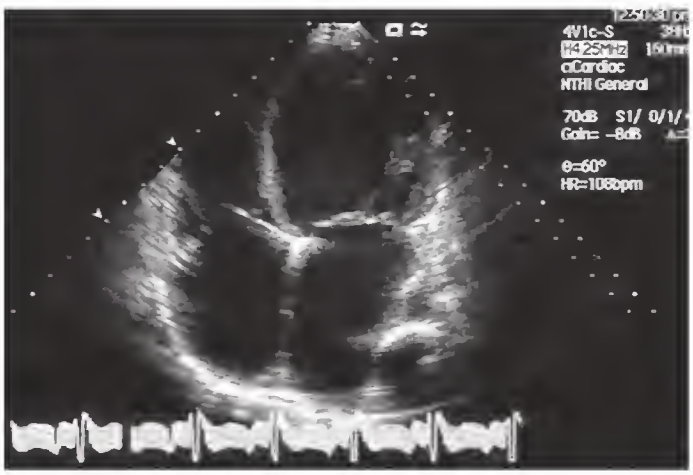


Figure 2: 2D echocardiographic image (apical 4-chamber view) showing dilatation of all four cardiac chambers in a patient with DCM.

Pathology

Grossly, there is cardiomegaly with increase in myocardial mass and marked chamber dilatation (**Figure 3**). Mural thrombi are seen frequently at various stages of organisation.



Figure 3: Gross photograph showing left-side of the heart with dilated cavity, endocardial sclerosis and mural thrombus in DCM.

Microscopic findings are non-specific and consist of myocyte hypertrophy, myocyte atrophy and interstitial fibrosis. Characteristic histologic findings in certain secondary forms of DCM include lymphocytic infiltration in myocarditis, granulomas in sarcoidosis and intramyocellular iron deposition in haemochromatosis.

Treatment

Treatment is directed to control heart failure symptoms. Diuretics, β-blockers, angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) and digoxin form the mainstay of treatment. Diuretics and digoxin provide symptomatic relief whereas β-blockers, ACEIs/ARBs and spironolactone improve survival as well. Therapy with β-blockers and ACEIs/ARBs should be initiated in lowest dose and then gradually up-titrated to maximum tolerated dose. Counselling regarding the natural history of the disease and the need for long-term treatment goes a long way in ensuring compliance to medications. Salt and fluid intake is restricted. All patients with prior ventricular fibrillation/sustained ventricular tachycardia should be offered implantable cardioverter defibrillator (ICD). Implantation of ICD also improves survival in patients with left ventricular ejection fraction less than 30%. In patients with left bundle branch block (LBBB) with wide QRS (>120 ms) and left ventricular ejection fraction (LVEF) ≤35%, who remain symptomatic despite maximum medical therapy, cardiac resynchronisation therapy (CRT) using

biventricular pacing improves survival, functional status, exercise tolerance and ejection fraction. Patients who have progressed to end-stage disease are candidates for heart transplantation. Anticoagulation is indicated in patients with mural thrombus and prior thromboembolism. Arrhythmias should be aggressively treated. In patients with atrial fibrillation, amiodarone is an effective drug and may restore normal sinus rhythm in some.

MYOCARDITIS

Myocarditis is defined as a disease process characterised by non-ischaemic inflammatory cellular infiltration of the myocardium with or without associated myocyte necrosis (Dallas criteria).

Aetiology

The most common underlying aetiology of myocarditis is common viral infections (coxsackie virus A and B, echovirus, adenovirus, poliovirus, parvovirus B-19, influenza virus, HIV and others). Less commonly, myocarditis results from other infections (bacterial, fungal, parasitic or rickettsial), toxic or hypersensitive drug reactions, collagen vascular disorders, snake/insect bites, radiation injury or electric shock.

Pathogenesis

Myocyte injury may result from direct cytopathic effect of inciting agent, cell-mediated cytotoxicity or autoantibody-mediated damage.

Clinical Presentation

Clinical presentation of myocarditis is variable and includes asymptomatic presentation with ECG abnormalities, sub-acute presentation with symptoms and signs of heart failure and ventricular dilatation (resembling DCM), and fulminant presentation with severe LV dysfunction without chamber dilatation. Symptoms may include dyspnoea, orthopnoea, chest pain, cough, fatigue, palpitations and syncope. A viral prodrome with fever, myalgia, and respiratory or gastrointestinal symptoms may precede the development of cardiac symptoms. Atrial and ventricular arrhythmias are common. Conduction blocks, including complete heart block, may be seen. Acute coronary syndrome remains an important differential diagnosis.

Investigations

Electrocardiography shows tachycardia with non-specific ST-segment and T-wave abnormalities, occasionally mimicking acute myocardial infarction. Cardiac biomarkers like troponins and CK-MB are elevated. Echocardiography reveals globally decreased ventricular function with chamber dilatation. However, in fulminant myocarditis, ventricular cavity may be small with increased wall thickness. Contrast-enhanced magnetic resonance imaging (MRI) reveals delayed gadolinium enhancement of the myocardium in T2-weighted images and suggests myocarditis. Coronary angiography is done to rule out CAD. Endomyocardial biopsy is the gold standard for diagnosis of myocarditis but has limited sensitivity and specificity. It is indicated in patients with unexplained rapidly progressive heart failure of less than 2 weeks duration refractory to conventional treatment and in those with unexplained heart failure associated with life-threatening ventricular arrhythmias or conduction system disease. Detection of viral antigen in EMB specimen confirms a viral aetiology.

Pathology

Gross

During the active phase, the gross appearance of the heart is variable as the myocardial involvement may be focal, patchy or diffuse. The myocardium is often mottled with pale foci and hyperaemic-haemorrhagic areas. Mural thrombi may be present, especially in dilated hearts.

Histopathology

There is interstitial mononuclear inflammatory infiltrate predominantly lymphocytic, with damage to adjacent myocytes (**Figure 4**). This may be focal, multifocal or diffuse. The nature of myocarditis can be confirmed by immuno-histochemical and molecular work-up. The most common viral cause of myocarditis is coxsackie virus B as confirmed by molecular analysis. Lately, parvovirus is emerging as an important cause of viral myocarditis.

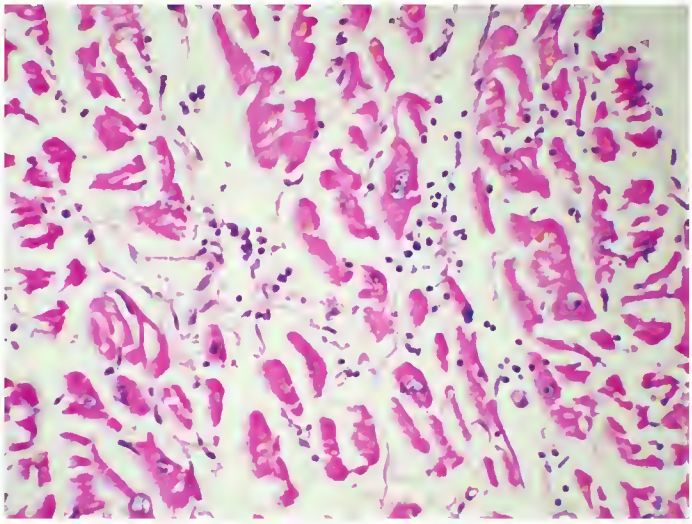


Figure 4: Microphotograph showing myocarditis with lymphocytic infiltrate and myocyte necrosis (H and E X 280).

Treatment

Treatment is supportive with diuretics, ACEIs and β-blockers. In patients who worsen on medical therapy, mechanical circulatory assist devices may be used as a bridge for transplantation or recovery. About 40% of patients recover uneventfully with supportive treatment. Antiviral therapy is being evaluated in patients with positive viral antigen in EMB specimen and immunosuppressive therapy in patients with negative viral antigen.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a primary genetic cardiac disorder resulting from mutation in genes encoding sarcomeric proteins. The hallmark of HCM is left (± right) ventricular hypertrophy in the absence of chronic pressure or volume overload. HCM has intrigued clinicians and researchers for decades due to its heterogenous expression, unique pathophysiology and variable clinical presentation. It is known by various other names like hypertrophic obstructive cardiomyopathy (HOCM), idiopathic hypertrophic subaortic stenosis (IHSS), and asymmetric septal hypertrophy (ASH). Hypertrophic cardiomyopathy is the most common inherited cardiovascular disorder with a prevalence of 0.2% (or 1 in 500) in the general population.

The HCM phenotype usually manifests during adolescence with marked increase in wall thickness accompanying adolescent growth spurt. Differentiating HCM from physiological hypertrophy in 'athlete's heart' is important for clinical implications (**Table 2**). Apical HCM (wall thickening confined to the left ventricular apex) is a morphological variant characterised by spade-shaped ventricular cavity (**Figure 5**) and giant symmetrical T wave inversions in lateral precordial leads on ECG (**Figure 6**). This variant has a benign course and good prognosis.

Table 2: Differentiating Hypertrophic Cardiomyopathy from Athlete's Heart

	HCM	Athlete's Heart
Family history of HCM	+	–
Marked LVH or unusual patterns of hypertrophy	+	–
LV cavity dilatation	–	+
LA enlargement	+	–
Abnormal ECG patterns	+	–
Abnormal LV filling pattern on pulse Doppler interrogation of mitral inflow velocities	+	–
Female gender	+	–
Thickness with deconditioning	–	+

Aetiology: Genetics

Hypertrophic cardiomyopathy is inherited as an autosomal dominant trait with positive family history in over 60% of cases. The remainder of the cases arise from *de novo* mutations in known or as yet unknown genes or may include other causes of LV hypertrophy like Fabry's disease and glycogen storage disorders. More than 450 mutations in 13 sarcomeric genes have been implicated.

Pathophysiology

Diastolic dysfunction

Diastolic dysfunction is seen in 80% of patients and manifests as dyspnoea and exercise intolerance. This is related to LV

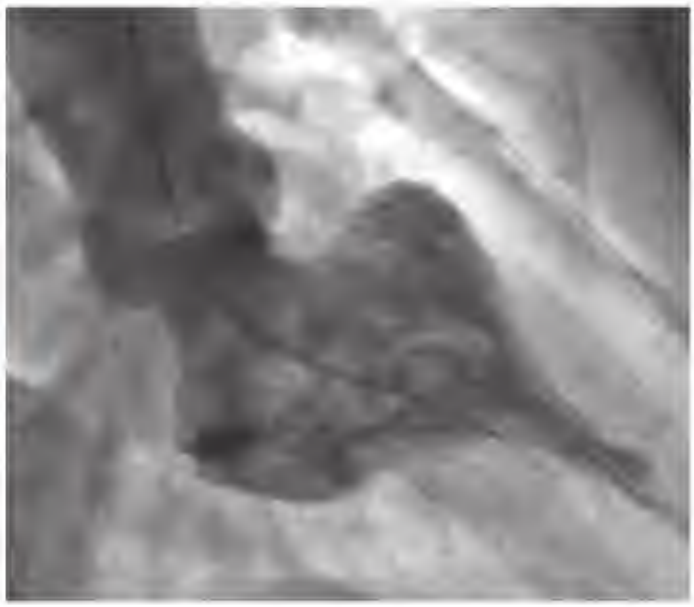


Figure 5: Left ventriculogram at end diastole showing 'spade-shaped ventricular cavity' in a patient with apical HCM.

hypertrophy, interstitial fibrosis, myocardial ischaemia and abnormal calcium influx. Systolic function is normal or increased in HCM.

Left ventricular outflow tract obstruction

Left ventricular outflow tract obstruction (defined as gradient ≥30 mm) in HCM is dynamic and varies with changes in preload, afterload and contractility (**Table 3**). It is seen at rest in 25% of individuals and that at rest or on provocation in 70%. It is produced by systolic anterior motion (SAM) of the mitral valve and mid-systolic contact with hypertrophied septum and is an independent predictor of heart failure and cardiovascular deaths.

Myocardial ischaemia

Myocardial ischaemia in HCM results from multiple mechanisms —reduced arteriolar density, myocardial hypertrophy, micro-

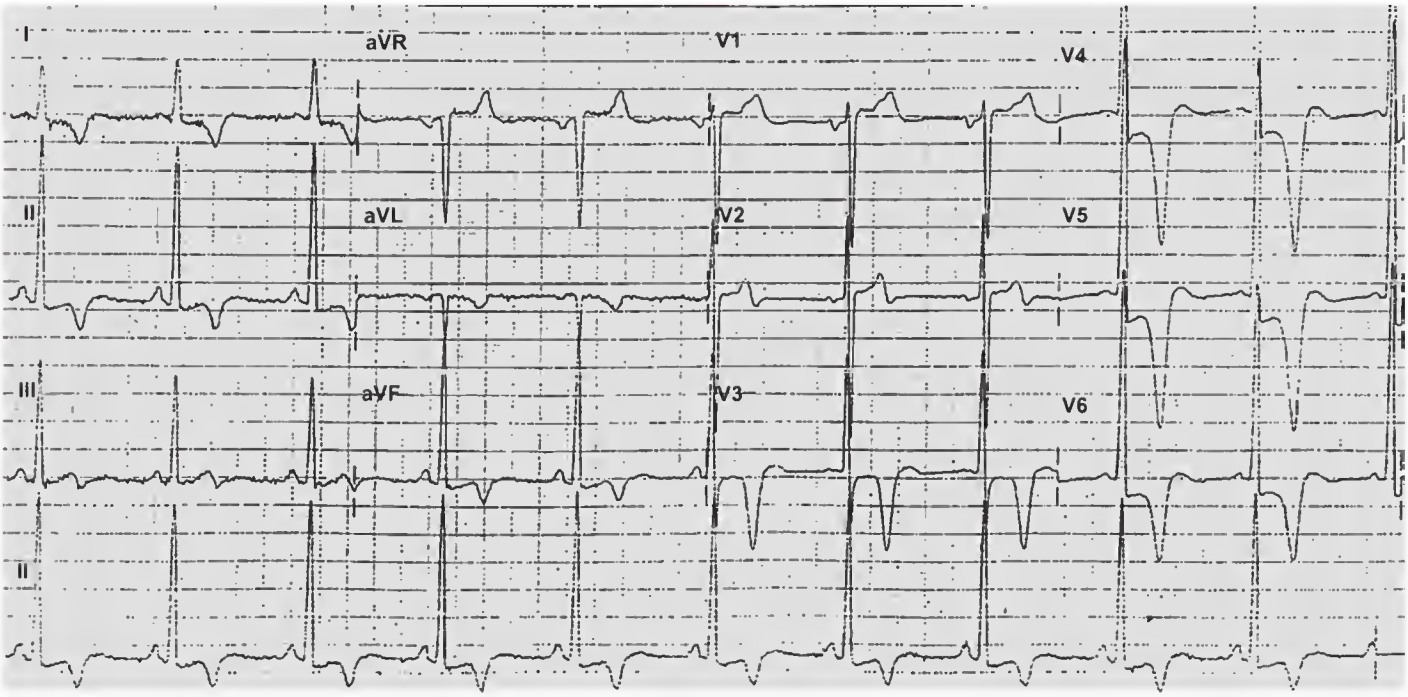


Figure 6: ECG of a patient with apical HCM showing giant T wave inversions (defined as ≥5 mm in limb leads and ≥10 mm in chest leads) with tall R waves.

vascular dysfunction, left ventricular outflow tract obstruction (LVOTO) and diastolic dysfunction.

Table 3: Effect of Changes in Preload, Afterload and Myocardial Contractility on LVOT Gradient and HCM Murmur

Manoeuvres increasing LVOT Gradient and Intensity of Murmur	Manoeuvres Decreasing LVOT Gradient and Intensity of Murmur
I **Decreased preload**	I **Increased preload**
Valsalva manoeuvre	IV fluids
Standing	Supine position
Nitrates	II **Increased afterload**
II **Decreased afterload**	Squatting
ACEIs/ARBs	Isometric handgrip
Amyl nitrite/Nitroglycerine	
III **Increased myocardial contractility**	
Premature ventricular contractions	
Exercise	

Natural History

Natural history of HCM is variable. Some patients remain asymptomatic throughout life, whereas in others, clinical course is marked by occurrence of symptoms of heart failure, atrial arrhythmias or sudden cardiac death (SCD). Symptoms may develop at any age. Hypertrophic cardiomyopathy related mortality in the community is about 1% per year in adults and 2% per year in children. Three per cent of patients develop end-stage disease characterised by wall-thinning and systolic dysfunction mimicking dilated cardiomyopathy.

Clinical Presentation

Most common presenting symptoms in affected patients include dyspnoea on exertion, angina, fatigue, presyncope or syncope and palpitations. Syncope may result from sudden reduction in cardiac output secondary to atrial or ventricular arrhythmias or significant LVOTO. Physical examination in patients without obstruction may just reveal brisk carotid upstroke and a left-sided fourth heart sound. In patients with LVOTO physical examination demonstrates a prominent 'a' wave in jugular venous waveform, bifid carotid pulse with brisk upstroke and a secondary shoulder, double or triple apical impulse, reversed splitting of second heart sound and a dynamic ejection systolic murmur at the left lower sternal border and apex. Ejection systolic murmur varies in intensity with the magnitude of LVOTO (**Table 3**). Pansystolic murmur (PSM) of mitral regurgitation is heard at the apex in some patients with obstruction.

Investigation

Electrocardiographic abnormalities are seen in 90% to 95% of patients with HCM which include LV hypertrophy, left atrial enlargement, ST segment and T wave abnormality, prominent Q-waves and diminished R-waves in lateral precordial leads. Periodic ambulatory Holter monitoring detects atrial or ventricular arrhythmias and helps risk stratify patients for SCD. Failure of blood pressure to increase during cardiopulmonary exercise testing identifies a subset with increased risk for SCD.

Echocardiography is the 'gold standard' for diagnosis of HCM and for screening asymptomatic relatives. Classical 2D echocardiography findings include asymmetrical septal hypertrophy (**Figures 7 and 8**), small LV cavity, LA enlargement and SAM of anterior mitral leaflet. Doppler echocardiography can assess diastolic dysfunction, measure left ventricular outflow tract (LVOT) pressure gradient and quantify mitral regurgitation. Since LVOT gradient is dynamic, Doppler assessment should be done both at rest and after provocative manoeuvres like Valsalva and exercise. Magnetic resonance imaging (MRI) is useful when hypertrophy is confined to unusual areas like apex or anterolateral free wall, which are difficult to image adequately with echocardiography.

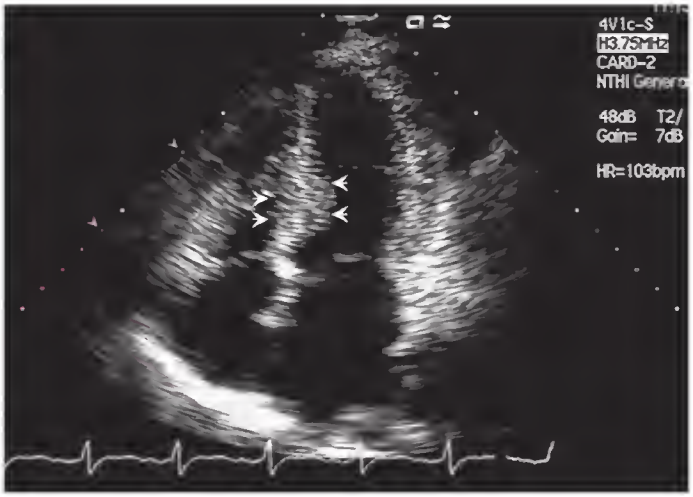


Figure 7: 2D echocardiographic image (apical 4-chamber view) showing hypertrophied basal septum (arrows) in a patient with HCM.

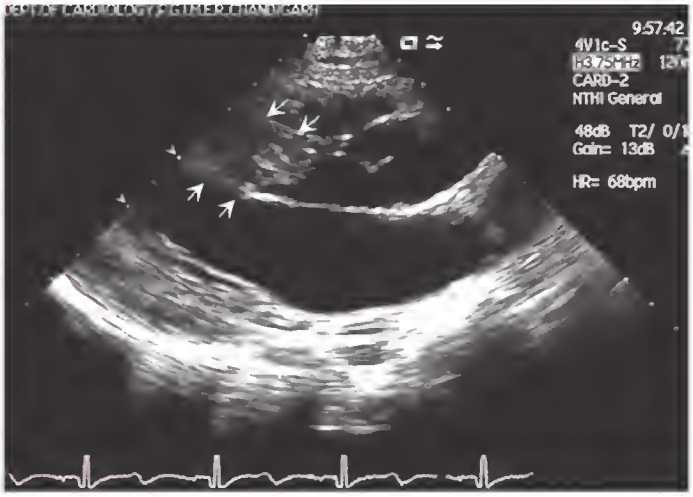


Figure 8: 2D echocardiographic image (parasternal long-axis view) showing hypertrophied basal septum (arrows) in a patient with HCM.

Cardiac catheterisation is indicated in patients with chest pain and atherosclerotic risk factors to exclude epicardial coronary artery disease. It can quantify LVOT gradient at rest or with provocation in patients with LVOTO (**Figure 9**).

Pathology

Grossly the heart is overweight and bulky with regional or concentric left ventricular hypertrophy. Myocardial hypertrophy is strikingly variable in extent and distribution. Asymmetric patterns of hypertrophy are more common, often confined to basal anterior septum, but occasionally to posterior septum, anterolateral free wall or apex. In some patients, disease involves both the ventricles or is confined only to the right ventricle. The magnitude of hypertrophy may vary from minimal to marked (wall thickness up to 60 mm), even in patients with similar genotypes. Mitral valve is elongated and enlarged in two-thirds

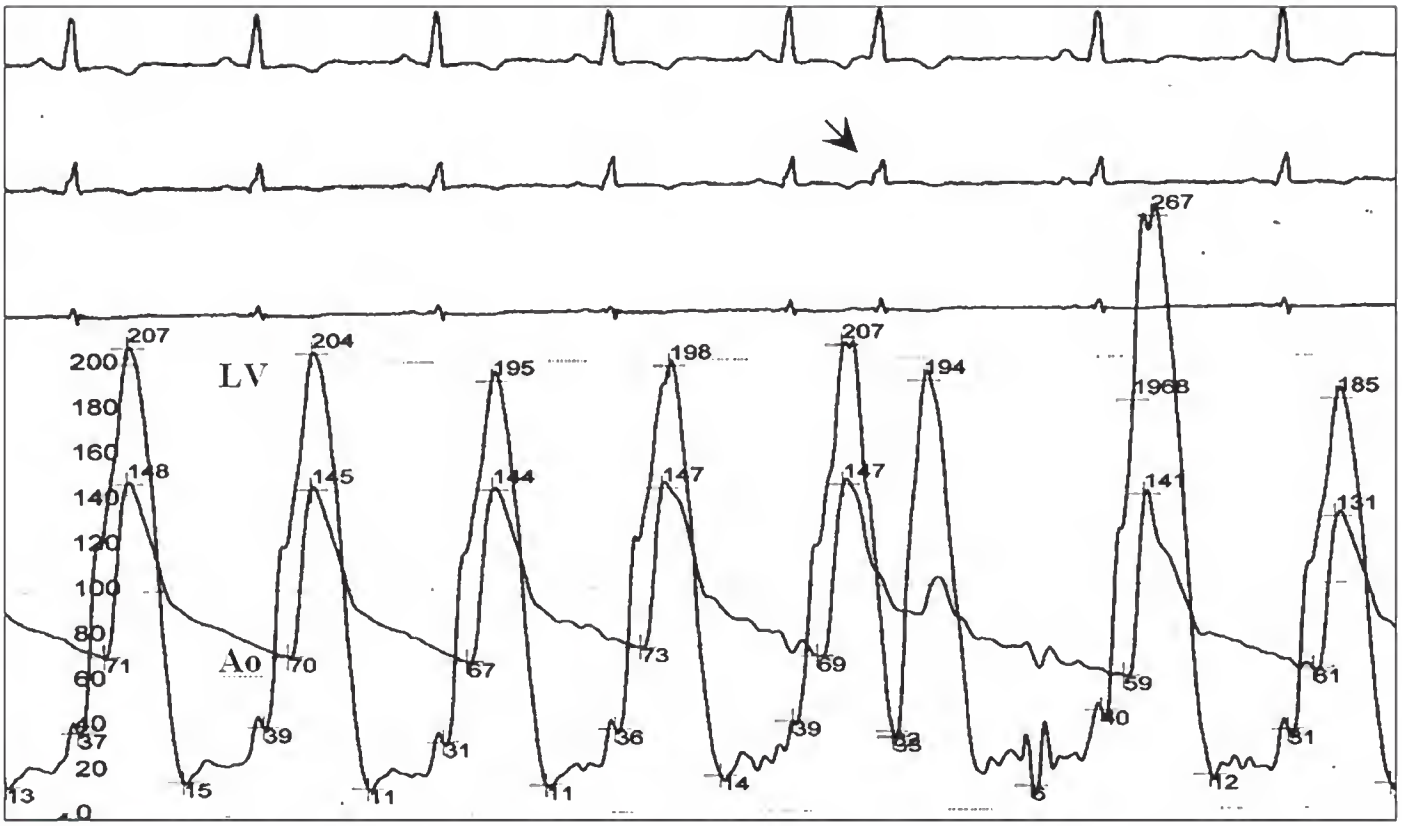


Figure 9: Simultaneous LV and aortic (Ao) pressure tracings in a patient with obstructive HCM showing marked increase in LV-aortic pressure gradient and decrease in pulse pressure following a premature ventricular contraction—the Brockenbrough Braunwald phenomenon.

of patients. This along with basal anterior septal hypertrophy narrows the left ventricular outflow tract and contributes to left ventricular outflow tract obstruction. The subepicardial coronary arteries are usually normal.

Myocyte disarray with myocardial hypertrophy is appreciable at light microscopy. The myocytes display bizarre forms with herringbone pattern. Myocyte disarray is characteristic and occupies at least 20% of one or more tissue blocks. The interstitial arteries are thickened with smooth muscle proliferation.

Risk Stratification and Sudden Cardiac Death

Sudden cardiac death in HCM is most common in adolescents and young adults and has a predilection for early morning hours. Hypertrophic cardiomyopathy is the most common cause of SCD in competitive athletes. Major underlying mechanism of SCD in these patients is ventricular tachyarrhythmias. Several risk factors for SCD have been identified (**Table 4**). The incidence of SCD is 1% per year in patients with ≤1 risk factors and 3% per year in patients with ≥2 risk factors.

Table 4: Risk Factors for SCD in HCM

Proven Risk Factors
Aborted cardiac arrest
Spontaneous sustained ventricular tachycardia
Family history of premature SCD
Unexplained syncope
LV wall thickness ≥30 mm
Multiple repetitive non-sustained VT on Holter monitoring
Abnormal BP response to exercise

Treatment

Affected individuals should be counselled to avoid strenuous exercise and competitive sports. Symptomatic patients with LVOTO are first managed medically. Medical therapy consists of β-blockers, calcium channel blockers and disopyramide. β-blockers are used as first-line agents. They improve disabling symptoms and limit the latent outflow gradient provoked during exercise when sympathetic tone is high by virtue of their negative ionotropic and chronotropic effects. β-blockers lessen LV contractility and myocardial oxygen demand and possibly reduce microvascular myocardial ischaemia. β-blockers are less effective in patients with obstruction under basal condition. Disopyramide is an important agent in such patients. It decreases both resting and provocable gradients but has anticholinergic side effects which should be watched for. It should be avoided in patients with benign prostatic hypertrophy and glaucoma. Disopyramide can result in fast ventricular response if patient develops atrial fibrillation (AF) and should always be used with β-blockers. Angiotensin converting enzyme inhibitors increase outflow tract obstruction and should be avoided. Patients with obstructive HCM who remain symptomatic despite medical therapy can be treated with surgical myomectomy or alcohol septal ablation. In alcohol septal ablation, selective injection of 1 to 2 mL of absolute alcohol in first septal branch of left anterior descending artery causes infarction and necrosis of hypertrophied part of the septum and relieves outflow obstruction. Elderly patients with obstructive HCM or patients with mid-cavitary obstruction may benefit from dual chamber pacing with short AV delay. Patients with ≥1 major risk factors for SCD should be offered ICD. Prospective screening of family members of affected individuals should be done with yearly 12-lead ECG and echocardiography

beginning at 12 years of age and continued up to 18 to 21 years of age and thereafter every five years.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM), a less common form of cardiomyopathy, is characterised by increased ventricular stiffness that results in impaired diastolic filling of the ventricle. The systolic function remains normal in early stages of the disease process. The ventricular wall thickness is either normal or increased depending on the underlying aetiologies.

Aetiology

Restrictive cardiomyopathy can occur in an idiopathic form or as part of specific disorders (**Table 5**). Idiopathic RCM is most common (50% of all cases) and can be familial with autosomal dominant mode of inheritance. Among the specific forms of RCM, amyloidosis is the most common outside the tropics. Endomyocardial fibrosis (EMF) is particularly common in the tropics.

Table 5: Secondary Causes of Restrictive Cardiomyopathy

Amyloidosis
Endomyocardial fibrosis
Sarcoidosis
Storage disorders: Haemachromatosis, Fabry's disease, Glycogen storage disorder
Drugs: Anthracyclines, Serotonin, Methysergide
Others
Gaucher's disease
Scleroderma
Hurler's syndrome
Hunter's syndrome
Pseudoxanthoma elasticum
Hyper-eosinophilic syndrome
Carcinoid heart disease
Metastatic cancer
Radiotherapy

Clinical Presentation

Patients with RCM can present with symptoms and signs of right or left ventricular failure. Right-sided symptoms and signs predominate in most patients. Left-sided involvement gives rise to dyspnoea on exertion, paroxysmal nocturnal dyspnoea and orthopnoea. Thromboembolic complications are common. Conduction blocks are common in amyloidosis and sarcoidosis whereas atrial fibrillation (AF) is seen in idiopathic form.

Physical examination reveals tachycardia. JVP is elevated with rapid 'x' and 'y' descents. Kussmaul's sign is present in some patients. Hepatomegaly, peripheral oedema and ascites are often present. Cardiovascular findings include third and fourth heart sounds and pansystolic murmurs of mitral and/or tricuspid regurgitation. Cardiomegaly is characteristically absent. It is important to accurately differentiate RCM from constrictive pericarditis (**Table 6**) which can present with similar findings but can be cured surgically.

Investigations

Electrocardiography shows non-specific ST- and T-wave abnormalities. There may be evidence of left ventricular hypertrophy, AF or conduction abnormalities. In amyloidosis, ECG may reveal low voltage in limb leads and normal or increased voltage in precordial leads. Chest X-ray may show evidence of atrial enlargement with pulmonary venous congestion. Cardiac size is within normal limits. Echocardiography reveals normal-sized ventricles with biatrial enlargement and evidence of atrioventricular valve regurgitation (**Figure 10**). Ventricular walls may be thickened in patients with infiltrative disorders and may show characteristic granular and sparkling appearance and thickened interatrial septum in amyloidosis (**Figure 10**). Doppler echocardiography reveals characteristic restrictive pattern of mitral inflow velocity (**Figure 11**). Cardiac catheterisation shows characteristic 'dip and plateau' configuration in ventricular pressure tracing. Endomyocardial biopsy may reveal specific causes of RCM like amyloidosis, sarcoidosis and storage disorders. CT chest for pericardial thickness and calcification should be done in every case to rule out constrictive pericarditis.

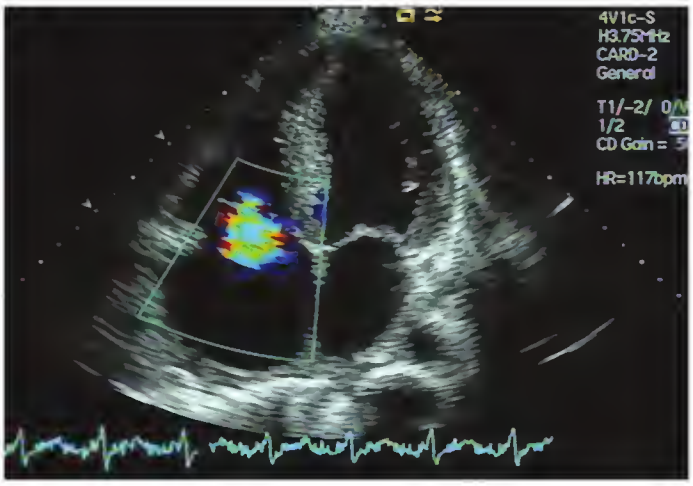


Figure 10: 2D echocardiographic image (apical 4-chamber view) showing dilatation of both the atria with normal-sized ventricles and mild tricuspid regurgitation in a patient with amyloidosis. Note the granular and sparkling appearance of interventricular septum.

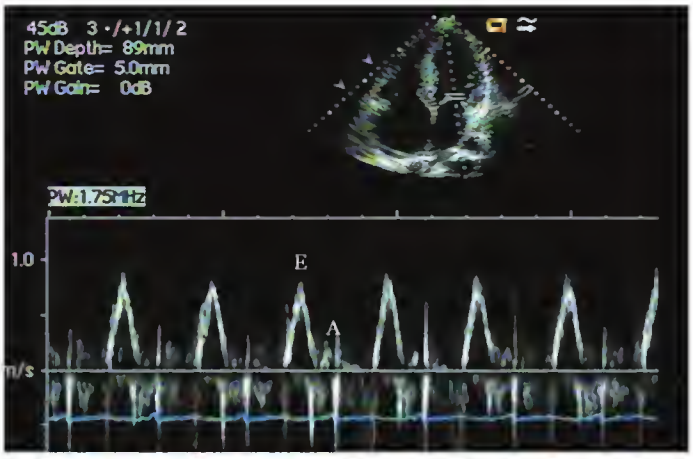


Figure 11: Pulse wave Doppler interrogation of mitral inflow velocities showing restrictive LV filling pattern (E > A) in a patient with RCM.

Pathology

Based on pathological involvement, RCM can be divided into two groups—with predominant endocardial involvement, or myocardial involvement. Conditions causing predominant endocardial involvement include EMF, Loeffler's endocarditis, carcinoid heart disease, metastatic cancers, radiation and drugs. Conditions with predominant myocardial involvement include idiopathic RCM, infiltrative disorders (amyloidosis, sarcoidosis) and storage disorders (haemachromatosis, Fabry's disease).

Table 6: Differentiating Restrictive Cardiomyopathy from Constrictive Pericarditis

	Restrictive Cardiomyopathy	Constrictive Pericarditis
Physical Examination		
JVP	Kussmaul's sign may be present	Kussmaul's sign usually present
Pulsus paradoxus	Absent	Present in one-third of cases
Apical impulse	Prominent	Usually not palpable
S2	Loud with narrow splitting	Wide split
S3	Present	Absent
Pericardial knock	Absent	Present
Murmur of MR/TR	Common	Uncommon
Electrocardiography	Conduction blocks common	Conduction blocks uncommon
Chest X-ray	No cardiomegaly; no pericardial calcification; signs of pulmonary venous congestion present	Pericardial calcification may be seen
2D-Echocardiography		
Posterior wall flattening in mid/late diastole	Absent	Present
Septal bounce	Absent	Present
Atrial enlargement	Marked	Mild
Pericardial thickness	Normal (<2 mm)	Increased
Doppler Echocardiography		
Significant respiratory variation in mitral (>25%) and tricuspid inflow velocities (>40%)	Absent	Present
Hepatic-vein diastolic flow reversal	More in inspiration	More in expiration
MR/TR	Common/Moderate-to-severe	Uncommon/Mild
Catheterisation		
Difference between LVEDP and RVEDP	>5 mm Hg	≤5 mm Hg
RV systolic pressure (RVSP)	>50 mm Hg	<50 mm Hg
RVEDP/RVSP	<one-third	>one-third
Endomyocardial Biopsy	Abnormal; may reveal aetiological diagnosis	Usually normal
CT/MRI	Pericardium usually normal	Pericardium is thickened

Characteristic gross examination findings in EMF and Loeffler's endocarditis include diffuse mural thrombi in ventricles obliterating the apices. In amyloidosis, the heart appears tan, firm and rubbery (**Figure 12**).

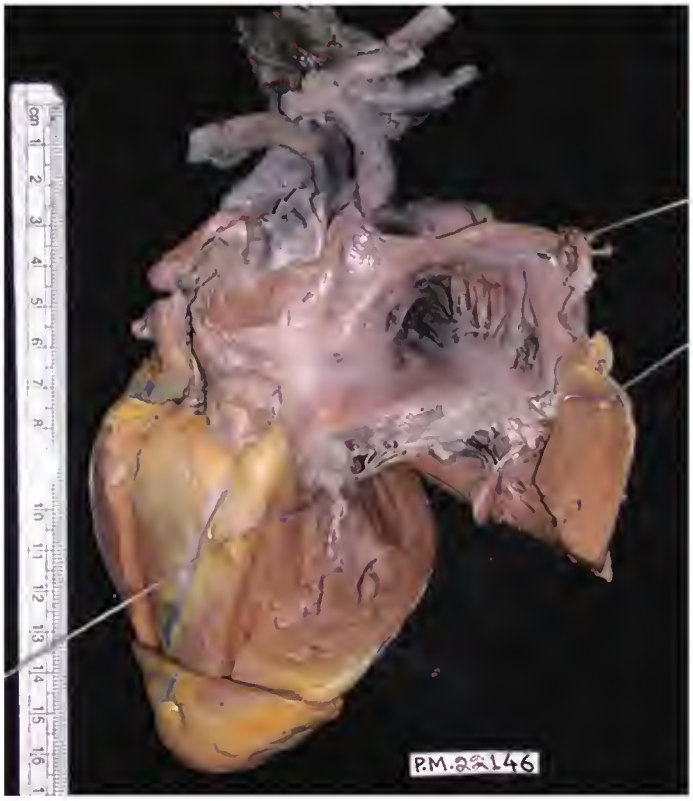


Figure 12: Gross photograph showing normal-sized left ventricle with tan, firm and rubbery myocardium and dilated left atrium in a patient with amyloidosis.

Microscopically, Loeffler's endocarditis is characterised by eosinophilic necrotising myocarditis. Amyloid deposits appear as hyaline eosinophilic material surrounding myocytes in the interstitium. This material is congophilic and gives apple green birefringence on polarised light (**Figure 13**).

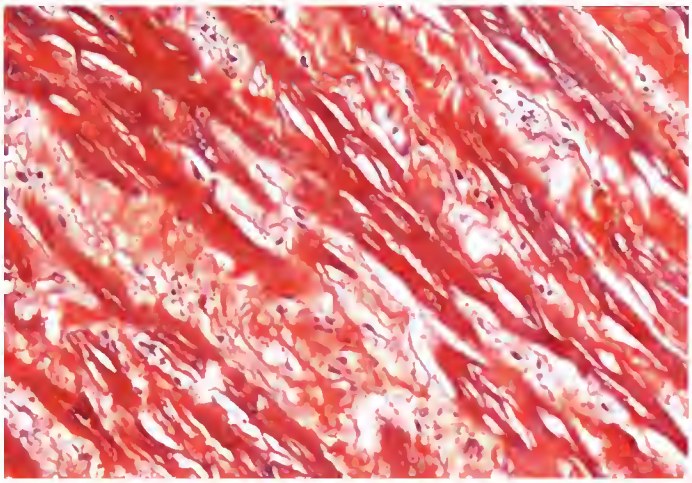


Figure 13: Microphotograph showing amyloid material deposited in the interstitium and myocytes (Congo Red X 140).

Treatment

Diuretics are used to treat pulmonary and systemic venous congestion. Atrial fibrillation is poorly tolerated due to loss of atrial contribution to ventricular filling and rapid ventricular response. Attempt should be made to maintain sinus rhythm by electrical cardioversion or anti-arrhythmic drugs. Digoxin should be used with caution in patients with amyloidosis due to its arrhythmogenic potential. Patients with AF, valvular

regurgitation and low ejection fraction are at increased risk of thromboembolism. They should be treated with oral anticoagulation. Patients with conduction blocks may require pacemaker implantation. ICD is indicated in patients with sustained ventricular arrhythmias.

Therapies for secondary forms of RCM are tailored to the underlying aetiologies—chemotherapy and autologous stem cell transplantation for amyloidosis, enzyme replacement therapy for Fabry's disease, iron chelation for haemachromatosis and immunosuppressive therapy for sarcoidosis.

Prognosis

Prognosis in RCM is variable depending on the underlying aetiology. RCM secondary to amyloidosis has poor prognosis with a median survival of less than two years. Idiopathic RCM has intermediate prognosis with five years survival of 64%.

Endomyocardial Fibrosis

Endomyocardial fibrosis (EMF) is characterised by fibrotic thickening of the endocardium and obliteration of right, left or both the ventriclular cavities. The disease has predilection for involvement of apices and inflow portion of the ventricles resulting in atrioventricular (AV) valve regurgitation. Right ventricular involvement is most common followed by left ventricular and biventricular involvement. Endomyocardial fibrosis is common in Brazil, Uganda, Nigeria, Ivory Coast and Kerala in Southern India. Several hypotheses have been proposed to explain the aetiology of EMF. They include hyper-eosinophilia, excessive consumption of plantains rich in serotonin, excessive consumption of cassava tubers which are rich in vitamin D, or a diet rich in thorium and deficient in magnesium (geochemical hypothesis). Endomyocardial fibrosis differs from other forms of RCM by the presence of marked cardiac enlargement due to AV valve regurgitation. Echocardiography reveals aneurysmal atria and small ventricles with apical fibrosis and cavitary obliteration. Intra-atrial thrombi and AV valve regurgitation are common findings. Endo-cardiectomy ± AV valve repair or replacement is the surgical treatment of choice in patients with advanced disease. Mild cases are treated conservatively with diuretics and digoxin.

OTHER SPECIFIC FORMS OF CARDIOMYOPATHY

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is characterised by development of left ventricular systolic dysfunction and symptoms of heart failure between the last month of pregnancy and the first five months postpartum. Incidence rates vary from 1 in 1,485 to 1 in 15,000 live births. Proposed aetiopathogenesis include myocarditis, abnormal immune response to pregnancy, nutritional deficiencies, abnormal prolactin levels and maladaptive response to the haemodynamic stresses of pregnancy. Peripartum cardiomyopathy is more common with advanced maternal age, multiparous state, multiple gestation, obesity, black race and pre-eclampsia. Clinical presentation and treatment are similar to that in DCM. Dopamine agonist, bromocriptine has shown encouraging results in pilot studies. Mortality is 25% to 50%. Fifty per cent of patients experience resolution of symptoms with normalisation of chamber dimensions and systolic function. Patients with persistent LV systolic dysfunction are at increased risk of death in subsequent pregnancy and should be advised to avoid pregnancy.

Alcoholic Cardiomyopathy

Long-term alcohol consumption is an important cause of dilated cardiomyopathy accounting for 3.8% of all cases. Alcohol is a myocardial toxin which causes myocyte apoptosis and changes in many aspects of myocyte function ultimately leading to chamber enlargement and systolic dysfunction. Asymptomatic alcoholic cardiomyopathy is seen in patients consuming >90 g of alcohol a day for >5 years. Patients who continue to drink develop symptoms of heart failure. Treatment includes standard heart failure therapy and abstinence from alcohol. Prognosis of alcoholic cardiomyopathy patients with abstinence is similar to idiopathic DCM whereas patients who continue to drink fare worse.

Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia or cardiomyopathy (ARVD/C) is a familial cardiomyopathy, mainly affecting the right ventricle (RV). Most common mode of inheritance is autosomal dominant. It is characterised by fibrofatty replacement of the myocardium. The disease typically affects inflow, apical, and outflow portions of the RV ('triangle of dysplasia'). Sudden cardiac death due to arrhythmias originating from right ventricle is the most common mode of presentation. Progressive right heart failure develops in late stages of the disease. Echocardiography and MRI form the main stay of diagnosis. Fatty replacement of RV myocardium can be reliably detected by MRI. Therapeutic options in patients with ARVD/C include β-blockers, anti-arrhythmic drugs, or an ICD. Patients with progressive right or biventricular systolic dysfunction are treated with standard therapy for heart failure.

Tako-Tsubo Cardiomyopathy

Tako-tsubo cardiomyopathy is characterised by transient apical ballooning of left ventricle and masquerades as an acute coronary syndrome. Ninety per cent of cases involve post-menopausal women. In majority of cases, symptoms are precipitated by physical or emotional stress. Catecholaminergic surge is incriminated in the pathophysiology of the disease. Presentation is with chest pain and dyspnoea, ST-segment elevation on ECG and elevated cardiac enzymes. Echocardio-graphy shows akinetic/hypokinetic apical portion of LV with hyper contractile basal regions. The shape of LV resembles an octopus pot ('tako-tsubo'). Coronary angiography reveals normal coronaries. Treatment is supportive and prognosis is good.

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12.29 Diseases of the Pericardium

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INTRODUCTION

The pericardium is a fibrous sac surrounding the heart, the thicker, outer parietal pericardium and an inner, thinner visceral layer. The two layers are separated by small amount of pericardial fluid (25 to 50 mL) produced by the visceral pericardium. It is an ultrafiltrate of the plasma and is resorbed by the lymphatics. The pericardium prevents friction between the heart and surrounding structures, acts as a mechanical and immunological barrier, and limits distention of the heart thereby maintaining a relatively fixed maximal heart volume.

Only the lower two-third of the parietal pericardium is sensitive to pain, the pain sensation being carried by the phrenic nerves. Inflammation of the pericardial layers is usually caused by infection (viral, bacterial, etc.), but can also have a non-infectious aetiology. Chronic inflammation with fibrosis and calcification can lead to a rigid, thickened and calcified pericardium, with progression to pericardial constriction. The most common forms of pericardial diseases include acute and recurrent pericarditis, isolated pericardial effusion with or without cardiac tamponade, and constrictive pericarditis.

PERICARDITIS

Pericarditis is inflammation of the pericardium with or without an associated pericardial effusion.

It can be of three types:

1. Acute (dry or effusive) pericarditis
2. Recurrent pericarditis
3. Chronic (effusive, adhesive, or constrictive)—lasting three months or more.

Aetiology

Pericarditis has a vast array of causes that can be separated into infectious and non-infectious categories. While in west idiopathic causes account for a greater number of cases, with viral infections being the most frequent cause; in the developing countries, tuberculosis accounts for 60% to 80% of the acute pericarditis (dry or effusive). Non-infectious pericarditis can be subdivided into immunoreactive, neoplastic, traumatic and metabolic causes. Some of the common causes are listed in **Table 1**.

ACUTE PERICARDITIS

Acute pericarditis may be either dry or effusive. Bread and butter pericarditis is another name given to dry pericarditis because of the typical appearance when the two layers are separated. Effusive pericarditis involves presence of fluid in excess of 50 mL in the pericardial cavity. Pericardial effusion may be transudate (hydropericardium), exudate, pyopericardium or haemopericardium, or a combination of these.

Clinical Features

Symptoms

Most patients with acute pericarditis experience sharp retrosternal chest pain, but in some cases it may be asymptomatic. Pericardial pain is usually worse with inspiration and when supine, and is relieved by sitting forward. Typically, the pain is referred to the scapular ridge, presumably due to irritation of the phrenic nerves, which pass adjacent to the pericardium. Dyspnoea can occur with acute pericarditis but is common with large pericardial effusions. Patient may experience constitutional symptoms like fever, bodyache, malaise, joint pain, and anorexia.

Signs

Inspection of the praecordium is normal but on palpation pericardial rub may be felt in left parasternal area and apex of the heart. The characteristic sign of acute pericarditis is the 'pericardial rub' heard on auscultation. It is a high-pitched, to-and fro-scratchy sound, heard both in systole and diastole. It is best audible in the third, fourth and fifth left intercostal spaces near the sternal edge, though the location may change with the position of the patient. It is better heard when the patient sits up, leans forward and is heard louder if the diaphragm of stethoscope is pressed harder to the chest wall. Sometimes only the systolic or the diastolic component may be heard and so the rub can be mistaken for a murmur.

Table 1: Aetiology of Pericarditis

Idiopathic or non-specific pericarditis	
Infections	Bacterial, tuberculous, viral (coxsackie, influenza, HIV, etc.), fungal, rickettsial, mycoplasma, leptospiral, listeria, parasitic and others
Vasculitis and connective tissue disease	Rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus, scleroderma, giant-cell arteritis, polymyositis (dermatomyositis), Behçet's syndrome, familial Mediterranean fever and others
Diseases in adjacent structures	Myocardial infarction, aortic dissection, pneumonia, pulmonary embolism, empyema
Metabolic disorders	Uraemia, dialysis-related, myxoedema
Neoplastic disorders	Primary: Mesothelioma, sarcoma, fibroma, lipoma and others Secondary (metastatic or direct spread): Lung carcinoma, lymphoma, carcinoid and others
Trauma	Direct: Pericardial perforation (penetrating injury) and cardiac injury (cardiac surgery, percutaneous procedures) Indirect: Radiation, non-penetrating chest injury
Association with other syndromes	Post-myocardial and pericardial injury syndromes, inflammatory bowel disease, Loffler syndrome, Stevens-Johnson syndrome, giant-cell arteritis, hypereosinophilic syndromes, acute pancreatitis, others

The pericardial rub arises from the inflamed visceral and parietal layers of the pericardium rubbing together but most patients with acute pericarditis (including those with audible rubs) have at least a small pericardial effusion. The pericardial friction rub can be differentiated from a pleural rub, which is absent during held respiration, whereas the pericardial rub is unaffected.

Diagnosis

The diagnosis of acute pericarditis is based on three simple criteria—typical pericardial chest pain, pericardial friction rub and typical electrocardiographic changes. The echocardiographic finding of pericardial effusion, which is not an accepted diagnostic feature, is justified considering that it is a confirmatory finding when present (**Table 2**).

Investigations

Patients with acute pericarditis usually have evidence of systemic inflammation, i.e. leucocytosis, elevated erythrocyte sedimentation rate, and increased C-reactive protein. Troponin levels may also be elevated in acute pericarditis due to some involvement of the myocardium by the inflammatory process.

Electrocardiography

Early in the course of acute pericarditis, the ECG typically shows diffuse ST elevation in association with PR-segment depression (**Figure 1**). The ST elevation is usually present in all leads except for aVR, but in post-myocardial infarction pericarditis the changes may be more localised. Classically, the ECG changes of acute pericarditis evolve through 4 progressive stages shown in **Table 2**.

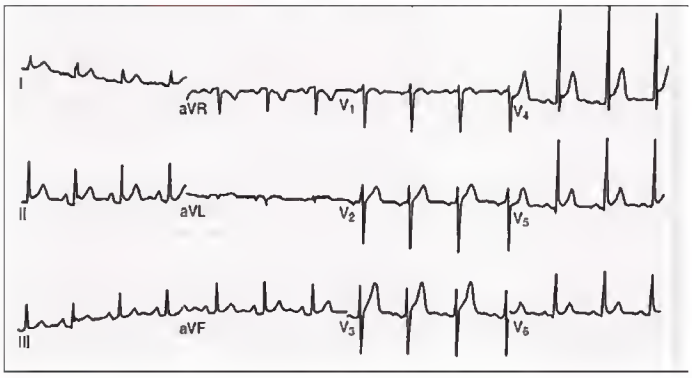


Figure 1: ECG in acute pericarditis. Diffuse ST segment elevation with PR segment depression.

Table 2: Diagnostic Pathway in Acute Pericarditis

Diagnostic Measure	Characteristic Findings
Auscultation	Pericardial rub
ECG	Stage I, diffuse ST segment elevation and PR segment depression
	Stage II, normalisation of the ST and PR segments
	Stage III, widespread T wave inversions
	Stage IV, normalisation of the T waves
Echocardiography	Pericardial effusion
Blood Analysis	Raised ESR, CRP, LDH, leucocytes (inflammation markers)
	Troponin I, CK-MB (markers of myocardial involvement)
Chest X-ray	Ranging from normal to 'water bottle' shape
	Performed primarily to reveal pulmonary or mediastinal pathology

Echocardiograhy

Echocardiography usually demonstrates at least a small pericardial effusion or it may be normal.

Prognosis

Prognosis depends on the aetiology of acute pericarditis. Acute benign or idiopathic forms have an excellent prognosis, while the uraemic pericarditis is usually a harbinger of death. Pericarditis due to rheumatic fever also has a good prognosis.

Treatment

Treatment for pericarditis should be targeted towards the specific aetiology but most cases are idiopathic or viral, so an empirical therapy is required. Empirical therapy in form of NSAIDs or aspirin is the first-line approach and mainstay of treatment. Anti-tubercular and antibiotic treatment should be instituted whenever required along with supportive therapy in the form of salicylates and corticosteroids to bring about early relief and to prevent formation of adhesions. Symptomatic treatment for the relief of fever and pain may be provided with analgesics. Rest and avoidance of physical activity are useful adjunctive non-pharmacologic measures that should be adopted until active disease is no longer evident, especially in case of rheumatic pericarditis.

PERICARDIAL EFFUSION

Pericardial effusion occurs when fluid accumulates in the intrapericardial space. It can occur with or without evidence of inflammation and pericarditis. Idiopathic aetiology is less common in patients with isolated pericardial effusion (**Table 3**).

Pathology

Under normal conditions, the space between the parietal and visceral pericardium contains only a small amount of fluid, usually up to 50 mL or less. In pericardial effusion, the quantity may vary from 200 mL to well over a litre. The fluid may be an exudate or a transudate or may contain blood, pus or chyle.

Clinical Features

Symptoms

They are essentially the same as those of acute pericarditis, but the dyspnoea may be more marked. Dyspnoea is thought to be due to compression of the lungs and bronchi and also due to encroachment on the intrathoracic space. Leaning forward may relieve this dyspnoea. This is because the fluid then gravitates forwards and downwards, exerting lesser pressure on the lungs and bronchi. If the effusion is large and produces sufficient pressure on the bronchi and oesophagus, it may result in a dry hacking cough, hoarseness of the voice and difficulty in swallowing.

Signs

On inspection, a cyanotic tinge may be observed in large effusions. Examination of the heart reveals the apex beat to be either weakly palpable or it may not be palpable at all. Bulging of the praecordium and the xiphisternum may be seen. There are very few or no palpable precordial pulsations.

Percussion of the heart reveals an increase in the area of the cardiac dullness especially on the left-side. Percussion of the back reveals an area of dullness in the left infrascapular region with bronchial breathing and aegophony (Ewart's sign). This is due to a compression of the base of the left lung. On auscultation, the heart sounds are muffled. A pericardial rub may be occasionally heard, though it tends to disappear with the accumulation of fluid (**Table 3**).

Table 3: Pericardial Effusion: Salient Features

Silent praecordium
Tachycardia
Ewart's sign
Muffled heart sounds

CARDIAC TAMPONADE

Cardiac tamponade is a medical emergency and its diagnosis is of major clinical importance. It has been described as 'an impaired diastolic filling of the ventricles due to raised intrapericardial pressure as a result of fluid accumulation in the intrapericardial space'.

Aetiology

Pericardial disease of almost any aetiology can produce cardiac tamponade by effusion accumulation and increased intrapericardial pressure. The most common causes are idiopathic, malignancy, tuberculosis, radiation, myxoedema, post-cardiotomy and lupus.

Haemodynamics

Cardiac tamponade occurs when fluid accumulation in the intrapericardial space is sufficient to raise the pressure surrounding the heart to the point where cardiac filling is altered. Ultimately, compression of the heart by a pressurised pericardial effusion results in markedly elevated venous pressures and impaired cardiac output producing shock. Because of its lower pressures, the right heart is most vulnerable to compression by a pericardial effusion, and abnormal right heart filling is the earliest sign of a haemodynamically significant pericardial effusion.

The increased pericardial pressure in cardiac tamponade accentuates the interdependence of the cardiac chambers as the total cardiac volume is limited by the pericardial effusion. The volume in any cardiac chamber can only increase when there is an equal decrease in the volume in other chambers. Because the total intrapericardial volume is fixed by the effusion, the increased inspiratory right ventricular filling crowds the left ventricle and impairs its filling (**Figure 2A**). Thus, in tamponade, left heart filling occurs preferentially during expiration when there is less filling of the right heart. The small normal respiratory variation in left ventricular stroke volume and systolic arterial pressure is markedly accentuated in cardiac tamponade, resulting in the clinical finding of 'paradoxical pulse'. Owing to decreased cardiac output a compensatory tachycardia ensues. Eventually, the systemic pressure falls (**Figure 2B**).

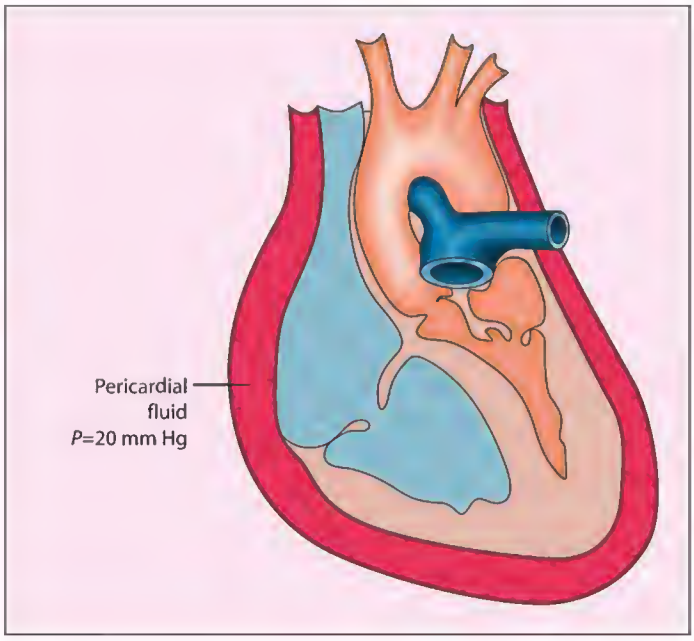


Figure 2A: Schematic illustration of leftward septal shift with encroachment of left ventricular volume during inspiration in cardiac tamponade.

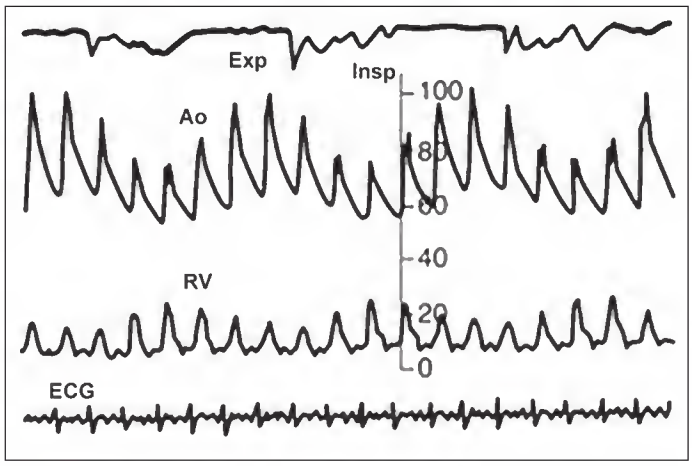


Figure 2B: Respiration marker and aortic and right ventricular pressure tracings in cardiac tamponade. A paradoxical pulse and marked, 180-degree, out-of-phase respiratory variation exists in right- and left-sided pressures.

Clinical Features

Symptoms

Cardiac tamponade is a treatable cause of cardiogenic shock that can be rapidly fatal if unrecognised. Patients with impending or early tamponade are usually anxious and may complain of dyspnoea and chest pain. Other symptoms include cough, fatigue and presyncope. With progression, patient presents with shock, altered mental status and pulseless electrical activity.

Signs

Cyanosis may be present and the patient usually sits up and leans forward or may assume a knee-chest position. Cardiac tamponade is suspected in a patient who runs a rapid downhill course and exhibits the tetrad of rising venous pressure, fall in arterial pressure, small quiet heart and tachycardia.

The increased venous pressure is usually apparent as jugular venous distension. The X-descent is typically the dominant jugular venous wave with little or no Y-descent. The heart sounds are classically soft or muffled; especially if there is a large pericardial effusion. The hallmark of cardiac tamponade is a paradoxical pulse. A paradoxical arterial pulse with a diminution in the volume during deep inspiration is quite characteristic of large effusions. This may be further corroborated by the use of a sphygmomanometre, i.e. reduction of >10 mm Hg in systolic pressure during inspiration.

Investigations for Pericardial Effusion and Cardiac Tamponade

General investigations for pericardial effusion and cardiac tamponade include routine blood counts and ESR. There may be leucocytosis and neutrophilia and the sedimentation rate may be high.

Electrocardiography

ECG can be normal or non-specific ST-T-wave changes are seen, total electrical alternans is seen in large effusions and tamponade (**Figure 3**). Bradycardia and electromechanical dissociation are diagnostic of end-stage tamponades.

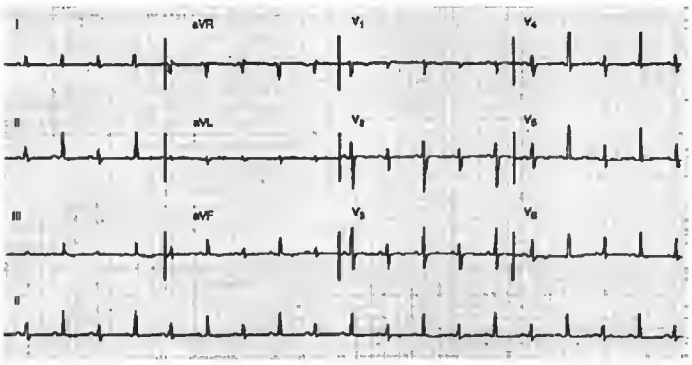


Figure 3: Total electrical alternans seen in large pericardial effusion and cardiac tamponade.

X-ray

In pericardial effusion, the cardiac silhouette will be increased in size. Enlarged cardiac silhouette with clear lungs on chest radiograph is very characteristic of large pericardial effusion (Money Bag appearance) (**Figure 4**). The individual chamber and blood vessel contours are lost.

Echocardiography

Echocardiography is an important part of the evaluation in patients with pericardial effusion and cardiac tamponade. The most important finding is the separation of the two pericardial layers by an 'echo-free' space. Small pericardial effusions are only seen posteriorly. Pericardial effusions large enough to produce cardiac tamponade are almost always circumferential (both anteriorly and posteriorly).



Figure 4: Enlarged cardiac silhouette with clear lung field in large pericardial effusion.

Echocardiography reveals the size of effusions:

1. Small (echo-free space in diastole <10 mm)
2. Moderate (at least >10 mm posteriorly)
3. Large (>20 mm)
4. Very large (>20 mm with compression of the heart)

In cases of gross effusion, the heart assumes a 'swinging' effect, wherein the heart seems to oscillate within the pericardial sac. Echocardiography also provides information on the significance of the pericardial effusion. In the presence of cardiac tamponade, there is diastolic collapse of the free walls of the right atrium and/or right ventricle (**Figures 5 and 6**). The collapse is exaggerated during expiration when right heart filling is reduced. Right atrial collapse is more sensitive for tamponade, but right ventricular collapse lasting more than one-third of diastole is a more specific finding for cardiac tamponade. On echo Doppler study, there can be marked reciprocal respiratory variation in mitral and tricuspid flow velocities reflecting the enhanced ventricular interdependence that is the mechanism of the paradoxical pulse.

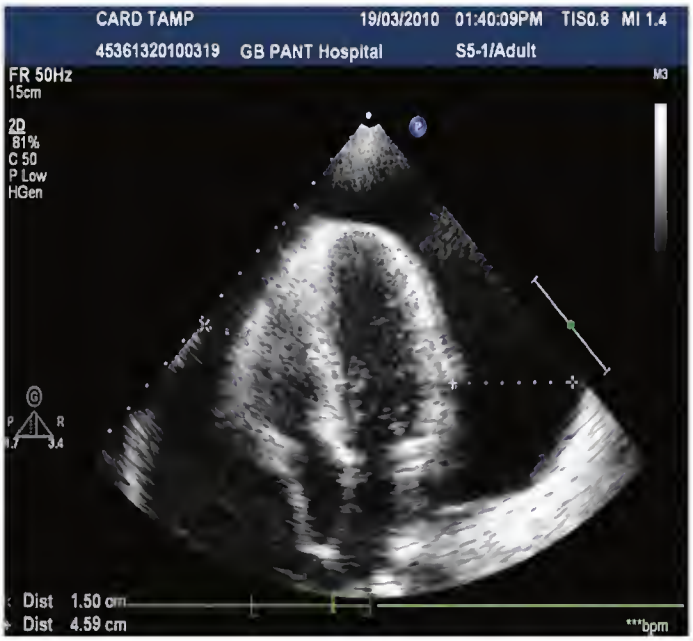


Figure 5: Echocardiography showing circumferential pericardial effusion with RA collapse (White or red arrow).

Diagnostic and Therapeutic Pericardiocentesis

Aspiration of the pericardial fluid will not only confirm the diagnosis but also help in detection of the aetiology. The aspirated fluid should be analysed and sent for bacteriological culture and sensitivity tests. If there is no haemodynamic compromise and the diagnosis can be established by other means, pericardiocentesis may not be necessary but it is generally advisable in patients with very large pericardial effusions (>20 mm on echocardiography), even in the absence of tamponade. It must be recognised that pericardiocentesis will not yield a diagnosis in most patients and, therefore, the reason for draining large effusions is to avoid potential progression to tamponade.

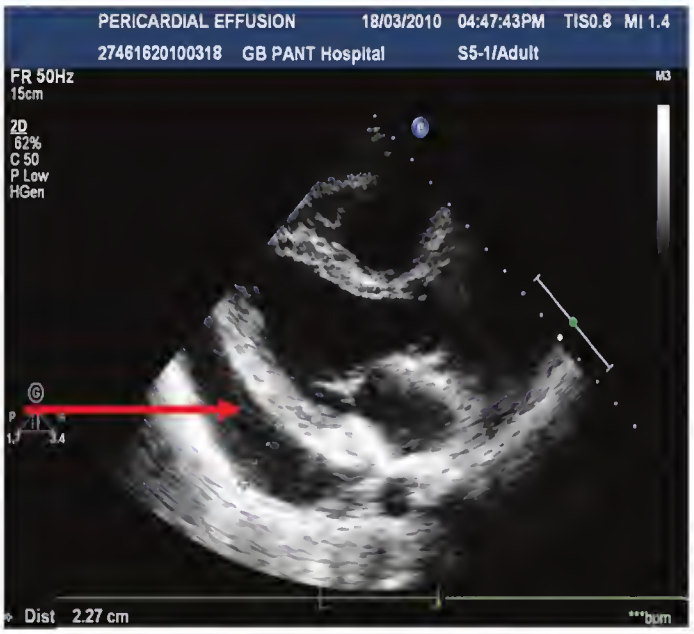


Figure 6: Echocardiography showing large posterior pericardial effusion (Red arrow).

Other Investigative Procedures

Computerised axial tomography and magnetic resonance imaging also help, especially when echocardiography does not reveal good images due to pulmonary disease.

Prognosis

This depends on the aetiological factor. Tuberculous pericardial effusion very often results in chronic constrictive pericarditis. Pericardial effusion in uraemia and neoplasms are harbingers of death. Purulent pericardial effusion, if not treated vigorously, may prove fatal.

Treatment

The treatment of pericardial effusion is two-fold; treatment of the aetiological factor and treatment of the effusion.

The treatment of cardiac tamponade is drainage of the pericardial effusion. Medical management is usually ineffective and should be used only while arrangements are being made for pericardial drainage. Fluid resuscitation may be of transient benefit if the patient is volume depleted. The use of inotropic agents is usually ineffective because there is already intense endogenous adrenergic stimulation.

PERICARDIOCENTESIS

Pericardiocentesis is the aspiration of the pericardial fluid for therapeutic as well as for diagnostic purposes. Indications for pericardiocentesis are: cardiac tamponade, diagnosis of the aetiology of pericardial effusion and introduction of drugs into the pericardial cavity (when indicated).

Procedure

Pericardiocentesis can be performed either using fluoroscopic (cardiac catheterisation laboratory) or preferably in the intensive care unit, under echocardiographic guidance. There are various sites for aspiration but the two commonest sites used are the subxiphoid and the left fifth intercostal space. The subxiphoid approach is the much preferred route, as one can aspirate fluid even in the case of small effusions. This route is extrapleural and avoids the coronary, pericardial, and internal mammary arteries. It is prudent to drain the fluid in stepped amounts of less than 1 litre at a time to avoid acute right ventricular dilatation.

The feasibility of pericardiocentesis is high (>93%) in patients with anterior effusion more than 10 mm, while the rate of success is only 58% with small, posteriorly located effusions. The most serious, but rare, complications are lacerations/perforations of the myocardium and the coronary vessels. In addition, patients can experience air embolism, pneumothorax, arrhythmias (usually bradycardia), and puncture of the peritoneal cavity or abdominal viscera.

If the fluid withdrawn is found to be purulent or there is large effusion then an indwelling pigtail catheter is left in pericardial cavity for drainage of residual or reoccurring effusion later on. Along with this, appropriate antibiotic therapy should be instituted.

SPECIAL FORMS OF PERICARDITIS

1. **Idiopathic Pericarditis**

   As the name suggests, the cause of this type of pericarditis is not known, though it is presumed to be viral. It affects all age groups and presents with fever, bodyache and chest pain. Pericardial effusion develops in about 75% of the cases.

   Treatment consists essentially of rest and analgesics. If pain is very severe and the effusion does not subside, then corticosteroids may be given. Very rarely, constrictive pericarditis may ensue.

2. **Rheumatic Pericarditis**

   This is seen in cases of acute rheumatic fever and is characterised by tachycardia, chest pain and fleeting joint pains. Usually, it is dry pericarditis ('bread and butter' pericarditis) but pericardial effusion may occur. There is complete regression with treatment and no sequelae are seen.

3. **Uraemic Pericarditis**

   Two forms of pericarditis have been described in renal failure:

   (a) Uraemic pericarditis

   Fibrinous inflammation with adhesions between the thickened pericardial membranes ('bread and butter' appearance) caused by the high degree of azotemia in advanced renal failure before dialysis is started or shortly, thereafter. This is seen usually in the terminal stages of uraemia. The pericarditis is of the dry type.

   (b) Dialysis-associated pericarditis

   Patients on maintenance haemodialysis, and occasionally with chronic peritoneal dialysis caused by inadequate dialysis and/or fluid overload.

   Most patients with uraemic pericarditis respond within 1 to 2 weeks to haemo or peritoneal dialysis, with resolution of chest pain and reduction of the pericardial effusion. To avoid intrapericardial haemorrhage, heparin-free haemodialysis should be used.

4. **Post-Infarction Pericarditis**

   Pericarditis may occur 'early' or be 'delayed' (Dressler's syndrome) after myocardial infarction. Early pericarditis occurs in the first few days of a transmural myocardial infarction, although early thrombolytic treatment has decreased its incidence. Dressler's syndrome occurs from

one week to several months after myocardial infarction and is considered to be an autoimmune phenomenon.

Aspirin, up to 650 mg every four hours for 2 to 5 days, has been successfully used to treat post-infarction pericarditis. Other nonsteroidal agents risk thinning the infarction zone. Corticosteroid treatment is used for refractory symptoms but can delay infarction healing.

5. Tuberculous Pericarditis

This is possibly the commonest cause of pericarditis and pericardial effusion in India. It is even more common after the advent of HIV infection and AIDS. Infection occurs through neighbouring structures, e.g. lungs, bronchi, lymph nodes or by blood-borne infection.

The patient may have vague complaints of fever, malaise, evening rise in temperature, loss of weight, etc. There may be no cardiac manifestations initially but later on, chest pain, cough and dyspnoea may appear due to an increase in the size of the effusion.

Aspiration of the fluid reveals either straw-coloured or blood-tinged exudative fluid. A systematic, multiple diagnostic approach is essential, e.g. sputum cultures, analyses of pericardial effusion by acid-fast staining, mycobacterial culture or radiometric growth detection (BACTEC-460), adenosine deaminase (ADA), pericardial lysozyme, and PCR for *Mycobacterium tuberculosis*. High ADA (>40 U/L) in pericardial effusion is diagnostic for tuberculous pericarditis (93% sensitivity, 97% specificity). The absolute criteria for diagnosis are the identification of *Mycobacterium tuberculosis* in the pericardial fluid or tissue, and/or the presence of caseous granulomas in the pericardium. However, pericarditis in proven extracardiac tuberculosis is strongly suggestive of a tuberculous aetiology. PCR is as sensitive (75% vs. 83%), but more specific (100% vs. 78%) for tuberculous pericarditis than ADA. Very often, even on a very close search, no evidence of tuberculosis may be found anywhere in the body.

Tuberculous pericarditis should be promptly treated with a combination of antitubercular drugs according to standard protocols. Prednisone should be administered along with antituberculous drugs as it reduces the host reaction to mycobacterial infections, minimises exudation, fibrin deposition, and proliferation of tuberculomas and may decrease symptoms and signs. However, despite combination therapy, many patients develop constriction and if untreated, it is one of the commonest causes of constrictive pericarditis in India.

6. Purulent Pericarditis

This is due to infection of the pericardium by organisms like the *Staphylococcus, Streptococcus, Pneumococcus, Meningococcus and Haemophilus*, etc. The infection may be either blood-borne, extension of an intrathoracic infection or from outside as in cases of stab wounds.

Patient presents with high-grade fever and appears very toxic. If the effusion accumulates very rapidly it may result in cardiac tamponade. Pericardial fluid aspirate should undergo urgent Gram's, acid-fast, and fungal staining followed by cultures for aerobes and anaerobes. Purulent effusions have significantly lower fluid glucose concentrations than non-infectious effusions.

Purulent pericarditis is an absolute indication for pericardial drainage and rinsing of the pericardial cavity, combined with high doses of systemic antibiotic treatment. A combination of antistaphylococcal antibiotic and aminoglycoside, followed by tailored antibiotic treatment according to the results of pericardial fluid and blood cultures, is mandatory.

7. Viral Pericarditis

This is a common cause of pericarditis and is clinically difficult to differentiate from idiopathic pericarditis. Viral pericarditis can be caused by direct viral attack (enterovirus, adenovirus, cytomegalovirus (CMV), Ebstein-Barr virus, herpes simplex virus, influenza virus, parvo B19, hepatitis C virus, HIV, etc.), the immune response or both. Initial presentation is the syndrome of acute pericarditis, often resolving within two weeks but may progress to pericardial effusion which may be serous, suppurative, or haemorrhagic.

The diagnosis depends on the demonstration of rising titers of specific antibodies in the serum. A four-fold rise in serum antiviral antibodies is suggestive but not diagnostic *per se*. In most patients, pericardial viral infection is self-limiting and no specific treatment is necessary.

8. Neoplastic pericarditis

Neoplastic pericarditis is also an important specific diagnosis to rule out in patients with pericarditis. It is responsible for about 5% of unselected cases of acute pericarditis and may metastasise to the pericardium, with the most common being lung and breast cancer and lymphomas. Lung cancer is the commonest malignancy giving early invasion of lymph nodes and thus being easily responsible for pericardial effusion. Primary tumours of the pericardium are less common.

9. Haemopericardium

Accumulation of blood in the pericardial cavity usually occurs after rupture of a cardiac chamber (after myocardial infarction), coronary artery or a dissecting aneurysm. Rarer causes include scurvy, neoplasms and leukaemia. Pericardial tamponade may occur and need drainage.

10. Pneumopericardium

Air in the pericardial cavity may result from stab wounds, perforation of an air-containing organ into the pericardium, by gas-forming organism or by introduction of air into the pericardial cavity. An X-ray of the chest reveals the presence of gas in the pericardial cavity. This usually does not require treatment, but the underlying cause requires treatment.

CHRONIC CONSTRICTIVE PERICARDITIS

Chronic constrictive pericarditis (CCP) is defined as a dense and rigid thickening of one or both layers of the pericardium with adhesions resulting in compression of the heart with impairment in the diastolic filling.

Aetiology

The most common causes include:

- Tuberculosis
- Idiopathic and viral pericarditis
- Chest irradiation
- Collagen vascular disease

- Post-cardiotomy
- Malignancy

In developing countries with high prevalence of tuberculosis, it is most common cause of CCP. In India, tuberculosis is responsible for nearly two-third of the cases of CCP. The aetiology of CCP in the western world has undergone a significant change, with tuberculosis reported in only 0% to 1% of cases. However, with emergence of the AIDS pandemic these numbers are likely to increase again. The leading identifiable causes of CCP in western world are following cardiac surgery and radiation therapy, besides viral pericarditis, but such cases are possibly missed in India.

Pathophysiology

The pericardium undergoes thickening and calcification (normal thickness of the pericardium is 3 to 5 mm). The thickened pericardium forms an encasement of the heart and is unable to stretch during diastole. The unyielding pericardium impairs the diastolic relaxation of the heart and thereby diminishes venous filling of the right ventricle. However, there is no interference with systole. The pathophysiological hallmark of pericardial constriction is equalisation of the end-diastolic pressures in all four cardiac chambers. This occurs because the filling is determined by the limited pericardial volume, not the compliance of the chambers themselves. Initial ventricular filling occurs rapidly in early diastole as blood moves from the atria to the ventricles without much change in the total cardiac volume. However, once the pericardial constraining volume is reached, diastolic filling stops abruptly. This results in the characteristic dip and plateau of ventricular diastolic pressures. The stiff pericardium also isolates the cardiac chambers from respiratory changes in intrathoracic pressures, resulting in Kussmaul's sign (**Figures 7 and Figures 8A and B**).

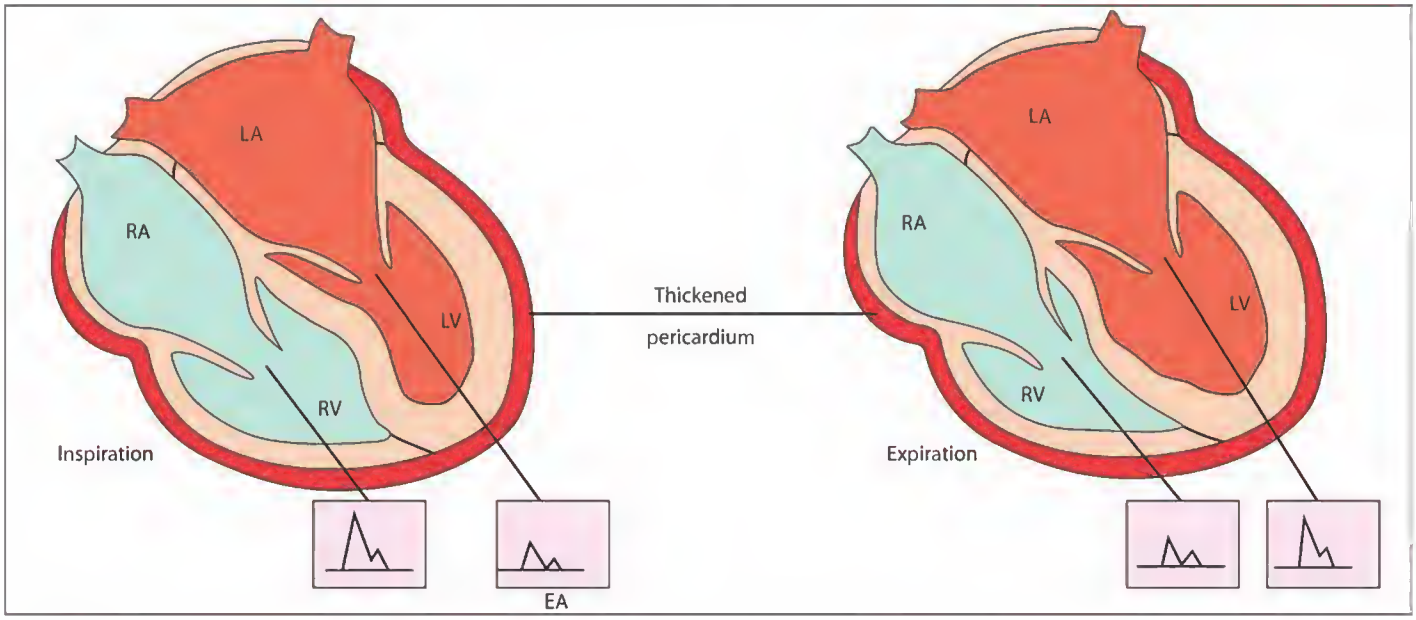
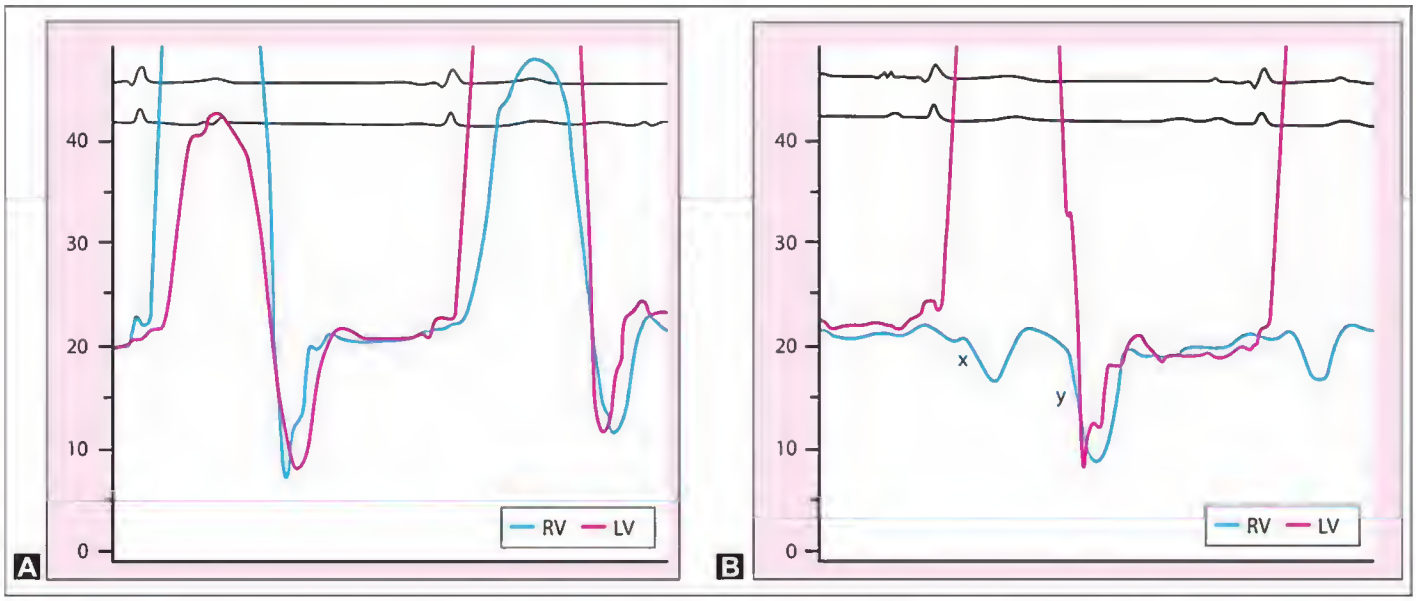


Figure 7: Schematic representation of transvalvular and central venous flow velocities in constrictive pericarditis. During inspiration, the decrease in left ventricular filling results in a leftward septal shift, allowing augmented flow into the right ventricle. The opposite occurs during expiration.

EA = Mitral inflow; LA = Left atrium; LV = Left ventricle; RA = Right atrium; RV = Right ventricle



Figures 8A and B: Pressure recordings in a patient with constrictive pericarditis. (A) Simultaneous right ventricular (RV) and left ventricular (LV) pressure tracings with equalisation of diastolic pressure, as well as 'dip and plateau' morphology. (B) Simultaneous right atrial (RA) and LV pressure with equalisation of RA and LV diastolic pressure. The y-descent is prominent.

Due to the reduction in venous filling, the stroke output falls and to compensate for decreased cardiac output the heart rate rises. The systemic pressure rises because of the limited cardiac filling. The liver and spleen are enlarged and the capsule is thickened as a consequence of chronic congestion.

Haemodynamics in cardiac tamponade and constrictive pericarditis are compared in **Table 4**.

Symptoms and Signs

The commonest complaint is the distension of the abdomen due to ascites and swelling of the feet. The next common complaint is dyspnoea and fatigue.

On inspection, the neck veins are engorged, even in the standing position. A deep 'y' descent (Frederick's sign) is seen. JVP is raised and increases/fails to decrease during deep inspiration (Kussmaul's sign). The arterial pulse is of a low volume and the rhythm may be irregular indicating the presence of atrial fibrillation.

Table 4: Haemodynamics in Cardiac Tamponade and Constrictive Pericarditis

	Tamponade	Constriction
Paradoxical pulse	Usually present	Present in ≈ 1/3
Equal left/right filling pressures	Present	Present
Systemic venous wave morphology	Absent *y* descent	Prominent 'y' descent (M or W shape)
Inspiratory change in systemic venous pressure	Decrease (normal)	Increase or no change (Kussmaul's sign)
'Square root' sign in ventricular pressure	Absent	Present

Inspection of the praecordium reveals a 'quiet' heart and prominent veins may be observed all over the chest. A systolic retraction at the apex may be observed. On palpation, a diastolic 'tap' or 'shock' may be palpated. It is due to the rapid filling of the right ventricle. The characteristic finding on auscultation is the 'pericardial knock'. This is a sound due to rapid filling of the ventricle in the early rapid filling phase. It occurs about 0.08 to 0.12 second after the second sound in contrast to the normal third sound, which occurs a little later (0.13 to 0.16 s). The heart sounds are normal and usually no murmur is heard.

Examination of the abdomen reveals an enlarged, smooth and tender liver. The chief finding in the abdomen, however, is the presence of ascites which is massive and out of proportion to the oedema on the legs (which may be minimal). It tends to refill very rapidly after aspiration.

Investigations

Electrocardiography

The ECG findings are not characteristic but include low voltage of the QRS complexes, flattening or inversion of the T-waves and occasionally atrial fibrillation.

X-ray

The heart size is usually normal or slightly smaller. The characteristic finding of constrictive pericarditis, however, is the calcification of the pericardium. This is best seen in the left lateral or oblique views and is present in about two-thirds of the cases. In the lateral view, if the calcification is seen in the entire pericardium (i.e. anteriorly, inferiorly and posteriorly) the appearance is termed as 'egg-shell pericardial calcification' (**Figure 9**). The lung fields remain clear. Severe venous engorgement may lead to pleural effusions.

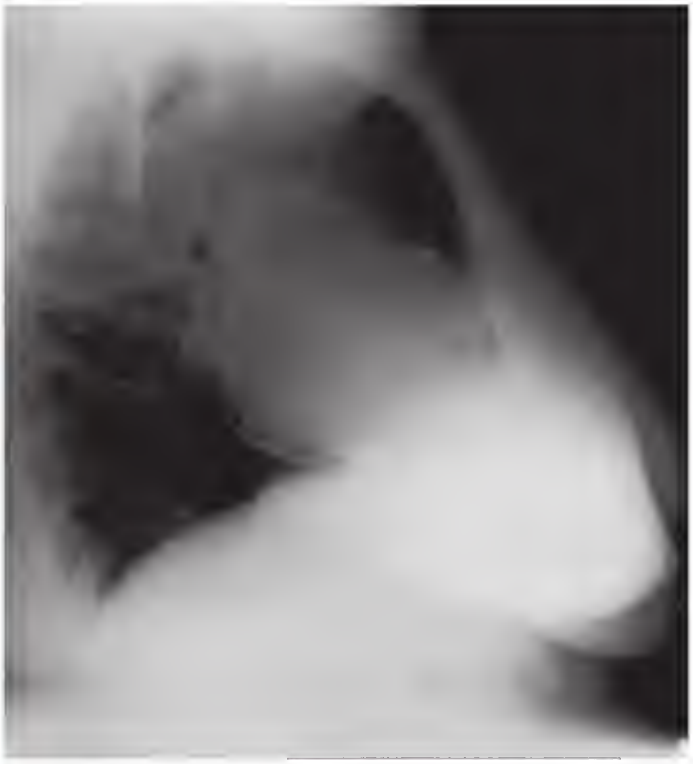


Figure 9: Chest radiograph showing marked pericardial calcifications in a patient with constrictive pericarditis.

Echocardiography

This is perhaps the most useful investigation to diagnose constrictive pericarditis. The presence of thickened and/or calcified pericardium clinches the diagnosis. However, increased pericardial thickness can be missed on a transthoracic echocardiogram. Transoesophageal echocardiography is more sensitive and accurate in determining pericardial thickness.

Doppler echocardiography is important in the evaluation of patients with suspected pericardial constriction. Doppler echocardiography frequently demonstrates restricted filling of both ventricles with a rapid deceleration of the early diastolic mitral inflow velocity (E wave) and small or absent a wave. In addition, there is substantial (>25%) respiratory variation of the mitral inflow velocity (**Figure 10**). There are signs of systemic venous congestion such as dilation of hepatic veins and distension of the inferior vena cava with lack of inspiratory collapse (**Figure 11**).

CT/MRI

CT and MRI allow accurate measurement of pericardial thickness and some assessment of diastolic filling patterns. Ancillary diagnostic findings include conical narrowing of the ventricles, atrial dilation, and enlargement of the inferior vena cava, hepatomegaly, and ascites. Excellent overall sensitivity (88%), specificity (100%), and accuracy (93%) have been reported for MRI. Increased pericardial thickening may not always imply

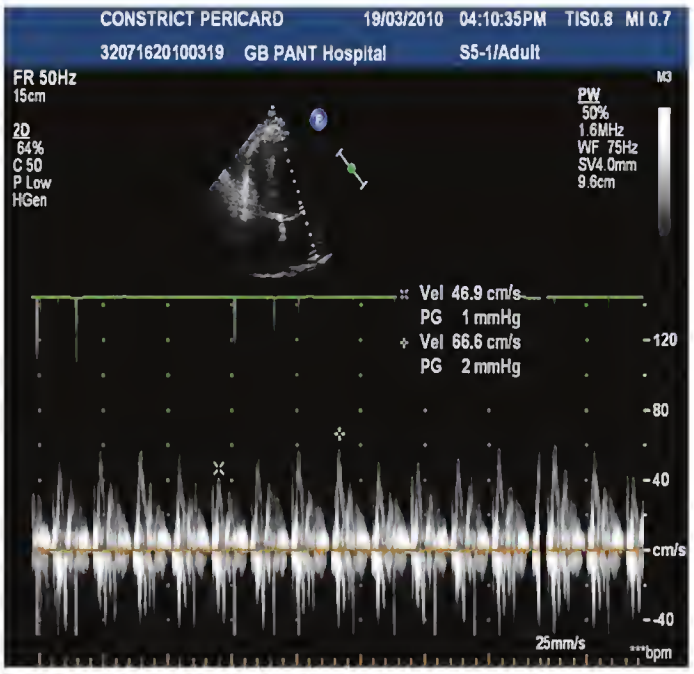


Figure 10: Doppler echocardiography showing respiratory variation of the mitral valve inflow velocity in a case of constrictive pericarditis.

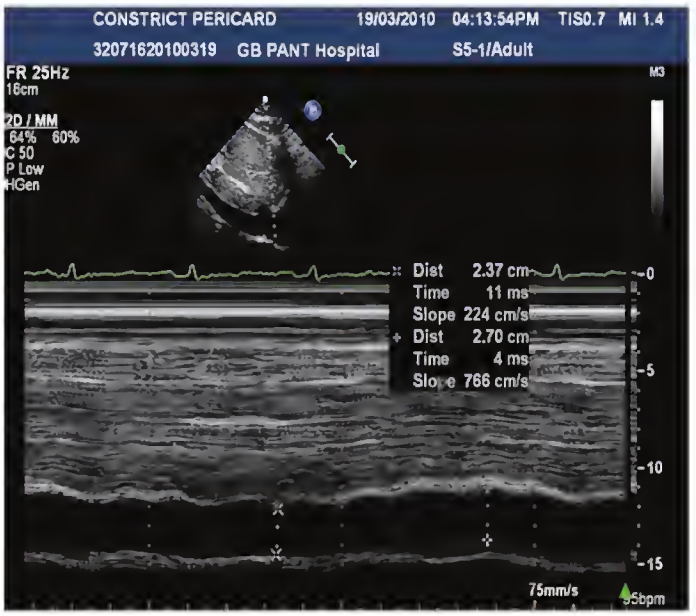


Figure 11: M mode showing dilated IVC with minimal respiratory variation in a case of constrictive pericarditis.

constriction, and conversely, constrictive pericarditis can present with normal pericardial thickness on non-invasive imaging, histology, or a combination of these.

Cardiac catheterisation

Though a very valuable tool in the diagnosis of constrictive pericarditis in the past, it is no longer used routinely after the advent of echocardiography. Catheterisation reveals an elevation of the right ventricular end-diastolic pressure, characterised by an early diastolic 'dip' and a late diastolic 'plateau'. The end-diastolic pressure is high due to incomplete relaxation of the ventricle during diastole and is usually more than one-third of the systolic pressure. The right atrial tracings show a 'M' or 'W' shaped pattern corresponding to the right ventricular pressures. It has been observed that the pulmonary wedge pressure, pulmonary artery diastolic pressure, right ventricular end-diastolic pressure, mean right atrial pressure and superior vena cava pressures tend to be equal or near-equal in constrictive pericarditis.

Diagnosis

The combination of pulsus paradoxus, neck vein signs, ascites and pericardial 'knock' should pose no difficulty in the diagnosis. However, similar clinical pictures may be seen in tricuspid valvular diseases, restrictive cardiomyopathies and cirrhosis of the liver. Tricuspid valvular defects have their characteristic murmurs, which increase in intensity on deep inspiration. Cardiomyopathies may be diagnosed on echocardiograms.

Prognosis

Without surgery the prognosis is poor. Long-standing cases of constrictive pericarditis develop hypoproteinaemia due to a protein-losing enteropathy. They also develop a myocardial failure (probably due to fibrosis) which does not respond to digoxin, even after pericardiectomy.

Treatment

Medical management of constrictive pericarditis, especially in less severe cases, is aimed at relief of fluid overload with careful administration of diuretics and is at best, palliative. Surgical pericardiectomy remains the only definitive management and should be done before calcification and myocardial involvement progresses. However, if the cause is thought to be tuberculosis, then a few weeks on antituberculous drugs should precede the surgery. The results of surgery are very gratifying. Other aetiological causes should get their respective treatments.

CONCLUSION

Pericarditis remains a common disorder, particularly as a complication of modern treatments such as cardiac surgery, percutaneous interventions, and radiation therapy. Pericardial effusion and constrictive pericarditis are infrequent sequelae that can be diagnosed accurately in most cases by use of modern imaging methods. Cardiac tamponade, a medical emergency should be promptly diagnosed and managed with urgent pericardiocentesis. Management of uncomplicated pericarditis rests largely on NSAIDs with the addition of colchicine for relapses. Pericardial effusion can be managed percutaneously in most cases, whereas definitive treatment for constriction remains surgery.

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12.30 Surgical Management of Heart Disease

Muhammad Abid Geelani, Nikhil Prakash Patil

INTRODUCTION

The era of cardiac surgery was ushered more than a century ago when Ludwig Rehn of Frankfurt operated to relieve cardiac tamponade and sutured a stab wound to the right ventricle in September 1896. However, 'open-heart surgery' as we know it today began a little over fifty years ago with the development of an artificial 'heart-lung machine' by John H. Gibbon, Jr. On May 6, 1953, the Gibbons-IBM oxygenator was successfully used for total substitution of the heart and lungs for 26 minutes, enabling correction of an atrial septal defect, and thereby the world's first successful open heart surgery. Since then, technological advances and myocardial protection techniques evolving continuously over the last six decades have enabled routine conduction of successful and complex cardiac surgery, totally bypassing the vital function of lungs and heart for hours to days.

Cardiac surgery broadly encompasses: surgery for congenital heart disease; surgery for valvular heart disease; surgery for ischaemic heart disease and cardiac transplantation and related heart failure surgery.

SURGERY FOR CONGENITAL HEART DISEASE

Congenital heart disease (CHD) has an overall incidence of 0.8%. The patient population is diverse. Defects, presentation, diagnosis, treatment and outcome differ widely according to age of presentation and complexity of lesions. These can be broadly classified into acyanotic and cyanotic heart defects.

A. Acyanotic

- Increased pulmonary blood flow (Left to Right shunt)
  - Atrial septal defect
  - Ventricular septal defect
  - Patent ductus arteriosus
  - Partial anomalous pulmonary venous connection

  All these patients must be operated upon before school-going age, unless progressive pulmonary arterial hypertension supervenes, in which case, early surgery is indicated to prevent the development of Eisenmenger complex.
- Normal pulmonary blood flow
  - Aortic stenosis/bicuspid aortic valve
  - Mitral regurgitation
  - Coarctation of aorta
  - Mitral stenosis

B. Cyanotic (Right to Left shunt)

- Increased pulmonary blood flow
  - Truncus arteriosus
  - Single ventricle
  - Transposition of great arteries
  - Total anomalous pulmonary venous connection
  - Hypoplastic left ventricle
- Decreased pulmonary blood flow
  - Tetralogy of Fallot
  - Pulmonary atresia
  - Tricuspid atresia with pulmonary stenosis
  - Total transposition of great arteries with pulmonary stenosis
  - Ebstein malformation

All blue babies must be closely observed for cyanotic spells. Severe and frequent spells constitute an indication for urgent operation. Early surgery is preferred as there is always a risk of paradoxical embolism with its complications.

Surgery may be classified into:

- Palliative, e.g. Blalock-Taussig shunt (BT shunt), cavo-pulmonary shunt (Bi-directional Glenn shunt), pulmonary artery banding.
- Corrective, e.g. atrial/ventricular septal defect repair, ligation of patent ductus arteriosus, arterial switch for simple transposition of great arteries.

Conditions such as patent ductus arteriosus, coarctation of the aorta, atrial septal defect, partial atrioventricular canal and tetralogy of Fallot can now have corrective surgery with hospital mortality ranging from 0% to 5% depending upon the age at surgery and the complexity of the condition. Many complex conditions such as pulmonary atresia, transposition of the great arteries, tricuspid atresia and many other conditions previously considered inoperable are now being successfully treated with acceptable mortality and satisfactory long-term results.

SURGERY FOR VALVULAR HEART DISEASE

Acquired disease of heart valves can be treated by repair procedures or by replacement with an artificial prosthesis (**Figures 1 to 3**). The valves commonly affected are the aortic, mitral and tricuspid valves; the commonest pathologies are rheumatic and degenerative disease. Rheumatic heart disease, which has been practically eradicated from Western countries, continues to be a problem in South Asian countries. Rheumatic mitral stenosis (MS) without mitral regurgitation (MR) may initially be treated by balloon mitral valvuloplasty (BMV) or rarely with closed mitral valvotomy when BMV is not possible because of difficulty in percutaneous access to mitral valve, e.g. in inferior vena cava obstruction or inability to puncture the interatrial septum. But when echocardiography suggests unfavourable anatomy (Wilkins score > 8)* or when a left atrial clot is present, it is best to do as an open-heart procedure and

* A scoring system exists to grade the morphological changes in the mitral valve during assessment with echocardiography. This takes into account 4 characteristics; leaflet mobility, leaflet thickening, valve calcification and involvement of the subvalvular apparatus. The involvement is graded from 0-4. A total score of more than 8 is predictive of a low success post percutaneous mitral valvuloplasty.



Figure 1: Tilting disc mechanical valve (TTK Chitra valve).



Figure 2: Bileaflet mechanical valve.



Figure 3: Bioprosthetic valve (Pericardial).

repair/replacement of the valve may be indicated. Nowadays, BMV is done even in presence of left atrial appendage clot after giving anticoagulation therapy for 6 weeks. All patients in New York Heart Association (NYHA) functional class II or above, having dyspnoea, orthopnoea, severe pulmonary hypertension, left atrial clot, must be referred for percutaneous/surgical intervention.

Mitral regurgitation may be caused by degenerative changes in the leaflet, prolapse of the leaflets, rupture of chordae tendineae or due to annular dilatation or tethering of the subvalvular apparatus secondary to ventricular dilatation. In such cases, a repair procedure may be considered. This is usually combined with implantation of a flexible or rigid annuloplasty ring to support the repair. All patients in NYHA class II and above, having orthopnoea, severe pulmonary hypertension, gradually dilating left ventricle and falling ejection fraction (LVEF), must be referred for early surgical procedure for better outcome.

If a repair is not possible and mitral valve replacement is indicated, there is a wide choice of prosthetic and bioprosthetic valves available. Mechanical heart valves have evolved from a ball and cage design to the tilting disc valve to the bi-leaflet prosthesis. Currently, the bi-leaflet pyrolytic carbon low profile mechanical prosthesis is the most commonly used prosthesis as it has the advantage of central flow and excellent long-term results. The preservation of posterior leaflet with/without anterior chordal apparatus provides better long-term result as it maintains left ventricular geometry. Lifelong anticoagulation is mandatory for all mechanical heart valves to prevent thromboembolic complications. In spite of this, the incidence of thromboembolic complications is 1.5% to 2% per patient year. The alternative to the use of mechanical prosthesis is the use of bioprosthetic valves, which have a biological origin. These are generally stent-mounted porcine valves or pericardium treated with buffered glutaraldehyde to promote cross linkages between the collagen bundles. Anticoagulation is not essential for recipients of bioprosthetic valves after 6 weeks of surgery unless they are in atrial fibrillation. The main disadvantage of bioprosthetic valves is their limited durability; many of them degenerate and even calcify in 10 to 15 years time. The long-term durability of these prostheses have been improved by the use of proprietary anti-calcification treatment and by the development of valves constructed from glutaraldehyde-treated bovine pericardium mounted within a specially designed stent. The hospital mortality for mitral valve replacement for primary non-ischaemic mitral valve disease is between 2% and 7%. The survival rate following surgery is 65% to 80% at 5 years, 50% to 60% at 10 years, and 30% to 40% at 15 years from several reported series.

Most patients who need replacement of the aortic valve are in the older age group and have calcific aortic stenosis. Aortic regurgitation is either due to rheumatic heart disease causing fibrosis and shrinkage of the leaflets or due to annular dilation as in cystic medial necrosis or in aortic aneurysms and dissections. Aortic valve replacement has better early and late survivals than mitral valve replacement because of afterload reduction and low thrombogenicity in a high flow area. Small aortic root and patient-prosthetic mismatch is still a concern which leads to higher gradient across aortic valve and poor exercise tolerance. It is better to use stentless valves in the aortic position (autografts as in the Ross operation, homografts or xenografts) or root enlargement techniques in such situations. Enlarging left ventricle, syncope or angina in aortic valve disease warrant early surgery.

The tricuspid valve is generally treated with repair procedures and the implantation of annuloplasty rings rather than valve replacement as prosthetic valves do not function well in this relatively low pressure area.

If the patients are offered surgery during late stages of the disease, the results of valve replacement are adversely affected because of left ventricular dilatation, pulmonary hypertension and congestive heart failure with hepatic and renal dysfunction. Surgery for valvular heart disease is now standardised in Indian centres but problems of late referrals, cost, maintenance of optimal anticoagulation and proper follow-up are the limiting factors.

SURGERY FOR ISCHAEMIC HEART DISEASE

Coronary artery bypass grafting (CABG) is one of the procedures with the highest impact in the history of medicine. CABG is based on the underlying principle that the symptoms and clinical events of coronary artery disease (CAD) are related to stenotic coronary lesions that can be identified by angiography, and if those lesions are bypassed, then those symptoms and clinical events become less common. Surgical attempts at increasing blood flow to the ischaemic myocardium originated a century ago when Alexis Carrel anastomosed a carotid artery segment between the descending aorta and the left coronary artery in a dog, for which he was later awarded the Nobel prize. Three decades later, Arthur Vineberg started implanting the left internal mammary artery (LIMA) into the anterior myocardial territory of patients with CAD in order to increase arterial inflow and relieve angina, with some experiencing prolonged symptomatic improvement. Surgery on the coronary arteries was introduced clinically in 1958 by William Longmire, who reported on the use of endarterectomy in five patients operated without cardiopulmonary bypass (CPB). The first reported successful CABG operation took place in 1964 in Leningrad, where Vasilii Kolesov grafted a LIMA to the left anterior descending (LAD) artery without CPB. The world's first CABG program started 3 years later in Cleveland, as Favaloro began to routinely use reversed saphenous veins for aortocoronary grafting. CABG today constitutes the keystone of adult cardiac surgery, but novel surgical, percutaneous, and medical alternatives loom large on the horizon. Yet CABG is constantly evolving and remains the most durable means of revascularisation for patients with CAD. Although CAD is largely diagnosed by conventional coronary angiography, evolving less invasive techniques like cardiac CT angiography may become the diagnostic modality of choice in the future.

CABG is indicated in patients with chronic stable angina and left main coronary artery stenosis ≥ 50%, left main equivalent (i.e. proximal stenosis of at least 70% of the proximal LAD and circumflex), three-vessel disease [especially if left ventricular ejection fraction (LVEF) is less than 0.50], and one- or two-vessel disease with either a large myocardial area at risk on non-invasive testing or depressed LVEF.

CABG may also be indicated for symptomatic improvement in low-risk patients with significant CAD who do not fulfil the above criteria but experience disabling myocardial ischaemia or unacceptable lifestyle restrictions on maximal medical therapy. CABG is not preferred over PTCA in patients with one- or two-vessel disease not involving the proximal LAD and with only a small area of viable myocardium or no objective evidence of ischaemia on non-invasive testing.

Several studies have shown that emergent surgery for relentless unstable angina or non-Q wave MI in the context of failed or unfeasible percutaneous coronary intervention (PCI) is associated with an increase in peri-operative mortality compared with semi-urgent CABG, although surgical revascularisation may still be preferable to a conservative strategy. Consequently, an attempt should be made at stabilising these patients with maximal medical therapy (and in some cases the temporary use of an intra-aortic balloon pump) to allow surgery to be performed on a non-emergent basis with a lower operative risk.

Intravenous thrombolytic therapy and primary PCI have supplanted CABG as the first line of therapy for patients in the acute period of ST segment elevation MI. As a result, residual ongoing ischaemia and cardiogenic shock despite maximal non-surgical therapy now constitute the main indication for emergent CABG in acute MI patients. Other acute indications include failed thrombolysis and demonstration of a large myocardial territory at risk in combination with an unsuitable anatomy for PCI, a left main coronary stenosis, an LV failure with severe coronary stenosis outside the initial infarct area, significant valve disease, or a mechanical complication of MI.

PCI may occasionally result in intractable coronary dissection or plaque haemorrhage, threatened proximal occlusion with a large myocardial area at risk, loss of a foreign body in a crucial anatomical position, or coronary rupture. These complications are indications for immediate surgical intervention, but in-hospital mortality is high in these patients (10% to 14%) because of unfavourable selection factors such as haemodynamic compromise and severe impairment of the coagulation system. CABG should NOT be attempted on an emergency basis in stable patients in whom PCI has failed because of unsuitable anatomy or no-reflow state.

Conduit Selection

The choice of conduit is determined by the quality of available conduit, the suitability of the target vessels and the age and co-morbidity of the patient.

Internal mammary artery grafts

The internal mammary artery (IMA) is the best conduit available for CABG and provides short- and long-term survival benefits in all patients subgroups, including those 75 years of age or older. Use of the LIMA to graft the LAD (or a main target vessel on the left coronary circulation if the LAD is free of disease) should be performed except in exceptional circumstances such as pre-existing or iatrogenic damage to the LIMA, poor flow from severe spasm, injury, or dissection, involvement of the LIMA in providing collateral supply to the lower extremity, mediastinal irradiation (if other arterial conduits are available), and emergency CABG with cardiogenic shock.

The use of bilateral IMAs should be considered over single IMA grafting whenever, possible in young patients, as they may lead to lower reoperation rates, decreased late PCI rates, and long-term survival benefits. Relative contraindications to the use of bilateral IMAs include emergency operation, advanced age,

diabetes mellitus, obesity, and severe COPD for which the patient requires systemic steroid therapy.

Radial artery grafts

The radial artery likely constitutes, after the left and right IMA, the next best conduit for CABG. Radial artery harvest is contraindicated in the presence of insufficient collateral supply to the hand or Raynaud's syndrome, in patients with high manual demands such as professional musicians, in the very elderly (who have a high prevalence of radial arteriosclerosis), during emergency operations, and in patients who are likely to require postoperative vasopressors such as those with very poor LV function.

Saphenous vein grafts

Saphenous veins are known not to be the conduit of choice for CABG due to proven lower short- and long-term patency than IMAs. Nevertheless, the long saphenous veins are still used in the majority of CABG operations by a large number of surgeons for practical reasons. They are also particularly useful for specific situations. They constitute the most readily available CABG conduit, provide immediate and reliable coronary flow with a low propensity for spasm or flow compromise during low-output states, and provide a time-honoured means of coronary revascularisation during emergency procedures or in patients with severe co-morbidity and limited life expectancy in whom procedural simplicity, expeditiousness, and reliability are most desirable.

Other conduits

The gastroepiploic artery, short saphenous vein and inferior epigastric artery constitute additional available conduits that are rarely needed for primary revascularisation, but which may be useful as a last resort in patients with severe conduit shortage, e.g. redo surgeries.

Off-pump: CABG versus CPB

CABG can be carried out with CPB (on-pump) or without (off-pump: OPCABG). Many surgeons elect to perform CABG on pump, until recently, the advantages of a still, clear operating field, myocardial protection and haemodynamic and respiratory control, appeared to outweigh the disadvantages of CPB. However, recent improvements in methods of stabilising the heart have led to some institutions adopting OPCABG expecting to see lower morbidity and mortality. OPCABG appears to offer favourable outcomes, leading to reductions in postoperative atrial fibrillation, transfusion requirements, inotrope requirements, ventilation times, length of hospital and intensive care unit stay, and cost compared to on-pump coronary artery surgery. But, till date, no randomised trial has been sufficiently powered to detect the widely expected difference in death or stroke at 30 days or one year. Nevertheless, OPCABG is a suitable alternative to CPB in experienced centres. It should probably be the technique of choice in patients with porcelain (calcified) aorta, poor LV function, renal dysfunction, pulmonary dysfunction and advanced age or other co-morbidity.

SURGERY FOR HEART FAILURE

Heart Transplantation

Dr. Christiaan Barnard performed the world's first human heart transplant operation on 3 December 1967. The patient, Louis Washkansky, was a 54-year-old grocer, suffering from diabetes and incurable heart disease. Washkansky survived the operation and lived for eighteen days. However, he succumbed to pneumonia induced by the immunosuppressive drugs he was taking. Barnard later wrote, 'For a dying man it is not a difficult decision because he knows he is at the end. If a lion chases you to the bank of a river filled with crocodiles, you will leap into the water, convinced you have a chance to swim to the other side.' Though the first patient with the heart of another human being survived for only a little more than two weeks, Barnard had passed a milestone in a new field of life-extending surgery. Since then, nearly 60,000 of these operations have been done worldwide, including over a hundred in Indian centres. The main limiting factor is the availability of suitable donors and the logistics of the procedure. The prognosis for heart transplant patients has greatly increased over the past 20 years. With the current immunosuppressive therapy using anti-thymocyte globulin, corticosteroids and azathioprine or mycophenolate survival is now 80% at 1 year, 70% at 5 years and 50% at 10 years. After the 20% mortality during the first year, the yearly mortality is approximately 4% per year. These results can be achieved only if the patients are carefully followed-up and monitored with percutaneous myocardial biopsy at appropriate time depending upon the clinical progress and modification of the immunosuppressive therapy based on the results of myocardial biopsy. Tony Huesman was the world's longest living heart transplant recipient, having survived for 31 years with a transplanted heart (he died on August 10, 2009 of cancer)—the operation was performed in 1978 at Stanford University by American heart transplant pioneer Dr. Norman Shumway.

In patients with severe pulmonary vascular disease heart-lung transplantation may be indicated but this operation is technically more difficult to perform and to manage post-operatively, and carries significantly lower survival rates.

Cardiomyoplasty using latissimus dorsi muscle is not used anymore but Myosplint and its modification, which prevent dilatation of LV, are currently undergoing clinical trials.

The artificial heart, which is essentially a 'bridge to transplantation', at present holds a very promising future as externally rechargeable energy sources are in the final stages of clinical trials.

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12.31 Diseases of the Aorta

Manotosh Panja

INTRODUCTION

The aorta is composed of a thin intima, a thick media and a thin adventitia. The media is composed of laminated but intertwining sheets of elastic tissue in a spiral manner that gives it not only tensile strength but also distensibility and elasticity. The aorta is divided anatomically into thoracic and abdominal segments. The thoracic aorta is further divided into ascending, arch and descending segments, while the abdominal aorta consists of suprarenal and infrarenal segments. Aortic isthmus is the point where aortic arch joins the descending aorta. This is especially vulnerable to trauma as it is the junction of the mobile ascending aorta and arch and relatively fixed descending aorta. This is also the site for coarctation of the aorta. Other aortic anomalies could be right-sided aortic arch, double aortic arches and cystic medial degeneration as in Marfan's syndrome and acquired degeneration of the aortic wall secondary to ageing, arteriosclerosis, hypertension and specific inflammatory, infectious or autoimmune diseases.

AORTIC ANEURYSMS

Aortic aneurysm is a localised dilatation of the aorta having a diameter at least 1.5 times that of the expected normal diameter of that given aortic segment. A true aneurysm involves all the three layers of the aortic wall. It is produced by the progressive distension of the aortic wall that is weakened by the degeneration of the tunica media. Sometimes, there may be a pseudoaneurysm or false aneurysm, which is actually a well-defined collection of blood and connective tissue outside the vessel wall as a consequence of a contained rupture of the aortic wall.

Morphologically, an aneurysm is either fusiform or saccular. Fusiform aneurysm is more common. It is a symmetrical dilatation of the full circumference of the aortic wall. Saccular aneurysm on the other hand involves more localised dilation appearing as an outpouching of only a portion of the aortic wall.

Incidence

The post-mortem incidence of aortic aneurysm is 1% to 3%. There has been a gradual decline in the incidence of syphilitic aneurysms, but this has been offset by an increase in the atherosclerotic variety.

ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms (**Figure 1**) are far more common than thoracic aneurysms. They are 8 to 10 times more frequent in men than in women. Their incidence shows a rapid rise after 55 years in men and 70 years in women.

Aetiopathogenesis

These aneurysms are usually atherosclerotic. Very rarely they may be traumatic, congenital or myxomatous. Most are infrarenal and fusiform, varying in size from a few millimetre to ten centimetre. Only 2% to 5% are suprarenal. Absence of vasa vasorum in the infrarenal aorta coupled with atherosclerotic thickening of intima may jeopardise nutrient and oxygen supply to the media of this segment. This may hasten degeneration of tunica media in genetically predisposed subjects due to increased elastolytic activity and lead to aneurysm formation. Surprisingly, diabetes mellitus patients are not prone to development of abdominal aortic aneurysm.



Figure 1: Post-mortem specimen of abdominal aortic aneurysm. Bilateral renal artery stenosis with infrarenal aortic involvement.

Clinical Features

Symptoms

Backache, abdominal pain, limb oedema and venous congestion are common. Acute pain and hypotension secondary to rupture may occur.

Signs

There is palpable pulsatile mass in the abdomen, presence of peripheral vascular disease, signs of distal embolisation, and haemodynamic collapse.

Majority of the cases are asymptomatic and are detected on incidental examinations like abdominal X-ray or ultrasound.

Younger patients (50 years old or less) are more likely to be symptomatic. The most frequent complaint is a steady, gnawing pain in the hypogastrium or lower back, lasting for several hours or days at a time and not affected by movement. A pulsatile mass extending variably from the xiphoid process to the umbilicus may be felt. Stagnation of blood in the aneurysmal sac forms mural thrombus which may embolise to distal arteries leading to absence of femoral and lower limb pulses and bruits over affected arteries. Rarely, an expending aneurysm can compress inferior vena cava or one of the iliac veins to produce lower limb oedema and venous congestion.

The major risk of abdominal aortic aneurysm is its rupture. Expansion or impending rupture are heralded by sudden onset of new or worsening pain that is characteristically constant, severe, localised to back or lower abdomen and sometimes radiating to the groin, buttocks and legs. The pulsatile abdominal mass, if present already, may become tender on palpation. Abrupt onset of back pain and abdominal pain with tenderness, and hypotension characterises actual rupture, but this pathognomonic sign is present in only one-third cases. In 80% of the cases rupture occurs in the left retroperitoneum and is signalled by haematomas in the flanks and groin. Most of the remainder rupture into the peritoneal cavity, causing uncontrolled haemorrhage and result in abdominal distension. Rupture into the duodenum presents as massive gastro-intestinal haemorrhage. Rarely, it may rupture into inferior vena cava, iliac or renal vein producing haemodynamic collapse and acute high-output cardiac failure. Rupture is associated with high mortality; 60% die before any medical intervention and 50% of those survive after operative correction.

Diagnosis and Size Estimation

Aneurysm may be detected and their size estimated by physical examination, routine roentgenography, abdominal cross-sectional ultrasonography, digital subtraction angiography, abdominal aortic angiography, CT scan and MRI.

In about 70% of cases, plain X-rays show a curvilinear or linear rim corresponding to the aneurysm wall. In fact aneurysm usually presents as a paravertebral soft tissue mass. With rupture, there is distortion of the psoas muscle shadow and absence of gas in the bowel over the aneurysm. Abdominal ultrasound is the most easily available and inexpensive way of detecting an aneurysm and assessing its size, wall thickness and presence of thrombus. Aortography is a risky procedure and is used in selective pre-operative cases to assess suprarenal extent of the aneurysm, any associated iliofemoral disease and for defining renal and mesenteric arterial anatomy. It may underestimate aneurysmal size in the presence of non-opacified mural thrombus lining its wall. CT scan is an extremely accurate method for both diagnosing and sizing the abdominal aortic aneurysms. MR angiography is also a highly effective method in delineating aneurysm anatomy pre-operatively and it is safe alternative to aortography. Pre-operative aortography is largely replaced by CT scan and MRI now-a-days considering their non-invasive nature and high sensitivity and specificity.

Treatment

Medical therapy with beta-blockers slows the expansion of aneurysm although its efficacy is less in aneurysm of bigger size. Aneurysmectomy and replacement by a synthetic prosthesis, usually Dacron, is advised for all abdominal aortic aneurysms 6 cm in diameter or wider since three-fourth of them will rupture. Operative mortality is 4% to 6% in elective repair. The benefit of surgery for asymptomatic aneurysms 4 to 5 cm in size is not yet established. Complications of surgery include stenosis or occlusion of the prosthetic graft, false aneurysm formation, infection and rupture. Endovascular treatment in the form of percutaneously implanted expanding endovascular stents are new interventional options for the treatment of abdominal aortic aneurysms not suitable for surgery (older patients, patients at higher risk for surgery). Endoleaks (persistent residual flow in aneurysmal sac) are a major disadvantage with this option.

THORACIC AORTIC ANEURYSMS

Thoracic aortic aneurysms are divided according to anatomical location into ascending arch and descending aortic aneurysms, each differing in aetiology, natural history and therapy.

Ascending aorta aneurysms most often result from cystic medial necrosis. Other causes are Marfan's syndrome, syphilis, mycotic aneurysm secondary to aortic bacterial endarteritis and rarely atherosclerosis. Aortic arch aneurysms may be due to atherosclerosis, cystic degeneration, syphilis or other infections while descending aortic aneurysms are predominantly atherosclerotic. The basic pathogenetic mechanism is progressive dilatation of the aortic wall weakened by tunica media degeneration.

Clinical Manifestations

Forty per cent of the patients are asymptomatic and are diagnosed on incidental physical examination or X-ray. Symptoms reflect either a vascular consequence of the aneurysm or a local mass effect. Vascular consequences are aortic regurgitation and secondary congestive heart failure due to aortic root dilatation, myocardial ischaemia due to coronary artery compression by enlarged sinuses of Valsalva, rupture of sinus of Valsalva into the right heart producing continuous murmur with congestive heart failure and thromboembolism causing stroke, lower extremity ischaemia, renal infarction or mesenteric ischaemia. Local mass-effects depend on anatomical location. Ascending aortic aneurysm may cause superior vena cava syndrome due to compression of the superior vena cava. Arch aneurysms cause superior vena cava syndrome; tracheal or main stem bronchus obstruction leading to wheeze, cough, dyspnoea (may be positional), haemoptysis and recurrent pneumonitis. Descending aortic aneurysms may cause trachea or main stem bronchus compression, oesophageal compression producing dysphagia or recurrent laryngeal nerve compression producing hoarseness.

Steady, deep, boring and sometimes excruciating chest or back pain develop due to compression of intrathoracic structures or due to erosion of adjacent bone. Aneurysms eroding through the chest wall are visible as pulsating masses. The most serious consequence of thoracic aneurysm is rupture that is heralded by sudden increase in the intensity of pain. Rupture most commonly occurs into the left intrapleural space or the intrapericardial space and presents as hypotension. Next common site is the oesophagus that presents as life-threatening haematemesis. Thoracic aneurysm may also develop aortic dissection.

Diagnosis

Many thoracic aneurysms, except for smaller ones, are evident on chest X-ray. Transthoracic Echocardiography (TTE) is useful in the imaging of aortic valve and proximal aortic root. Transoesophageal Echocardiography (TEE) can help in assessment of aneurysm of ascending and descending aorta but it cannot visualise aneurysm of the arch. Contrast CT-scan and MR angiography are very accurate in detecting and sizing aneurysms. Aortography was a preferred pre-operative modality to define the anatomy of the aneurysm. However, as in the case of abdominal aorta, CT and MR angiogram are now often sufficient in most of the cases to define aortic and branch vessel anatomy. MR angiography is preferable to CT scanning when the aortic root is involved.

Treatment

Medical therapy is directed towards risk factor reduction and control of blood pressure. Aneurysmectomy and replacement by a prosthetic sleeve or composite graft-valve (in case of ascending aorta) is indicated for aneurysms 6 cm or larger; however, in case of Marfan's syndrome, bicuspid aortic valve or rapidly growing aneurysms, early surgery is indicated. Propranolol may be used to delay the surgery in smaller aneurysms. Surgical repair of arch aneurysms is particularly challenging with high incidence of stroke. Descending thoracic aneurysmectomy may produce post-operative paraplegia due to interruption of spinal cord blood supply. Transluminally placed endovascular stent grafts is an alternative approach for treating descending aneurysms in patients with higher risk for surgery.

DISSECTION OF THE AORTA

Aetiopathogenesis

Aortic dissection is initiated by entry of blood through an intimal tear into a degenerated tunica media of the thoracic aorta. The medial degeneration may occur due to classical cystic medial necrosis or connective tissue disorders like Marfan's or Ehlers-Danlos syndrome. The blood jet divides the media into two producing a false lumen. The inner portion of the dissected wall forms an intimal flap. The intimal flap may be pushed into the true lumen, by the false lumen distended with blood, or it may be torn open by the blood jet producing an exit site. Old age (50 to 70 years), female sex, pregnancy, hypertension, bicuspid or unicuspid aortic valve, giant cell arteritis, Noonan and Turner syndromes and cocaine abuse may predispose to dissection. Aortic dissection occurs at a rate of 5 to 10 cases per million population per year.

Classification (Figure 2)

DeBakey classification

Type I: Begins in the ascending aorta and extends to the descending aorta and arch.

Type II: Confined to the ascending aorta.

Type III: Originates in the descending aorta and extends distally or rarely, retrograde into arch and ascending aorta.

Stanford classification

Type A: All dissections involving the ascending aorta, regardless of the site of origin.

Type B: All dissections not involving the ascending aorta.

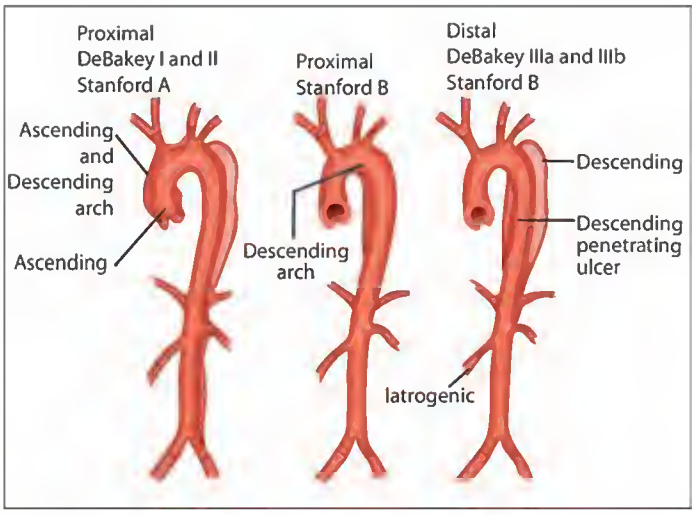


Figure 2: Schematic diagram of classification of aortic dissection.

Descriptive classification

Proximal: DeBakey types I and II or Stanford type A.

Distal: DeBakey type III or Stanford type B.

Proximal dissections are twice more common and more lethal than distal dissections.

Clinical Picture

A tearing, ripping or severe stabbing pain, from its initiation and with a tendency to migrate from its point of origin to other sites following the course of dissection is typically present in majority of cases except for those with chronic dissections. Severe pain from onset differentiates it from myocardial infarction. Anterior chest pain or neck, throat, jaw or face pain usually signifies ascending aorta involvement and inter-scapular or back, abdomen or lower limb pain that of descending thoracic aorta.

Obstruction of the branches by compression of the true lumen by the distended false lumen or by obstruction of the vessels orifices by a mobile intimal flap may produce pulse deficits, pseudohypotension, syncope, cerebrovascular accident, cardiac arrest or sudden cardiac death, ischaemic peripheral neuropathy and paraplegia. Pulse deficits and neurological manifestations are more common in proximal dissection. Hypertension is seen in 80% to 90% of distal dissection and hypotension is more common in proximal dissection.

Aortic regurgitation due to dilatation of aortic root and annulus, detachment of aortic leaflet or prolapse of a mobile intimal flap through aortic orifice is the characteristic of proximal dissection and results in congestive cardiac failure. The murmur has a musical quality and radiates along the right sternal border. Syncope without a focal neurological sign heralds rupture of a proximal dissection into pericardial sac producing cardiac tamponade or that of distal dissection into the intrapleural space.

Investigations

Anaemia may develop from significant haemorrhage or sequestration of blood in the false channel. A mild-to-moderate polymorphonuclear leucocytosis (10,000-14,000/mm^3) is common. Lactate dehydrogenase (LDH) and bilirubin levels are sometimes elevated. Serum glutamic oxaloacetic transaminase (SGOT) and CK-MB are usually normal, unless associated myocardial infarction develops along with

dissection. ECG abnormalities are particularly common in Stanford type A aortic dissections. ST depression is most common abnormality. Sometimes, patients present with inferior wall MI due to involvement of right coronary sinus. Chest X-ray may reveal widening of the aortic arch in 40% to 50% of cases, change in configuration of the aorta on successive X-ray, obliteration of the aortic knob with displacement of the trachea to the right, localised hump on the aortic arch and an increase in distance from intimal calcification to the outer edge of the aortic shadow of > 1 cm (calcium sign).

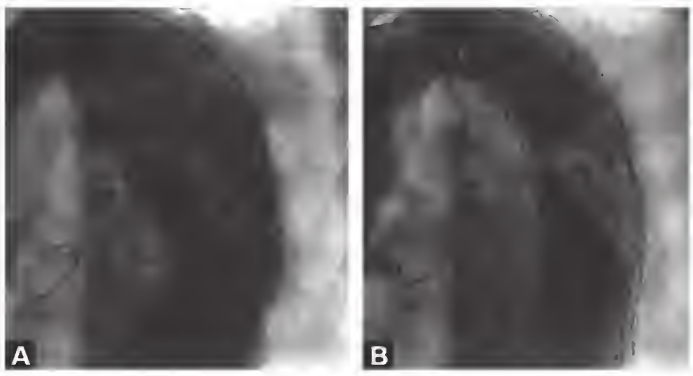
TTE is a useful tool for the diagnosis of ascending aortic dissections. However, it is limited by its inability to show the distal extent. TEE is highly sensitive and specific for evaluating proximal aortic dissection.

Development of helical CT with multiplanar and 3D reconstruction and CT angiography has made CT scan a highly sensitive (83% to 94%) and specific (87% to 100%) mode for diagnosis of aortic dissection. It is fast replacing the conventional angiography (**Figures 3A and B and Figure 4**) as a standard diagnostic test in many centres.

MRI although highly sensitive and specific it is used preferably for chronic aortic dissection and post surgical follow-up.

Treatment

Therapy is aimed at halting the progression of the dissecting haematoma. Without treatment 25% of the patients die within 24 hours, more than 50% within the first week, 75% within one month, and more than 90% within one year.



Figures 3A and B: Aortogram showing aortic dissection. (A) pre-stenting and (B) post-stenting.

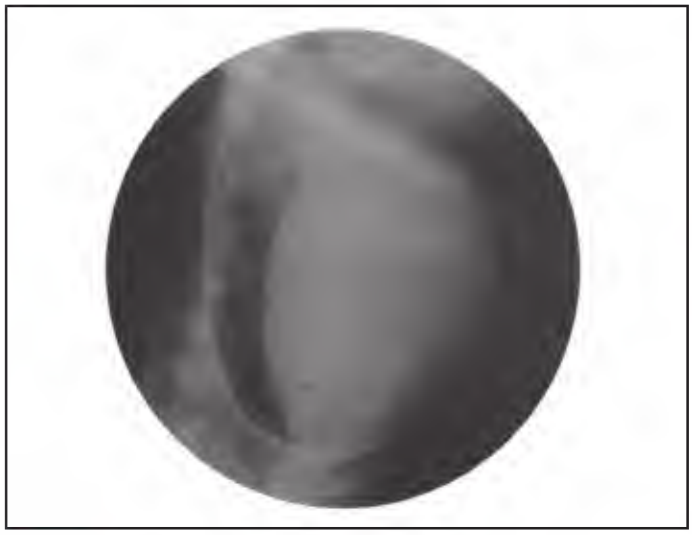


Figure 4: Aortogram showing dissection of aorta.

Early emergency treatment

All patients should be admitted immediately to an intensive care unit. Initial therapeutic goals are the elimination of pain and reduction of systolic blood pressure to 100 to 120 mm Hg with a potent vasodilator like sodium nitroprusside. Nitroprusside when used alone can cause increase in the dp/dt so it should be used with a beta-blocker.

Propranolol is used in incremental doses of 1 mg intravenous every five minutes until there is an evidence of satisfactory beta-blockade, usually indicated by a pulse rate of 60 to 80 beats/min. Labetalol and esmolol can also be used in this setting. Patients who have contraindication for beta-blocker therapy should be put on cardioselective calcium channel blockers. In chronic stable dissection propranolol is given orally in dose of 20 to 40 mg six hourly.

Definitive subsequent therapy

Results of surgical therapy is superior to medical therapy in acute (< 2 weeks) proximal dissection and, conversely medical therapy offers a relative advantage over surgery in most cases of uncomplicated acute distal dissection (**Table 1**).

Table 1: Indications for Definitive Therapy in Aortic Dissection

Surgical	
	Treatment of choice for acute proximal dissection
	Treatment of choice for acute distal dissection complicated by progression with vital organ compromise
	Rupture or impending rupture
	Aortic regurgitation (rare)
	Retrograde extension to the ascending aorta
	Dissection in Marfan's syndrome
Medical	
	Treatment of choice for uncomplicated distal dissection
	Treatment for stable, isolated arch dissection
	Treatment of choice for stable chronic dissection (uncomplicated dissection presenting two weeks or later after onset)

Long-term medical therapy to control hypertension and reduce dp/dt is indicated for all patients regardless of whether they have received definitive surgical or medical therapy. Follow-up of patients should include repeated physical examinations, periodic chest X-rays, CT scans or digital substraction angiograms (DSA) for evidence of localised aneurysm formation. MRI also promises to be a valuable tool for follow-up.

INTRAMURAL HAEMATOMA

It is an acute aortic syndrome which is typically characterised by haemorrhage within medial layer of aortic wall, but unlike classic aortic dissection, there is no evident tear in intimal layer. It is proposed that it results from the rupture of vasa vasorum within aortic wall although some believe that it results from intimal tear which is too small to be visualised. The risk factors, signs and symptoms resemble classic aortic dissection. Among the various available diagnostic modalities CT scan is the most preferred diagnostic tool to visualise the intramural haematomas.

The natural history of intramural haematoma is debatable but they can proceed in four possible ways absorption of

haematoma, persistence of haematoma, development of aortic aneurysm, and conversion to classic aortic dissection.

Treatment of this aortic syndrome is similar to classic aortic dissection in the sense that proximal aortic intramural haematoma should be operated while distal intramural haematoma should be managed medically.

AORTO ARTERITIS (TAKAYASU'S ARTERITIS)

Takayasu's arteritis (TA) is a chronic inflammatory disease of the aorta and its major branches. Though the disease was named after him, Takayasu was not the first to describe this disease entity. 'Pulseless' disease was reported by Adams way back in 1827. In 1908, Takayasu described a peculiar 'wreath-like' appearance of arteriovenous anastomosis around the optic papilla.

The disease has a worldwide distribution, though the majority of cases are seen in Japan, India, South Africa, Mexico and parts of South America. Mongoloid races are affected the most, followed by the Indo-Aryan. The disease predominantly affects young females. The female: male ratio being 7:1 in Japan, 5:1 in Mexico and 3:1 in India.

Aetiopathogenesis

The specific cause of the disease is not known, though the bulk of evidence favours an autoimmune aetiology. Association with rheumatic fever, streptococcal infection, rheumatoid arthritis, other collagen vascular disease and tuberculosis were described. The disease has two stages. The early active phase, there is non-specific granulomatous panarteritis involving all the layers of the wall of the aorta and its branches but unlike other forms of the aortitis, pulmonary artery may be involved in this disease. The disease progresses variably to a chronic sclerotic phase, characterised by intimal hyperplasia leading to purely stenotic lesion in 85% of the patients, purely dilatative in 2% and mixed lesion in 13% of the patients.

Classification

Lupi-Herrera *et al* in 1977, described four varieties of disease based on predominant site of involvement: Type I (Shimizu-Sano) aortic arch and its branches (**Figure 5**); Type II (Kimoto) thoraco-abdominal aorta and its branches; Type III (Inada) combines features of both Type I and Type II; and Type IV (Oata) pulmonary artery (**Figure 6**). Another variety of arteritis is proposed as Type V aorto-arteritis associated coronary artery (Panja *et al*) (**Figure 7**). Criteria of American College of Rheumatology for the Classification of Takayasu Arteritis (1990) are given in **Table 2**.

Clinical Manifestations

The disease affects teenagers in three-fourths of cases, though no age is immune to this disease. More than half of the patients present with features of active disease viz. fever, anorexia, malaise, weight loss, night sweats, arthralgias, pleuritic pain and fatigue. Localised pain and tenderness may be noted over the affected arteries. Occasionally, it may present as fever of unknown origin.

In the sclerotic phase, the manifestations include diminished or absent pulses in 96%, bruits in 94%, hypertension in 74% and heart failure in 28% patients. Retinopathy leading to retinal detachment and loss of vision is seen in 25% of the cases.

Patients with types I and III disease present as 'reverse coarctation' manifested by absent or diminished pulse and



Figure 5: Aortogram showing involvement of aortic arch with both common carotid arteries with aorto-arteritis.



Figure 6: Pulmonary artery involvement in a patient with aorto-arteritis.

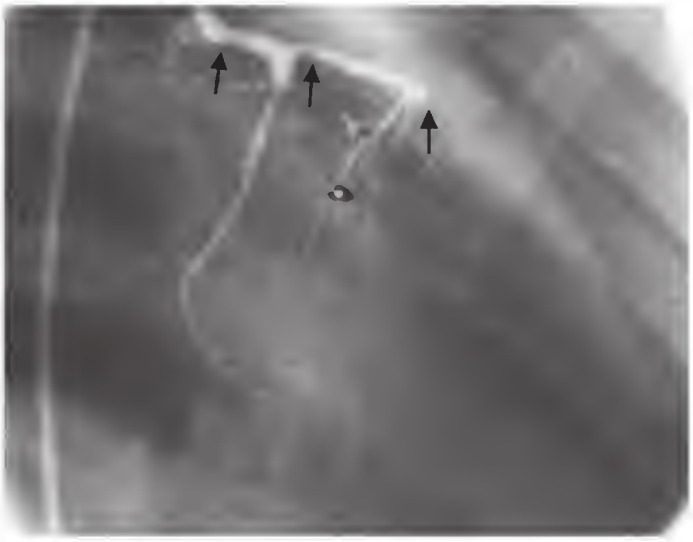


Figure 7: Severe coronary artery involvement in a patient of aorto-arteritis.

blood pressure in the upper limbs, bruits over diseased arteries and syncope. Type II disease is manifested by abdominal angina, claudication of limbs and hypertension due to renal artery involvement.

Hypertension, a major complication of this disease, arises due to renal artery stenosis (35.85%) (**Figure 8**), involvement of baroreceptors by aortitis, loss of elasticity of aorta and coarctation like lesion. Congestive heart failure occurs due to hypertension, dilated cardiomyopathy or more rarely aortic regurgitation. Coronary artery involvement may cause angina, myocardial infarction. Pulmonary artery involvement may result in a clinical picture similar to primary pulmonary hypertension.

Investigations

During the systemic phase, elevated ESR, low-grade leucocytosis and mild anaemia of chronic disease are frequent. IgG or IgM values are elevated in more than half of the patients. C-reactive protein may be elevated with increased anti-streptolysin titre, rheumatoid factor, anti-endothelial antibodies and elevated fibrogen levels.

Chest X-ray is usually unrevealing although a rim of calcification is sometimes seen in the walls of the affected arteries. Arteriography reveals irregular intimal surface with stenosis of the aorta or its branches, post-stenotic dilatation, saccular aneurysm and even complete occlusion of vessels. The affected thoracic aorta has been described as having a rat-tail appearance. Arterial biopsy may be positive in 20% to 35% of the cases. Gallium-67 radionuclide scan may demonstrate uptake in aorta and its branches. High resolution ultrasono-graphy is useful in monitoring disease of common carotid and subclavian arteries.

MRI, MR angiography and CT scan are useful for serial examination and diagnosis in early phase of Takayasu arteritis.



Figure 8: Bilateral renal artery involvement with left common iliac artery involvement in patient with aorto-arteritis.

Use of contrast may reveal inflammatory lesion prior to development of stenosis. Ishikawa and American College of Rheumatology have proposed criteria for the diagnosis of Takayasu arteritis (**Table 2**).

Table 2: 1990 Criteria of American College of Rheumatology for the Classification of Takayasu Arteritis

Criteria	Definition
Age of onset	Development of symptoms or findings related to Takayasu arteritis at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries
BP difference in arms	Difference of >10 mm Hg in systolic pressure between arms
Bruit	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arterio-sclerosis, fibro-muscular dysplasia, or similar causes: changes usually focal or segmental

For purposes of classification, a patient shall be said to have Takayasu's arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.

Natural History

The disease is basically progressive, though the rate of progression varies considerably. The cause of death is usually heart failure, encephalopathy, renal failure, rupture of aneurysms and cerebral haemorrhage.

Treatment

Medical treatment is recommended for those suffering from active and early lesions, those in whom surgery is not possible or considered too risky because of extensive and multifocal involvement of the arterial tree and where surgery is contra-indicated due to uncontrollable congestive cardiac failure or progressive renal failure. Steroids are often effective in relieving the constitutional symptoms. Cyclophosphamide, cyclosporine, mycophenolate mofetil and methotrexate can be tried in cases which fail to respond to steroids. Etanercept and infliximab may be used for inducing clinical remission in steroid-dependent patients. Anticoagulant anti-platelet and drugs like warfarin, aspirin and dipyridamole are recommended to treat transient ischaemic symptoms and to prevent progression. Aggressive treatment of hypertension is important. Surgical treatment for late complications includes endarterectomy, bypass of obstructed arteries especially renal arteries, resection of localised coarctation, excision of saccular aneurysms and rarely aortic valve replacement.

Percutaneous transluminal coronary angioplasty (PTCA) with or without stenting has emerged as a useful effective and less invasive therapeutic option for Takayasu's disease. This option is especially effective for discrete lesions.

CARDIOVASCULAR SYPHILIS

It is very rare as a result of aggressive antibiotic treatment of syphilis in its early stages. Cardiovascular complications occur in approximately 10% of cases of untreated syphilis. The latent period may extend from 5 to 40 years, with a usual time of 10 to 25 years. During the secondary phase of the disease the bacteria directly invade the aortic media. The direct infection and subsequent inflammatory response cause destruction of muscular and elastic media followed by its fibrosis.

Clinical Manifestation

In the absence of' aortic regurgitation an aneurysm may undergo significant enlargement without producing symptoms. Eventually it may expand to compress and erode contiguous structure, particularly the sternum and the anterior right thoracic cage. This causes pain at the point of involvement. Ascending aortic aneurysms and those involving the arch may cause a tracheal tug, stridor and dysphagia. There may be hoarseness due to compression of the left recurrent laryngeal nerve and cough from pressure against the left main stem bronchus. Patients may have anginal symptoms due to associated stenosis of the coronary ostia.

Diagnosis

There is a history of syphilis and other manifestations of tertiary syphilis in 10% to 30% of cases. About 15% to 30% of patients have negative routine serological tests for syphilis (Wassermann, Kahn and VDRL). Serological tests directed against a specific treponemal antigen are almost invariably positive. The chest X-ray may show calcification in the ascending aorta proximal to the brachiocephalic vessels.

Angiography may delineate the aneurysm and help to quantify the severity of aortic regurgitation. In patients suspected to have coronary ostial stenosis and in patients where surgical correction is contemplated, the coronary artery anatomy, and particularly the ostia, should be visualised by coronary angiography. CT and MRI are quite helpful in evaluating the aneurysm.

Treatment

All patients who are seen one year or more after the initial contact should be given a course of antibiotic therapy, i.e. injection benzathine penicillin 2.4 million units IM weekly for three weeks. For patients allergic to penicillin, tetracycline 500 mg four times daily for 30 days is recommended.

GIANT CELL ARTERITIS

This disease is found predominantly in elderly people and characteristically involves medium-sized arteries. The aorta and its branches are affected in about 15% cases. The aetiology of giant cell arteritis is unknown. However, the possibility of an autoimmune or infectious origin has been considered. The typical pathological lesion is granulomatous inflammation of the media of small-to-medium calibre arteries about the size of the temporal artery, with a special predilection for the vessels of the head and the neck.

Clinical Manifestations

It typically affects patients over the age of 50 years and occurs predominantly in females. The typical presentation consists of fever, malaise and headache. Other constitutional symptoms include anorexia, weight loss, myalgias, night sweats and lassitude. Headaches are often intense and unbearable and occur over the involved arteries, usually the temporal arteries, but occasionally over the occipital region. Blindness may occur due to involvement of the ophthalmic artery. The syndrome of polymyalgia rheumatica is seen in nearly 40% of these patients. Physical examination reveals the patient to be febrile. The involved vessels are thickened and tender, pulse may be lost and bruits may be heard over the sites of arterial occlusion.

Investigations

A high erythrocyte sedimentation rate (ESR) is virtually inevitable, normocytic, normochromic anaemia may be present. Antinuclear antibody and rheumatoid factor are not found. The diagnosis is usually confirmed by biopsy of the temporal artery (TA). Colour duplex ultrasonography of TA is a promising alternative for temporal artery biopsy. Angiography may help to confirm the diagnosis in cases of larger vessel and aortic involvement. CT, MRI are used as second-line diagnostic procedure.

Treatment

Treatment consists of prednisolone 60 to 80 mg per day for 1 to 2 years. With ESR as guide, steroid may be tapered to a maintenance dose of 5 to 15 mg per day for 1 to 2 years. Cyclosporine and azathioprine or cyclosporine and methotrexate are used in steroid-resistant cases. The overall prognosis with treatment is good.

OTHER ARTERITIS SYNDROMES

These may be seen in association with ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, and Reiter's syndrome.

AORTIC TRAUMA

Aortic injuries may occur with severe blunt trauma as in motor vehicle accident, blast injuries, crush injuries and severe falls. The most common site of tear is the aortic isthmus just distal to the origin of the left subclavian artery. Other sites include the supravalvular portion of the ascending aorta, the aortic arch, the innominate artery, abdominal aorta and combinations of these.

RECOMMENDED READINGS

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12.32 Vascular Disorders of the Extremities

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INTRODUCTION

Vascular disorders of the extremities can involve the arterial, venous or the lymphatic systems. These are generally more common in the lower limbs than in the upper limbs. These disorders can have an acute onset or may develop chronically. The diagnosis is made in most cases by a thorough clinical, ultrasonographic and Doppler evaluation. These abnormalities can be primary in origin or they may be manifestations of a systemic disorder.

ARTERIAL DISORDERS

Vascular occlusion, acute or chronic, is the major arterial disorder of the extremities. **Table 1** outlines the arterial disorders.

Table 1: Classification of Arterial Disorders

Occlusive
Acute occlusion (embolic, thrombotic, traumatic)
Chronic occlusion (Atherosclerotic, Takayasu's arteritis)
Gangrene
Wet (due to acute occlusion)
Dry (due to chronic occlusion)
Aneurysm
Arteriovenous fistula
Thromboangiitis obliterans (Buerger's disease)
Vasospastic disorders
Raynaud's disease
Livedo reticularis
Acrocyanosis

Chronic Arterial Occlusion

It presents less dramatically than acute occlusion and is much more common. Atherosclerotic peripheral arterial disease (PAD) affects the leg eight times more often than the arm. The pathophysiology of PAD is similar to coronary artery disease. The most important risk factors are smoking, diabetes, hyperlipidaemia and hypertension. The clinical manifestations depend on the anatomical site, the presence or absence of collateral supply, the rapidity of onset and the occurrence of external trauma.

Takayasu's arteritis (pulseless disease) is another common cause of chronic PAD involving the aorta and its major arteries. Most commonly upper limb vessels are affected. Its prevalence is high in young women of Indian, Japanese and Mexican descent. There is a panarteritis in the acute stage, culminating in fibrotic occlusion in the chronic stage. No definitive therapy is available for this disease. However, in acute stage steroids are of some use. Vascular interventions (balloon angioplasty and metallic stents) are often used with variable results.

In Indian subcontinent, diabetics form the largest group of patients with atherosclerotic PAD. The occlusive disease in diabetics is more extensive and complicated due to associated neuropathy and increased risk of infection. Most patients with chronic PAD have bad prognosis due to associated coronary and cerebral atherosclerosis. Diabetic foot is one of the dreaded complication with high rate of amputation. This can be managed with combined approach of preventive measures (education, foot care, special shoes) and treatment strategies (angioplasty ± stents). These have reduced the below knee amputation rate.

Patients often present with intermittent claudication when the limb ischaemia is less critical. This is a cramp-like pain felt in the calf muscles, brought on by walking and relieved on standing still. The distance walked is called 'claudication distance' and is relatively constant for a patient.

Patients with critical limb ischaemia (CLI) are defined as those with rest pain that is felt in the foot at rest and made worse by lying down or elevation of the foot. Characteristically, the pain is worse at night and relieved by hanging the foot out of the bed. Other changes include coldness, numbness, paraesthesias and colour change (ischaemic limbs become blanched on elevation and develop a purple discolouration on dependence). Severe arterial insufficiency can result in painful superficial erosions between the toes, on the dorsum of feet and around the malleoli. Later, this can progress to ulceration and frank gangrene (**Figure 1**). A severely ischaemic foot is frequently paralysed and cold but may feel warmer as it takes on the temperature of its surroundings.

In the upper limb, atheromatous occlusive disease can involve subclavian artery and may cause claudication and rarely frank ischaemia of an arm. The subclavian lesion may also cause distal embolisation and consequent loss of digits. Subclavian steal syndrome may occur if the first part of the subclavian artery is obstructed and the vertebral artery provides a collateral circulation into the arm by reversing its direction of blood flow. The classic syndrome of syncopal attack and visual disturbance associated with arm exercise and a diminished blood pressure in the affected limb is rare. Asymptomatic reversal of flow in the vertebral artery recognised by duplex scanning or angiography is much more common.

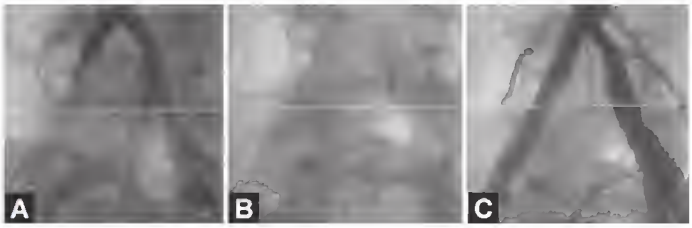
Relevant investigations include tests for diabetes mellitus, lipid abnormalities and anaemia. Doppler ultrasound is a very sensitive type of stethoscope that can be used in conjunction with a sphygmomanometer to assess the systolic pressure in relatively small vessels. Ankle: brachial pressure index (ABPI) is the ratio of systolic pressure in the ankle to that in the arm. Values under 0.9 indicate mild ischaemia whereas < 0.5 indicate severe ischaemia. Duplex imaging combines B-mode ultrasound with Doppler ultrasound to give detailed knowledge about vessel-wall thickness, blood flow and turbulence. The 'gold standard' for arterial occlusive disease is angiography, which involves the injection of radio-opaque dye in the vessels



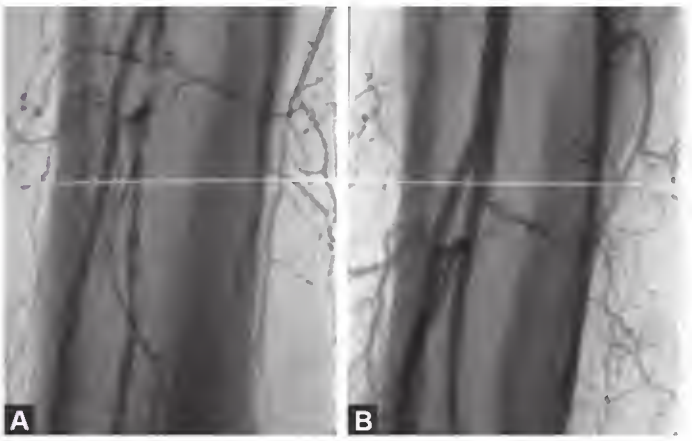
Figure 1: Patient with chronic arterial occlusion of left lower limb showing discolouration of left foot, thinning of ankle and foot, and dry gangrene of distal digits.

and then using a real time or single shot X-ray to detect the status of the vessels. Digital subtraction angiography (DSA) helps in better delineation of the vessels by subtracting the images of overlying tissues. More recently, ultra fast CT-angiography done by injection of intravenous contrast helps in studying the arterial tree without the need for arterial injection as in conventional angiography. Renal function test should be done before sending the patient for contrast imaging. Magnetic resonance angiography (MRA) provides multiplanar imaging without the need of ionising radiation.

Arterial occlusive disorders can be managed conservatively in most cases. Encouraging exercise within the limits of disability is a good way of increasing exercise capacity. Spontaneous improvement occurs after a few months due to formation of collaterals. Drugs that have a role in occlusive arterial disorders include those for underlying diabetes, hypertension and lipid abnormalities. Antiplatelet agents like aspirin (75 to150 mg od) or clopidogrel can be used. Cilostazol, a phosphodiesterase inhibitor with vasodilator and antiplatelet properties has been shown to improve claudication distance. Naftidrofuryl oxalate may alter tissue metabolism, thus increasing claudication distance. Pentoxifylline improves RBC rheology (flexibility) and has some blood thinning capacity, thus helping to improve circulation. Prostacyclins may have some minor role in the management of the critically ischaemic limb. Lumbar sympathectomy has been used for pain relief. In vessels with localised blocks, transluminal angioplasty and stenting may be performed by inserting a balloon catheter into an artery and inflating it within a narrowed or blocked area. In certain cases, a metallic stent may need to be inserted to keep the lumen patent (**Figures 2Ato C, and Figures 3A and B**). In feasible cases, a surgical vascular bypass may be performed around the occluded part of the vessel to permit distal perfusion. The long-term results of reconstructive aortoiliac surgery are good and they are usually only marred by a progressive disease producing femoro-popliteal occlusions at a later stage. Stem cell therapy (therapeutic angiogenesis) has generated a lot of interest. However, the results need to be documented in large randomised control trials.



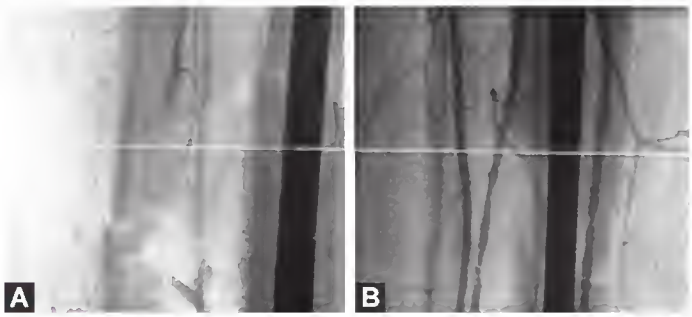
Figures 2A to C: (A) Bilateral common iliac stenosis, (B) Stents placed in both common iliac arteries, (C) Post-stenting angiogram showing normal flow.



Figures 3A and B: (A) Angiogram showing stenosis in the peroneal artery, (B) Post-angioplasty angiogram showing normal flow.

Acute Arterial Occlusion

Sudden occlusion of an artery may be due to emboli from a remote site, thrombus formation on a pre-existing atheroma or trauma (**Figures 4A and B**). The emboli can arise from an atrial source as in atrial fibrillation or left ventricular mural thrombus following myocardial infarction. These tend to lodge at vessel bifurcation. Acute occlusion is an emergency and threatens limb viability. It needs immediate diagnosis and early management since delay can compromise limb viability.



Figures 4A and B: This patient presented with a tibial fracture and absent distal pulses: (A) Angiogram showing sudden cut-off of arterial blood flow at the level of the fracture; (B) After stabilisation of the fracture, injection of local vasodilators and ballooning of the blocked segment, flow is restored.

The classical signs in the lower limb are the 6 P's – *pain, pallor, paresis, pulselessness, paraesthesia and poikilothermia*. The limb is cold and, almost immediately, the toes cannot be moved. Sensation to touch is soon lost and distal pulses become impalpable. B-mode ultrasound imaging shows lack of pulsation in arteries and Doppler confirms the diagnosis by showing lack of blood flow.

Appropriate treatment is the immediate intravenous administration of heparin. This can halt the extension of the thrombus and maintain patency in the surrounding vessels. Pain relief is essential because pain is severe and constant. Surgical embolectomy for larger vessels till the popliteal artery is the treatment of choice when done within 12 hours of ischaemia. Thrombolysis using streptokinase or urokinase is preferred for distal vessels. This has to be done within 6 to 12 hours to preserve limb viability. Patients presenting late often go on to develop gangrene of the distal toes and the feet.

Gangrene

The combination of rest pain, colour changes and hyperaesthesias with or without ischaemic ulceration is frequently referred to as pre-gangrene. Gangrene implies death of macroscopic portions of tissue. It is commonly seen affecting the distal part of the limb. A gangrenous part lacks arterial pulsation, venous return, capillary response to pressure (colour return), sensation, warmth and function. The colour changes from pale through dusky-gray to mottled until finally taking on the characteristic dark brown, green-black or black appearance.

Dry gangrene

This occurs when the tissues are desiccated by gradual occlusion of the vessels. It is typically due to atheromatous occlusion of the arteries. The affected part becomes dry and wrinkled, discoloured and greasy to touch.

Wet gangrene

This occurs when the artery is suddenly occluded and there is venous obstruction as well. Infection and putrefaction are present and the affected part becomes swollen and discoloured and the epidermis may be raised in blebs. Crepitus may also be palpated (**Figure 5**).

Treatment includes general measures like hydration, pain control and control of infection. Once gangrene has set in, the reestablishment of blood flow by percutaneous intervention or surgery does not help. Unviable portions of tissue need to be amputated to relieve pain and prevent the spread of infection and gangrene.

Aneurysm

An aneurysm is a localised dilatation of a segment of the arterial system. Aneurysms can be true (involving the vascular intima, media and adventitia) or false (with a fibrous wall). In appearance, they may be fusiform, saccular or dissecting. Aetiology can be atheromatous, traumatic, syphilitic or due to collagen disease.

These can present due to expansion, thrombosis or embolisation. Intrinsically, a pulsatile swelling is present along the course of an artery, which diminishes on application of proximal pressure. The sac is usually compressible unless thrombosed. A thrill may be felt and a systemic bruit auscultated.



Figure 5: Wet gangrene of both lower limbs due to acute arterial occlusion with blebs, denuded skin and blackish discolouration of both feet.

Extrinsically, pressure on veins or nerves may cause distal oedema or altered sensation.

Arteriovenous Fistula

This is a communication between an artery and vein. This may be congenital or acquired due to surgical trauma and catheter access. AV fistulas may also be created in the upper limb to facilitate haemodialysis. Haemodynamically significant fistulas may lead to a wide pulse pressure and a thrill is present. A continuous bruit can be heard over the fistula. Pressure on the artery proximal to the fistula may cause the swelling to diminish, the thrill and bruit to cease and the pulse rate to fall (Nicoladoni's or Branham's sign) and the pulse pressure to return to normal. Embolisation by autologous material (fat/muscle) or gelatine sponges, silicon spheres can obliterate the fistula. Large, painful or bleeding AV fistula can be managed surgically or with endovascular grafts/stents.

Thromboangiitis Obliterans

This involves occlusive disease of the small and medium sized arteries, thrombophlebitis of superficial and deep veins, and Raynaud's phenomenon. It is also known as Buerger's disease. It is most common in Asian males under the age of 30, generally smokers. Treatment is primarily cessation of smoking. This helps halt the progression of the disease but does not lead to reversal of the established occlusion. Sympathectomy for pain relief is also done. Stem cell therapy has also been tried.

Vasospastic Disorders

Raynaud's disease

It predominantly affects the upper limbs in young women. The peripheral pulses are normal. Due to an abnormal response to

cold temperature, the vessels constrict and then dilate. This produces a classic triphasic colour change; pallor, cyanosis followed by redness of the digits. This is often accompanied by pain.

Raynaud's syndrome shares the clinical features of Raynaud's disease but is much more severe. It is generally a manifestation of collagen vascular disease. It may also follow the use of vibrating tools and is then known as 'vibration white finger'. Treatment is primarily directed at the underlying condition. Calcium channel blockers may have a role in management.

Livedo reticularis

This involves purplish mottling of the skin due to spasm of dermal arterioles in lower extremities, especially on cold exposure.

Acrocyanosis

It is an uncommon condition seen in females and is characterised by bluish discolouration in hands and fingers. No specific therapy is required.

VENOUS DISORDERS

Blood returns from the limbs via the deep and superficial veins. In the upper limb, the superficial veins are more important. The superficial veins in the leg are the long and short saphenous veins, and they carry only 10% of the blood from the lower limbs.

There is a foot-pump that ejects blood from the plantar veins as pressure is placed on the foot during walking. On exercise, the thigh and calf muscles contract compressing the veins and ejecting blood towards the heart. Venous valves control the direction of flow of blood in the veins. During muscle relaxation phase, the pressure within the calf falls to a low level and blood from superficial veins flows through the perforating veins into the deep veins. Venous diseases are of two main types; venous thrombosis and venous incompetence.

Venous Thrombosis

Venous thrombosis of the deep veins involves the lower limbs more frequently than the upper limbs. In most cases, deep vein thrombosis (DVT) is asymptomatic and resolves without sequelae. However, often patients are left with a post-thrombotic limb that is persistently swollen, often complicated by venous ulceration. During the acute phase, DVT needs to be taken seriously since the thrombi can dislodge and embolise to the pulmonary circulation. A clot from the lower limb veins detaches from its site and passes via the inferior *vena cava* and right heart to the pulmonary arteries. It may totally occlude the perfusion to a part or all of one or both lungs. In 10% patients who die in the hospital, the cause of death is pulmonary embolism following a DVT.

The main causative factors are part of the Virchow's triad; stasis (slowing of the blood flow), hypercoagulability (increased tendency to clot) and vessel wall damage (which releases thrombogenic substances). The term 'thrombophilia' implies an increased tendency for clotting, often for prolonged periods of time. This can be inherited or acquired. The common genetic causes responsible for venous thromboembolism are mutations involving factor V Leiden (20% to 40%) and prothrombin (6%) genes. Inherited deficiency of protein C (3%), protein S (3%) and antithrombin III (1%) have also been shown to lead to venous thrombosis in young patients. Common acquired thrombophilic states are previous surgery (especially orthopaedic like joint replacement), trauma, pregnancy, certain malignancies, stroke, heart failure, prolonged immobilisation and drugs such as oral contraceptives and hormone replacement therapy (**Table 2**). Long haul air travel has been associated with an increased incidence of DVT due to the immobilisation.

Table 2: Predisposing Causes for Venous Thrombosis

Hypercoagulable states	
	Mutations of factor V (Leiden), prothrombin gene
	Deficiency of protein C, protein S, antithrombin III
	Antiphospholipid antibody
	Disseminated intravascular coagulation
Surgery	
	Orthopaedic, thoracic, abdominal
Neoplasia	
	Pancreas, lung, ovary, testes, breast
Trauma	
	Fractures, spinal injuries
	Immobilisation (any cause)
Hormonal	
	Pregnancy, oral contraceptives

The most significant clinical findings are tenderness in the calf and ankle oedema. Pain in the calf on dorsiflexion of the ankle (Homan's sign) is rare and often misleading. Other signs and symptoms are swelling, pain, redness, dilated superficial veins and low-grade pyrexia (**Figure 6**). Some



Figure 6: Superficial and deep vein thrombosis of right leg showing oedema and calf swelling due to DVT. There is an accompanying superficial vein thrombosis as evidenced by the linear redness and swelling.

patients with DVT may have no symptoms in the leg but initially present with sudden onset dyspnoea due to pulmonary embolism.

For diagnosis, a quantitative D-dimer analysis is done to measure the levels of fibrin degradation products. It is recommended to rule-out DVT in clinically suspicious patients. It is, however, not very specific and hence the value of a positive test is limited. The best method for diagnosis is B-mode and Doppler ultrasound in which we look for flow in the veins and augmentation on calf compression. Ascending phlebography is rarely done.

Immobilisation is usually needed only for first 24 hours. Treatment involves anticoagulation after the diagnosis is made. Standard treatment involves unfractionated intravenous heparin (UFH) with dose adjusted according to activated partial thromboplastin time (aPTT). The onset of action is rapid and it is given for about 5 days. The aim is to minimise the risk of pulmonary embolism and to encourage the resolution of the thrombus. Subcutaneous injections of low molecular weight heparin (LMWH) are an alternative method and have been found to produce reliable anticoagulation. These are given twice daily and are easier to administer. They also do not require aPTT monitoring. Many LMWHs are now commercially available and are preferred over UFH nowadays. At the same time, the patient should be started on oral anticoagulants (e.g. warfarin, acenocoumarol) to reduce risk of recurrence of DVT. Duration of treatment is usually for 6 to 12 months. Patients who have inherited thrombophilia require lifelong anticoagulation. The effect of warfarin is monitored by measuring the international normalised ratio (INR), which should be prolonged to 2.0 to 3.0 times the control values. Inferior *vena cava* (IVC) filters are implanted in patients with contraindication to oral anti-coagulants (GI bleed), recurrent DVT and high risk DVT. Retrievable filters are preferred over permanent ones.

Prevention of DVT can be done by both mechanical and pharmacological methods. Graduated elastic compression stockings have been shown to reduce the incidence of deep vein thrombosis. Intermittent pneumatic compression devices are used only peri-operatively. Pharmacological methods include UFH and LMWH. LMWHs are generally preferred. These are considered in all immobilised patients especially those with orthopaedic surgery, congestive cardiac failure and occlusive strokes. Prevention of thrombosis during long distance air travel requires the use of graduated compression stockings, exercise during the flight and avoidance of alcohol and sleeping tablets.

Superficial Vein Thrombosis

This is a frequent complication of varicose veins and may also follow cannulation of a vein for intravenous infusion. Spontaneous superficial thrombophlebitis may occur in the presence of polycythaemia, polyarteritis and Buerger's disease and may also herald the presence of a visceral cancer. This condition does not carry the risks of deep vein thrombosis and is normally treated symptomatically with simple analgesics and anti-inflammatory drugs.

Axillary Vein Thrombosis

This may occur following excessive exercise or as a complication of thoracic outlet syndrome. It is occasionally associated with a cervical rib. The arm becomes swollen and the superficial veins become distended. Early treatment with anticoagulants may result in rapid resolution. In severe cases, the use of fibrinolytic therapy, streptokinase or TPA may be considered. Definite treatment of thoracic outlet syndrome by surgical decompression of the subclavian may be needed, e.g. by resection of the first rib.

Venous Incompetence

Unidirectional venous flow requires the competence of the valves in the superficial and deep veins as well as the venous perforators. Dysfunction of these valves leads to venous incompetence and varicose veins. The incidence of varicose veins in developing countries is lower than in the western nations due to genetic, lifestyle and dietary differences. Varicose veins develop more frequently in people who stand during their work and during pregnancy under the influence of oestrogen and progesterone.

Symptoms include tiredness, aching, tingling, ankle swelling and a cramping sensation in the legs, which progressively worsen towards the end of the day and are relieved by elevating the leg. Patients with more severe venous disease may notice skin changes. Some patients may be asymptomatic and may present for cosmetic reasons.

On examination, there is an increase in size of the calf muscles, ankle oedema, and skin complications like brown pigmentation, eczema and severe ulcerations. Later on, lipodermatosclerosis may develop. Contraction of the skin and subcutaneous tissue is seen and the ankle becomes narrow. A combination of narrow ankle and prominent calf is often referred to as a champagne bottle leg. Venous ulceration may also develop in these areas. Diagnosis can be made by a thorough clinical examination and Doppler ultrasound evaluation.

The treatment depends on the size of the varices, their extent and the symptoms they produce. Compression stockings are used in early stages of disease. Injection sclerotherapy involves the injection of an irritant solution, sodium tetradecyl. Surgical treatment involves the ligation of the source of reflux (usually the saphenopopliteal or saphenofemoral junction) and removal of the incompetent saphenous trunks and the associated varices. Endovenous radio frequency and laser ablation have been used in patients with persistent symptoms and/or who develop ulceration.

LYMPHATICS DISORDERS

Lymphatic system is composed of interstitial fluid that bathes tissues of the body, lymphatic capillaries that collect interstitial fluid, transporting vessels and the lymph nodes. The lymphatic capillaries absorb interstitial fluid and empty into transporting vessels, which traverse the extremities and join with the visceral channels to form the cisterna chyli adjacent to the upper abdominal aorta. These pass through the diaphragm to become the thoracic duct. The thoracic duct empties into the left

subclavian vein. A separate smaller right lymphatic duct drains the right upper extremity and neck, and enters the right subclavian vein. Normally between 2 litres and 4 litres of interstitial fluid is filtered each day and returned to the vascular system by the lymphatic system. Diseases of the lymphatics include lymphoedema due to lymphatic obstruction, lymphangiomas and tumours.

Lymphoedema

Lymphoedema is caused by excessive accumulation of interstitial fluid in the extravascular, extracellular fluid compartment due to defects in the lymphatic transport system. Inadequate removal of the interstitial fluid by the lymphatic system may be the result of absent hypoplastic or obstructed lymphatic vessels. In the limb, interstitial fluid accumulates mainly in the cutaneous tissues and presents as a swollen extremity. In the early stages, the oedema is pitting but later it typically becomes non-pitting. The skin becomes thickened, hypertrophic and hyperkeratotic. It should be distinguished from other causes of unilateral leg swelling such as DVT (**Table 3**). Lymphoedema may be primary or secondary (**Table 4**).

Table 3: Differences Between Swelling of the Extremity Due to Lymphatic and Venous Obstruction

Lymphatic Obstruction	Venous Obstruction
Swelling typically involves the distal aspect of the extremity and characteristically involves the dorsum of the feet and toes	Swelling is present distal to the site of obstruction and uniformly involves the extremity uniformly
Swelling is usually painless. Pain and redness occur only if there is associated cellulitis	There is pain, redness and dilated superficial veins in the affected extremity
Oedema is pitting in nature and responds to limb elevation, however later on it characteristically becomes non-pitting and does not respond to limb elevation	Oedema is pitting in nature in the initial phase and responds to limb elevation
Due to lymphoedema, skin becomes thickened, hypertrophic and then hyper-keratotic	Due to increase in foot vein pressure, skin around the ankle becomes pigmented due to leakage of blood and fibrin into the surrounding tissues. With passage of time, the skin becomes eczematous and ulcerated

Table 4: Types of Lymphoedema

Primary
- Lymphoedema congenita
- Lymphoedema precox
- Lymphoedema tarda

Secondary
- Filariasis
- Tuberculosis
- Neoplasia
- Recurrent lymphangitis
- Surgery
- Radiotherapy

Primary lymphoedema

This is relatively uncommon and often associated with inherited disorders like Turner's and Klinefelter's syndromes. 'Lymphoedema congenita' is a severe form of lymphoedema that is usually apparent at birth or during early infancy. Familial cases are termed as Milroy's disease. These patients have associated lymphatic abnormalities such as intestinal and pulmonary lymphangiectasia.

'Lymphoedema precox' presents at about the time of puberty and is the most common form of primary lymphoedema accounting for >80% of the cases. 'Lymphoedema tarda' refers to lymphoedema that appears at about the third or fourth decade of life.

Secondary lymphoedema

It is usually due to acquired lymphatic obstruction. The causes of obstructive lymphoedema are infiltration of regional lymph nodes by tumour, surgical excision of regional lymph nodes in the treatment of malignancy, repeated infections, inflammatory processes causing fibrosis and irradiation.

In tropical and subtropical countries infestation by filarial parasites is the most frequent cause of secondary lymph-oedema. Eight filarial species infect humans out of which only two; *Wuchereria bancrofti* and *Brugia malayi* are found in India and South-East Asia. *W. bancrofti* is the most widely distributed human filarial parasite. In India, the disease is rampant in Uttar Pradesh, Bihar, Andhra Pradesh, Orissa, Tamil Nadu, coastal Kerala and Gujarat. Tuberculous lymphangitis may also cause lymphoedema. In Western countries lymphoedema occurs most commonly in the arm after surgical excision of lymph nodes for carcinoma of the breast.

Lymphangiography is used to diagnose lymphoedema and to demonstrate the nature of lymphatic abnormality. However, as this procedure is invasive and because of the risk of oil embolism, it is being replaced by isotope lymphangiography. MRI imaging has also been employed to investigate the lymphatic system.

Treatment includes prolonged bed rest, limb elevation, elastic stockings, meticulous skin hygiene, avoidance of local injury and prompt treatment with antibiotics if cellulitis occurs. Surgery is reserved for those with severe disabling lymphoedema. It includes the excision of hypertrophic tissue, pedicle transfer of normal lymphatic bearing tissue and microvascular bypass.

Lymphangiomas

Lymphangiomas are benign overgrowths of lymphatic vessels. It is not certain whether these are congenital malformations, hamartomas or true neoplasms.

Capillary lymphangiomas are small, circumscribed, pale-white to pink lesions composed of network of endothelium-lined, thin-walled lymphatic spaces separated by lymphoid

aggregates. These mainly involve skin or mucous membranes of the head and neck.

Cavernous lymphangiomas are more common than the capillary variety. They are slow growing, congenital lesions and are composed of numerous dilated lymphatic channels filled with lymph and often surrounded by a fibrous capsule.

Lymphangiosarcoma

It is a rare malignant lesion that develops in a lymphoedematous/ extremity. Malignant transformation is more frequent in cases of secondary lymphoedema. It appears as purple-red nodules in the skin. It is an aggressive and rapidly fatal tumour.

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12.33 Pregnancy and Heart Disease

Amal Kumar Banerjee

INTRODUCTION

Management of pregnancy in patients with heart disease continues to pose a challenge to the clinicians. Heart disease is the third leading cause of death in 25 to 44-year-old women. Because it is relatively common in women of childbearing age, heart disease of varying severity complicates about one per cent of pregnancies. Rheumatic heart disease accounts for most of the cases and mitral stenosis being the commonest lesion, in India.

NORMAL PHYSIOLOGIC CHANGES IN PREGNANCY

There is an increase in blood volume, by about 50%, and relatively haemoglobin concentration falls, causing the physiological anaemia of pregnancy. Cardiac output increases as early as 5 weeks after the last menstrual period and rises to 45% above baseline at 24 weeks' gestation. Increased cardiac output is achieved by an increase in heart rate, which rises progressively until 32 weeks' gestation, and in stroke volume, which begins to increase by 8 weeks and peaks as early as 20 weeks. Twin pregnancies result in an additional 15% rise in cardiac output in mothers. The cardiovascular system is taxed further by stage one of labour, which is associated with an additional 12% increase in demand for cardiac output. This demand increases to a mean of 34% above the already increased baseline value as labour progresses to its final stages. After delivery stroke volume decreases by 2 weeks post-partum, but a small further reduction occurs up to 6 months after delivery. The stroke volume remains at pregnancy levels for the first 2 days post-partum and then falls dramatically. Heart rate remains elevated for 2 days post-partum and returns to the baseline by 10 days after delivery. Cardiac output similarly decreases from pregnancy levels to normal levels between 24 hours and 10 days post-partum. Systemic vascular resistance and diastolic blood pressure decrease as a result of changes in aortic compliance and arterial venous shunting in the uterus.

DIAGNOSIS OF HEART DISEASE

Many of the physiological changes of normal pregnancy tend to make the diagnosis of heart disease more difficult due to alterations in the physical examination of the pregnant patient (**Table 1**). Symptoms and clinical findings that may indicate heart disease (**Table 2**), should be carefully recognised. Pregnant women who have none of these findings, rarely have serious heart disease.

Diagnostic Studies

The physiologic changes associated with pregnancy may also alter the results of non-invasive evaluations of the heart (**Table 3**).

In most cases, conventional testing including electrocardiography, Doppler echocardiography and chest radiography will provide necessary data. If indicated, right-heart catheterisation can be performed with limited X-ray fluoroscopy. All X-ray procedures should generally be avoided, particularly early in pregnancy.

Table 1: Physical Findings During Normal Pregnancy

Mild jugular venous distension
Lower-extremity oedema
Decreased breath sounds at bases
Upward and leftward deviation of point of maximal impulse
Volume-loaded ventricle (active praecordium)
Increased valve closure sounds
'Flow' murmurs (pulmonic and aortic)
Mammary soufflé (left sternal border)
Wide pulse pressure
Increased heart rate

Table 2: Some Clinical Indicators of Heart Disease During Pregnancy

Symptoms
Progressive dyspnoea or orthopnoea
Nocturnal cough
Haemoptysis
Syncope
Chest pain
Clinical Findings
Cyanosis
Clubbing of fingers
Persistent neck vein distension
Systolic murmur grade 3/6 or greater
Diastolic murmur
Cardiomegaly
Persistent arrhythmia
Persistent split-second sound
Criteria for pulmonary hypertension

Table 3: Changes in Non-invasive Test Results That Occur During Pregnancy

Test	Changes
Electrocardiography	Leftward axis deviation
	Increased ventricular voltage
	Increased rate
	Repolarisation changes
Chest X-ray film	Upward diaphragm displacement
	Horizontal heart placement
	Enlarged pulmonary silhouette
Echocardiography	Increased left ventricular diastolic dimension
	Increased left ventricular wall thickness
	Mild increase in contractility

GENERAL MANAGEMENT

Poor maternal functional class, cyanosis, myocardial dysfunction, left-heart obstructive lesions, prior arrhythmia, and prior cardiac events are prognostic of complications during pregnancy. The

likelihood of cardiac complications during pregnancy is 3%, 30% and 66% when none, one or more than one of these are present.

A three tiered risk classification of maternal mortality (**Table 4**), has been developed. This will help in counselling the woman regarding advisability of conception or continuation of pregnancy.

Most current management recommendations have been based on expert opinion and/or retrospective series. To date, there has been only one large multicenter study to prospectively ascertain maternal and foetal outcomes in women with cardiac disease. This Canadian study also derived and validated a risk index for the prediction of maternal cardiac complications during pregnancy (**Table 5**).

Women with heart disease who are at intermediate or high-risk for complications should be managed in a high-risk pregnancy unit by a multidisciplinary team from obstetrics, cardiology, anaesthesia, and paediatrics.

Table 4: Risks for Maternal Mortality Caused by Various Heart Disease

Cardiac Disorder	Mortality (%)
Group 1 – Minimal Risk	0 to 1
Atrial septal defect	
Ventricular septal defect	
Patent ductus arteriosus	
Pulmonary or tricuspid disease	
Tetralogy of Fallot, corrected	
Bioprosthetic valve	
Mitral stenosis, NYHA classes I and II	
Group 2 – Moderate Risk	5 to 15
2A:	
Mitral stenosis, NYHA classes III and IV	
Aortic stenosis	
Aortic coarctation without valvular involvement	
Tetralogy of Fallot, uncorrected	
Previous myocardial infarction	
Marfan's syndrome, normal aorta	
2B:	
Mitral stenosis with atrial fibrillation	
Artificial valve	
Group 3 – Major Risk	25 to 30
Pulmonary hypertension	
Aortic coarctation with valvular involvement	
Marfan's syndrome with aortic involvement	

NYHA = New York Heart Association.

Table 5: Risk Factors for Maternal Cardiac Adverse Events During Pregnancy

Adverse Maternal Cardiac Event	Risk Factor
Pulmonary oedema	General
Arrhythmia	NYHA functional class III or IV or cyanosis
Stroke	Systemic ventricular EF < 40%
Death	Mitral valve area < 2 sq cm, aortic valve area < 1.5 sq cm, peak left ventricular outflow gradient > 30 mmHg
	Cardiac event (arrhythmia, stroke, pulmonary oedema) prior to pregnancy

The general risk factors can be used to create a maternal risk index for adverse cardiac events related to pregnancy: 0 risk factors < 5% risk, 1 risk factor = 27% risk, ≥ 2 risk factors = 75% risk.

Congestive Heart Failure

Management of congestive heart failure (CHF) during pregnancy, is not much different from that at other times. Salt restriction and limitation of activity to a level below that, which causes symptoms are appropriate. In a woman with significant symptoms or pulmonary oedema, standard therapy can be used with the exception of ACE-inhibitors. Congestive heart failure is one situation, where maintaining a woman in supine position may be beneficial by causing preload reduction with obstruction of return of blood from the inferior vena cava to the heart.

Low-Cardiac-Output Syndrome

A low cardiac output is an ominous sign in pregnancy with heart disease. Although potentially treatable causes such as tamponade or severe valvular stenosis should be considered, it is most often due to intravascular volume depletion. This should be prevented when possible and corrected when recognised.

Thromboembolic Complications

The risk of venous thromboemboli increases five-fold during and immediately after pregnancy, and there is an increase in arterial emboli as well. Prevention is optimal, and prophylactic full-dose heparin or low-molecular-weight heparin is indicated in those at high-risk of a thromboembolic complication. If a thrombus or embolus is identified, 5 to 10 days of intravenous heparin therapy followed by full-dose subcutaneous heparin is recommended. If a thromboembolus is life-threatening, like a massive pulmonary embolus or a thrombosed prosthetic valve, thrombolytic therapy can be used.

Pulmonary Hypertension

Pulmonary hypertension, whether primary or secondary, is associated with 30% to 70% maternal mortality and even with maternal survival, foetal loss exceeds 40%. The mother is most vulnerable during labour and in the first post-partum week. If detected early in pregnancy, interruption is advised. When detected late in pregnancy, close follow-up is necessary. Intravascular volume depletion should be promptly corrected, since it puts these patients at greatest risk. Systemic vascular resistance and pressure must be maintained in patients with pulmonary hypertension who have a right-to-left shunt, and meticulous attention is necessary to avoid air or thrombus emboli from intravenous catheters, which may lead to systemic emboli. At the time of labour and delivery, a central venous line allows adequate fluid administration, and a radial artery catheter makes determinations of blood pressure and oxygen saturation easier. These lines should be continued for 48 to 72 hours post-delivery.

Arrhythmias

The rules for the treatment are the same as in the non-pregnant patient, with the possible exception that a rhythm causing haemodynamic instability should be treated more promptly and aggressively because of the concern about diversion of blood flow away from the uterus.

Complete heart block, which in this age group is most likely to be of congenital origin, is consistent with a successful pregnancy. If required, a permanent pacemaker can be implanted.

Endocarditis

Infective endocarditis is uncommon during pregnancy and the puerperium. The clinical presentation and management of endocarditis during pregnancy is the same as at other times.

SPECIFIC FORMS OF HEART DISEASE

Rheumatic Heart Disease

Rheumatic mitral valve disease continues to be the most prevalent heart disease encountered in pregnant women in India. Women with rheumatic valvular heart disease (VHD), have high rate of clinical deterioration and a marked increase in morbid events during pregnancy, including CHF, arrhythmias and need to either initiate or increase cardiovascular drug therapy or to hospitalise patients during pregnancy. Pregnancy with VHD, may be associated with an increased incidence of intrauterine growth restriction (IUGR), preterm deliveries, and lower birth weight, especially in cases with moderate and severe stenosis of the mitral or aortic valve.

Acute Rheumatic Fever

This disease occurs only rarely during pregnancy and management is similar to that of non-pregnant patients.

Mitral Stenosis

This is the commonest VHD in pregnancy and represents a common health problem in our country. The increased preload of normal pregnancy, as well as other factors that require increased cardiac output, may cause ventricular failure with pulmonary oedema in these women with relatively fixed cardiac output. About 25% of women with mitral stenosis experience cardiac failure for the first time during pregnancy. In some cases, this may be confused with idiopathic peripartum cardiomyopathy. The most prominent complaint is dyspnoea due to pulmonary venous hypertension and pulmonary oedema. Other common symptoms are fatigue, palpitations, cough and haemoptysis.

The therapeutic approach is to reduce the heart rate and decrease blood volume. Limited physical activity is generally recommended. Prophylactically beta-blocking agents can be used and digoxin may be considered in patients with AF. For chronic AF, anticoagulation with heparin is also indicated. If symptoms of pulmonary congestion develop, activity is restricted even more, dietary sodium is restricted and diuretic therapy is started. Labour and delivery are particularly stressful for women with tight stenosis. Epidural analgesia for labour, with strict attention to avoid intravenous fluid overload, is ideal. Vaginal delivery is preferable. In symptomatic patients with moderate-to-severe stenosis (mitral valve area < 1.5 cm^2), haemodynamic monitoring is indicated during labour and delivery with haemodynamic optimisation by diuretics, beta-blockers, digoxin or nitroglycerin. Intrapartum endocarditis prophylaxis is required.

Closed mitral commissurotomy is associated with only minimal risk to the foetus and therefore, preferable to the open technique. It should be recommended only in centres where it is done routinely.

The safety and efficacy of percutaneous balloon mitral valvuloplasty (PBMV) has been reported by several investigators. Now, PBMV during pregnancy has been reported without foetal loss and should be the preferred modality of treatment in this subset of patients. Mitral valve repair or replacement during pregnancy should be considered only in cases with severe stenosis (mitral valve area < 1.0 cm^2), refractory to optimal medical therapy, PBMV is not feasible or when close follow-up during pregnancy, labour and delivery is not possible. When valve replacement is indicated, selection of the type of prosthesis should be based on its haemodynamic profile and durability and the need for anticoagulation.

Mitral Regurgitation

This condition is well tolerated in pregnancy. In symptomatic patients, diuretics are indicated, and digoxin may be beneficial in cases with impaired left ventricular systolic function.

Aortic Stenosis

Rheumatic aortic stenosis is unusual finding in pregnancy and may occur in conjunction with mitral valve disease in about 5% of pregnant patients with rheumatic valvular disease. Most patients with aortic stenosis (Valve area > 1.0 cm^2), tolerate pregnancy well. But patients with more severe stenosis may experience clinical deterioration with exertional dyspnoea, near-syncope or syncope and pulmonary oedema. Serious symptoms during pregnancy, if resistant to medical treatment, may necessitate termination of pregnancy or repair of the valve either surgically (valve replacement) or by percutaneous balloon valvuloplasty. For women with critical aortic stenosis, intensive monitoring during labour is necessary and epidural analgesia seems ideal, thus avoiding potentially hazardous hypotension.

Aortic Regurgitation

This condition is well tolerated in pregnancy. Symptoms necessitate salt restriction, diuretics and digoxin.

Prosthetic Valve Disease

A prosthetic valve is a relative contraindication to pregnancy. Maternal mortality is 3% to 4% with mechanical valves and foetal, loss is common. The critical issue is anticoagulation in cases with mechanical prosthesis. Full anticoagulation throughout pregnancy is recommended with subcutaneous heparin, maintaining anticoagulation at the high therapeutic level by following levels of factor Xa. Just before delivery, heparin is stopped. Protamine sulphate may be used to counter excessive bleeding. Anticoagulant therapy with warfarin or heparin may be restarted 6 hours following vaginal delivery. But anticoagulation should be withheld for at least 24 hours, following caesarean delivery. Antibiotic prophylaxis is necessary during labour.

Mitral Valve Prolapse

Pregnant women with mitral valve prolapse, rarely have cardiac complications. For women who are symptomatic, beta-blockers are used. Antibiotic prophylaxis for labour and delivery in patients with mitral valve prolapse, accompanied by valve thickening and/or regurgitation, seems warranted.

Congenital Heart Disease

A good maternal outcome can be expected in most cases with acyanotic congenital heart disease. Maternal functional capacity and cyanosis determine foetal outcome. Foetal wastage is about 45% in cyanotic mothers compared with 20% in acyanotic mothers with congenital heart disease. Prematurity and IUGR are common in cyanotic mothers. Risk of congenital heart disease is increased for the offspring of mothers with congenital heart disease with a reported incidence of 4% to 8%.

Elective induction of labour, when foetal maturity is confirmed, may be used in high-risk patients for better planning of haemodynamic monitoring. Vaginal delivery is preferred for

most patients, and caesarean section is indicated in stable patients only for obstetric reasons. Oxygen should be given to hypoxaemic mother during labour. Haemodynamic and blood gas monitoring is necessary in patients with impaired functional capacity, cardiac dysfunction, pulmonary hypertension, and cyanotic malformations. Blood loss should be treated promptly.

Antibiotic prophylaxis for vaginal delivery in all patients with congenital heart disease (except secundum type of ASD, 6 months or more after repair of septal defects or surgical ligation and division of patent ductus arteriosus), is necessary.

Atrial Septal Defect

Atrial septal defect is well tolerated in pregnancy. Pulmonary hypertension and atrial arrhythmias occur rarely and antibiotic prophylaxis is not indicated.

Ventricular Septal Defect

Isolated ventricular septal defect is usually well tolerated in pregnancy. The occasional congestive heart failure or arrhythmias, developing during pregnancy, can be managed in the usual manner. The incidence of ventricular septal defect in the offspring has been reported to be 4% to 11%. Volume depletion during or after delivery, may lead to shunt reversal, in patients with pulmonary hypertension. Prompt volume replacement is necessary to prevent further complications.

Patent Ductus Arteriosus

A patent ductus arteriosus is tolerated well during pregnancy. On occasion, congestive heart failure can occur, but standard treatment is effective. Antibiotic prophylaxis is recommended. Peripartum decrease in systemic blood pressure should be promptly corrected.

Congenital Aortic Valve Disease

Most patients with mild aortic stenosis have favourable outcome of pregnancy, provided that they are diagnosed early. Appropriate care, including haemodynamic monitoring during labour and delivery and appropriate anaesthesia are associated with favourable outcomes. Moderate and severe aortic stenosis may be associated with symptomatic deterioration during pregnancy and may lead to maternal morbidity and even mortality. Exertional dyspnoea, chest pain, light headedness, and syncope may develop in the second or third trimester. Increased incidence of cardiac defects has been reported in live born infants of mothers with left ventricular outflow obstruction. Optimal management strategies of a pregnant woman with severe aortic stenosis include early abortion followed by valve replacement and repeat pregnancy, and continuation of pregnancy and plan for percutaneous balloon valvuloplasty or surgical intervention who show clinical deterioration not controlled by medical therapy. These procedures have been performed successfully in pregnant women but are not free from complications. So, these interventions should be reserved for patients with severe disease, not manageable by medical therapy and should be avoided during first trimester.

Coarctation of Aorta

Both maternal and foetal outcome is usually favourable. In case of severe hypertension, congestive heart failure and aortic dissection may occur. To prevent aortic dissection and rupture of cerebral aneurysm, physical activity should be limited and blood pressure must be adequately lowered. Surgical correction can be performed successfully in patients with severe, uncontrolled systolic hypertension or heart failure.

Pulmonic Stenosis

Isolated pulmonic stenosis is usually well tolerated in pregnancy. Occasionally, progressive right ventricular failure, symptoms related to stenotic valve or intracardiac shunt at either the atrial or ventricular level with cyanosis may develop. Percutaneous balloon valvotomy should be considered in such situations.

Tetralogy of Fallot

Successful pregnancy can be achieved, but maternal mortality is high and foetal loss can exceed 50%. During labour and delivery, right to left shunt may increase. Maternal haematocrit above 60%, arterial oxygen saturation below 80% and syncopal episodes are poor prognostic signs. In cyanotic women, the rate of spontaneous abortion, premature deliveries and IUGR is high. Close monitoring of systemic blood pressure and blood gases during labour is necessary for cyanotic or symptomatic patients. Incidence of cardiac defects reported born to such mothers infants ranges between 3 and 17%.

Patients who have significant residual defects after repair, such as residual ventricular septal defect, pulmonic stenosis or regurgitation, and ventricular dysfunction, are still at higher risk during pregnancy. Patients who had undergone shunt procedures to improve cyanosis, may develop pulmonary hypertension, which increases the risk of pregnancy. After surgical repair, maternal and foetal outcomes improve markedly.

Eisenmenger's Syndrome

This condition leads to poor foetal outcome, with high incidence of foetal loss, prematurity, IUGR and perinatal death.

Since there is a high-risk of maternal mortality, patients with Eisenmenger's syndrome should be advised against pregnancy, and early abortion should be recommended for those who are already pregnant. In an overview of 125 pregnancies in patients with Eisenmenger's syndrome, primary and secondary pulmonary hypertension, maternal mortality was uniformly high at 36%, 30% and 56% respectively. The overall neonatal mortality was 13%.

Management of a patient who decides to proceed to term, must include close follow-up for early recognition of clinical deterioration. Anticoagulation is necessary in the third trimester and 4 weeks post-partum, to prevent peripartum thrombo-embolism. Since premature delivery is common, patients should be hospitalised for any sign of premature uterine activity. Early hospitalisation ensures restricted activity and close follow-up. Spontaneous delivery is preferred to induction, and should lower the chance of prematurity or the need for caesarean section. Blood pressure, ECG and blood gas monitoring are essential during labour and delivery to ensure early detection and correction of problems. High concentration of oxygen may be beneficial. Most patients with stable condition, tolerate vaginal delivery, but an attempt is to be made to shorten the second stage of labour by the use of forceps. A planned caesarean section is often preferred, to avoid risk of foetal distress during vaginal delivery and potential need for emergency caesarean section. Swan-Ganz catheter should be avoided.

Ebstein's Anomaly

Pregnancy with acyanotic Ebstein's anomaly is well tolerated. But in cyanotic cases, pregnancy is associated with increased risk of maternal heart failure, prematurity and foetal loss. The management during labour and delivery in symptomatic or cyanotic cases, includes antibiotic prophylaxis, oxygen inhalation, haemodynamic and blood gas monitoring, and measures to prevent a fall in systemic blood pressure due to peripheral vasodilatation or blood loss.

Complex Cyanotic Congenital Heart Disease

In India, very few successful pregnancies have been reported in patients with partially corrected and uncorrected cyanotic heart disease, like pulmonary and tricuspid atresia, transposition of great vessels, truncus arteriosus, single ventricle, double-outlet right ventricle and double-inlet left ventricle. A report (outside India) has demonstrated complications like, heart failure, thromboembolic events, supraventricular tachycardia, peri-partum infective endocarditis, high incidence of foetal wastage, premature deliveries, IUGR and both cardiac and non-cardiac congenital malformations, in such situations.

Marfan's Syndrome

In this condition, pregnancy may be associated with cardiovascular complications and a high-risk of having a child who will inherit the condition. Cardiovascular complications include dilatation of ascending aorta, leading to aortic regurgitation and congestive heart failure, and proximal and distal dissections of aorta with occasional involvement of the iliac and coronary arteries. Patients with aortic diameter less than 40 mm, usually tolerate pregnancy well. Marfan's syndrome may be associated with cervical incompetence, abnormal placental site and post-partum haemorrhagic complications. Women with Marfan's syndrome should be advised to avoid pregnancy and if already pregnant, interruption is recommended. Preconception echocardiographic assessment of the aorta and periodic follow-up during pregnancy are necessary and transoesophageal echocardiography is preferred. During pregnancy, physical activity should be restricted and beta-blockers should be administered. Substantial dilatation of aorta, necessitates therapeutic abortion or surgical intervention. Caesarean section should be preferred to minimise, haemodynamic stresses of vaginal delivery.

Hypertrophic Cardiomyopathy

In this condition, pregnancy is associated with a favourable outcome in most cases but there may be increased morbidity and even mortality. If congestive heart failure or abnormal rhythms occur, standard therapy is appropriate. Hypovolaemia should be avoided. Beta-blockers or calcium channel blockers may be used if necessary. Vaginal delivery is safe and second stage of labour may be shortened by the use of forceps. Antibiotic prophylaxis is necessary during labour and delivery.

Peripartum Cardiomyopathy

Symptoms usually occur during last trimester and is detected in the early peripartum period. The clinical presentation and haemodynamic changes are same as in other forms of dilated cardiomyopathy. The incidence is greater in elderly multiparous women with pre-eclampsia and twin pregnancies. There is relatively rapid recovery of cardiac size and function in large number of patients with recurrence of left ventricular dysfunction in subsequent pregnancies. About 50% to 60% of the patients show complete or near complete recovery of clinical status and cardiac function, usually within first 6 months post-partum. Rest of the patients demonstrate either further clinical deterioration, leading to early death or persistent left ventricular dysfunction and chronic heart failure.

Acute heart failure necessitates prompt treatment with oxygen, diuretics, digoxin and vasodilator agents. Anticoagulant therapy is necessary. The temporary use of an intra aortic balloon pump or left ventricular assist device may help stabilise the patient's conditions pending improvement. Intravenous immune globulin use, has shown a favourable effect on recovery of left ventricular dysfunction. Subsequent pregnancies should be discouraged.

CONCLUSION

With important exceptions, most women with cardiac disease can be expected to do well during pregnancy with appropriate management based on systematic risk stratification. Pregnancies deemed to be at intermediate or high-risk should be managed and delivered in a tertiary care setting. More thorough pre-pregnancy cardiovascular evaluations, is likely to better identify patients who are capable of proceeding safely with pregnancy and delivery. Best outcome is based on the strong relationships between physicians in cardiology and in high-risk obstetrics.

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Section 13

Gastroenterology

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13.1 Clinical Approach—Gastrointestinal Disorders

AC Anand

Patients with gastrointestinal diseases can have varied presentations. Symptoms like dysphagia, heartburn, abdominal pain, nausea, vomiting and haematemesis point to diseases of the upper gastrointestinal tract, while constipation, diarrhoea and haematochezia are commonly due to disease of the lower gastrointestinal tract. Diagnosis from individual gastrointestinal symptom may however be difficult at times as symptoms may overlap in a variety of diseases. For example, even the classic symptoms of peptic ulcer such as relief of pain by antacids or food and nocturnal pain are commonly seen in functional dyspepsia.

DYSPHAGIA, ODYNOPHAGIA AND HEARTBURN

Dysphagia, odynophagia and heartburn point towards oesophageal diseases as a cause of the symptoms. Dysphagia is difficulty in passage of solids or liquids from the mouth to the stomach. It should be distinguished from odynophagia, which is pain on swallowing. Heartburn is a burning sensation behind the sternum.

It is important to differentiate dysphagia into causes that mostly affect the pharynx or proximal oesophagus (high/oropharyngeal dysphagia) and low oesophageal dysphagia. Oropharyngeal (transfer) dysphagia is due to diseases of the neuromuscular mechanism of the pharynx and cricopharyngeus. The patient is unable to initiate and execute the swallow mechanism. There may be coughing or regurgitation of fluids from the nose while swallowing besides associated features of cranial nerve palsies in the form of dysarthria and hoarseness of voice. Low oesophageal dysphagia is due to diseases involving the body of the oesophagus and gastro-oesophageal junction.

The common causes of dysphagia are given in **Table 1** and the approach to a patient with dysphagia is summarised in **Figure 1**. The diagnosis can be confirmed by barium swallow, upper GI endoscopy and oesophageal motility study as indicated.

NAUSEA, RETCHING AND VOMITING

Nausea is an unpleasant feeling of wanting to vomit; this may be associated with autonomic features like increased salivation and sweating. Retching is a strong involuntary effort at vomiting. Vomiting is associated with bringing out of gastric contents through the mouth.

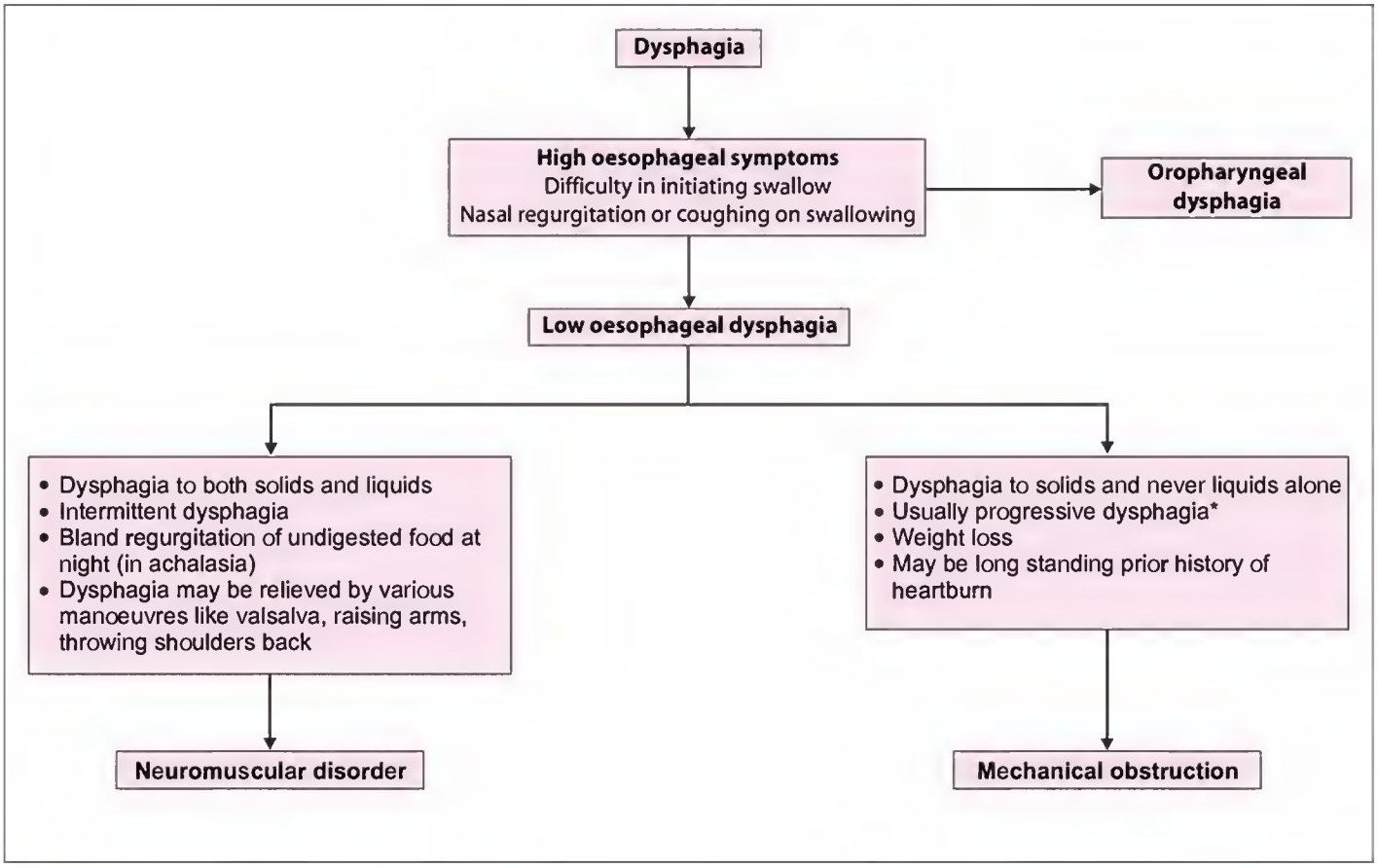


Figure 1: Approach to a case with dysphagia.
** May be intermittent dysphagia in an oesophageal ring.*

Gastrointestinal disorders causing vomiting include infections, bowel obstruction, cholecystitis, pancreatitis, infectious hepatitis, appendicitis and peptic ulcer. Vomiting may also be due to drugs, motion sickness, raised intracranial tension, meningitis, azotaemia, pregnancy, systemic illness and psychogenic causes.

Associated symptoms like abdominal pain and constipation point to a gastrointestinal aetiology. Vomitus may be projectile in raised intra-cranial tension. There may be stale food in vomitus in gastric outlet obstruction. The vomitus is bilious in obstruction distal to the duodenum. Vomiting of psychogenic aetiology occurs during or soon after a meal.

Table 1: Causes of Dysphagia

Oropharyngeal or high dysphagia	Neurological	Cerebrovascular accident Motor neurone disease Parkinson's disease Multiple sclerosis Myasthenia gravis
	Anatomical or muscular	Oropharyngeal malignancy (uncommon) Zenker's diverticulum Retropharyngeal abscess Cervical osteophyte
Low oesophageal dysphagia	Motility disorder	Achalasia Scleroderma Chagas disease Diffuse oesophageal spasms
	Mechanical obstruction	Webs Schatzki ring Neoplasm Strictures Dysphagia lusoria (due to aberrant subclavian artery)

DYSPEPSIA

Dyspepsia comprises of a group of upper abdominal symptoms including bloating, pain, postprandial fullness, heartburn and belching. Dyspepsia is defined as chronic or recurrent pain or discomfort centred in the upper abdomen. The first step in assessment is to select patients who will require early endoscopy and/or investigations to rule out serious diseases such as malignancy. The warning signs and symptoms that should alert the physician to a possibility of malignant disease are shown in **Table 2**.

Table 2: Alarm Symptoms in a Patient with Dyspepsia that Indicate High Risk for Serious Underlying Disease

Anaemia
Weight loss
Gastrointestinal bleed
Recent onset of progressive symptoms
Age >45 years
Dysphagia

ABDOMINAL PAIN

Abdominal pain can have three broad patterns: visceral, parietal, and referred.

Visceral Pain

Visceral pain is dull crampy and poorly localised. It is often in the midline because abdominal organs transmit afferents to both sides of the spinal cord. Pain location corresponds to those dermatomes that match the innervation of the diseased organ. Generally, visceral pain from abdominal organs proximal to the ligament of Treitz is felt in the epigastrium; pain from organs between the ligament of Treitz and the hepatic flexure of the colon is felt in the periumbilical region; and that from organs beyond the hepatic flexure is perceived in the lower abdomen midline. Pain arising in hollow organs may wax and wane due to peristaltic waves.

Parietal Pain

Parietal pain is well localised and sharp and is due to peritoneal irritation by the inflamed organ, e.g. appendicitis.

Referred Pain

Referred pain may be seen, for example, as shoulder pain due to liver abscess causing diaphragmatic irritation.

Assessment of cause of abdominal pain includes a careful history of onset, duration, progress, location, radiation, character and aggravating and relieving factors.

Clinical examination starts with inspection, which may show scars, hernias, splinting of abdominal movements, and visible peristalsis. A patient with peritonitis would lie still and the abdomen would be tender and would appear rigid. In contrast, a patient with ureteric colic may be rolling in bed due to pain. Visible peristalsis may be seen in bowel obstruction. Palpation may show a lump or tenderness. Guarding or rebound tenderness may be seen in peritonitis. Percussion may show ascites or obliteration of hepatic dullness in bowel perforation. Auscultation may reveal hyperactive or absent bowel sounds, besides bruits. Rectal examination can reveal a rectal growth or a pelvic abscess.

GASTROINTESTINAL BLEEDING

Bleeding from the GI tract can present as melaena, haematochezia or haematemesis; patients with occult bleed may present only with anaemia.

Melaena is black, tarry foul-smelling stool and usually signifies the presence of >50 mL of blood. It usually implies a proximal GI source. It takes about 12 hours of transit time for melaena to develop. It can rarely develop as a result of bleeding from right colonic sources.

Haematochezia (maroon bloody stools) can come from a proximal GI source if intestinal transit is rapid but usually signifies a lower GI source. Fresh red blood is commonly due to rectal or left colonic disease.

Haematemesis is blood in vomitus. It may be fresh bright-red or older coffee-ground material and signifies an upper GI bleed. The presence of haematemesis or melaena signifies an upper GI source but patients with rapid upper GI bleed may present with haematochezia.

Preliminary clues to the site of haemorrhage include the presence of haematemesis, hyperactive bowel sounds, and increased blood urea nitrogen out of proportion to creatinine (upper GI), or fresh rectal bleeding (colonic). Insertion of a nasogastric tube and aspiration may help in localisation of bleeding. However, it may be negative in some cases of upper GI bleed.

In upper GI bleeding, from a management point of view, it is important to differentiate between variceal and non-variceal aetiology. The clinical evaluation of upper GI bleed is shown in **Table 3**. Gastrointestinal endoscopy is usually required to make a definitive diagnosis. In obscure GI bleeding, one may need an isotope scan, angiography, or capsule or double-balloon enteroscopy to determine the source of bleeding.

Table 3: Differentiating Variceal from Non-Variceal Bleed

Variceal source suspected if GI bleeding is associated with
Jaundice
Ascites
Splenomegaly
Past history of treatment for liver disease
Clinical stigmata of chronic liver disease (spider naevi, palmar erythema, testicular atrophy, gynaecomastia, etc.)
Non-variceal source is suspected if bleeding is associated with
Absence of the above
History of epigastric pain
Past history of peptic ulcer
Recent NSAID intake
Recurrent vomiting/retching (Mallory-Weiss tear)

CONSTIPATION

Patients usually define constipation not only by infrequent stools (typically fewer than three per week), but also by associated symptoms which are equally important, and probably more important, such as: hard stools, the need for excessive straining, a sense of incomplete bowel evacuation, and excessive time spent on the toilet or in unsuccessful defaecation.

Constipation is a common symptom, more so in the elderly. A number of commonly used drugs in the elderly often aggravate constipation, including calcium supplements, iron supplements, diuretics, calcium-channel blockers, etc. A history of recent onset of constipation and/or blood mixed with stool raises the possibility of a malignant colonic lesion.

A thorough physical examination should be performed to exclude systemic or neurological illnesses that may cause constipation. Abdominal examination may reveal abdominal mass or palpable stools. Anorectal examination may reveal fissures, haemorrhoids, lack of anal sphincter tone or a rectal stricture.

Stool for occult blood is a useful screening test, while colonoscopic examination would be required to rule out local diseases.

DIARRHOEA

Diarrhoea is defined as increase of volume, frequency or fluidity of stool. It could be acute or chronic. Acute diarrhoea (< 4 weeks) is usually due to infections and is often self-limited. It may be associated with fever, pain in abdomen or dehydration.

Chronic diarrhoea (>4 weeks) may be associated with malabsorption and weight loss.

Evaluation of a case of chronic diarrhoea requires detailed clinical history. Malabsorption will be associated with semisolid (occasionally watery) stools that are bulky, float on water, and stick to the pan. The stools may be explosive in character and be associated with flatulence and borborygmi. It may contain undigested food particles, increase with lactose intake, and decrease on fasting. There may be mild periumbilical pain relieved by passage of flatus or stools. Small volume stools associated with blood, mucous and tenesmus are suggestive of large bowel diarrhoea. The clinical clues to aetiology of chronic diarrhoea are given in **Table 4**.

The approach to chronic diarrhoea (>4 weeks) should follow the following steps:

Table 4: Chronic Diarrhoea: Clinical Clues

Clubbing: Immunoproliferative small intestinal disease, Crohn's disease, coeliac disease
Fever: Tuberculosis, lymphoma, Whipple's disease, Crohn's disease/ulcerative colitis
Response to antibiotics: Bacterial overgrowth, giardiasis, tropical sprue, Whipple's disease
Response to steroids: Inflammatory bowel disease (IBD), microscopic colitis, eosinophilic gastroenteritis, Addison's disease
Arthritis: IBD, coeliac disease, Whipple's disease, collagen disorder
Lymphadenopathy: HIV, Whipple's disease, tuberculosis, lymphoma
Dermatitis herpetiformis: Coeliac disease
Pyoderma gangrenosum: IBD
Abdominal mass: Crohn's disease, lymphoma, tuberculosis

Step 1: Rule-Out Irritable Bowel Syndrome

Red flag symptoms that are against the diagnosis of irritable bowel syndrome are shown in **Table 5**.

Table 5: Red Flag Symptoms that make the Diagnosis of Irritable Bowel Syndrome Unlikely

Fever
Weight loss
Nocturnal diarrhoea
Blood in stools
↓ Haemoglobin, ↓ albumin, ↑ ESR
Recent symptoms in middle age/elderly

Step 2: Large Bowel versus Small Bowel (Table 6)

Table 6: Large Bowel Diarrhoea versus Small Bowel Diarrhoea

Large bowel diarrhoea	Small bowel diarrhoea
Presence of blood and mucous	Malodorous, floating, greasy, containing undigested food particles
Rectal/anal symptoms such as tenesmus/dyschezia	Large-volume stools
Small-volume jelly-like stools	Mid-abdominal cramps with borborygmi
Associated hypogastric cramps	

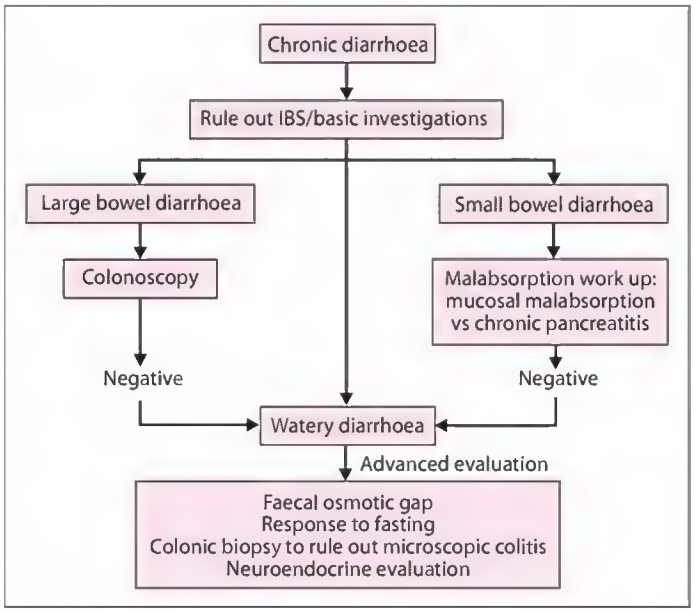


Figure 2: Approach to chronic diarrhoea: Basic clinical segregation of patient into small bowel diarrhoea and large bowel diarrhoea is usually adequate in directing evaluation. A small subgroup of patients with watery diarrhoea, in whom evaluation for the above have been negative, require advanced evaluation.

Step 3: Chronic Pancreatitis versus Mucosal Malabsorption

Features of carbohydrate malabsorption with lactose intolerance causing explosive stool with flatulence are suggestive of mucosal malabsorption. This can be confirmed by an abnormal d-xylose test. In chronic pancreatitis, classical history of pancreatic pain with radiation to back and imaging evidence of chronic pancreatitis are often clearly evident. The d-xylose test would be normal in chronic pancreatitis and faecal fat excretion is often more than 14 gm/day, much more than that seen in mucosal malabsorption. A clinical approach to chronic diarrhoea is shown in **Figure 2**.

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13.2 Investigations—Gastrointestinal Disorders

Ashok Chacko

INTRODUCTION

The gastrointestinal (GI) tract can be evaluated by examination of luminal contents, upper and lower GI endoscopy and various laboratory tests which may help in establishing diagnosis. In this chapter, author discusses about tests for luminal contents and laboratory tests while the endoscopy of GI tract has been covered in next chapter (see Chapter 3 Endoscopy—Diagnostic and Therapeutic Utility).

STOOL EXAMINATION

Stool examination must be performed in all patients with abdominal symptoms, especially diarrhoea. Stool inspection, often neglected, is important as it gives information regarding volume, consistency and presence of blood and mucous.

Stool microscopy helps in detection of RBC and pus cells—suggesting bacillary dysentery and inflammatory bowel disease, parasitic ova/cysts, and fat in stools (Sudan stain) suggesting malabsorption. In immunocompromised patients with diarrhoea, stool evaluation for parasites like *Cryptosporidium, Microsporidium, Isospora belli* and *Cyclospora* should be performed. Stool culture is not done routinely except in persistent diarrhoea. Stool positive for occult blood suggests GI blood loss and warrants further evaluation.

Acidic stools (pH <6) suggests carbohydrate malabsorption. Increased stool alpha 1-antitrypsin clearance helps in diagnosis of protein losing enteropathy. Stool DNA tests (k-ras, APC, p53) are promising screening tests for diagnosis of sporadic colorectal cancer.

Stool osmotic gap (290 - 2 [$Na^+ + K^+$]) is useful to distinguish osmotic from secretory diarrhoea. An osmotic gap >50 mOsm/kg is characteristic of osmotic diarrhoea whereas secretory diarrhoea has osmotic gap <50 mOsm/kg.

GASTRIC ACID SECRETION

Measurement of gastric acid output to evaluate peptic ulcer disease is not relevant now. It is occasionally used to distinguish Zollinger-Ellison syndrome (ZES) from achlorhydria in patients with elevated serum gastrin. Basal acid output (BAO) > 15 mmol per hour suggest ZES (normal BAO <5 mmol/h). Low values are seen in achlorhydria.

ABSORPTION

Tests of absorption are shown in **Table 1**. In assessment of suspected malabsorption, blood tests (CBC, folate, vitamin B12, albumin, anti TTG/endomysial antibody), barium meal follow through and endoscopy with distal duodenal biopsy are performed in most cases.

PANCREATIC EXOCRINE FUNCTION

Tests to evaluate pancreatic exocrine function are shown in **Table 2**. Clinical use of the tests are limited because stimulation tests need intubation and tubeless tests are not sensitive to diagnose early chronic pancreatitis.

Table 1: Tests of Small Intestinal Absorption

Absorption	Test	Method	Comments
Xylose (measures small bowel absorptive surface area)	Blood/urine xylose	Quantification in blood (1h) or urine (5 h collection) after ingestion of 5 g xylose Normal: Blood >0.55 mmol/L Urine >20% of ingested xylose	Rapid small bowel transit, renal failure, *ascites*, incomplete urine collection give false positive results
Fat	72 h faecal fat	Quantification of stool fat while patient ingests 50 g fat/d Normal: <6 g per day	Non-invasive, slow, unpleasant
	^{14}C triolein breath test	Measurement of $^{14}CO_2$ in breath after ingestion of ^{14}C triolein	Non-invasive, fast, not quantitative
Vitamin B12	Schilling test	Quantification of ^{57}CO and ^{58}CO (used to label free vitamin B12 and vitamin B12 - intrinsic factor complex) in 24-hour urine Normal: >10% with equal ratio of both isotopes after antibiotics	*Gastric disease*: Free vitamin B12 absorption decreased *Ileal disease*: Free vitamin B12 and vitamin B12 - IF factor complex absorption decreased *Bacterial overgrowth*: vitamin B12 normal
Lactose	Breath hydrogen	Measurement of breath hydrogen every 30 min for 2 hours after 50 g of lactose Hypolactasia >20 ppm	Early rise of breath H_2 in small bowel bacterial overgrowth
Bile acids	^{75}SeHCAT test	Isotopic quantification of 7 days whole body retention of oral dose ^{75}SeHCAT	Accurate and specific
		Normal: >15%	Involves radiation
		Abnormal: <5%	Slow

Table 2: Tests of Exocrine Pancreatic Functions

Test	Method	Comment
Secretin stimulation test	Injection secretin intra-venously followed by duodenal aspiration Aspirate assayed for bicarbonate	Invasive, expensive Chronic pancreatitis: low volume, low bicarbonate
Pancreolauryl test	Pancreatic esterases cleave fluorescein dilaurate after oral ingestion. Fluorescein absorbed and quantified in urine	Avoids duodenal intubation Test takes 2 days Low sensitivity for early chronic pancreatitis
NBT-PABA test	Pancreatic chymotrypsin releases PABA which is assayed in urine	Less reliable as compared to pancreolauryl test
Faecal chymotrypsin/ elastase	Immunoassay of chymotrypsin/elastase in stool	Simple, quick, does not detect mild disease

TESTS FOR MUCOSAL PERMEABILITY

Mucosal permeability of small bowel can be evaluated by ^{51}Cr-EDTA and sugar tests (lactulose-rhamnose). Urinary quantification of label after oral ingestion of ^{51}Cr-EDTA is performed. Increased level of label in urine suggests increased intestinal permeability.

The small intestine absorbs monosaccharides but not undigestable disaccharides (lactulose) unless mucosa is leaky. Lactulose-rhamnose test detects increased intestinal permeability and is abnormal in IBD, coeliac disease, tropical sprue, NSAIDS. The test is rarely used clinically as it is not specific.

MUCOSAL BIOPSY

If is obtained either by 'cupped biopsy forceps' passed through an accessory channel of an endoscope or by Crosby capsule per orally under fluoroscopic guidance. It provides definite histological diagnosis of the diseases of oesophagus, stomach, small bowel (duodenum, proximal jejunum), distal ileum and colon. Detection of *Helicobacter pylori* in stomach is rapidly performed by placing two gastric biopsy specimens (antrum, body) into a container using rapid urease kit which changes colour in a few minutes from yellow to red.

TESTS OF GASTROINTESTINAL MOTILITY

Radiological, manometric and radioisotope tests are used for evaluation of gut motility.

Oesophageal Motility

A careful barium swallow (using video fluoroscopy and bread barium) may give information about oesophageal motility. Oesophageal manometry which measures peristaltic performance, contraction wave configuration (amplitude, velocity), basal and post-swallow lower oesophageal sphincter pressure is the 'gold standard' test to evaluate motor disorders of oesophagus, like achalasia cardia and diffuse oesophageal spasm.

Monitoring gastro-oesophageal acid reflux with pH sensitive electrodes over 24 hours distinguishes refractory gastro-oesophageal reflux from other causes of chest pain and in relating atypical symptoms to episodes of reflux. A small portable recording device allows time of symptoms, meals and sleeping to be recorded which can be correlated with episodes of low pH.

Gastric Emptying

Delayed gastric emptying due to diabetic gastroparesis or gastric surgery may cause bloating, early satiety, nausea and vomiting. Endoscopy and barium studies are often normal. Gastric transit can reliably be measured by calculating the amount of radio isotope retained in the stomach after a test meal of solids and liquids labelled with different isotopes (Technetium/Indium).

Small Intestinal Transit

Oro-caecal transit can be estimated by lactulose-hydrogen breath test. Lactulose, a non-absorbable disaccharide reaches the colon intact. Bacterial metabolism of lactulose in the colon produces hydrogen. The time interval between ingestion of lactulose and rise in breath hydrogen give a measure of oro-caecal transit. Radionuclide techniques can also measure small bowel transit. Small bowel transit is seldom measured in clinical practice.

Colonic and Anorectal Motility

Total and segmental colon transit can be measured by plastic radio-opaque marker technique. The test is useful for evaluation of chronic constipation and helps differentiate slow transit constipation from obstructed defaecation. Obstructed defaecation and anorectal physiology are assessed by defaecating proctography and anorectal manometry.

BREATH TESTS

Breath tests are enlisted in **Table 3**.

Table 3: Breath Tests

Test	Indication	Positive Test
Hydrogen breath test		
Glucose	Small bowel bacterial overgrowth	>12 ppm rise over baseline within 120 min.
Lactulose	Small bowel transit	Time to first sustained response within 3-5 hours
Lactose	Hypolactasia	20 ppm rise over baseline within 3 h.
^{14}C-Xylose breath test	Bacterial overgrowth	$^{14}CO_2$ > 0.3% at 2-3 h
^{14}C-Glycocholic acid breath test	Bacterial overgrowth	$^{14}CO_2$ > 0.3% at 2-3 h
^{14}C-triolein breath test	Fat malabsorption	Breath $^{14}CO_2$ < 0.0005%
^{13}C or ^{14}C-Urea breath test	Confirm *H. pylori* eradication	$^{13/14}CO_2$ > 5-fold baseline at 20 min.

RADIOISOTOPE TESTS

Radioisotope tests are shown in **Table 4**.

Table 4: Radioisotope Tests

Test	Isotope	Indication
Gastric emptying	^{99m}Tc pertechnetate ^{111}In-DTPA	Gastroparesis
Urea breath test	^{14}C/^{13}C Urea	Confirm *H.pylori* eradication
Meckel's scan	^{99m}Tc-pertechnetate	Meckel's diverticulum in obscure GI bleed
Labelled red cell scan	^{51}Cr labelled erythrocytes	Obscure GI bleed
Labelled leucocyte scan	^{111}In or ^{99m}Tc HMPAO labelled leucocytes	Distribution of activity (extent) in inflammatory bowel disease
Albumin tagged scan	^{125}I-Albumin, ^{51}Cr-Albumin	Protein losing enteropathy

TUMOUR MARKERS

CA 19:9	Pancreatic and biliary malignancy
CEA	Colonic malignancy
Chromogranin	Neuroendocrine tumour

Molecular Tests

Disorder	Gene Affected
Familial adenomatous polyposis	APC
Multiple endocrine neoplasia	Menin
Hereditary non-polyposis colon cancer	hMSH 2, hMLH1
Peutz-Jegher syndrome	LKB1

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13.3 Endoscopy—Diagnostic and Therapeutic Utility

Gourdas Choudhuri

INTRODUCTION

Advancement in endoscopy has revolutionised our approach to diagnosis and management of various gastrointestinal disorders. The word endoscopy is derived from Greek, 'end' meaning within and 'skopein' meaning to view or observe. In this chapter upper gastrointestinal endoscopy, colonoscopy and endoscopic retrograde cholangio-pancreatography (ERCP) will be discussed in brief.

HISTORY

The first attempt at looking into the body cavity was made by Adolf Kussmaul who devised the first gastroscope in 1868, made up of a rigid metal tube. Subsequently Rudolf Schindler (1888-1968) improved this instrument but it was Basil Hirschowitz who pioneered the use of fibre optics (glass fibre that conduct light) that greatly improved the flexibility and manoeuvrability of the instrument. In 1957 he himself swallowed the first fibre optic gastroscope. The use of electronic chips (charge couple devices or CCD) to transmit the image from the tip of the endoscope to a video screen resulted in the present generation of video endoscopes since the 1980s.

UPPER GASTROINTESTINAL ENDOSCOPY (UGIE)

Indications

This largely depends on the suspected diagnosis, availability of facilities and expertise, and patient's choice. The common diagnostic and therapeutic indications for UGIE are given in **Table 1** and shown in **Figures 1 to 6**.

Contraindications

The absolute contraindications are given in **Table 2**. Apart from these conditions special precautions should be taken in patients with Zenker's diverticulum, compromised cardiovascular and pulmonary reserve and coagulopathy. Taking biopsy should be avoided in patients with coagulopathy. Pregnancy is not a contraindication for UGIE, but should only be performed for pressing indications.

Table 1: Indications for Upper Gastrointestinal Endoscopy

Diagnostic	Upper gastrointestinal bleeding: past or present
	Patients with splenomegaly or suspected chronic liver disease: for presence and grading of oesophago-gastric varices
	Upper abdominal distress that persists despite an appropriate trial of therapy
	Upper abdominal distress associated with symptoms or signs that suggest serious organic disease.
	Dysphagia or odynophagia
	Oesophageal reflux symptoms that are persistent or recurrent despite appropriate therapy
	Persistent nausea and vomiting of unknown cause
	Surveillance for malignancy
	Gastric or oesophageal ulcers
	Familial adenomatous polyposis
	Adenomatous gastric polyps
	Barrett's oesophagus
	Occult gastrointestinal bleeding
	Small bowel biopsy
	Cirrhotic patients in whom prophylactic therapy is considered
	After caustic ingestion to assess for acute injury
Therapeutic	Treatment of bleeding lesions
	Sclerotherapy or banding of varices
	Removal of foreign bodies
	Removal of selected polypoid lesions or superficial neoplasms
	Placement of feeding or drainage tubes
	Dilation of stenotic lesions
	Palliative treatment of stenosing neoplasms
	Drainage of pancreatic pseudocysts

Table 2: Contraindications for Upper Gastrointestinal Endoscopy

The risks to patient health or life are judged to outweigh the most favourable benefit of the procedure.
Adequate patient cooperation cannot be obtained.
A perforated viscus is known or suspected.



Figure 1: Upper gastrointestinal endoscopy showing large oesophageal varices with red colour signs.



Figure 2: Upper gastrointestinal endoscopy showing polypoidal, ulcerated growth suggestive of oesophageal cancer.



Figure 3: Upper gastrointestinal endoscopy showing a benign gastric ulcer.



Figure 4: Oesophageal variceal sclerotherapy. Note the blue scleropathy needle.



Figure 5: Glue injection being done in a patient with large, bleeding fundal varices.

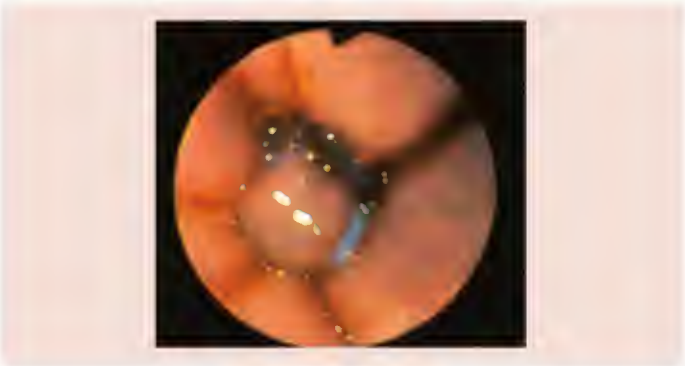


Figure 6: Oesophageal variceal band ligation. Note the blue 'O' ring on one of the varix.

Preparation and the Procedure

The procedure is performed after anaesthetising the pharynx with lignocaine spray or gel. Tense and apprehensive patients may need intravenous sedation with midazolam or propofol. The procedure is performed with the patient lying in the left lateral position. The endoscope is inserted through the mouth, pharynx, oesophagus, stomach and then further down to the second part of the duodenum under vision.

Complications of UGIE

Endoscopic examination of the upper gastrointestinal tract is a fairly safe procedure with overall complications being less than 1% and mortality rate <0.01%. Serious complications following diagnostic UGIE like perforation (0.01% to 0.11%) and bleeding (0.03% to 0.1%) are rare. Pulmonary complications like aspiration, decreased oxygen saturation and pulmonary infection are known to occur. The cardio-pulmonary complications include premature beats, arrhythmias and respiratory depression, which occur mostly due to use of pre-medications at the time of UGIE. There is a small risk of transmission of diseases like hepatitis B, hepatitis C, *Helicobacter pylori*, *Pseudomonas*, *Salmonella* and mycobacteria. Transient bacteraemia has been reported following oesophageal dilatation and sclerotherapy in up to 30% of cases; it has importance for patients with valvular heart disease who need prophylaxis with antibiotics for prevention of sub-acute bacterial endocarditis.

COLONOSCOPY

Since early 1970s colonoscopy is in common use in gastro-enterology. Although it is a more difficult and time consuming procedure compared to UGIE, it has become widely accepted as the most useful test for evaluation of the colon and terminal ileum.

Indications

The indications can be divided into two categories; diagnostic and therapeutic (**Table 3**) and shown in **Figures 7 to 9**.

Table 3: Indications for Colonoscopy

Diagnostic	Unexplained rectal bleeding
	Unexplained lower gastrointestinal symptoms and signs, such as recent onset constipation or feeling of incomplete evacuation, especially in the elderly
	Non-diagnostic radiographic examination
	Polyp and cancer screening or follow-up
	Inflammatory bowel disease
	Stricture or colonic narrowing (with and without inflammatory bowel disease)
	Diverticular disease
	Infectious colitis
	Radiation colitis
	Ischaemic colitis
	Endometriosis
	Pneumatosis cystoides intestinalis
Therapeutic	Polypectomy
	Foreign body removal
	Dilation of strictures in colon or terminal ileum
	Therapeutic: Haemostasis
	Tumour resection (palliative)
	Colonic decompression (volvulus and pseudo-obstruction)
	Placement of stents for non-resectable malignant obstruction

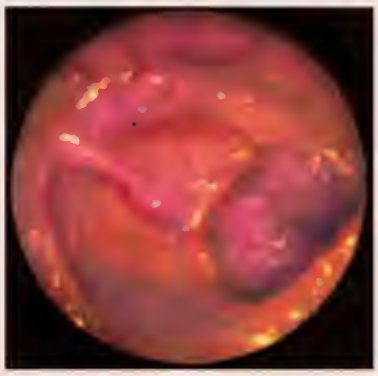


Figure 7: Colonoscopy showing a nodular polypoidal growth in the rectum suggestive of rectal cancer.



Figure 8: Colonoscopy showing ulcerations and pseudopolyps in a patient with ulcerative colitis.

Patient Preparation

A clean colon is mandatory for proper evaluation. Various agents are used to prepare the bowel for colonoscopy; they include polyethylene glycol (PEG) with electrolytes or sodium picosulphate. Before giving peroral bowel preparation in any patient, overt or impending bowel obstruction should be ruled out, to avoid precipitating acute intestinal obstruction.

Sedation and analgesics are more frequently used during colonoscopy than during UGIE. Most centres use midazolam alone or in combination with pentazocine.

Contraindications

Contraindications are listed in **Table 4**.

Table 4: Contraindications to Colonoscopy

Acute inflammation of the colon (fulminant), including ulcerative colitis, Crohn's colitis, ischaemic colitis, diverticulitis, and radiation colitis
Peritonitis
Suspected or impending intestinal perforation
Pregnancy (second and third trimester)
An uncooperative patient
Bleeding disorder
Acute cardiorespiratory disease or recent myocardial infarction
Shock
Large aortic or iliac artery aneurysm
Recent pelvic or colonic surgery

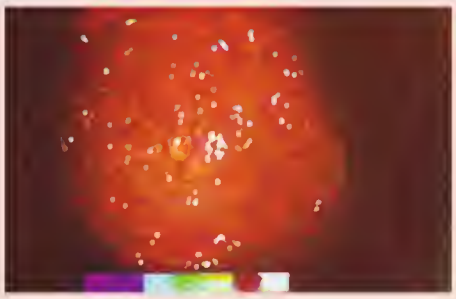


Figure 9: Colonoscopy showing multiple large polyps.

Complications

Apart from side-effects of sedatives and analgesics used and complications of peroral bowel preparation, some serious complications can occur during colonoscopy (**Table 5**).

Table 5: Complications of Diagnostic and Therapeutic Colonoscopy

Diagnostic Colonoscopy	Therapeutic Colonoscopy
Complications of bowel preparation	Perforation
Premedication related problems	Haemorrhage
Bacteraemia	Mucosal burns
Haemorrhage	Incomplete polypectomy
Perforation	Explosion
Diastatic serosal tears	Accidental removal of a urete-rosigmoidostomy stoma
Post-colonoscopy distension	Accidental removal of an intussuscepted appendiceal stump
Vaso-vagal reflex	Electrical ileal perforation
Splenic trauma	
Cardiac and electrocardiographic abnormalities	
A dynamic ileus	
Pneumatosis cystoides intestinalis	
Incarceration or impaction of an instrument in a hernia	
Aortic aneurysm dissection	
Cardiopulmonary problems	

The incidence of perforation and haemorrhage increase from <0.07% during diagnostic colonoscopy to 2.2% following therapeutic procedures like polypectomy. Deaths have rarely been reported following colonoscopy (<0.01%). Bacteraemia following colonoscopy has been reported in up to 27% of cases. Rarely transmural burns and explosion can occur after using electro-surgical instruments.

ENDOSCOPIC RETROGRADE CHOLANGIO-PANCREATOGRAPHY (ERCP) (FIGURES 10 and 11)

Endoscopic retrograde cholangio-pancreatography is a procedure by which the biliary and pancreatic ductal systems are visualised by injecting radio-opaque contrast solutions after endoscopic cannulation of the duodenal papilla. This is a difficult and potentially risky procedure which should be undertaken only by a properly trained and experienced endoscopist. In expert hands the procedure is successful more than 95% of times.

Indications

List of indications for diagnostic and therapeutic ERCP is given in **Table 6**.

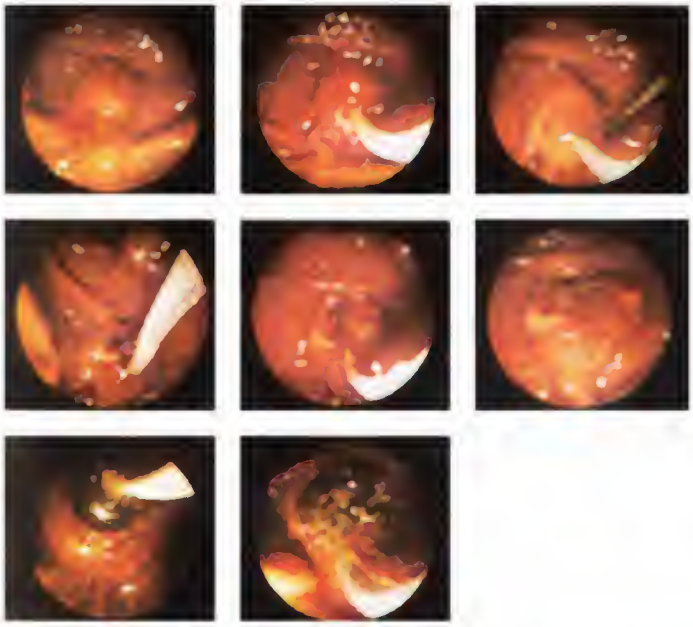


Figure 10: Impacted stone at the ampulla of vater being extracted during ERCP.



Figure 11: Biliary stent inserted during ERCP.

Table 6: Indications for ERCP

Diagnostic	Cholestatic jaundice
	Acute cholangitis
	Choledocholithiasis
	Sphincter of Oddi manometry
	Suspected sclerosing cholangitis
	Choledoschoscopy
	Bile for cytology and other studies
	Evaluation of peri-ampullary neoplasm
	Biliary pancreatitis, recurrent acute pancreatitis, chronic pancreatitis
	Evaluation of pancreatic pseudocyst
	Pancreatic fistula, pancreatic ascites
	Pancreatic juice aspiration for study
	Taking brush cytology or biopsy for confirmation of diagnosis
Therapeutic	Biliary drainage for cholangitis, pruritus, post-operative bile leak
	Extraction of stones, round worms or hydatid daughter cysts from bile duct
	Bile duct stricture dilatation
	Pancreatic duct stone extraction, pancreatic duct stricture dilatation
	Pancreatic duct stenting for pain in chronic pancreatitis, pancreatic ascites and fistula

Contraindications

The contraindications are same as those for upper gastrointestinal endoscopy. With advancement in non-invasive imaging such as MRCP or endoscopic ultrasound, ERCP is rarely required at present for diagnostic purposes. It should be undertaken in patients with suspected biliary obstruction only with sufficient preparations to drain the biliary system as well. The procedure also requires fluoroscopic guidance and hence contraindicated during early pregnancy.

Complications of ERCP

ERCP is a potentially risky procedure especially when therapeutic biliary and pancreatic procedures are performed. The complication rates are high if ERCP is done as an emergency procedure and by an inexperienced endoscopist. The complication rate is 5% to 10% and mortality is 0.5% to 1%. Major complications include post-ERCP pancreatitis in about 5%, haemorrhage (following sphincterotomy) in 2% to 3%, cholangitis 1% to 3% and retro-duodenal perforation in 1%. The list of complications of ERCP is given in **Table 7**.

Table 7: Complications of ERCP

Exposure to radiation	Perforation of duodenum
Pancreatitis	Haemorrhage
Allergy to contrast	Biliary/pancreatic sepsis
Trapped dormia basket	Splenic trauma
Subcapsular biloma of liver	Emphysematous cholecystitis

In addition to the three common standard procedures mentioned above, several new ones are now gaining importance.

1. Endoscopic ultrasound (EUS) is an instrument with a high frequency ultrasound probe mounted on the distal tip of a video-endoscope, and has emerged as the most accurate method for loco-regional staging of upper GI and pancreatobiliary tumours and for imaging the wall of the upper GI tract. It provides high resolution cross sectional imaging and is especially useful for imaging sub-mucosal or intramural lesions.
2. Enteroscopes are long video-endoscopes specially designed to inspect the small intestine. There are 2 types depending on whether it has a double or single balloon. These ballon enteroscopes can be used to inspect up to the mid ileum from the peroral route or from the anal route. They also have an operating channel for fulgurating bleeding lesions, removing polyps or taking biopsy.
3. Cholangioscope is a thin instrument that can be passed into the bile duct for imaging of stones or tumours. A variety of thin instruments can be passed through the operating channel of the ERCP scope, and can be useful for managing tight biliary obstruction due to cholangiocarcinomas or large biliary stones.
4. Contrast endoscopy: There are several new techniques that sharpen the distinction between normal and abnormal mucosa, facilitating better recognition and assessment of extent, as well as more accurate targeting of biopsy. They include chromoendoscopy or narrow band imaging.
5. Confocal endomicroscopy provides very high magnification and enables the cells of the surface layer to be viewed for

diagnosing dysplastic or anaplastic changes. Using this instrument one can diagnose a malignancy during the endoscopic procedure itself, without having to wait for the histopathology report.

FUTURE OF ENDOSCOPY

Endoscopes are now being used to enter the peritoneal cavity by producing a controlled gastric perforation. Having reached there, a diseased appendix or gallbladder can be removed through the natural orifice, i.e. mouth without an external scar. Thus, the procedure is called NOTES (Natural Orifice Trans Endoscopic Surgery). It is being actively developed in several advanced centres and holds promise in the near future.

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13.4 Diarrhoea and Malabsorption

BS Ramakrishna

Diarrhoea and malabsorption are disorders that are common in India possibly because of the prevailing lower levels of hygiene and unsafe water supplies. Diarrhoea is characterised by increased liquidity of stool or increased frequency of stool and is defined in different ways depending on the context in which the definition is required. For field studies of the prevalence or incidence of diarrhoea, diarrhoea is defined as three or more stools, taking the form of the container into which they are passed, in a 24 h period. For hospital-inpatient studies, diarrhoea is defined by a stool weight greater than 400 g/24 h (cf. Western definition of 200 g/24 h). In the outpatient clinic, diarrhoea is diagnosed when there is an increase in the frequency and liquidity of the stool compared to an earlier time period. Diarrhoea is categorised as 'acute' or chronic' depending on whether it has lasted less than 2 weeks or more than 4 weeks. In the setting of infectious gastroenteritis, diarrhoea lasting longer than 2 weeks is labelled as 'persistent' diarrhoea. Malabsorption syndromes are one of several causes of chronic diarrhoea. This chapter will review the causes and diagnostic pathways for diarrhoea and malabsorption especially as they pertain to India.

ACUTE DIARRHOEA

Acute diarrhoea is usually due to acute infectious gastroenteritis, although several other causes are shown in **Table 1**. Acute infectious gastroenteritis is a major cause of morbidity and childhood mortality. Over 1.5 million children (approximately 500,000 in India) continue to die worldwide each year because of the consequences of acute diarrhoea. This is significantly less than diarrhoea mortality of five million children per year twenty years ago. Currently, it is estimated that over a half of the diarrhoea deaths in children are associated with malnutrition.

Clinical Features

Acute diarrhoea presents with two basic syndromes—*watery diarrhoea* and *blood and mucous diarrhoea* (also called *dysentery*). When vomiting is very prominent and overshadows diarrhoea, the possibility of viral gastroenteritis or of food poisoning must be considered first. Watery diarrhoea is due to excessive fluid secretion from the small and/or large intestine. In its most dramatic form it is seen in cholera, where the patient may typically lose several litres of fluid in the stool in hours and present to the emergency department with peripheral vascular collapse and un-recordable blood pressure. Cholera, enterotoxigenic *Escherichia coli* infection, and viral gastroenteritis present with acute severe watery diarrhoea. The fluid secretion in watery diarrhoea is due to the effect of enterotoxins that increase the mucosal concentrations of cyclic nucleotides—cyclic AMP and cyclic GMP—which inhibit sodium absorption while turning on chloride secretion in the intestine. These ion movements lead to excessive retention and secretion of fluid into the lumen of the intestine. While cholera toxin and *E. coli* heat-labile enterotoxins were the prototypic enterotoxins, it is now shown that even viruses (rotavirus) and protozoan parasites (*Cryptosporidium*) produce enterotoxins that drive fluid secretion. Rotavirus infection is one of the most common causes of acute diarrhoea in infants and children and is a major cause of childhood deaths due to diarrhoea.

Acute blood and mucous diarrhoea (or dysentery) is usually due to invasive bacteria such as *Shigella* species, or enteroinvasive *E. coli*, as well as due to the protozoan pathogen, *Entamoeba histolytica* that causes amoebic dysentery. Bacillary dysentery is characterised by frequent small volume stools which are mostly a

Table 1: Causes of Acute Diarrhoea

Condition	Proximate Cause or Agent		
Infectious gastroenteritis	**Bacteria** *Vibrio cholerae* *Shigella* species - *S. dysenteriae*, *S. flexneri*, *S. boydii*, *S. sonnei* Pathogenic *Escherichia coli* (enterotoxigenic, enteroinvasive, enterohaemorrhagic, enteroaggregative) *Salmonellae* (non-typhoidal) *Campylobacter jejuni* *Clostridium difficile* *Aeromonas* species *Plesiomonas* species *Yersinia enterocolitica*	**Viruses** Rotavirus Calicivirus Enteric adenovirus Astrovirus	**Parasites** *Entamoeba histolytica* *Giardia intestinalis*
Antibiotic-associated diarrhoea	Alteration in commensal flora of gut Overgrowth of *Clostridium difficile*		
Traveller's diarrhoea	Altered bacterial flora in upper gut Pathogen (e.g. *Giardia*, enterotoxigenic *Escherichia coli*)		
Post-operative and nosocomial diarrhoea	Alteration in commensal flora of gut Drugs including antibiotics Enteral feeding		

mixture of blood and pus with little faecal matter. Fever and lower abdominal pain relieved by bowel movement may occur. Amoebic dysentery is characterised by fewer stools (frequency of 4 to 6 per day) which are larger in volume and contain mostly dark blood.

Diagnosis

In acute watery diarrhoea it is generally not necessary to investigate for the cause. Examination of the stool by dark field microscopy of a hanging drop shows actively motile bacteria in cholera infection. Stool culture establishes a bacterial aetiology when present, while rotavirus is diagnosed by enzyme immunoassay of the stool for rotavirus antigen. In patients with dysentery, it is very necessary to examine stool or a rectal swab smear under the microscope for evidence of pus cells, macrophages that have ingested red blood cells (bacillary exudate) and presence of *E. histolytica* trophozoites that have ingested RBCs. Presence of amoebic cysts alone does not establish a diagnosis of amoebic dysentery, since there are non-pathogenic amoebae in the intestine. Stool culture is necessary for the diagnosis of invasive bacterial pathogens. *Clostridium difficile* infection, that causes antibiotic-associated diarrhoea and colitis, is diagnosed by detecting toxin in the stool using enzyme immunoassay.

Complications

Haemoconcentration, pre-renal uraemia and renal failure due to acute tubular necrosis may occur as a consequence of acute watery diarrhoea. Death in acute gastroenteritis is usually due to the excessive loss of fluid with electrolyte imbalance, principally hypokalaemia and acidosis since the intestinal secretion is rich in potassium and bicarbonate. Persistent diarrhoea leading to malnutrition is another cause of death in children presenting with acute infective gastroenteritis. Complications associated with a dysenteric illness include sepsis, encephalopathy, haemolytic uraemic syndrome with renal failure, and rarely toxic megacolon, all of which may be associated with mortality. It is recently recognised that a significant number of individuals are afflicted with post-infective irritable bowel syndrome following an episode of acute gastroenteritis.

Management

In resource-poor settings, it is generally not necessary to investigate patients with acute watery diarrhoea before initiating therapy. It is necessary to evaluate the patient for evidence of dehydration. In adults, presence of tachycardia and orthostatic or postural hypotension signifies 10% loss of blood volume, while supine hypotension indicates loss of over 20% of circulating blood volume. In children and adults with severe dehydration, the lost fluid has to be replaced quickly by the intravenous route over a period of four to six hours. In cholera and severe diarrhoea, the choice of replacement fluid is Ringer's lactate solution which is similar in composition to the fluid lost in the stool and corrects the electrolyte losses. A volume equivalent to 10% of the body weight is infused over 4 hours in such individuals, the first 30% in one hour and remaining 70% in three hours. In patients with mild dehydration, it is sufficient to rehydrate the patient through the oral route. Oral rehydration therapy, which is based on the fact that glucose-linked sodium absorption in the small intestine is preserved in most patients with acute gastroenteritis even when sodium absorption in the absence of glucose is impaired, efficiently rehydrates patients with mild dehydration and prevents mortality. When oral rehydration solution (ORS) cannot be taken orally as in patients with profuse vomiting, intravenous rehydration is indicated. Antibiotics are not necessary in most patients with acute watery diarrhoea with the exception of cholera where antibiotic treatment significantly shortens diarrhoea. In suspected cholera it is usual to treat patients with an antibiotic to which the *Vibrio* in that geographic region is considered to be sensitive, either doxycycline 300 mg stat or ciprofloxacin 500 mg twice daily for three days or azithromycin 500 mg stat can be used. Antibiotics prolong faecal excretion of non-typhoidal *Salmonella* in immunocompetent individuals, and are therefore not administered. However, antibiotics need to be given to the very young and the elderly patient with salmonellosis, as well as to patients who have a prosthetic joint or valve.

The management of dysenteric illnesses is with an antibiotic to which the organism is sensitive, such as metronidazole 800 mg three times daily for amoebic dysentery or ciprofloxacin 500 mg twice daily for shigellosis. Patients with amoebic dysentery should typically receive diloxanide furoate for two weeks after treatment with metronidazole in order to ensure that the cyst forms of the parasite are eradicated. Antibiotics are used with care in enterohaemorrhagic *E. coli* infection since there is some evidence that some antibiotics may paradoxically worsen illness.

Prevention

Handwashing before and after eating or feeding a child is the most effective preventive intervention. Disinfection of drinking water at home is achieved by a variety of means. Safe drinking water and implementation of safe food handling practices are very important in a general context when eating out. Rotavirus vaccines have been introduced in several parts of the world. The first vaccine to be widely used was withdrawn because of development of intussusception in some patients. Rotavirus vaccines have now been shown to protect against severe diarrhoea in Mexico and Africa but are not yet included in the extended primary immunisation schedule in India. Cholera vaccines using an attenuated strain (Dukoral) are not widely available. A new killed whole cell vaccine has been shown to be effective in a large trial in India and may be widely available soon.

CHRONIC DIARRHOEA

Diarrhoea lasting longer than four weeks is termed as chronic diarrhoea. Infections, tropical sprue, coeliac disease and bacterial overgrowth in the small intestine are the major causes of chronic diarrhoea seen in clinical practice. These and rarer causes of chronic diarrhoea are listed in **Table 2**. This section will briefly describe an approach to the diagnosis of chronic diarrhoea but will not elaborate on the individual diseases.

Clinical Features

Patients with chronic diarrhoea must be carefully evaluated in order to separate functional from organic disease. The duration of the history, associated symptoms, co-morbid illnesses, diet history, medication history and family history are all important. A nutritional evaluation is important. The presence of nocturnal diarrhoea, presence of blood in the stool, and evidence of nutritional deficiencies suggests an organic cause such as malabsorption or inflammatory bowel disease. In order to facilitate investigation, it is usual for the specialist to categorise chronic diarrhoea as either small bowel or large bowel in origin.

Small bowel diarrhoea may be either secretory (large volume watery stool) or suggestive of steatorrhoea (pale, bulky, frothy, foul smelling) and is often not accompanied by pain. Large bowel diarrhoea is small in volume and is usually associated with abdominal pain, localised to the iliac fossae and relieved by defaecation, and with mucous and/or blood in the stool.

Table 2: Causes of Chronic Diarrhoea and Malabsorption

Tropical sprue Coeliac disease	Small intestinal mucosal atrophy
Small intestinal bacterial overgrowth	Strictures in small intestine, Motility disorders of gut Surgical bypass of gut with blind loop
Inflammatory bowel disorders	Tuberculosis Crohn's disease Ulcerative colitis Collagenous enteritis and colitis Microscopic colitis
Infections	Strongyloidiasis Capillariasis Isosporiasis Cryptosporidiasis Microsporidiosis HIV enteropathy
Chronic pancreatitis	Alcoholic, idiopathic and tropical pancreatitis
Malignancies	Lymphoma Carcinoid syndrome Pancreatic endocrine neoplasm (VIPoma)
Infiltrative disorders	Whipple's disease Eosinophilic gastroenteritis
Drug-related diarrhoea Laxative abuse	Antibiotics, chemotherapeutic agents, laxatives
Idiopathic bile acid malabsorption Factitious diarrhoea	

Diagnosis

Routine haematology and clinical chemistry are useful to separate organic from functional disease. Normal haemoglobin and red cell parameters, normal leucocyte counts, sedimentation rate, faecal examination for parasites and faecal occult blood, and liver function tests usually indicate absence of significant organic pathology in an untreated patient with chronic diarrhoea. Faecal testing for occult blood and for parasites (routine microscopy and special stains for protozoan parasites) is usually done on three consecutive samples. Further testing is usually dependent on clinical judgement of the cause of chronic diarrhoea. Where appropriate, patients may be tested for antibodies to the human immunodeficiency virus after counselling and for antibodies to tissue trans-glutaminase (to exclude coeliac disease). Patients with small bowel type of diarrhoea may undergo testing for malabsorption and imaging studies of the small bowel and lymph nodes followed by endoscopy and biopsies of the small intestine. In patients with large bowel type diarrhoea, the directed investigation consists of either sigmoidoscopy and rectal biopsy or ileocolonoscopy and biopsies. A significant minority of patients with chronic diarrhoea of organic nature will remain undiagnosed after all the above tests. In this group, unusual causes of chronic diarrhoea such as a pancreatic endocrine tumour or idiopathic bile acid malabsorption may need to be considered.

MALABSORPTION

Malabsorption syndromes are encountered not uncommonly in specialist gastroenterology practice in India. Over the last few decades, the profile of such diseases has changed significantly. Tropical sprue, once common all over India, has been replaced as the most common malabsorption syndrome by coeliac disease particularly in children in the Northern states of India. **Table 3** lists several malabsorption syndromes that occur in India.

Table 3: Malabsorption Syndromes and their Diagnosis

Syndrome	Diagnosis
Tropical sprue	Establish malabsorption Exclude other causes Demonstrate villus atrophy in small bowel biopsy
Coeliac disease	IgA antibody to tissue transglutaminase Small bowel biopsy showing increased intraepithelial lymphocyte number and villus atrophy Clinical, haematological, biochemical or histological response to gluten withdrawal
Parasites	Examination of wet mounts (stained and unstained) of stool or jejunal fluid for helminths larva or ova and protozoan cysts Examination of faecal smears with special stains—safranin, methylene blue, modified AFB stain EIA of faeces for antigens of *Giardia*, *Cryptosporidium*, microsporidia Small bowel biopsy
Bacterial overgrowth	Low serum vitamin B12 with normal or high folate Glucose breath hydrogen test Quantitative culture of jejunal fluid or mucosal biopsy
Pancreatic insufficiency	Increased faecal fat Pancreolauryl test Faecal chymotrypsin and elastase Pancreatic calcification on radiology
Eosinophilic gastroenteritis	Peripheral eosinophilia Small bowel biopsy showing increased eosinophilic infiltration
Immuno-proliferative small intestinal disease and lymphoma	Immunochemical detection of alpha heavy chain in serum Barium meal showing picket fence appearance of mucosa, and aneurysmal dilatation in frank lymphoma CT appearances of uniform thickening of bowel wall with lymph node involvement Small bowel biopsy showing characteristic effacement of crypts by lymphoplasmacytic infiltrate ranging from benign looking cells to lymphosarcoma
Intestinal lymphangiectasia	Duodenoscopy showing milky white spots especially after high fat meal Small bowel biopsy demonstrating dilated lymphatics in villi
Whipple's disease	Small bowel biopsy showing infiltration of lamina propria by PAS positive macrophages
Abetalipo-proteinaemia and hypobeta-lipoproteinaemia	Acanthocytosis on peripheral blood smear Small bowel biopsy demonstrating vacuolisation of surface epithelial cells

Clinical Features

Patients with malabsorption usually present with gastrointestinal symptoms, particularly chronic diarrhoea and weight loss. The basis for diarrhoea and other manifestations of malabsorption is shown in **Table 4** which will help the physician to understand why symptom constellations and specific physical signs are associated with particular disease processes. Although diarrhoea is the most common symptom in patients with malabsorption, earlier recognition of the malabsorption disorders in recent years has led to the emergence of atypical presentations without diarrhoea.

Table 4: Symptoms and Signs in Malabsorption and their Genesis

Symptom	Correlating physical sign	Pathophysiology
Diarrhoea	Dehydration Hypotension	Water malabsorption due to unabsorbed osmolytes, e.g. sugars Water secretion due to unabsorbed bile acids or fatty acids
Steatorrhoea	Reduction of skinfold thickness Loss of buccal fat pad	Fat malabsorption due to mucosal disease Fat maldigestion due to pancreatic insufficiency
Borborygmi, flatulence, bloating	Abdominal distension	Carbohydrate malabsorption due to mucosal disease or disaccharidase deficiency
Weight loss	Reduction of skinfold thickness Loss of buccal fat pad	Energy, fat and protein malnutrition Inflammation
Tiredness and weakness	Muscle wasting	Vitamin and mineral deficiency
Night blindness	Bitot's spots, keratomalacia	Vitamin A malabsorption due to steatorrhoea or bile salt deficiency
Bone pain	Bone tenderness, rickets	Vitamin D and calcium malabsorption
Burning in mouth	Glossitis, stomatitis	Vitamin B deficiencies
Tingling and numbness in feet and hands	Loss of ankle jerks Loss of proprioception	Vitamin B deficiencies
Anaemia	Flat nails, koilonychias Hyperpigmentation	Iron deficiency due to duodenal mucosal disease or blood loss Vitamin B12 deficiency in bacterial overgrowth, ileal disease Folate deficiency due to mucosal disease in upper gut
Amenorrhoea	Delayed secondary sexual characteristics	Secondary hypopituitarism
Stunting	Height for age Z score <-2	Secondary hypopituitarism
Skin lesions	Pellagra, nutritional dermatoses Acrodermatitis Dermatitis herpetiformis	Vitamin and essential fatty acid deficiencies Zinc deficiency Association with coeliac disease

Tropical sprue, also called idiopathic tropical malabsorption, is a disorder characterised by chronic diarrhoea, steatorrhoea, abdominal distension, prominent borborygmi, glossitis and multiple nutrient deficiencies. Tropical sprue occurred as epidemics in south India in the 1960s and 1970s but then disappeared. Sporadic tropical sprue was very common in the 1960s to 1980s but has gradually declined or disappeared in recent years.

Coeliac disease, caused by allergy to gliadin in wheat gluten, is particularly common in Western countries. While it has been reported in Indians since the 1960s, in the last two decades, the incidence of the disease has dramatically increased particularly in the northern states of Punjab, Uttar Pradesh and Delhi where the largest number of cases have been reported. Atypical presentations with anaemia, bone disease, short stature and menstrual disorders are described from India as in other countries.

Parasitic infestations also rank as a common cause of malabsorption in India. Helminth parasites that cause malabsorption include *Strongyloides stercoralis* and *Capillaria philippinensis* and these may affect immunocompetent individuals. Protozoan infections that cause malabsorption include *Giardia intestinalis*, *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora cayetanensis*, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. The last two are now thought to be fungi rather than protozoans. These usually cause malabsorption only in immunocompromised individuals including those with acquired immunodeficiency syndrome (AIDS) or with congenital immunodeficiencies such as common variable immunodeficiency.

Small intestinal bacterial overgrowth is another cause of malabsorption. Normally, the bacterial population of the small intestine is kept to a minimum by peristalsis. Bacterial overgrowth occurs primarily in conditions where the clearance of bacteria from the gut is impaired as in obstructive strictures due to tuberculosis or Crohn's disease, in diseases where gut motility is impaired such as diabetic autonomic neuropathy or progressive systemic sclerosis, and following surgical bypass of the gut with blind loops.

Infiltrative disorders of the intestine cause malabsorption, but are rarer. These include eosinophilic gastroenteritis, immunoproliferative small intestinal disease which includes the stage of immunoblastic lymphoma, and Whipple's disease.

A variety of other disorders cause malabsorption in infancy and childhood including abetalipoproteinaemia, lymphangiectasia, and disaccharidase deficiencies.

Diagnosis

Initial investigation includes the demonstration of nutrient deficiencies, e.g. anaemia, hypoalbuminaemia, by appropriate testing, along with faecal examination for parasites and occult blood. Detection of the protozoan parasites that cause malabsorption is facilitated by the use of special stains such

as safranin-methylene-blue and modified acid fast stains. Xylose, a pentose sugar that is not metabolised in humans, is given orally and 5-hour urine excretion (greater than 20% of dose ingested) is estimated as a direct measure of small intestinal sugar absorption. Faecal fat (normal <7 g/day) can be measured chemically by collecting stool collectively for three days while ingesting 50 to 100 g/day fat. Breath hydrogen excretion after oral ingestion of a digestible sugar such as lactose may be used as a measure of malabsorption but is fraught with inconsistencies. Breath hydrogen measurement after oral glucose is used to measure bacterial overgrowth in the upper small intestine. Serum iron, ferritin, vitamin B12 and folate, calcium and phosphorus are commonly measured in these patients. If malabsorption has been established, the next step is to image the small bowel by radiology (barium meal follow through or CT enteroclysis) or by endoscopy (enteroscopy) to exclude ulcerative or infiltrative disease. Mucosal biopsies are obtained from the third or fourth part of the duodenum or from the jejunum in order to elucidate the diagnosis.

Tropical sprue is essentially a diagnosis of exclusion, confirmed by the absence of parasites, tuberculosis or inflammatory bowel disease, and negative coeliac serology, with the presence of villous atrophy, crypt elongation and inflammatory cell infiltration of the lamina propria on small bowel biopsy. Coeliac disease diagnosis may be established by the finding of partial or complete villous atrophy and increased intraepithelial lymphocytes on small bowel biopsy, the presence of positive coeliac serology, and clinical and/or histological response to gluten withdrawal. The serological test used most commonly for the diagnosis of coeliac disease is IgA antibody to human tissue transglutaminase (anti-tTG), while anti-endomysial antibody is more specific but also not widely available. Pancreatic insufficiency used to be diagnosed by measuring duodenal trypsin after a fatty meal (Lundh test) but this is given up for tubeless tests such as the pancreolauryl test where fluorescein dilaurate is cleaved by a pancreatic enzyme cholesterol ester hydrolase and fluorescein measured in the urine. Faecal chymotrypsin and elastase are used also as measures of pancreatic insufficiency.

Management

Nutrient deficiencies that need to be urgently corrected include deficiencies of potassium and divalent cations (Ca, Mg) in patients with significant chronic diarrhoea. Megaloblastic anaemia due to vitamin B_{12} or folate deficiency also needs to be urgently treated with the appropriate vitamin given orally or parenterally. Adequate calorie and protein intake, with restriction of long chain triglycerides in patients with symptomatic steatorrhoea, must be maintained. Medium chain triglycerides may be used in patients with malabsorption due to pancreatic insufficiency. Fat-soluble vitamins, A, D and K, need to be given orally or parenterally in patients with significant long-term steatorrhoea.

Specific therapy depends on the nature of the condition causing malabsorption. Tropical sprue is treated with long-term antibiotics, typically tetracycline in a dose of 250 mg four times daily for up to 6 months. Coeliac disease is treated with strict gluten restriction, which has to be explained to the patient and family and monitored. Treatment of parasitic infections causing malabsorption depends on the specific parasite. *Strongyloides* and *Capillaria* infestations may be treated with albendazole or ivermectin, while protozoan infections are treated with co-trimoxazole, ciprofloxacin, or nitazoxanide in appropriate dose. Treatment needs to be for longer periods of time than uncomplicated infection, and in the case of the protozoan parasites it may also involve maintenance therapy since these occur in patients with immunodeficiency. Bacterial overgrowth is treated with periodic administration of antibiotics such as metronidazole, ciprofloxacin or with the non-absorbable antibiotic rifaximin.

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13.5 Constipation—Diagnosis and Management

Uday Chand Ghoshal

DEFINITION AND EPIDEMIOLOGY

The daily stool frequency in healthy population differs from thrice a week to twice a day in different geographical and ethnic groups. The Rome II consensus criteria based on western stool frequency, defines constipation as less than three stools per week with straining, excessively hard stool, unproductive urges and feeling of incomplete evacuation. However, many individuals would report themselves as constipated with stool frequency of three or more per week. Therefore, in Rome III criteria, stool frequency has not been given much importance while defining constipation. The stool frequency in India is different from that of the West. Therefore, the definition based on the frequency proposed for Western population does not hold true for Indian population. Hence, Asian consensus on irritable bowel syndrome proposed a definition based on the Bristol stool pattern (**Figure 1**). Passage of type 1 or 2 stool should be considered as constipation.

A second point to consider is difficulty in evacuating the bowel. Patients with this symptom often complain of stool that is hard to pass or pebble-like. This may suggest an outlet obstruction such as an intra-rectal intussusception or anismus. A third pattern is a combination of infrequency and dyschezia. Constipation-predominant irritable bowel syndrome may not fulfil the definition of constipation and has other gastrointestinal and extra-gastrointestinal symptoms in addition.

Constipation is a common symptom at all ages. In a study on 4500 adults from Indian community, 43 (1%) reported passing less than three stools per week. Although the exact frequency of constipation using various definitions in the Indian population is not known, it is likely to be common, but many individuals manage it on their own and do not consult doctors for the same. The perceptions of individuals and doctors about constipation differ, making an exact definition difficult.

AETIOPATHOGENESIS

Of the causes (**Table 1**) and types of constipation, many occur in the elderly. The important practical point is to identify the potentially serious causes. Pathophysiologically, constipation may result from slow colonic transit, faecal evacuation disorders (e.g. anismus or puborectal dyssynergia, rectocoele and perineal descent syndrome) and various combinations of these causes.

CLINICAL FEATURES

A careful history and physical examination usually give adequate pointers to the likely mechanism and type of constipation. Many patients, due to the chronic nature of the disease, tend to take a number of home remedies and seek a medical consultation only when a fresh set of symptoms supervene or the old symptoms get aggravated often due to refractoriness to laxative self-medication. This history is, therefore, important. Some of these fresh symptoms, particularly loss of body weight, rectal bleeding and constipation with spurious diarrhoea, may point to neoplastic disorder. History also helps in classifying the mechanism of constipation, like colonic inertia and functional outlet obstruction. Symptoms predict well colonic transit disturbances, but are relatively insensitive to suspect pelvic floor problems. Digital evacuation, passage of ribbon-like stool, feeling of rectal prolapse, and ability to pass stool in postures different from the usual posture, while pressing in and around the anus and supporting rectovaginal wall with fingers in the vagina may suggest functional disorder of faecal evacuation. A feeling that the

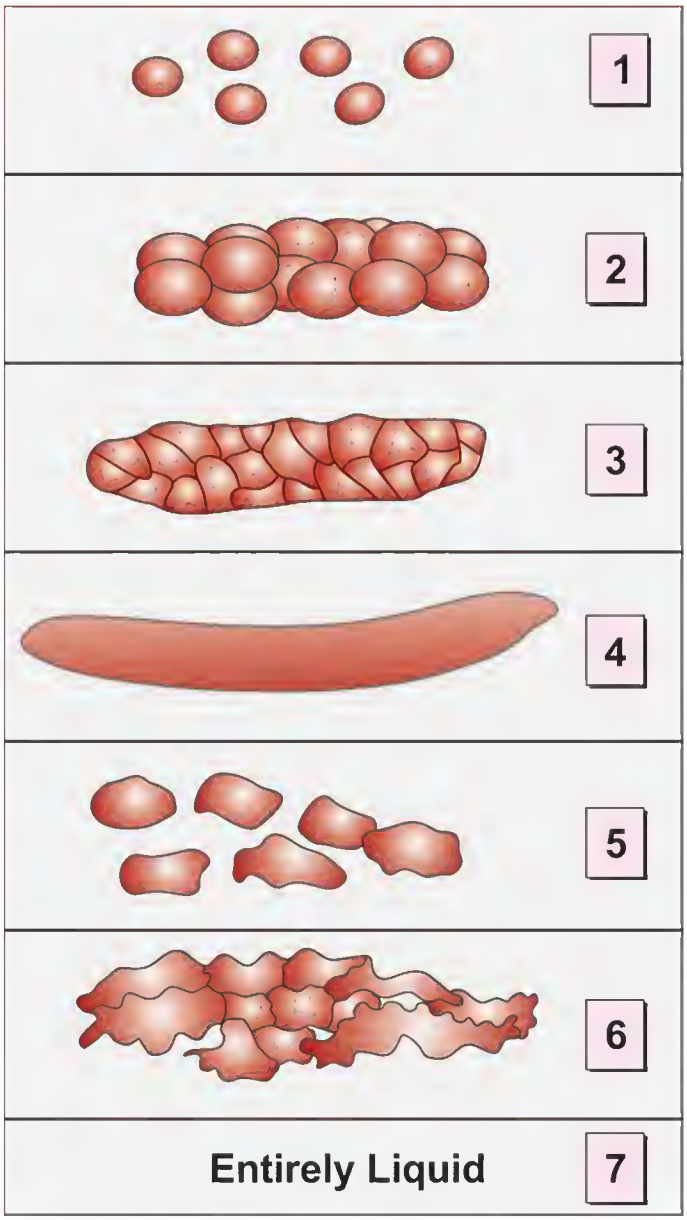


Figure 1: Bristol stool chart.

rectum is loaded with stool with urge to pass and repeated attempt for evacuation and straining at stool may also suggest functional disorder of faecal evacuation. Associated psychosocial disorders are common in these patients.

Table 1: Classification and Mechanisms of Constipation

Classification	Causes
Primary (idiopathic)	
Colonic inertia	Limited to colon or part of a global disorder
Functional outlet obstruction	Anismus Hypertonic internal anal sphincter Solitary rectal ulcer Mucosal intussusception Rectal prolapse
Secondary	
Endocrine/metabolic diseases	Diabetes mellitus Hypothyroidism Hypercalcaemia Porphyria
Neurogenic disorders	Spinal lesions: cauda equina syndrome and tumour Multiple sclerosis Autonomic neuropathy Parkinson's disease Hirschsprung's disease
Rectoanal disease	Anal fissure, haemorrhoids, strictures
Iatrogenic disease	Drugs, surgery
Dietary factors	Low-residue diet

Physical examination: A good physical examination should enable the physician to detect primary diseases like endocrinopathies and neurological disorders leading to constipation. Anorectal examination helps in diagnosing pelvic floor muscle weakness, sphincter disturbances, rectal sensitivity, stool consistency and faecal impaction. Per rectal examination may reveal low resting sphincter pressure due to weakness of the external anal sphincter; this may be related to pudendal neuropathy secondary to stretching of pudendal nerve from long-standing and prolonged straining during defaecation. Unusually high squeeze pressure during per rectal examination and anorectal manometry may suggest anismus, which is best diagnosed by defaecography.

MODALITIES OF DIAGNOSIS

In most patients with mild constipation, not many investigations are required. However, in patients with severe and refractory constipation several tests may be necessary to know the cause. **Table 2** shows the diagnostic tests useful in various forms of constipation and **Figure 2** shows a flow chart to diagnose various causes of constipation. Since a neoplastic disease always looms in the diagnosis of constipation in the elderly, the first investigations should always be proctosigmoidoscopy or if necessary colonoscopy and barium enema. Assessment of colonic transit by radio-opaque markers (**Figures 3A to E**) not only helps in diagnosis of slow-transit constipation but also gives suggestion about faecal evacuation disorder. Balloon expulsion test (**Figure 4**), in which the patient is asked to expel a latex balloon tied on a thin catheter that is placed inside rectum and

Table 2: Criteria for Diagnosis of Functional Anorectal Disorders Causing Constipation

Disorders	Diagnostic criteria
Anismus	Resting anal sphincter pressure >100 mmHg Abnormal balloon expulsion test
Puborectal dyssynergia	Failure of anorectal angle to open by >15° during defaecography between resting and defaecatory position No relaxation or increase in pressure on attempted defaecation Abnormal balloon expulsion test
Perineal descent syndrome	Failure of anorectal angle to open by >15° during defaecography between resting and defaecatory position Descent of perineum >4 cm during defaecation
Rectocoele	Herniation of rectal wall with either preferential filling during defaecography or failure to empty during defaecation
Non-specific syndrome	Symptoms, abnormal balloon expulsion test, but other criteria not fulfilled

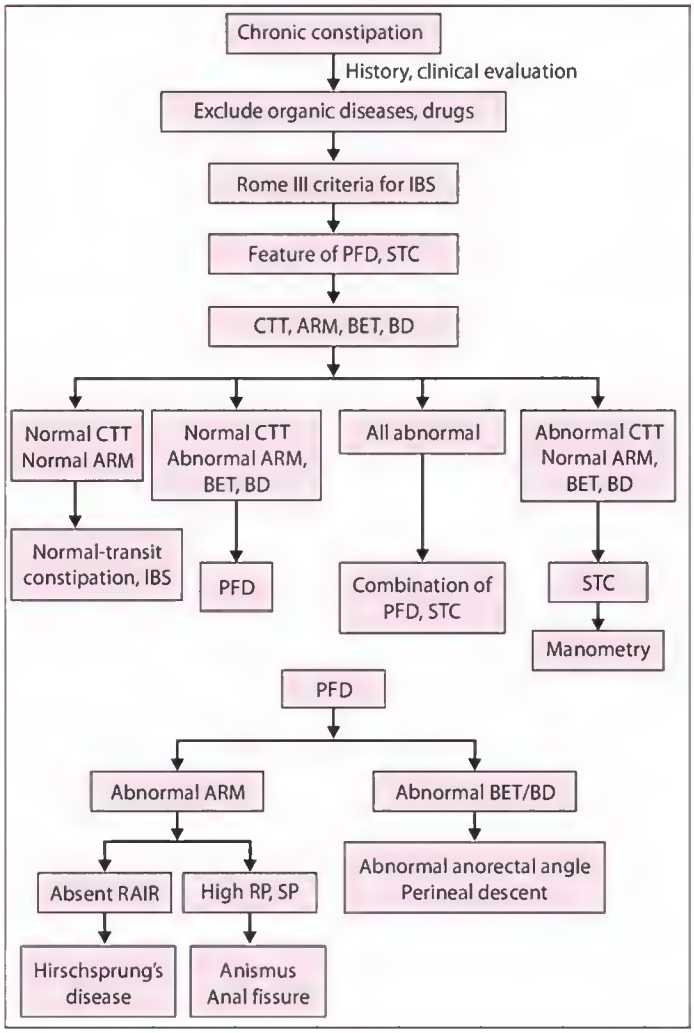
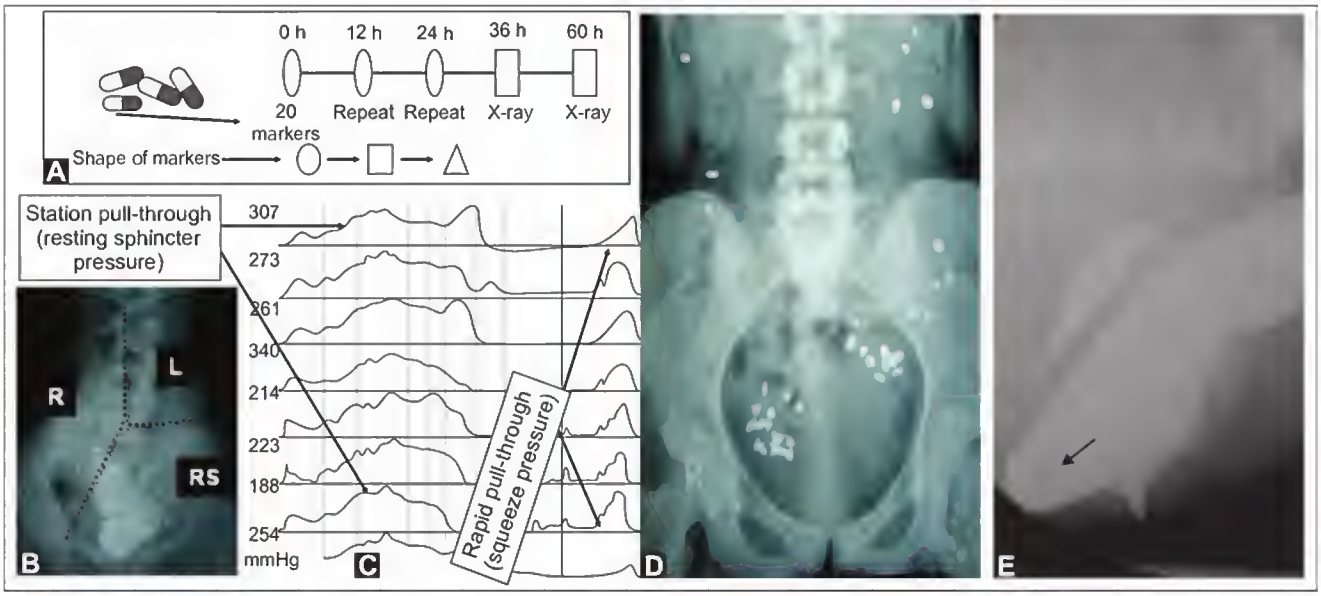


Figure 2: Flow chart showing a protocol for work-up for patients with refractory constipation.

IBS = Irritable bowel syndrome; PFD = Pelvic floor disorder; STC = Slow-tronsit constipotion; CTT = Colonic tronsit time; ARM = Anorectal monometry; BET = Bolloon expulsion test; BD = Borium defoecogrophy; RAIR = Rectoonol inhibitory reflex; RP = Resting pressure of anal sphincter; SP = Squeeze pressure.



Figures 3A to E: (A) Protocol for evaluation of colonic transit using radio-opaque markers (*SG-mark*), in Indian context. (B) sixty hours abdominal radiograph of a patient with constipation studied using such protocol, which shows that most of the markers are retained in the recto-sigmoid segment (RS) suggesting faecal evacuation disorder. Also note that there is retained barium inside rectum from the study done previously, which also suggest evacuation disorder. (C) Anorectal manometry of the same patient showed very high resting and squeeze sphincter pressure and hence, anismus was diagnosed. The patient improved with repeated sessions of biofeedback and osmotic laxative. (D) sixty hours abdominal radiograph of another patient with constipation studied using *SG-mark*, which shows that most of the markers are retained diffusely suggesting slow transit constipation. (E) Defaecography of a patient with constipation, showing a large rectocoele (marked with an arrow). (Reproduced from reference 7).

then filled with 60 mL of water while the patient is lying in the left lateral position, is a good screening test for faecal evacuation disorders. Faecal evacuation disorders are best diagnosed by barium (**Figures 3A to E**) or magnetic resonance defaecography, which helps in picking up intrarectal intussusception, pelvic floor descent, puborectal dyssynergia and rectal prolapse. The other techniques include anorectal ultrasonography for sphincter anatomy, and anorectal manometry. One should also look for systemic disorders causing constipation, such as hypothyroidism, diabetes mellitus, systemic amyloidosis and hypercalcaemia, when indicated.

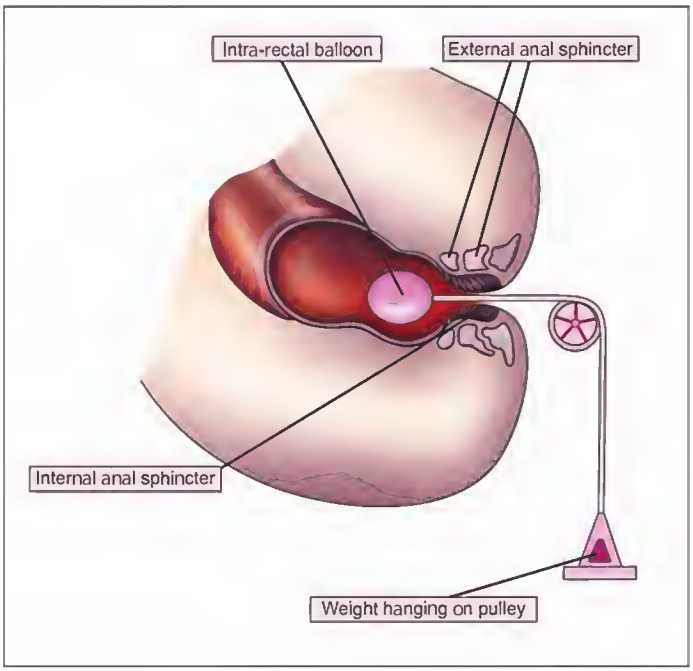


Figure 4: Balloon expulsion test.

TREATMENT

Treatment of primary constipation basically aims at symptom relief and improving quality of life. **Figure 5** outlines treatment protocol for patients with constipation.

Non-Pharmacological Treatment

Adequate diet replete with nutrition, liquids and fibre and physical activity are essential to ensure proper bowel function. Fibre intake must be at least 20 gm/day. It may be necessary to

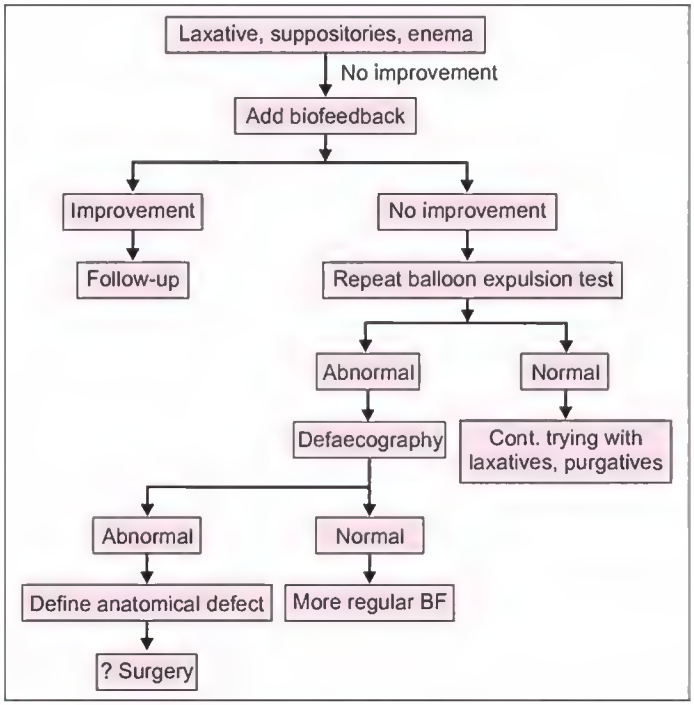


Figure 5: Outline of treatment protocol for faecal evacuation disorders. (Reproduced from reference 7).

BF = Biofeedback.

supplement with fibre-rich food or fibre medication. Physical activity is important to ensure general interest and zest for life, but attention to abdominal wall and pelvic floor muscles may actively help in initiating defaecation. Existing therapy may need to be modified; for instance, if the patient is on opioids for pain, the drug may have to be discontinued.

Pharmacological Treatment (Table 3)

Laxatives are needed in almost all patients with significant constipation. They help in improving the frequency and bulk of stools and thus ease bowel movements. Patients with colonic inertia are best treated with bulking agents like isphagula (15 to 20 gm daily) and methylcellulose (10 gm/day). Bulk laxatives may lead to bloating and excessive gas formation and precipitate intestinal obstruction in those with incipient gut obstruction. Patients with outlet obstruction are best treated with osmotic agents such as magnesium sulphate (15 to 45 mL/day), lactulose (15 to 45 mL/day) or polyethylene glycol (17 to 34 gm/day) (Table 3). These are poorly absorbed osmotically active substances that draw water into the lumen. They modify stool consistency effectively and ease bowel movements. Milk of magnesia is a cheap and safe medication. Other agents are equally effective and safer but more expensive. Stool softeners and stimulants are best avoided because of the danger of cathartic colon or melanosis coli, as with senna. Mineral oil and enemas should be avoided as regular therapy, but may be necessary in some patients infrequently. Mineral oils have a particular problem of depleting fat-soluble vitamins, which should then be supplemented.

Table 3: Commonly Available Agents for the Management of Constipation

Agents	Usual adult oral dose
Ispaghula husk	15 to 20 gm/day
Natural (e.g. psyllium husk)	7 gm/day
Synthetic (e.g. methylcellulose, polycarbophil)	4 to 6 gm/day
Osmotic laxatives	
Polyethylene glycol	8 to 25 gm/day
Lactulose	15 to 30 mL/day
Lactitol	10 to 20 gm/day
Sorbitol (70%)	15 to 30 mL/day
Magnesium hydroxide	2.4 gm (30 mL)
Magnesium citrate	200 mL/day
Stimulant laxatives	
Anthraquinones: Senna	8.5 to 17 mg/day
Diphenylmethanes: Bisacodyl	10 to 15 mg or 10 mg suppository/day

Biofeedback Programmes

Biofeedback has been proved to be useful in faecal evacuation disorders in about half to two-thirds of patients. Its role in the treatment of constipation due to other causes remains to be proved.

Surgery

Surgical treatment may be rarely necessary to correct anatomical problems like stenotic diverticulitis or outlet problems. Patients with colonic inertia due to visceral myopathy may also require surgical treatment such as colectomy in the long run. Surgical treatment, however, is best avoided as long as possible. Injection of botulinum toxin into the puborectal sling has been found to be useful in the treatment of puborectal dyssynergia.

COMPLICATIONS

Most causes of constipation usually do not produce major complications though these impair the quality of life. However, prolonged constipation and straining at stool can be complicated with haemorrhoids, anal fissure and faecal incontinence due to development of pudendal neuropathy. Also, sometimes patients may experience symptoms of large bowel obstruction. Megarectum can also develop due to prolonged constipation. Faecal evacuation disorders may be complicated with solitary rectal ulcer syndrome.

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13.6 Gastrointestinal Bleeding

Rakesh Kochhar, Mohd. Talha Noor

Gastrointestinal (GI) bleeding is a common and potentially life-threatening problem. Mortality rate of upper GI bleeding (6% to 10%) has remained unchanged over the years. Lower gastrointestinal bleeding requiring hospitalisation is only one-fifth as common as upper GI bleeding.

GENERAL FEATURES

GI bleeding may manifest in several ways. Haematemesis is defined as vomiting of blood. Gastric acid may alter the colour of the vomited blood. If vomiting occurs shortly after the onset of bleeding, the vomitus appears red. Precipitated blood clots and acid-degraded blood produce a characteristic 'coffee-ground' appearance of the vomitus. Haematemesis usually indicates a source of bleed proximal to the ligament of Trietz. Melaena is black, tarry, foul-smelling stool that results from formation of acid haematin and bacterial degradation of haemoglobin in the gastrointestinal tract. Melaena usually occurs due to bleed proximal to the ligament of Trietz but may at times be due to bleed from the small bowel or ascending colon if gastrointestinal transit time is prolonged. Approximately 60 mL of blood is required to produce a single melaenic stool. Melaena can persist for up to one week after an episode of massive upper GI bleed.

Haematochezia, the passage of bright red or maroon blood per rectum, generally signifies a bleeding source distal to the ligament of Trietz. However, brisk bleeding from a proximal source can also cause haematochezia due to rapid transit. Occult GI blood loss is evidence of blood as identified by laboratory testing of stool. Finally, patients with gastrointestinal blood loss may present with symptoms of blood loss, such as light-headedness, syncope, dyspnoea, angina, or even shock.

Initial Assessment

It is necessary to determine whether bleeding is acute or chronic and whether the patient is haemodynamically stable or not. The presence of GI bleeding should be confirmed by inspection of the stool or nasogastric aspirate. Careful assessment of the vital signs is the best way to judge a patient's stability. Blood loss of less than 500 mL is rarely associated with systemic signs. A postural fall in systolic blood pressure of >10 mmHg usually indicates a 20% or greater reduction in blood volume (**Table 1**). Concomitantly, the patient may have symptoms like light-headedness, syncope, nausea, diaphoresis and thirst. Shock frequently results when the blood loss is more than 25% of the blood volume. Patients may occasionally experience a vasovagal reaction with bradycardia during bleeding episodes. Haematocrit is used to assess the degree of blood loss. However, it does not fall immediately with haemorrhage because of proportionate reduction of plasma and red cell volumes and it reflects the true magnitude of bleed only after a period of 24 to 48 hours. Hence, during this time, the severity of bleeding must not be underestimated. With administration of intravenous fluids as well as entry of extravascular fluid into the vascular space to restore volume, the haematocrit falls. Serial haematocrit measurements are helpful in following a patient's course.

Table 1: Patient's Haemodynamic Status with Degree of Blood Loss

Patient's haemodynamic status	Blood loss %
Resting hypotension	>26
Postural hypotension	10-20
Normal	<10

Resuscitation

Insertion of two large-bore intravenous cannulae is recommended. Saline or lactated Ringer's solution should be infused to stabilise vital signs. Administration of supplemental oxygen may be of benefit in patients with inadequate oxygenation. Airway protection with endotracheal intubation to prevent aspiration should be strongly considered in patients with ongoing haematemesis if mental or respiratory status is altered. Those patients who are in shock have very low haematocrit (less than 20% to 25%), have symptoms related to poor tissue oxygenation (e.g. angina) or those who continue to bleed despite therapy are candidates for transfusion. The target to which the haematocrit value should be raised varies; in elderly it should be 30%; in younger and otherwise healthy patients it should be 20% to 30% and in patients with portal hypertension, it should not exceed 27% to 28%, so as not to raise portal pressure. Transfusion of packed red blood cells is preferred. Warmed blood should be administered to patients who require massive transfusion (i.e. >3,000 mL). Fresh frozen plasma (FFP) or platelets may be required in patients with coagulopathy or severe thrombocytopaenia, and in patients who require ten or more units of blood.

Differentiating Upper from Lower GI Bleeding

After resuscitation, the source of bleeding must be localised to direct further management. A nasogastric lavage must be performed irrespective of the probable site of the bleed. A bloody or a coffee ground aspirate confirms an upper GI source but their absence does not rule it out. A clear aspirate may be seen in up to 10% to 20% of patients with bleeding from a duodenal source. However, the presence of bile in the clear aspirate rules out a duodenal source. Other clues to upper GI bleeding include hyperactive bowel sounds and an elevation in blood urea nitrogen (BUN); the latter results from volume depletion and breakdown of blood proteins in the gut. Patients with lower GI bleed are less likely to present with shock or orthostatic symptoms as compared to patients with upper GI bleed. They have higher haemoglobin levels at presentation and also lower transfusion requirements.

DIAGNOSTIC EVALUATION OF PATIENTS WITH GI BLEEDING

Acute Upper Gastrointestinal Bleeding

History and physical examination

A history of prior episodes of bleeding, illnesses such as ulcers, cirrhosis, cancer or bleeding disorders, prior surgery (such as for peptic ulcer), consumption of excess of alcohol, and medications like nonsteroidal anti-inflammatory drugs (NSAIDs) and anti-coagulants should be elicited. Oesophago-gastric variceal bleed is painless and massive. A bleeding episode preceded by abdominal pain usually indicates underlying peptic ulcer disease. A history of retching and vomiting prior to haematemesis may indicate Mallory-Weiss syndrome. Examination of the skin may reveal cutaneous stigmata of cirrhosis. Rarely, evidence of underlying cancer (e.g. acanthosis nigricans), tumours (e.g. neurofibromatosis, blue rubber bleb nevus). Henoch-Schönlein purpura or vascular anomalies may be found. Skin and musculoskeletal abnormalities of pseudoxanthoma elasticum or Ehlers-Danlos syndrome may be diagnostic. Further clues on systemic examination include lymphadenopathy or abdominal masses, malignancy, abdominal tenderness (peptic ulcers, pancreatitis) and splenomegaly with or without prominent abdominal wall veins (cirrhosis, portal/splenic vein thrombosis).

INVESTIGATIONS

Endoscopy plays a major role in diagnosing the cause of GI blood loss. Other tests that may help include USG abdomen, CT scan of the abdomen and angiography.

Endoscopy

Endoscopy should be performed only after the patient has been haemodynamically stabilised. However, if the patient is bleeding massively and responding to resuscitative measures, endoscopy can be performed at the bedside provided adequate support personnel and with resuscitative facilities. Repeated gastric lavage prior to urgent endoscopy helps in clearing the stomach of blood clots, thereby providing a better field of view. Intravenous erythromycin can help clear the stomach if given half an hour before endoscopy. There is no role of cold saline lavage in controlling gastrointestinal bleeding. At endoscopy, detailed evaluation of the oesophagus, stomach and duodenum is carried out.

A majority of the bleeds occur from peptic ulcers, varices and erosions (**Table 2**). If there is no evidence of any of these, other uncommon lesions, especially vascular malformations should be carefully looked for. Endoscopy is superior to barium studies as it detects more lesions, it permits mucosal biopsy of suspicious lesions; it may act as a therapeutic modality; presence of active bleeding or stigmata or recent haemorrhage can provide prognostic information; and results of endoscopy guides the decision on the level of hospital care, on when to resume feeding and on length of hospitalisation. Endoscopic Forrest classification of peptic ulcer is useful for stratifying patients into high and low risk of rebleeding. Patient with Forrest 1a (active bleeding) and Forrest 1b (oozing vessel) at the time of endoscopy have high risk of rebleeding. Patients with Forrest 2a (visible vessel), Forrest 2b (adherent clot) and Forrest 2c (pigmented base) have moderate risk of rebleeding. Patients with Forrest 3 (clean base) have low risk of rebleeding. Patients in Forrest class 1, 2a and 2b benefit from endotherapy.

Other Diagnostic Tests

Ultrasound of the abdomen can provide evidence of portal hypertension in the form of coarsened liver echotexture, dilated splenoportal axis, presence of collaterals and splenomegaly, it should be carried out in all patients.

Computed tomography (CT) of the abdomen is useful to look for any evidence of pancreatitis, tumour or haemosuccus pancreaticus, CT angiography is useful in the diagnosis of visceral aneurysms.

AETIOLOGY AND MANAGEMENT OF UPPER GI BLEED

The various causes of upper GI bleed and management are given in **Table 2** and **Figure 1**. In India, most common aetiology is oesophageal variceal bleeding, other common causes are duodenal ulcer, gastric ulcer and gastritis.

Table 2: Causes of Upper Gastrointestinal Bleeding

Common causes
Peptic ulcer disease
Oesophageal and gastric varices
Oesophagitis
Gastric erosions
Duodenitis
Mallory-Weiss tear
Gastrointestinal malignancies
Uncommon causes
Angiodysplasia
Dieulafoy lesion
Cameron ulcers
Gastric antral vascular ectasia
Portal hypertensive gastropathy
Gastric polyps
Aortoenteric fistula
Haemobilia
Haemosuccus pancreaticus
Foreign bodies
Iatrogenic-nasogastric tube erosions, endoscopic polypectomy, sphincterotomy

Acute Variceal Haemorrhage

In India, non-cirrhotic portal hypertension (NCPF) account for up to 25% of portal hypertension, and they have a better prognosis than cirrhosis. Oesophageal varices are the site of bleeding in most patients. Bleeding from gastric varices can occur in patients with active as well as thrombosed oesophageal varices. Some patients may bleed from portal hypertensive gastropathy and gastric antral vascular ectasia. Treatment options for bleeding oesophageal varices include pharmacotherapy, balloon tamponade, endoscopic, transjugular intrahepatic portosystemic shunt and surgery. In the emergency room, if clinical suspicion of bleed being variceal is high, patients can be started on intravenous terlipressin 1 mg every 4 to 6 hourly or octreotide 50 to 100 µg bolus, followed by infusion at 50 µg/hour. Continuation of these drugs for 3 to 5 days after endoscopic treatment reduces chances of rebleeding. If the patient is bleeding actively and immediate endotherapy is not possible, an alternative of endoscopic therapy is balloon tamponade with Sengstaken Blakemore tube. It has two balloons, oesophageal and gastric, control of haemorrhage requires inflation of gastric balloon with 250 mL of air, oesophageal balloon is usually not inflated as it is associated with risk of oesophageal rupture. It is very effective in immediate controlling of bleeding in over 80%

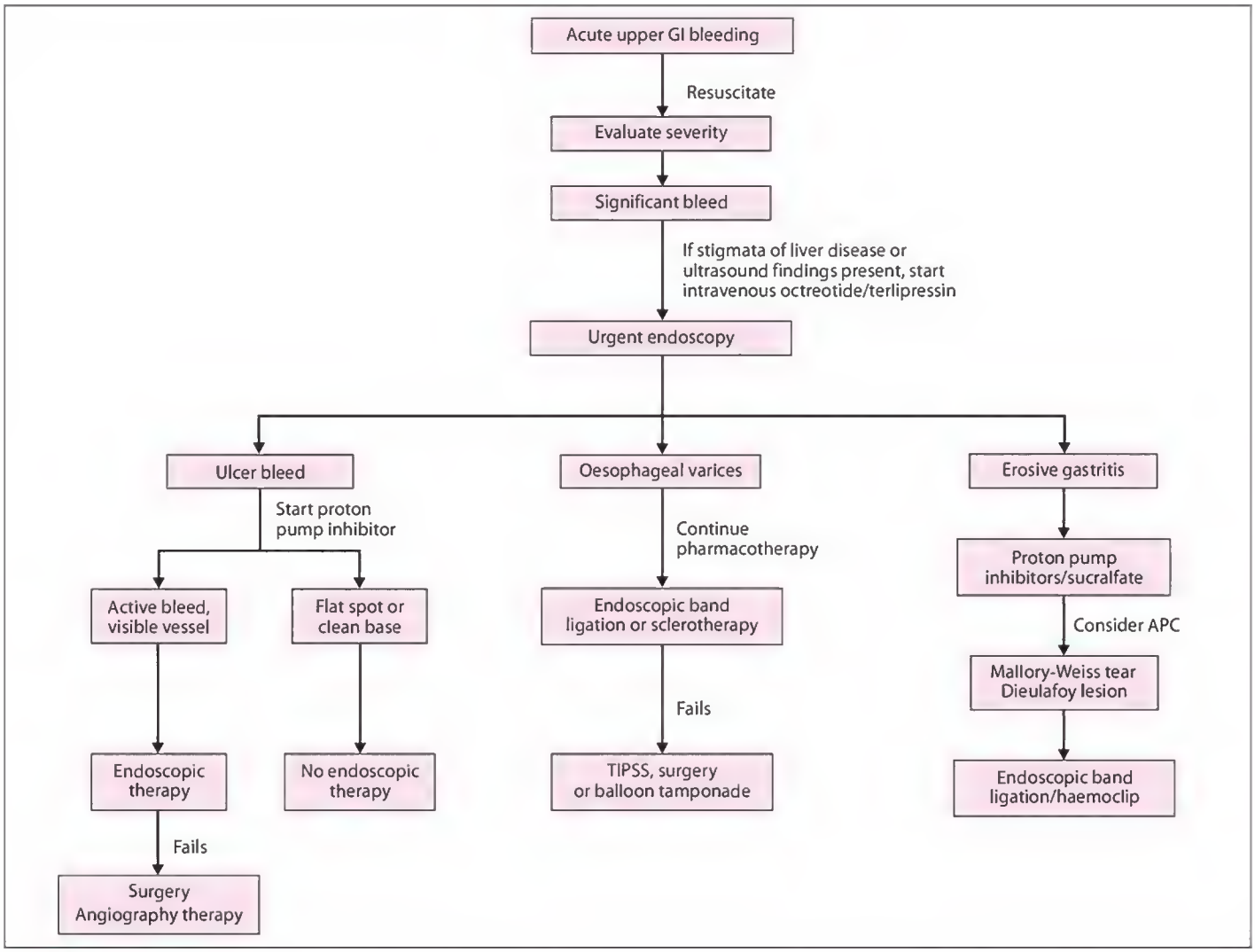


Figure 1: Algorithm for managing acute upper GI bleeding.

TIPSS = Transjugular intrahepatic porto-systemic shunt; APC = Argon plasma coagulation.

of patients. It is associated with 50% rebleeding after deflation of balloon. It is also associated with risk of oesophageal rupture, ulceration and aspiration pneumonia. Though associated with significant complications, balloon tamponade can be instituted even by primary physicians.

Endoscopic treatment options for bleeding oesophageal varices are endoscopic variceal ligation (EVL) and endoscopic sclerotherapy (ES). Both have an efficacy of about 90%. Endoscopic sclerotherapy involves visualisation of the varix during endoscopy, followed by injection of a sclerosing agent into the varix or into the adjacent tissue. Various sclerosing agents include sodium tetradecyl sulphate, polidocanol, sodium morrhuate and ethanol. Variceal obliteration is usually achieved after 3 to 6 sclerotherapy sessions at periodic intervals. Complications associated with ES include retrosternal pain, oesophageal ulcers and oesophageal stricture. EVL was first reported in 1989. The technique involves the placement of rubber bands around a portion of the varix containing oesophageal mucosa. The varix is sucked into a hollow, clear plastic cylinder attached to the tip of the endoscope. Once suctioned into the sheath, a trigger device allows deployment of the band around the varix. The blood flow is completely interrupted, producing ischaemic necrosis of the mucosa and submucosa. Later granulation takes place with sloughing of the rubber rings and necrotic tissue, leaving shallow mucosal ulcerations that heal in 14 to 21 days. Application of the bands is started at the gastroesophageal junction and progresses cephalad in a helical fashion. EVL sessions are repeated at approximately 2-week intervals until varices are obliterated, usually requiring 2 to 4 ligation sessions. Complications are less frequent than with endoscopic sclerotherapy.

Transjugular intrahepatic porto-systemic shunt (TIPSS) is a procedure in which a self-expanding metal stent is placed radiologically between the portal and hepatic veins. It is highly effective in reducing portal pressures and rebleeding and in controlling acute variceal haemorrhage. TIPSS is, however, associated with a risk of encephalopathy and shunt stenosis, although the latter risk is reduced with the use of the newer polytetrafluoroethylene covered stents. Recently a removable self-expanding oesophageal metal stent has also been used effectively in patients with variceal bleeding refractory to other treatment modalities.

Nowadays surgery is rarely needed for variceal bleeding. Surgical options include shunt and non-shunt procedures. The shunts are either total or selective. Total shunts include porta-caval, mesocaval and central splenorenal, selective shunt include distal splenorenal shunt. Non-shunt operations are gastroesophageal devascularisation or disconnection procedures.

For bleeding gastric varices, injection of N-butyl-cyanoacrylate can be made into the varices with good results. This modality can be used in actively bleeding gastric varices as well as to prevent rebleeding; 1 to 2 mL of cyanoacrylate is injected into the varix using a 21 gauge sclerotherapy needle. In refractory cases TIPSS is an effective treatment modality; it controls acute gastric variceal bleeding in over 90% patients. Balloon-occluded retrograde transvenous obliteration (B-RTO) is a new technique; it is highly effective in controlling acute gastric variceal bleeding. Bleeding from portal hypertensive gastropathy and gastric antral vascular ectasia is not massive but difficult to treat. Treatment of portal hypertensive gastropathy is directed towards underlying portal hypertension. First line therapy for gastric antral vascular ectasia (GAVE) is argon plasma coagulation. Recently, endoscopic variceal ligation has also been used for its treatment successfully. Apart from the treatment mentioned above, broad spectrum of antibiotics for a week have been shown to improve survival of these patients.

After control of initial haemorrhage, prevention of variceal rebleeding is an important aspect of the management of portal hypertension. Non-selective beta-blockers reduce cardiac output and cause splanchnic vasoconstriction, reducing portal venous pressure. Several randomised controlled trials comparing propranolol or nadolol with placebo have shown a reduction in rebleeding and mortality with beta blockers. Addition of isosorbide mono nitrate to beta-blockers enhances the efficacy of therapy but offers no survival advantage and reduces tolerance to therapy.

Peptic Ulcer Disease (PUD)

Most ulcer bleeds are from duodenal ulcers, though in patients on NSAIDs, bleeding from gastric ulcers is more common. An ulcer bleeds when it erodes into the lateral wall of a blood vessel. Ulcers located high on the lesser curve of stomach or on the posteroinferior wall of the duodenal bulb are most likely to bleed. *Helicobacter pylori* infection, NSAID use, and stress due to critical illness contribute to the development of ulcers.

Up to 80% of duodenal ulcers are caused by *Helicobacter pylori*, whereas about 50% of gastric ulcers are associated with this infection. NSAIDs constitute the most important cause of PUD after *H. pylori* infection, all patients who have PUD should be carefully questioned about NSAIDs use. NSAIDs induced ulcers may be painless because analgesic properties of NSAIDs can mask the pain of ulcers. Concurrent aspirin and oral anti-coagulant use increase the risk of bleeding. Other risk factors are cardiovascular or cerebrovascular disease and hospitalisation.

Bleeding stops spontaneously in 80% of instances. Patients with ongoing bleed, haemodynamic compromise, and high transfusion requirements mandate urgent endoscopic therapy, which can achieve haemostasis in more than 90% of cases. Surgical intervention is indicated in patients whose bleeding is refractory to endoscopic therapy.

Proton pump inhibitors (PPI) are the mainstay of pharmacological treatment. Proton pump inhibitors elevate the pH, thus, enhancing clot formation and platelet aggregation. PPI should preferably be given intravenously, though oral administration is also shown to be effective. High dose intravenous (IV) omeprazole or pantoprazole (80 mg IV bolus followed by 8 mg per hour for 72 hours) has been shown to reduce rebleeding rate and the need for surgery. Lansoprazole and esomeprazole are the other PPIs available for intravenous use. After the patient's condition stabilises, intravenous PPI therapy may be switched to oral PPI therapy.

Endoscopic therapy is accepted as the most effective method for controlling acute ulcer bleeding and for preventing rebleeding. Depending on the endoscopic appearance of the ulcer, different endoscopic modalities are applied. High risk ulcers are those that are bleeding actively and those with a non-bleeding visible vessel. These patients are shown to benefit the most from endoscopic therapy. Management of ulcers with adherent clots was controversial earlier, but now it has been shown that endoscopic therapy is superior to medical therapy for preventing recurrent haemorrhage in patients with bleeding peptic ulcers with adherent clots. Ulcers with flat pigmented spots or those with clean base have no additional benefit from endotherapy. The most popular endoscopic therapy is injection therapy using epinephrine (1:10,000). Other injection therapies include use of sclerosants, including sodium tetradecyl sulphate, polidocanol or ethanol. Biologic agents like thrombin, fibrin sealant and cynoacrylate glue can also be utilised. The assistant projects the needle, originally designed for injection sclerotherapy, about 5 mm beyond the plastic sheath, injects the solution, multiple injections are given around the ulcer to provide tamponade effect. Thermal methods for controlling bleeding include laser, electrocoagulation and heater probe. These can be combined with injection therapy. Newer techniques include application of metal clips, band ligation, argon plasma coagulation and endoloops. In patients with rebleeding, repeat endoscopy appears to be useful. Presence of hypotension at admission and an ulcer size larger than 2 cm are independent predictors of failure of endoscopic therapy.

Eradication of *H. pylori* and stopping NSAIDS are two factors shown to prevent recurrent bleeding. Relook endoscopy with retreatment in peptic ulcer bleeding significantly reduces the risk of recurrent bleeding, although it does not substantially reduce the need for subsequent surgery or mortality. In summary management of bleeding peptic ulcer include initial resuscitation, pharmacotherapy with proton pump inhibitors, endoscopic therapy and in refractory cases, surgery should be considered. Indications for surgery include failure of endoscopic therapy, large ulcer (>2 cm), massive bleeding and development of complications like perforation. Transcatheter arterial embolisation is reserved for patients who have exceptionally high risks for surgery (e.g. acute myocardial infarction).

Erosive Gastropathy

Erosive gastropathy refers to endoscopically visualised subepithelial haemorrhages and erosions that may account for upper GI bleeding in 15% to 25% of cases. Antacids, H_2 receptor blockers, proton pump inhibitors and sucralfate decrease bleeding from gastric erosions. Endoscopic, argon plasma coagulation has been found to be useful in the treatment of severe bleeding.

Mallory-Weiss Syndrome

Recurrent vomiting or retching can lead to mucosal tears at the gastro-oesophageal junction causing haematemesis. Bleeding

is usually not massive and stops spontaneously. Occasionally injection therapy or haemoclips may be required to control the bleeding.

Dieulafoy's Lesion

Dieulafoy's lesions are prominent submucosal vessels, usually found in the proximal stomach with no surrounding ulceration. These lesions are difficult to identify if they are not bleeding actively during endoscopy. Standard endoscopic injection, thermocoagulation, haemoclip, argon plasma coagulation or band ligation can successfully achieve haemostasis.

Gastrointestinal Malignancies

Endoscopy is used for diagnosis and for taking biopsies but it is usually ineffective in controlling the bleed.

ACUTE LOWER GASTROINTESTINAL BLEEDING

History and Physical Examination

Passage of drops of blood either separately or coating the stool may indicate bleeding from an anorectal source, especially haemorrhoids. Bloody diarrhoea with or without pain occurs in infective colitis or inflammatory bowel disease. Associated weight loss or recent change in bowel habits suggests colorectal cancer. A history of radiation therapy suggests radiation proctitis. The abdomen should be carefully examined to detect tenderness, organomegaly or a mass. A per rectal examination should always be performed to look for prolapsed haemorrhoids, mass polyp or ulcer.

Proctoscopy and Sigmoidoscopy

Patients with presumed lower GI bleeding must undergo early proctoscopy and sigmoidoscopy for the detection of obvious, low-lying lesions such as bleeding haemorrhoids, anal fissure, rectal ulcer, proctitis or rectal cancer.

Colonoscopy

If procto-sigmoidoscopy is not informative, colonoscopy is the next logical investigation. It is superior to barium enema since it can detect vascular lesions and allows biopsies to be taken. As 5% to 10% patients with upper GI lesions present with haematochezia, it is prudent to perform upper GI endoscopy before undertaking extensive investigations. Urgent colonoscopy in lower GI bleeding is safe with high likelihood of making a specific diagnosis (75% to 100%). Performance of colonoscopy requires preparation of the patient with purgatives, polyethylene glycol and sodium phosphate are the commonly used purgatives.

Angiography

Angiography is helpful in detecting the site of bleed in actively bleeding patients. Angiodysplasias are the commonest lesions detected by angiography. It may also show vascular malformations or tumours, even if extravasation of contrast material is not noted.

Radionuclide Scanning

It involves intravenous administration of ^{99m}Technetium tagged sulphur colloid or RBCs followed by imaging with an external gamma camera to detect intestinal extravasation of the substrate. It can detect bleeding even at a slower rate than that detected by angiography.

AETIOLOGY AND MANAGEMENT OF SPECIFIC CAUSES OF LOWER GI BLEED

The various causes and management of lower GI bleed are given in **Table 3** and **Figure 2**.

Table 3: Causes of Lower Gastrointestinal Bleeding

Common causes	Relative frequency in India
Colonic sources	*70% to 90%*
Haemorrhoids	30% to 40%
Inflammatory bowel disease	30% to 40%
Neoplasms	15% to 20%
Arteriovenous malformation, angiodysplasia	2% to 5%
Diverticula	2% to 5%
Small bowel source	*10% to 20%*
Meckel's diverticulum or other diverticula	
Vasculitis	
Ulcers, e.g. typhoid	
Less common causes	*2% to 5%*
Solitary rectal ulcer syndrome (SRUS)	
Infectious enterocolitis	
Ischaemic colitis	
Aortoenteric fistula	
Colonic varices in portal hypertension	
Radiation proctitis	
Lesions associated with use of NSAIDs	

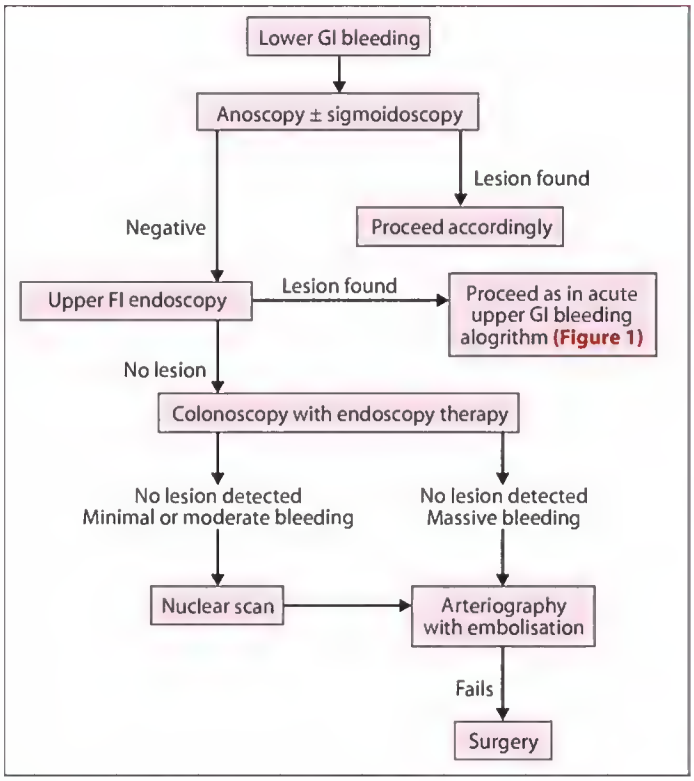


Figure 2: Algorithm for managing acute lower GI bleeding.

Anorectal Lesions

Haemorrhoids are the most common cause of lower GI bleed. Treatment may be in the form of sclerotherapy, banding, and cryotherapy. Surgery is required for large and prolapsed haemorrhoids. Solitary rectal ulcer syndrome (SRUS) is a benign condition in young individuals, which presents as rectal

bleeding, tenesmus and mucous discharge. Sigmoidoscopy with biopsy is essential for diagnosis. Treatment consists of avoiding digital rectal manipulation, laxatives and sucralfate enemas.

Inflammatory Bowel Disease (IBD)

Patients with IBD have a history of recurrent episodes of bloody diarrhoea. Colonoscopy with biopsy is required to differentiate IBD from other forms of colitis. Steroids and 5-aminosalicylic acid usually control the disease. Colectomy is required for massive bleeding not responding to medical management.

Polyps

Adenomatous colonic polyps can present with occult or overt rectal bleeding (if they are larger than 1 cm). Juvenile polyps are hamartomas occurring in the first two decades of life. Colonoscopic polypectomy is the treatment of choice. Bleeding from malignant colonic polyps requires colectomy.

Infectious Enterocolitis

Various invasive organisms viz. *Shigella, Salmonella, Campylobacter,* enteroinvasive *E. Coli, Clostridium difficile* and *Entamoeba histolytica* present with bloody diarrhoea. Diagnosis is usually made by routine examinations and culture of the stool. Treatment is with antibiotics.

Colonic Diverticula

Colonic diverticula are less frequent in the Indian population as compared to the West. However, in elderly patients especially those with complications, diverticular disease should be considered and looked for. Bleeding is abrupt in onset, usually painless and often massive, but ceases spontaneously in 80% of patients. Colonoscopy is required for diagnosis. Vasopressin infusion controls bleed temporarily. Segmental surgical resection is indicated for ongoing bleed.

Angiodysplasia

Angiodysplasia or arteriovenous malformations are also less frequent in Indians as compared to Western population. Bleeding from angiodysplasia is painless, trivial to massive in amount, recurrent and usually resolves spontaneously. Colonoscopic diagnosis and treatment by endoscopic electrocoagulation are generally successful in identification and definitive management of these lesions.

Ischaemic Colitis

Ischaemic colitis usually occurs in the elderly due to occlusion of a major vessel or low cardiac output. It usually presents with sudden, crampy, left lower abdominal pain and passage of bright red or maroon blood mixed with the stool. Bleeding is usually moderate. The splenic flexure, descending colon and sigmoid colon are most commonly affected. Colonoscopy shows segmental haemorrhagic mucosa with or without ulcerations. CT angiography is a non-invasive test which helps in diagnosis. Colectomy is required only if there are signs of bowel infarction.

Radiation Colitis

Symptoms of radiation colitis may occur few months to many years after abdominopelvic radiation usually for cancer of the cervix or prostate. Treatment using laser, argon plasma coagulation or sucralfate enema is effective.

Rectal Varices

Rectal varices are an uncommon cause of lower gastrointestinal bleeding, seen in patients with portal hypertension particularly extrahepatic portal venous obstruction. They can be successfully treated by endoscopic variceal ligation.

Postpolypectomy Bleeding

Postpolypectomy bleeding is the most frequent complication of colonoscopy and is seen in 0.2% to 1.8% cases of colonoscopic polypectomy. Delayed bleeding may occur up to 14 days after polypectomy. Endoscopic clipping is an effective treatment modality.

SMALL INTESTINAL BLEED

Only 3% to 5% of all GI bleeding arises between the second portion of the duodenum and the ileocaecal valve. Bleeding from this site is difficult to diagnose, since the small bowel is relatively inaccessible. Patients present either with chronic occult blood loss or with recurrent episodes of melaena. Repeated endoscopies and barium studies are often negative. Various causes of small intestinal bleed are given in **Table 4**. Vascular ectasias are the commonest cause of small intestinal bleed. Benign small bowel tumours (usually leiomyomas) are the second most common cause. Meckel's diverticulum is the cause of bleeding in two-third of males younger than 30 years presenting with small bowel bleeding. Bleeding is almost always brisk, resulting from ulceration within the diverticulum or the adjoining ileal mucosa.

Table 4: Differential Diagnosis of Occult-GI Bleeding

Mass lesions in colon or small intestine
Carcinoma
Adenoma
Inflammation
Erosive oesophagitis/gastritis
Ulcer (any site)
Coeliac disease
Inflammatory bowel disease
Colitis (non-specific)
Worm infestation (hookworm, whipworm, strongyloidiasis, ascariasis)
Tuberculous enterocolitis
Amoebiasis
Other causes
Drug intake
Haemosuccus pancreatitis
Haemobilia
Vascular disorders (haemangioma, Dieulafoy's lesion)

GASTROINTESTINAL BLEEDING OF OBSCURE ORIGIN

Obscure bleeding is defined as recurrent bouts of acute or chronic GI bleeding for which no definite source has been discovered by routine endoscopic and barium contrast studies. Obscure gastrointestinal bleeding can be overt or occult, depending upon the presence or absence of clinically evident bleeding. Causes of gastrointestinal bleeding that are commonly missed on upper gastrointestinal endoscopy are Cameron's erosion, gastric varices, Dieulafoy's lesion, angiodysplasia, oesophagitis, portal hypertensive gastropathy and gastric antral vascular ectasia. Therefore, upper gastrointestinal endoscopy should be repeated, if it is negative then a cause in the small bowel should be looked

for. The most common cause of obscure GI bleeding is vascular ectasia of the small bowel. Certain lesions are difficult to diagnose because of their rarity or their subtle appearance; and some lesions are detectable only if active bleeding is seen endoscopically (e.g. Dieulafoy's lesion). Tubercular enteritis/colitis is another cause of obscure GI bleed in our country. Worm infestation, especially with hookworms, is a common cause of anaemia in India. With a heavy parasite load, some patients may have continuous ooze from the small intestine and may have positive stool occult blood. Stool examination is diagnostic. An approach to management of obscure gastrointestinal bleeding is given in **Figure 3**.

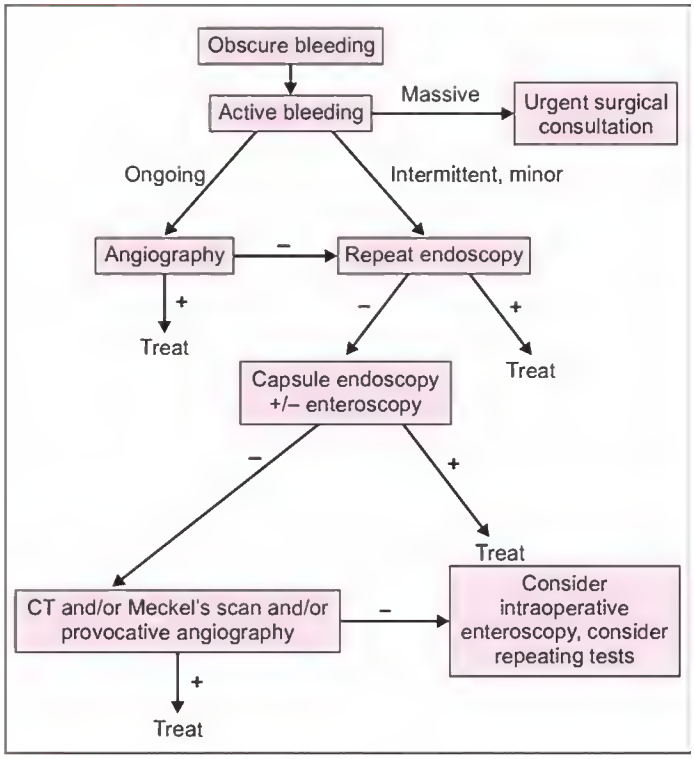


Figure 3: Algorithm for managing obscure gastrointestinal bleeding.

Angiography is performed only if bleeding is likely to be beyond duodenum and is so massive that endoscopy cannot be safely or satisfactorily performed and surgery is contraindicated. Blood loss must be greater than 0.5 mL/min for angiography to detect the site of bleed. Selective mesenteric angiography usually localises the site of bleeding in about 75% of such patients. Radionuclide imaging studies are not useful in the evaluation of upper GI bleeding.

Radionuclide scanning is a sensitive method for detecting gastrointestinal bleeding at a rate of 0.1 mL/min. This technique is more sensitive, but less specific than angiography. The major disadvantages are that nuclear imaging localises bleeding only to an area of the abdomen and the intraluminal blood is moved away by intestinal motility leading to false localisation. For proximal small bowel push enteroscopy permits inspection of the entire duodenum and part of the jejunum.

Capsule endoscopy (CE) was launched at the beginning of this millennium and since then it has had a very important impact on managing obscure gastrointestinal bleeding. Before the advent of CE, small bowel was an organ which was very difficult to explore with available endoscopic, radiological and nuclear medicine techniques. Wireless CE is simple, safe, non-invasive, reliable procedure, well accepted and tolerated by the patient. This technique evaluates with high resolution images, the whole small bowel, avoiding surgery or radiation exposure. In this technique a small capsule camera is swallowed by the patient (capsule enteroscopy). It takes up to 50,000 photographs of the entire small intestine and transmits the images to a data recorder externally, enabling visualisation of areas where the endoscope cannot reach.

Double-balloon enteroscopy is another new technique that allows access to the whole of the small bowel with the added advantage of therapeutic option, like haemoclip application or polypectomy, etc. As inferred from its name, the two inflatable balloons are the crux of the double balloon system. An overtube is backloaded onto the endoscope before intubation. The distal ends of the overtube and of the endoscope are fitted with inflatable/deflatable air-filled latex balloons. When inflated to 45 mmHg, the balloons grip the intestinal lumen, providing traction against the wall without undue pressure. Exploratory laparotomy with intra-operative endoscopy is indicated in patients with severe recurrent or persistent bleeding in whom all other investigative modalities have proved unsuccessful. Scintigraphy and mesenteric angiography can also be done to guide the surgeon in patients prior to exploratory laparotomy.

Faecal Occult Blood

Various causes of occult gastrointestinal bleeding are given in **Table 4**. An important cause of chronic occult bleeding is NSAIDs intake. Other causes are polyps and carcinoma of the colon. Faecal occult blood loss in normal individuals varies from 0.5 to 1.5 mL per day. Faecal occult blood tests are to detect blood not visible overtly. The classic faecal occult blood tests are of guaiac based type. They are based on haemoglobin pseudoperoxidase activity, guaiac turns blue after oxidation by oxidants or peroxidases in the presence of an oxygen donor such as hydrogen peroxide. Various factors influence the result of guaiac test, presence of animal haemoglobin and dietary peroxidases leads to false positivity while presence of vitamin C results in false negativity. Immunological faecal occult blood tests detect human globin epitopes and are highly sensitive for detection of blood. They are more specific than guaiac based tests; their results are not affected by dietary factors. Haem-porphyrin based test relies on spectrofluorometric method to measure porphyrin derived from haem, they provide a highly accurate determination of total stool haemoglobin. Intraluminal degradation of haemoglobin or interfering peroxidase producing substances do not effect the haem-porphyrin assay, although myoglobin, a haem containing protein found in red meats interferes with its result. The initial investigation for evaluation of occult bleeding is colonoscopy which should be followed by an upper GI endoscopy to rule out gastroduodenal pathology. If these tests are unrevealing, small intestinal causes of bleed should be considered.

PROGNOSIS OF GASTROINTESTINAL BLEEDING

Mortality of each episode of variceal bleed in cirrhotics is 30% to 50%. Variceal bleeding in non-cirrhotic causes of portal hypertension, however, carries a good prognosis. Mortality for ulcer bleed is much lower (3% to 10%). Lower GI bleed is usually less life-threatening than upper GI bleed. Risk factors for increased mortality are presentation with shock, active bleeding at presentation, advanced cirrhosis, old age, co-morbid medical illnesses, occurrence of rebleeding and failure of endoscopic methods to control bleed.

FUTURE PROSPECTS

Steady progress in engineering including microelectrical systems will affect the performance of capsule endoscopy. With the advent of robotic capsule in near future, it will be possible to perform drug delivery and tissue sampling, robotic capsule will be equipped with microelectrical system for directed therapy. Natural orifice transendoscopic surgery (NOTES) is a stimulating advancement. Development of endoscopic suturing devices to close gastrointestinal perforations is equally exciting. These techniques will be increasingly adapted to control gastrointestinal bleeding in future.

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13.7 Oesophageal Disorders

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SYMPTOMS

Oesophageal disorders are one of the commonest disorder of the GI tract. The description is given in next chapters. The passage of food through the body of the oesophagus is not sensed by an individual in normal circumstances. The major symptoms of oesophageal diseases are heartburn, chest pain, regurgitation and dysphagia.

Heartburn (pyrosis) is defined as retrosternal burning pain that travels cephalad. It is exacerbated by bending or lying down, and is worse after meals. It is relieved by upright posture, by swallowing of saliva or water, or more reliably by antacids or acid-inhibiting drugs. Heartburn is a characteristic symptom of gastro-oesophageal reflux (GOR), and may be associated with regurgitation.

Regurgitation is described as effortless appearance of acid or a bitter taste in the mouth. It occurs in GOR, and may result in laryngeal aspiration with spells of coughing and choking which awaken the patient from sleep.

It may also result in aspiration pneumonia. Regurgitation of bland food suggests that an obstruction exists in the lower oesophagus; in GOR, bland regurgitation occurs when acid secretion has been inhibited by drugs.

Dysphagia, or difficulty in swallowing, is a sensation of obstruction to the passage of food through the mouth, pharynx or oesophagus due to a significant problem in the anatomy or motility of these organs. Dysphagia could be oropharyngeal (transfer) or oesophageal. Oropharyngeal dysphagia occurs due to neuromuscular or structural abnormalities of mouth, hypopharynx or upper oesophagus; these patients have difficulty in initiating the swallow. Oesophageal dysphagia is classified as mechanical or motor. Mechanical oesophageal dysphagia is initially to solids only. It could be intermittent (webs or Schatzki ring) or progressive from solid to blenderised food and finally to liquids (stricture, malignancy). The severity of dysphagia in mechanical obstruction varies with the degree of luminal narrowing, type of food bolus, and presence of associated oesophagitis. On the other hand, dysphagia due to motor disorders is equal for solids and liquids, may increase with intake of very cold foods and it could be slowly progressive (achalasia cardia) or intermittent (less specific motility disorder). Non-obstructive dysphagia occurs in patients with reflux disease who have oesophageal inflammation associated with a motility disorder.

Odynophagia or painful swallowing is due to mucosal non-infectious inflammation. Causes could be infectious (candidiasis, herpes, cytomegalovirus, Epstein-Barr virus, etc.) or non-infectious like corrosive intake, pill oesophagitis, radiation oesophagitis, severe GOR disease and rarely osesophageal carcinoma.

Chest pain of oesophageal origin described as squeezing or burning sensation, is similar to cardiac angina and may not be related to swallowing. Almost 90% of times it is associated with other oesophageal symptoms. More than 50% of cases of non-cardiac chest pain have GOR disease; other causes are oesophageal spasm, achalasia cardia, nutcracker oesophagus and sometimes panic disorders. Water brash is reflex salivary hypersecretion that occurs in response to GOR. It should not be confused with regurgitation. Globus sensation is a feeling of food stuck at the pharyngeal level, but occurs between meal times.

MOTILITY DISORDERS

Skeletal Muscle Disorders

Pharyngeal paralysis may occur following neuromuscular diseases; laryngeal and orofacial muscles also may be involved. It is characterised by transfer dysphagia, laryngeal aspiration and nasal regurgitation. Barium swallow with cineradiography is the investigation of choice, and reveals poor contraction of pharyngeal constrictors, barium in the valleculae and pyriform sinuses, and nasal and tracheal aspiration. Oesophageal motility studies may reveal reduced amplitude of contraction wave in pharynx and proximal oesophagus, reduction in upper oesophageal sphincter (UOS) resting tone, and incoordination between the pharynx and oesophagus during a swallow.

Patients who have pharyngeal paralysis due to myasthenia gravis or polymyositis respond to treatment of the primary disease. In other patients, swallowing exercises usually help. In patients with a cerebrovascular accident, the extent of impairment of swallowing and its subsequent recovery depend on the type and extent of lesion. In severe cases, a permanent feeding gastrostomy may be required. In patients with UOS spasm, botulinum toxin injection or cricopharyngeal myotomy may be helpful.

Cricopharyngeal achalasia is a disorder of unknown cause, and occurs due to failed relaxation of the UOS and can be associated with Zenker's diverticulum. Dysphagia and choking are the predominant symptoms. On radiography, a prominent bar representing the contracted UOS may be seen. Cricopharyngeal myotomy may be helpful in selected cases, but should not be done in patients with associated GOR, because of increased risk of pulmonary aspiration post-operatively.

Smooth Muscle Disorders

Achalasia cardia

Achalasia cardia is a motor disorder of the oesophageal smooth muscle in which the oesophageal body is aperistaltic, the lower oesophageal sphincter (LOS) may be hypertensive and does not relax completely with swallowing. In addition, because of the non-relaxing LOS, the intra-oesophageal pressure is higher than the gastric pressure.

The underlying abnormality is defective innervation of the smooth muscle portion of the oesophageal body and the LOS.

Classic achalasia shows a marked reduction in myenteric neurons. Secondary achalasia may be caused by gastric carcinoma infiltrating the oesophagus, lymphoma, Chagas disease, neuropathic chronic intestinal pseudo-obstruction syndrome, irradiation and certain toxins and drugs.

Dysphagia, chest pain and regurgitation are the main symptoms of achalasia. Dysphagia occurs with both liquids and solids. Various manoeuvres designed to increase intra-oesophageal pressure, including the Valsalva, may help passage of the bolus into the stomach. Regurgitation and pulmonary aspiration occur because of retention of large volumes of saliva and ingested food in the oesophagus. The overall course is usually chronic over months to years.

Chest X-ray may show absence of the gastric air bubble. In advanced cases, an air-fluid level in the mediastinum in the upright position represents retained food in the dilated oesophagus. Barium swallow shows oesophageal dilatation and a persistent beak-like narrowing, representing the non-relaxing LOS, in the lower oesophagus (**Figure 1**).

Oesophageal manometry shows the defining feature of distal body aperistalsis and incomplete or absent swallow induced relaxation of LOS. Other features are hypertensive LOS and low amplitude simultaneous onset oesophageal body contractions. An increased intra-oesophageal basal pressure that exceeds intragastric pressure is commonly seen. High resolution oesophageal manometry with contour plot topographical analysis has found three variants of achalasia (**Figures 2A and B**), type 1—no significant oesophageal pressurisation; type 2—rapidly progressive compartmentalised pressurisation, either localised to distal oesophagus or throughout the whole oesophagus; and type 3—rapidly progressive pressurisation attributable to spastic contractions. This classification is also helpful in prognosticating outcomes with type 2 responding best to therapy; type 3 achalasia does not respond well, and type 1 has intermediate response to any form of treatment.

Endoscopy is helpful in excluding the causes of secondary achalasia, particularly gastric fundal carcinoma.

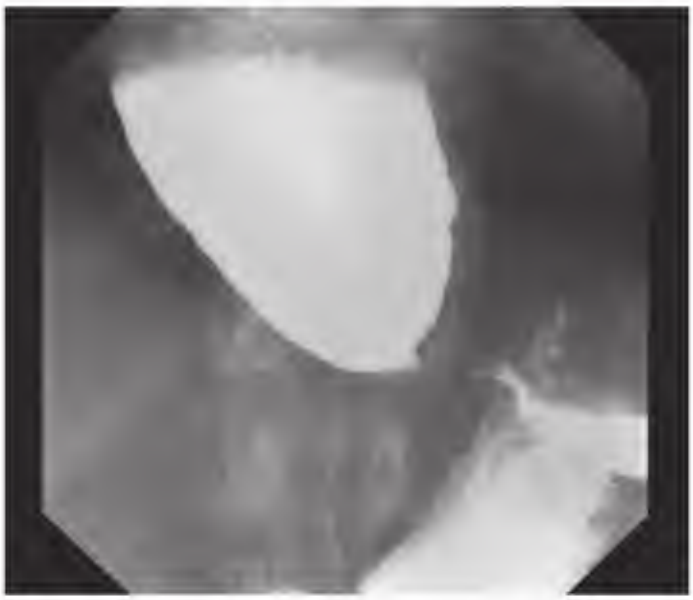
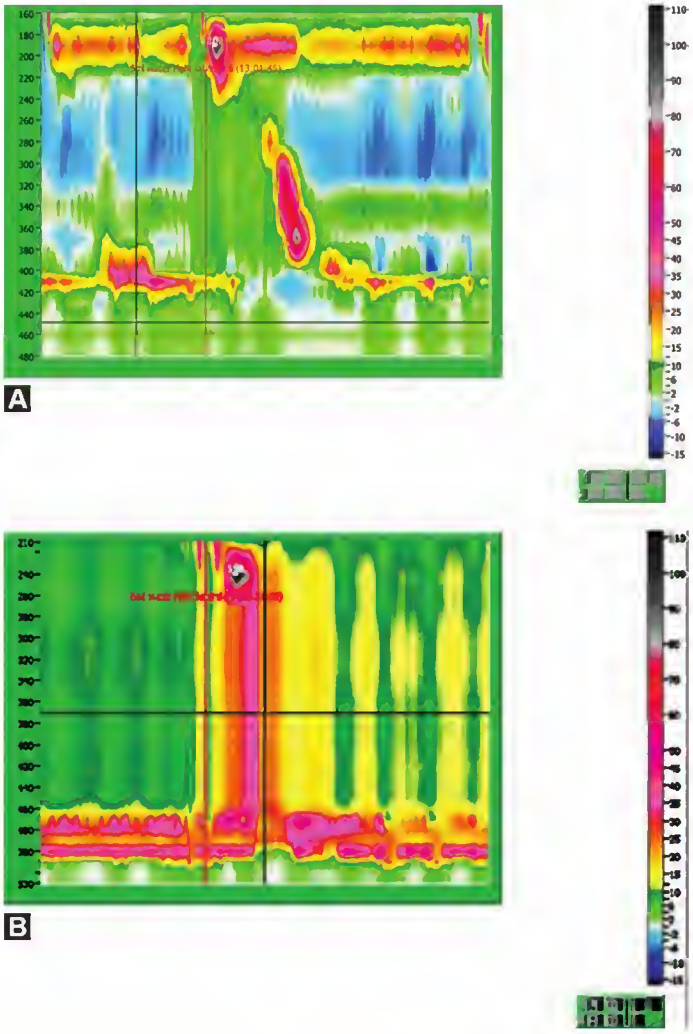


Figure 1: Barium swallow showing dilated oesophagus with bird beak appearance at the lower end and fluid level in the oesophagus, suggestive of achalasia cardia.



Figures 2A and B: (A) High resolution manometry shows normal peristaltic wave after a swallow. (B) Manometry shows aperistalsis in oesophageal body after a swallow with elevated lower oesophageal sphincter pressure suggestive of achalasia.

Medical treatment using nitrates is usually unsatisfactory. Calcium-channel antagonists such as nifedipine have been used with some success; these need to be administered sublingually 15 to 30 min prior to a meal. The best available non-surgical therapy involves endoscopy-assisted balloon dilatation of the LOS; this reduces the basal LOS pressure by tearing muscle fibres. Endoscopic injection of botulinum toxin into the LOS is effective in the short term. Heller's extra-mucosal myotomy of the LOS in which the circular muscle layer is incised, is equally effective. Reflux oesophagitis and peptic stricture may develop after successful treatment of achalasia; this complication is more frequent after surgery than with balloon dilation. Surgery is increasingly being performed laparoscopically; additionally, fundoplication is often done to prevent GOR.

Spastic Disorders of Distal Oesophagus Other than Achalasia

This section includes a spectrum of disorders ranging from diffuse oesophageal spasm, nutcracker oesophagus, non-specific spastic disorders and hypertensive LOS. These are differentiated on the basis of manometry findings (**Figure 3**). They all are present with history of chest pain, occasional dysphagia and rarely regurgitation. Pain is very similar to angina, may occur at rest or after swallowing, and may radiate to the back or neck. These disorders are associated with other functional bowel disorders and have high association with anxiety

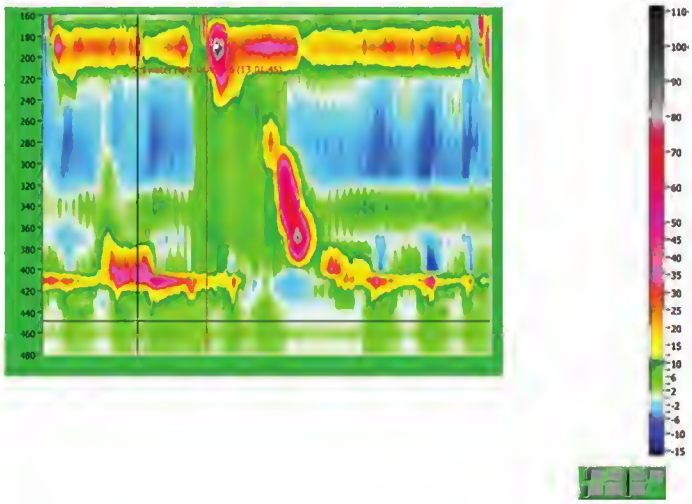


Figure 3: High resolution manometry shows simultaneous and prolonged contraction of oesophageal body suggestive of diffuse oesophageal spasm.

disorders, depression and other psychological abnormalities. The pathogenesis of these disorders is not known, probably functional with no anatomic abnormalities found.

Diffuse oesophageal spasm is characterised by non-peristaltic responses of normal amplitude after 30% or more of swallows with a normally relaxing LOS. Barium swallow may reveal intermittent areas of oesophageal spasm that produce an appearance of a corkscrew oesophagus (**Figure 4**).

Treatment includes ruling out the possibility of ischaemic heart disease; smooth muscle relaxants like nitrates and calcium channel blockers are beneficial in a few cases. Anti-depressants like imipramine, trazodone and sertraline have been found to be useful in a number of patients with chest pain. Pneumatic dilatation of LOS has been found to be beneficial in cases with associated LOS hypertension. In refractory cases, long oesophagomyotomy has been tried with some success.



Figure 4: Barium swallow showing appearance of a corkscrew oesophagus.

Systemic diseases like scleroderma and diabetes mellitus also cause motor disorders of the oesophagus. Scleroderma oesophagus is typically one with a low LOS pressure and aperistalsis. There is atrophy of the smooth muscle. The patient presents with severe gastro-oesophageal reflux disease with complications. Diabetes mellitus, when complicated by autonomic neuropathy, may have associated oesophageal dysmotility. The patients are rarely symptomatic, but may have occasional dysphagia and heartburn. Candidal infection should also be considered; if present, patients may have odynophagia.

GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux (GOR) is defined as backward flow of gastric contents into the oesophagus. A small amount of GOR occurs in normal individuals. GORD (gastro-oesophageal reflux disease) is defined as a condition which develops when stomach contents cause troublesome symptoms or complications, and adversely affects an individual's quality of life. The typical reflux syndrome is defined by presence of troublesome heartburn and/or regurgitation. GORD is the most common oesophageal disorder, accounting for nearly 75% of all patients with oesophageal disorders. In Western studies, 15% to 20% of the general population suffers from GORD. The prevalence of GORD in Asia is lower (2.3% to 8%), probably due to higher prevalence of *Helicobacter pylori*, lower body mass index, low fat consumption in diet and genetic diversity. Adenocarcinoma of the oesophagus is on the rise in the Western world. Barrett's oesophagus, which is a recognised precursor to adenocarcinoma is strongly associated with GORD.

Pathophysiology

The normal anti-reflux barrier at the gastro-oesophageal junction is a zone whose functional integrity is maintained by the LOS pressure, extrinsic compression of the LOS by the crural diaphragm, the intra-abdominal location of the LOS, integrity of the phreno-oesophageal ligament, and maintenance of the acute angle of His.

Transient LOS relaxation is one of the most important causes for GORD; it is not associated with a swallow. It is more harmful because it is longer in duration (>10 seconds) compared with swallow-induced LOS relaxation, accompanied by relaxation of crural diaphragm and not associated with peristalsis. It is usually stimulated by gastric distension due to food or gas, or rarely fat and stress. Small amount of reflux occurs during swallow induced LOS relaxation. The role of hypotensive LOS seems to be present only in patients with severe oesophagitis.

Hiatus hernia is seen in 60% to 90% of patients with reflux oesophagitis, especially in patients with peptic stricture or Barrett's oesophagus. Hiatus hernia breaches the anti-reflux barrier by displacing the LOS from crural diaphragm. Loss of the intra-abdominal segment of LOS increases transient LOS relaxation and impairs oesophageal acid clearance.

Impaired oesophageal motor function resulting in inadequate volume clearance occurs in oesophagitis; peristaltic dysfunction increases with increasing severity of oesophagitis. The layer of mucous carpeting the mucosa and mucosal bicarbonate also constitute an important line of defence against acid injury.

If acid injury and cell necrosis occur, the rate of regeneration plays a role in determining the severity of lesions.

There is no increase in gastric secretions in GORD patients, but there is a pocket of acid in the distal oesophagus which escapes the buffering action of food; hence the predilection for oesophagitis at this location. Animal and human studies have demonstrated that acid and pepsin are responsible for the mucosal injury. Other factors implicated are duodenogastric reflux, with conjugated bile acids and trypsin as possible culprits. Gastroparesis is found in 6% to 38% of patients with GORD.

Helicobacter pylori infection is currently believed to lower the frequency of GORD. This is backed by epidemiological data of low prevalence of GORD in areas with high prevalence of *H.pylori* and vice versa. Prevalence of more virulent strains of *H. pylori* in developing countries results in corpus or pangastritis, thus reducing gastric acid secretion and resulting in decreased symptoms of GORD.

Pathology

Grossly, the spectrum of oesophageal mucosal appearances varies from normal appearing mucosa (40% to 80%) to mucosal injuries of varying severity-erosions to ulcerations. The earliest finding, seen on electron microscopy, is dilated intercellular spaces, at least three times greater than controls; this is reversible on administering proton pump inhibitors. Light microscopy shows papillary height more than half, and basal zone thickness more than 1/6th of total mucosal thickness. Acute inflammation with neutrophils and eosinophils is seen in up to 40% of cases but is not specific for GORD.

Development of columnar-lined mucosa, with specialised intestinal metaplasia is the defining feature of Barrett's oesophagus, visible on endoscopy when normal squamous mucosa is replaced by salmon pink columnar mucosa. This can progress from low grade to high grade dysplasia, and later to adenocarcinoma of the oesophagus.

Clinical Features

Symptom complex of GORD has been divided into oesophageal and extra-oesophageal syndromes. Oesophageal syndromes include the typical reflux syndrome and reflux chest pain syndromes.

Typical reflux symptoms are heartburn, a burning sensation in the retrosternum and regurgitation—a perception of flow of gastric contents into the mouth or hypopharynx. The prevalence of these is 75% to 98% and 48% to 91%, respectively. GORD can be diagnosed by these two symptoms without the need for endoscopy. Reflux chest pain can be indistinguishable from pain of ischaemic heart disease, but is usually associated with other symptoms of GORD. GORD is the most common oesophageal cause of chest pain. Sleep disturbance is often associated with GORD. In patients with minimal symptoms, exercise has been found to worsen symptoms of GORD.

Dysphagia in a patient with GORD could be a marker of peptic stricture or development of malignancy. Dysphagia may also occur because of reflux oesophagitis and motor functional abnormalities. Barrett's oesophagus is an endoscopic diagnosis (**Figure 5**) confirmed on histology showing specialised intestinal metaplasia. There are no symptoms which herald the development of Barrett's oesophagus. Increasing age, male gender, long duration of GORD symptoms, obesity and smoking are risk factors for Barrett's oesophagus. Adenocarcinoma may develop in patients with Barrett's oesophagus especially high grade dysplasia.



Figure 5: Endoscopy shows evidence of Barrett's metaplasia in the oesophagus. The normal squamous mucosa of the oesophagus is replaced by columnar gastric mucosa.

Extra-oesophageal syndromes are classified as those with established associations and those with proposed associations. Established associations include reflux cough, reflux laryngitis, reflux asthma and reflux dental erosions. These syndromes usually occur with the concomitant manifestation of typical reflux oesophageal symptoms and rarely in their absence. Reflux is rarely the only cause for these extra-oesophageal symptoms. They have been found to respond to treatment of GORD. Other symptoms with proposed associations are sinusitis, pulmonary fibrosis, recurrent otitis media and pharyngitis. The degree of evidence for this last group is minimal, epidemiologically or treatment-response wise.

Investigations

The diagnosis of GORD is made on the basis of clinical history and confirmed by response to medications. Diagnostic testing is done to avert misdiagnosis, to identify complications of GORD and to evaluate the reason for failure of standard therapy. To avert misdiagnosis and identify reflux complications, the concept of alarm symptoms has been introduced; these include gastrointestinal blood loss, involuntary weight loss, dysphagia and anaemia. In these conditions an endoscopy is warranted. In case any lesion is seen, biopsies should be taken from it. Less than 50% of patients with GORD have endoscopic features of oesophagitis; visible breaks in mucosa is the most reliable marker of reflux oesophagitis. This does not correlate with the frequency or severity of reflux symptoms. Reflux stricture seen in less than 5% of GORD patients is defined by a persistent narrowing in the lumen of the oesophagus and manifests as troublesome mechanical dysphagia. If endoscopy is normal, the patient should be treated empirically as GORD, and further investigated if the symptoms do not resolve. Manometry is useful in detecting severe peristaltic dysfunction which is a contraindication for anti-reflux surgery. Investigations to demonstrate excessive oesophageal acid exposure are conventional catheter based pH-metry or wireless capsule pH-metry, and impedence-pH monitoring.

Therapy

Treatment is directed towards decreasing GOR and improving oesophageal clearance. The aim is to alleviate symptoms, heal oesophagitis and prevent complications.

Treatment usually begins with dietary and lifestyle modifications. The patient should be asked to avoid food items that increase reflux (fatty or fried food, caffeinated drinks, chocolate, mint) and decrease intake of acidic foods (citrus fruits, spicy food, carbonated drinks, tomatoes, onions). Lifestyle modifications include weight reduction in those who are obese, elevation of the head end of the bed and avoiding eating within 3 hours of bedtime in those with night time symptoms. Patients with postprandial symptoms are advised to take small frequent meals.

Empirical initial management with acid reduction is the accepted approach currently in patients with uncomplicated heartburn. Evidence suggests that acid reduction helps healing of oesophagitis and relief from symptoms. Meta-analysis of randomised control trials show that proton pump inhibitors (PPIs) are more effective than H_2 receptor antagonists (H_2RAs) in treating oesophagitis and ameliorating symptoms. PPIs as a class (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are all equally effective in standard doses. There does not appear to be any additional benefit of higher dosage/twice daily dosing of PPIs or adding a H_2RA, except in cases of severe oesophagitis. Patients whose heartburn has not responded to twice daily PPIs are considered treatment failures. Preference of a PPI over another is primarily to ameliorate the side-effects of the PPI need earlier. Patients with reflux chest pain can be given a trial of PPI once ischaemic heart disease has been ruled-out. Patients with extra-oesophageal symptoms require high doses.

Maintenance therapy is usually necessary as GORD is a chronic disease, the lowest possible dose of PPI should be titrated for symptom control in patients with definite oesophagitis. PPIs have been shown to reduce the development of reflux strictures, but there is no evidence that they reduce the risk of Barrett's oesophagus or adenocarcinoma. In patients with extra-oesophageal symptoms, maintenance therapy is indicated only to control oesophageal symptoms. Long-term PPI therapy is potentially safe though there is a theoretical risk of hypergastrinaemia, pneumonia, *Clostridium difficile* colitis and hip fractures.

Anti-reflux surgery and PPIs have equal efficacy for control of oesophageal reflux symptoms. Surgery should be offered when an individual is intolerant to PPIs, or when a patient with oesophageal reflux syndrome has troublesome regurgitation. The potential side-effects of anti-reflux surgery include excessive flatulence, inability to belch, dysphagia and recurrence of symptoms post-surgery (30% over 5 years). Patients well controlled on PPIs should not be offered surgery. The surgery recommended is laparoscopic fundoplication.

INFECTIOUS OESOPHAGITIS

Infectious oesophagitis can be due to viral, bacterial and fungal causes. With an increase in the number of patients with immunocompromised states, there has been an increased frequency of oesophageal infections.

Infections of the oesophagus present with acute dysphagia, odynophagia and chest pain. In patients with severe ulceration of the mucosa, bleeding may occur; this is usually self-limiting and small in quantity, but life-threatening haemorrhage may occur.

Viral Oesophagitis

Herpes simplex virus (HSV) type 1 or 2 may cause oesophagitis in immunocompromised individuals. Systemic manifestations like nausea, vomiting and fever may be present. On endoscopy, the oesophageal mucosa has 1 to 3 mm vesicles and small, discrete, punched-out lesions, which may proceed to confluent ulcers and diffuse erosive oesophagitis. These lesions may get superinfected by bacteria or fungi. Biopsy or cytology may show ballooning degeneration, ground-glass change in nuclei with eosinophilic inclusions (Cowdry type A) and giant cell formation. Culture may be positive. Treatment consists of acyclovir 250 mg/m^2 intravenous 8 hourly. As the patient improves, oral therapy may be started with 200 to 400 mg acyclovir 5 times a day. Symptoms resolve within a week. Ulcers take a longer time to heal.

Varicella-zoster virus occasionally produces oesophagitis in children with chicken pox and adults with herpes zoster. The oesophageal lesions are similar to those of HSV, and necrotising oesophagitis may occur in a severely compromised patient. Biopsy from the edge of the ulcer shows findings similar to those of HSV, and differentiation requires culture studies. Acyclovir, in doses higher than for HSV, is required for treatment.

Cytomegalovirus infection occurs only in the immuno-compromised host. Endoscopy shows serpiginous ulcers which are large and deep with surrounding normal mucosa. In the distal oesophagus the ulcers may coalesce. Biopsy should be taken from the centre of the ulcer and reveals intranuclear and small cytoplasmic inclusions in fibroblasts and endothelial cells of blood vessels. Early diagnosis may be made by immuno-histochemistry using monoclonal antibodies to CMV. Ganciclovir is the treatment of choice. Complete healing may take a few weeks to months and treatment should be continued until then.

HIV causes oesophagitis during seroconversion and during inversion of T-cell helper: suppressor ratio. The oesophagitis is self-limiting. Steroids may help in this condition.

Bacterial oesophagitis is very rare. However, patients with AIDS may develop oesophagitis due to *Cryptosporidium* or *P. carinii*.

Tuberculosis of the oesophagus is rare and is almost always due to contiguous spread from the lung or mediastinal lymph nodes.

Fungal Oesophagitis

Candidiasis of the oesophagus occurs in immunodeficiency disorders like diabetes mellitus, chronic renal failure, and AIDS. Individuals receiving steroids or immunosuppressive chemotherapy for malignancy and those with underlying oesophageal diseases that cause stasis of food (achalasia or scleroderma) may also develop candidiasis.

Candida is present in the non-pathogenic form in the oral flora in normal individuals. Patients who develop oesophagitis may be asymptomatic, or may have odynophagia and dysphagia. Rarely, bleeding may occur, and the deep ulcers may perforate or may form a stricture. Systemic invasion from oesophageal candidiasis is also reported.

Oral *candidiasis*, if present, suggests the diagnosis by its white flake's appearance. Endoscopy reveals raised white pseudo-membranous plaques with mucosal erythema. In severe cases, confluent linear and nodular plaques with underlying ulcerations may be present. A smear taken from these plaques may reveal hyphae. Treatment in mild cases is with 10 to 20 mL of oral nystatin (100,000 units/mL) 6 hourly, or oral clotrimazole (10 mg 6 hourly), or fluconazole 100 mg per day for 7 days. If symptoms persist, endoscopic biopsy and culture are

recommended. If anti-fungal resistance is demonstrated, caspofungin may be effective. Narcotics are recommended for patients with severe odynophagia.

Corrosive Injury

Corrosive is any substance which causes tissue injury upon contact. Caustic injury of the oesophagus occurs following ingestion of strong alkali or acid, most often accidentally or with suicidal intent. Sodium hydroxide is the most frequent cause of alkaline injury. Hydrochloric and sulphuric acids are the common acids causing injury. Most corrosives are available as over-the-counter drain cleaners, dish washing detergents, bleaches, battery fluids, button batteries, nail polish removers, etc.

Alkali ingestion provokes liquefaction or saponification necrosis of the oesophageal wall and thrombosis of blood vessels. Acids cause coagulative necrosis. Severity of tissue injury depends upon factors like substance pH, physical state (solids adhere to mucosa and cause more damage), quantity, intention (quantity is usually larger in suicidal cases), tissue contact time and concentration. There is an acute inflammatory response with mucosal necrosis, followed by sloughing of necrotic tissue and ulceration over 4 to 15 days. Risk of perforation is maximum up to 7 days. After 3 to 4 weeks, cicatrisation begins. Significant oesophageal strictures develop when there is circumferential damage.

In the oesophagus, corrosives pool at the post-cricoid area, level of aortic arch, tracheal bifurcation, and lower oesophageal sphincter. These are common locations for strictures. In severe cases, there may be perforation into the mediastinum or pleural cavity or development of a tracheo-oesophageal fistula. The damage is mainly in the antrum in the fasting stomach, and in the gastric corpus if the patient has ingested a meal prior to corrosive ingestion.

Symptoms include burning pain in the mouth and throat, odynophagia, excessive salivation, stridor, hoarseness, dysphagia and chest pain. Gastric involvement leads to abdominal pain and vomiting, and occasionally symptoms and signs of perforation. There may be oedema and ulceration of the lips, tongue and pharynx. Airway obstruction from severe epiglottic and laryngeal oedema may occur. As the acute inflammatory reaction subsides, odynophagia and dysphagia decrease; with the development of oesophageal stricture, dysphagia gradually returns, usually within 1 to 3 months after the accident. Mortality rate is of 1%, usually due to mediastinitis or peritonitis resulting in multi-organ failure.

The aim of therapy in the acute phase is resuscitation and supportive care. Assessment of the severity of damage is most important after resuscitation of the patient. Clinical features do not correlate with severity of damage. X-ray films of chest and abdomen are taken to check for perforation, pneumo-mediastinum or pneumoperitoneum, which if present can be confirmed by CT scan. If there is evidence of perforation, patient should be referred for surgery (oesophagectomy or gastrectomy). Flexible endoscopy should be done at the earliest or up to 96 hours of corrosive ingestion, after ruling out a perforation and is the best way to assess the severity of mucosal damage. Endoscopic grading is helpful in management and prognostication. Patients who have minimal injury can be started on oral liquids by 48 hours and can be discharged early; they also have a low risk of complications. In patients with advanced damage, a nasojejunal tube can be placed over a guide wire during endoscopy; this serves as a route for maintaining nutrition and also provides a lumen for dilatation in future as these patients are prone to develop strictures. Measures which have shown to be of no use or are harmful are administration of activated charcoal, pH neutralisation or dilution, by inducing emesis, and intravenous steroids. Antibiotic therapy is required only if secondary infection sets in.

Early dilatation of the oesophagus has been associated with a high-risk of perforation, and is therefore not recommended. Stricture of the oesophagus is the major long-term complication. Caustic strictures are often extensive and multiple, involving most of the lower oesophagus. They respond to repeated dilatation, and the frequency of dilatation may decrease over time. Recently, self-expandable plastic stents have been placed at the site of stricture for 6 to 8 weeks, with good results. Oesophageal resection with colon or gastric tube replacement may be necessary in cases where the lumen is too small for dilatation, or in cases of extensive damage. Oesophageal squamous cell carcinoma is a potential long-term complication of corrosive injury.

Pill-Induced Oesophageal Injury

Pill-induced oesophageal injury results from damage due to ingestion of certain medications which cause injury by either production of caustic solution, hyperosmolar solution or direct drug damage. Drugs commonly implicated are tetracycline, doxycycline, potassium chloride, nonsteroidal anti-inflammatory drugs, alendronate, ferrous sulphate, theophylline, quinidine, etc. The injury is more common in individuals with anatomic or motility abnormalities of oesophagus. It could be predisposed by taking inadequate water or assuming recumbent posture immediately after taking the pill. Symptoms include severe chest pain, odynophagia and dysphagia. Endoscopy may reveal an ulcer, diffuse oesophagitis or pseudomembrane at the site of damage. Withdrawal of the offending medication, viscous lignocaine solution, adequate hydration, and use of PPIs to reduce acid exposure results in healing of the lesion. Rarely there can be perforation, oesophago-respiratory fistula or a chronic stricture at the site of the ulcer. The disorder is preventable in most cases.

Eosinophilic Oesophagitis

Eosinophilic oesophagitis (EO) is a disease characterised by eosinophilic infiltration of the oesophageal mucosa. Identified in 1978, the incidence of EO has been increasing in the Western world. Familial clustering and seasonal variation have been noted in patients with EO. Almost 80% of children and 40% to 60% of adults have history of allergies. It is postulated to be IgE or non-IgE mediated. Sensitisation could be via food or inhaled allergens. EO appears to be a Th2 mediated immune response; IL-5 and IL-13 appear to play a key role in pathogenesis.

The pathognomonic feature of EO is eosinophilic infiltration of ≥15 eosinophils/HPF in the oesophageal mucosa; eosinophils should be counted in the most densely inflamed part of the biopsy (X 400). Other features are eosinophilic micro-abscesses, superficial infiltration of eosinophils in the upper half of mucosa, basal zone hyperplasia and papillary lengthening.

Most of the patients are men with a male to female ratio of 3:1, in the third or fourth decade of life. Presentation varies from dysphagia (60% to 90%), food impaction (50% to 60%), heartburn

and regurgitation (24% to 50%), refractory GORD, chest pain, abdominal pain, diarrhoea and weight loss. Children present with poor feeding, vomiting, regurgitation and failure to thrive.

Endoscopic findings include oesophageal rings (felinisation or trachealisation), raised white specks, longitudinal furrows, whitish exudates and a friable mucosa which may tear by passage of endoscope. Normal mucosa can be seen in up to a third of the patients. Strictures could be seen in any part of the oesophagus. Multiple (>5) biopsies from different levels of the oesophagus should be taken. Oesophageal pH monitoring should be done in difficult cases to rule-out GORD, or biopsies should be repeated after 6 weeks of PPI treatment. Barium swallow may reveal strictures, Schatzki's ring or a diffuse narrowing of the oesophagus. Allergic testing by skin prick, skin patch test or food specific radioallergosorbent testing can be done.

Treatment

Treatment is to control the inflammation using systemic steroids, prednisolone 1 to 2 mg/kg, tapered over 6 weeks in patients with severe dysphagia, weight loss and refractory oesophageal strictures. Steroids should not be used for maintenance therapy. Other steroids used are swallowed topical fluticasone propionate (440 to 500 µg/day) twice daily for 6 weeks, swallowed budesonide mixed with sucralose and beclomethasone have also been used. Symptoms recur in 50% of patients when treatment is stopped and can be managed with reintroduction of same therapy or, use of steroid-sparing drugs like azathioprine. Leukotriene receptor antagonist montelukast 10 to 40 mg/day has been used with some success. Endoscopic dilatation of strictures should be preferably limited to patients after a trial of medical therapy, because of the risk of perforation. Dietary therapy by eliminating foods like dairy, peanuts, soy, fish, eggs wheat and other foods identified by allergic testing has been found to be successful in 70% of paediatric cases. Because of poor tolerability, dietary therapy should be used in individuals not responding to medical and endoscopic treatment. Studies with targeted therapies to IL-5 are underway.

Hiatus Hernia

Herniation through the oesophageal hiatus occurs in two forms: axial or sliding type in which both the distal oesophagus and a varying portion of the stomach (i.e. the entire oesophago-gastric junction) are situated above the diaphragm, and para-oesophageal or rolling type in which the lower most oesophagus and the oesophago-gastric junction retain their position below the diaphragm, while a portion of the proximal stomach protrudes into the thorax alongside the oesophagus.

The size of the sliding hernia alone does not predict the presence or severity of symptoms; larger, long-standing hernias are more likely to be associated with symptomatic GOR.

In the less common para-oesophageal or rolling hernia, the less-than-atmospheric intrathoracic pressure is transmitted directly through the pleura to the peritoneal sac. With positive intra-abdominal pressure exerting an upward push, this hernia tends to enlarge progressively. The typical para-oesophageal hernia is rarely associated with GOR; however, it can get incarcerated and strangulation or bleeding may occur.

The management of symptomatic sliding hiatus hernia is similar to that of GORD. Para-oesophageal hernia needs surgical correction to avoid complications.

OESOPHAGEAL WEBS, RINGS AND DIVERTICULA

Oesophageal webs usually occur in the upper oesophagus, but may occur in the mid or lower oesophagus as well. They are thin horizontal membranes of stratified squamous epithelium, usually protrude from the anterior wall, rarely complete and are best demonstrated on the lateral view in the barium swallow. They are usually acquired, but webs in the upper third may be congenital in origin (**Figure 6**). A syndrome of cervical oesophageal web, anaemia and platonychia, which occurs mainly in middle-aged women, is called the Patterson-Kelly or Plummer-Vinson syndrome.



Figure 6: Barium swallow shows a web in upper oesophagus.

Oesophageal rings are found near the lower oesophageal sphincter (LOS). They are of 2 types. Type A is a muscular ring, 4 to 5 mm thick and is the hypertrophied upper portion of LOS. Type B ring, or Schatzki ring, is a mucosal ring at the squamo-columnar junction; its upper surface is squamous epithelium and undersurface is columnar. It is usually associated with GORD or rarely EO.

Rings and webs present with intermittent dysphagia to solid food. Rarely, dysphagia progresses to a severe state. Treatment consists of breaking the web or ring by dilatation; webs may rupture even during a diagnostic endoscopy. The underlying disorder like anaemia or GOR needs appropriate treatment.

Diverticula are outpouchings of the oesophageal wall from an area of muscular weakness. Zenker's diverticulum occurs due to weakness in the posterior hypopharynx; patients present with dysphagia and regurgitation. Treatment consists of cricopharyngeal myotomy. Epiphrenic diverticula occur in the distal oesophagus and are associated with oesophageal motility disorders.

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13.8 Diseases of the Stomach and Duodenum

Pankaj Dhawan

The stomach is a J-shaped organ continuous with the oesophagus proximally and the duodenum distally. It is divided from the proximal to distal end into the cardia, fundus, body or corpus, antrum and pylorus (pyloric channel). The duodenum is the first part of the small intestine and is in continuity with the pylorus of the stomach proximally and the jejunum distally. It forms a C-shaped loop around the head of the pancreas.

The arterial blood supply of the stomach is derived from the coeliac artery and its major branches, the common hepatic, splenic and left gastric arteries while the duodenum receives additionally from the superior mesenteric artery. The venous drainage is into the portal vein or its tributaries, the superior mesenteric and splenic veins. The lymphatic drainage of the stomach is to the coeliac lymph nodes. The autonomic innervation stems from both the sympathetic (coeliac plexus) and the parasympathetic (right and left vagus nerves) nervous systems. The latter synapses with ganglion cells in the submucosa (Meissner's plexus) and myenteric plexuses (Auerbach's plexus). From these plexuses fibres are distributed to secretory components including cells and glands as well as to the gastric smooth muscle.

MOTOR PHYSIOLOGY

The motor function of the gastrointestinal (GI) tract is controlled at 3 levels. The first is the extrinsic neural control from the parasympathetic pathways via the vagus nerve and the sympathetic supply through the coeliac ganglion. The second level is provided by the enteric nervous system, which constitutes the complex network of ganglion cells in the layers of the gut wall. The third level of control of GI motility is in the excitable smooth muscle cells. Specific receptors in the cell membrane of the smooth muscle bind to amines, peptides, and other transmitters that reach the smooth muscle membrane via neurocrine, endocrine and paracrine routes. The main transmitters involved in excitation of the gastric muscle are acetylcholine and tachykinins, such as substance P and substance K. The main inhibitory transmitters are nitric oxide and vasoactive intestinal peptide (VIP).

GASTRIC SECRETION

The human stomach secretes water and electrolytes (H^+, Na^+, K^+, Cl^- and HCO_3^-), enzymes (pepsins and gastric lipase) and glycoproteins (intrinsic factor and mucins). The gastric exocrine secretions have a variety of functions.

Acid Secretion

The most important secretion of the stomach is gastric acid, secreted from parietal cells in the fundus and body of the stomach. Parietal cells have on their basolateral membrane receptors for 3 stimulants: histamine (H_2) receptor for histamine released from ECL cells and possible mast cells, a muscarinic (M_3) type of cholinergic receptor for acetylcholine released from post-ganglionic neurons and a cholecystokinin (CCK) receptor for gastrin released from pyloric and duodenal G cells.

Hydrogen ions are generated in the parietal cell from water. The corresponding hydroxyl ions combine with cellular carbon dioxide (CO_2) to form HCO_3. This reaction is catalysed by carbonic anhydrase. HCO_3 ions are exchanged at the basolateral membrane for Cl^- ions, which are ultimately secreted by the parietal cells. Hydrogen ions are exchanged for K^+ catalysed by the magnesium dependant H^+-K^+ ATPase pump. The H^+-K^+ ATPase is inhibited by covalent antagonists such as the substituted benzimidazoles (e.g. omeprazole). The apical membrane of the parietal cell is impermeable to H^+ and Cl^- and hence, it does not diffuse back from the lumen into the cell.

Other Secretions

The other important gastric secretion is pepsinogen (PG). This is a proenzyme S which gets activated to pepsin in the gastric lumen by the gastric acid. Two types of pepsinogen are PG I and PG II.

The gastric mucosa also secretes bicarbonates through the surface cells that are rich in carbonic anhydrase. Under most conditions, luminal HCO_3 is overwhelmed by luminal H^+ and is converted to CO_2. Therefore, HCO_3 is not ordinarily present in gastric juice. The other secretory products are gastric mucin and intrinsic factor. The role of intrinsic factor in vitamin B12 absorption is discussed elsewhere.

GASTRITIS

Gastritis is acute or chronic inflammation of the stomach and is most often diffuse. It is usually diagnosed on upper GI endoscopy and can be confirmed and classified histologically by performing a gastric biopsy. A detailed system for classification (Sydney system) has been adopted recently.

Acute Gastritis

This is also called erosive or haemorrhagic gastritis. Of these, the most common cause is use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). These agents cause gastric mucosal damage by inhibiting prostaglandins, gastric bicarbonate and mucous, disrupting epithelial tight junctions and altering gastric mucosal micro-circulation. The mucosal damage can result in either slow upper GI bleeding which can be detected as positive faecal occult blood test or can manifest as massive upper GI bleeding. In some patients, epigastric discomfort, anorexia and nausea may be present. Treatment includes omission of the offending agent, acid-suppressive agents such as H_2 receptor antagonists and proton-pump inhibitors, prostaglandin analogues such as misoprostol (more useful for prevention) and cytoprotective agents, such as sucralfate.

Chronic Gastritis

Chronic gastritis progresses over years in three stages. In chronic superficial gastritis, there is infiltration of lymphocytes and plasma cells in the lamina propria; however, the mucosal thickness is normal. In atrophic gastritis, there is reduction in the gastric glands (parietal and chief cells) along with infiltration of plasma cells and lymphocytes. When there is associated polymorphonuclear cells infiltration, gastritis is termed active. In gastric atrophy, glands are lost, mucosal thickness is reduced, infiltration of lymphocytes and plasma cells is minimal and there may be foci of intestinal metaplasia.

The two main types of chronic gastritis are autoimmune (formerly type A) and *H. pylori*-associated (formerly type B). Autoimmune gastritis involves the gastric body and spares the antrum. Parietal cell and intrinsic factor antibodies are serum markers of autoimmune chronic gastritis. Patients present with pernicious anaemia (megaloblastic anaemia with absolute achlorhydria) and features of vitamin B_{12} deficiency. Also, autoimmune chronic gastritis is a pre-malignant condition and can progress to gastric cancer. *H. pylori*-associated chronic gastritis usually involves the antrum but over a period of time may involve the body as well (*see Infection Section*).

An uncommon cause of chronic gastritis is Menetrier's disease (hypertrophic gastritis). The most common presentation is in middle age with features of protein-losing enteropathy. On upper GI endoscopy, enlarged rugal folds in the fundus and body are evident. Histologically, gastric pits and glands are elongated and tortuous and the parietal and chief cells are replaced by mucous-secreting glands. Treatment with proton-pump inhibitors may decrease protein loss. However, in patients who do not respond, gastric resection may become necessary.

PEPTIC ULCER DISEASE

Peptic ulcers are defects in the GI mucosa that result when injury occurs due to the effects of acid and pepsin in the GI lumen. Although the term 'peptic ulcer' is commonly used to describe ulcers in the stomach (**Figure 1**) and duodenum (**Figure 2**), peptic ulcers can develop in any portion of the GI tract exposed to acid and pepsin such as the oesophagus, Meckel's diverticulum or site of gastrojejunostomy (**Figure 3**). In the early part of the 20th Century, stress and diet were thought to be important pathogenetic factors. During the 1980s, it was established that most peptic ulcers were related to either *H. pylori* infection or due to consumption of NSAIDs. This revolutionised the management of peptic ulcer disease.



Figure 1: Benign gastric ulcer at incisura.

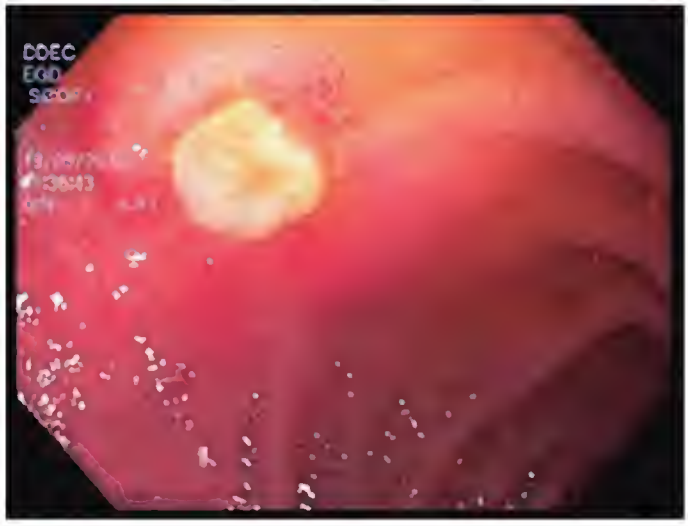


Figure 2: Duodenal ulcer in first part of duodenum.



Figure 3: Barium meal showing an anastomotic ulcer at the gastro-jejunostomy site.

Pathophysiology

Peptic ulcer occurs when the deleterious effects of acid and pepsin overwhelm the ability of the mucosa to resist these effects.

Defence Mechanisms

The mechanisms that normally enable the mucosa to resist acid-peptic attack can be divided into three components: pre-epithelial, epithelial and post-epithelial defence mechanisms.

Pre-epithelial defence mechanisms

A prominent coat of mucous and a layer of unstirred water rich in bicarbonate constitutes this component. Within the mucous layer glycoprotein form a physical barrier to the diffusion of pepsin. Mucous also contains phospholipids which protect the mucosa by forming a hydrophobic layer.

Epithelial defence mechanisms

The apical cell membranes and the tight junctional complexes between the surface cells limit the diffusion of hydrogen. Excess hydrogen ions can be removed actively by ion pumps in the basolateral membrane, such as Na^+/H^+ exchanger and Cl^-/HCO_3^- exchanger. Mucosal cell restitution regulated by growth factors (epidermal and fibroblast growth factors) also plays a part.

Post-epithelial defence mechanisms

Mucosal blood flow comprises the post-epithelial defence mechanism.

Abnormalities in Gastric Acid Secretion, Acid Homeostasis and Gastroduodenal Motility

In 1910, Schwarz proposed his famous dictum 'no acid, no ulcer'. This followed numerous studies on abnormalities in acid homeostasis in peptic ulcer. After the discovery of *H. pylori* it has been shown that many of these abnormalities may not be the primary defects but reversible consequences of infection with *H. pylori*.

Abnormalities associated with duodenal ulcer

Studies have shown these patients to be hypersecretors of gastric acid with an increase in the number of parietal cells. This may be related to *H. pylori* induced increases in cytokines such as tumour necrosis factor which stimulates gastrin release from G cells and *H. pylori* mediated decrease in somatostatin, a peptide which suppresses gastric release. Also an increased rate of liquid gastric emptying with increased acid burden in duodenum has also been described.

Abnormalities associated with gastric ulcer

Whereas the mucosa of the fundus and body is acid secreting (oxyntic) mucosa with abundant parietal cells, the gastric antrum is normally lined by a columnar epithelium that does not secrete gastric acid. The majority of gastric ulcers occur in the non-acid secreting epithelium at or near its junction with oxyntic mucosa. Long standing gastritis as occurs in *H. pylori* infection can cause atrophy of oxyntic mucosa with development of intestinal metaplasia and extension of the non-acid secreting epithelium into the proximal stomach. Patients who have gastric ulcers in the proximal stomach have chronic gastritis, substantial gastric atrophy and low gastric acid outputs.

Helicobacter pylori

H. pylori is associated with more than 80% of duodenal ulcers and more than 60% of gastric ulcers patients. Host factors as well as bacterial virulence factors (such as cagA positive *H. pylori*) may determine disease predisposition in those who are *H. pylori* positive.

Nonsteroidal Anti-Inflammatory Drugs

A large number of peptic ulcers not related to *H. pylori* are related to NSAIDs use. Typically NSAIDs-induced ulcers are asymptomatic, but may cause symptoms as well as complications such as, bleeding, perforation and obstruction. Asymptomatic ulcers can be endoscopically documented in 15% to 45% of patients receiving chronic NSAID therapy. However, 1% to 4% of patients receiving NSAIDs for 1 year will experience serious GI complications.

The major mechanism of NSAIDs-induced injury appears to be due to its topical effects leading to ulcers, erosions and sometimes acute haemorrhages. Most NSAIDs are weak organic acids that in acidic gastric juice become unionised, and thus, are freely lipid soluble. These diffuse across the gastric epithelium into the cytoplasm. Uncoupling of oxidative phosphorylation resulting in decreased mitochondrial energy production, reduction in cellular integrity and increase in cellular permeability. Attenuation of the gastric mucous gel layer also occurs. Enteric coated NSAIDs produce considerably less acute topical erosive injury than non-enteric coated formulations over short term (1 to 2 weeks) usage.

Injury also occurs through its systemic effects. Peptic ulcers will develop after intravenous or rectal suppository further supporting a systemic effect. Cyclo-oxygenase (COX) is the rate limiting enzyme for prostaglandin synthesis. Most NSAIDs (excepting the specific COX-2 inhibitors) reduce mucosal prostaglandin. A small dose of 10 mg of oral aspirin can decrease gastric prostaglandin levels by 60% and can cause gastric ulcers. Levels do not recover till 5 to 8 days. Animal experiments indicate that for gastric ulcers to occur both COX-1 and COX-2 must be inhibited. Hence, theoretically, COX-2 specific inhibitors are associated with improved GI toxicity profile.

Besides COX inhibition NSAIDs increase gastric acid secretion, decrease gastric mucosal blood flow, decrease mucous production and duodenal bicarbonate. Nitric oxide (NO) protects the GI mucosa from NSAIDs-induced injury. Nitric oxide donating NSAIDs or COX inhibiting nitric oxide donating drugs (CINODs) exhibit reduced GI toxicity in animal and human trials.

Other Ulcerogenic Drugs

Besides NSAIDs the other ulcerogenic drugs are 5-fluorouracil, potassium chloride, mycophenolate mofetil, and bisphosphonates (alendronate and risedronate).

Hypersecretory Conditions

These should be considered in any patient who has peptic ulcer not associated with *H. pylori* or NSAIDs. Other clues include severe complicated disease, ulcers in the post-bulbar duodenum and diarrhoea. Hypersecretory conditions include gastrinoma, systemic mastocytosis and myeloproliferative disorders with basophilia, and antral G cell hyperfunction.

Epidemiology

It has been observed that there is a declining prevalence of peptic ulcer disease, in part related to falling prevalence of *H. pylori*. In contrast ulcer related complications as well as hospitalisation is on the rise, particularly in elderly due to increased use of NSAIDs.

Cigarette smoking is a risk factor for peptic ulcer disease and its complications. It slows healing and predisposes to relapses. However, if *H. pylori* is eradicated, smoking does not influence relapses.

As far as alcohol is concerned, wine and beer are potent acid secretagogues but its importance in pathogenesis of peptic ulcer is dubious. There is no study which has clearly demonstrated a link between diet and peptic ulcer disease. Coffee (both caffeinated and decaffeinated), tea and colas are potent acid secretagogues. Amongst the diseases associated with peptic ulcer are alcoholic cirrhosis, chronic pulmonary disease and chronic renal failure. Despite popular belief, there is no role of emotional stress and peptic ulcers. Some studies have suggested that genetics may predispose to peptic ulcer disease.

Clinical Features of Uncomplicated Peptic Ulcer Disease

The main symptom of peptic ulcer disease is abdominal pain. Patients with duodenal ulcer describe burning or gnawing epigastric pain. Pain occurs 2 to 3 hours after a meal and is relieved after food or with antacids. Pain may occur in the night. Anorexia and weight loss are uncommon. Patients with gastric ulcers may have pain indistinguishable from duodenal ulcer. Peptic ulcers may be asymptomatic. Symptoms are neither specific nor sensitive for diagnosing peptic ulcers. If peptic ulcer is suspected, investigations must be carried out. Increase in severity of pain, radiation of pain to the back, pallor, vomiting or bleeding should point to the development of complications. It should be remembered that the symptoms of gastric cancer may be very similar to those of peptic ulcer. Presence of alarm signs like increased severity of pain, pallor, weight loss, vomiting, high ESR and presence of occult blood in stool should prompt investigations. In uncomplicated peptic ulcer the clinical examination will be unremarkable or the only sign will be tenderness in the epigastrium or slightly to the right of the midline in the upper abdomen.

Diagnostic Tests

Upper GI endoscopy has become the gold standard for diagnosis of peptic ulcer. Barium-meal is a far less sensitive investigation. Also endoscopy allows an opportunity for mucosal biopsy. Studies of acid secretion have little role in the diagnosis of peptic ulcer. However, these are useful in the work up of hypergastrinaemia, and to assess the completeness of vagotomy in recurrent ulcer. In patients with refractory peptic ulcer, serum calcium and fasting serum gastrin are indicated.

Treatment

The treatment of peptic ulcer has dramatically changed over the years. From bed rest and prescription of 'bland diets' came the era of antacids. The discovery of H_2 receptor antagonists and later of proton pump inhibitors (PPIs) achieved greater ulcer healing rates. The real revolution occurred, however, with discovery of the link between *H. pylori* and peptic ulcer.

Acid lowering drugs

These are not routinely required for patients with uncomplicated *H. pylori* ulcers in whom the bacterium has been successfully eradicated. However, anti-ulcer drugs are important for healing of large ulcers, management of complicated ulcer disease such as bleeding, reducing the risk of ulcer relapse in patients on NSAIDs and treating idiopathic ulcers.

Antacids: Besides increasing the gastric pH, antacids have a variety of cytoprotective effects. At present, they are used mainly for relieving symptoms. Side-effects include diarrhoea (magnesium containing) or constipation (aluminium containing). Antacids must be used cautiously in patients with renal insufficiency.

Histamine (H_2) receptor antagonits

These include cimetidine, ranitidine, famotidine, roxatidine and nizatidine. These agents competitively inhibit histamine stimulated acid secretion. All of them decrease basal as well as meal stimulated acid output. These agents are well absorbed after oral dosing and are not affected by food. All of them are eliminated by a combination of renal excretion and hepatic metabolism. H_2 receptor antagonists are remarkably safe and well tolerated. Overall incidence of side-effects is less than 4% and serious side effects are very uncommon. A variety of central nervous system symptoms have been rarely reported; these include headache, dizziness, depression. Drug interactions (inhibiting elimination of theophylline, phenytoin, lidocaine, quinidine and warfarin) have been reported due to binding of hepatic cytochrome P450 (CYP) system. Tolerance appears to develop quickly and frequently.

Proton pump inhibitors

These agents decrease gastric acid by inhibiting the H^+/K^+ ATPase pump of the parietal cell. Currently five PPIs are available; omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. They are all substituted benzimidazoles and are weak bases. They are prodrugs and are acid labile. PPIs are most effective when administered immediately before meals. If the dose is once daily, it is preferable to administer immediately before breakfast. Single dose may inhibit gastric acid secretion for more than 24 hours. Newer PPIs inhibit H^+/K^+ ATPase more rapidly than omeprazole. PPIs are remarkably safe. Common side-effects are headache and diarrhoea. No dose adjustment is required in patients with renal or hepatic impairment. Elevation of gastric pH can interfere with absorption of drugs such as ketoconazole (decrease) and digoxin (increase). Drug interactions are uncommon. Potential interactions may occur since PPIs are metabolised by CYP system. One such example is reduction in the effect of clopidogrel. Although PPIs cause hypergastrinaemia, there is no human report of development of gastric carcinoid tumours. Tolerance to the anti-secretory effects of PPIs is not seen. There is no need for routine *H. pylori* eradication prior to initiating treatment with PPIs.

Mucosa protective agents

Sucralfate: This is a complex metal salt of sulphated sucrose and aluminium hydroxide. When exposed to gastric acid, the aluminium hydroxide dissociates, leaving sulphate anions that can bind electrostatically to positively charged proteins in damaged tissue. It forms a protective layer over the ulcer craters. Other beneficial effects include increase in mucosal prostaglandins, stimulation of mucous and bicarbonate secretions, binding of bile salts and promotion of angiogenesis. It is effective in promoting healing when given in a dose of 1 g four times a day. Since it is not absorbed, there is no systemic toxicity.

Bismuth: The two commonly used preparations are colloidal bismuth subcitrate and bismuth subsalicylate. The bismuth component forms complexes with mucous and coats the ulcer

craters. Also bismuth has anti-microbial action against *H. pylori*. Bismuth is unabsorbed if given over a short duration and systemic toxicity is rare.

Prostaglandin E analogues: Prostaglandin E2 regulates mucosal blood flow, epithelial cell proliferation, epithelial restitution, mucosal immunocyte function, mucous and bicarbonate secretion, and basal acid secretion. Misoprostol, a prostaglandin analogue is used for prevention of NSAIDs-induced ulcer disease. It is well absorbed after oral administration. Dose related diarrhoea is observed in nearly one-third of the patients. It is contraindicated in pregnant women.

Ulcers associated with H. pylori

Peptic ulcer management was revolutionised after discovery of *H. pylori*. It is well established that *H. pylori* eradication not only heals ulcers but also prevents relapses. *H. pylori* is associated with 70% to 90% of duodenal ulcers and 40% to 70% of gastric ulcers. For uncomplicated duodenal ulcers, additional anti-secretory treatment is not required. For large gastric ulcers additional anti-secretory treatment may promote ulcer healing. For large gastric ulcers, biopsy must be taken to exclude malignancy. After successful eradication, maintenance therapy with anti-secretory agents is not required.

Ulcers associated with NSAIDs

In this situation NSAIDs should be discontinued, if possible. PPIs are more effective than H_2 receptor antagonists or misoprostol for healing of NSAIDs-induced ulcers. There is little role of substituting a selective COX 2 inhibitor in place of conventional NSAIDs once an ulcer develops. *H. pylori* needs to be eradicated if present in these patients.

Prophylaxis of NSAIDs ulcers

H_2 receptor antagonists reduce the risk of duodenal ulcers but not gastric ulcers. Misoprostol reduces the risk of NSAIDs-induced gastric and duodenal ulcers. Higher dose (800 µg/day) of misoprostol reduced ulcer complications. PPIs are very effective in reducing the risk of NSAID-induced gastric and duodenal ulcers. COX 2 inhibitors induced fewer ulcers than conventional NSAIDs. New data suggest that a combination of non-selective NSAIDs with PPI is as effective or better than using selective COX 2 inhibitors in prevention of NSAIDs-ulcers. Also studies have shown increased serious cardiovascular events with the use of COX 2 inhibitors. If *H. pylori* is present, it needs to be eradicated. This is also recommended for patients on long-term, low-dose aspirin. In patients with risk factors for ulcer complications (**Table 1**), co-therapy with a PPI is recommended.

Table 1: Risk Factors for NSAIDs-Induced Ulcer Complications

History of peptic ulcer complication
Increasing age
Use of steroids
Use of anti-coagulants
Use of combination NSAIDs
Co-morbid diseases
Smoking

Refractory Peptic Ulcers

Most peptic ulcers heal with 8 to 12 weeks of anti-secretory therapy. If this does not occur, consider the following: lack of compliance, failed *H. pylori* eradication, ongoing NSAIDs, smoking, hyper-secretory condition and other aetiologies (neoplastic, infective).

Complications

The complications of peptic ulcer are penetration, perforation, haemorrhage and obstruction.

Penetration refers to the extension of the ulcer through the bowel wall into the adjacent structures without producing free perforation into the peritoneal cavity. The ulcer can penetrate into the pancreas, biliary tract, omentum or colon. Perforation into the colon leads to gastro-colic fistula. Symptoms of penetration vary depending on the organ involved. It manifests as increase in severity and duration of pain and failure of pain relief with antacids or food.

Bleeding from peptic ulcer is a life-threatening complication. The patient may present with melaena, haematemesis or both. When the bleeding is massive haematochezia will be present. Old age, shock at the time of admission and massive bleeding necessitating transfusion of more than five units of blood indicate poor prognosis, and surgery should be considered in these situations. The first step in the management is resuscitation of the patient by replacing the blood volume and managing haemodynamic instability. Upper GI endoscopy should be done as soon as the patient is stable. This will show the site of bleed. Active bleeding or the presence of high-risk lesions—visible vessel or adherent clot (**Figure 4**)—call for endoscopic management. Injection of saline or dilute adrenaline (**Figure 5**), application of heater probe, endoscopic application of clips (**Figure 6**) can all arrest the bleeding. Anti-secretory treatment (intravenous, continuous infusion of PPI) should be started.



Figure 4: Duodenal ulcer with stigmata of recent bleed (black base).

Perforation of peptic ulcer is an emergency. The patient presents with sudden onset of abdominal pain; peritonitis and free gas in the peritoneum are present. Patients who present late and those who develop perforation while in the hospital have a poor prognosis. Surgical treatment, which involves closure of the perforation with an omental patch is the procedure often employed. Effective treatment of *H. pylori* infection and strong acid suppressants are available now, and



Figure 5: Injection sclerotherapy being done for bleeding duodenal ulcer with stigmata of recent bleed (visible vessel).



Figure 6: Haemoclips applied to base of bleeding ulcer.

hence, a definitive surgical treatment may not be necessary in selected patients; small leaks into peritoneum can be managed conservatively.

Obstruction in peptic ulcer may be due to fibrosis, inflammation or spasm. It is the pyloric channel ulcers or ulcers in the first part of duodenum that develop gastric outlet obstruction. Gastric outlet obstruction (pyloric stenosis) (**Figure 7**) presents with post-prandial bloating, fullness and vomiting. Vomiting brings out food consumed several (>6) hours ago. Foul smelling eructations may be present. Examination reveals a visibly dilated stomach, visible peristalsis or succussion splash. Barium meal shows a dilated stomach with delayed emptying. Endoscopy should be performed after thorough cleaning of the stomach. Carcinoma of the stomach should be excluded in every patient with gastric outlet obstruction as malignancy is seen in about half of such cases. Management includes gastric lavage to remove food debris, correction of fluid and electrolyte disturbances and metabolic consequences of prolonged vomiting and loss of gastric acid. Anti-secretory drugs should be administered parenterally since absorption is poor. *H. pylori* infection and NSAID intake should be looked for and managed. If the symptoms fail to respond, surgery is indicated. Endoscopic balloon dilatation of the narrowed segment has also been used successfully (**Figure 7**).



Figure 7: Endoscopic balloon dilatation for pyloroduodenal stenosis.

Ulcers in the lower end of the oesophagus may in the long run lead to peptic strictures and dysphagia. Endoscopic balloon dilatation gives symptomatic relief to these patients. Fibrosis during healing of gastric ulcers may result in rare deformities of the stomach like 'tea-pot stomach' or the 'hour-glass stomach'.

Recurrent ulcer is the term used for recurrence of ulcers after surgical treatment of duodenal ulcer. Incomplete vagotomy and retained antrum are the most common causes.

Duodenal ulcer does not turn malignant. *H. pylori* is implicated as an aetiological agent in carcinoma stomach. In spite of the high prevalence of *H. pylori* in persons with peptic ulcer, duodenal ulcer is not a risk factor for the cancer of the stomach or of the duodenum. However, persons who had undergone surgery (partial gastrectomy) for duodenal ulcer are at increased risk of developing cancer in the post-operative stomach.

GASTRIC VOLVULUS

Twisting of the stomach upon itself leads to gastric volvulus which can present clinically either acutely or as chronic volvulus. Three types have been described—organoaxial volvulus is the most common; in this type the stomach twists along its long axis (cardiopyloric line); mesenteroaxial volvulus is one in which the stomach falls on itself along an imaginary line drawn from the mid-point of the lesser curvature to the mid-point of the greater curvature and is the least common of the three; mixed gastric volvulus is a combination of organoaxial and mesenteroaxial types. Anatomical anomalies such as ligamentous laxity, paraoesophageal hiatus hernia, eventration of the diaphragm, extrinsic compression from adjacent organs or submucosal tumours of the stomach can cause gastric volvulus.

Patients with acute gastric volvulus present as an acute abdomen with the classical triad of violent retching and little vomiting, severe epigastric pain and inability to advance a nasogastric tube into the stomach. In patients with chronic volvulus the major symptoms are epigastric pain, bloating and eructations.

Barium-meal examination usually demonstrates the twisted stomach. Acute volvulus is an emergency and usually requires an emergent laparotomy although endoscopic derotation of the

volvulus is sometimes successful. Recurrent symptoms in patients with chronic volvulus need surgical treatment wherein the stomach is fixed to the anterior abdominal wall by performing a gastropexy. Recently, percutaneous endoscopic gastrostomy has been found to be an alternative to surgical gastropexy.

BEZOARS

These have been classified into two main groups: hair or trichobezoar and plant or phytobezoars. Other materials such as chemical concretions, food boluses and foreign bodies may also cause bezoars. For phytobezoars, hypochlorhydria, gastroparesis and incomplete mastication are important predisposing factors. In patients with trichobezoar, underlying neuropsychiatric disturbances may be present. Bezoars present with pain in the upper abdomen, periodic attacks of nausea and vomiting and a lump in the abdomen. Complications such as gastric ulcer, perforation and peritonitis may occur. Plain X-ray abdomen in the standing position occasionally demonstrates a mass invading the gastric air bubble. Barium-meal examination demonstrates a barium shell coating an irregular large filling defect. In most cases upper GI endoscopy is diagnostic. For treating phytobezoars, endoscopic internal fragmentation using forceps and polypectomy snares may be tried. Chemical dissolution using papain, cellulase and acetylcysteine is sometimes successful. If these methods fail, surgical removal needs to be done. In most cases of trichobezoars, surgery is required.

DUODENAL DIVERTICULUM

It is usually single and present along the medial wall of the duodenum. It is acquired as an outpouching of the duodenal mucosa at the point of maximum weakness. Most often this diverticulum is asymptomatic and incidentally detected during a barium-meal examination or Upper GI endoscopy (**Figure 8**). Rarely, duodenal diverticulum may perforate retroperitoneally, cause upper GI bleeding or obstruct the bile duct or pancreatic duct. The treatment of a complicated duodenal diverticulum is surgical.



Figure 8: Barium-meal examination showing duodenal diverticulum along medial wall.

RECOMMENDED READINGS

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13.9 Diseases of the Pancreas

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ACUTE PANCREATITIS

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems.

Mild acute pancreatitis consists of minimal or no organ dysfunction and an uneventful recovery. Severe pancreatitis manifests as organ failure and/or local complications such as necrosis, abscess, or pseudocyst (**Table 1**). Overall, about 20% of patients with acute pancreatitis have a severe course, and 10% to 30% of those with severe acute pancreatitis die.

Table 1: Criteria of Severe Acute Pancreatitis

Organ failure
Shock: Systolic blood pressure of <90 mm Hg
PaO_2 <60 mmHg
S. Creatinine >2 mg/dL
Gastrointestinal bleed of >500 mL in 24 hours
And/Or local complications
Necrosis
Abscess
Pseudocyst
Unfavourable prognostic signs
>3 Ranson's signs
>8 APACHE II points

Aetiopathogenesis

The gallstone disease and alcohol are the two most common causes for AP (**Table 2**). The initial step in the pathogenesis of acute pancreatitis is conversion of trypsinogen to trypsin within acinar cells. Trypsin, in turn, catalyses conversion of pro-enzymes, including trypsinogen and inactive precursors of elastase, phospholipase A_2, and carboxypeptidase, to active enzymes. Active enzymes autodigest the pancreas and initiate a cycle of releasing more active enzymes. Factors that may initiate gallstone pancreatitis include reflux of bile into the pancreatic duct or obstruction of the pancreatic duct at the ampulla by a stone(s) or oedema resulting from the passage of a stone. The pathophysiology of acute pancreatitis includes microcirculatory injury, leucocyte chemoattraction and release of cytokines, oxidative stress, and bacterial translocation.

Clinical Features

Abdominal pain is present at the onset, but the timing of abdominal pain is variable. Biliary colic may herald or progress to acute pancreatitis. Alcohol-related acute pancreatitis frequently occurs 1 to 3 days following drinking. The pain radiates to back and is associated with nausea and vomiting. Its onset is rapid and reaches maximal intensity in 10 to 20 minutes. Occasionally, pain takes several hours to reach maximum intensity. It is steady and moderate to very severe in intensity.

Physical findings depend on the severity of an attack. Patients with mild pancreatitis may not appear acutely ill and have mild abdominal tenderness. In severe pancreatitis, patients look severely ill and often have abdominal distention, especially epigastric, which is due to gastric ileus or dilatation of the transverse colon. Bowel sounds are reduced and may be absent.

Table 2: Aetiology of Acute Pancreatitis

Gallstones
Biliary sludge and microlithiasis
Alcohol
Mechanical obstruction of ampulla
Metabolic: Hypertriglyceridaemia and hypercalcaemia
Infections: Mumps, HIV, CMV, EBV, Clonorchiasis, and Ascariasis
Toxins: Scorpion venom, organophosphorous insecticides
Trauma
Post ERCP
Pregnancy
Post-operative
Hereditary
Ischaemia
Drugs: Pentamidine, didanosine, salicylates, sulindac, frusemide, thiazides
Sulphasalazine, mesalamine, L-asparaginase, azathioprine, valproic acid, ACE-inhibitors

Diagnosis

Acute pancreatitis can be diagnosed by the presence of typical clinical features along with corroborative laboratory findings of elevated serum enzymes (amylase/lipase) and/or imaging features. It needs to be differentiated from other abdominal causes which may present as an acute abdomen.

Investigations

Blood investigations

The white blood cell count is usually elevated, markedly so in severe pancreatitis. A raised haematocrit, indicative of haemo-concentration, may indicate severe disease.

Serum amylase is the most frequently ordered test. However, hyperamylasemia can also occur in other conditions. In acute pancreatitis, the serum amylase concentration is usually more than three times the upper limit of normal. Measurement of serum lipase is performed less frequently. Amylase levels tend to return to normal faster than lipase levels, so that measurement of the latter is particularly useful in patients who present several days after the onset of pain. An increase in serum alanine aminotransferase (ALT) 3 to 4 times the base-line level suggests gallstone-induced pancreatitis.

Imaging

There can be localised ileus of a segment of small intestine ('sentinel loop') or the colon cut-off sign on a plain radiograph of the abdomen. Thirty per cent of patients with acute pancreatitis have abnormalities in chest radiograph in the form of elevation of a hemi-diaphragm, pleural effusion(s), basal or

plate-like atelectasis secondary to limited respiratory excursion, and pulmonary infiltrates.

Transabdominal ultrasonography is the best initial imaging modality. It is used during the first 24 hours of hospitalisation to search for gallstones, dilatation of the common bile duct due to choledocholithiasis and ascites. Pancreas is usually diffusely enlarged and hypoechoic.

A contrast enhanced computed tomography (CECT) scan of the abdomen is the most important imaging test for the diagnosis of acute pancreatitis and its intra-abdominal complications and is also used to assess the severity of the disease.

Magnetic resonance imaging (MRI) shows the pancreas as well CT scan. In addition, it has certain advantages over the latter. It does not carry the potential nephrotoxicity of the contrast required to perform CECT, better than it avoids the radiation exposure of CT scan and finally, it shows a greater ability than CT scan to distinguish necrosis from fluid.

Endoscopic ultrasound (EUS) helps in timely diagnosis of common bile duct (CBD) or ampullary stones in the setting of acute gallstone pancreatitis; hence it can be used instead of diagnostic endoscopic retrograde cholangio-pancreatography (ERCP) to identify patients who would likely benefit from therapeutic ERCP.

Treatment

The algorithm for treatment of acute pancreatitis is outlined in **Figure 1**.

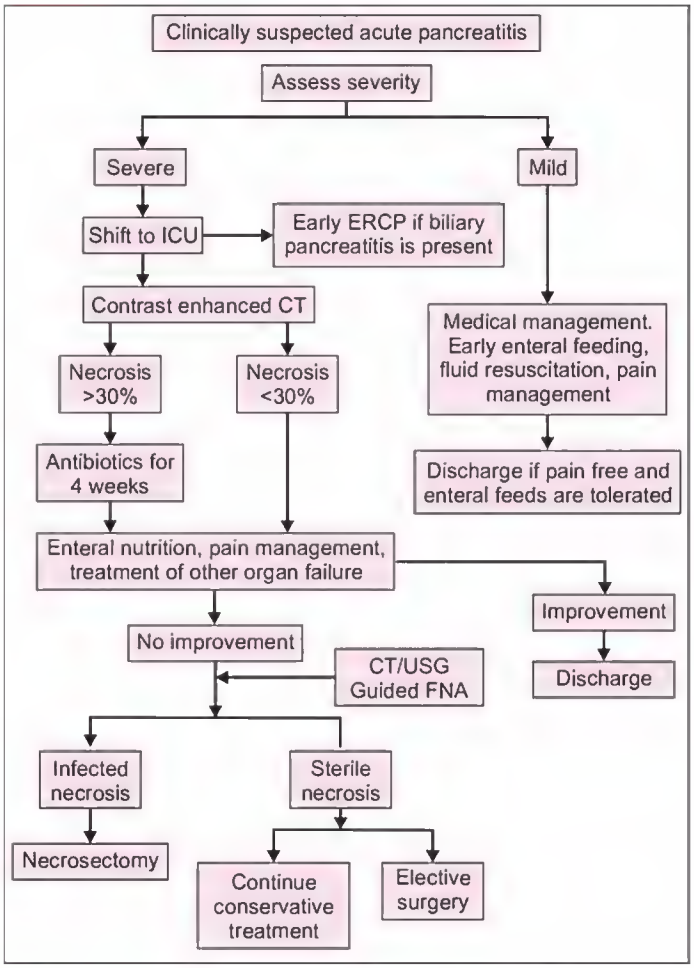


Figure 1: Algorithm for management of pancreatitis.

Mild acute pancreatitis

The prognosis of mild pancreatitis is good and can be managed in a regular hospital ward with fluid administration, bowel rest and analgesics. Fluid resuscitation is important to replace low intravascular volume due to vomiting, diaphoresis, and third-space losses. Abdominal pain is treated with parenteral analgesics. Most patients require no further therapy and recover within a week.

Severe acute pancreatitis

Patients with signs of severe acute pancreatitis should be identified early and admitted promptly to an intensive care unit. The goal is to provide supportive care and treatment of complications when they develop. Maintaining adequate intravascular volume may require 5 to 10 litres of fluid daily for the initial few days. Hypoxaemia (oxygen saturation <90%) requires oxygen, ideally by nasal prongs or by facemask. If nasal oxygen fails to correct hypoxaemia or if there is fatigue and borderline respiratory reserve, endotracheal intubation and assisted ventilation are required early. Nutritional support via nasojejunal feedings should be initiated. Hyperglycaemia may present during the first several days of severe pancreatitis but usually normalises as the inflammatory process subsides. Blood sugar levels can be variable, and insulin should be administered cautiously.

Sterile pancreatic necrosis is managed conservatively. Bacterial infection of pancreatic and peripancreatic tissues develops usually after one week in approximately 30% of severe acute pancreatitis. Three approaches to decrease bacterial infections in acute necrotising pancreatitis are used; they are selective decontamination of the gut with non-absorbable antibiotics, prophylactic systemic antibiotics, and enteral feeding to avoid catheter-related infections associated with a central line, to maintain gut barrier integrity, and to decrease bacterial translocation.

Infected pancreatic necrosis should be suspected in patients with worsening of symptoms after initial improvement; and in those who develop new fever, marked leucocytosis, positive blood cultures, or other evidence of sepsis. The important organisms causing infection in necrotising pancreatitis are from the gut (*Escherichia coli*, *Pseudomonas*, *Klebsiella*, and *Enterococcus* species). Standard regimens include imipenem 500 mg intravenously three times a day; pefloxacin (fluoroquinolone) 400 mg intravenously two times a day; or metronidazole 500 mg three times a day for 10 to 14 days. Infected pancreatic necrosis usually requires minimally invasive debridement via endoscopic or surgical approaches.

Urgent therapeutic ERCP should be performed in patients with suspected or proven biliary pancreatitis, who satisfy the criteria for predicted or actual severe pancreatitis; or when there is cholangitis, jaundice, or a dilated common bile duct.

Adequate supply of nutrients plays an important role early in management. Enteral feeding is safe and as effective. However, total parenteral nutrition may be necessary for patients who cannot obtain sufficient calories through enteral nutrition or in whom enteral access cannot be maintained; but carries an increased risk of infection.

Prognostic indicators

These include use of single markers like C-reactive protein (CRP), trypsin activation peptide (TAP), procalcitonin, etc. as well as

scoring systems like Ranson's score, Glasgow score, acute physiology and chronic health evaluation (APACHE) II, among others (**Tables 3 and 4**). A new prognostic scoring system, the bedside index for severity in acute pancreatitis—BISAP (blood urea nitrogen >25 mg/dL, impaired mental status, systemic inflammatory response syndrome (SIRS), age >60 years, and pleural effusions) was comparable to existing scoring systems.

Table 3: Complications of Acute Pancreatitis

Local
- Pseudocyst
- Necrosis
- Abscess
- Gastrointestinal bleed due to ulcerations, gastric varices and pseudoaneurysm rupture

Systemic
- Shock
- Coagulopathy
- Respiratory failure
- Renal failure
- Metabolic: Hyperglycaemia, hypocalcaemia
- Subcutaneous nodules
- Retinopathy
- Psychosis

Table 4: Ranson's Criteria for Assessing Severity of Acute Pancreatitis

	Non-gallstone pancreatitis	Gallstone pancreatitis
On Admission		
Age (years)	>55	>70
WBC (/cmm)	16000	18000
Glucose (mg/dL)	>200	>220
LDH (IU/L)	>350	>400
AST (IU/L)	>250	>250
Within 48 hours of admission		
Haematocrit fall	>10	>10
BUN rise (mg/dL)	>5	>2
Calcium (mg/dL)	<8	<8
PO_2 mmHg	<60	—
Base deficit (mEq/L)	>4	>5
Fluid deficit	>6L	>4L

CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is characterised by pancreatic inflammation and fibrosis, the end point of which is destruction of pancreatic parenchyma with eventual loss of exocrine and endocrine function.

Aetiology

The aetiologic risk factors associated with chronic pancreatitis is given in **Table 5**.

Alcohol

The most common cause of chronic pancreatitis in the Western world and in Japan is excessive alcohol consumption. In most patients, at least five years of alcohol intake exceeding 80 g/day is required prior to the development of chronic pancreatitis.

Tropical pancreatitis

Tropical pancreatitis (TCP) remains an important form of chronic pancreatitis in certain areas of India. The exact aetiopathogenesis of TCP remains unknown. Nutritional deficiencies, especially of micronutrients and antioxidants or/and dietary toxins such as cyanogenic glycosides (cassava or tapioca), have been considered as likely aetiological factors.

Hereditary pancreatitis

Hereditary pancreatitis is a rare autosomal dominant disorder with approximately 80% penetrance. It presents typically in childhood or early adulthood with abdominal pain and recurrent acute attacks of pancreatitis.

Table 5: Aetiologic Risk Factors Associated with Chronic Pancreatitis: TIGAR-O Classification System

Toxic-metabolic

Alcohol, tobacco smoking, hypercalcaemia (hyperparathyroidism), chronic renal failure, medications (phenacetin), toxins (organotin compounds, e.g. DBTC)

Idiopathic

Early onset, late onset

Tropical (tropical calcific pancreatitis, fibrocalculous pancreatic diabetes)

Genetic

Autosomal dominant (Cationic trypsinogen codon 29 and 122 mutations)

Autosomal recessive/modifier genes (CFTR mutations, SPINK1 mutations

Cationic trypsinogen codon 16, 22, 23 mutations, α1-antitrypsin deficiency)

Autoimmune

Isolated autoimmune chronic pancreatitis

Syndromic autoimmune chronic pancreatitis (Sjögren syndrome-associated chronic pancreatitis, inflammatory bowel disease-associated chronic pancreatitis

Primary biliary cirrhosis—associated chronic pancreatitis)

Recurrent and severe acute pancreatitis

Post-necrotic (severe acute pancreatitis), recurrent acute pancreatitis, vascular diseases/ischaemic, post-irradiation

Obstructive

Pancreatic divisum, sphincter of Oddi disorders, duct obstruction (e.g. tumour)

Pre-ampullary duodenal wall cysts, post-traumatic pancreatic duct scars

Obstructive chronic pancreatitis

Obstruction of the main pancreatic duct by tumours, scars, cysts, or stenosis of the papilla of Vater or minor papilla can produce chronic pancreatitis in the parenchyma upstream of the obstruction. Blunt and penetrating trauma to the pancreas can also lead to pancreatic duct strictures.

Autoimmune pancreatitis

This is characterised by presence of autoantibodies, elevated levels of immunoglobulins especially IgG4, enlargement of the pancreas (diffuse or focal), pancreatic duct strictures, and pathologic features of a dense lymphocytic infiltrate. A common presentation is that of a pancreatic mass mimicking cancer. It is often steroid responsive. Low dose steroids or immunomodulators may be needed to maintain remission.

Idiopathic chronic pancreatitis

Idiopathic chronic pancreatitis accounts for 10% to 30% of all cases of CP in the West and 40% to 60% in India, and appears to occur in two forms, early onset and late onset type.

Pathophysiology

The pathophysiology of CP remains incompletely understood. Four major theories include toxic-metabolic, oxidative stress, stone and duct obstruction, and necrosis-fibrosis.

Pathology

In early CP, areas of interlobular fibrosis are seen, with the fibrosis often extending to the ductal structures. Infiltration of the fibrotic area and lobules with lymphocytes, plasma cells, and macrophages is seen. In affected lobules, acinar cells are replaced by fibrosis. As the disease progresses, fibrosis within the lobules and between lobules becomes more widespread. The pancreatic ducts become more abnormal, with progressive fibrosis, stricture formation, and dilation. Protein plugs may calcify and obstruct major pancreatic ducts.

Clinical Features

The cardinal symptom of CP is abdominal pain. Fat malabsorption leading to steatorrhoea and weight loss is common in CP. Steatorrhoea does not occur until pancreatic lipase secretion is reduced to less than 10% of normal. Diabetes in CP is considered as a secondary form of diabetes mellitus. Weight loss is most commonly due to decreased intake in episodes of acute exacerbation. Weight loss may also occur owing to the development of small bowel bacterial overgrowth, malabsorption, uncontrolled diabetes or pancreatic or extrapancreatic malignancy.

Physical examination might show evidence of nutritional deficiencies. Complications of common bile duct obstruction or a pseudocyst may produce physical findings of jaundice, or a palpable swelling in the epigastrium. Ascites may rarely follow a leak from a ruptured pancreatic duct. A palpable spleen may be seen following thrombosis of the splenic vein (**Table 6**).

Diagnosis

Serum amylase or lipase may be found to be elevated only during acute exacerbations. A full diabetic work-up should be done for all patients with suspected pancreatitis. A prediabetic stage has been well described.

Imaging

The demonstration of pancreatic calcification on imaging is pathognomonic of CP. Diagnosis is difficult in early cases of pancreatitis where the patient may have typical symptoms but lack diagnostic imaging features on ultrasonography (USG)/CT. In such cases, an endoscopic retrograde pancreatography (ERP) or a EUS may be helpful.

Pancreatic calcifications are most common in alcoholic, late-onset idiopathic, hereditary and especially in tropical pancreatitis and may be detected on abdominal radiograph.

Ultrasonography findings indicative of CP include dilation of the pancreatic duct, pancreatic ductal stones, gland atrophy or enlargement, irregular gland margins, pseudocysts and changes in the parenchymal echotexture.

CECT scan of the abdomen is superior to USG. The sensitivity of CT for CP is 75% to 90% and specificity 85% or more.

ERCP is considered the most specific and sensitive test of pancreatic structure. The sensitivity of ERCP is between 70% and 90%, with a specificity of 80% to 100%.

Magnetic resonance cholangiopancreatography (MRCP) agrees with ERCP in 70% to 80% of findings. MRCP is non-invasive, avoids ionising radiation and contrast administration, and does not routinely require sedation, making it a diagnostic procedure of choice in some groups of patients, particularly children.

EUS is the best among currently available tests for the detection of early changes of CP. Typical findings in CP include parenchyma features like hyperechoic strands, hyperechoic foci, lobularity, cysts; and ductal features like stones, main duct irregularity, hyperechoic main duct, visible side branches, main duct dilatation.

Table 6: Complications of Chronic Pancreatitis

No.	Complication	Signs and Symptoms	Treatment
1.	Pseudocyst	Increased abdominal pain, nausea, vomiting, jaundice, palpable mass, bleeding, increase in amylase and lipase	Endoscopic drainage (transmural or transpapillary) Surgical drainage (cyst-gastrostomy or cyst-jejunostomy) Percutaneous drainage
2.	Biliary obstruction	Jaundice, biliary pain, cholangitis, pruritus	Drainage of obstructing pseudocyst Endoscopic decompression Surgical decompression Surgical biliary bypass, either with a cholecystojejunostomy or choledochojejunostomy
3.	Gastric outlet obstruction	Abdominal pain, early satiety, nausea and vomiting	Drainage of pseudocyst Surgical gastrojejunostomy
4.	Pancreatic adenocarcinoma	Increased pain, weight loss, jaundice, elevated Ca 19-9	Whipple's or modified Whipple's surgery Palliation if advanced disease
5.	External pancreatic fistula	Consequence of surgical or percutaneous therapy for chronic pancreatitis or pseudocyst	NPO, parenteral nutrition, octreotide and endoscopic stent placement Surgical treatment includes pancreatic resection (if the fistula is in the tail) or a fistulojejunostomy, in which the fistula tract is 'capped' with a defunctionalised limb of jejunum
6.	Pancreatic ascites	Increased abdominal girth, high ascitic fluid amylase typically greater than 4000 units/L	Endoscopic stent placement, total parenteral nutrition
7.	Pleural effusion	Shortness of breath, high amylase in pleural fluid typically greater than 4000 units/L	Therapeutic thoracentesis, endoscopic stent placement, total parenteral nutrition
8.	Splenic vein thrombosis	Bleeding from gastric varices	Splenectomy

Treatment

Continued alcohol abuse hastens the development of pancreatic dysfunction and continued alcohol abuse, along with smoking, increases mortality. Moreover, smoking is one of the risk factors for the progression to pancreatic cancer. There are good reasons, therefore, to encourage patients to stop drinking and smoking.

Relief of pain

Analgesics like acetaminophen for mild pain or non-narcotic agents for moderate to severe pain are usually used. If non-narcotic agents fail, it is useful to begin with the less potent opioid agents like propoxyphene napsylate or tramadol before starting morphine. Pancreatic enzyme preparations, particularly those with high protease content and antioxidants may also help to relieve pain. Failure of medical management necessitates use of interventions like coeliac plexus block, extra-corporeal shock wave lithotripsy (ESWL), endoscopic therapy or surgery.

Correction of maldigestion

Pancreatic enzymes (~ 30,000 units of lipase) have to be given along with each meal. The enzyme activity tends to be degraded by the gastric acid, especially in case of non-enteric coated preparations; hence it is better to also administer proton pump inhibitors or H_2 receptor antagonists.

Management of diabetes

A few newly detected diabetics in CP can be controlled with diet and regular exercise. The majority can be managed with oral hypoglycaemic agents for varying periods. A large group will require insulin for glycaemic control.

Endotherapy

The general goal of endoscopic therapy is to improve drainage of the pancreatic duct by relieving obstruction. Patients with a solitary stone or a few small stones in the head region with a dilated proximal duct are the ideal candidates. Sphincterotomy, with pancreatic duct stenting, sometimes undertaken after ESWL to crush the stones, is the usual procedure.

Surgery

Surgery is indicated for intractable abdominal pain that has failed medical therapy. Other indications for surgery include complications involving adjacent organs (duodenal, splenic vein, or biliary obstruction), pseudocysts failing endoscopic or radiologic management, internal pancreatic fistulas, and suspected or proven malignancy. Surgical options for pain can include pancreatic ductal drainage, resection of all or part of the pancreas, or both. If there is suspicion of a malignancy in the head, a pancreaticoduodenectomy should be undertaken.

PANCREATIC CANCER

Pancreatic cancer remains a leading cause of death with 5-year survival rates of less than 5%. Despite advances in diagnosis and staging, most cancers are diagnosed in an advanced stage and are suitable only for palliative treatment.

Pathophysiology

Approximately 75% of all pancreatic carcinomas occur within the head or neck of the pancreas, 15% to 20% occur in the body of the pancreas, and 5% to 10% occur in the tail. It is a very aggressive neoplasm. At the time of diagnosis, 80% will already have metastasised.

Clinical Features

The presenting symptoms of pancreatic carcinoma are generally non-specific. Cancer that originates from the head of the pancreas can produce obstructive jaundice, epigastric pain and weight loss. The presence of pain is a late symptom and back pain typically signifies advanced disease. Jaundice is usually progressive and associated with pruritus, which can often be severe. Dyspepsia and early satiety may be present due to delayed gastric emptying (gastroparesis). Vomiting may be present if the tumour has invaded or compressed the second portion of the duodenum, creating a partial or complete intestinal obstruction.

The patient is usually jaundiced and may be anaemic or cachectic. There may be an epigastric mass or an irregular, enlarged liver because of metastases. There may be a palpable gallbladder secondary to common bile duct obstruction. Other findings include left supraclavicular lymphadenopathy (Virchow's node) and superficial thrombophlebitis (Trousseau's sign).

Investigations

The lesion may have a variable appearance on ultrasonography; it may be hypoechoic, isoechoic, or hyperechoic as compared to normal pancreas. Pancreatic ductal dilatation and biliary ductal dilatation are easily demonstrated in patients with a tumour in the head of pancreas. Lymphadenopathy, relation of the tumour to peripancreatic vessels, and the tumour margins are demonstrated less reliably with sonography.

CECT scan of abdomen using a pancreas protocol is the most useful and widely used imaging modality especially when some intervention is planned. Features on CT scan include: alterations in morphology of the gland with abnormalities of CT attenuation values, obliteration of peripancreatic fat, loss of sharp margins with surrounding structures, involvement of adjacent vessels and regional lymph nodes, pancreatic ductal dilatation, pancreatic atrophy, and obstruction of the common bile duct. Tumours less than 1 cm are readily visualised with EUS.

ERCP has a sensitivity of 95% and a specificity of 85% for pancreatic malignancy. MRCP is a non-invasive alternative to ERCP.

Serum carbohydrate antigen (CA) 19-9 has an overall sensitivity of approximately 80% and specificity of 90%.

Treatment

Surgery is the mainstay of treatment, but it is of value only if the primary tumour is less than 3 cm, free of major blood vessels and if there is no metastatic spread (**Tables 7 and 8**). Suitable patients undergo Whipple's procedure, which involves excision of the head of the pancreas, the distal common bile duct, the gall bladder, the duodenum and distal stomach, followed by anastomosis of the pancreatic duct, the common hepatic duct, and the distal stomach to a loop of jejunum. Perioperative mortality is less than 5% in experienced hands. Modified Whipple's procedure involves preservation of the distal stomach and pylorus, which may have long-term nutritional benefits. Distal pancreatectomy may be suitable for carcinoma of the body or tail.

Table 7: American Joint Committee for Cancer (AJCC) Staging of Carcinoma of the Pancreas (2002)

T stage
TX – Primary tumour cannot be assessed
T0 – No evidence of tumour
Tis – Carcinoma *in situ*
T1 – Tumour limited to the pancreas, 2 cm or less in greatest dimension
T2 – Tumour limited to the pancreas, more than 2 cm in greatest dimension
T3 – Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4 – Tumour involves the coeliac axis or the superior mesenteric artery (unresectable primary tumour)

N Stage
NX – Regional lymph nodes not assessed
N0 – No regional lymph node metastasis
N1 – Regional lymph nodes involved

M stage
MX – Distant metastases cannot be assessed
M0 – No distant metastases
M1 – Distant metastases present

Table 8: TNM Staging of Pancreatic Cancer

Stage	Classification	Clinical classification	5-year survival rate
0	Tis, N0, M0	Resectable (7.5%)	15.2%
1A	T1, N0, M0		
1B	T2, N0, M0		
IIA	T3, N0, M0		
IIB	T1-3, N1, M0	Locally advanced (29.3%)	6.3%
III	T4, any N, M0		
IV	Any T, any N, M1	Metastatic (47.2%)	1.6%

Palliative Treatment

Jaundice is palliated by stenting the biliary stricture. Both plastic and self-expandable metal stents (SEMS) have been used for palliation of jaundice. When endoscopic biliary drainage is unsuccessful or contraindicated, percutaneous transhepatic biliary drainage is done.

Pain requires graded use of analgesic agents. Coeliac plexus block (percutaneous or EUS guided) and splanchnectomy are useful interventions for palliation of pain.

Gemcitabine is the standard chemotherapeutic agent used for pancreatic cancer. Other drugs are capecitabine, 5-fluorouracil, cisplatin and oxaliplatin.

RECOMMENDED READINGS

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13.10 Functional Gastrointestinal Disorders

Philip Abraham

The term 'functional gastrointestinal disorders' is used for a group of conditions with clinical manifestations in the absence of obvious organic disease in gastrointestinal (GI) tract. These disorders constitute the most common gastrointestinal cause for consultation. The characterisation and classification of these disorders is based on predominant symptoms (which may suggest region of origin in the GI tract), because no single aetiological factor or investigative pattern has been identified in any subgroup.

CLASSIFICATION

For the sake of convenience, the disorders have been broadly classified as due to upper or lower GI disturbance. Although each subgroup has distinct features, many subjects have overlapping symptoms, suggesting that the disorder may be more diffuse than implied by the predominant symptom. Thus, patients with the irritable bowel syndrome (IBS), a predominantly lower GI disturbance, often have dyspeptic symptoms in addition. Also, in IBS, what is considered abnormal bowel frequency by the patient may overlap what is considered normal by a segment of the general population, suggesting visceral hypersensitivity in the patient.

The Rome III criteria for functional bowel disorders (**Table 1**) are an attempt to improve on several previous classifications.

FUNCTIONAL DYSPEPSIA

(Synonyms: Idiopathic, essential or non-ulcer dyspepsia)

Functional dyspepsia is a chronic or recurrent heterogeneous symptom complex that has its origin in the upper gastrointestinal tract, is localised to the upper abdomen, and is generally meal-related. The Rome III criteria identifies two primary symptom groups, namely, epigastric pain or burning (the epigastric pain syndrome) and meal-related early satiety or postprandial fullness (the postprandial distress syndrome).

The diagnosis of functional dyspepsia ideally requires that organic conditions with similar symptoms (peptic ulcer disease, gastro-oesophageal reflux disease, giardiasis, pancreatic and biliary diseases) be excluded first. In clinical practice, however, a normal upper gastrointestinal endoscopy is generally taken as adequate evidence, unless the suspicion of pancreatic or biliary disorder is strong enough to merit investigation. The likelihood of endoscopy detecting an organic lesion is low if it is undertaken as a regular practice.

Aetiopathogenesis

Recent data implicates phenotypic changes in acid secretion; alterations of fundic accommodation, antro-duodenal motility and gastric emptying; gastric hypersensitivity triggered by chemo- or mechanoreceptors; and hormonal disturbances; as the possible causes of dyspepsia, but each of these is present in only a proportion of the patients. A possible role of alpha-adrenoceptor gene polymorphism has also been suggested.

Table 1: Rome III Diagnostic Criteria for Functional Bowel Disorders

Functional Dyspepsia

At least 3 months, with onset at least 6 months previously, of one or more of the following:

- Bothersome postprandial fullness
- Early satiation
- Epigastric pain
- Epigastric burning
- No evidence of structural disease (including an upper GI endoscopy) that is likely to explain the symptoms

This is subclassified into:

Epigastric pain syndrome

At least 3 months, with onset at least 6 months previously, with all of the following:

Pain and burning that is:

- Intermittent
- Localised to the epigastrium of at least moderate severity, at least once per week,
- And not:
  - Generalised or localised to other abdominal or chest regions
  - relieved by defaecation or flatulence
  - Fulfilling criteria for gall bladder or sphincter of Oddi disorders

Postprandial distress syndrome

At least 3 months, with onset at least 6 months previously, of one or more of the following:

- Bothersome postprandial fullness occurring after ordinary-sized meals at least several times a week

or

- Early satiation, which prevents finishing a regular meal and occurs at least several times a week

Cyclic vomiting syndrome

At least 3 months, with onset at least 6 months previously, of:

- Stereotypical episodes of vomiting regarding onset (*acute*) and duration (*less than 1 week*)
- Three or more discrete episodes in the prior year
- Absence of nausea and vomiting between episodes

Supportive criteria: History of migraine headaches or a family history of migraine headaches

Chronic idiopathic nausea

At least 3 months, with onset at least 6 months previously, of:

- Bothersome nausea, occurring at least several times per week in the last 3 months
- Not usually associated with vomiting
- Absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea

Irritable Bowel Syndrome

At least 3 months, with onset at least 6 months previously, of recurrent abdominal pain or discomfort* associated with two or more of the following:

- Improvement with defaecation; *and/or*
- Onset associated with a change in frequency of stool; *and/or*
- Onset associated with a change in form (appearance) of stool

** Discomfort means an uncomfortable sensation not described as pain.*

It is generally agreed that *Helicobacter pylori* has a poor or irrelevant role in the pathophysiology. Gastric acid secretion is normal in most patients although acid-related symptoms may be present. Non-painful dyspeptic symptoms are suggestive of motor disorder. Post-prandial fullness and vomiting have been associated with delayed gastric emptying of solids, and early satiety to postcibal impaired accommodation of the gastric fundus. Many patients with this condition implicate particular articles of diet as cause of symptoms. Higher anxiety and neuroticism scores have also been described.

Investigations

Investigations are mandatory in the following situations ('alarm' or 'red flag' features): recent onset, late age at onset of symptoms (>40 years), weight loss, no response to adequate standard therapy, and any abnormality on physical examination.

The utility of routine laboratory testing is debated. Haematocrit, stool examination (including test for occult blood in the elderly), and liver and renal profiles are used as screening tests. Diagnostic oesophago-gastroduodenoscopy with or without biopsy-based testing for *H. pylori* should be considered with the slightest suspicion of organic disease. The most common finding is antral gastritis; its relevance in the absence of *H. pylori* infection is not clear. Ultrasound screening for biliary and pancreatic diseases is done when suspicion exists.

Specialised tests (antro-duodenal manometry, electro-gastrography, radionuclide evaluation of gastric emptying) are confined to the research setting.

Management

Simple dietary precautions may go a long way in alleviating symptoms. Regular meal timings; having unhurried meals; not habitually sipping fluids during meals; avoidance of excessively spicy and fatty food; restricting intake of caffeinated and aerated beverages may all be helpful to the patients. 'Avoid what you cannot tolerate' is a better advice than a blanket ban on food items; this also leaves the patient feeling in charge of himself. Tobacco in any form, and immoderate alcohol consumption, should be avoided.

The most common medication used is antacid; since most of the commercial preparations are antacid-antiflatulent combinations, they may alleviate a wide range of symptoms. When this is not effective (its long-term use is also not desirable), a histamine H_2-receptor antagonist (ranitidine, famotidine) can be substituted in patients with acid-peptic symptoms. More powerful acid suppressants (proton pump inhibitors) are seldom required.

In patients with symptoms of gastroduodenal dysmotility (bloating, early satiety) a prokinetic agent (metoclopramide, domperidone, mosapride, itopride, levosulpiride) may be beneficial; cisapride may be preferred when the patient has additional lower gastrointestinal symptoms (constipation, incomplete evacuation); its use is, however, restricted by fears of cardiotoxicity. There is no evidence to show that treatment for *H. pylori* is indicated.

Other distinct functional upper gastrointestinal conditions with features suggesting dysmotility have been described, but these are uncommon in clinical practice. These include:

Idiopathic gastroparesis

As the term implies, these patients have defective gastric contraction and emptying. While this may be a consequence of systemic diseases, e.g. diabetes mellitus, acute viral infections, or of drug therapy (beta-adrenergic agonists, dopamine D2 agonists such as bromocriptine, levodopa and opioids), in some cases no cause is identified.

These patients may present with dyspepsia-like symptoms (early satiety, bloat, nausea and occasional vomiting) acutely over months or years.

The diagnosis rests on documenting delayed gastric emptying by radionuclide scan or other appropriate techniques. More frequent small meals, liquids or soft solids, and prokinetic drugs are the mainstay of therapy.

Aerophagia and belching syndrome

Aerophagia is the semivoluntary swallowing of abnormal amounts of air while eating or drinking. When this results in increased intragastric air volume, belching occurs. Patients with the syndrome voluntarily aspirate air into the oesophagus, and then expel it loudly. Frequent swallowing is an accompanying feature. Some of them push the air further into the stomach and present with bloat and discomfort. Anxiety may aggravate the condition, which takes on the nature of a compulsive tic. Gastric hypomotility has been documented in such subjects, but whether this is a cause or effect is not known. Management is empirical, and should include a search for psychological factors.

Cyclic vomiting syndrome

This condition is characterised by stereotypic episodes of vomiting, with absence of nausea and vomiting in between episodes. Sometimes it is confused with other functional gastrointestinal syndromes because abdominal pain is not uncommon when episodes occur. The causes remain unclear, but some investigators have considered it to represent a migraine variant.

Antral hypomotility and delayed emptying have been recorded in some patients. Nutritional compromise may occur in the long term. Available evidence suggests poor response to prokinetics. Anti-depressants work in some individuals, suggesting a central origin for the symptoms.

Rumination syndrome

Rumination is a process by which food from the stomach is brought back into the mouth; some of the food is chewed and re-swallowed, and the process is repeated. Contraction of abdominal muscles and simultaneous relaxation of the lower oesophageal sphincter seem to occur as an effortless, semivoluntary action. A psychological element seems to be underlying. Apart from erosion of tooth enamel and bad breath (halitosis), this condition may also lead to nutritional deficiencies because patients tend to be withdrawn. Psychological support and physical training to overcome the muscle activity may be helpful.

IRRITABLE BOWEL SYNDROME (IBS)

The terms spastic colon, mucous colitis, irritable colon, among others were used to describe this condition earlier. While each of them reflected the predominant symptom or the

understanding of the condition at that time, they all reflect the recognition that the symptoms arise primarily in the colon.

Patients with IBS report with abdominal pain and altered bowel habits. The earlier criteria laid down by Manning *et al* for its diagnosis have been supplemented by the recent Rome III symptom criteria (**Table 1**). These identified pain or discomfort as an overwhelming symptom and introduced a time factor for diagnosis.

It is accepted now that a positive clinical diagnosis of IBS can be made and the condition need not be a diagnosis established by absence of evidence for structural disease. The presence of certain 'alarm' features (**Table 2**), however, requires that the patient be investigated.

Table 2: Features Against Diagnosis of IBS

History
- Late age (>40 years) at onset of symptoms
- Large-volume diarrhoea or steatorrhoea
- Frequent nocturnal symptoms
- Blood in stools (except from anal lesions, e.g. haemorrhoids, fissure)
- Fever, dehydration
- Significant weight loss
- Progression of symptoms or development of new symptoms

Physical examination
- Abdominal mass
- Signs of malabsorption, bowel obstruction, thyroid dysfunction
- Extraintestinal manifestations (arthritis, skin lesions)

Laboratory findings
- Occult blood in stools

Epidemiology

About 15% of the general population have symptoms that justify a diagnosis of IBS; however, only about 20% of these will seek medical opinion, prompting a suggestion of hypersensitivity in them. IBS is the most common single reason for referral to gastroenterologists. In Western series, female patients predominate; in South Asia and in India, most reporting patients are young men. The reason for this difference is not known.

Clinical Features

Pain (or discomfort) is an important feature of IBS, and is localised to the periumbilical region or lower abdomen, especially the left side. Altered bowel habit is the other symptom. While Indian patients generally do not have the alternating diarrhoea and constipation pattern described from the West, whether diarrhoea or constipation predominates varies regionally within the country. Abdominal pain and other accompanying features like gas bloat are usually relieved temporarily by defaecation.

In patients with constipation, sense of incomplete evacuation is a particularly distressing symptom; since these patients actually have increased attempts at defaecation, they may wrongly be labelled as having diarrhoea and are treated accordingly, with worsening of symptoms. Some of them attempt digital evacuation of the anal canal; these patients often have a profusion of mucous, and may develop ulcers in the anal canal or lower rectum (solitary rectal ulcer syndrome). Many patients with straining at stools as their only complaint may actually have an evacuation disorder.

Stool consistency may vary from small-quantity semisolid or liquid with mucous in those with diarrhoea, to hard, pellet-like with mucous in constipated subjects. Blood in stools may take the form of streaks or fresh drops after defaecation; the former are due usually to anal fissures and the latter to haemorrhoids, two conditions these patients are predisposed to.

Though the predominant symptoms arise from the colon, up to one-third of patients have accompanying upper gastrointestinal symptoms like dyspepsia, heartburn and bloat. Extraintestinal symptoms like dysmenorrhoea, dyspareunia, urinary frequency and headache are also common in female patients. Abnormal psychological features have been reported in over 70% of patients; stressful life events are also reported with increased frequency. However, a cause and effect relationship is not certain.

Pathophysiology

The pathophysiology of IBS is considered to be multifactorial, generated by interplay between genetic, psychosocial and environmental factors. These produce abnormalities in central nervous system processing as well as in the periphery, where they generate abnormal motility and possibly abnormal secretory activity. No consistent anatomic, physiological or microbiological abnormality has, however, been demonstrated; it is unlikely there is a single unifying explanation. Alterations in bowel motility and transit, as a consequence of abnormal myoelectric rhythm, are the most common features identified.

In a subgroup of patients the onset of symptoms follows an episode of infective diarrhoea (post-infective IBS). These and other patients with documented bacterial overgrowth may benefit from short courses of antibacterial treatment. This response to drugs, including a nitroimidazole, has often led to a wrong label of 'chronic amoebiasis', especially when this is associated with incidental stool detection of amoebae.

As stated earlier, a proportion of individuals from the general population have symptoms overlapping those of IBS, but do not consult a physician. Whether this represents a non-complainant group, or suggests that visceral hypersensitivity plays a role in distinguishing 'patient' from 'normal', is an open question.

Investigations

The diagnosis is generally based on history with normal physical examination (at most, tenderness in the lower abdomen, especially on the left side). Finding anal fissures or haemorrhoids on proctoscopic examination confirms the source of local pain and bleeding. Twenty four hours stool weight is recorded to rule out causes of large-volume (small intestinal or pancreatic) diarrhoea; stool weight in normal Indian subjects and those with IBS is less than 350 g/24 hours. Routine stool examination is done for amoebae and giardia. Sigmoidoscopy or colonoscopy is done when features against the diagnosis of IBS exist (**Table 2**). Recent Western studies suggest that routine investigation of all patients with diarrhoea predominance may identify a small number with unsuspected coeliac disease, bacterial overgrowth syndrome, or inflammatory bowel disease.

Management

The most important component of management is reassurance and psychological support. Cancer phobia is often the reason for medical consultation, and some investigations may become necessary if only to allay this fear. Despite the lasting discomfort and morbidity, patients should be assured that no complications arise out of IBS. Tranquilisers or anxiolytics may be required in the highly apprehensive patients (**Table 3**). Non-pharmacological relaxation modalities like yoga and biofeedback may also help.

Dietary advice should include restriction on items known to aggravate symptoms. Thus, milk and spicy food may need to be restricted in those with diarrhoea; milk, legumes and cabbage in those with gas bloat. Patients often report relief by eliminating meat from the diet. Obviously, advice will have to be individualised.

High-fibre diets are most effective in patients with constipation; when adequate fibre is already being consumed in the diet with no relief (as often happens in Indian patients), fibre supplementation may be tried. Commercially available isaphgol husk preparations can be taken with meals; usually 1 to 2 teaspoons of the refined preparations are given with breakfast and dinner, to ensure an additional 15 to 20 g fibre/day. These hydrophilic agents bind water and so prevent stool dehydration and add bulk. They may also help in patients with diarrhoea. One side-effect of fibre supplementation that is particularly distressing to patients with IBS is bloat. Relief can be obtained by combining this with preparations of simethicone or methylpolysiloxane. An alternative is the fibre substitute calcium polycarbophil.

Drugs that have the potential for use in the treatment of IBS are listed in **Table 3**. Tegaserod, a specific serotonin ($5\text{-}HT_4$) agonist, can improve symptoms in patients with IBS and constipation. Lactulose, lactitol and oral solutions containing polyethylene glycol (PEG) have been associated with improvement in stool frequency and consistency. Bowel retraining may improve bowel regularity.

Patients with diarrhoea may benefit from a morning dose, or if necessary thrice-daily doses, of the anti-diarrhoeal agent loperamide; milder symptoms may be controlled with racecadotril. Abdominal pain may require anti-spasmodics (e.g. mebeverine, dicyclomine).

Table 3: Drugs with Potential for Use in Treatment of IBS

Predominantly centrally acting drugs
- Selective serotonin-reuptake inhibitors (SSRIs)

Centrally and peripherally acting drugs
- Neurokinin-receptor antagonists
- Serotonin-receptor (mainly 5-HT3 and 5-HT4) modulators: alosetron, tegaserod, prucalopride
- Drugs with opioid (mu, kappa, delta) action: diphenoxylate, loperamide
- Neurotrophins
- Corticotrophin-releasing factor (CRF) antagonists
- Somatostatin analogues

Predominantly peripherally acting drugs
- Antibiotics (rifaximin) and probiotics
- Selective chloride-channel activators: lubiprostone
- Cholecystokinin (CCK) antagonists
- Peripheral receptor modulators: guanylate cyclase

FUNCTIONAL ABDOMINAL PAIN SYNDROME

Many of these patients are young women with other features to suggest psychological problems, including somatisation. Where suspicion is strong, investigation for the rare metabolic cause, e.g. porphyria, or poisoning (lead) should be done. The more common metabolic causes of abdominal pain (diabetes mellitus, uraemia) usually have other characteristic features present. The diagnosis of functional abdominal pain should be entertained only after organic causes are eliminated with reasonable certainty.

Management includes reassurance, psychologic support measures, anxiolytics if necessary, and spasmolytics, antacids, analgesics or other similar drugs depending on the type of pain described by the patient.

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13.11 Abdominal Tuberculosis

Govind K Makharia

INTRODUCTION

About 20% of patients with tuberculosis (TB) have extra-pulmonary TB and 7% to 10% of them have abdominal TB. While abdominal TB continues to be a common problem in the developing countries including India; increasing population migration, epidemic of acquired immunodeficiency syndrome (AIDS) and use of more potent chemotherapeutic agents led to resurgence of this disease in regions where TB had previously been largely controlled. Reliable epidemiologic data on abdominal TB from India is lacking. Of all hospital admissions, nearly 0.8% is reported to be due to intestinal TB. Three per cent to twenty per cent of all intestinal obstruction and 5% to 7% of intestinal perforation are due to intestinal TB in India.

In the abdomen, TB infection can involve many organs including gastrointestinal (GI) tract, peritoneum and many others (**Table 1**). In an analysis of 6 reports including 596 patients, Marshall *et al* reported that 42%, 50% and 8% had peritoneal, GI and lymph node TB, respectively and only a minority had combined peritoneal and GI TB.

Table 1: Classification of Abdominal Tuberculosis

- Gastrointestinal tuberculosis
  - Intestinal (both small and large)
  - Gastroduodenal tuberculosis
  - Oesophageal tuberculosis
- Peritoneal tuberculosis
  - Acute tuberculosis peritonitis
  - Chronic peritoneal tuberculosis
    - Ascitic form
    - Encysted (loculated) form
    - Dry type
- Tuberculosis of the solid viscera
  - Hepatobiliary
  - Spleen
  - Pancreas
- Tuberculosis of the abdominal lymph nodes
  - Tubercular mesenteric lymphadenitis
  - Tubercular retroperitoneal lymphadenitis
- Genitourinary tuberculosis

INTESTINAL TUBERCULOSIS

Site of Involvement

While any part of GI tract may be involved by the TB infection, the most common site of involvement is ileocaecum (ileum, ileocaecal valve and caecum). Other common sites of involvement are the colon (where the frequency decreases segmentally from the ascending colon to the rectum), appendix, jejunum, stomach, duodenum and oesophagus. The preferential location of ileo-caecum is because of a number of reasons including: the abundance of lymphoid tissue, relative physiologic stasis, higher electrolyte and water absorption, and minimal digestive activity, permitting greater contact time of the acid-fast bacilli (AFB) with the mucosal surface.

Pathogenesis

The mycobacterial infection can develop primarily within the intestinal tract or secondary to a focus elsewhere in the body. There are 4 possible ways by which an infection can reach GI tract: direct invasion by the ingested mycobacteria, transport by the way of infected bile, extension from adjacent diseased organs or tissues and spread through mycobacterial bacteraemia. Animal studies have shown that intestinal TB can result from ingestion of food containing tubercle bacilli, especially milk. With widespread pasteurisation of milk, milk is not a significant cause of TB. Secondary infection of the GI tract may arise from contamination of enteric chyme by bacteria from another site, usually the lungs, through swallowing of infected sputum. Intestinal involvement is probably related to the number and virulence of the ingested organisms and the nutritional status of the patient. Invasion of the intestine does not seem to occur when there is TB involvement of the peritoneum. Generalised tuberculous peritonitis is usually not associated with intestinal TB other than as a consequence of the extension of the infectious process transmurally or from an infected, ulcerating lymph node to the serosal surface.

Pathology

Traditionally, intestinal TB is described as of three types—ulcerative, hypertrophic and ulcero-hypertrophic. The ulcerative form of the disease is mainly due to deprivation of blood supply, because of endarteritis. In GI TB, ulcerogenesis is relatively slow, and an inflammatory wall develops ahead of the advancing ulcer. Thus, most perforations are confined. There is an accumulation of collagenous tissue during the process of ulcer healing that subsequently contracts and cause circumferential stricture of the intestinal lumen. The diseased segment is moderately indurated and the serosa is studded with nodules. The mesenteric lymph nodes are usually enlarged. The mucosal surface may show single or multiple ulcers, and skip areas may be present with normal appearing mucosa between involved segments. The ulcers are characteristically transverse and circumferential, but may be round, stellate, or longitudinal. The ulcers are deep, these however, generally do not penetrate the muscularis propria. In the acute phase, there may be a functional stenosis of the involved segment because of the spasm. In the more chronic phase, circumferential strictures may develop. The hypertrophic form of the disease, there is a marked inflammatory fibroblastic reaction in the submucosa and subserosa of the involved segment mostly ileocaecum.

Caseating granulomas (**Figure 1**) are the histologic hallmark of TB. The granulomas in intestinal TB are usually larger (>200 µm), multiple in number (>5/section) and confluent (**Figure 1**). Careful scrutiny should be made of acid-fast stained tissue for

tubercle bacilli. The ulcers usually do not penetrate beyond the muscularis and are lined by non-specific inflammatory granulation tissue. It must be emphasised that the histologic features of intestinal TB may be altered and may remain undiagnostic in patients who have received anti-tuberculosis drugs earlier or where tissue specimen is small.

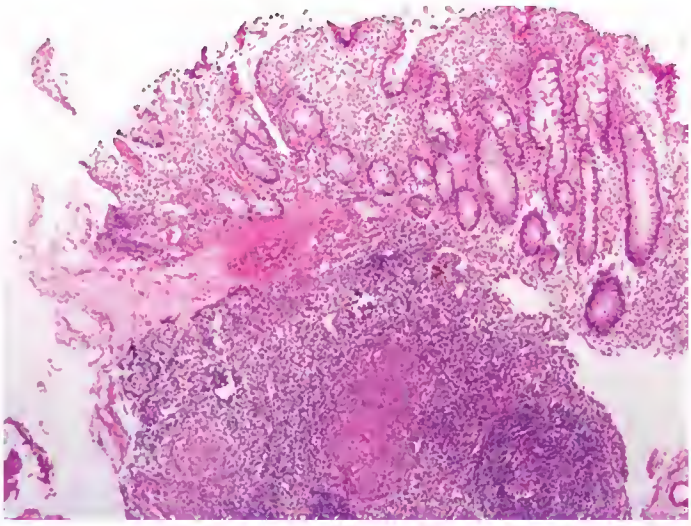


Figure 1: Photomicrograph showing caseating granuloma, multiple submucosal large (> 200 μm diameter) epitheloid cell granuloma with lymphocytic cuffing. Focally, the granuloma show central necrosis and presence of Langhan's giant cells (Haematoxylin and Eosin x 40).

Clinical Features

The most common age of patients with intestinal TB is between 20 to 40 years it, however, can occur in any age. Intestinal TB may have symptoms arising from the (a) intestinal ulcero-constrictive disease (intestinal colic, abdominal distension, nausea, vomiting, constipation, bleeding manifestations); (b) symptoms due to chronic inflammatory process (fever, weakness, weight loss, night sweats); (c) symptoms due to associated adjacent tissue involvement (ascites, lymph node enlargement or tubo-ovarian symptoms); and (d) coincident pulmonary TB (chronic cough, expectoration, haemoptysis).

The symptoms of GI TB will depend upon the site(s) of involvement of the GI tract and also the type of lesions it produces. As discussed earlier in the pathogenesis, ileocaecal area is the most common site of involvement in patients with intestinal TB, and most of the lesions are ulcerative or ulcero-constrictive. Abdominal pain is the most common manifestation and occurs because of stricture of the lumen, stretch on the surrounding tissue, mesenteric inflammation and peritoneal involvement. While the pain arising from the intestine is mostly colicy in nature, the pain arising from mesentery or peritoneum is diffuse and dull ache. As disease advances with time, the severity and frequency of pain increases. Therefore, the patient may initially present with occasional episodes of intestinal colic only, which may be disregarded by a physician as an episode of GI infection. As the stricture advances, the patient may develop partial intestinal obstruction (abdominal distension, gurgling in the abdomen, partial or complete cessation of flus, vomiting or movement of ball of wind in the abdomen). Diarrhoea is seen in 20% to 30% of patients and can be because of both small and large intestinal involvement. Malabsorption results from: (a) decreased small intestinal mucosal surface, (b) lymphatic obstruction, (c) fistula formation between the small and large intestine, (d) deconjugation of bile salts secondary to bacterial overgrowth, and (e) decreased bile salt pool because of impaired active absorption in the distal ileum. Bleeding per rectum is seen in 10% to 15% of patients with intestinal TB and occasionally massive bleeding. Almost half of patients have constipation. Constitutional symptoms in the form of fever, malaise, night sweats, anorexia, and weight loss are reported by 40% to 70% of patients with intestinal TB. A few patients may have active TB elsewhere especially lungs.

On examination, there are no characteristic signs. Most patients appear sick, poorly nourished and febrile. Doughy consistency of abdomen (due to extensive fibro-adhesive inflammation) is infrequent and non-specific. Abdominal tenderness is frequently present in the right lower quadrant. Palpable mass, which is a conglomerate of adhered bowel loops, lymph nodes and sometimes mesentery, may be observed in 10% to 20% patients.

Complications

The complications of intestinal TB are partial or complete intestinal obstruction, lower GI bleeding, intra-abdominal abscess, malnutrition and at occasions intestinal perforation. Intestinal obstruction occurs due to contraction of intestine following healing of circumferential tuberculous ulcers, bowel wall thickening, kinking of the intestine by intra-peritoneal adhesions, retraction of the mesentery and obstruction at the ileocaecal junction (due to changing the angle of entrance of the ileum into the colon of 90° to nearly 180°). Malnutrition occurs because of anorexia, inadequate food intake (because of sitophobia and poverty), and malabsorption.

Investigations

The haemogram in patients with intestinal TB shows a mild-to-moderately severe normochromic, normocytic anaemia, thrombocytosis and a normal white cell count with relative lymphocytosis. The erythrocyte sedimentation rate is almost always raised. Mantoux test is positive in over 70% of patients but high prevalence of Mantoux positivity in developing countries (≈ 60%) limits its usefulness. False-negative result is often seen in the elderly, malnourished, immunosuppressed, or in patients with disseminated disease. Pulmonary lesions on chest radiograph may be noted in a quarter of subjects; recognition of active pulmonary disease reduces the cost and expedites the diagnosis. Plain radiograph abdomen should be done in those who present with intestinal obstruction and may reveal air-fluid level and dilated bowel loops. One should review the radiograph properly to see other suggestive evidences, such as calcified lymph nodes, calcified granuloma in the spleen, liver and pancreas and enteroliths.

The aims of the investigations in patients suspected to have intestinal TB are detection of lesion, site and extent of the lesion, type of lesion, detection of any associated complication, histological diagnosis, microbiological confirmation and detection of TB either active or healed elsewhere, most commonly lungs. Intestinal imaging includes: luminal imaging (endoscopic, barium studies), and imaging of the wall and extra-intestinal extent which is detected by cross sectional imaging, such as CT scan and MRI. Both these techniques may be combined in one, such as CT-enteroclysis or MR-enteroclysis.

Endoscopic Investigation

Since ileocaecal area is involved in the majority of the patients with intestinal TB, colonoscopy with retrograde ileoscopy is the investigation of choice. Colonoscopic examination provides an opportunity to visualise the lesion directly and one can obtain biopsies from the lesions at the same time. The morphological appearance of intestinal TB depends upon the stage of the disease. The lesions may vary from mild lesions, such as loss of vascular pattern, erythema, small ulcerations and superficial ulcerations, to more advanced lesions including deep ulcerations, nodularity and strictures. One should realise that the evolution of intestinal TB takes from months to years. The classical morphological features described in the textbooks are seen in advanced cases. Some of the patients may present in early stages of evolution of the disease, thereby one may not find classical lesions and instead finds minute lesions. The wisdom lies in identifying these minute lesions so that the progression of the disease can be prevented. Common colonoscopic features of intestinal TB include deep ulcers (50% to 80%), nodules (30% to 60%) and strictures (**Figure 2**). One should take multiple biopsies from the lesion for not only histological examination but also for *M. tuberculosis* culture, PCR and AFB staining.

For small intestinal lesions, newer endoscopic techniques such as single and double balloon enteroscopic examination can be done. Capsule endoscopic examination is generally not done for those patients where obstructive lesion such as intestinal TB is suspected.

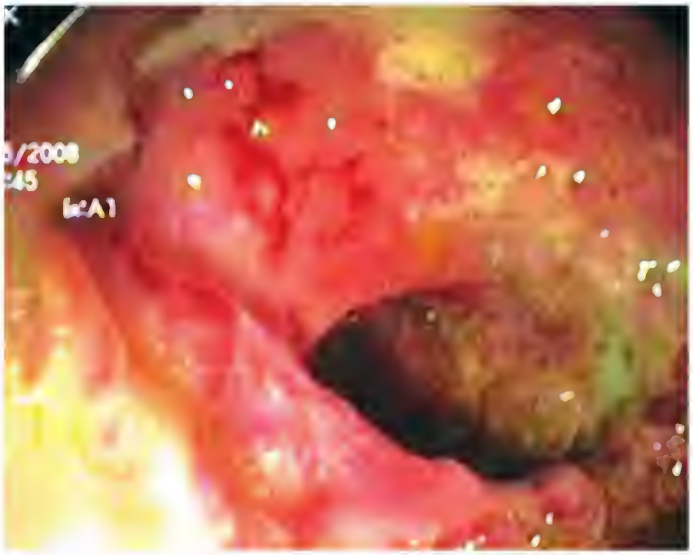


Figure 2: Colonoscopic picture showing ulceration of the ileocaecal valve in a patient with intestinal tuberculosis.

Radiological Investigations

Although there are many suggestive features on radiological investigations, none however is diagnostic of intestinal TB. The radiological features depend upon the stage of the disease, site of involvement and severity of the disease. In the early stage of mucosal invasion and ulceration, barium findings of ileocaecal TB are non-specific and include spasm and hyper-motility of the intestinal segment, oedema of the ileocaecal valve and mucosal thickening. Tubercular ulcers are circumferential or transverse in orientation. With progression of the disease, the ulcers become confluent. In patients with TB, barium findings in the advanced stage of fibrosis are more definitive. There is a thickening of the ileocaecal valve with narrowing of the terminal ileum (Fleischner or inverted umbrella sign). In further advanced disease, the characteristic deformity include symmetric, annular stenosis with obstruction, and shortening of the intestine and the colon. The caecum classically becomes conical, shrunken, and pulled up from the iliac fossa due to contraction of the mesocolon. There may be a loss of the normal ileocaecal angle (**Figure 3**). A localised narrowing opposite the ileocaecal valve with a rounded smooth caecum and a dilated terminal ileum is termed as 'purse string stenosis'. Spasm of the distal ileum and the ascending colon with contraction of the caecum (Stierlin sign) may be seen in association with shrunken ascending colon. The ileocaecal valve classically becomes incompetent, rigid and fixed with an irregular outline. Tubercular strictures are typically short and multiple separated by unaffected segments. Enteroliths may form proximal to the



Figure 3: Barium-meal follow through study showing contracted and pulled up caecum with narrowing of the ileocaecal junction and loss of the normal ileocaecal angle. The terminal ileum appears suspended and hanging from the caecum.

strictures and may vary from a single large lamellated calculus to multiple small stones visible on the radiograph.

CECT or CT-enteroclysis/MR-enteroclysis is essential for the evaluation of extra-luminal, peritoneal, nodal and visceral involvement. CT is more accurate than ultrasonography in detecting most of these manifestations including peritoneal and intestinal involvement. CECT/CT enteroclysis may show intestinal wall thickening (unifocal or multifocal), stricture with proximal dilation of the intestine, and regional lymphadenopathy. The pattern of lymphadenopathy in TB may vary widely, including increased number of normal sized nodes, mildly enlarged nodes to large confluent nodal masses. The involved lymph nodes typically show hypodense centre and peripheral enhancement in 40% to 70% cases; which reflects central necrosis (**Figure 4**).

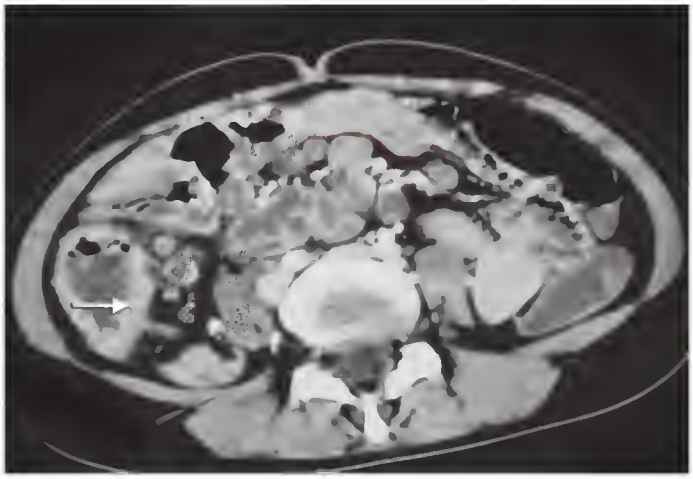


Figure 4: A contrast enhanced computerised tomography showing enlarged mesenteric lymph nodes with central hypodensity and thickening of the caecum (arrow) in a patient with abdominal tuberculosis.

Microbiological Tests

Isolation of *M.tuberculosis* using culture is the most specific method for diagnosis of active TB. It can detect 10-100 bacilli per mL of the sample. The most commonly used solid media is the Lowenstein-Jensen medium, on which it usually takes 4 to 6 weeks to grow. Radiometric (BACTEC) method and MGIT culture system can grow *M. tuberculosis* in shorter period of time, however, these are expensive. PCR using *M. tuberculosis* specific primer shows a positivity varying from 20% to 65%. Identification of acid-fast bacilli (AFB) on microscopy is presumptive for TB infection as saprophytic mycobacteria may give false-positive result.

Serological Tests

Although enzyme-linked immunosorbent assay (ELISA) using semi-purified antigens has sensitivity of 80% in abdominal TB; however, it fails to distinguish active from the past infection and it has high false positive rate. At present, there is no role of commercially available ELISA in making diagnosis of TB. One should not base one's decision of starting anti-tuberculous treatment (ATT) on ELISA report unless there are enough clinical, endoscopic and histological evidences.

Diagnostic Criteria for Tuberculosis

At least one of the following criteria must be met:

1. Culture of tissue (colonic biopsy, lymph nodes) resulting in growth of *M. tuberculosis.*
2. Histological demonstration of typical ATB.
3. Histological evidence of necrotising granuloma.
4. Definite response to ATT in a patient with probable TB based on clinical, endoscopic, histological features (Logan's modification).

Differential Diagnosis

Crohn's disease (CD) and intestinal TB are granulomatous diseases of the intestine. The clinical, morphological and histological features of intestinal TB and Crohn's disease are so similar that it becomes difficult to differentiate between these two entities. In geographical regions like Asia where both Crohn's disease and intestinal TB are prevalent, differential diagnosis between the two may be challenging. In Asia, intestinal TB is common, but CD is also being increasingly reported from all over Asia. Natural history of CD is quite different from that of intestinal TB. While intestinal TB gets cured by appropriate ATT, CD has a remitting/relapsing or persistent course and usually stays lifelong. Because of similarity in the clinical presentation and morphology of these two entities, at times such patients are treated empirically with anti-tuberculous drugs. The clinical, endoscopic and histological features which can differentiate these two diseases are summarised in **Table 2**.

Table 2: Clinical, Endoscopic and Histological Differentiation between Intestinal Tuberculosis and Crohn's Disease

Variables	Intestinal Tuberculosis	Crohn's Disease
Symptoms		
Chronic diarrhoea	20 to 40%	60 to 80%
Blood in the stools	10 to 20%	50 to 70%
Abdominal pain	90%	60 to 80%
Constipation	50%	10 to 30%
Partial intestinal obstruction	50 to 60%	20 to 30%
Peri-anal disease	5%	30 to 80%
Fever	40 to 70%	30%
Loss of appetite	40 to 80%	40 to 60%
Weight loss	60 to 90%	50 to 60%
Extra-intestinal manifestations	10%	20 to 50%
Involvement of the Intestine		
Anal canal	<5%	15 to 50%
Rectum	10 to 20%	40 to 60%
Sigmoid colon	5 to 10%	10 to 50%
Descending colon	5 to 10%	10 to 50%
Ascending colon	40 to 60%	50 to 70%
Ileocaecal area	70 to 90%	60%
Ileum	10 to 20%	20 to 40%
Endoscopic Features		
Aphthous ulcers	5 to 10%	30 to 50%
Linear ulcers	5%	20 to 30%
Deep ulcers	50 to 70%	30 to 40%
Nodularity	50%	20%
Cobblestoning	None	15 to 20%
Histological Features		
Granuloma	30 to 60%	30%
Necrosis in the granuloma	10 to 30%	None

PERITONEAL TUBERCULOSIS

The peritoneum is another common extra-pulmonary site for TB infection. Tuberculous peritonitis frequently complicates patients with underlying end-stage renal or liver disease. The disease can present in three different forms which are: the ascitic form (wet

type), encysted (loculated) form and dry type. All of them have almost similar clinical manifestations except for abdominal distension which does not occur in the dry type tuberculous peritonitis. Abdominal pain (60% to 70%) is a common presenting symptom and frequently accompanied by abdominal distension. It is usually non-localised and vague in nature. The pain is largely due to the tuberculous inflammation of the peritoneum and mesentery. Less often, it could be due to involvement of intestine as described in the above segment. Tenderness on palpation is common in tuberculous peritonitis and occurs in almost half of patients. Rebound tenderness is rare as the presence of ascitic fluid prevents approximation of the parietal with the visceral peritoneum. A smaller percentage of patients (5% to 10%) present with the classical 'doughy' abdomen. This is described as the dry or plastic type of tuberculous peritonitis.

The ascitic fluid is usually straw coloured. Although, red blood cells (RBCs) are frequently seen on microscopic examination, frank haemorrhagic, however, is uncommon. The ascitic fluid white blood cells (WBC) in tuberculous peritonitis varies widely from <100 cells/mm^3 to 5000 cells/mm^3. However, most patients have cell counts between 500 and 1500 cells/cmm. The WBCs are predominantly lymphocytes with the possible exception of patients with underlying renal failure where, for unknown reasons, the cells are mostly neutrophils. The protein content of ascitic fluid is high (> 2.5 g/dL) and have low glucose. The serum ascites albumin gradient (SAAG) has more diagnostic yield than ascitic fluid total protein measurement. It is calculated by measuring both serum and ascitic fluid albumin on the same day and subtracting the ascitic albumin from the serum albumin concentration. While tuberculous peritonitis has low SAAG (<1.1 g/dL), a high SAAG (>1.1 g/dL) suggests portal hypertension.

Adenosine deaminase (ADA) is an enzyme that converts adenosine to inosine and its activity is more in activated T lymphocytes than in B lymphocytes. There is an increase in number of activated T-cells in closed cavity infection, such as tubercular ascites or pleural effusion. With attrition of these lymphocytes, ADA along with other enzymes and end products are released in the closed compartment and, therefore, there is an increase in the ADA levels. A high value of ADA in any fluid cavity is not diagnostic of TB infection; in fact it is a reflection of high T-cell activity. An ADA value more than 32 IU/L in ascitic fluid has been reported to have high sensitivity and specificity for the diagnosis of tubercular ascites. High ADA may be seen in malignant ascites and even ascites due to cirrhosis. Interferon-γ (IFN-γ) has also been reported to be higher in tubercular ascites compared with malignant and cirrhotic ascites. The clinical significance and utility of estimating IFN-γ in ascitic fluid for diagnostic purposes is not very clear. While at least 5000 bacilli/mL of specimen is required for a positive smear, only a few bacilli/mL may be sufficient for a positive culture and for detection by PCR. Ziehl-Neelsen staining of the ascitic fluid for mycobacterial detection has a very low yield (3% to 5%) in proven patients with tuberculous peritonitis. In order to increase the yield, it is recommended that a larger volume of ascitic fluid should be sent to the laboratory and the fluid should be centrifuged before staining. There is a lack of reliable data on the sensitivity of PCR in tuberculous peritonitis, however, PCR is expected to show a higher yield.

Direct inspection and biopsy of the peritoneum are perhaps the most effective method of diagnosing peritoneal TB. The laparoscopic examination can show thickened, hyperemic peritoneum with ascites and whitish miliary nodules (<5 mm) scattered over the parietal peritoneum, omentum and intestinal loops in two-third of patients. The diagnostic yield of laparoscopic examination is very high. Peritoneal carcinomatosis, and sarcoidosis may have same features such as that seen in tuberculous peritonitis. Therefore, one should always take peritoneal biopsy during laparoscopic examination. In a patient with lymphocytic, exudative ascites with low SAAG and high ADA; tuberculous peritonitis is the most likely cause. However, one should remember the possibilities of fungal peritonitis, and malignant ascites.

OESOPHAGEAL TUBERCULOSIS

TB of the oesophagus is uncommon. Oesophageal involvement in TB occurs usually due to direct extension of infection from adjacent affected structures, such as mediastinal lymph nodes or the lung. Less frequently, oesophageal involvement occurs in the absence of TB elsewhere in the body. Upper part of the oesophagus is more often involved than the lower part. The main presenting features are dysphagia, odynophagia, chest discomfort, and systemic symptoms. Some of these patients may develop trachea-oesophageal or broncho-oesophageal fistula. The lesion can be seen by endoscopic examination and the diagnosis can be achieved by histological and microbiological evaluation of the biopsies. The endosonographic examination can help in imaging the mediastinal lymph nodes and one can obtain the fine needle aspiration from these nodes using endosonography. One can also do a CECT of the chest to look for the extent of involvement including mediastinal lymph nodes.

GASTRODUODENAL TUBERCULOSIS

Because of acidic environment, stomach and duodenum are generally spared by TB infection. The TB lesion produces ulcerations and stricture in the duodenum and rarely in the stomach. Therefore, symptoms include abdominal pain, nausea, vomiting, GI bleeding, fever and weight loss. Once there is obstruction to the lumen because of the lesion, the patient presents with obstructive features such as copious vomiting of stale food (food eaten four hours earlier). Endoscopic examination is the best investigation wherein one can see the lesion and obtain appropriate biopsies. If the lesion is out of reach of a routine upper GI endoscope, one can still see the lesion using enteroscope, if available. Otherwise radiological investigations such as barium-meal or barium-meal follow through can be done. Many patients respond to ATT and to endoscopic dilation of stricture while some may require surgery for obstructive symptoms.

HEPATOBILIARY TUBERCULOSIS

Liver is involved in TB infection in two forms. More commonly liver is involved in TB as part of miliary or disseminated disease. There may not be any specific signs or symptoms related to the liver except the hepatomegaly and liver biopsy may show presence of granuloma. The second form, which is seen less often, is localised form of TB involving liver and biliary ducts. Localised hepatobiliary tuberculosis occurs as: (i) localised

solitary or multiple nodules, tuberculoma and tuberculous hepatic abscess without bile duct obstruction; (ii) and bile ductal epithelium involvement producing inflammatory strictures with obstructive jaundice; and (iii) enlarged lymph nodes at porta causing obstruction to the bile duct. Obstructive jaundice is more common in those who have biliary system involvement. Most patients have an increase in alkaline phosphatase and gamma glutamyl transferase in addition to a mild rise in serum transaminases. Ultrasonography and subsequently CECT are required for complete imaging. In suspected patients, the bile ductal abnormality (stricture, unifocal or multifocal; ductal irregularity) can be seen by MRCP or ERCP.

SPLENIC TUBERCULOSIS

As liver, spleen can also be involved by TB infection in two ways mostly as a part of disseminated or miliary form of the disease and occasionally as isolated splenic TB. Most of these patients are immunocompromised; splenic TB, however, has been reported in otherwise immunocompetent individuals. Most of the cases of splenic TB are recognised on imaging and sometimes as surprise on operated splenectomy specimen. In those with disseminated form of the disease, there are enough clinical clues in other organs; there is no specific feature in isolated splenic TB to suggest a clinical diagnosis of splenic TB. Fever, left upper quadrant abdominal pain, weight loss, splenomegaly and or hepatomegaly are usual features. On imaging (US or CT), spleen may be enlarged and there may be one or multiple lesions. The treatment is similar as elsewhere except that a splenectomy may be required in a few patients where spleen is studded with TB abscesses.

PANCREATIC TUBERCULOSIS

Pancreatic TB is uncommon. Pancreatic TB is most often the result of lymphatic or haematogenous dissemination or direct spread from other adjacent organs. The involvement of pancreas by TB infection can occur as part of miliary or disseminated form of TB or as isolated pancreatic TB. The usual lesion in such patients is a pancreatic mass and, therefore, symptoms depend upon the type and site of the mass. As other sites, anorexia, malaise, low-grade fever, weight loss, night sweats are seen in majority of the patients. The specific symptoms include abdominal pain and obstructive jaundice if pancreatic head is involved. The imaging shows mass in the pancreas which is a conglomerate of lesions in the pancreas and peri-pancreatic lymph nodes. Therefore, pancreatic TB mimics pancreatic malignancy. A fine needle aspiration cytology and a guided biopsy helps in differentiating TB from pancreatic malignancy. One must always should culture the tissue for *M. tuberculosis*. The other differential diagnosis include pancreatic lymphoma, chronic pancreatitis, and sarcoidosis.

TREATMENT OF TUBERCULOSIS

Medical Treatment

All patients with abdominal TB should be treated with standard anti-tuberculous drugs. The treatment of TB includes multiple drugs for a prolonged duration. Treatment using more than one drug is based on two principles: preventing acquired drug resistance and enhancing efficacy. Tubercle bacilli undergo random chromosomal mutations that make them resistant to drugs used to treat TB. Fortunately, these mutations are infrequent. Because they are unlinked (in terms of chromosomal location or function) and specific to a drug or drug class, spontaneous generation of an organism with multi-drug resistance is extremely uncommon. Acquired drug resistance for TB is almost always caused by inadequate treatment. Most of the guidelines on the treatment of TB suggest that short course treatment for 6 months is sufficient for extra-pulmonary TB except for bone TB and tuberculous meningitis. Despite these recommendations, many physicians treating abdominal TB use ATT for 9 months, sometimes even 12 months without any scientific justification. In a randomised controlled trial, Balasubramaniam *et al* showed almost equal efficacy of ATT given for 6 months (99%) versus 12 months (94%) in the treatment of abdominal TB.

The role of corticosteroid treatment in patients with abdominal TB is not well-established and these should not be routinely-administered to all patients.

Surgical Treatment

Surgery is required only in small number of patients with intestinal TB and other solid organ TB. The indications for surgery in intestinal TB are generally for the complications of the disease such as free perforation, confined perforation with abscess or fistula formation, intestinal obstruction not responding to usual conservative measures, and massive haemorrhage. A subset of patients despite effective ATT continue to have episodes of intestinal obstruction. This may occur because of two reasons: failure of ATT or residual tight fibrotic strictures. In such cases, the stricture is required to be removed. Stricturoplasty or resection of the diseased segment with end-to-end anastomosis is the routinely done procedure. Surgical procedures such as bypass surgery (entero-enterostomy, ileo-transverse colostomy) are not recommended for obstructive lesions as these procedures may facilitate the formation of blind loops leading to obstruction, malabsorption, or both. Strictures at ileocaecal region may be treated by limited ileocaecal resection with a 5 cm margin from a visible abnormal tissue or a limited right hemicolectomy and end-to-end anastomosis. Perforating ulcers are treated by excision of the perforated segment with primary anastomosis. Wherever appropriate, elective surgery should be performed after four to six weeks of ATT. Even after surgery, the course of medical treatment for TB should be completed.

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13.12 Inflammatory Bowel Disease

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INTRODUCTION

Chronic inflammatory bowel disease (IBD) includes ulcerative colitis (UC), a disorder in which inflammation affects the mucosa and submucosa of the colon, and Crohn's disease (CD), in which inflammation is transmural and may involve any or all segments of the gastrointestinal tract. Patients who have features of IBD but cannot be clearly categorised into any of these two diseases are labelled as having indeterminate colitis (IC).

EPIDEMIOLOGY

Both UC and CD are worldwide disorders, although the precise incidence varies considerably in different countries. The United States, Northern Europe and Scandinavian countries have higher rates compared to countries in Southern Europe, South Africa and Australia. In Asia, the disease was thought to be uncommon, but recent reports have highlighted the increasing incidence of the disease. The rapid changes in incidence and prevalence in Asia may point to environmental changes associated with the so-called 'Westernisation' of lifestyle (e.g. dietary changes, smoking, etc.) as potential risk factors.

IBD typically affects young people, but may have a bimodal incidence with a second peak in later life. Crohn's disease is frequently diagnosed in late adolescence or early adulthood, with a median age of diagnosis in the third decade. Men are slightly more likely to be affected with UC whereas women with CD.

AETIOPATHOGENESIS

Despite improved understanding of the mechanisms of intestinal inflammation, the aetiology and pathogenesis of IBD remain obscure. The pathogenesis involves an interplay of genetic, environmental, microbial and immune factors, which in combination result in chronic intestinal inflammation.

The most firmly established risk-factor for developing IBD is a positive family history. The incidence of IBD among first-degree relatives of IBD patients is 30 to 100 times that of the general population. Approximately 15% of patients with IBD have a first-degree relative suffering from either UC or CD; the risk being higher in patients with CD. Other factors suggesting genetic susceptibility are higher concordance amongst monozygotic than dizygotic twins, and ethnic differences in disease prevalence. However, no clear cut Mendelian pattern of inheritance has been established. Genome scans reveal that IBD is a complex genetic disorder with several predisposing genes. Linkage analyses have identified 16 susceptibility loci, of which those on chromosomes 1, 5, 6, 12, 14, 16 and 19 are important. The actual identification of NOD2/CARD15 within the IBD gene locus is an important breakthrough in genetic research for unraveling the aetiology of CD. The major histocompatibility complex or HLA genes on chromosome 6 have a greater role in modifying the IBD phenotype than overall disease susceptibility.

A dramatic rise in the incidence in recent decades points to environmental factors as potential risk factors for disease occurrence. Westernisation of lifestyle, such as changes in diet and variance in exposure to sunlight, pollution, and industrial chemicals, has been postulated to be responsible for the rising incidence. It is postulated that improved hygiene alters the intestinal flora by decreasing exposure to certain bacteria. This may explain the higher frequency of both UC and CD in higher socioeconomic groups. Studies seeking to link diet and IBD are generally inconclusive. There is some evidence that a higher intake of fatty acids increases the risk of IBD. Similarly, frequent fast-food intake confers a 3- to 4-fold greater risk of IBD. It has been observed that smoking is protective against UC while patients with CD who smoke are more likely to have frequent relapses. Appendicectomy has been reported to be a potential protective factor for UC. Other factors that may have a role in pathogenesis or precipitation of relapse are use of drugs like oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics and seasonal variation and mental stress.

Over the past decades, various pathogenic agents have been implicated including *Mycobacterium paratuberculosis*, *Listeria monocytogenes*, *Chlamydia trachomatis*, cytomegalovirus, measles virus, *Saccharomyces cerevisiae* and certain strains of *Escherichia coli*, *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*. However, these data have not been confirmed and antibiotics have not been effective in treating IBD. It has been postulated that the normal local flora may play an important role in the development and perpetuation of the disease. This is supported by the observation that surgical exclusion of small bowel loops resulting in loss of contact of bowel contents, can lead to disappearance of inflammatory changes in these bowel segments. On re-establishing the continuity, recurrence of inflammatory changes occur. In most animal models for experimental colitis, animals do not develop inflammation when they are maintained free of bacteria.

Unlike in healthy individuals, the equilibrium between pro- and anti-inflammatory cytokines is significantly deranged. This dysregulation of the immune reaction leads to excessive activation of pro-inflammatory cytokines. Excessive and prolonged activation of bowel-associated immune system may result in causation of IBD.

CLINICAL FEATURES

Symptoms suggestive of IBD include watery stools, blood or mucus in the stool, diarrhoea persisting for more than 4 weeks, crampy abdominal pain, nocturnal defaecation and fever. Weight loss is significant. Anal fissures, anal fistulae, frank bleeding per rectum and abdominal masses can occur. Symptoms are generally recurrent. Ulcerative colitis is a recurrent inflammatory disease of the colon and rectum

characterized by mucosal inflammation and ulceration. The disease starts in the rectum and spreads to a variable extent in a proximal direction. The inflammation is continuous and affects the entire circumference of the mucosal membrane. Pathological and histological features include diffuse inflammation of the mucosal membrane with ulceration, crypt abscesses, infiltrates and reduced number of goblet cells. The terminal ileum is rarely involved (backwash ileitis). The disease activity is categorised as active colitis or flare (active disease), remission (quiescent phase) or chronic continuous disease (partially active disease). The disease extent is variable and can be confined to the rectum (proctitis), rectum and sigmoid colon (proctosigmoiditis), may reach upto the splenic flexure (left-sided colitis) or may involve the transverse colon or beyond (pancolitis). Disease severity is categorised as mild, moderate or severe according to Truelove-Witts criteria (**Table 1**).

Crohn's disease is segmental, non-continuous, subacute or chronic inflammation that can affect any part of the digestive tract from the mouth to the anus, with a predilection for the distal ileum and colon. The inflammation is transmural and this can lead to internal abscesses and fistulae. The fistulae can be entero-enteric, entero-cutaneous, entero-vesical or entero-vaginal. The deeper layers of the intestinal walls may be more severely affected. Creeping fat around the diseased part of the intestine is very suggestive of CD.

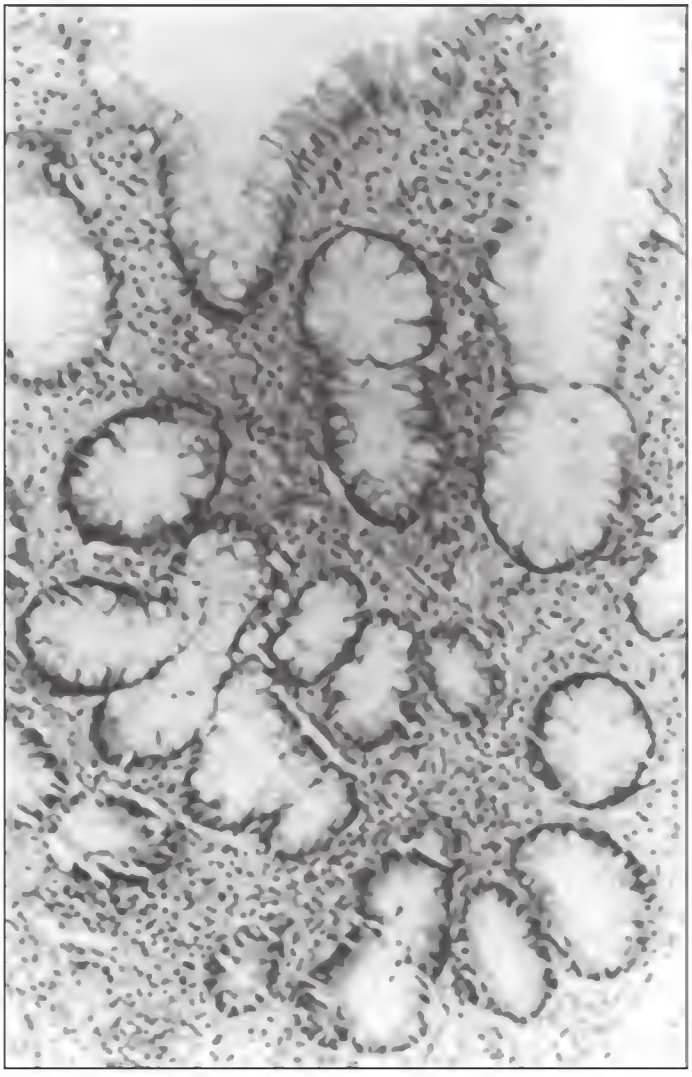


Figure 1: Microphotograph showing cryptitis, crypt abscess, crypt distoration and crypt branching along with villiform surface (x 550).
Courtesy Dr Ritambhara Nada.

Pathological and histological features include segmental transmural inflammation with micro-erosions, fissures, ulcerations, granulomas, infiltration, and dilated lymph vessels (**Figure 1**). The disease is most common in distal ileum and colon (50% of patients), small intestine only (25% to 30%), colon only (20% to 25%), rectum (10% to 15%) or gastroduodenal (3% to 5%). Anorectal disease like anal fistulae, anal fissures, perianal abscess can occur in 30% to 40% of patients. Comparative features of UC and CD are shown in **Table 2**.

Table 1: Severity of Ulcerative Colitis (Based as Truelove-Witts Criteria)

Features	Mild	Moderate	Severe
Bowel frequency	<4/day	4-6/day	>6/day
Rectal bleeding	Intermittent	Usual	Common
Fever	No	Possibly	Yes
Pulse	Normal	May be >90/min	>90/min
Abdominal tenderness	Absent	Often present	Present
Haematocrit	Normal	>30%	<30%
ESR	<30 mm		>30 mm

Table 2: Comparative Features of Ulcerative Colitis (UC) and Crohn's Disease (CD)

Features	Ulcerative colitis	Crohn's disease
Fever	Less common	Common
Abdominal pain	Mild	Moderate-to-severe
Diarrhoea	Common	Less common
Rectal bleeding	Very common	Less common
Perianal disease	Rare	Common
Abdominal mass	No	Common
Extent	Continuous, starts from rectum	Discontinuous, segmental
Rectal involvement	>90%	<50%
Ileal involvement	<10% (backwash ileitis)	Up to 50%
Anal lesions	Up to 25%	Up to 75%
	Acute fistula formation	Chronic fissures and fistulas
Bowel wall-thickness	Normal to slightly increased	Slight to significant thickening, fibrosed
Mucosa/submucosa	Haemorrhagic, oedematous,	Cobble stones, skip lesions
	Ulcerated	Aphthotic ulcerations
		Fissures
Pseudopolyps	Frequent	Rare
Hyperaemia	Significant	Slight, only in acute flare
Strictures	Rare	Frequent
Fistulae	None	Frequent
Bowel shortening	Yes (fibrous, segmental)	Yes Muscular
Toxic megacolon	Rare (<5%) More common in pancolitis	Rare (<5%)

EXTRAINTESTINAL MANIFESTATIONS

Both CD and UC may be accompanied by extraintestinal manifestations. In CD, nearly 40% of patients experience extraintestinal disease manifestations while this rate is significantly lower in UC. The symptoms can occur as initial symptoms, during the course of the disease or may even follow surgical removal of the diseased bowel. The various extraintestinal manifestations and complications are shown in **Tables 3 and 4**.

Table 3: Extraintestinal Manifestations

Skin	Erythema nodosum Pyoderma gangrenosum
Joints	Arthritis, ankylosing spondylitis, sacroilitis
Eyes	Iridocyclitis, uveitis
Lung	Alveolitis, lung fibrosis
Heart	Myocarditis
Liver	Primary sclerosing cholangitis, fatty liver
Blood	Thromboembolic complications Autoimmune haemolytic anaemia
Tissue	Amyloidosis

Table 4 : Extraintestinal Complications

Deficiencies

- Vitamin deficiency (A, B12, C, D, E, K): Osteomalacia, muscular atrophy, night blindness, hyperkeratoses and anaemia
- Mineral deficiency (iron, calcium, magnesium, zinc): Anaemia, osteomalacia, growth retardation, oligospermia, immune-deficiency
- Protein deficiency: Oedema

Absorption changes

- Hyperoxaluria, water loss: Kidney stones
- Bile acid deficiency: Gallstones

DIAGNOSIS

Chronic pattern of symptoms (persisting for more than 4 weeks), abdominal pain, diarrhoea, with or without blood, weight loss or growth disturbance raises a suspicion of IBD. The diagnosis is made on the basis of careful medical history, close observation of the clinical picture, the evaluation of endoscopic, histological and radiological findings and, finally, the results of laboratory investigations. Laboratory abnormalities include elevated ESR and C-reactive protein, thrombocytosis, anaemia, leucocytosis and hypoalbuminaemia. Stool examination is required to look for pus cells, RBC's, infective organism and markers of inflammatory exudation in the bowel like faecal calprotectin, α_1-antitrypsin and lactoferrin. Differentiation of CD and UC on the basis of laboratory parameters alone, however, is difficult. Antibodies such as p-ANCA (increased in UC) and anti- *Saccharomyces cerevisiae* antibody (ASCA, primarily in CD) shows too much overlap in the distribution to permit exact differentiation.

A plain X-ray film of the abdomen is indicated in patients with severe disease when there is suspicion of complications like toxic megacolon, ileus or perforation. Double contrast (**Figure 2**) barium examination of the colon used for long has been replaced by endoscopy. Small bowel series or enteroclysis is primarily used for evaluation of the small bowel. Although aphthoid and small erosions usually escape detection with these methods, enteroclysis effectively visualises ulcerations, cobblestoning, strictures and fistulae.

Computer tomography (CT) is sensitive in detecting both luminal and extra-luminal disease in patient with CD. It can recognise extra-intestinal complications with high sensitivity. However, subtle mucosal changes may escape detection with CT. MRI (magnetic resonance imaging) has, in comparison to CT, significantly better tissue contrast and because of the lack of radiation exposure has gained wide acceptance. In addition, MRI is more sensitive for detecting anorectal lesions. The main disadvantages of MRI in comparison with CT are poorer resolution and longer duration of examination. Both CT and MRI can be utilised for enteroclysis examination and mucosal details are delineated better.

The diagnosis of IBD is facilitated by direct inspection of mucosal membrane and stepped biopsies, which permit exact determination of the extent of disease. In early stages, the diagnosis is only possible using endoscopy, since small discrete mucosal lesions may not be visualised using radiology. Endoscopic findings in ulcerative colitis include pale mucosa, erythema, granularity, loss of mucosal visible vessels, ulcerations and contact and spontaneous bleeding. Pseudopolyps may be noticed in patients with chronic disease. The typical endoscopic characteristic of CD is the discontinuous spread of the disease: healthy mucosa alternates with affected segments and lesions are distributed asymmetrically. Endoscopic findings include aphthoid lesions in normal mucosa (early sign), bizarre 'map-like' ulcers and fissures, cobblestoning of mucosa which is caused by deep fissures, ulcerations and intact mucosa. Pseudopolyps are less common but an inflammatory mass may at times simulate growth. Wireless capsule endoscopy (CE), allows direct visualisation of the small bowel mucosa. Tight stricture or visceral fistulous communications should be excluded before planning CE. Enteroscopy (double balloon or



Figure 2: Double contrast barium enema showing multiple pseudopolyps in a patient of ulcerative colitis.
Courtesy: Dr B Nagi

single balloon) can be planned after localising the disease with more basic radiological investigations.

COMPLICATIONS

Ulcerative colitis can be associated with complications like massive haemorrhage, toxic megacolon, perforation, stricture and colo-rectal carcinoma. Toxic megacolon occurs when inflammation extends beyond the mucosa and the colon dilates excessively (transverse colon diameter >6 cm on plain X-ray). Clinical features suggestive of toxic megacolon include fever, tachycardia, leucocytosis and abdominal tenderness and distension. Perforation of the colon may complicate toxic megacolon but can also occur in cases of severe UC without toxic megacolon. Benign strictures are rare. The risk of development of colo-rectal carcinoma is high in patients with long standing disease, young age of onset of disease, pancolitis and presence of sclerosing cholangitis. Free perforation is less common with CD as serosal adhesions provide pathways for fistulae formation. Intestinal obstruction due to strictures occur more often in patients with CD. Malabsorption and nutritional deficiencies develop in patients with extensive small bowel involvement.

DIFFERENTIAL DIAGNOSIS

The diagnosis of UC or CD can be made when, after careful work-up, other causes of colitis or ileocolitis have been ruled-out. Many disorders can mimic the clinical, endoscopic or radiological picture of UC or CD (**Table 5**).

Table 5: Differential Diagnosis of UC and CD

- Bacterial infections
  - Tuberculosis
  - Campylobacter
  - *Salmonella* and *Shigella*
  - *Yersinia enterocolitica*
- Viral infections
- Parasitic infections
- Pseudomembranous colitis
- Ischaemic colitis
- Radiation enterocolitis
- Diverticulitis
- Primary intestinal lymphoma
- Behcet's disease
- Eosinophilic gastroenteritis
- Scleroderma
- Drug-induced colitis

MANAGEMENT

As the aetiology of IBD has not yet been established, curative therapy is yet not available. Treatment is aimed to eliminate symptoms during an acute flare or exacerbation as well as to maintain remission. The principal classes of drugs used in IBD are: 5-aminosalicylic acid (5-ASA) derivatives, corticosteroids and immunosuppressants. In recent years, anti TNF-α antibodies have been introduced in the therapy of IBD. They can be successful in corticosteroid-refractory disease. Therapeutic response leading onto remission occurs in nearly 75% of the patients with these drugs.

General Measures

No major dietary modification is required. Patients with strictures should avoid high-residue foods. Iron, calcium and vitamins supplements may be required if there is evidence of deficiency. Extensive terminal ileal resection may lead to vitamin B_{12}, fat and bile salt malabsorption, and hence vitamin replacement and low fat diet is recommended. Parenteral nutrition may be required in patients with fulminant disease.

Medical Therapy (Tables 6 and 7)

Sulphasalazine (SLZ)/5-aminosalicylic acid (5-ASA)

These agents are the mainstay of therapy for mild-to-moderate disease. Sulphasalazine (SLZ) consists of sulphapyridine and 5-ASA joined by a diazo bond, which is cleaved by colonic bacteria, releasing the active 5-ASA molecule and the inert antibiotic moiety. Sulphasalzine is started at low doses and is gradually increased to 4 to 6 gm per day and can be tapered by 1 to 2 gm per day during remission. Maximum dose of mesalamine is upto 4.8 gm for active disease while for maintenance, 800 to 1200 mg may be sufficient. Their role in maintenance of remission in Crohn's disease is less convincing. Main side-effects of SLZ are nausea, vomiting, headache, abdominal discomfort and haemolysis. Other side-effects include reduced sperm count, which is reversible after stopping the therapy. Side-effects are less with non-sulpha based 5-ASA agents, but nephrotoxicity is known to occur.

Table 6: Ulcerative Colitis—Therapeutic Options

Active disease	Maintenance therapy
Mild flare	
Mesalazine or sulphasalazine, olsalazine	Mesalazine or sulphasalazine Probiotics Azathioprine/6-MP
Moderate flare	
Mesalazine or sulphasalazine Corticosteroids Oral Topically acting, e.g. hydrocortisone, budesonide	
Severe flare	
Corticosteroids—intravenous Mesalazine or sulphasalazine Parenteral or enteral nutrition Intravenous cyclosporine A Anti-TNF-α antibodies Surgery	

Table 7: Crohn's Disease—Therapeutic Options

Active disease	Maintenance therapy
Mild-to-moderate flare	
Mesalazine or sulphasalazine Corticosteroids Topically acting: For example, budesonide Systemically acting: For example, prednisolone	Mesalazine (after surgery) Azathioprine/6-MP
Severe flare	**Chronic active course, steroid dependence and fistulae**
Corticosteroids Systemically acting: e.g. prednisolone Immunosuppressants Elemental diet Biologicals	Azathioprine Methotrexate If no response to immunosuppressants: Anti-TNF-α antibodies

Corticosteroids

Corticosteroids are effective in inducing remission but should not be used for maintenance of remission. Oral steroids are used for moderately active disease while severe disease generally requires intravenous administration. Steroid enema can be effective in treating left-sided UC. As systemic absorption of the steroid enaema is significant, long-term use should be avoided. Corticosteroids also produce remission in cases of CD; however, the presence of abscess should be excluded to minimise the risk of septicaemia. Oral prednisolone is usually started at the dose of 40 to 60 mg/day and gradually tapered off over the next 8 to 12 weeks.

The potential side-effects of corticosteroids are multiple and quite severe. They suppress intrinsic adrenal function and immune function. They may also induce hyperglycaemia, truncal obesity, cataracts, abdominal striae, myopathy, psychiatric disturbances, and avascular necrosis. Budesonide is a steroid having increased first-pass metabolism in the liver, and this results in less systemic toxic effects. Budesonide is preferred to conventional corticosteroids in patients with ileal and right colonic disease.

Immunomodulators

The role of immunologic mechanisms in the pathogenesis of IBD forms the basis for using immunomodulators. Azathioprine (AZA) and 6-mercaptopurine (6-MP) are useful for patients with UC who are steroid-dependent and suffer frequent relapses or are steroid-refractory. These agents also are beneficial in healing fistulae in CD. One major limitation of these agents is their delayed onset of action of 3 to 6 months. For this reason the primary role of these agents is in maintenance of remission and not to induce remission. Major side-effects of these drugs include nausea, vomiting, bone marrow toxicity, hepatitis, pancreatitis, alopecia and infections. Regular blood count and liver biochemical tests are recommended to detect toxic effects. The doses for 6-MP and AZA are 1.5 mg/kg/day and 2.5 mg/kg/day, respectively.

Cyclosporine (CSA), which is a potent inhibitor of T cells, has been found to be useful for patients with severe UC who do not respond to glucocorticoids. Cyclosporine may be able to avert colectomy in these patients. Patients require concomitant therapy with AZA/6-MP. Cyclosporine has not shown convincing efficacy in CD. Methotrexate (MTX) is a folic-acid antagonist and has both immunomodulatory and anti-inflammatory properties. Patients who do not tolerate AZA/6-MP may benefit from MTX. Mycophenolate mofetil and tacrolimus are other agents which have been tried with limited success. Infliximab is a mouse-human chimeric monoclonal antibody directed against tumour necrosis factor (TNF-α). This is effective in inducing remission in patients with refractory CD, in healing fistulae, and as maintenance therapy for CD. It has been used in UC also, but the results are less convincing. Reactivation of tuberculosis is known to occur with these biological drugs. These drugs may increase the risk of lymphoma.

Antibiotics/probiotics

Broad-spectrum antibiotics are required for treating complications of CD like abscess and perianal disease and small intestinal bacterial overgrowth which occur from stasis proximal to strictures. Metronidazole and ciprofloxacin have been shown to be beneficial. Antibiotics are not very useful in the treatment of UC. Probiotics are live bacteria that are non-pathogenic and confer health benefits beyond their nutritional value. *Escherichia coli*, Nissle, 1917 and VSL#3 are the probiotic preparations that have shown promise in the treatment of UC.

Miscellaneous agents

Nicotine patch has been shown to induce remission in patients with UC. Anti-diarrhoeal agents (loperamide, diphenoxylate), which may reduce stool frequency, and anti-cholinergic drugs, which can reduce pain and cramps, should be avoided in severe disease because of the risk of developing toxic megacolon.

Surgery

Patients with severe UC not responding to medical therapy or those who develop complications like toxic megacolon, perforation, massive haemorrhage, high-grade dysplasia or colon cancer need surgery. Ileal pouch-anal canal anastamosis is the procedure of choice for most patients. Surgery can be curative for patients with UC. Indications for surgery in CD include disease intractability, failure of medical therapy, intestinal obstruction, persistent fistulae, and abscess formation.

PREGNANCY AND IBD

Most pregnant women with IBD can carry their pregnancy normally, although the incidence of spontaneous abortion is slightly higher than that in the general population. Medical therapy which has achieved remission in such cases should not be stopped. However, drugs like CSA and infliximab should be avoided, if possible. Methotrexate is contraindicated during pregnancy.

RECOMMENDED READINGS

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13.13 Ischaemic Bowel Disorders

Deepak Kumar Bhasin

Gastrointestinal ischaemia is a rare disorder that is seen infrequently in routine clinical practice and, therefore, a high index of suspicion is required to diagnose it correctly that too in the early phase of intestinal ischaemia so that appropriate therapeutic measures can be instituted in time. The ischaemic bowel disease can be caused by occlusion of the supplying arteries or draining veins and the onset can be acute or chronic. The ischaemia can also be caused by physiological vasoconstriction during low perfusion states. Each subtype of intestinal ischaemia requires its own diagnostic and therapeutic plan. Earlier digital subtraction angiography (DSA) was the mainstay for diagnosis of intestinal ischaemia but recently computed tomography (CT) and magnetic resonance (MR) angiography have emerged as effective alternatives for imaging splanchnic vessels. Because of rarity of intestinal ischaemia there are no randomised controlled trials. The treatment protocols are usually based on case series and clinical experience. The treatment of intestinal ischaemia is individualised and is mainly based on precise vascular anatomy, co-morbidity and severity of ischaemia. The advancement in therapeutic angiography has revolutionised the management of these disorders.

CLINICAL ANATOMY

Stomach, small intestine and colon are supplied by three major arteries. Celiac artery supplies stomach, proximal duodenum, liver and spleen. Superior mesenteric artery (SMA) supplies distal duodenum, rest of the small intestine, right colon and upto proximal two-thirds of the transverse colon. Inferior mesenteric artery (IMA) supplies from the distal third of the trasnverse colon to the proximal rectum. Distal rectum is supplied by the inferior rectal branch of the internal iliac artery. Splenic flexure and sigmoid colon have limited anastomosis; thus, ischaemic injury is more common in these areas. There are three pathways of communication between SMA and IMA: (i) marginal artery of Drummond which runs parallel to the intestinal wall, (ii) arch of Riolan, and (iii) central anastomotic artery.

PATHOPHYSIOLOGY

Splanchnic circulation receives one-fifth of the cardiac ouput, and this blood flow can increase up to 2 L/min post-prandially. The bowel can tolerate three-fourths reduction in its blood supply for up to 10 to 12 hours after which vasoconstriction and ischaemic injury develop. This is secondary to hypoxia and re-perfusion injury that sets in due to the reactive oxygen species following establishment of the blood flow.

CLINICAL FEATURES

Gastrointestinal ischaemia can be acute or chronic and both of these can be due to occlusive and non-occlusive lesions of the blood vessels known as non-occlusive mesenteric ischaemia (NOMI). Early diagnosis of mesenteric ischaemia is the key for successful management of these potentially catastrophic disorders.

Acute Mesenteric Ischaemia (AMI) or Acute Splanchnic Syndrome

It is by far more common than chronic mesenteric ischaemia. It is most commonly due to an embolism into the SMA that arises from the heart in about a half of the cases. Many of them also have a history of previous peripheral arterial emboli. These emboli lodge at the normal anatomical narrowing. Emboli are labeled major when they are lodged proximal to the origin of ileocolic artery. The most important symptom of acute mesenteric arterial occlusion is severe abdominal pain, which is out of character to the physical findings early in the course of the illness. This difference between the patient's presenting complaints and the lack of physical findings, which usually is responsible for delay in establishing the correct diagnosis is the most important feature of AMI. When physical findings arise that usually denotes that bowel infarction has set in.

Non-Occlusive Mesenteric Ischaemia (NOMI)

It occurs because of compromise of intestinal blood flow in the absence of an anatomic arterial occlusion or venous thrombosis as a result of severe mesenteric vasoconstriction. This usually occurs in the setting of low cardiac output or diseases associated with dehydration or hypo-perfusion like septicaemia, haemorrhage, shock, severe diarrhoea and those diseases where third-space fluid sequestration occurs, such as pancreatitis and burns. Because of more focus on underlying condition, the correct diagnosis of NOMI is ignored and delayed.

Mesenteric Venous Thrombosis (MVT)

It is predisposed by underlying hypercoagulable states, inflammatory conditions like diverticulitis, portal hypertension, etc. Selective mesenteric angiography can differentiate venous from arterial thrombosis. CT and MR can also demonstrate thrombus in the mesenteric veins.

Acute Superior Mesenteric Artery Thrombosis (SMAT)

It occurs in the areas of severe atherosclerotic narrowing. On angiography absence of collateral vessels denote acute occlusion.

Ischaemic Colitis and Colonic Ischaemia

These can have a spectrum of presentation in the form of: (i) transient colitis, (ii) chronic colitis, (iii) reversible colopathy, (iv) stricture, (v) gangrene, and (vi) fulminant universal colitis. Changes of ischaemia can vary from mild form of mucosal oedema to transmural infarction. In most cases of colonic ischaemia a specific cause cannot be identified. Patients most commonly present with sudden onset of crampy pain in the left lower abdomen followed by diarrhoea with bright red or maroon blood. Watershed areas of splenic flexure and rectosigmoid are involved in non-occlusive ischaemic injury.

Chronic Mesenteric Ischaemia [Chronic Splanchnic Syndrome (CSS), Intestinal Angina]

Patients typically have post-prandial pain which can last for 1 to 3 hours. There is fear of eating because of pain, resulting in weight loss. They can also have pain in the abdomen after exercise, history of nicotine abuse, classical abdominal angina and bruit on auscultation of the abdomen. Uncommonly they may have unexplained gastric ulcers or gastroparesis. It can be a single-vessel disease or multi-vessel disease former can be due to atherosclerosis or compression by the crus of the diaphram. Since there are a large number of collaterals, it is considered that single-vessel stenosis is usually asymptomatic. A classical example is coeliac artery compression syndrome. In multi-vessel disease, symptoms are as mentioned above and it is a big challenge even for the most experienced clinician to make a diagnosis as presentation can mimic simple dyspepsia and unexplained diarrhoea.

DIAGNOSIS

Routine blood investigations early in the course of intestinal ischaemia are usually normal. The findings of leucocytosis, acidosis, and elevated amylase level usually suggest advanced intestinal ischaemia and likely infarcted bowel.

Plain radiograph of the abdomen may show evidence like formless loops of intestine and thumb printing. In AMI it may show gas in the portal venous system. The main role of abdominal radiography lies in ruling-out other causes of acute abdomen. Duplex ultrasound is most frequently used modality for diagnosis. Air filled stomach, at times interferes in the visualisation of coeliac artery and SMA. Blood flow pattern and velocity can be measured to diagnose stenosis of arteries. It is recommended that duplex ultrasound should be done in fasting as well as post-prandial status.

CT angiography performed on multi-slice CT scanner can detect abnormalities in splanchnic arteries, veins and collaterals. Beside this, it can rule out alternate possibilities, such as perforation, pancreatitis, etc. MR angiography with contrast enhancement has been used to assess narrowing of splanchnic arteries. It has a sensitivity and specificity of more than 90%, but there is marked inter-observer variation in interpretation of stenosis. Digital subtraction angiography can detect lesions which can be treated in the same session and it provides a road, map for operative revascularisation. Thus it is the investigation of choice.

Endoscopy is preferred to barium studies. In colonic ischaemia it may show areas of haemorrhagic nodules, ulceration, friability which are segmental thus differentiating it from ulcerative colitis. Care should be taken not to overdistend the colon with air. Upper gastrointestinal endoscopy may reveal gastric ulcers.

In ischaemia there is increased carbon dioxide tension in the tissue. Tonometry measures the difference in luminal and arterial pCO_2. In chronic ischaemia gastric tonometry has been used following exercise to increase the yield of diagnosis.

Other investigations include serum D-lactate and I-FABP (intestinal fatty acid binding protein) have been used as markers for intestinal ischaemia.

MANAGEMENT

It is important to diagnose these patients before infarction of intestine sets in. It is necessary to use angiography judiciously and to relieve vasoconstriction by intra-arterial infusion of papaverine. We have to decide whether we are dealing with acute or chronic ischaemia, if chronic, which and how many vessels are involved, are there any co-morbid conditions, has infarction of intestine got established.

Acute Mesenteric Ischaemia (AMI)

Resucitate the patient, correct underlying hypovolaemia, treat underlying conditions like congestive heart failure, start broad-spectrum antibiotics. Confirm the diagnosis by CT angiogrpahy, contrast enhanced MRI, or selective angiography. Based on findings of angiography, plan further treatment and also infuse papaverine at the rate of 30 to 60 mg per hour to keep the blood vessels patent. In case infarction of intestine has set in proceed for surgical treatment.

For patient with SMA emboli, if peritoneal inflammation has set in, embolectomy and bowel resection is performed. Continue intra-arterial papaverine before, during and up to 24 hours in the post-operative period. If there are no features of peritoneal inflammation cases with minor emboli can be treated by intra-arterial infusion of papaverine, vasodilators and thrombolytic agents like streptokinase, urokinase, recombinant tissue plasminogen activator. Patients with major emboli may need surgical exploration.

Non-Occlusive Mesenteric Ischaemia (NOMI)

Intra-arterial infusion of papaverine should be given and if peritoneal signs are present, resect the necrotic bowel. When peritoneal signs are absent, patients can be managed with intra-arterial infusion of papaverine. Apart from treating underlying conditions, nitrates, ketanserin and sympathetic alpha receptor blockers have been tried with some benefit.

Acute SMAT

An attempt is made to place angiography catheter in proximal SMA and papaverine infusion is started. Thrombolytic agents and percutaneous angioplasty have also been employed.

Acute MVT

In case peritoneal signs are present, laparotomy and resection of the infarcted bowel is performed. In the absence of peritoneal signs immediate heparinisation followed by oral anti-coagulation for 3 to 6 months is used.

Chronic MVT

The main aim is to control the bleeding from varices by endoscopic banding and sclerotherapy.

Colonic Ischaemia

If there are signs of gangrene and infarction of bowel, patient should be operated upon. In the absence of these signs parenteral fluids and broad-spectrum antibiotics should be administered. Rectal tube should be inserted if colonic distension is present. Underlying cardiac failure and arrhythmia should be treated. In half of the cases of colonic ischaemia disease is reversible.

In patients with ischaemic stricture of colon, surgery is required in case of symptomatic obstruction. Endoscopic balloon dilatation can be used to relieve the obstruction.

Chronic Magnetic Ischaemia (Chronic Splanchnic Syndrome)

Single-vessel disease

In coeliac artery compression syndrome, relief of compression from diaphragmatic crus tends to relieve the symptoms.

Multi-vessel disease

Patients can proceed to acute splanchnic syndrome. Aim of treatment is to relieve obstruction and prevent acute splanchnic syndrome. Patients are strongly advised to stop smoking. Revascularisation can be done by surgery or percutaneous transluminal mesenteric angioplasty with or without stent placement.

Angioplasty is a recent advancement and high-risk patients not fit for surgery can undergo this form of therapy. However, recurrence of symptoms are more when compared to surgical revascularisation.

Follow-up

A severe reperfusion injury can set in, manifesting with nausea, abdominal pain, diarrhoea. Massive ascites may develop. To distinguish reperfusion injury from vessel re-occlusion, CT or MR angiography should be used to assess the patency of the vessel.

CONCLUSION

The wide spectrum of ischaemic bowel disease includes a number of disorders and each type of requires its own plan of management. The hallmark of diagnosis is high index of suspicion.

Aim should be to diagnose and manage the patient before intestinal infarction sets in. Mesenteric angiography (conventional or CT or MR angiography) should be done if no cause for the pain is found on plain radiographic film of the abdomen or CT in a patient suspected to have mesenteric ischaemia. Treatment options, including non-invasive, minimal invasive and classical open vascular reconstructive techniques, are available and require a multi-disciplinary team-approach for selection of appropriate case for appropriate treatment. The role of anti-coagulants and thrombolytics in mesenteric ischaemia is evolving.

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13.14 Gastrointestinal Symptoms in Systemic Diseases

Rakesh Tandon, Sudeep Khanna

Gastrointestinal (GI) symptoms may be a manifestation of an extra-abdominal or a systemic disease, the prime examples being chronic diarrhoea in diabetes or hyperthyroidism and constipation in hypothyroidism. It is important to keep this fact in mind while doing the clinical examination of a patient who presents with abdominal pain, nausea, vomiting, diarrhoea, constipation or jaundince.

Given below are some diseases that should be considered while investigating the patients presenting with the common gastrointestinal symptoms.

ABDOMINAL PAIN

Abdominal but Extra-Gastrointestinal Causes of Pain

1. ***Diseases of kidney, ureters and urinary bladder***

   Pyelonephritis: The patient may be a diabetic who presents with flank pain or a diffuse abdominal pain. The pain may radiate downwards. Fever may or may not be present. Urine examination will show pus cells. CECT should be diagnostic.

   Cystitis: Depending upon the clinical scenario, this may be bacterial, viral or fungal infection of the bladder. The patient may have an underlying immunocompromised state. The pain is generally localised to the lower abdomen.

   Ureteric stone: Sudden onset, shooting pain with difficulty in passing urine, haematuria and radiation to the testis is highly suggestive of ureteric colic.

2. ***Gynaecological conditions***

   Endometritis: The pain is generally associated with onset of menstruation and would disappear during pregnancy. MRI pelvis may pick-up the diagnosis. Laparoscopy may however, be needed to confirm.

   Acute salpingitis with or without tubo-ovarian abscess: Acute lower abdominal pain may be the first presentation. History of multiple sexual partners or sexually transmitted diseases may be forth coming. CT scan and/or MRI are good radiological modalities to pick-up the pathology.

   Ovarian cysts or torsion: Sudden onset tearing pain in pelvis is the hallmark. CECT is the investigation of choice. Surgery is curative.

   Ectopic pregnancy: The patient will present with acute lower abdominal pain and vaginal bleeding. There is a history of amenorrhoea. Ultrasonography (USG) may pick-up the ectopic pregnancy. If not, CECT/MRI may be done. Urine pregnancy test will be positive.

3. ***Abdominal aortic aneurysm***

   The pain is sudden acute, severe, constant, localised to the mid-abdomen or paravertebral or flank areas. The pain is tearing in nature and associated with prostration, light-headedness, and diaphoresis. If the patient does not sccumb to it on the way to the hospital, shock is the most common presentation. Physical examination reveals a pulsatile, tender abdominal mass in about 90% of cases. The classic triad of hypotension, a pulsatile mass, and abdominal pain is present in 75% of cases and mandates immediate surgical intervention.

Extra-Abdominal Causes of Acute Abdominal Pain

Cardiac

1. Myocardial ischaemia and infarction
2. Congestive heart failure (CHF)
3. Endocarditis
4. Myocarditis

Epigastric pain is classical of inferior wall ischaemia. It is important to think of it in the elderly, diabetic, hypertensive patient or the patient with a known history of coronary artery disease. The excruciating nature of the pain and associated symptoms like rapid or irregular heart beat, nausea/vomiting or pain radiation to chin or left arm may further alert the clinician to this possibility.

CHF may present with right upper quadrant pain and a tender hepatomegaly. Presence of pedal oedema and fullness of neck veins suggest the diagnosis of CHF. Pulse may be irregular in any of the above conditions. Past-history may be contributory. ECG, Echocardiogram, Trop-T tests will clinch the diagnosis.

Thoracic

1. Oesophageal rupture and spasm
2. Empyema, pneumonia and pneumothorax
3. Pulmonary embolism and infarction
4. Abdominal aortic aneurysm

All the above-mentioned conditions would be generally associated with chest pain. History of fever with cough may suggest empyema and lower lobe pneumonitis. Sudden onset pain and breathlessness would favour the diagnosis of pneumothorax and pulmonary embolism in the appropriate clinical setting.

Haematological causes

1. Haemolytic anaemia, e.g. sickle cell anaemia
2. Henoch-Schönlein purpura (HSP)
3. Haemolytic uraemic syndrome

Patients with HSP may present with the classical triad of palpable purpura (**Figure 1**), abdominal pain and arthritis. Renal involvement and GI bleeding may occur (**Figure 2**). Haemolytic uraemic syndrome is characterised by haemolytic anaemia, thrombocytopaenia and renal failure. It is a disease of children and abdominal manifestations include bloody diarrhoea, abdominal pain and vomiting.



Figure 1: Palpable purpura on lower extremities in a patient with HSP.

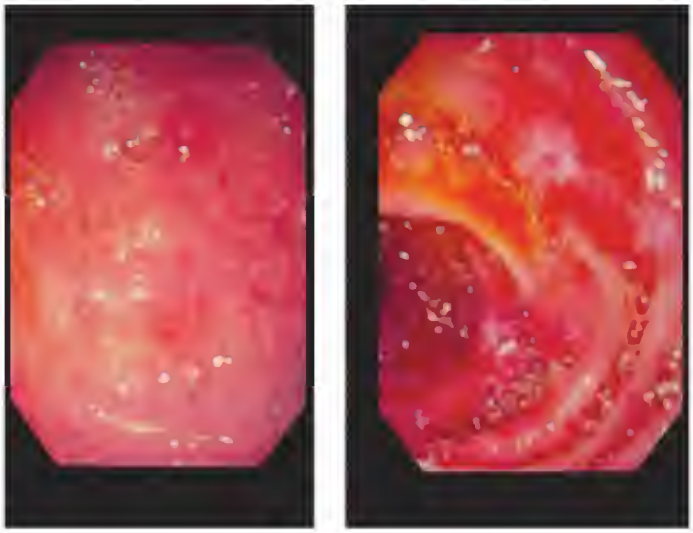


Figure 2: Erosions and erythema in duodenum and stomach in HSP.

Haemolytic anaemias may present as cholecystitis due to pigment gall stones, pain due to splenic infarct and abscess specifically with underlying sickle cell disorder.

Metabolic disorders

1. Acute adrenal insufficiency (Addison's disease)
2. Diabetes mellitus (especially with ketoacidosis)
3. Hyperlipidaemia
4. Hyperparathyroidism
5. Porphyria
6. Uraemia

Acute adrenal insufficiency may present as non-specific abdominal pain with vomiting and/or diarrhoea. There may be significant hyponatraemia. History of autoimmune disorders, tuberculosis, sarcoidosis may be present. Diabetes may present as abdominal pain due to neuropathy or more importantly due to uncontrolled sugar levels with sepsis and ketoacidosis. Acidotic breathing will give a clue. Blood sugar levels, arterial blood gases and urine ketones will clinch the diagnosis. Hypertrighlyceridaemia level (>1,000 mg/dL) can cause acute pancreatitis and, thus, present with severe epigastric pain with radiation to the back and vomiting. Hyperparathyroidism (primary) is seen most frequently in post-menopausal women. Most of the patients are asymptomatic. Among the symptomatic patients the presentation may be with acute epigastric pain of pancreatitis or dull to severe epigastric or right upper quadrant pain of gastric or duodenal ulcers. Involvement of kidneys, nervous system and musculoskeletal system will provide further clues to the diagnosis. Elevated serum ionised calcium levels, low serum phosphorus and normal or elevated serum alkaline phosphatase are also present.

Abdominal pain is present in more than 90% of patients during an acute attack of porphyria, followed in frequency by tachycardia and dark urine in about 80% of patients. Neuropsychiatric features include hysteria, depression, psychosis, confusion, hallucinations, seizures, and coma. Other features are constipation, pain in extremities, paraesthesias, nausea, vomiting, urinary retention, hypertension, peripheral sensory deficits (often in a 'bathing trunk' distribution), and weakness leading to ascending paralysis or quadriplegia. These neurologic attacks appear to be related to the over-production of ALA and porphobilinogen (PBG), which leads to higher serum and tissue levels of these neurotoxic products.

Patients with underlying chronic kidney disease (CKD) can present with acute abdominal pain secondary to ulcer disease or pancreatitis which are more common in this setting. Past-history of CKD and a serum creatinine level will give the clue towards the diagnosis.

Neurological conditions

1. Herpes zoster
2. Abdominal epilepsy
3. Transverse myelitis
4. Radiculopathy

Abdominal epilepsy is an exceptionally rare syndrome of epilepsy that is more likely to occur in children than adults. Very little is known about abdominal epilepsy. There have only been 36 cases reported in medical journals in the last 40 years. With abdominal epilepsy, seizure activity causes abdominal symptoms. For example, it may cause pain and nausea. Anti-convulsant medications can improve the symptoms.

With abdominal epilepsy, the seizures are thought to affect primarily the digestive system, resulting into the following GI symptoms:

(a) Abdominal pain, usually sharp or cramping and lasting seconds to minutes
(b) Nausea and/or vomiting
(c) Fatigue, lethargy, or sleep following seizures
(d) Altered level of consciousness, such as confusion or unresponsiveness, and
(e) Convulsive seizures known as generalised tonic-clonic seizures

People with reported abdominal epilepsy have different patterns of symptoms. Symptoms may also vary in the same person from one time to the other. For example, a person might have convulsive seizures and abdominal pain during one episode. Then the person may only have abdominal pain during another seizure.

Herpes zoster presents with severe pain/paraesthesia along a dermatomal distribution. One needs to think about it in the

differential diagnosis so that unnecessary tests are not conducted.

Miscellaneous causes

1. Narcotic withdrawal
2. Familial mediterranean fever
3. Muscle contusion, subcutaneous/parietal haematoma
4. Heat stroke
5. Psychiatric disorders

Narcotic drugs produce their effect by stimulating opioid receptors in the central nervous system (CNS) and surrounding tissues. The abuse of narcotics occurs as a result of the euphoria and sedation that narcotics produce within the central nervous system. Narcotics used for short-term medical conditions rarely require weaning since stopping the medication after a brief period rarely produces adverse effects.

The withdrawal syndrome from narcotics generally includes signs and symptoms opposite of the drug's intended medical effects. The severity of the withdrawal syndrome increases as the drug dose increases. The longer the duration of the physical dependence, the more severe is the withdrawal syndrome. Although uncomfortable, acute narcotic withdrawal for adults is not considered life-threatening unless the person has a medical condition that compromises his/her health (for example, if someone has severe heart disease). Some of the signs and symptoms of narcotic withdrawal include: anxiety, irritability, increased respiratory rate, yawning, rhinorrhoea, goose bumps, hypersalivation, nausea, vomiting, abdominal cramps, muscle cramps, diarrhoea, confusion, etc.

Familial mediterranean fever (FMF) is an inherited disorder featuring short recurring crises of severe abdominal pain and bouts of fever. Other symptoms include arthritis, chest pain from inflammation of the lung cavity and skin rashes. In between the attacks, the patient looks and feels healthy. Amyloidosis (the abnormal deposition of a particular protein, called amyloid, in various tissues of the body) is a potentially serious complication and can develop without overt attacks of FMF. The kidney is a prime target for the amyloid.

Daily use of the drug colchicine prevents attacks of fever in 60% of patients and significantly reduces the number of attacks in another 20% to 30% of patients.

Heat exhaustion results from prolonged heavy activity in a hot environment with subsequent dehydration, electrolyte loss and rectal temperature more than 37.8°C but less than/equal to 40°C. Heat stroke is a continuum of heat exhaustion with core temperature more than 40°C and neurological manifestations. Nausea, vomiting and abdominal cramps can be seen in both the conditions.

NAUSEA AND VOMITING

Nausea, retching, and vomiting may occur separately or together. Vomiting is a complex act that requires central neurologic coordination, whereas nausea and retching do not imply activation of the vomiting reflex. Nausea is an unpleasant subjective sensation that most people have experienced at some point in their lives and usually recognise as a feeling of impending vomiting in the epigastrium or throat. Retching consists of spasmodic and abortive respiratory movements with the glottis closed. When part of the emetic sequence, retching is associated with intense nausea and usually ends in vomiting.

Principal Extra-Gastrointestinal Causes of Nausea and Vomiting

Drugs

1. Aspirin and other NSAIDs
2. Anti-tuberculosis drugs
3. Steroids
4. Antibiotics, e.g. nitrofurantoin, clarithromycin, doxycycline, etc.
5. Anti-diabetic drugs, specifically metformin
6. Oral contraceptives
7. Theophyllines
8. Chemotherapeutic agents
9. Anti-retrovirals
10. Anti-arrhythmics, e.g. quinidine, digoxin
11. Antiprotozoals
12. Azathioprine
13. Sulphasalazine

Non-gastrointestinal systemic infections

1. Pneumonias
2. Meningitis
3. Urinary tract infections
4. Myocarditis

Patients with pneumonia may complain of associated pleuritic pain, cough with expectoration and breathlessness. Those with meningitis would present with fever, headache, neck rigidity and neurological signs. Urinary tract infections may be associated with burning micturition and flank pain along with fever.

Metabolic and endocrine causes

1. Addison's disease
2. Porphyrias
3. Diabetic ketoacidosis
4. Hypercalcaemia
5. Hyponatraemia

Labyrinthine disorders

1. Labyrinthitis
2. Meniere's disease
3. Motion sickness
4. Otitis media

History of related specific ear complaints will give a clue, e.g. presence of tinnitus, vertigo, ear discharge, etc.

Neurological disorders

1. Hydrocephalus due to any cause including tuberculous meningitis, normal pressure hydrocephalus
2. Brain abscess
3. Large infarct
4. Intracerebral bleed
5. Subdural haematomas

The onset of neurological signs will give a clue. Presence of projectile vomiting without nausea is characteristic of a

neurological illness. There will be presence of focal neurological signs.

Other causes include cyclical vomiting syndrome (there are days of vomiting followed by months of no episodes of vomiting during which the patients gain weight lost during the acute episode), eating disorders [bulimia (binge eating followed by induced vomiting)], alcohol binge, radiation therapy.

DIARRHOEA

Metabolic and Endocrine Disorders

1. Addison's disease
2. Diabetic autonomic neuropathy
3. Amyloidosis
4. Hyperthyroidism
5. Medullary carcinoma of thyroid
6. Phaeochromocytoma

Diarrhoea in diabetic autonomic neuropathy is either due to intestinal hurry or bacterial growth. Secondary amyloidosis may present as chronic diarrhoea with features of malabsorption. Renal involvement in the form of proteinuria is a prominent feature. Patients with hyperthyroidism will have associated tachycardia, tremor, hyper-reflexia, anxiety, heat intolerance, sweating, weight loss, etc. Patients with phaeochromocytoma presenting with diarrhoea will have associated hypertension (which may be sustained or paroxysmal), headache, palpitation and hyperhidrosis during the attack.

Drugs (need to be considered while taking the clinical history)

1. Antacids containing magnesium
2. Anti-arrhythmics (quinidine)
3. Antibiotics
4. Anti-neoplastic agents
5. H2-receptor antagonists, protein pump inhibitors
6. Theophylline
7. Various herbal preparations, etc.

CONSTIPATION

The various non-GI causes of constipation that need to be considered in differential diagnosis include:

Metabolic and Endocrinologic Disorders

Diabetes mellitus, hypothyroidism, hyperthyroidism, hypokalaemia, hypercalcaemia, pregnancy, phaeochromocytoma, panhypopituitarism, porphyria, heavy metal poisoning.

Medications

Calcium channel blockers, mu-opioid agonists (e.g. loperamide, fentanyl, morphine), anticholinergic agents (e.g. antispasmodics, anti-psychotics, tricyclic anti-depressants, etc.), anti-convulsants (e.g. phenytoin, carbamazepine, etc.), antacids, diuretics, NSAIDs.

Neurologic and Myopathic Disorders

Progressive systemic sclerosis, amyloidosis, dermatomyositis, multiple sclerosis, Parkinsonism, intestinal pseudo-obstruction, etc.

FAECAL INCONTINENCE

Among the systemic diseases which may cause faecal incontinence, the predominant ones are various neurological disorders including: dementia, mental retardation, stroke, brain tumour, spinal cord lesions (e.g. multiple sclerosis, *tabes dorsalis*), peripheral nervous system disorders including *cauda equina* lesions, diabetes mellitus, various polyneuropathies, sedation and hypothyroidism.

1. *Endocrinopathies:* Hyperthyroidism, Addison's disease, various neuroendocrine tumours (discussed earlier), medullary carcinoma thyroid, mastocytosis and phaeochromocytoma.
2. *Disordered motility:* Post-vagotomy diarrhoea, post-sympathectomy diarrhoea, diabetic autonomic neuropathy.
3. *Infiltrative diseases like lymphoma.*

The disease-symptom associations given above are only a few examples of the wide variety of manifestations of the diseases. Metabolic and endocrine disorders are the commonest in this category and some of them have been cited above. Neoplasia and connective tissue disorders are other groups of diseases that often manifest with GI symptoms. Intestinal metastases occur in up to 20% of all non-gut cancers. Breast, lung, ovarian cancer and melanoma are the commonest source. Serosal metastases may cause pain, *ascites*, obstruction or recurrent GI bleeding. Paraneoplastic pseudo-obstruction is a rare feature of small cell lung cancer. Chemotherapy can cause diarrhoea due to *Clostridium difficile* infection (especially, with neutropaenia), mucositis or autonomic neuropathy.

Connective tissue disorders such as rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus may present with dysphagia or other GI manifestations like diarrhoea or malabsorption or abnormal liver function tests, particularly raised serum alkaline phosphatase. Behcet's syndrome is a rare cause of ileocolic disease.

The clinician should, thus, always keep in mind that the gastrointestinal or abdominal symptoms may reflect diseases pertaining to organs away from the gastrointestinal tract.

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Section 14

Hepatology

Section Editors: Rajesh Upadhyay and S.K. Sarin

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14.1 Basic Considerations of Hepatobiliary Disorders

Vivek Anand Saraswat

INTRODUCTION

The normal liver occupies the right upper quadrant, extending from the 5th intercostal space in the midclavicular line to the right costal margin. With a median weight of 1800 g in men and 1400 g in women, the liver is the largest organ in the body and accounts for 4% to 5% of total body weight at birth and 2% to 3% after the first year of life. It is strategically situated, being the first organ to receive nutrient-enriched blood supply from the portal system, and its unique vascular structure provides hepatocytes with unparalleled access to nutrients and xenobiotics absorbed from the intestinal lumen, enabling it to serve key functions in critical metabolic and synthetic pathways.

FUNCTIONS OF THE LIVER

The liver is a factory, a storehouse, a filter, a policeman and above all, orchestrator and regulator of the complex ballet of metabolic functions that keeps the body running. It is an excretory organ, an endocrine organ, an immune organ, at times a haemopoeitic organ. Its various functions include processing and redistribution of metabolic fuels such as glucose and fatty acids, and modification and detoxification of compounds absorbed from the small intestine for which the liver contains a host of biochemical pathways. The functions are summarised in **Table 1**.

Table 1: Functions of the Liver

Regulation of *intermediary metabolism* ensures a constant supply of fuel (glucose, ketone bodies) to the entire body during periods of fasting and stress
Lipid and cholesterol metabolism and reverse cholesterol transfer
Interorgan *trafficking of aminoacids* and *synthesis of essential aminoacids*
Excretion of endogenous and exogenous toxins, directly through bile or indirectly by converting to polar compounds excreted through the kidneys
Storage of excess energy fuels (e.g. glycogen, fats) and vitamins (e.g. vitamin A)
Synthesis of plasma proteins, e.g. albumin, coagulation factors, complements C3, C4, α1-antitrypsin, caeruloplasmin, transferrin, ferritin, orosomucoid, haptoglobin, serum amyloid A protein, etc.

Intermediary Metabolism

A major responsibility of the liver is to provide a continual source of energy for the entire body. The liver's ability to store and modulate the availability of systemic nutrients is regulated by numerous local factors and the requirements of peripheral organs for energy sources. Hepatic metabolic function is subject to hormonal modulation by endocrine organs, such as the pancreas, adrenal gland, and thyroid, as well as to neuronal regulation. The liver regulates nutrient flux during periods of nutrient absorption (meals), when absorbed nutrients are metabolised, modified for storage in the liver and fatty tissue, or made available to the remaining organs as sources of energy metabolism, and during non-absorptive periods (fasting), when metabolic requirements need to be maintained from stored fuel sources or by synthesis. The regulation of these metabolic pathways involves complex interactions among the nutrient content of the blood, end-products of nutrient metabolism that are present in the blood and represent precursors for hepatic synthesis, and hormonal regulation.

Ammonia Handling by the Liver

Liver is the principal site of conversion of ammonia to urea. Nearly one-fourth of the nitrogen incorporated into urea comes from ammonia generated in the splanchnic viscera by bacterial degradation of luminal urea in the colon and from breakdown of glutamine extracted from the arterial blood by small intestinal enterocytes. The rest of the urea nitrogen comes from the breakdown products of aminoacids (alanine and glutamine) transported to the liver. In the liver, there are two methods of ammonia disposal: a low-affinity, high-capacity urea synthesis localised to the periportal hepatocytes and a high-affinity, low-capacity glutamine synthesis by the perivenous hepatocytes. Since the synthesis of each mole of urea utilises 2 moles of bicarbonate, the liver also plays an important role in pH regulation. The urea cycle and synthesis of glutamine illustrate how compartmentalisation of hepatic metabolic pathways in different zones leads to efficient utilisation of metabolic by-products. Ammonia is converted to urea by the concerted activity of urea cycle enzymes in the liver. This high-capacity, low-affinity system is located predominantly in the periportal and central zones of the liver acinus. These same populations of cells also are the principal sites of ammonium generation as a by-product of amino acid metabolism. Glutamine synthesis utilises ammonium and is catalysed by glutamine synthetase, which is expressed exclusively in hepatocytes lining the pericentral vein. Pericentral hepatocytes thus scavenge ammonium and convert it to glutamine, thereby eliminating toxic ammonium from the systemic circulation.

Bilirubin Handling by the Liver

Jaundice or icterus is the hallmark of hepatobiliary disease and reflects a breakdown in the orderly sequence of bilirubin production, transport and biliary excretion that keeps serum bilirubin levels within a narrow range of 0.2 to 0.8 mg/dL.

Bilirubin Metabolism

Briefly, bilirubin is mainly produced in the spleen from the break down of the haem moiety of haemoglobin derived from senescent red cells. It is transported to the liver bound to albumin and is taken up by the hepatocytes where it undergoes microsomal conjugation to bilirubin mono- and diglucuronides. These conjugates are then actively transported to the biliary canaliculus, then through the intra- and extra-hepatic biliary

channels to the intestine, from where they are largely excreted in faeces (**Figure 1**). A small amount undergoes bacterial deconjugation and conversion to urobilinogen that undergoes enterohepatic circulation and renal excretion. Perturbations at each of these steps, which are elaborated below, may result in the clinical outcome of jaundice.

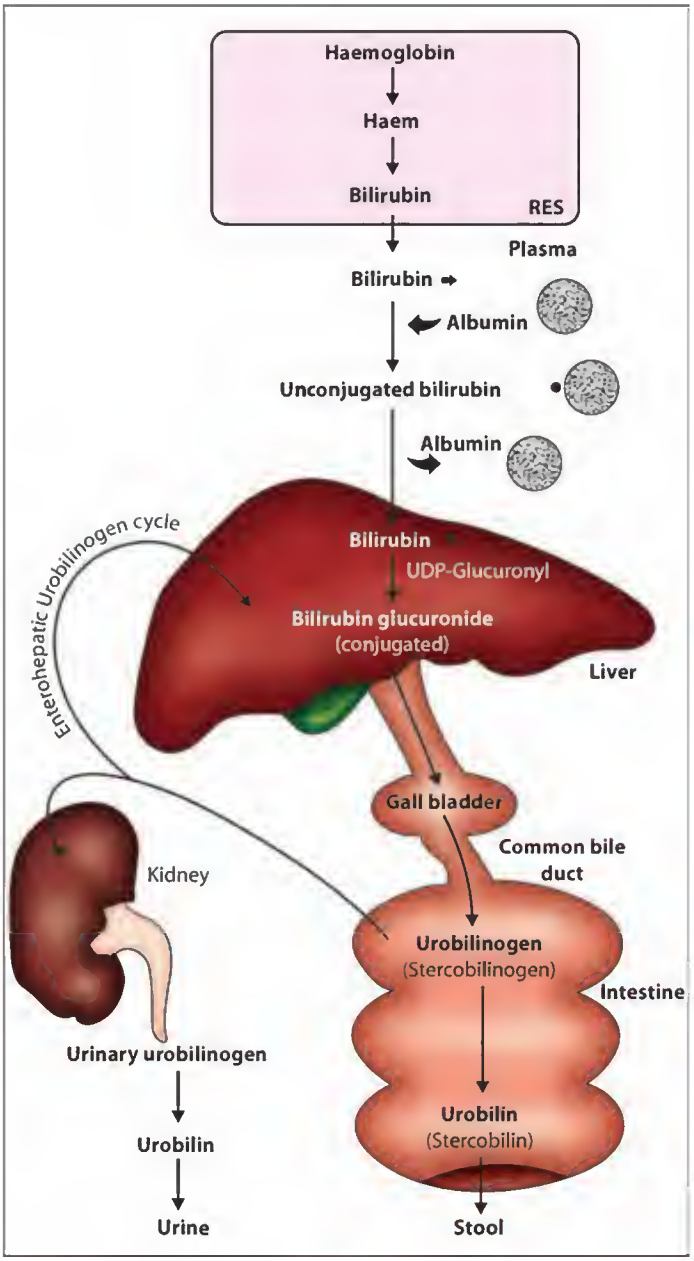


Figure 1: Bilirubin metabolism.

Bilirubin production

Under steady state normal metabolic conditions, about 3.9 mg/kg or 250 to 350 mg of bilirubin is produced each day, nearly 80% of which is derived from haemoglobin. The closed tetra pyrole ring of haem is opened up by microsomal enzymes haem oxygenase, with nicotinamide adenine dinucleotide phosphate hydrogenase (NADPH) and molecular oxygen used as co-factors. This reaction is the rate limiting step in haem catabolism. Each gram of haemoglobin produces 36.3 mg of bilirubin.

Biliverdin, a green pigment which is the predominant bile pigment in avian and fish bile, is converted to bilirubin in mammals by biliverdin reductase, a cytosolic enzyme that uses NADPH as co-factor. Using radio-labelled precursors of haem, two-phase elimination of bilirubin has been identified. Approximately 20% is excreted within 24 to 72 hours as an early peak or early labelled bilirubin (ELB) while 80% is excreted during late-phase elimination at about 110 days. The ELB consists of an initial 'fast' fraction, derived from hepatic haem containing proteins, and a slower fraction derived from *ineffective erythropoiesis* or destruction of maturing erythroid precursors in the bone marrow. Ineffective erythropoiesis markedly increases in conditions like porphyria, sideroblastic anaemia, megaloblastic anaemia and lead poisoning. Bilirubin derived from senescent red blood cells at the end of their life span appears over a broad range of 90 to 150 days.

Bilirubin transport

Lipophilic unconjugated bilirubin circulates in the blood and body fluids bound tightly and reversibly to albumin, which solubilises it in aqueous solutions. Albumin binding also protects against kernicterus by preventing entry of unconjugated bilirubin into the brain when its levels are elevated or when the blood-brain barrier is immature. The likelihood of developing kernicterus in Crigler-Najjar syndrome therefore is influenced by serum albumin levels. Drugs such as sulphonamides and long chain fatty acids used in parenteral nutrition may displace bilirubin from albumin binding sites, resulting in an increase in free unbound bilirubin in plasma.

Hepatic uptake

On reaching the liver, albumin-bound unconjugated bilirubin dissociates and is taken up by the hepatocyte across the sinusoidal membrane (**Figure 2**). While some uptake of unconjugated bilirubin across the cell membrane occurs by passive diffusion, active uptake against a concentration gradient is most important, particularly at low plasma bilirubin concentrations, and is mediated by *organic anions transporting protein 2* (OATP2). Conjugated bilirubin shares the same transporter for hepatic uptake. Thus, in predominantly conjugated hyperbilirubinaemic conditions, elevation of unconjugated bilirubin also occurs because of a competitive uptake defect.

Intrahepatocytic transorganelle trafficking

Within the hepatocyte, unconjugated bilirubin is bound to intracellular transport proteins called *ligandins* that play an important role in preventing reflux back to plasma. Intrahepatocytic movement of bilirubin from the plasma membrane to the endoplasmic reticulum for conjugation and to the canalicular membrane for export is predominantly carried out by organelle-dependent tubulovesicular transport. The most important event occurring within the hepatocyte is conjugation of bilirubin with activated sugar (predominantly glucuronic acid, also glucose, xylose) to make it water soluble for efficient biliary excretion.

Conjugation and the diphosphoglucuronyl transferase gene

In conjugation, propionic acid side chains of bilirubin are esterified by activated uridine diphosphoglucuronic acid (UDPG) to produce first bilirubin mono- and then diglucuronide, in a reaction catalysed by the microsomal enzyme uridine diphosphoglucuronyl transferase (UGT). Bilirubin diglucuronide is the predominant form of conjugated bilirubin in human bile, though increase in monoglucuronides is seen in Crigler-Najjar

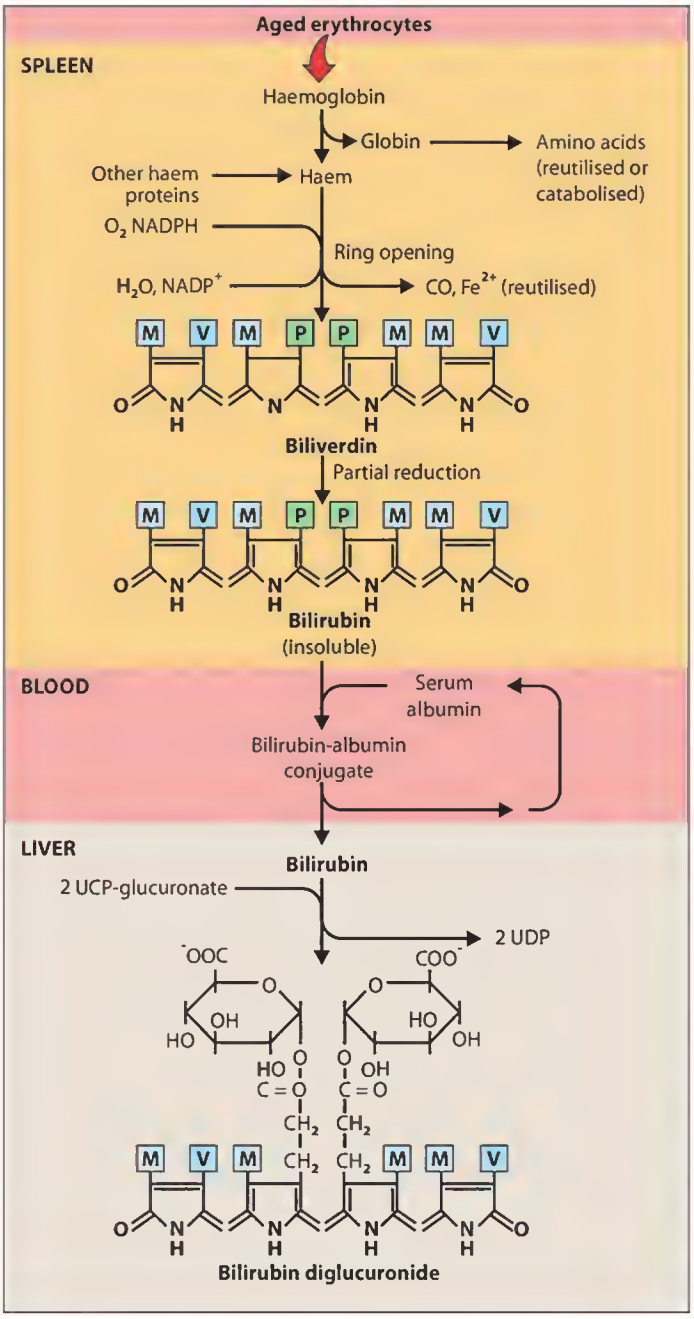


Figure 2: Bilirubin transport.

syndrome when glucuronidation is impaired. Though several independently regulated UGT isoforms are expressed from the human UGT1A locus, only bilirubin UGT1 (BUGT1, also termed UGT1A1) contributes significantly to bilirubin glucuronidation. The UGT1 gene has been mapped to chromosome 2q 37. It belongs to a superfamily of genes that are important in detoxification, encoding more than 10 isoforms with varying substrate specificity. Apart from bilirubin, bile acids, phenol, steroids and various drugs and toxins are substrates for UGT1.

Canalicular export

Transport across the canalicular membrane to the biliary canaliculus is an active carrier mediated process, utilising ATP in the presence of Mg^{++} ions, that transports substances against a steep concentration gradient. The transport protein multiple drug resistant protein 2 (MDR2/MRP2) functions as the canalicular transporter of bilirubin, bromsulphthalein, glutathione and glucuronide conjugated drugs and xenobiotics. MDR2/MRP2 is also called canalicular multispecific organic anion transporter (cMOAT) and belongs to a class of membrane transporters that forms a superfamily called ATP binding cassette (ABC) proteins.

Intestinal phase

Though conjugated bilirubin is not absorbed to any significant extent from the intestinal tract, it is deconjugated by bacterial glucuronidases, yielding urobilinogens that can be absorbed from the intestine and undergo enterohepatic circulation and renal excretion. Urobilinogen is colourless but is converted to urobilins that are yellow coloured. Absence of urobilinogen from stool may be indicative of complete biliary obstruction.

Molecular Mechanism of Inherited Disorders of Bilirubin Metabolism

With rapid advances in the understanding of genetic regulation of bilirubin homeostasis, molecular mechanisms of inherited disorders characterised by unconjugated and conjugated hyperbilirubinaemia have been elucidated. Inherited unconjugated hyperbilirubinaemic conditions are the result of impaired or absent conjugation due to abnormalities of UGTI AI. Gilbert's syndrome (GS), Crigler-Najjar syndrome type II (CN II), and Crigler-Najjar syndrome type I (CN I) form a spectrum in terms of increasing degree of enzyme deficiency. Dubin Johnson and Rotor syndrome are inherited, conjugated hyperbilirubinaemias.

Gilbert's syndrome

Gilbert's syndrome is the most common among these and is characterised by mild persistent unconjugated hyperbilirubinaemia (usually less than 5 mg/dl), normal liver structure and function, no evidence of haemolysis and an excellent prognosis. The genetic defect in GS lies in the promoter region upstream of exon I. Normal TA/TAA repeats are of the sequence (TA)6TAA. GS patients are homozygous for a longer sequence, (TA)7TAA. This dinucleotide polymorphism reduces the expression of a structurally normal UGTI gene to less than 30% of the normal and results in higher levels of bilirubin monoglucuronides (14% to 34%) in bile in GS patients, normal range being 0% to 7%. It is interesting to note that mere presence of the GS genotype may not be sufficient to produce clinically evident hyperbilirubinaemia. Variations in the amount of bilirubin production may also be important for phenotypic expression, accounting for clinical observations such as GS being uncommon in females who produce less bilirubin than males and commoner after fasting, exercise and following intercurrent infections.

Crigler-Najjar syndrome

In the Crigler-Najjar syndromes, hyperbilirubinaemia is more severe due to more pronounced deficiency of UGT. In CN II, some residual enzyme activity remains (partial deficiency) and serum bilirubin fluctuates between 7 and 20 mg/dl. Bile contains high concentration of bilirubin monoglucuronides. Prognosis in CN II is generally good, but intercurrent infection and debility might precipitate bilirubin encephalopathy even in this relatively benign phenotype. On the other hand in CN I, absence of UGT1 results in high levels of unconjugated hyperbilirubinaemia and kernicterus, unless phototherapy is instituted soon after birth. In both the CN syndromes, there are mutations involving the

coding region (exons 2 to 5) of the UGT1A1 gene. These may take the form of nonsense or missense mutations, insertions, deletions as well as a premature stop codon. In CN I, genetic lesions are widespread, involving more than one exon at critically important sites for enzyme less in number, leading on to diminished but not absent UGT activity. Interestingly, in India, presence of Gilbert's type promoter abnormality in one gene together with coding region mutation in the other (compound heterozygosity) might be an important genetic mechanism producing the CN II phenotype. Apart from its significance in inherited hyberbilirubinaemias, it has been shown that the Gilbert's type promoter abnormality might be responsible for the high serum bilirubin levels seen in some patients with chronic hepatitis.

Dubin Johnson and Rotor syndromes

A number of inherited disorders are characterised by conjugated hyperbilirubinaemia including Dubin Johnson syndrome, Rotor syndrome and progressive familial intrahepatic cholestasis (PFIC). The molecular defect in Dubin Johnson has been found to be associated with abnormal structure of MRP2, due to mutations that alters protein assembly. As a result canalicular export of bilirubin glucuronides and other organic anion is hampered. In PFIC–1, there is a defect in canalicular bile salt transporter.

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14.2 Hepatobiliary Disorders—A Clinical Approach

Nagaraja Rao Padaki

INTRODUCTION

Liver is considered as a major metabolic organ in the body performing diversified functions, namely metabolisms of carbohydrate, protein and fat, regulation of coagulation and detoxification of toxic substances. In addition, being an organ enriched with reticuloendothelial functions, it is the site of immunological activity. It is no surprise that liver is involved whenever any of these functions are deranged. The symptoms and signs may be very minimal or even absent despite advanced, compensated state of liver disease. In addition patients with a liver disease can present signs or symptoms relating to other systems for example pruritus as initial or the only manifestations of many cholestatic diseases. Liver disease, quite frequently is detected incidentally on routine master health check-up or while investigating other symptoms. Hence, the clinician should be aware of various manifestations of acute and chronic liver disease. The presence of liver disease may be indicated by an abnormal laboratory test, incidental finding at endoscopy or ultrasonogram or even surgery done for some other purpose.

In patients with liver disease particularly in jaundiced patient, it is possible to arrive at accurate diagnosis in nearly 85% of patients with a careful history, physical examination and standard laboratory tests.

HISTORY IN LIVER DISEASE

Like in any other system, the importance of history taking can not be underestimated in liver disease. Presence of dark urine, jaundice, haematemesis, and melaena will obviously point towards liver disease. One should be aware of certain non-specific symptoms which may escape from the notice of the physician. These include fatigue, pruritus, anorexia, weight loss or gain and abdominal pain.

Fatigue

This apparently non-specific symptom of fatigue may be present for many years in patients with undiagnosed liver disease. The severity of fatigue in these conditions is thought to be out of proportions to severity of the liver disease. The fatigue associated with liver disease is central fatigue and is thought to be due to abnormal functioning of hypothalamic-pituitary-adrenal axis and or altered opiate mediated neurotransmission. Two important disease states particularly important to remember in this aspect are hepatitis C and cholestatic disorders. The other reasons for fatigue in any liver disease are loss of muscle mass and poor nutrition.

Pruritus

The symptom of pruritus associated with jaundice are easy to point towards extra-hepatic or intra-hepatic cholestasis. One should remember that in primary biliary cirrhosis and benign recurrent intra-hepatic cholestasis, pruritus can be the initial manifestation without jaundice or overt signs or symptoms of liver disease for a long time. Pruritus, or itching, is a common symptom in patients with cholestatic liver disease. The pathophysiology of pruritus is poorly understood. It may be mediated centrally through opioid receptors. The itching typically affects the extremities more than the trunk and face and is usually worse at night. The scratching associated with pruritus may cause fleeting skin excoriations. Non-hepatic systemic causes of pruritus include chronic renal failure, thyroid dysfunction, malignancy, human immunodeficiency virus (HIV) infections, pregnancy and ovarian hormones abnormalities.

Anorexia

Anorexia is common in patients with acute viral hepatitis and in those with neoplasms of the liver, biliary tree, pancreas. Onset of nausea and vomiting during second or third trimester of pregnancy should alert one to the possibility of acute fatty liver of pregnancy. Anorexia in liver disease contributes to muscle wasting further by interfering with nutrition.

Weight Loss or Gain

Weight loss occurs in cirrhosis due to loss of muscle mass which may be secondary to poor nutrition. Characteristically these patients loose fat from face, extremities and chest and do so progressively and rather insidiously. Weight gain in patients with advanced liver disease is typically caused by *ascites* and oedema and may precede other symptoms of the liver disease. At times pedal oedema on prolonged dependency may be the only manifestation of the liver disease.

Abdominal Pain

Abdominal pain is a common complaint in patients with liver disease and is typically located in the right upper quadrant of the abdomen below the right rib cage. The pain tends to be constant and worse with movement as a result of the stretching of the liver capsule in inflammatory conditions like acute viral hepatitis, amoebic liver abscess. Biliary colic in patients with symptomatic gallstones is typically acute in onset and steady in nature, in right upper quadrant or epigastric regions. The pain attacks often occur after a meal or in the early hours of the morning lasting for 30 to 90 minutes. In contrast, the pain due to acute cholecystitis is steady right upper quadrant pain that may radiate to the right shoulder and is often exacerbated by respiration because of diaphragmatic irritation. This may be associated with fever or rigors.

A rapidly enlarging liver resulting from tumour growth, inflammation, or congestion. Slow onset of right upper quadrant pain over several weeks should suggest tumour growth or hepatic congestion. Sometimes pain over left upper quadrant may be due to splenomegaly as a result of portal hypertension. Generalised abdominal discomfort may be due to *ascites* in initial onset when abdominal muscles are not stretched enough to accommodate even smaller amount of fluid accumulation. Pain all over abdomen particularly tenderness may be the manifestation of ensuing

spontaneous bacterial peritonitis. A tense *ascites* merely due to large volume causes generalised pain all over the abdomen. Focal pain over the liver, with associated point tenderness on examination, can occur with liver abscesses and tumours.

OTHER IMPORTANT POINTS IN THE HISTORY

Icterus and Jaundice

Jaundice is a characteristic presentation of liver disease and refers to the yellow colouration of the patient's skin caused by the deposition of bilirubin glucuronides in the tissues. Icterus is the term used to denote yellow sclerae resulting from hyperbilirubinaemia. The jaundice noticed by friends or relatives is usually due to malignancy of extrahepatic biliary tree like slow growing sclerosing cholangiocarcinoma or ampulla of Vater.

Abnormal Stool

A mild increase in the frequency or decrease in the consistency of bowel movements is often seen in patients with liver disease; constipation is infrequent. Diarrhoea may result from a decrease in the concentration of intestinal bile salts, leading to an increase in faecal fat.

In patients with cholestasis or acute hepatitis, the stool is typically pale or "clay-coloured" as a result of decreased bilirubin excretion into the intestinal lumen. It is important to question patients with chronic liver disease about malaena (dark, tarry stool) which indicates upper gastrointestinal bleeding. Sometimes slow bleed from gastric fundal varices can have only slow onset anaemia due to malaenic stool without any other features of the liver disease.

Sleep Disturbance

In patients with known or suspected end-stage liver disease, a disruption of the normal sleep pattern may be the earliest symptom of hepatic encephalopathy. Patients may have trouble falling asleep, interrupted sleep at night, or day-time somnolence. The sleep disturbance is thought to result in part from changes in melatonin secretion in cirrhotic patients.

Change in Mental Status

Patients with worsening hepatic encephalopathy may experience mental impairment, ranging from lethargy and confusion to stupor and coma. Encephalopathy can be associated with personality changes, depression, irritability, and inappropriate and disinherited behaviour. These symptoms are typically not noted by the patient but reported by friends and family. The diagnosis of minimal hepatic encephalopathy (MHE) rests on the confirmation of a disease that can cause MHE, such as, cirrhosis or presence of portosystemic shunt, exclusion of normal mental status, on clinical examination, demonstration of abnormalities of cognition and/or neurophysiological variables and exclusion of concomitant neurological disorders.

Leg Cramps

Patients with end-stage liver disease have a high frequency of muscle cramps, typically in the legs and mostly at night.

ROLE OF PHYSICAL EXAMINATION IN LIVER DISEASE

General inspection of the patient gives several clues. Icterus which is evident if bilirubin is more than 3.0 mg/dL should be seen in day-light so as not to miss. Wasting is indicative of advanced liver disease or malignancy. Presence of skin excoriations confirms pruritus. Interscapular area which the patient cannot access will be devoid of excoriations. **Table 1** lists common clinical features present in liver diseases.

Table 1: General Physical Examination in Liver Disease

Manifestations	Key Points-Significance
Ocular manifestations	
Jaundice, be aware of	Non-hepatic causes of jaundice Haemolytic jaundice Heredofamilial causes Gilberts syndrome/Crigler-Najjar type 2 syndrome Dubin-Johnson syndrome Systemic causes of febrile jaundice Primary biliary cirrhosis Long-standing obstructive jaundice
Cutaneous manifestations	
Spider angioma	Cirrhosis-hormonal changes
Palmar erythema	Cirrhosis-vasodilatation
Spontaneous bruising	Cirrhosis-impaired coagulation
Petichae	Thrombocytopaenia
Palpable purpura	Polyarteritis nodosa (Hepatitis B virus related) Cryoglobulinaemia (Hepatitis C virus related)
Excoriations	Cholestatic liver disease
Endocrine and other manifestations	
Gynaecomastia	Indicative of advanced liver disease Spironolactone induced (tender and painful) Non-hepatic systemic causes include: Physiological at neonatal and puberty Hormone producing neoplasms Renal disease, hyperthyroidism
Testicular atrophy	Advanced liver disease
Dupuytren's contracture	Thickening of flexor tendons of hand-disease advanced liver
Parotid enlargement	Indicative of alcoholic liver disease
Asterixis (liver flaps, flapping tremors)	Indicative of early hepatic encephalopathy, seen also in advanced cardiac, renal, pulmonary failures
Lymphadenopathy	Not a usual finding in liver disease, suggests Epstein-Barr virus infection, lymphoma

LIVER FUNCTION TESTS: SOME PRACTICAL POINTS

Liver performs various complex synthetic, metabolic or excretory functions. All these functions can not be assessed by any single or group of tests. Biochemical liver function tests popularly known as "LFT" are frequently used as screening tests in asymptomatic or symptomatic subjects. The pattern of abnormalities noted usually give a clue towards predominantly, haemolytic or obstructive nature of jaundice.

Causes of isolated unconjugated hyperbilirubinaemia include Gilbert's syndrome (<6 mg/dL), Crigler-Najjar I (25 to 48 mg/dL), Crigler-Najjar II (6 to 25 mg/dL), haemolysis (<5 mg/dL), ineffective erythropoiesis, neonatal jaundice and sepsis, congestive heart failure, and some drugs like pregnanediol, chloramphenicol, novobiocin, rifampicin, probenecid.

Some practical points to remember about liver functions are presented in **Tables 2 to4**.

Table 2: Abdominal Examination of Liver Disease

Manifestation	Key Points-Significance
Engorged abdominal veins	Typical caput medusae is rare More prominent in *ascites* Seen only in intra-hepatic and supra-hepatic causes of portal hypertension Absent in extra-hepatic portal vein thrombosis due to collapsed umbilical vein which joins L portal vein Veins over the back suggests Budd-Chiari syndrome Longitudinal veins along side of abdomen suggest IVC obstruction
Hepatomegaly	
Left lobe alone palpable	Indicates cirrhosis or mass lesion in the left lobe
Generalised tender enlargement	Acute hepatitis, hepatic congestion
Localised tenderness	Liver abscess
Splenomegaly	Large spleen suggests EHPVO/NCPF
Palpable gall bladder	Courvoiseur's law/hypothesis Indicates obstruction below the level of cystic duct
Ausculatatory findings	
Hepatic bruit	Alcoholic hepatitis, hepato-cellular carcinoma Hepatic artery aneurysm, Traumatic A-V fistula
Venous Hum	Cruveihier-Baumgarten syndrome/ disease Portal hypertension
Hepatic rub	Liver abscess, hepato-cellular carcinoma

ICV = Inferior vena cava; EHPVO = Extra-hepatic portal vein obstruction; NCPF = Non-cirrhotic portal fibrosis.

Table 3: Clinical Significance of AST/ALT Ratio

Clinical Status	AST/ALT	Remarks
No underlying liver disease	0.8	
Alcoholics without liver disease	<1.0	
Alcoholic liver disease	>2	ALT <300 U/L
Non-alcoholic liver disease	>1	Indicates underlying cirrhosis (specifically 94% to 100%) and sensitivity 44% to 75%
NAFLD	<1	

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; NAFLD = Non-alcoholic fatty liver disease.

Table 4: Non-Hepatic Causes of Elevation of Transaminases

Clinical Status	Remarks
Hyperthyroidism	Both AST and ALT
Strenous exercise	AST elevation can cap up to 3-fold
Muscle injury Rhabdomyolysis Polymyositis Muscular dystrophy	
Diurnal variation	ALT lowest at night and highest in the afternoon
Coeliac disease	
Haemolysis	

ROLE OF IMAGING PROCEDURES IN DIAGNOSIS OF LIVER DISEASE

If clinical and laboratory features are suggestive of acute liver disease, ultrasound may not help further. Some characteristic but not pathognomonic findings in ultrasonogram in acute hepatitis include oedematous gall bladder wall and portal lymph-adenopathy. However, an ultrasonogram of the abdomen will be helpful in acute presentations of underlying chronic disease, like flares in chronic hepatitis B and acute on chronic liver disease.

In a patient with jaundice, if the biochemistry is suggestive of obstructive type (grossly elevated alkaline phosphatase with ALT/AST less than 300 U/L ultrasonogram is helpful. It has been observed that if the bilirubin is more than 10 mg/dL for atleast 2 weeks, the sensitivity and specificity of ultrasonogram in differentiating intra-hepatic from extra-hepatic cholestasis is 95%.

If an ultrasonogram reveals dilated intra-hepatic bile ducts then an additional imaging procedures like computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasonography (EUS) with or without biopsies are often necessary to establish the cause of the obstruction.

On the other hand, if bile ducts are not dilated, i.e. medical jaundice is considered, then liver biopsy is helpful if not contraindicated otherwise.

If cholelithiais is suspected, ultrasonography is sufficient along with liver function tests. If choldocholithiasis is suspected then ERCP is indicated especially if cholangitis is suspected since a therapeutic intervention like NBD, papillotomy and retrieval of stone can be done. In doubtful cases a prior EUS is likely to give some guidance.

In new onset ascites a color Doppler ultrasound will be helpful in evaluating the portal and hepatic venous systems. Ascitic fluid analysis to differentiate high and low SAAG is of immense immediate value in diagnosing portal hypertension.

In patients with obstructive jaundice due to suspected pancreatic carcinoma, EUS is superior to CT with regard to detecting a pancreatic mass, tumour staging. While predicting operability, both are comparable.

DIFFERENTIAL DIAGNOSIS OF LIVER DISEASE

If the patient is jaundiced, a reliable history, physical examination, and standard biochemical tests are sufficient to make near accurate diagnosis in about 85% of the cases. Splenomegaly, ascites and prominent veins over the anterior abdominal wall are good indicators of presence of portal hypertension.

If you have two physical findings like *ascites* and asterexis and two laboratory values like hypoalbuminaemia and prolonged prothrombin time are sufficient to make, one have sufficient evidence to make a diagnosis of cirrhosis. Parotid swelling, gynaecomastia and Dupuytren's contracture are more or less certain pointers towards alcoholic aetiology.

But nowadays with increasing awareness and excellent imaging modalities, the challenge is diagnosing and differentiate between various liver diseases early enough to prevent disease progression.

When confronted with a clinical scenario of a liver disease, be it incidental detection of abnormal liver tests, acute hepatitis or chronic hepatitis, one should differentiate between a predominantly hepatocellular disease or cholestatic disease or a mixed pattern on the basis of liver functions.

Hepatocellular

When hepatocytes are mainly affected, it results in hepatocellular jaundice and is characteristically but not always associated with predominant elevation of aminotransferases.

The next step is to decide if it is acute hepatitis, chronic hepatitis or acute or chronic liver disease. Some common causes of acute and chronic hepatitis are listed in **Table 5**.

Table 5: Common Causes of Hepatitis

Causes	Clinical Clues	Diagnostic Clues
Acute hepatitis		
Hepatitis A	Exposure to travel, etc	IgM, anti HAV
Hepatitis B	Injection sexual risk factors	HBsAg, IgM anti HBV
Hepatitis C	Injection sexual risk factors	Anti HCV, HCV, RNA
Ischaemic hepatitis	Vascular occlusion/low BP	Very high AST, ALT elevation with rapid decline, elevated LDH
Alcoholic hepatitis	History of alcohal abuse - associated large tender liver	AST: ALT > 2, AST < 400
Drug induced	History of drug intake/other corroborative evidence	None, improvement on withdrawal
Chronic hepatitis including cirrhosis		
Hepatitis B	Features of cirrhosis, non-specific	HBsAG, HBeAg, HBV DNA
Hepatitis C	Features of cirrhosis, non-specific	Anti HCV, HCV RNA
Alcoholic liver disease	Features of cirrhosis, non-specific	AST: ALT >2, AST <400
NAFLD/NASH	Obesity abdominal girth	Metabolic syndrome
Autoimmune hepatitis	Female gender, other auto-immune diseases	ANA, ASMA, LKM
Wilson's disease	KF ring in eyes, young age	Caeruloplasmin, urinary copper
Haemochromatosis	Diabetes, arthritis, family history	Iron studies, HFE genetic studies
Alpha-1 anti-trypsin	Young age	AAT levels and phenotype

Note: Liver biopsy desirable but not feasible at times, may not be required
Metabolic syndrome: Increased abdominal girth, elevated triglyceride, blood sugar, hypertension, low HDL (International Diabetic Federation 2007)
IgM = Immunoglobulin M; HAV = Hepatitis A virus; HBV = Hepatitis B virus; NAFLD = Non-alcoholic fatty liver disease; NASH = Non-alcoholic steatohepatitis; KF = Kayser-Fleischer; HCV = Hepatitis C virus; RNA = Ribonucleic acid; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; DNA = Deoxyribonucleic acid; ANA = Anti-nuclear antibodies; ASMA = Anti-smooth muscle antibody; LKM = Liver kidney microsome; HFE = Haemochromatosis gene; AAT = Alpha-1 Anti trypsin.

Cholestatic Liver Disease

When biliary tract is affected predominantly it results in cholestatic liver disease (pruritus, high coloured urine, markedly elevated alkaline phosphatase). The first step is to rule out extra-hepatic biliaty obstruction by stone or tumour by appropriate imaging modalities. The common causes of intra-hepatic cholestasis include primary biliary cirrhosis, primary sclerosing cholangitis and drug induced (**Table 6**).

Table 6: Common Causes of Cholestatic Liver Disorders

Causes	Clinical Clues	Diagnostic Clues
Primary biliary cirrhosis	Middle aged female, other autoimmune diseases	Antimitochondrial antibodies
Primary sclerosing cholangitis	Association with ulcerative colitis	Cholangiography
Drug induced	History of drug toxicity/abuse	None, improvement on withdrawal
Systemic infectious association	Symptoms of organ sepsis	Appropriate bacterial cultures

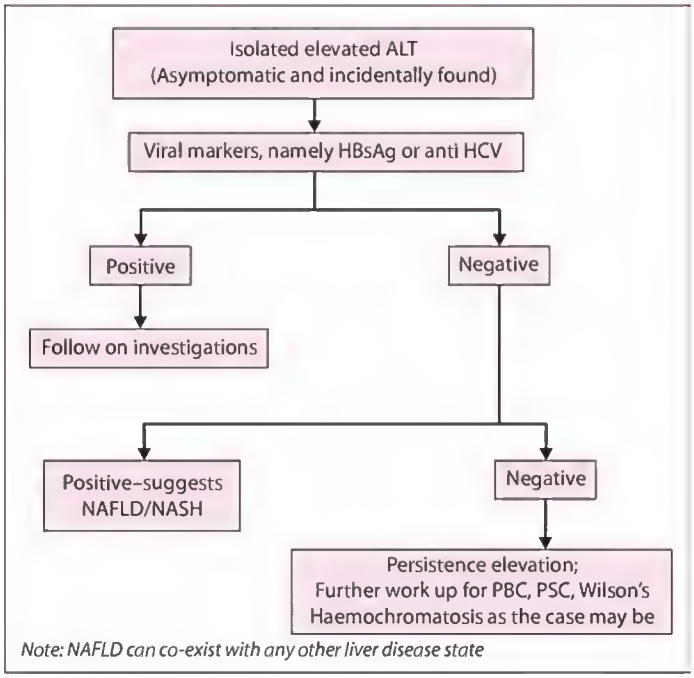


Figure 1: An approach to isolated elevation of ALP.

It is not always possible to differentiate haemolytic, extra-hepatic and intra-hepatic causes of jaundice despite making use of all biochemical and imaging investigations and liver biopsy may become mandatory. There could be a mixed situation like choledocholithiasis in a patient with cirrhosis, haemolysis due to G6PD deficiency with acute viral hepatitis, etc.

INCIDENTALLY FOUND ABNORMAL LIVER FUNCTIONS

Sometimes one could come across clinical situations like pre-anaesthetic, pre-employment, master health check etc with abnormal liver functions (isolated or mixed).

It has been found that atleast 6% to 25% of asymptomatic individuals have abnormal liver tests. Atleast one-third of such patients will have normal enzymes on subsequent testing.

On the other hand, prevalence of significant liver disease in general population is significantly low. The commonest abnormal biochemical liver functions are hyperbilirubinaemia, elevated ALT/AST and elevated alkaline phosphatase. The following algorithmic approaches are general guidelines that can be followed (**Figures 1, 2 & 3**).

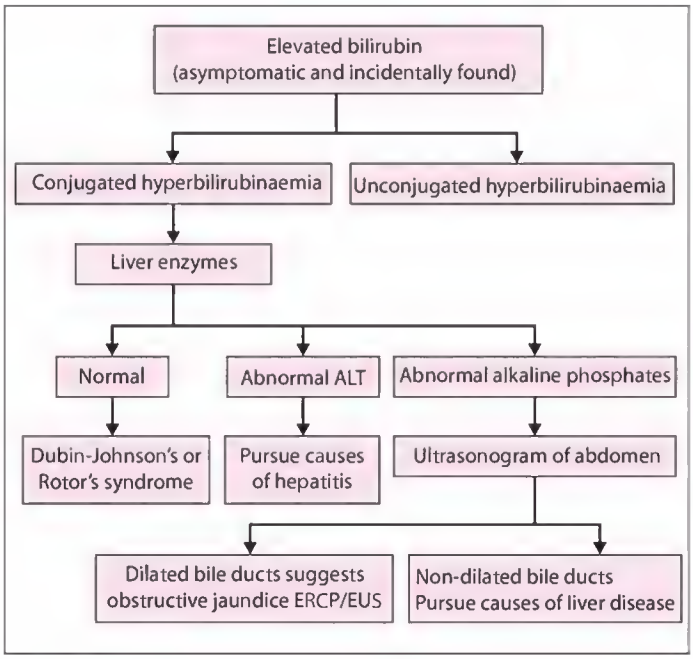


Figure 2: Approach to conjugated hyperbilirubinaemia.

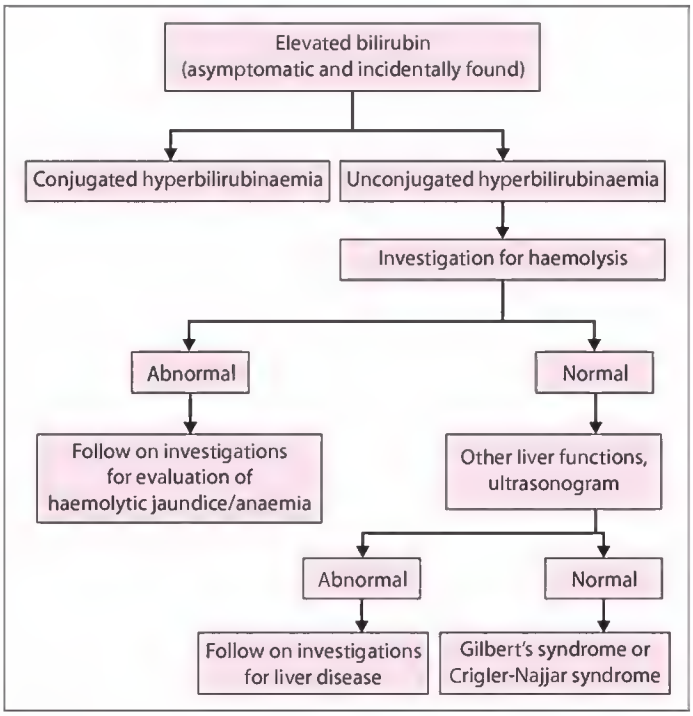


Figure 3: Approach to unconjugated hyperbilirubinaemia.

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14.3 Hepatobiliary Disorders—Investigations

Radha K Dhiman

INTRODUCTION

A number of investigations can be performed in patients with liver disorders. In this chapter, we will discuss liver function tests indicative of hepatocellular necrosis, cholestasis and biosynthetic functions and utility of liver biopsy.

BIOCHEMICAL MARKERS

Several biochemical tests are useful in the evaluation and management of patients with hepatic disorders. Accurate interpretation of these biochemical tests in the context of a carefully obtained history and thorough physical examination is crucial because non-specific aberrations in these tests can occur. Biochemical test abnormalities can have patterns that suggest predominantly hepatocellular or cholestatic liver injury or a mixed pattern. Therefore, it is best to use these tests as a battery, rather than rely on a single test.

Markers of Hepatocellular Necrosis

Aminotransferases

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are sensitive indicators of hepatocellular injury of diverse causes, such as viral hepatitis, liver ischaemia, or toxin or drug-induced injury. ALT is primarily found in liver and is confined to the cytoplasm, whereas AST is found in liver, myocardium, skeletal muscles, pancreas, kidney, brain and blood cells and is present in both cytoplasm and mitochondria.

Hepatocyte injury results in leakage of these enzymes into circulation. However, there is a poor correlation between the degree of liver cell injury and the serum levels of amino-transferases. Serum levels of aminotransferases can be in the normal range in patients with advanced fibrosis or cirrhosis. Various liver disorders are associated with typical ranges of AST and ALT. The highest ALT levels, usually more than 10,000 U/L, are found in patients with acute toxic injury as a result of acetaminophen overdose or acute ischaemic insult. ALT levels often rise to 1000 to 5000 U/L in patients with acute viral hepatitis. AST and ALT levels fall rapidl1y after an acute insult. Among patients with alcoholic hepatitis or biliary obstruction serum transferase levels are usually less than 300 U/L. However, during the acute phase of biliary obstruction, the AST or ALT levels may go up transiently to 1000 to 2000 U/L.

Clinical history should focus on prodromal illness for acute viral hepatitis, alcohol intake, intravenous drug abuse, hepatotoxic drug intake, family history of liver disease, etc. Further investigations should be based on suspected hepatic disorder (**Figure 1**).

Aspartate aminotransferase/alanine aminotransferase ratio

The relative levels of AST and ALT also provide some useful information. AST/ALT ratio of ≤1 indicates acute hepatocellular injury with an exception of alcoholic hepatitis. An AST/ALT ratio of ≥2:1 is suggestive and a ratio of ≥3:1 is highly suggestive of alcoholic liver disease (**Table 1**). A lower level of ALT than AST in patients with alcoholic liver disease is due to associated pyridoxine deficiency and poor nutritional status of these patients. Supplementation with pyridoxine in patients with alcoholic liver disease results in increased serum ALT levels and a reduction in AST/ALT ratio. An AST/ALT ratio of >1:0 is also seen in patients with cirrhosis due to any cause and in Wilson's disease.

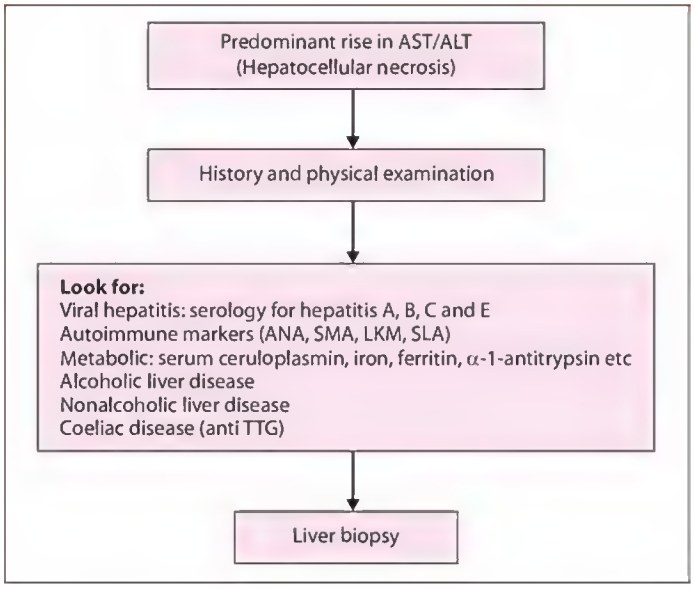


Figure 1: Algorithm for the management of hepatic disorder with raised transaminases.

AST = Aspartate aminotransferase; ALT = Alanine aminatransferase; ANA = Anti-nuclear antibody; SMA = Smooth muscle antibody; LKM = Liver kidney micrasamal antibody; SLA = Soluble liver antigen antibody, anti-TTG.

Table 1: Clinical Significance of AST/ALT Ratio

Clinical Status	AST/ALT	Remarks
No underlying liver disease	0.8	
Alcoholics without liver disease	<1.0	
Alcoholic liver disease	>2	ALT < 300 U/L
Non-alcoholic liver disease	>1	Indicates underlying cirrhosis (specificity 94% to 100%) and sensitivity 44% to 75%
NAFLD	<1	

AST = Aspartate aminatransferase; ALT = Alanine aminatransferase; NAFLD = Nan-alcahalic fatty liver disease.

Markers of Cholestasis

Alkaline phosphatase (ALP), 5'-nucleotidase and gamma glutamyl transpeptidase (GGT) are markers of cholestasis. ALP and 5'-nucleotidase are present near the canalicular membrane of the hepatocytes, whereas GGT is located in the endoplasmic reticulum and in the bile duct epithelium.

Alkaline phosphatase

ALP consists of several isoenzymes present in liver, bone, leucocytes, placenta, intestine, etc. ALP levels are physiologically elevated in children and adolescents during periods of rapid bone growth and in pregnant women, due to ALP of bone and placental origin, respectively. The ALP levels may rise after a fatty meal; hence, its determination should be done in the fasting state. If the origin of an elevated ALP level is in doubt, then serum 5′-nucleotidase and GGT should be measured; elevation of these enzymes suggests liver origin of ALP. **Figure 2** has shown an algorithmic approach for patients with isolated or predominantly elevation of ALP.

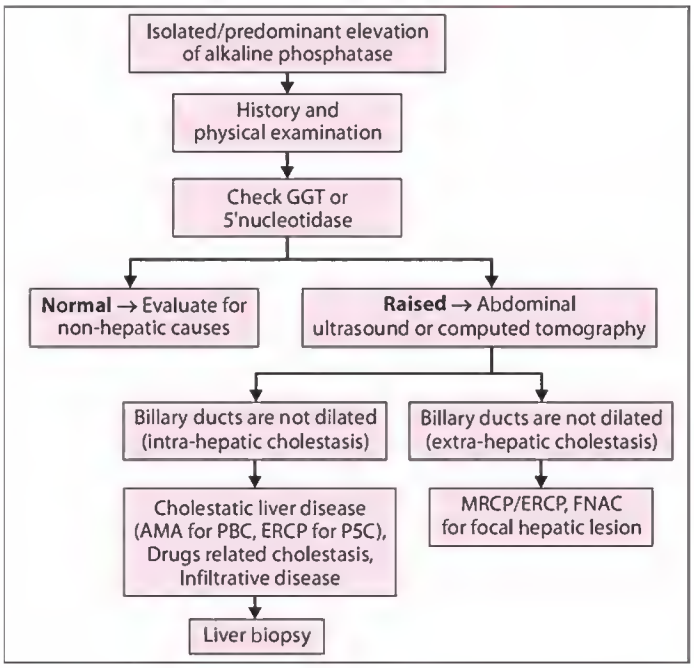


Figure 2: Algorithm for the management of isolated or predominant elevation of alkaline phosphatase.

GGT = Gommo-glutamyl tronspeptidose; AMA = Anti-mitochondrial antibody; PBC = Primory biliory cirrhosis; PSC = Primory sclerosing cholongitis; MRCP = Mognetic resononce cholongiopancreatogrophy; ERCP = Endoscopic retrogrode cholongioponcreotogrophy; FNAC = Fine needle aspirotion cytology.

Gamma glutamyl transpeptidase

GGT is a microsomal enzyme, which can be induced by stimulants, such as alcohol, phenytoin, phenobarbital, warfarin, etc. In addition to liver, GGT is also present in kidney, pancreas, spleen, heart, lung and brain. However, it is not present in the bone; this helps in distinguishing whether elevated ALP in a person is from a liver source or from a bone source.

Elevated GGT level has also been used as a marker of occult alcohol use. However, lack of specificity makes its use for this purpose unreliable.

5′-Nucleotidase

5′-nucleotidase is found in several tissues, which include liver, myocardium, brain, pancreas, etc. An elevated 5′-nucleotidase is commonly associated with liver disease. In biliary obstruction, the rise in serum 5′-nucleotidase may lag behind elevations in ALP and GGT.

Serum bilirubin

Bilirubin, a breakdown product of heme, is found in the blood in two forms: conjugated (direct) and unconjugated (indirect).

Unconjugated bilirubin is conjugated with glucuronic acid in hepatocytes by uridine diphosphate glucuronosyl (UDPG) transferase enzyme to increase its water solubility and is then rapidly transported into the bile. The rate-limiting step in bilirubin metabolism is not conjugation of bilirubin but its excretion from the hepatocytes (excretory capacity). Thus, liver disease is associated with elevated serum levels of conjugated bilirubin. However, this elevation does not appear until the liver has lost at least 50% of its excretory capacity. In healthy persons conjugated bilirubin is not detectable.

Serum bilirubin level is an indicator of prognosis in parenchymal liver diseases; the higher the level, the worse is the prognosis. However, familial defects in hepatic excretory function, such as Dubin-Johnson's and Rotor's syndromes, can result in isolated conjugated hyperbilirubinaemia without any abnormality in other routine laboratory tests.

Isolated unconjugated hyperbilirubinaemia results from either increased bilirubin production due to haemolysis, ineffective erythropoiesis or muscle injury, or from defects in hepatic uptake or conjugation (**Figure 3**). Careful history and physical examination may provide diagnostic clues to the presence of haemolysis, which can be confirmed further by specific diagnostic tests.

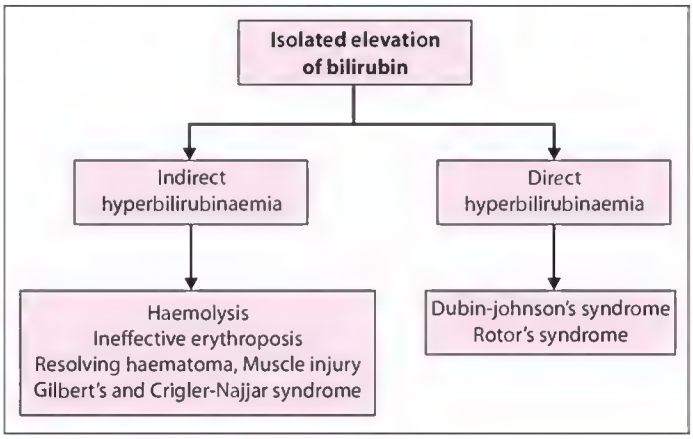


Figure 3: Algorithm for the management of isolated elevation of serum bilirubin.

Urinary bilirubin

Only conjugated bilirubin is filtered by the kidneys. Therefore, any bilirubin found in the urine is conjugated bilirubin and its presence implies presence of conjugated hyperbilirubinaemia and liver disease.

Markers of Biosynthetic Functions

Prothrombin time

All clotting factors, except factor VIII, are synthesized exclusively in the liver by hepatocytes. Prothrombin time collectively measures the activity of factors II, V, VI, IX and X. Prothrombin time does not become abnormal until more than 80% of liver synthetic capacity is lost. Therefore, prothrombin time prolongation may be considered as a sign of advanced liver dysfunction. Factor VII is sensitive to rapid changes in liver synthetic function because it has a short half-life of 6 hours. Hence, it is a useful marker of recovery from acute liver failure.

Biosynthesis of factors II, V, IX and X depends on vitamin K. Consequently, vitamin K deficiency can result in prolongation

of prothrombin time; however, this abnormality is corrected by vitamin K injections. Marked prolongation of prothrombin time, not corrected by vitamin K, indicates hepatocellular disease.

Albumin

Serum albumin is synthesised exclusively in the liver. It has a long half-life of about 3 weeks, making it a poor indicator of acute/mild liver dysfunction. Low serum level of albumin is more common in chronic liver disease, such as cirrhosis, and usually indicates advanced disease.

QUANTITATIVE ASSESSMENT OF HEPATIC FUNCTION

Quantitative liver function tests are helpful for determining the severity of liver disease, long-term prognosis, disease progression, surgical risk and in monitoring treatment. The most frequently used tools are: galactose elimination capacity to assess hepatocyte cytosol activity; indocyanine green clearance (ICG) to assess excretory function; monoethylglycinexylidide (MEGX) test and; aminopyrine breath-test to estimate microsomal activity. The role of these tests for routine use in clinical practice, however, remains undefined.

USE OF LIVER FUNCTION TESTS FOR THE ASSESSMENT OF PROGNOSIS

Serum bilirubin level and markers of hepatic biosynthetic functions, such as albumin and prothrombin time, are useful for predicting prognosis in liver disorders. Child-Turcotte-Pugh (CTP) scoring system includes all these three parameters along with two clinical parameters (presence or absence of ascites and hepatic encephalopathy) and conveys information about overall liver function and prognosis (**Table 2**).

Table 2: Clinical Staging of Cirrhosis by Child-Turcotte-Pugh Classification

Factor	Points		
	1	2	3
Bilirubin	<2.0 mg/dL	2.0 to 3.0 mg/dL	>3.0 mg/dL
Albumin	>3.5 g/dL	3.0 to 3.5 g/dL	<3.0 g/dL
Prolongation of prothrombin time	0 to 4 sec	4 to 6 sec	>6 sec
International Normalised Ratio	<1.71	1.71 to 2.20	>2.20
Ascites	Absent	Easily controlled	Poorly controlled
Encephalopathy	Absent	Minimal	Advanced coma

CTP score can range from 5 to 15. Based on this score, patients can be classified into CTP A (score 5 to 6), B (score 7 to 9), or C (score 10 to 15). A score of more than 7 indicates decompensation, and is used as a criterion for listing the patient for liver transplantation.

The model for end-stage liver disease (MELD) is a survival model based on a composite of three laboratory variables: serum creatinine, serum bilirubin, and International Normalised Ratio (INR) for prothrombin time. MELD is better than the CTP score in stratifying patients according to mortality, and has replaced the latter to prioritise allocation of cadaveric livers for transplantation in many countries. It can be calculated using an online calculator http://www.mayoclinic.org/meld/mayomodel7.html. Severity of alcoholic hepatitis is calculated using "Maddrey discriminant function". It is calculated with the following formula.

Maddrey discriminant function = 4.6(prothrombin time prolongation) + (serum bilirubin in mg/dL)*

A value above 32 signifies severe alcoholic hepatitis.

LIVER BIOPSY

Liver biopsy is the ultimate and most specific investigation for assessing the nature and severity of the liver disease. It is a safe procedure and can be done through percutaneous, laparoscopic and transjugular approaches.

Liver biopsy is indicated in the following situations: grading and staging of liver diseases, unexplained hepatomegaly, hepatocellular disease of unknown aetiology including infiltrative hepatic disorders, unexplained splenomegaly, pyrexia of unknown origin, hepatic malignancies, autoimmune and cholestatic liver disease, and to assess the effectiveness of treatment for liver disease.

Grading refers to an assessment of the severity or activity of liver disease (inflammation, liver cell necrosis) such as mild, moderate or severe. Staging refers to an assessment of the disease as early or advanced in terms of fibrosis score (e.g. Ishak scoring system).

Percutaneous liver biopsy should not be performed in an uncooperative patient, patients with prothrombin time more than 3 seconds over control or International Normalised Ratio (INR) $\geq$1.5, patients with platelet counts less than 80,000/mm^3 and inability to tackle complication as a result of the procedure.

Liver biopsy carries a small but definite risk of mortality and complications, with rates of approximately 0.01% and 0.1 to 0.3%, respectively. The common complications include pain arising from pleura, peritoneum or diaphragm, intra-peritoneal haemorrhage, intra-hepatic haematoma, haemobilia, bile peritonitis, infection, etc. These complications can be managed using intravenous analgesics, blood transfusions, and radiological or endoscopic interventions. Surgical intervention is rarely required.

Transjugular liver biopsy is used in patients with abnormal coagulation, massive ascites or small liver, or those who need measurement of hepatic venous pressures. It does not carry the risk of bleeding complications, but is costly and needs a trained operator.

IMAGING STUDIES

These are discussed in chapter on "Hepatobiliary Disorders—Imaging".

HAEMODYNAMIC STUDIES

A balloon catheter is introduced into the hepatic vein via the femoral or internal jugular veins. Pressure measurements are taken in the hepatic veins by inflating [wedged hepatic venous pressure (WHVP)] and deflating [free hepatic venous pressure (FHVP)] the balloon catheter. The hepatic venous pressure gradient (HVPG) represents the difference between the WHVP and the FHVP, and is a measure of portal hypertension.

The normal value for HVPG is less than 5 mm Hg. The HVPG value more than 5 mm Hg signifies "portal hypertension" and more than 10 mm Hg signifies "clinically significant portal hypertension". Increase in value above 10 mm Hg is required for the development of oesophageal varices and above 12 mm Hg for the appearance of other complications, such as variceal bleeding. Decline of HVPG below 12 mm Hg or through more than 20% of the baseline level is associated with prevention of variceal bleeding, and at times with a reduction in size and possibly disappearance of varices. The achievement of these haemodynamic targets also lowers the risk of developing ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome and death.

RECOMMENDED READING

1. Boyer TD, Wright TL, Manns MP, editors: *Zakim and Boyer's Hepatology: A Textbook of Liver Disease*; 5th Ed. Philadelphia: Saunders; 2006.

14.4 Hepatobiliary Disorders—Imaging

Shrinivas B Desai

Imaging plays a crucial role in the management of hepatobiliary diseases. This topic can be divided into imaging in liver diseases and imaging of the biliary system.

IMAGING IN LIVER DISEASES

Techniques for studying the liver include plain radiograph, ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), angiography and radionuclide scanning.

Abdominal Radiograph

The liver casts an appreciable soft tissue density shadow, with its borders outlined against fat and gas in adjacent organs. Hepatomegaly can be made out on plain radiographs of the abdomen by noting the displacement of gas in the adjacent gas-filled organs. Riedel's lobe, a normal variant seen commonly in women, is an inferior tongue-like projection of the right lobe. Focal hepatic lesions may distort one or more hepatic margins or may be seen as diffuse hepatomegaly on the plain radiograph.

Calcification within the liver may be localised or diffuse. Hydatid disease is the commonest cause. Other causes include old abscess or granuloma (single or multiple foci), hepatocellular carcinoma (stippled or sunburst type) and metastasis from mucous secreting adenocarcinoma and medullary carcinoma of the thyroid gland (faint fluffy calcification).

Gas is normally not seen in the liver. It may be seen confined to the parenchyma (e.g. abscess), within the biliary tree (e.g. after bilioenteric anastomosis or endoscopic papillotomy) or within the portal vein radicals (e.g. necrotising enterocolitis). Distribution of air helps in differentiation between air in the biliary tree (centrally located) and that in the portal veins (more peripherally distributed).

FOCAL HEPATIC LESIONS

Simple Liver Cyst

A liver cyst is a fluid-filled space with an epithelial lining. On sonography, liver cysts appear as anechoic, thin-walled lesions with posterior acoustic enhancement. On CT, they appear as well-defined, non-enhancing and thin walled cystic lesions. On MRI, they are hypointense on T1 WI images and hyperintense on T2 WI images.

Haemangioma

It is the most common benign tumour of the liver. On sonography, these appear as well-defined homogenously hyperechoic lesions (**Figure 1**). On non-enhanced CT (NECT) (**Figure 2**), they are seen as hypodense well defined mass lesions. Following contrast administration, there is filling in of the contrast from the periphery. On MRI, haemangiomas show a characteristic very long T2 relaxation time and therefore appear hyperintense on T2 WI images. On labelled RC SPECT scans, they appear as filling defects on early scans with prolonged and persistent radiotracer uptake on delayed scans.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is a developmental hyperplastic lesion comprising of hepatocytes, Kupffer cells, biliary ducts and components of portal triads. It appears as a well-defined mass

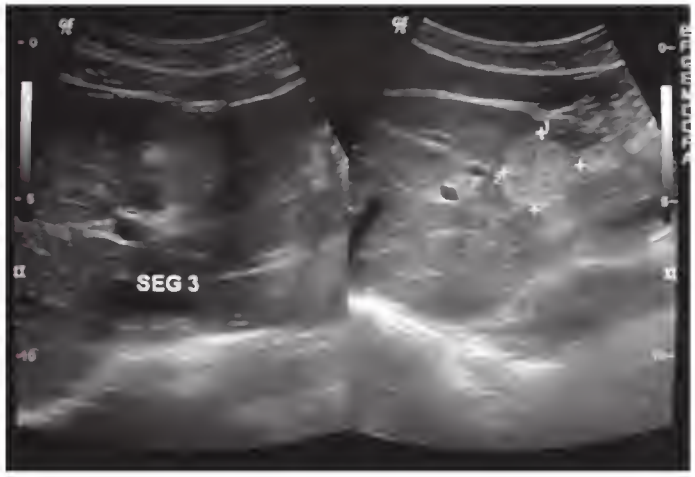
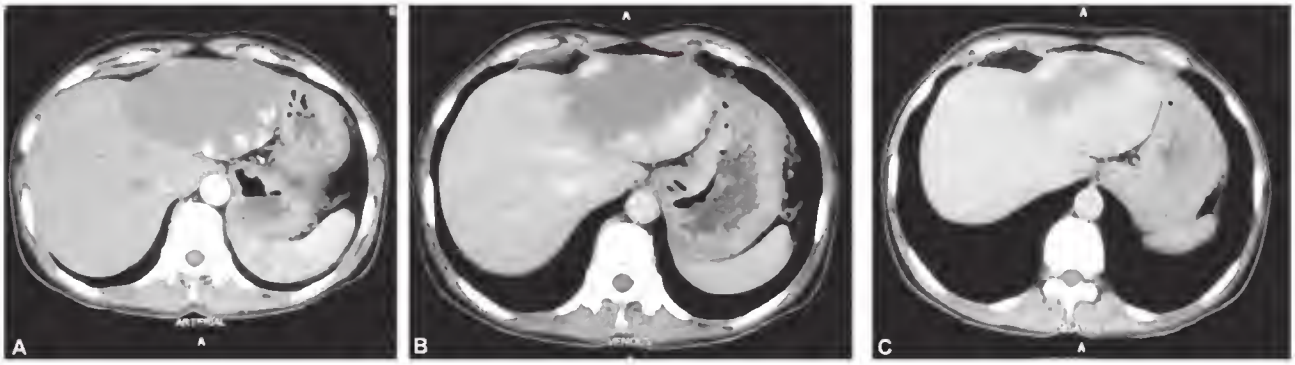


Figure 1: Ultrasound showing a hyperechoic lesion in segment 3 of left lobe of liver. Diagnosis: Haemangioma.
Courtesy: Dr Raju Sharma, AIIMS.



Figures 2A to C: Triple phase CT of the abdomen. Arterial phase (A) shows peripheral nodular discontinous enhancement with progressive centripetal extension on venous (B) and delayed (C) phase. Retention of contrast in the lesion is seen on the delayed image (C). Diagnosis: Liver haemangioma.
Courtesy: Dr Raju Sharma, AIIMS.

lesion with a central stellate scar that is isoechoic with the liver parenchyma on USG. The central scar appears hyperechoic with significant vascularity on Doppler imaging. On NECT, these lesions are iso- to hypodense to the liver parenchyma with a hypoattenuating central scar. Being highly vascular, these lesions show marked enhancement on arterial phase of contrast-enhanced CT (CECT) with rapid washout of the contrast, whereas the scar shows persistent enhancement. On T1 WI images, FNH appears iso- to slightly hypointense and turns iso- to slightly hyperintense on T2 WI images. The central scar is typically hypointense on T1 and hyperintense on T2 WI images. On administration of gadolinium contrast agents, the enhancement pattern is similar to that seen on CECT. On sulphur colloid scan, 50% of these lesions take up sulphur similar to adjacent normal liver and 10% appear as hot spots.

Hepatocellular Adenoma

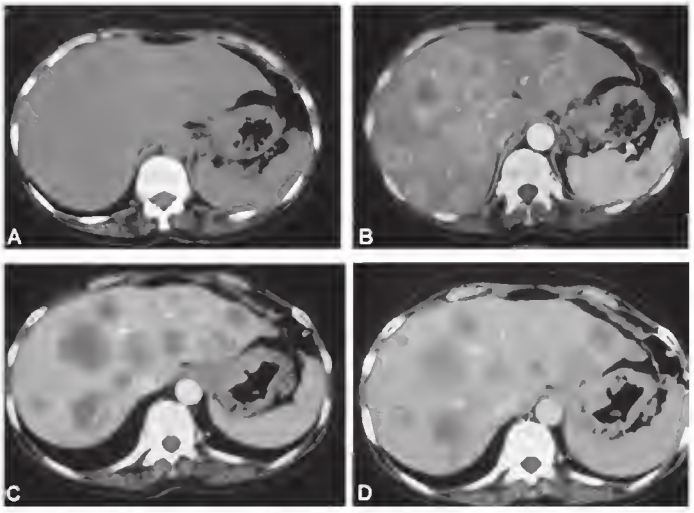
It is a benign neoplasm that contains hepatocytes with dilated sinusoids but lacks bile duct components. The lesions are very heterogeneous on imaging due to the presence of fat, old or fresh blood and necrosis. Majority of adenomas are hyperintense to surrounding liver parenchyma on T1 WI images, and iso- to hyperintense on T2 WI images. They show marked contrast enhancement and are seen as cold spots on sulphur colloid scans.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a common malignant tumour. It can be solitary, multifocal or a diffusely infiltrating tumour. The sonographic features of HCC are very variable. It can be hypoechoic, echogenic or complex. In smaller tumours, there is seen a hypoechoic halo corresponding to fibrous capsule. Portal vein thrombosis is a frequent feature. The CT appearance is also variable. Most HCC are hypodense to the liver parenchyma on NECT, show enhancement on arterial phase and become iso- to hypodense on portal venous phase. As they are vascular tumours supplied by the hepatic artery, hypertrophy of the hepatic artery may be noted. Calcification is seen in 5% to 10% of HCC. Portal and hepatic vein thrombosis and arterioportal shunting may also be seen. On MRI, they are seen to be iso-, hypo- or hyperintense to the liver parenchyma on T1 WI images, and usually hyperintense on T2 WI images. They are heterogeneous with intratumoural septations. Fibrolamellar HCC is a histological subtype that shows no gender predilection and occurs in a younger age group. It arises commonly in non-cirrhotic livers. It is a vascular mass with a central scar, which is often calcified. On MRI, it is hypointense on T1 and hyperintense on T2 WI images, whereas the central scar remains hypointense on both sequences and shows no contrast enhancement.

Metastatic Tumours

They are usually multiple and hypoechoic on USG. Hyperechoic lesions are seen with GIT and urogenital tumours. Occasionally, metastatic disease may be seen as target lesions. They are typically hypodense to the liver parenchyma on NECT and show peripheral rim enhancement on arterial phase in CECT (**Figure 3**). Hypervascular metastases may become isodense to liver on portal venous phase and may be visualised on arterial phase as hyperdense lesions. Therefore, it is necessary to do dual phase imaging of the liver when looking for metastatic disease. On MRI, they are usually hypointense on T1 and hyperintense on T2 WI images and show an enhancement pattern similar to CT.



Figures 3A to D: Triple phase CT of the abdomen. Non-contrast CT (A) shows no lesion. Arterial phase (B) shows multiple hypodense lesions with thick rim enhancement. Portal venous phase (C) and delayed phase (D) shows washout from these lesions. Diagnosis: Liver metastases.
Courtesy: Dr Raju Sharma, AIIMS.

Liver Abscess

Liver abscesses may be pyogenic, amoebic (**Figure 4**) or fungal in nature. They are seen as hypoechoic lesions. As liquefaction sets in, the abscesses become more echo poor. Fungal abscesses show a hyperechoic central punctum, which represents an artery plugged by the fungus. On CT and MRI, they are seen as necrotic lesions with thick enhancing capsule.

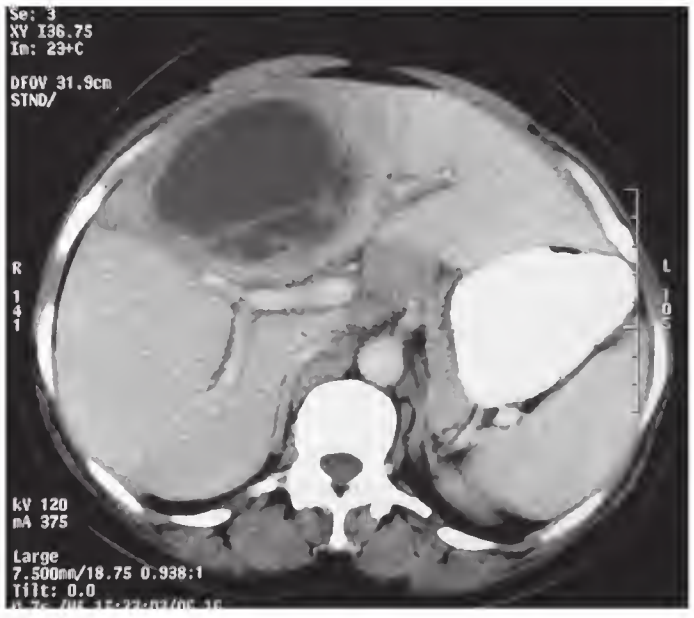


Figure 4: CT scan shows a hypodense lesion in segment IV of liver with thick peripheral enhancement and oedema in adjacent liver. Diagnosis: Amoebic liver abscess.
Courtesy: Dr Raju Sharma, AIIMS.

Hydatid Disease

Liver presents as a hypodense mass with multiple daughter cysts (water lily sign) (**Figures 5 to 7**). Hydatid cysts can rupture into the peritoneal cavity, biliary tree or pleural cavity with resultant pleural effusion. Calcification can be noted in longstanding hydatid cysts.

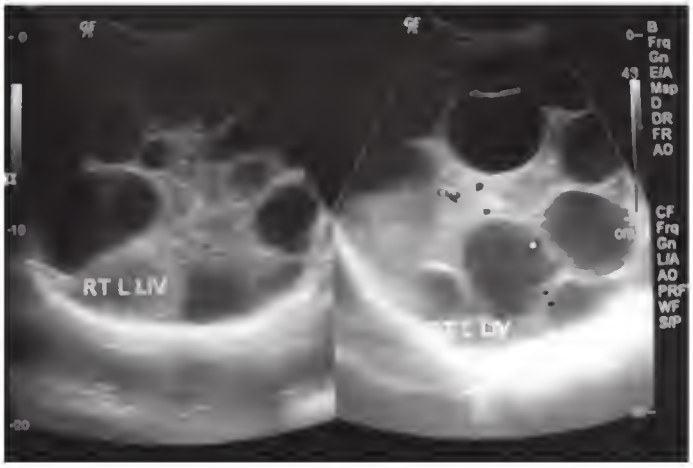


Figure 5: Ultrasound shows a multiloculated mass with daughter cysts in the periphery. Diagnosis: Hydatid cyst.
Courtesy: Dr Raju Sharma, AIIMS.



Figure 6: Hydatid cyst: CT scan shows a multilocular lesion in the left lobe of the liver. Density of daughter cysts is less than the centre of the lesion.
Courtesy: Dr Raju Sharma, AIIMS.

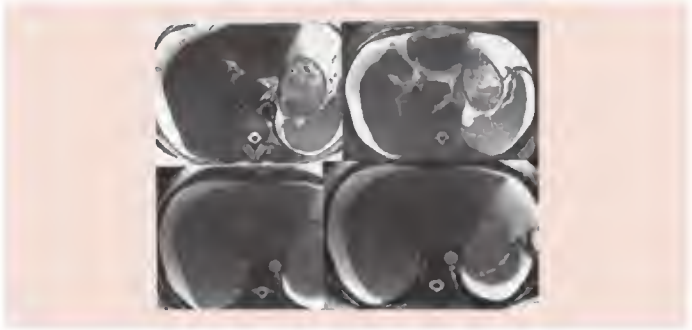


Figure 7: Hydatid cyst: Ultrasound reveals a right lobe cyst with multiple daughter cysts, pre and post aspiration.

DIFFUSE DISEASE OF THE LIVER

Fatty Liver

On USG, this is seen as diffuse increase in the echogenicity of the liver with poor visualisation of intrahepatic vessels and diaphragm. On CT (**Figure 8**), it is seen as a generalised low attenuation of the liver. MRI can confirm the diagnosis by utilising chemical shift imaging. On opposed phase images, areas of fat deposition show signal drop-out. In focal fatty deposition, focal deposits of fat stand out against the background of normal liver parenchyma; the reverse occurs in focal fatty sparing. None of above the imaging methods can differentiate simple fatty liver from those with steatohepatitis and fibrosis.

Ultrasound elastography (Fibroscan) is a new non-invasive method for assessment for hepatic fibrosis. It uses a modified



Figure 8: CECT scan shows liver is markedly hypodense as compared to the spleen suggestive of diffuse fatty change.
Courtesy: Dr Raju Sharma, AIIMS.

ultrasound probe to measure the velocity of a shear wave created by a vibratory source. Estimates of stiffness (fibrosis) of the liver by ultrasound correlate with fibrosis stage, and values above 12.5 kPa are indicative of cirrhosis. This technique is used in fatty liver/chronic hepatitis for separating patients with minimal or no fibrosis from those with significant fibrosis or cirrhosis. A linear correlation with increasing fibrosis has not been demonstrated, and 15% discordance between elastography scores and histologic fibrosis has been observed.

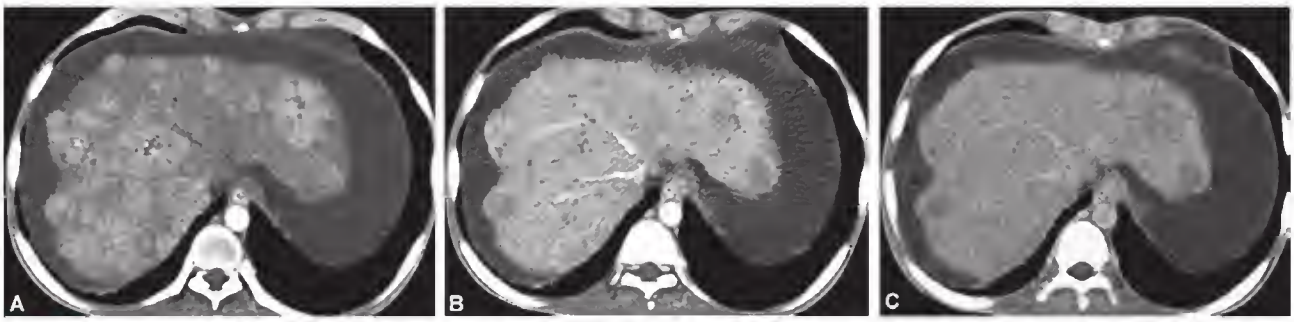
Cirrhosis

Sonographic features of cirrhosis include coarse echogenic echotexture, nodular surface and regenerating nodules surrounded by fibrous septae. The nodules are seen as iso- to hypoechoic lesions with echogenic borders corresponding to fibrous septae. There may be features of complication of cirrhosis in the form of portal hypertension or HCC. The caudate lobe to right lobe liver ratio of >0.65 is highly specific for cirrhosis.

CT and MRI show similar features (**Figure 9**). Regenerating nodules appear iso- to hyperdense to liver on NECT. Better appreciated on MRI, they are seen as hyperintense lesions on T1 and hypointense lesions on T2 WI sequences, and show an enhancement pattern similar to the rest of the liver. These features help in differentiating metastases and hepatomas from regenerating nodules. Of the various imaging techniques, MRI is the most sensitive and specific for this differentiation.

Viral Hepatitis

Imaging has little role in the diagnosis of viral hepatitis, and may reveal hepatomegaly, diffuse fatty change, periportal oedema and gall bladder (GB) wall thickening in the acute phase.



Figures 9A to C: Triple phase CT abdomen. Arterial phase (A) shows multiple lesions showing homogeneous arterial enhancement with washout in venous phase; (B) with suggestion of a peripheral capsule around some lesions.; (C) Background changes of cirrhosis in the form of nodular liver and ascites are noted. Diagnosis: Multifocal HCC in cirrhotic liver.

Courtesy: Dr Raju Sharma, AIIMS.

VASCULAR DISORDERS

Portal Hypertension

Ultrasonography may show features of underlying liver disease, collaterals, splenomegaly and ascites. Colour Doppler imaging is a non-invasive modality for studying portal haemodynamics (**Figure 10**). A portal vein diameter of >13 mm is characteristic of portal hypertension. Portal venous velocity is reduced in portal hypertension. Colour Doppler imaging can demonstrate the direction of flow in the portal vein. When paraumbilical vein is the major decompressive collateral, the flow in portal vein is hepatopetal. When other collateral channels open up, if the resistance to portal venous flow exceeds that in the collateral bed, the flow in portal vein becomes hepatofugal.

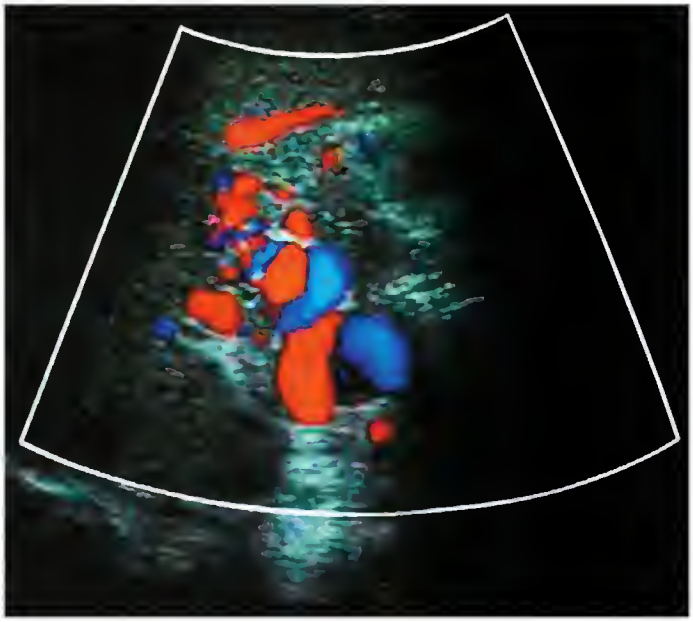


Figure 10: Colour Doppler in portal hypertension: Multiple tortuous serpiginous periportal collateral channels.

Portal vein thrombosis can be well evaluated by sonography. A portal cavernoma comprises multiple tubular structures in the porta hepatis. A pulsed Doppler spectral waveform of portal flow from multiple tubular channels at the porta is highly diagnostic of a portal cavernoma. In portal hypertension, variability of calibre of the splenic and superior mesenteric veins with respiration is lost.

Colour Doppler imaging can also be used to assess surgical porto-system shunts for patency. CT with angiography and portovenography can show the collateral circulation, and the presence of underlying cirrhosis, splenomegaly and ascites. It can also effectively monitor for development of hepatoma in the cirrhotic liver. The currently available 3D CT techniques can provide excellent three-dimensional images of the portal venous system with the entire collateral circulation, and have replaced splenoportograms (**Figure 11**).



Figure 11: Contrast-enhanced computed tomography in a patient with portal hypertension: Multiple tortuous serpiginous splenic hilar, lienorenal gastric bed and paraoesophageal collateral channels.

Budd-Chiari Syndrome

Obstruction to the hepatic venous outflow either due to hepatic veno-occlusive disease or due to IVC obstruction can be well evaluated by colour Doppler, CT, MRI and inferior venacavogram. The flow on Doppler imaging in IVC and hepatic veins changes from the normal phasic flow to absent, reversed, turbulent or continuous flow. In long standing disease, changes of cirrhosis and porta hypertension may set in. In the acute stage, NECT shows a large liver with generalised hypoattenuation, due to congestion and ascites. CECT shows patchy parenchymal enhancement and thrombosis of the IVC or the hepatic veins. In chronic stages, caudate lobe hypertrophy and dilated azygous and hemiazygous veins can be seen. MRI is very sensitive in Budd-Chiari syndrome and shows hepatomegaly, reduction in calibre or non-visualisation of hepatic veins, IVC thrombosis and generalised increase in signal intensity on T2 WI images due to congestion in the acute stage. Once the disease becomes chronic, the hepatic signal is low on both T1 and T2 WI images. Caudate lobe hypertrophy, dilated azygous and hemiazygous venous systems, and comma-shaped foci of signal void representing intrahepatic collaterals are seen.

IMAGING OF THE BILIARY SYSTEM

The various imaging modalities available today for studying the biliary system include plain radiographs, USG (trans-abdominal and endoscopic), endoscopic retrograde cholangiopancreaticography (ERCP), CT, MRI, MR cholangiopancreaticography (MRCP) (**Figure 12**), percutaneous transhepatic cholangiography (PTC), T-tube cholangiograms and radionuclide imaging.

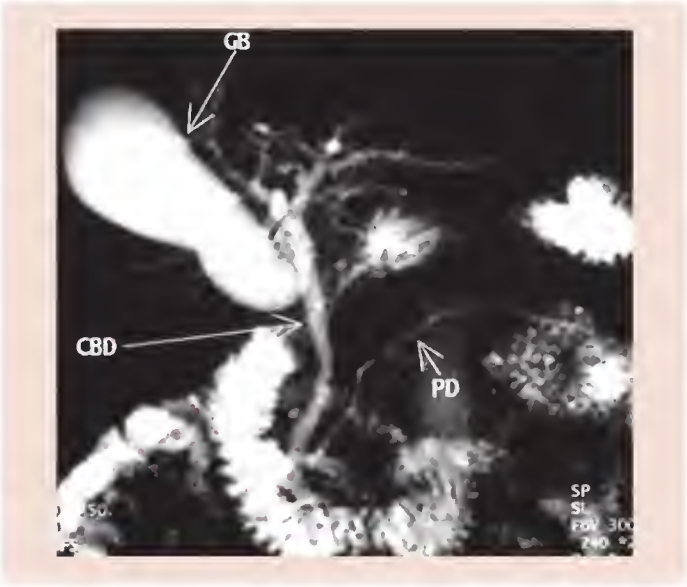


Figure 12: MRCP: Rare sequence delineating normal pancreatico-biliary tree.

Oral and IV cholangiography are of historical interest today, and CT cholangiography is hardly used in India.

Plain Radiographs

Gall stones

Approximately 20% to 30% of gallstones are radio-opaque and are seen on plain radiographs. A characteristic feature is the presence of central stellate fissure that contains gas (Mercedes Benz sign).

Limey bile

On horizontal ray projections, a horizontal level representing layered high-density bile, that contains a mixture of calcium carbonate and calcium phosphate, is seen.

Porcelain gall bladder

The GB wall shows calcification, as a result of chronic inflammation.

Emphysematous cholecystitis

Seen particularly in diabetics and following hepatic artery embolisation, this condition is a severe form of cholecystitis with gas-forming organisms. On plain radiographs, air is identified within the GB wall.

Air within the biliary tree

This will be seen as a centrally-located branching pattern of air confined to the biliary tree. The causes include bilio-enteric fistulae caused by gallstones, perforated peptic ulcer, and malignant diseases. It may also occur following biliary surgery or ERCP, and in elderly persons with physiological laxity of the biliary sphincter (old age).

Ultrasonography (USG)

The free availability, low cost, lack of ionising radiation and high sensitivity and specificity in detecting biliary diseases make USG a favoured imaging modality. The biliary system can be visualised by subcostal scanning. The normal GB is well distended after a fast of 8 to 12 hours and its wall should not be >3 mm in thickness. The GB should be scanned in two planes and in two patient positions so as not to miss any disease. The intrahepatic biliary ducts are seen as tubular structures accompanying the portal vein. Normally, they are 2 mm or less in diameter. The entire extrahepatic biliary tree can be well visualised on sonography. The normal mean duct diameter of common bile duct (CBD) is 4 mm at age 40, 5 mm at age 50, 6 mm at age 60 years, and so on.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

It involves cannulation of the major minor duodenal papilla under endoscopic visualisation and injection of iodinated contrast medium into the bile duct and pancreatic duct under fluoroscopic monitoring. Spot films in multiple projections are obtained. ERCP has the advantage of allowing collection of brushings and biopsy for cytological and histopathological examination, respectively, as also therapeutic procedures such as biliary stenting, balloon dilatation of strictures and extraction of stones.

CT and MRI

These are non-invasive and highly sensitive methods of determining the level and nature of biliary obstruction, and the extent of the disease process. They also play a useful role in postoperative evaluation. The normal GB is seen on CT as an oval structure located along the inferior surface of the liver, with a density (0 to 20 HU) similar to that of water. On MRI, it is seen as a bile-filled structure, bile in a non-fasting patient is hypointense on T1WI and hyperintense on T2WI images as compared to liver parenchyma. In fasting patents, bile gets concentrated and appears hyperintense to liver on both T1WI and T2WI sequences.

Magnetic Resonance Cholangiopancreatography

This is a non-invasive technique for visualisation of the biliary tree and pancreatic ducts which is based on heavily T2WI sequences. It does not require the use of any contrast medium. Magnetic resonance cholangiopancreatography (MRCP) has 95% accuracy in differentiating normal from dilated ducts, 100% accuracy in determining the level of biliary obstruction and 96.4% accuracy in determining the cause of obstruction.

Percutaneous Transhepatic Cholangiography

Percutaneous transhepatic cholangiography (PTC) is an interventional technique in which the biliary tree is punctured percutaneously using a Chiba needle under fluoroscopic guidance. After ensuring a secure access to the biliary system, iodinated contrast medium is injected and spot films of the opacified biliary stem are taken. It also permits therapeutic procedures like drainage of the obstructed biliary system and stenting of strictures.

Biliary Scintigraphy

99mTc-labelled N-substituted iminoacetic acid compounds (99mTc-HIDA) are used for imaging the hepatobiliary tree. After a

2 hour fast, 3 to 10 mCi of 99mTc-HIDA is administered intravenously and sequential images obtained with a gamma camera at 1-minute intervals over the first 1 hour and then at longer intervals over 24 hours. Functional and morphological information about the hepatic parenchyma is obtained over the first 10 minutes and about of the extrahepatic biliary tree over the next 10 minutes; normally, the dye reaches the bowel by 1 hour.

Biliary Disorders

Biliary atresia

Features on sonography include non-visualisation of the GB or a hypoplastic thick GB, non-visualisation of the common hepatic duct and presence of intra- or extra-hepatic cysts.

Choledochal cyst

Choledochal cyst, or cystic dilatation of extrahepatic bile ducts, is seen on CT as a hypodense (0-20 HU i.e. water density) lesion, which does not enhance on contrast administration. The lesion runs along the course of the CBD, and a separate CBD is not seen. On MRI, it appears as a fluid intensity lesion, which is hypointense on T1 WI images and markedly hyperintense on T2 WI images.

In patients without cholangitis, calculi or history of previous surgery, presence of contrast enhancement, or focal or diffuse thickening of the cyst wall should arouse a suspicion of carcinoma. In a large majority of cases, a long common channel with the pancreatic duct is seen which supports the hypothesis of reflux of pancreatic juice into the CBD as a causative factor in the development of choledochal cyst.

Based on the cholangiographic features, choledochal cysts are divided into five types (Todani classification; **Table 1**). Knowledge of the type of choledochal cyst (**Figure 13**) aids in planning surgery.



Figure 13: MRI of choledochal cyst: fusiform dilatation of the common hepatic duct and the common bile duct.

Table 1: Todani's Classification of Choledochal Cysts, based on Cholangiographic Features

Type 1a	–	Cystic dilatation of the CBD
Type 1b	–	Focal segmental dilatation of distal CBD
Type 1c	–	Fusiform dilatation of both CHD and CBD
Type 2	–	True diverticulum arising from the CBD
Type 3	–	Choledochocoele of the intraduodenal portion of CBD
Type 4a	–	Intra- and extrahepatic cysts
Type 4b	–	Extrahepatic cysts
Type 5	–	Intrahepatic bile duct cysts

Gall stones

USG is very sensitive in detecting gallstone disease. On sonography, the typical feature is that of a mobile highly reflective echo with posterior acoustic shadowing. CT is less sensitive than USG for this purpose, but is better for detecting calcified gallstones. On MRCP, gallstones produce no signal, and therefore, appear as inclusion defects against the background of bright bile; it is very sensitive in detecting gallstones in the lower CBD (**Figure 14**). Endoscopic USG also permits good evaluation of the lower CBD, which may be obscured by bowel gas or obesity on a transabdominal USG.



Figure 14: MRCP showing gall bladder calculi.

Cholecystitis

USG features of acute cholecystitis include presence of gallstones, oedema of the GB wall (wall thickness > 3 mm with a hypoechoic rim around it), calcific inclusion defect in the GB, probe tenderness over the GB, pericholecystic fluid collection, GB enlargement and gas in the GB wall (emphysematous cholecystitis). In chronic cholecystitis, the GB is contracted and has a thickened wall which may get calcified (porcelain GB). HIDA scan may show obstruction of the cystic duct. CT is more sensitive in picking up features of acute cholecystitis, which include pericholecystic fluid, GB wall thickening, GB enlargement, GB or CBD calculi, pericholecystic abscess, and gas within GB wall. It also helps to exclude other diseases that mimic cholecystitis.

GB carcinoma

CT and MRI usually show a soft tissue mass within the GB or in the GB fossa with direct extension into the adjacent liver. Lymphadenopathy may be present. Occasionally, there may only be focal or diffuse thickening of the GB wall (**Figure 15**). These tumours are usually hypodense and show heterogeneous enhancement. On T1 WI images they appear hypointense and hyperintense on T2 WI sequences. Fat-suppressed gadolinium-enhanced images are the best for detecting local invasion.

Bile duct tumour

They are usually adenocarcinomas of the scirrhous or papillary type. On imaging, there is proximal biliary dilatation with an abrupt cut-off due to a soft tissue mass that may occasionally be entirely intraluminal or may be apparent only as thickening of the bile duct wall. On non-enhanced CT, these tumours are frequently isodense to the liver and show minimal enhancement. On MRI, they are usually low signal on T1 WI and bright on T2 WI sequences. Fat-suppressed, gadolinium-enhanced images are the best for detection of periductal extent of the tumour.

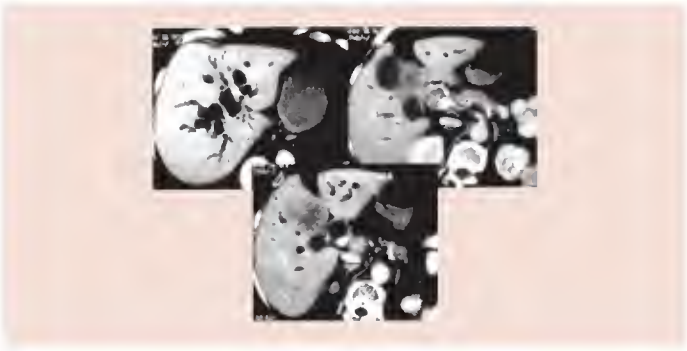


Figure 15: Carcinoma of gall bladder: Enhancing mass arising from GB wall with infiltration of porta hepatis and segment 4B of liver with resultant marked intrahepatic biliary radical dilatation.

Primary sclerosing cholangitis

In this condition, bile ducts have multiple strictures with focal areas of ductal dilatation leading to a beaded appearance on cholangiography (**Figure 16**). There may also be evidence of cirrhosis or portal hypertension. It predisposes to malignancy and there is an association with ulcerative colitis, retroperitoneal and mediastinal fibrosis, Riedel's thyroiditis and orbital pseudotumour.

Biliary parasitic infestations

Parasites that commonly infest the biliary tree include *Clonorchis sinensis*, *Ascaris lumbricoides* and *Echinococcus granulosus*. The infestation may be asymptomatic or may present with cholangitis. On MRCP, ascariasis is seen as linear filling defects within the bile duct or GB. Presence of fluid (bile) within the intestine of the round worm appears as a hyperintense line within the linear filing-defect. *Clonorchis sinensis* infestation may be associated with intrahepatic biliary structures and intraductal calculi (**Figure 17**).



Figure 16: Colour Doppler in porta hypertension: Mutiple tortuous serpiginous periporta collateral channels.

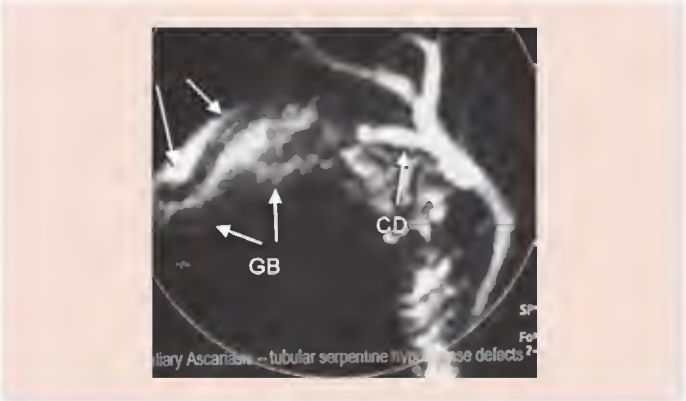


Figure 17: Contrast-enhanced computed tomography in a patient with portal hypertension: Multiple tortuous serpiginous splenic hiar, lienorenal, gastric bed and paraoesophageal collateral channels.

14.5 Acute Viral Hepatitis

Deepak Amarapurkar

INTRODUCTION

Acute viral hepatitis (AVH) was known to mankind since the middle ages. During the second world war, AVH was described to be of two types: (1) infectious hepatitis transmitted through contaminated water, (2) serum hepatitis transmitted by percutaneous exposure. The landmarks in the history of AVH are discoveries of Australia antigen by Barry Bloomberg in 1965, hepatitis A virus (HAV) by Feinstone in 1973, hepatitis C virus (HCV) by Hougton and colleagues in 1989, and hepatitis E virus (HEV) in 1990 by Reys *et al.*

Acute hepatitis is characterised by the parenchymal liver damage by any agent on an underlying normal liver which produces similar clinical and biochemical features. It can be caused by viral infections, non-viral infections, drugs,toxins, alcohol, metabolic diseases and ischaemia. A proper history and serological tests for infectious agents and assays for identifying drugs/poisons are required to diagnose the cause. When viral hepatitis is suspected, special emphasis should be given in history taking on blood transfusion, intravenous drug use, sexual practices, contact with jaundice person, needle stick exposure, working in hospitals in the areas like dialysis, trauma units, shared razors or tooth brushes, body piercing, tattooing, type of domestic water supply, and history of travel to the endemic areas for Hepatitis A and E. Sometimes, acute hepatitis may be first manifestation of underlying occult chronic liver disease e.g. acute exacerbation of chronic liver disease, or acute hepatitis may bring to light underlying chronic liver disease e.g. AVH occurring on underlying undiagnosed Wilsons' disease.

AETIOPATHOGENESIS

AVH is a systemic infection mainly affecting liver caused by hepatotropic viruses (hepatitis A to E). Other viruses like cytomegalovirus (CMV), herpes simplex, Coxsackie and adenovirus can also cause hepatitis in certain situations. AVH caused by hepatitis A to E is most common cause of liver disease worldwide and is a major public health problem in India. AVH leads to 1 to 2 million deaths annually worldwide.

The agents causing AVH are classified into two groups: (1) enterically transmitted (HAV and HEV) and (2) parenterally transmitted (HBV, HCV and HDV). Enterically transmitted viruses are not enveloped viruses, they are shed in faeces, survive intact when exposed to bile, do not cause chronicity and do not have prolonged viremia or carrier state. HAV and HEV are highly endemic in India. HEV is the main cause of most of the epidemics in India and accounts for 30% to 70% cases of acute sporadic hepatitis and a major cause of acute liver failure especially in pregnant women in India. In paediatric population, HAV is predominant cause of AVH. Dual infections with HAV and HEV have been reported in children and adolescents especially in acute liver failure in India.

Parenterally transmitted hepatitis viruses are HBV, HDV and HCV which are enveloped viruses which can cause chronicity and be associated with persistent viraemia and carrier state. About 15% to 30% of acute cases in India are due to HBV infection. HDV infection is found in less than 10% patients with HBV infection. HCV is rarely a cause of icteric AVH.

Majority of the AVH episodes are anicteric or subclinical; but when symptoms appear they are all similar in different types of AVH. The symptoms are characterised by prodrome of fever, anorexia, nausea, vomiting, mild abdominal pain, dark coloured urine followed by development of scleral icterus. AVH is characterised by 5 to 10 times elevation in serum alanine transaminases (ALT) with or without rise in serum bilirubin. However, the levels of ALT do not reflect the severity of AVH. To determine the severity of AVH estimation of prothrombin time (PT) (expressed as INR) is essential. PT expressed as INR more than 1.5 is considered severe acute hepatitis. Majority of the AVH are self limiting. Chance of fulminant liver failure varies from 0.01% to 1%.

HEPATITIS A VIRUS (HAV)

Virology and Modes of Transmission

HAV is a RNA virus belonging to Picorna virus family which is non enveloped, 27 nano micron size, has 7.5 kb genome. HAV is transmitted faeco orally. In rare instances, parenteral transmission via blood transfusion has been documented. Incubation period for HAV is 15 to 50 days with an average of 30 days.

Epidemiology

HAV has worldwide distribution and highly endemic in developing countries. India is hyperendemic region for HAV. There are estimated 1.5 million cases of HAV annually worldwide. Most of these cases occur in areas of poor hygiene and poor sanitation. Risk factors for HAV are children living in unhygienic condition, poor sanitation, consumers of high risk food, e.g. raw shell fish, people travelling to endemic areas and those participating in anal sex, intravenous drug abuses.

Natural History and Clinical Course

Main symptoms of HAV are fatigue, abdominal pain, anorexia, nausea, fever, dark coloured urine, jaundice, and diarrhoea. Rarely, HAV is associated with prolonged cholestasis leading to prolonged icetric illness. HAV never causes chronic infection and produces life long immunity. The risk of fulminant hepatic failure (FHF) is 0.01% to 0.1% which increases with age and patients having pre-existing liver disease (**Figure 1**).

Diagnosis

HAV is diagnosed by serological tests. IgM anti-HAV suggests acute infection; IgG anti-HAV suggests previous infection or vaccine acquired immunity. HAV RNA can be detected in blood, stool and liver during early part of the illness, but this test is not used in clinical practice.

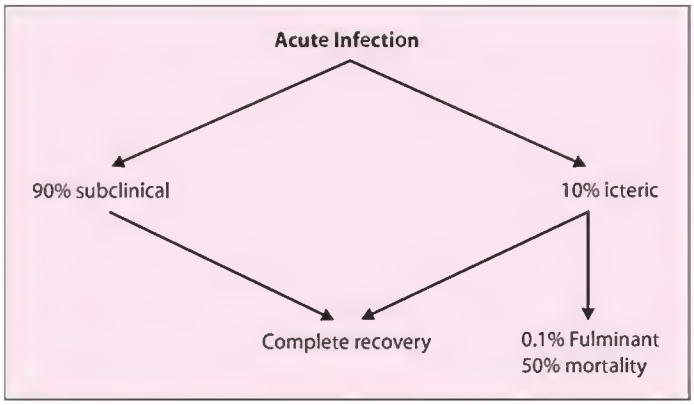


Figure 1: Natural history of hepatitis A virus infection.

Treatment

Management of HAV includes symptomatic and supportive measures; no specific antiviral treatment is required. Majority of the patients do not require hospital admission. Patients should be advised rest and given normal hygienic diet. Antiemetics may be given for nausea and vomiting. Patients with severe AVH and patients with HAV super imposed on underlying chronic liver disease require hospitalisation. Patients with HAV should be advised to avoid hepatotoxic agents such as alcohol, oral contraceptive medicines, paracetamol and non-steroidal anti-inflammatory drugs.

Prevention

Provision of clean drinking water, proper sewage disposal, public education about the hygiene are the mainstay for prevention of HAV infection. Infection with HAV provides long term immunity. Highly effective active and passive immunisation are available. Pre-exposure prophylaxis with inactivated vaccines can give protection up to 20 years. Passive immunisation is used for post-exposure prophylaxis within two weeks and should be accompanied with active vaccination (**Table 1**).

Table 1: Immunisation for Hepatitis A

Indication for active vaccination
Travellers to high risk area
Homosexual men
Injection drug users
Children and young adults when there is community outbreak
Susceptible patients with chronic liver disease
Food handlers
Children in the area of high endemicity
Schedule for hepatitis A vaccination
Children over two years of age, 3 dose regime
Inactivated HAV vaccine (360 ELISA units) 0, 1 and 6 to 12 months
Two dose regime : Inactivated HAV vaccine (720 ELISA units) 0, 6 to 12 months
Adults above 19 years of age
Inactivated HAV vaccine (1440 ELISA units) 0–6 to 12 months
Combined hepatitis A and B vaccine also can be used containing 20 mu/g HBsAg protein and more than 720 ELISA units of inactivated hepatitis A vaccine scheduled at 0, 1 and 6 months.
Post-exposure immunoprophylaxis—0.02 mL/kg body weight immunoglobulin specific to HAV on deltoid as early as possible after the exposure.

HEPATITIS B VIRUS (HBV)

Virology and Pathogenesis

HBV is a single-stranded DNA virus, with particle size 22 to 42 nano micron with 3.2 kb circular DNA genome. HBV replicates through an RNA intermediate using a virus-encoded reverse transcriptase enzyme. HBV genome has four genes, namely: surface, core, DNA polymerase and X. Four antigens HBsAg, HBcAg, HBeAg and HBxAg that have been identified in relation to HBV. Antibodies against this can be detected in the blood and are useful in diagnosis of various phases of HBV infection. There are at least 7 HBV genotypes (from A to G). Genotype D and A are more common in India. In immunocompetent persons, HBV is not cytopathic, and liver damage in this infection is caused through an immune-mediated mechanism directed against HBV-infected hepatocytes. However, in post-transplant patients, the virus appears to produce liver damage via a cytopathic effect.

Modes of Transmission

HBV is transmitted by blood-borne route, such as transfusion of infected blood and blood products, intravenous drug use, haemodialysis, sexual contact, percutaneous exposure (like needle-stick injuries, shared razor blades and tooth brushes, tattooing, acupuncture, etc.), and mother-to-newborn (i.e. perinatal) transmission. In India, a majority of chronic HBV infections are acquired horizontally, and less than 20% of chronic HBV infections results from vertical mother-to-child transmission.

Epidemiology

Acute hepatitis B is generally seen in patients with high risk behaviour for parenteral transmission in the western countries while in endemic region it can be seen in family contacts of patients infected with hepatitis B. More than one million people are infected with hepatitis B annually. In India 15% to 30% of the acute hepatitis cases are due to HBV infection.

Natural History and Clinical Presentations

Incubation period of HBV varies from 15 to 180 (average 60 to 90) days. In adults, almost 70% of acute infections are silent and subclinical; 30% develop icteric hepatitis. The proportion with clinical illness is smaller when infection occurs in early life. Thus, perinatal or childhood HBV infections are usually asymptomatic. About 1% of patients with acute hepatitis B develop fulminant hepatic failure (**Figure 2**).

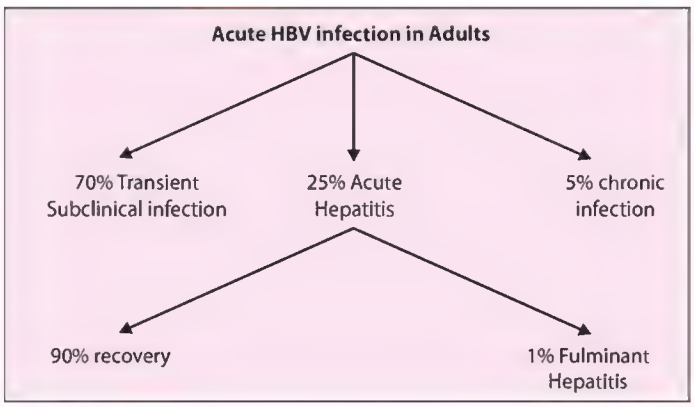


Figure 2: Natural history of hepatitis B virus infection.

HBV viraemia lasts for weeks to months after infection. Infection persisting beyond 6 months is labelled as chronic HBV. Risk of developing chronic HBV infection after acute exposure is dependent on age at the time of acquisition of infection; thus, nearly 90% of neonates, around 50% of young children aged 1 to 5 years, and 1% to 5% of adults with acute HBV infection develop chronic infection and persistent viraemia. The risk of chronic HBV infection is higher among immunocompromised individuals like HIV-infected, patients under immunosuppressive therapy and haemodialysis patients.

Diagnosis

Diagnosis of HBV infection is based on detection of various antigens and antibodies in the serum, or of HBV-DNA in serum or liver tissue. Presence of HBsAg in the blood suggests the presence of HBV infection. Presence of HBeAg in blood suggests active viral replication. IgM anti-HBc antibodies indicate recent (acute) infection. Anti-HBc IgG antibodies persist in the blood life-long after exposure to HBV. Anti-HBs antibodies appear with the clearance of HBV infection, and their presence suggests complete recovery. Detecting the presence and quantity of HBV-DNA in blood by polymerase chain reaction is useful in assessing whether virus is actively replicating, judging the need for and response to treatment. More specialised tests are used to detect mutant virus strains. Diagnosis of acute HBV is based on detecting IgM anti HBc in the blood.

Treatment

Acute HBV infection in adults is mostly a self-limiting disease and hence does not require any specific anti-viral treatment. The patients should be followed up to detect those in whom the infection becomes chronic; this is particularly important for children. Treatment with oral antivirals like Lamivudine, Telbivudine or Entecavir is indicated in patients with fulminant HBV, protracted severe HBV infection in immunosuppressed patients.

Prevention

HBV infection can be prevented by screening the transfused blood and blood products for HBsAg, using disposable needles and syringes, using safety precautions and practicing safe sex. Both active and passive immunisation are available. HBV vaccines, recombinant as well as plasma-derived, have more than 95% efficacy and are very safe. Hepatitis B immunoglobulin is useful for post-exposure prophylaxis (i.e. within 48 hours) and prevents mother-to-child transmission. HBV vaccination has been shown to reduce chronic HBV infection rate, and the incidence of hepatocellular carcinoma. HBV vaccination should be integrated into routine infant immunisation programme (**Table 2**).

HEPATITIS C VIRUS (HCV)

Virology and Pathogenesis

HCV is a single-stranded, enveloped RNA virus with a single open reading frame and 9.5 kb linear RNA genome. The anti HCV antibody has been used for the diagnostic purposes and does not have a protective value. The viral strains have significant genetic variability and have been grouped into six genotypes. In India, genotype 3 is the commonest; it is characterised by a good response to interferon treatment.

The exact mechanism of hepatocellular injury in HCV infection is unknown. Initially, HCV-induced liver injury was considered to be cytopathic in nature but current data suggest that host immune responses to HCV-infected hepatocytes play a major role in the pathogenesis of chronic hepatitis C.

Table 2: Immunisation for Hepatitis B

Indication for active vaccination	
	Universal infant immunisation shortly after the birth
	Catch up vaccination for adolescents if not previously vaccinated
	High risk groups
	Household contacts of HBV carriers
	Health care professionals
	Injection drug abusers
	Homosexual men
	Individual with multiple sex partners
	Haemodialysis patients
	Patients with chronic liver disease
HBV vaccine schedule	
	Below the age of 19 years 10 mu intramuscularly on deltoid at 0, 1, 6 months
	Above the age of 19 years 20 mu intramuscularly on deltoid at 0, 1, 6 months
	Accelerated schedule of 0, 1, 2, 12 also can be used
	Post exposure prophylaxis
	0.04 – 0.07 mL/kg HBIG intramuscularly within 48 hours alongwith the first dose of active vaccine. Further doses of active vaccine at 1 and 6 months should be continued.
	In neonates born to HBsAg positive mothers should be vaccinated at a dose of 0.5 ml of HBIG within 12 hours of birth along with the first dose of active vaccination. Futher doses of active vaccine at 1 and 6 months should be continued.

Mode of Transmission

Similar to HBV infection, HCV is also transmitted by blood-borne routes. Transmissibility of HCV is much lower than that of HBV. Recipients of infected blood and blood products, intravenous drug abusers, and haemodialysis patients form the major HCV risk groups. Sexual and perinatal transmission of HCV is uncommon. More than 80% of Indian patients with chronic HCV infection are either transfusion recipients or undergoing haemodialysis.

Epidemiology

Worldwide prevalence of HCV infection is around 1% with marked geographical variation. HCV carrier rate in India is around 1% to 2%, thereby meaning that 15 million people in India are infected with this virus. HCV is responsible for 20% to 30% of patients with chronic liver disease in India.

Natural History and Clinical Presentation

Incubation period of HCV ranges from 15 to 160 days. Prolonged viremia and persistent infection are common. More than 75% of acute HCV infections are silent. Only 25% acute HCV infections manifest as clinical hepatitis. In the stage of acute hepatitis, patients should be monitored for spontaneous viral clearance. Patients with symptomatic acute hepatitis and female gender are more likely to clear the virus. Fulminant hepatic failure due to HCV infection alone is extremely uncommon. Nearly 50% to 85% of patients with HCV infection develop chronic infection;

of these, 60% to 70% develop chronic hepatitis, 30% develop cirrhosis and 15% develop hepatocellular carcinoma. Average time duration between acquisition of infection and development of chronic hepatitis, cirrhosis and HCC is 10 years, 20 to 30 years and 40 years, respectively.

Diagnosis

Diagnosis of HCV infection depends on detection of anti-HCV antibodies, using third generation enzyme immunoassays (EIAs); the current tests for this purpose are highly sensitive and specific. In acute HCV infection serum HCV RNA are detected within 1 to 2 weeks of exposure while elevation in ALT occurs 2 to 8 weeks after exposure. Anti HCV antibody develop 4 to 6 weeks after exposure to hepatitis C.

Treatment

More than 50% patients with acute HCV infection develop chronicity. Treatment of acute HCV infection after 12 weeks is recommended as spontaneous resolution at this stage is unlikely. The objective of antiviral treatment in acute HCV infection is to prevent chronicity. Interferon alpha, peg interferon alpha and peg interferon alpha + ribavirin have been shown to be highly effective in treatment of acute HCV infection.

Prevention

Use of blood from voluntary blood donors (as opposed to professional donors) and screening of blood and blood products using an anti-HCV antibody test prior to blood transfusion can bring down HCV transmission dramatically. Use of disposable syringe and needles is also helpful. Currently, no active or passive immunisation is available for preventing HCV infection.

HEPATITIS D INFECTION (HDV)

HDV is an incomplete enveloped virus with particle size of 35-37 nano microns, 1.7 kb circular RNA genome. It uses HBsAg of HBV as its envelope protein, and hence can cause infection only in the presence of HBV infection. Infection with both HDV and HBV may be acquired simultaneously (known as delta-coinfection); alternatively, HDV infection may occur in a person previously having chronic HBV infection (delta-superinfection). HDV is transmitted by parenteral and sexual routes; vertical transmission is extremely rare. HDV infection is prevalent worldwide. However, its frequency has shown a decline globally, as well as in India.

HDV coinfection has a good prognosis with 80% to 90% of patients showing complete recovery. Fulminant hepatic failure is seen in 5% to 10% of patients as compared to only 1% of those with isolated acute HBV infection. HDV superinfection in a chronic HBV infected person is associated with increased rates of progression to cirrhosis, decompensation, development of hepatocellular carcinoma and death as compared to isolated chronic HBV infection. Clinical presentation of HDV infection varies from asymptomatic carrier stage, acute hepatitis, fulminant hepatitis, chronic hepatitis, cirrhosis decompensation and HCC. Acute deterioration in chronic stable HBV infection should lead to suspicion of delta superinfection. Diagnosis of HDV infection depends on demonstration of anti-HDV antibodies in the serum and HDV-RNA in serum or liver tissue.

Response of HDV infection to interferon as well as lamivudine is suboptimal. Since HDV depends on HBV for survival and multiplication, it can be prevented using methods to prevent the latter.

HEPATITIS E VIRUS (HEV)

Virology and Modes of Transmission

HEV is a positive stranded 7.6 kb base non enveloped RNA virus and belongs to family of calcivirus. The particle size of HEV virus is 32 to 34 nano microns. HEV antibodies have protective value are also used for the diagnostic and epidemiological purpose. HEV is predominantly transmitted by faeco-oral route with incubation period of 2 to 9 weeks with mean of six weeks. Rarely parenteral transmission, person to person transmission and mother-foetal transmission has been documented.

Epidemiology

HEV infection is most common cause of acute sporadic and epidemic viral hepatitis in India. Contamination of drinking water due to sewage has been the important source of majority of these epidemics. Faecal contamination may be due to backflow during the floods, leaking sewers located close to the corroded drinking water pipes and contamination of well water during raining seasons.

Natural History and Clinical Course

Clinical manifestation of HEV infection ranges from asymptomatic to icteric hepatitis to fulminant hepatic failure (FHF). Prodromal symptoms are similar to other forms of AVH. Cholestatic hepatitis with striking jaundice and itching may last for several months in 20% to 30% patients with acute HEV infection. By and large HEV is a self-limiting acute infection. 1% of the patients with HEV can develop FHF. Pregnant females (especially during 2nd and 3rd trimester) have high attack rates and 10% to 12% chance of FHF (**Figure 3**).

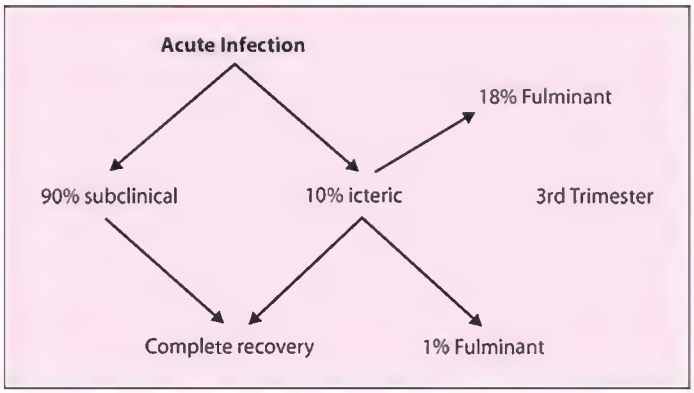


Figure 3: Natural history of HEV infection.

Diagnosis

IgM anti HEV antibodies are available for diagnosing of acute HEV infection. IgG anti HEV antibodies can be used for the sero-epidemiological studies. The virus can be identified in faeces, bile and the liver but this is not used in clinical practice.

Treatment

Treatment is supportive as described initially.

Table 3: Acute Viral Hepatitis in Special Situations

Specilist	HAV	HEV	HBV	HCV
Children	Benign course	Infrequently affected	Chance of chronicity is high	Chance of chronicity is high
Adolescents	Benign course Severe disease above the age of 40 years	Common benign course	Need to exclude underlying chronic hepatitis B	Chance of chronicity
Pregnant females	Course similar to non pregnant	Increase attack rate and increased chance of fulminant failure in 3rd trimester Increased foetal loss, possibility of transmission to foetus	Perinatal transmission to foetus likely Active and passive vaccination to child immediately at birth should be given	Chance of transmission to foetus if mother is coinfected with HIV
Immunosuppressed patients	Course can be severe	Course can be severe, can become chronic in post transplant period	High risk of chronicity may need antiviral treatment. Risk of chronicity in post treatment situation	High risk of chronicity, may need antiviral treatment. Risk of chronicity in post treatment situation

Acute Viral Hepatitis in Special Situation

The general clinical features of acute viral hepatitis have to kept in mind while dealing with such group. The clinical features and investigations are delineated in **Tables 3 and 4**.

Prevention

The best way of avoiding HEV infection is using safe drinking water, uncooked shell fish and foods which are contaminated. HEV vaccine has been recently shown to be effective and is awaiting commercial availability.

In conclusion, all forms of AVH in immune competent persons are self limiting. They do not require any specific therapy other than stopping hepatotoxic medications, including oral contraceptives and paracetamol. There is no role of vitamin supplementations, hepato-protective medications and dietary restrictions like avoiding proteins, fats and tamarind. Patients can start their routine work as soon as they feel fit to do so. Dietary restrictions and alternative medications may have deleterious course in AVH.

Table 4: Diagnostic Tests for Acute Viral Hepatitis

Hepatitis	Diagnostic Test For Acute Stage
HAV	IgM Anti HAV
HBV	IgM Anti HBc, HBsAg
HDV	Anti HDV in presence of IgM Anti HBc +ve
HCV	No antibody test to determine acute stage HCVRNA +ve in the absence of Anti HCV +ve in immune competent phase suggestive of acute infection
HEV	IgM anti HEV

RECOMMENDED READINGS

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2. Heathcote J, Elewaut A, Fedail S, *et al*. Management of Acute Viral Hepatitis World Gastroenterology Organization Practice Guidelines.
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14.6 Chronic Viral Hepatitis

Rajesh Upadhyay, Nitin Gupta

Chronic hepatitis is defined as hepatic necro-inflammation (detectable by biochemical or histological methods) continuing for more than 6 months. The condition may be self-limiting but usually progresses to fibrosis and subsequent architectural distortion with regenerating nodules leading to cirrhosis. There are many diverse causes of chronic hepatitis which can be broadly categorized into viral and non-viral causes (**Table 1**). This chapter presents an overview on chronic viral hepatitis.

Table 1: Causes of Chronic Hepatitis

Viral	Non-Viral
Chronic hepatitis B	Alcoholic hepatitis
Chronic hepatitis C	Non-alcoholic steatohepatitis
Chronic hepatitis D	Wilson's disease
	Drugs
	Auto-immune hepatitis
	Others

AETIOLOGY

Chronic viral hepatitis may be caused by hepatitis B, hepatitis C and hepatitis D. Of these, hepatitis B and C are the two most common viruses. In India, deaths from chronic hepatitis B (HBV) and chronic hepatitis C (HCV) infections are increasing over the years.

Hepatitis B Virus (HBV)

Epidemiology

HBV is a ds DNA virus belonging to Hepadnaviridae family of viruses. Hepatitis B is endemic throughout the world (350 million infected worldwide) especially in countries like Bangladesh, Thailand and Myanmar which have HBsAg carrier rates as high as 9 to 12%. In India, the carrier rate has been found to be around 4 to 7% with an estimated 45 million infected individuals. HBV is present in the blood, saliva, semen, vaginal secretions, and menstrual blood and, to a lesser extent, perspiration, breast milk, tears and urine of infected individuals. The virus can survive outside the body and is easily transmitted through contact with infected body fluids. The pattern of infection differs in developed and developing nations. Sexual transmission is common in the western world, whereas in developing countries like India, vertical transmission (mother to child at birth) and early childhood infections predominate.

Chronic infection leads to cirrhosis and hepato-cellular carcinoma (HCC) in 15 to 40% patients.

Clinical features and outcome

The clinical presentation of chronic viral hepatitis is similar for both HBV and HCV.

Chronic HBV infection is usually asymptomatic and is commonly detected on routine blood testing or during evaluation of incidental, unexplained elevation in alanine aminotransferase (ALT) levels. The clinical symptoms, when present, are generally mild and non-specific such as fatigue, mild right upper quadrant pain, nausea, weight loss, weakness, pruritus, etc. Patients with more advanced disease may have jaundice, abdominal swelling, gastrointestinal (GI) bleed or hepatic encephalopathy. Sometimes, the condition is diagnosed when the patient presents with an acute hepatitis illness which is due to reactivation of chronic hepatitis B.

Physical examination is usually unremarkable but stigmata of chronic liver disease may be present. Hepatomegaly with or without splenomegaly may be present depending on the stage of disease.

The outcome of chronic HBV infection depends on the age of acquisition of infection. Most patients are infected in early childhood and initial infection leads to inactive HBeAg-positive disease with high-level viraemia and minimal liver damage (immune tolerant phase). With advancing age, many patients develop an immune response (immune clearance phase) that leads to liver inflammation with progressive disease (high AST/ALT levels) and often seroconversion to HBeAg-negative phase of infection with low-level viraemia and normal liver function tests (LFT) (inactive replicative phase). A proportion of patients have reactivation of infection (reactivation phase) and develop HBeAg negative disease with fibrosis progression. The stages of chronic hepatitis B infection are shown in **Figure 1**.

Diagnosis

When chronic viral disease is suspected, the next step involves work-up of viral hepatitis using serological or molecular biological methods.

Patients with chronic hepatitis B (CHB) are diagnosed when hepatitis B surface antigen (HBsAg) persists in serum for more than 6 months. There are two main forms of chronic hepatitis B: (a) HBeAg-positive form associated with wild-type infection; and (b) HBeAg negative form associated with core promoter and/or pre-core mutant viruses.

Hepatitis B core antibody (Total) is present in CHB infection and presence of HBeAg or high HBV-DNA are markers of replicative virus. The transaminases (AST, ALT) are typically elevated usually 1 to 5 times the upper limit of normal with ALT> AST, whereas the alkaline phosphatase level is only mildly elevated. The albumin: globulin ratio remains normal except in advanced stages of disease where reversal of A:G ratio may be seen.

Abdominal ultrasonography (USG) is the most commonly used imaging modality although it is not useful in making the diagnosis. Its importance, however, lies in distinguishing patients with cirrhosis (small, shrunken nodular liver or atrophy of right lobe with hypertrophy of caudate/left lobe) or those with portal hypertension. It is also a useful screening test for

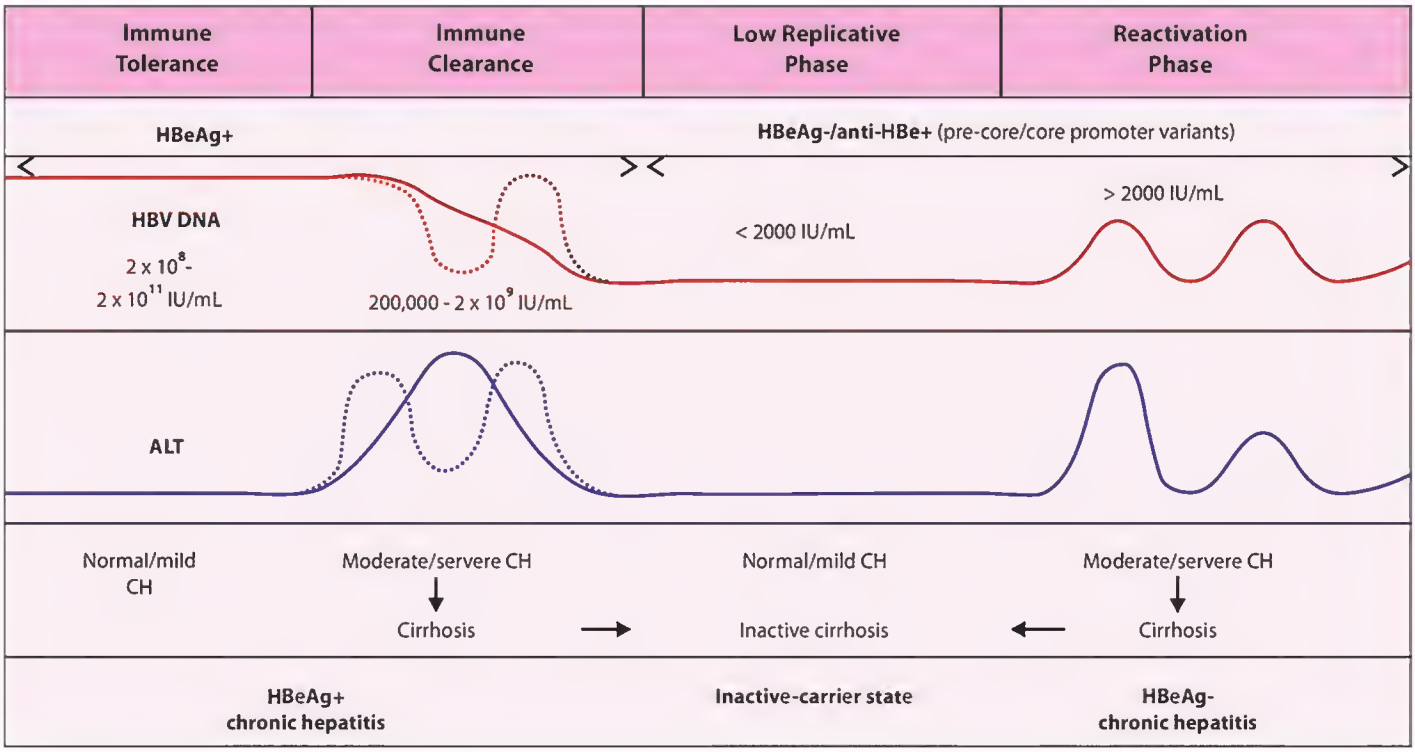


Figure 1: Stages of chronic hepatitis B infection.

hepato-cellular carcinoma. (USG) elastography (fibroscan) is a new non-invasive imaging modality used for assessment of fibrosis (stiffness) in chronic hepatitis. It may be useful in detecting patients with advanced fibrosis.

Chronic hepatitis is a necro-inflammatory process that may be complicated by fibrosis. A hallmark of chronic hepatitis is portal inflammation (portal hepatitis), predominantly lymphocytic. These changes are common to all aetiologies of chronic hepatitis. Certain changes are characteristic, but not pathognomonic, of chronic HBV. "Ground-glass" hepatocytes are a hallmark of hepatitis B infection which is due to proliferation of smooth endoplasmic reticulum containing HBs antigens.

Liver biopsy is not required for diagnosis of chronic viral hepatitis. Its usefulness lies in the histological assessment of liver for severity of necro-inflammation (grading) and degree of fibrosis (staging). Several histological classification systems are used for this purpose, e.g. Knodell-Ishak score, Scheuer score, Metavir score, etc. Such information is often useful for making therapeutic decisions.

Treatment

Treatment for chronic HBV infection should be restricted to patients with active inflammation and high replicative state (HBeAg positive or high level HBV-DNA). Such patients have higher risk of progressive disease leading to cirrhosis and hepato-cellular carcinoma.

Inflammation may be assessed indirectly by elevated ALT or directly by assessing liver biopsy specimen. Biopsy is usually not required for patients with ALT more than two times upper limit of normal. It may be considered in patients with borderline elevated ALT levels. Current guidelines advocate treatment in patients with HBV-DNA >20,000μ/ml in HBeAg-positive patients and HBV-DNA >2000μ/ml in HBeAg-negative patients.

The short-term goal of treatment is to convert patients from the high replication phase (HBeAg-positive or high HBV-DNA) to the low replication phase characterized by the appearance of HBeAb (called as seroconversion) or disappearance of HBV-DNA. This end-point is associated with lower or normal ALT levels and histological improvement. The long-term goals are to delay or prevent histological progression to cirrhosis and hepato-cellular carcinoma leading to improved survival. The ideal aim of treatment is HBsAg/HBsAb seroconversion which is difficult to achieve.

Treatment options include interferon injections (both standard and pegylated) and anti-viral drugs, such as nucleoside or nucleotide inhibitors. Currently used oral anti-viral drugs include lamivudine, adefovir, emtricitabine, entecavir and tenofovir. Interferon therapy is of finite duration, whereas a long-term therapy should be planned when using nucleoside analogues. The usual regimen for Peg-interferon is a weekly dose for 12 months. Nucleoside treatment should be continued for at least 6 months (preferably 12 months) after seroconversion in HBeAg-positive patients, or after HBV DNA levels have become undetectable in HBeAg-negative patients. Interferons should be avoided in HBeAg-negative patients as the results are disappointing and the end-points of treatment are not well defined. The problem with oral anti-viral drugs is the long duration of treatment and the risk of resistance (albeit low with newer anti-virals).

Hepatitis C Virus

Epidemiology

Hepatitis C virus is an RNA virus belonging to the Flaviviridae family of viruses. It was first identified in 1989. About 3% of the world population is infected with HCV and among them 170 million individuals are chronic carriers, and at risk of developing cirrhosis and liver cancers. In India, the prevalence of HCV

antibodies has been found to be 2% in voluntary blood donors, and 42% of patients with hepato-cellular cancer. The prevalence of HCV infection is also age-related with children and adolescents exhibiting very low rates (0.4%). The hepatitis C virus is blood borne and in the developed world transmission is common in IV drug abusers sharing contaminated needles or those who received blood or blood products before screening for HCV was introduced. The routes of transmission are diverse and include contaminated medical equipment (used in treatment or immunization) as well as contaminated non-medical equipment (such as barbers' razors).

Clinical features

Acute infection with hepatitis C leads to chronicity in almost 85% of the patients. Chronic infection leads to a slowly progressive hepatitis that can cause significant liver disease including cirrhosis and sometimes hepato-cellular carcinoma over 15 to 30 years. The disease is usually asymptomatic and detected during routine testing or during evaluation for asymptomatic elevation of transaminases. Sometimes it is present with icteric hepatitis and a few patients may present for the first time with decompensated cirrhosis.

The differentiation of acute from chronic HCV infection depends on the clinical presentation, namely the presence of symptoms and whether or not there was a prior history of ALT elevation and its duration.

The clinical features of chronic hepatitis C are similar to those of CHB infection. However, these patients are less likely to present with a past history of icteric hepatitis compared to patients with chronic hepatitis B.

Diagnosis

The diagnosis is based on the presence of both anti-HCV and HCV-RNA. These assays have no role in the assessment of disease severity. After acute exposure, HCV-RNA can be identified as early as 2 weeks following exposure whereas anti-HCV is generally not detectable before 8 to 12 weeks. Careful analysis of both these markers helps in diagnosis of acute or chronic HCV infection or resolved HCV infection (**Table 2**).

Table 2: Serology in the Diagnosis of HCV Infection

Anti-HCV	HCV-RNA	Analysis
Yes	Yes	Active infection (acute or chronic)
Yes	No	Resolved HCV infection
No	Yes	Early acute infection, false positive serology
No	No	No HCV infection

The pattern of LFT abnormality, use of imaging modalities and assessment of liver histology in chronic hepatitis C is similar to that in chronic hepatitis B (CHB).

Treatment

All anti-HCV positive patients with detectable HCV-RNA are potential candidates for treatment. Patients suspected of having acute or chronic HCV infection should first be tested for anti-HCV. HCV-RNA testing should be performed in patients with a positive anti-HCV test especially in whom, antiviral treatment is being considered. HCV genotyping should be performed in all HCV-infected persons prior to treatment. This helps to plan for the dose and duration of therapy and to estimate the likelihood of response. Treatment decisions should be individualized based on the severity of liver disease (decompensated liver disease is a contraindication to treatment), the potential for serious side effects and the presence of co-morbid conditions (like HIV co-infection).

The optimal therapy for chronic HCV infection is the combination of peginterferon alfa and ribavirin. Peginterferon alfa 2a is given as a fixed dose and alfa 2b is given according to body weight. Genotype 1 and 4 patients are treated with 48 weeks of treatment while genotype 2 and 3 patients are treated with 24 weeks of treatment. The finding of undetectable levels of HCV-RNA levels at 24 weeks after completion of treatment (sustained virological response) ensures that the treatment can be considered curative. The expected response rate is lower with genotype 1 and 4 patients (55 to 60%) compared to genotype 2 and 3 (75 to 80%).

In view of the poor response rate, especially in genotype 1 and 4, a number of drugs, such as telaprevir, are being currently tried in combination with pegylated interferon and ribavirin with encouraging results.

Hepatitis D Virus

This is uncommon in India but is more commonly seen in West Africa, Mediterranean and in parts of South America.

HDV (hepatitis delta virus) is a RNA virus discovered in 1977 and causes infection which requires HBV particles to infect the liver. The viral transmission is similar to HBV (blood borne and sexual). HDV infection may either be co-infection with HBV (simultaneous infection) or superinfection (HDV in chronic HBV carrier).

Chronic hepatitis D occurs in less than 5% of co-infected patients and in 80% of superinfected patients. The clinical features are similar to chronic HBV or HCV. The disease is progressive and 60 to 70% develops cirrhosis over 5 to 10 years. HCC also occurs with same frequency as in HBV or HCV infection.

The diagnosis is confirmed with a positive test for anti-HDV and HDV-RNA by RT-PCR. No specific treatment is available

14.7 Chronic Non-Viral Hepatitis

CE Eapen

When hepatic inflammation when continued for more than 6 months duration, the disease process is termed as chronic hepatitis. Progression of chronic hepatitis can lead onto cirrhosis and, less commonly, hepatocellular carcinoma. This section presents an overview of chronic non-viral hepatitis and discusses auto-immune hepatitis (AIH) in detail.

CHRONIC NON-VIRAL HEPATITIS

Aetiology

Hepatitis viruses B, C and D are important causes of chronic hepatitis, which are discussed separately in chapter 6, section 14. The important non-viral causes of chronic hepatitis are Wilson's disease, AIH, non-alcoholic steatohepatitis (NASH), drug-induced hepatitis, iron overload and unexplained/cryptogenic chronic hepatitis.

Clinical Features

Chronic hepatitis may be asymptomatic, with the disease being detected on routine blood tests. Patients may also present with non-specific symptoms, like fatigue or joint pains. Some patients may present with features of portal hypertension (like oesophageal variceal bleed) or liver cell failure. Physical examination may be normal. Some patients have jaundice, peripheral stigmata of liver cell failure, like spider nevi and splenomegaly.

Clinical clues may suggest the aetiology of chronic hepatitis. Acne may be a prominent feature of AIH, however it may also occur in other causes of chronic hepatitis (like Wilson's disease). Other autoimmune diseases like Hashimoto's thyroiditis, pernicious anaemia, insulin dependent diabetes mellitus or coeliac disease may be seen in AIH.

Kayser-Fleischer rings in eyes, neurological features (extra-pyramidal involvement: tremors, drooling of saliva, pseudo-Parkinsonian features) or psychiatric illness point to a diagnosis of Wilson's disease. Family history of liver or neurological illness also favours a diagnosis of Wilson's disease. Being an autosomal recessive disorder, Wilson's disease is more often seen in children born to parents of consanguineous marriage.

Chronic hepatitis in a patient with metabolic syndrome (obesity, diabetes mellitus, hypertension) is likely to be due to NASH.

A detailed drug history should be obtained in a patient with chronic hepatitis. Hepatotoxicity is a well recognised side-effect of some drugs, for example, anti-tuberculosis drugs like isoniazid, rifamipicin and pyrazinamide are a common cause of drug-induced hepatitis in India. In patients with drug-induced hepatitis, inadvertent continued use of the drug or repeated exposure to the drug may lead to more severe liver injury.

Hepatic iron overload may either be due to genetic haemochromatosis (clinical clues: family history of similar illness, presence of hyperpigmentation, diabetes mellitus, cardio-myopathy or hypogonadism) or haemosiderosis (example: a patient with thalassaemia who has been multi-transfused).

It is also possible that more than one hepatotoxic factor may be operant in an individual with chronic hepatitis (for example, a patient with metabolic syndrome and NASH, who develops alcoholic hepatitis).

Investigations

Persistent elevation of serum transaminases for more than 6 months raises the possibility of chronic hepatitis. Serum (AST to ALT) ratio is useful to distinguish NASH (AST: ALT ratio < 1) from alcoholic liver disease (ratio >/= 2). Viral markers (serology, molecular tests) are used to rule out hepatitis viral infections. Specific tests are done to look for the different causes of chronic non-viral hepatitis. For example, serum caeruloplasmin, urine copper and slit lamp examination of the eye for Kayser-Fleischer rings are done to look for Wilson's disease.

Liver Biopsy

The liver histology shows hepatic necro-inflammation with infiltration of portal tracts by chronic inflammatory cells—lymphocytes, plasma cells and varying degrees of fibrosis. Histological changes in chronic viral hepatitis are scored by 'grading' (degree of necro-inflammation) and 'staging' (degree of fibrosis).

Mallory hyaline bodies can be seen in a variety of conditions (for example, Wilson's disease, alcoholic hepatitis, NASH). Eosinophilic infiltrate may suggest drug-induced hepatitis. Special stains for copper (Rhodanine stain) and copper associated protein (orcein stain) help diagnose copper overload. Iron deposits are detected on Perl's Prussian blue stain.

Treatment

If an aetiological factor for chronic hepatitis is identified, specific treatment can be given. With effective treatment of Wilson's disease, the affected patients (often children or young adults) can be expected to outlive their doctors! Medications to reduce the copper overload state (for Wilson's disease), immuno-suppressive treatment (for AIH), stopping the offending drug (in drug-induced hepatitis), measures to reduce insulin resistance (for NASH) and iron chelation (in iron overload states) are examples of specific treatment when the cause for chronic non-viral hepatitis is identified.

AUTOIMMUNE HEPATITIS

This is an uncommon type of chronic hepatitis that improves after treatment with corticosteroids and other immuno-suppressive drugs. The other autoimmune liver diseases are primary sclerosing cholangitis, primary biliary cirrhosis and overlap syndrome. In a series of patients with autoimmune liver

disease from Delhi, AIH was seen in 78%, primary sclerosing cholangitis (10%), primary biliary cirrhosis (8%) and overlap syndrome (4%).

Epidemiology

AIH comprised 2% to 6% of the causes of acute and chronic liver diseases in reports from North and Western India. The disorder can occur at any age but has a predilection for girls and young women. The mean age of presentation of adults with AIH in India is between 31 and 36 years with female preponderance (male: female ratio is 1:3).

Pathogenesis of Autoimmune Hepatitis

A young lady on minocycline for treatment of acne who presents with chronic hepatitis could be having AIH. What predisposes an individual to develop AIH? One explanation is an interaction between human leukocyte antigens (HLA), hepatocyte antigens and receptors on T-lymphocytes (**Figure 1**). Candidate self-antigens are asialoglycoprotein receptor (located on hepatocyte surface) in AIH type 1 and cytochrome P450 2D6 (in hepatocyte microsomes) in AIH type 2. HLA-DR3 and DR-4 increase the risk of AIH type 1. In Western India, AIH type 1 is associated with HLA DRB1*0301, DRB1*1301, DRB1*14 and DRB1*1501.

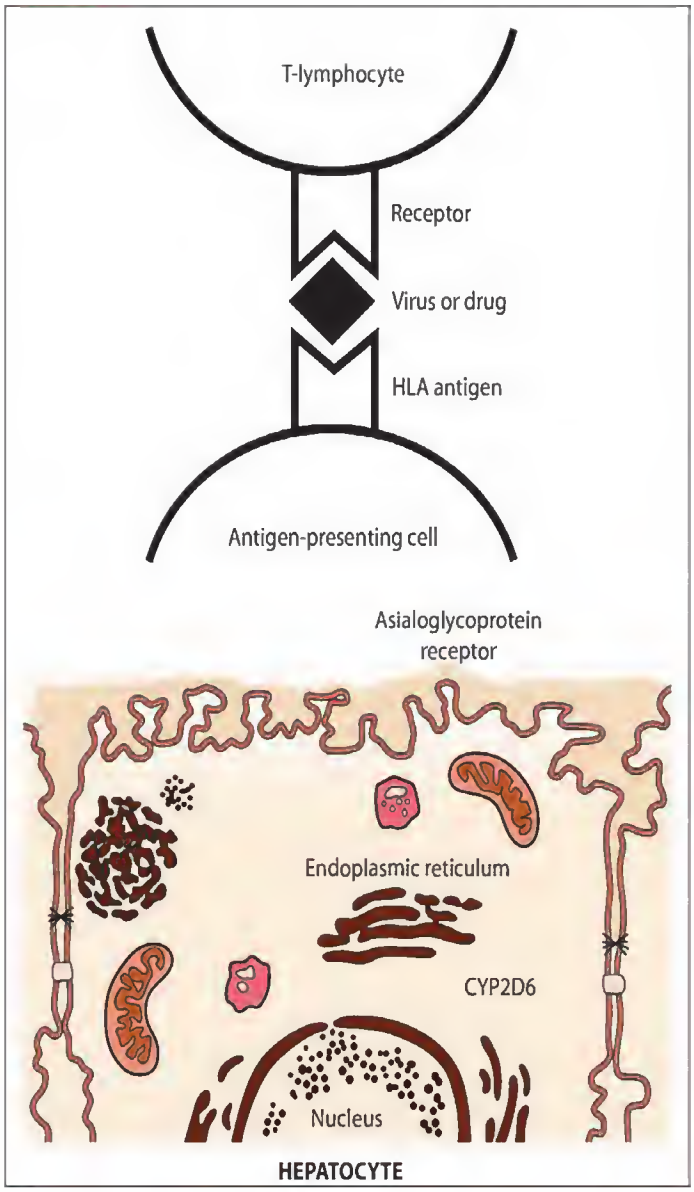


Figure 1: Pathogenesis of autoimmune hepatitis.

Molecular mimicry between viruses (hepatitis A, B, C, Epstein-Barr, measles virus) or drugs (minocycline, atorvastatin, methyldopa, nitrofurantoin) and hepatocyte antigens is a possible mechanism of pathogenesis. In genetically predisposed individuals this may result in an inappropriate immune response against the hepatocyte, even after elimination of the virus or cessation of the drug.

Clinical Features

The majority of patients present insidiously with malaise, anorexia and arthralgia while some may have features similar to acute hepatitis. Some patients may be asymptomatic. Fulminant hepatic failure is an uncommon presentation. In a report from Lucknow, patients with AIH presented with chronic hepatitis (50%), cirrhosis (34%), acute hepatitis (13%) and cholestatic hepatitis (3%).

Associated Autoimmune Diseases

About 40% of Indian patients with AIH have other autoimmune disorders. It is important to look for these disorders in patients with AIH. Fatigue in a patient with AIH may be attributed to the liver disease, while undiagnosed coeliac disease, hypothyroidism or vitamin B12 deficiency may be the cause of fatigue. In a report of 38 patients with AIH from Lucknow, other autoimmune diseases seen were diabetes mellitus (4 patients), hypothyroidism (3 patients), vitiligo (2 patients), thrombocytopaenia (2 patients), rheumatoid arthritis (2 patients), Sjögren's syndrome (1 patients) and autoimmune polyglandular syndrome III (1 patients).

Diagnosis

The diagnosis is based on clinical features and laboratory abnormalities. Elevation of serum transaminases is more than the elevation of alkaline phosphatase. Hyper-globulinaemia, increased serum immunoglobulin (Ig)G levels, positive autoantibodies: anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal antibody (anti-LKM), or anti-liver cytosol-1 (anti-LC1) and interface hepatitis on biopsy are the key tests to confirm the diagnosis. The levels of elevation of serum transaminases or serum globulins do not reflect severity of changes seen on liver biopsy. Making a confident diagnosis of AIH is difficult at times. A composite score to make the diagnosis of AIH has been proposed and presented in **Table 1**.

Types of Autoimmune Hepatitis

Autoantibody profiles are used to classify AIH into two types; however, these antibodies may not be involved in pathogenesis of AIH. Type 1 or classic AIH is characterised by the presence of ANA and/or ASMA. Anti-LKM-1 and anti-LC1 are found in type 2 AIH. Classic (type 1) AIH occurs predominantly in women in all age groups, while type 2 AIH is generally a disease of girls and young women.

Table 1: International Diagnostic Criteria for Diagnosis of AIH

	Parameter	Score
Female sex		+2
Ratio of elevation of serum alkaline phosphatase *vs* transaminase	>3.0	−2
	1.5 to 3	0
	<1.5	+2
Serum globulin or IgG (times upper limit normal)	>2.0	+3
	1.5 to 2.0	+2
	1.0 to 1.5	+1
	<1.0	0
ANA, SMA or LKM-1	>1:80	+3
	1:80	+2
	1:40	+1
	<1:40	0
AMA positive		-4
Hepatitis viral markers	Negative	+3
	Positive	−3
Drug history	Yes	−4
	No	+1
Alcohol	<25 g/day	+2
	>60 g/day	−2
HLA DR3 or DR4		+1
Other autoimmune diseases		+2
Response to therapy	Complete	+2
	Relapse	+3
Liver histology	Interface hepatitis	+3
	Predominant lympho-plasmacytic infiltrate	+1
	Rosetting of liver cells	+1
	None of above	−5
	Biliary changes	−3
	Other changes	−3
Seropositivity for other defined autoantibodies		+2

Definite AIH: totol score >15 before treotment ond >17 ofter treatment; Probable AIH: totol score 10-15 before treotment and 12-17 ofter treotment.
AIH = Autoimmune hepotitis; IgG = Immunoglobulin G; ANA = Anti-nuclear ontibody; SMA = Smooth muscle ontibody; LKM-1 = Liver kidney microsomol-1; AMA = Anti-mitochondrial ontibody; HLA = Humon leucocyte ontigen.

Differential Diagnosis

The other viral and non-viral causes of chronic hepatitis need to be ruled out before diagnosing AIH.

Treatment

Appropriate treatment for AIH can improve the quality of life, prolong survival and delay the need for liver transplantation. The benefits of achieving control of disease activity with immunosuppression has to be weighed against the potential side-effects of immunosuppression. Treatment decisions are thus individualised. Asymptomatic patients with minimal disease activity on liver biopsy or inactive cirrhosis may not need immunosuppression.

Corticosteroids are the mainstay of treatment. Prednisolone only regimen (1 mg/kg/day or 60 mg once daily) or combination of Prednisolone (0.5 mg/kg/day or 30 mg once daily) along with Azathioprine at 50 mg once daily are standard regimens to start treatment. In patients with uncontrolled disease despite steroids and azathioprine, treatment with cyclosporine, mycophenolate, tacrolimus and methotrexate have been tried.

Immunosuppression is tapered down once control of liver disease is achieved and low dose prednisolone and/or azathioprine is given as maintanence treatment for prolonged time periods. The end point of immunosuppressive treatment is sustained remission without need for medications, however this may be possible in only 10% to 40% of patients.

Patients with decompensated autoimmune cirrhosis do well after liver transplantation.

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14.8 Alcoholic Liver Disease

Rajesh Upadhyay

INTRODUCTION

World Health Organization (WHO) estimates that about 2 billion people worldwide consume alcoholic beverages and 76.3 million have diagnosable alcohol-use disorders. India has also, unfortunately, witnessed a steadily increasing consumption of alcohol in the last 2 decades, attributable to socio-economic and demographic changes in population. The per capita consumption of alcohol in India has risen to 4 litres per year although it is still less than in US (16.2 litres per year). The National Family Health Survey (NFHS) 2007 reported that 30% of adult Indians have been consuming alcohol and of which 4% to 13% are daily users. **Table 1** shows some recent trends in alcohol consumption in India.

Table 1: Recent Changes in Alcohol Consumption Patterns

Emergence of wine and beer drinking
Increased drinking among women
Decreasing age of initiation
Shift from urban to rural areas
More 'binge drinking'
Greater social acceptability

PREVALENCE AND RISK FACTORS

There is a high prevalence of alcoholic liver disease (ALD) in India and about 50% cases of cirrhosis in India may be due to alcohol abuse. The quantity and duration of alcohol intake are the most important risk factors for the development of ALD. Different alcoholic beverages contain varying quantities of alcohol (**Table 2**) and the quantity is expressed as units (1 unit = 10 g alcohol). A high daily intake of alcohol (>60 g in males and 20 g in females) taken for more than 6 to 8 years significantly increases risk of ALD. Indians develop cirrhosis with smaller quantity and duration of alcohol intake. Other risk factors also influence the development of ALD in different individuals given the same dose or duration of alcohol intake (**Table 3**).

Table 2: Content and Quantity of Alcohol in Different Alcoholic Beverages

Beverage	Alcohol Content (per cent)	Serving Size (in mL)	Quantity of Alcohol (in grams)
Beer	5	350	13.85
Wine	12	120	10.7
Hard liquor	40	30	10.0

PATHOPHYSIOLOGY

A simple model explaining alcohol related hepatic injury is the three hit explanation: 1. lipogenic hit, 2. inflammatory hit and 3. fibrogenic hit.

Liver and gastrointestinal (GI) tract are the main sites of alcohol metabolism. Within the liver, there are two main pathways of alcohol metabolism, alcohol dehydrogenase and cytochrome P-450 (CYP) 2E1. Alcohol dehydrogenase is an enzyme that converts alcohol to acetaldehyde. Acetaldehyde is subsequently metabolised to acetate via the acetaldehyde dehydrogenase. CYP 2E1 also converts alcohol to acetaldehyde.

Table 3: Factors Increasing Risk of Alcoholic Liver Disease

Quantity of alcohol (>60 g in male and >20 g in female)
Duration of intake (High risk cirrhosis with >10 years intake)
Sex (Females susceptibility twice as males)
Hepatitis C co-infection (in up to 20% case)
Genetic factors
Malnutrition
Obesity
Smoking
Iron overload

Lipogenic Hit

Alcohol dehydrogenase and acetaldehyde dehydrogenase leads to reduction of nicotinamide adenine dinucleotide (NAD) to NADH. The altered ratio of NAD/NADH promotes fatty acid accumulation through the inhibition of gluconeogenesis and fatty acid oxidation.

Inflammatory Hit

The CYP 2E1, which is up-regulated in chronic alcohol use, generates free radicals through the oxidation of NADPH to NADP. Chronic alcohol exposure also activates hepatic macrophages, which produce tumour necrosis factor-alpha (TNF-α). TNF-α increases the production of reactive oxygen species. This oxidative stress promotes hepatocyte necrosis and apoptosis, which is exaggerated in the alcoholic, who are deficient in antioxidants, such as glutathione and vitamin E. Free radicals initiate lipid peroxidation, which causes inflammation and fibrosis. Inflammation is also incited by acetaldehyde that, when bound covalently to cellular proteins, forms adducts that are antigenic. Alcohol also increases permeability of intestine thereby releasing endotoxins which ignites Kupffer cells to initiate inflammatory cascade.

Fibrogenic Hit

The stellate cell is the major source of collagen production which leads to fibrosis. It is normally in a quiescent state and serves as a storehouse for vitamin A. The cytokine tumour growth factor-beta (TGF-β) is a major stimulus for stellate cell activation and collagen production. Other cytokines, such as platelet derived growth factor; connective tissue growth factor and oxidative stress also stimulate stellate cells to produce fibrosis.

A simplified pathogenic mechanism for ALD is shown in **Figure 1**.

SPECTRUM OF LIVER DISEASE

Chronic alcohol abuse leads to a spectrum of liver disease ranging from fatty liver, alcoholic hepatitis to cirrhosis and hepato-cellular carcinoma. Fatty liver is the earliest change and is almost universally present in heavy alcoholics. It is generally

a benign condition and usually reverses with abstinence. Alcoholic hepatitis (AH) occurs in 10% to 35% of heavy drinkers who develop necro-inflammation with or without fat infiltration and fibrosis. AH is a precursor of cirrhosis (9 times higher than patients with fatty liver alone) and patients with severe AH have extremely high short-term mortality. Cirrhosis occurs in 8% to 20% of heavy drinkers. It is advanced, irreversible stage of the disease characterised by hepatic fibrosis and regenerating nodules (micro- or macro-nodular). Hepato-cellular carcinoma may develop in this setting. The spectrum of alcoholic liver disease and the inter-relationship is shown in **Figure 2**.

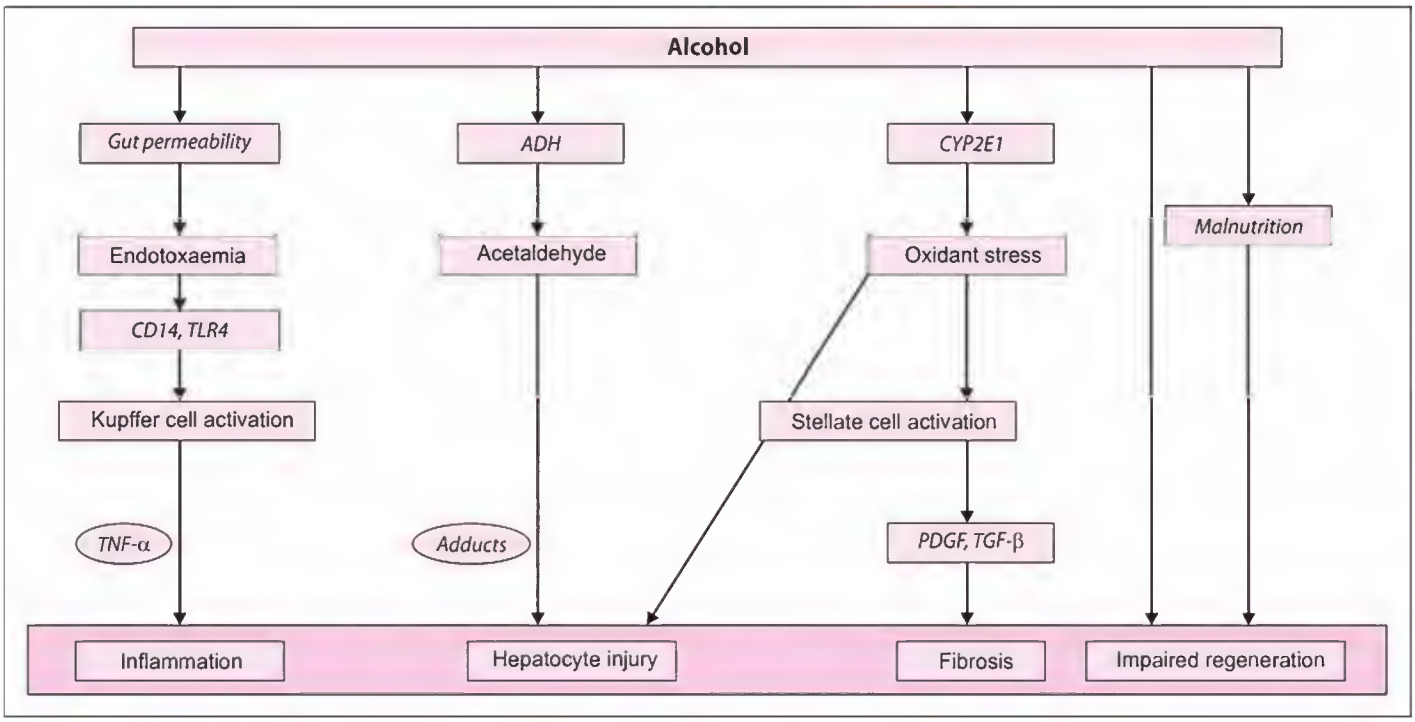


Figure 1: Pathogenic mechanisms of alcoholic liver disease.

ADH = Alcohol dehydrogenase; CYP2EJ = Cytochrome P2EJ; TNF-α = Tumour necrosis factor-α; PDGF = Platelet-derived growth factor; TGF-β = Tumour growth factor-beta.

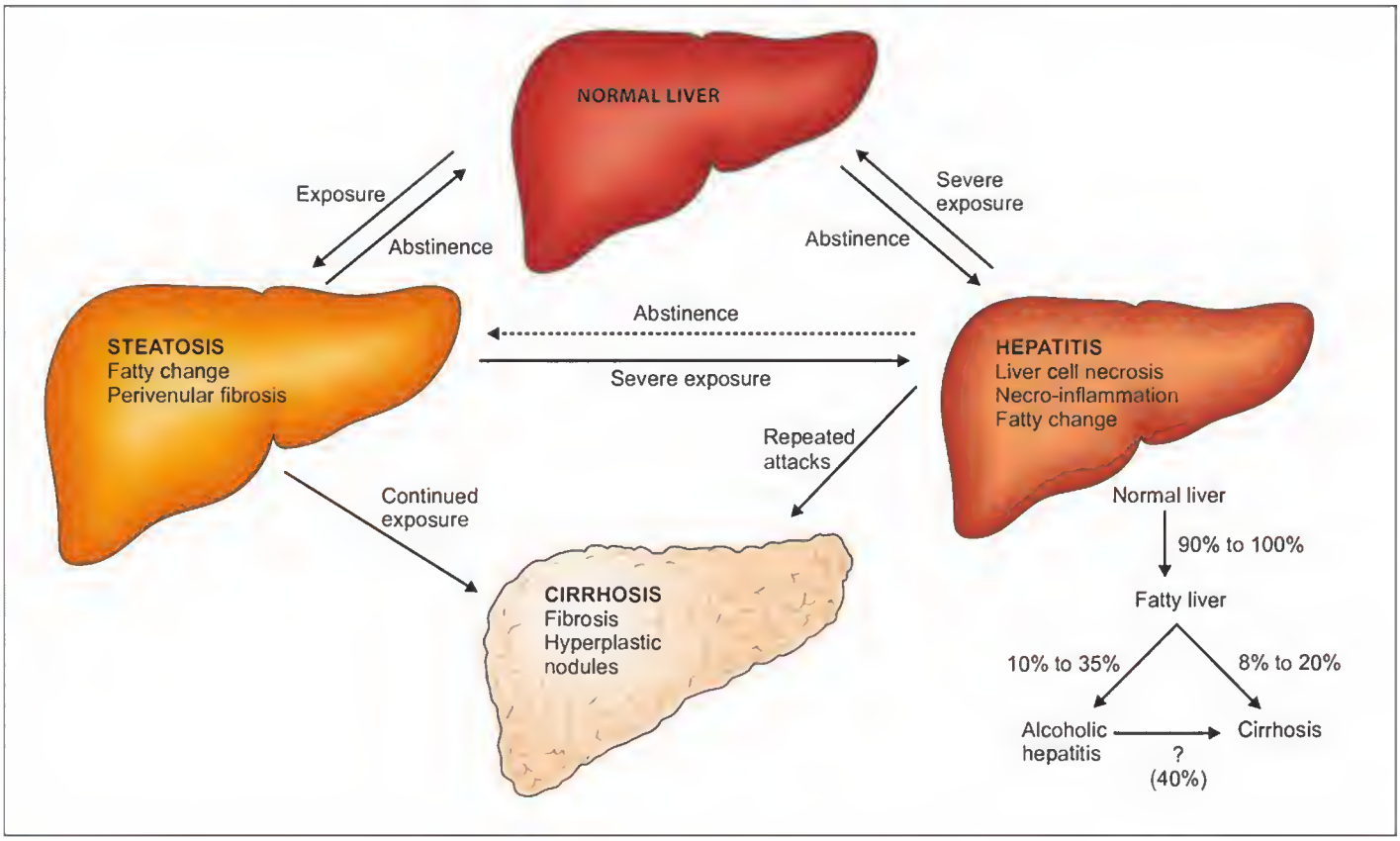


Figure 2: The spectrum and inter-relationship of alcoholic liver disease.

Prognosis and Assessment of Severity

The prognosis is dependent on the many factors such as severity of liver disease, nutritional status, continued alcohol ingestion, presence of co-morbid conditions, e.g. hepatitis B or C, hepatotoxic drugs, development of complications of cirrhosis (e.g., *ascites*, encephalopathy, variceal bleed), increasing age and acute severe AH.

Survival rate at 5 years is as follows: fatty liver – 70% to 80%, AH or cirrhosis – 50% to 75% and cirrhosis with AH – 30% to 50%. Overall one year survival rate is 80% which drops down to 50% at 5 years.

Clinical and laboratory features are powerful prognostic indicators for short-term mortality in acute AH. The Maddrey's score or discriminant, function [DF = 4.6 (patient's prothrombin time – control time) + serum bilirubin (mg/dL)]. Patients with DF > 32 (severe AH) have a one-month mortality of approximately 50%. AH patients with hepatic encephalopathy and hepato-renal syndrome have a mortality of 50% and 75%, respectively. Other prognostic indicators used to predict outcome are model for end stage liver disease (MELD) and Glasgow alcoholic hepatitis score (GAHS). The MELD score is calculated based on a patient's prothrombin time, serum creatinine and bilirubin and is equally sensitive and specific as DF but is more difficult to calculate at bedside.

The Childs Pugh score and MELD remain the most widely used systems for the assessment of outcome in patients with alcoholic cirrhosis.

CLINICAL FEATURES AND DIAGNOSIS

The key to diagnosis is a history of excessive alcohol intake along with features of liver disease (symptoms, physical signs, laboratory data and imaging). Patients frequently deny or understate alcohol abuse, and hence, a clinical suspicion should be confirmed by thorough questioning of family members and close friends as well.

Patients with fatty liver and most patients with mild/moderate AH are usually asymptomatic. Some patients have vague symptoms such as anorexia, malaise, nausea or right hypochondrial discomfort/pain. Physical examination in these patients is unremarkable although a mild smooth, non-tender hepatomegaly without any signs of chronic liver disease (CLD) may be present. Patients with more severe AH usually present with fever and signs of hepato-cellular failure, such as jaundice, ascites and encephalopathy. Patients with cirrhosis may remain asymptomatic and others have vague symptoms, such as tiredness, malaise or features of hepato-cellular failure, such as jaundice, *ascites*, peripheral oedema, etc. Physical signs of CLD is usually present in patients with cirrhosis and can broadly be divided into the following:

1. Signs of portal hypertension, i.e. *ascites*, splenomegaly and prominent abdominal wall veins.
2. Signs of alcoholism and liver disease, such as jaundice, telangiectasia, palmar erythema, parotid enlargement, clubbing, Dupuytren's contracture, neuropathy, etc.
3. Signs of hormonal dysfunction (feminisation), such as hypogonadism and gynaecomastia.

None of these signs are specific for ALD but parotid enlargement, feminisation and Dupuytren's contracture are seen more commonly in ALD. Other signs of extra-hepatic involvement in ALD, such as cardiomyopathy, muscular wasting, pancreatic dysfunction and neuropathy may also be present.

LABORATORY TEST

Liver Function Test (LFT)

The ratio of SGOT: SGPT >2:1 or higher is suggestive of ALD (present in >70% of the cases). Characteristically the SGOT is <400 and SGPT <200 u/l and higher levels should suggest an alternative diagnosis or a superimposed hepatic insult, such as viral infection or drug effect. Gamma GT is neither specific nor sensitive for the diagnosis of ALD. Macrocytosis is common and the combination of macrocytosis with high GGT may have a higher sensitivity for diagnosis. Leucocytosis is a common finding in acute AH and may be difficult to differentiate from associated infection. Laboratory tests which are useful in diagnosis are shown in **Table 4**.

Table 4: Typical Laboratory Abnormalities in Alcoholic Liver Disease

Liver Function Test	
	AST >ALT (AST usually <400 IU and ALT <200 IU)
	Serum albumin, prothrombin time, and serum bilirubin may be normal until significant liver injury is present
	Alkaline phosphatase, GGT levels usually elevated to a variable degree
Haematologic Abnormalities	
	Mild anaemia common (usually macrocytic)
	Platelets (normal to markedly decreased)
	Elevated white blood cell count
	Leukemoid reactions associated with alcoholic hepatitis
Metabolic Alterations	
	Hyperglycaemia
	Hypertriglyceridaemia
	Electrolyte abnormalities
	Low levels of potassium, magnesium and phosphorus

Liver Biopsy in Alcoholic Liver Disease

The overall clinical diagnosis of ALD, using a combination of physical findings, laboratory values, and clinical acumen is fairly accurate. However, liver biopsy may be required in select cases of ALD in order to confirm or exclude other diagnosis when in doubt. In addition, liver biopsy is also useful for the assessment of the disease severity, prognostication and guiding therapeutics. There are no pathognomonic histological features of ALD and the biopsy findings have to be corroborated with other evidences of ALD. The histological features on liver biopsy in different phases are shown in **Table 5**.

Imaging in Alcoholic Liver Disease

Imaging does not have a specific role in establishing alcohol as the cause of liver disease. The major role of imaging is to exclude other causes of abnormal LFT such as biliary obstruction, infiltrative and neoplastic conditions in an alcohol abuser.

Abdominal ultrasound is the first-line and the most cost-effective imaging modality. An increased echogenicity of liver is sensitive for fatty liver but does not help in diagnosing steatohepatitis. The presence of splenomegaly, *ascites*, dilated portal vein and collaterals suggest portal hypertension. Computed

Table 5: Histological Features of Alcoholic Liver Disease	
Fatty liver	Accumulation of microvesicular lipid droplets in hepatocytes, chronic intake leads to macrovesicular globules Perivenular fibrosis Macroscopically large, heavy (4 to 6 kg), soft, yellow and greasy liver
Alcoholic hepatitis	Hepatocyte swelling and necrosis Mallory bodies Neutrophilic reaction Fibrosis
Cirrhosis	Macroscopically the liver is brown and shrunken Regenerative activity of entrapped parenchymal cells with fibrous bands generate uniform micronodules With time nodules become more prominent and gives 'Hob nail' appearance (macronodular cirrhosis with higher risk of hepato-cellular carcinoma)

tomography (CT) and magnetic resonance imaging (MRI) are more sensitive in diagnosis of cirrhosis and demonstrate liver surface nodularity and altered density of the liver. Ultrasound elastography (Fibroscan) has recently been used as a non-invasive method to establish the presence of hepatic fibrosis (by assessing the elasticity of the liver).

Endoscopy in Alcoholic Liver Disease

Upper GI endoscopy is useful in the diagnosis of portal hypertension in patients with ALD. It can demonstrate oesophageal, gastric or duodenal varices and portal congestive gastropathy suggestive of portal hypertension. It also has a diagnostic and therapeutic role in alcoholic patients with upper GI bleed which is usually due to varices but may be due to a variety of causes, such as Mallory-Weiss tear, peptic ulcer, erosive mucosal disease or congestive gastropathy.

TREATMENT

The treatment depends on the stage of the disease and presence of complications of hepatic cirrhosis, such as GI bleed, *ascites* or encephalopathy. It includes certain general measures and specific treatment.

General Measures

Abstinence

This is the cornerstone of management. Abstinence improves survival, improves hepatic histology, reduces portal pressure and progression to cirrhosis. Patients should be encouraged to abstain but they are often unable to achieve complete and durable alcohol abstinence and psychiatric help is often required. Drugs which may help to sustain abstinence are naltrexone and acamprosate.

Nutritional support

There is a high prevalence of protein-calorie malnutrition in patients with ALD. The degree of malnutrition correlates directly with mortality. At one year from the time of diagnosis of AH, patients with mild malnutrition have a 14% mortality rate, compared with a 76% in those with severe malnutrition. In general, enteral nutrition is preferable over parenteral supplementation, and protein should be supplied (1 to 1.5 g/kg body weight/day) to provide positive nitrogen balance. Branched-chain amino-acids are useful as a supplement to maintain positive nitrogen balance in patients who do not tolerate liberal protein intake because of the development of encephalopathy. Nutritional supplementation may improve LFT, but mortality remains unaffected. Patients may also have depletion of potassium, magnesium and phosphates which may require replacement.

Alcohol withdrawal

This is commonly seen and needs aggressive management with intravenous glucose and thiamine supplementation (to prevent Wernicke's encephalopathy). Drugs, such as chlordiazepoxide, benzodiazepines may be required.

Specific Therapies

Fatty liver

Abstinence is the key intervention in management of fatty liver and leads to normalisation of LFT and imaging/histology. Overweight patients should lose weight with diet and exercise. Any associated metabolic abnormalities, such as diabetes or hyperlipidaemia, should also be treated aggressively.

Alcoholic hepatitis

Most patients with AH are associated with fatty liver and have a mild form of the disease requiring no specific treatment except the general measures. Other patients with more severe acute AH require specific treatment with anti-inflammatory agents, e.g. steroids and anti-cytokine therapy, e.g. pentoxifylline, infliximab, etc.

Corticosteroids

Steroids suppress inflammatory and immune responses in AH and has been the most extensively studied drug. Its efficacy remains controversial but overall evidence suggests that it reduces short-term mortality (although about 7 to 8 patients are required to be treated to prevent 1 death). The beneficial effect is limited to patients with severe disease (DF > 32 ± enceph-alopathy). Steroids, however, have a high rate of side-effects particularly infections, and hence should be used only in patients with no evidence of infection or GI bleed and where the diagnosis is definite (ideally biopsy proven). Predinosolone is given at 40 mg for 4 weeks, followed by tapering over the next 4 weeks.

Pentoxifylline

Pentoxifylline is a phophodiesterase inhibitor and also reduces the production of TNF-α and other pro-inflammatory cytokines. At a dose of 400 mg thrice daily, it significantly reduces mortality in patients with acute AH as compared to placebo (24% *versus* 46%, respectively). The drug is inexpensive and fairly well tolerated and is therefore preferred in management.

Infliximab and etanercept

These anti-TNF-α therapy have been used but remain controversial. Small trials with these anti-TNF-α drugs have shown beneficial effect but the cost and side-effects, especially a high incidence of infections, remains a concern for routine clinical use.

Other drugs

A large number of other drugs have also been studied in the management of ALD with variable levels of evidence for efficacy. Some are effective and others are still under evaluation stage (**Table 6**).

An algorithm for the management of acute AH is shown in **Figure 3**.

Table 6: Drugs Used in Alcoholic Liver Disease (Evidence based)

Beneficial	Likely to be Beneficial	Unlikely to be Beneficial
Corticosteroids Pentoxifylline	Infliximab Etanercept Antioxidants S-Adenosyl L-Methionine Silymarin	Colchicine Propylthiouracil Anabolic steroids Polyenylphosphatidylcholine

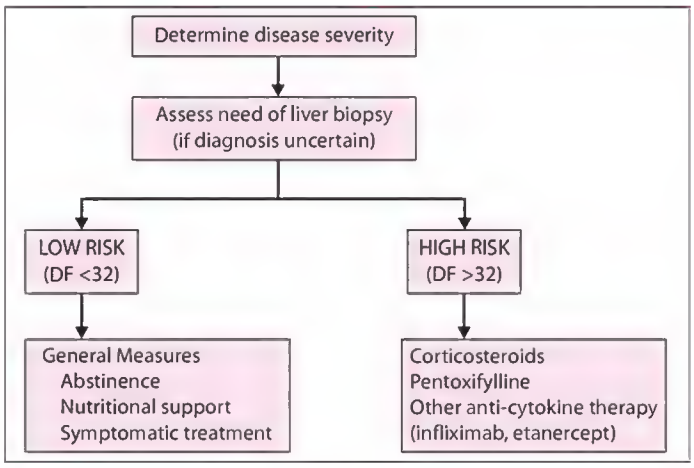


Figure 3: Therapeutic algorithm for alcoholic hepatitis.

Alcoholic cirrhosis

No specific treatment is available for alcoholic cirrhosis. Abstinence and correction of nutritional deficiencies are the major components of management to prevent disease progression. Management of alcoholic cirrhosis and its complication is same as with other forms of cirrhosis and is discussed in another chapter.

Liver Transplantation in Alcoholic Liver Disease

Acute AH, no matter how severe, is a contraindication for liver transplantation. Patients with end-stage ALD should be considered for liver transplant. Generally 6 months of abstinence is considered necessary as eligibility for liver transplantation. This requirement theoretically has a dual advantage of predicting long-term sobriety and allowing recovery of liver function from acute AH. Survival of patients post-transplant is similar to those with non-alcoholic cirrhosis (70% 5-year survival). However, alcohol use after transplantation for alcohol-related liver disease approaches 50% during the first 5 years, and abuse occurs in up to 15% of the patients.

CONCLUSIONS

Although 90% to 100% of heavy drinkers show evidence of fatty livers, only 10% to 35% develop AH and 5% to 15% develop cirrhosis. The daily intake of alcohol that results in liver injury varies and depends on a number of factors. ALD develops at lower doses in South Asians, women and patients with hepatitis C infection. Abstinence and correction of nutritional deficiencies are major components in the long-term management of ALD. Anti-inflammatory therapy with corticosteroids and anti-cytokine therapy with pentoxifylline are effective in patients with severe AH. Liver biopsy may be required when diagnosis is in doubt and is of importance when corticosteroids are being considered for treating AH. Patients with end-stage ALD should be considered for liver transplantation.

RECOMMENDED READINGS

1. Bell H *et al.* Long-term prognosis of patients with alcoholic liver cirrhosis: A 15-year follow-up study of 100 Norwegian patients admitted to one unit. *Scand J Gastroenterol* 2004; 9:858.
2. Levitsky J, Mailliard ME. Diagnosis and therapy of alcoholic liver disease. *Semin Liver Dis* 2004; 24:233.

14.9 Cirrhosis of the Liver

Philip Abraham

DEFINITION

Cirrhosis is a diffuse process of fibrosis that converts the liver architecture into structurally abnormal nodules. In most if not all cases, the process follows or is accompanied by hepato-cellular necrosis.

Hepato-cellular necrosis can heal in one of two ways: complete regeneration and restitution of normal architecture (as occurs after recovery from fulminant hepatitis); or replacement by collagen, leading to fibrosis, as in cirrhosis. By this stage, evidence of the initial insult and necrosis may have disappeared.

Focal conditions like focal nodular hyperplasia need to be differentiated from the diffuse nodular process in cirrhosis. Fibrosis without nodularity (as in non-cirrhotic portal fibrosis and schistosomiasis) and nodularity without fibrosis (nodular regenerative hyperplasia) are also known to occur and should be differentiated from cirrhosis. Congenital hepatic fibrosis includes fibrosis and nodules, but the lobular architecture is maintained within the nodules.

CLASSIFICATION

Morphologically, cirrhosis is classified as:

1. *Micronodular*, in which all or nearly all the nodules are <3 mm in diameter and are surrounded by thick fibrous septa. This is often an early stage in the development of the disease. The liver is usually normal in size or enlarged.
2. *Macronodular*, where the nodules are more variable in size, with many being >3 mm in diameter, some up to several centimetres. Some nodules may contain normal lobules. The liver size is usually reduced.
3. *Mixed nodular*, in which micro- and macronodules are present in almost equal numbers.

AETIOLOGY

The commonest causes of cirrhosis worldwide are alcohol abuse and viral hepatitis (B and C). In urban centres in India, alcohol abuse accounts for more than 50% of cases. Hepatitis B accounts for 30% to 70% of cases, with hepatitis C following in frequency. About 30% of alcoholics also have markers of hepatitis virus infection; the relative contribution of viral infection and alcohol in such patients is variable.

An average daily intake of 80 gm of alcohol for 10 to 20 years is required for the development of cirrhosis in Western populations. It appears that Indians develop cirrhosis with smaller quantities of alcohol and over shorter durations; possible reasons include their smaller build, poor nutrition, adulterants in the illicit country liquor commonly consumed and higher frequency of concurrent hepatitis virus infection.

The other causes of cirrhosis are listed in **Table 1**. Malnutrition and mycotoxins (especially aflatoxin) may initiate or aggravate cirrhosis but are not recognised as independent causes of the disease.

Table 1: Causes of Cirrhosis

Alcohol*
Viral hepatitis (B and C)*
Metabolic disorders
Wilson's disease*
Haemochromatosis
Alpha-1 antitrypsin deficiency
Cystic fibrosis
Glycogen storage diseases
Galactosaemia
Autoimmune hepatitis*
Venous outflow obstruction
Budd-Chiari syndrome*
Veno-occlusive disease
Cardiac failure
Biliary obstruction
Primary sclerosing cholangitis
Primary biliary cirrhosis
Extrahepatic biliary obstruction (unrelieved obstruction for 3 months or more)
Unknown causes
Cryptogenic cirrhosis* (increasingly attributed to non-alcoholic steatohepatitis)
Indian childhood cirrhosis (infrequently reported now)
Sarcoidosis, Sjögren's syndrome, scleroderma, psoriasis, sickle cell disease
Drugs
Methotrexate, oxyphenisatin

**Common causes.*

PATHOLOGY AND PATHOGENESIS

The major pathways leading to cirrhosis are:

Hepatitis

Lobular hepato-cellular necrosis and central-portal bridging necrosis with fibrosis are important routes; piecemeal necrosis of hepatocytes may also be important. These changes of chronic hepatitis occur in viral hepatitis and in several other causes of cirrhosis.

Fatty liver

Ballooned hepatocytes containing Mallory bodies and macrovesicular fat deposits, surrounded by neutrophils and lymphocytes and collagen deposits, is the predominant route in alcoholics. Severe steatohepatitis may lead to fibrous septa, which contract and accentuate the architectural distortion caused by necrosis. A similar picture is seen in non-alcoholic steatohepatitis, which, as a part of the metabolic syndrome, is being increasingly incriminated as a major cause of 'cryptogenic' cirrhosis.

Portal and centrilobular fibrosis

Bile duct disease causes cirrhosis by initiating fibrosis in the portal tracts, with linking of these tracts ultimately. A similar process of fibrosis sets in the centrilobular area in patients with venous outflow obstruction.

The end-result of all these pathways is fibrosis and scarring with distortion of the architecture (**Figure 1**). Regeneration of hepatocytes may proceed simultaneously with the necrosis. Intrahepatic portal-systemic shunting of blood is a consequence of the necrotic bridges. Portal hypertension follows collagen deposition in the space of Disse and compression of the vasculature by regenerative nodules, fibrosis and hepatocyte enlargement.

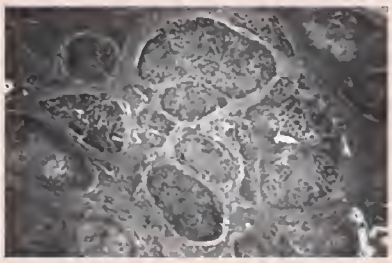


Figure 1: Histology of liver showing cirrhosis.
Courtesy: Dr. IM Vora

CLINICAL FEATURES

About one-third of patients with cirrhosis are *asymptomatic* because just 10% of the liver cell mass is adequate to maintain metabolic functions, and because the liver has a unique regenerative capability. *Weakness* and *fatigability* are common in decompensated cirrhosis, which carries a poorer prognosis; muscle wasting is evident. Overall *weight loss* may be masked by fluid retention. The clinical features associated with hepatocellular failure are depicted in **Table 2**.

Table 2: Clinical Features of Hepatocellular Failure

Jaundice
Foetor hepaticus
Parotid enlargement
Spider naevi, bruises and purpura
Loss of axillary and pubic hairs
Breast atrophy, gynaecomastia/testicular atrophy
Dupuytren's contracture, flaps, white nails with clubbing
Pedal oedema

Spider angiomas (naevi) and *palmar erythema* are seen in alcoholics. The naevi consist of a central arteriole with radiating capillaries; pressure on the arteriole with a pinhead obliterates the naevus. Such naevi vary in size from a few millimetres to a centimetre, are found commonly on the face, chest and upper limbs, and can rarely spurt blood. They can also be found uncommonly in normal subjects, especially in pregnancy, in rheumatoid arthritis and in patients on oestrogen therapy. Palmar erythema appears as reddening of the thenar and hypothenar eminences and finger pulp, with sparing of the rest of the palm.

Gynaecomastia in men is believed to be due to increased conversion of androgens into oestrogens in the peripheral tissues; spironolactone therapy can also induce gynaecomastia. *Hypogonadism* manifests in men by testicular atrophy and loss of libido, especially in alcoholics, and in women by oligomenorrhoea or amenorrhoea. *Infertility* is common in both sexes.

Anaemia in cirrhosis is due to several factors: nutritional iron or folate deficiency, blood loss, bone marrow hypofunction, hypersplenism, and haemolysis. *Impaired coagulation* due to decrease in the synthesis of coagulation factors in the liver, disseminated intravascular coagulopathy, and thrombocytopaenia secondary to hypersplenism may manifest with ecchymosis, purpura or gingival haemorrhage.

Low-grade fever, white opaque nails, clubbing of nails, Dupuytren's contracture (in alcoholics), *cyanosis* (central and peripheral), and *foetor hepaticus* (ammonical smell of breath in hepatic encephalopathy) are infrequent manifestations. The *Kayser-Fleischer corneal ring* should be looked for in all young cirrhotics, in whom Wilson's disease should be suspected.

The other major manifestations in decompensated cirrhosis are features of hepatocellular failure and portal hypertension, viz. jaundice, ascites and hepatic hydrothorax, gastrointestinal (GI) bleeding, and encephalopathy. *Jaundice* is usually due to failure of hepatocytes to excrete bilirubin, with resulting conjugated hyperbilirubinaemia. Except in the presence of ongoing histologic activity, jaundice is absent or mild; severe jaundice is a poor prognostic feature.

Ascites is frequently associated with oedema of the feet. Distension of abdomen, anorexia and fullness after small meals are the presenting symptoms. Occasionally, umbilical or inguinal hernia may be the presenting feature. Ascites is a sequel of portal hypertension (high hydrostatic pressure), along with decreased serum albumin levels (low osmotic pressure) due to low functional hepatocyte mass. Both hepatic and splanchnic lymph spillover may contribute to its formation.

On examination, the abdomen is distended with bulging of the flanks. The abdominal wall is thin due to loss of subcutaneous fat and muscle mass. Veins in the wall may therefore appear prominent and should be distinguished from the dilated veins of intrahepatic portal hypertension and inferior vena cava block. *Dilated veins* radiating from the umbilicus (caput medusa), when present, help to differentiate patients with intrahepatic causes of portal hypertension (in whom they may be present) from those with prehepatic causes (where they do not occur).

The puddle sign around the umbilicus can detect small amounts of fluid, but is inconvenient to elicit and unreliable. Flank dullness (indicating at least 1500 mL of fluid) and shifting dullness are other signs in ascites. A fluid thrill can be elicited when the abdomen is tense. Tense ascites is diagnosed when organomegaly cannot be detected despite deep palpation. About 5% to 10% of patients with ascites have pleural effusion ('hepatic hydrothorax'), on the right side in about 70% of them. The fluid is drawn up through defects in the diaphragm by the negative intrathoracic pressure.

The most common source of *upper GI haemorrhage* in cirrhosis is oesophageal varices, which are collateral vessels decompressing the portal hypertension. Less commonly, varices in the gastric fundus or body may bleed. Portal hypertensive ('congestive') gastropathy, gastric antral vascular ectasias, gastric erosions and peptic ulcers are other potential sites of bleed in cirrhosis. Ectopic varices may be found elsewhere in the alimentary tract, especially in the anorectum, but these seldom bleed.

Hepatic (portal-systemic) encephalopathy may occur spontaneously due to poor hepatocyte function and portal-

systemic shunting, or may be precipitated by various factors (**Table 3**). Ammonia is the best-characterised neurotoxin in the spontaneous cases; mercaptans and phenolic compounds are others. Synergism may exist between these factors. Gamma aminobutyric acid (GABA), the most important inhibitory neurotransmitter, is activated. Hyperammonaemia is associated with depletion of glutamate, the most important excitatory neurotransmitter. Decrease in concentrations of the branched-chain amino acids (valine, leucine and isoleucine) as a consequence of increased levels of aromatic amino acids has also been implicated as a mechanism.

Table 3: Precipitating Factors for Hepatic Encephalopathy

High-protein diet
Constipation
GI bleeding
Infection, including spontaneous bacterial peritonitis
Excessive diuretics causing hyponatraemia, hypokalaemia, renal failure
Sedatives and hypnotics
Interventional procedures
Surgical porto-systemic shunts

An entity of minimal hepatic encephalopathy is now being increasingly recognised on psychometric tests in 30% to 65% of patients with cirrhosis who do not have overt encephalopathy. Its clinical importance is still under evaluation, although recent data suggest that it impairs quality of life and the individual's ability to perform skilled work.

Recent evidence suggests that *cirrhotic cardiomyopathy* and *osteodystrophy* may be subclinical in most cases but are important determinants of mortality and morbidity.

INVESTIGATIONS

Among biochemical investigations, decreased serum albumin level and increased serum globulin may be the only abnormalities. Serum bilirubin and aminotransferases may be elevated in the presence of histologic activity. An AST:ALT ratio >1 in patients with chronic viral hepatitis and non-alcoholic fatty liver disease may suggest the presence of cirrhosis, particularly if associated with low platelet count. In alcoholic liver disease, the ratio is >2 even in the absence of cirrhosis. Elevated gamma-glutamyl transferase is suggestive of alcohol abuse. Serum alkaline phosphatase is elevated markedly in patients with biliary cirrhosis or sclerosing cholangitis.

Tests for hepatitis B and C viruses; autoantibodies; serum copper and caeruloplasmin and urinary copper; serum iron and transferrin; and alpha-1 antitrypsin levels should be undertaken based on the clinical suspicion of aetiology of the disease.

Psychometric tests in early cases, electroencephalography and evoked potentials may be required for the evaluation of hepatic encephalopathy. Tests for serum or cerebrospinal ammonia and glutamate are not routinely done and may be of more relevance when studied sequentially.

Imaging techniques useful in the diagnosis and evaluation of cirrhosis include ultrasonography, computed tomography (CT scan), radionuclide scan and MRI. Of these, ultrasonography is the most informative and is the least costly: apart from assessing liver size and shape, it can detect fatty infiltration, hepato-cellular carcinoma, ascites, portal hypertension and collateral circulation. Radionuclide scan can reliably differentiate cirrhosis from non-cirrhotic portal hypertension.

Endoscopy is performed to detect oesophageal varices (a reliable sign of portal hypertension) and other potential sites of bleeding. When indicated, endoscopic therapeutic measures can be instituted.

Ascitic fluid paracentesis is done to determine the characteristics of the fluid. In most of the uncomplicated cases, the fluid has low protein concentration (<2.5 g/dL) and few cells. However, in up to one-third of uncomplicated cases the protein content may be higher. A high protein level may be seen in patients on diuretics. Serum ascites albumin gradient (SAAG) of >1.1 g/dL is highly specific for ascites due to portal hypertension, even in the presence of complicating factors. Rarely (in <2% of cases), the fluid may be bloody.

A high ascitic fluid polymorphonuclear cell count (>250/mm^3) suggests spontaneous bacterial peritonitis, a complication seen more frequently in patients with low fluid protein level (<1 g/dL). Fluid adenosine deaminase levels (in tuberculous peritonitis), amylase levels (in pancreatic ascites), and cytology (in malignant ascites) should be tested when clinical suspicion exists.

Liver biopsy is the most reliable test for the diagnosis of cirrhosis but is not required if other evidence is available. It is done by the percutaneous route, usually with a biopsy gun or Tru-cut needle (suction techniques, as with the Menghini needle, are not used now). In patients with coagulopathy or ascites, transjugular biopsy is preferred. Laparoscopy with biopsy is an alternative choice. If an additional focal lesion, like hepato-cellular carcinoma, is suspected, imaging-guided biopsy is indicated.

The tissue obtained at biopsy is often fragmented. Microscopic features to be looked for include:

1. *Fibrosis*, resulting from collapse of the reticulin framework as well as replacement of the necrosed hepatocytes by collagen. The normal relationship between the vascular channels is disrupted and these may lie randomly in the fibrous septa or enclosed nodules.
2. *Activity*, manifest by parenchymal inflammatory cell infiltration and necrosis. This is considered as a sign of ongoing liver injury and hence may represent one of the indications for therapeutic intervention to arrest progression of the disease. Simultaneous regeneration may result in large binucleated cells and two-cell-thick hepatocyte plates (versus the normal one-cell-thick plates in adults). The regenerating nodules aggravate the architectural distortion caused by fibrosis.
3. *Fatty infiltration*, which when associated with Mallory hyaline bodies, neutrophilic infiltration and pericellular fibrosis, is evidence of alcohol aetiology and, in non-alcoholics, of non-alcoholic steatohepatitis. Mallory bodies are also seen in chronic cholestasis and Wilson's disease.

Positive staining with orcein occurs with hepatitis B surface antigen (HBsAg) or copper-associated protein. The latter is seen in Wilson's disease, Indian childhood cirrhosis and

chronic cholestasis. Special stains are used to detect iron (in haemochromatosis) and alpha-1 antitrypsin bodies. Bile duct damage and progressive bile duct loss are seen in primary biliary cirrhosis and sclerosing cholangitis.

Markers that have been used as surrogate for biopsy include: indirect markers (AST:ALT ratio, AST to platelet ratio index [APRI], FibroTest, and ActiTest), direct markers of extracellular matrix turnover (hyaluronic acid), and ultrasonographic evaluation of liver stiffness (Fibroscan).

MANAGEMENT

There is as yet no specific treatment for cirrhosis. Increasing evidence suggests though that the fibrosis in cirrhosis may be reversible, especially when specific therapy is available for the aetiology. Liver transplantation is the only definitive treatment for advanced disease.

A balanced diet with 1 gram protein and 30 kcal per kg body-weight per day must be ensured; malnourished patients may need more protein. Institution of adequate nutritional support actually improves morbidity and survival. The addition of choline, methionine or the other dietary 'hepatoprotective agents' has not shown any benefit. No item of diet (except salt in the salt-retaining state) needs to be restricted. Alcohol should be avoided even in non-alcoholic cirrhosis.

Hepatoprotective agents like ursodeoxycholic acid (UDCA), silymarin, and phosphatidyl choline have given variable results; theoretically, these drugs are more likely to benefit patients with precirrhotic liver disease, although UDCA has shown beneficial effects on the fibrosis in primary biliary cirrhosis. Colchicine has been used with some benefit in primary biliary cirrhosis and as an anti-fibrotic agent; however, more data are required.

Some causes of cirrhosis have specific therapy available; for example, antiviral agents in cirrhosis with activity due to hepatitis B and C, D-penicillamine or zinc therapy in Wilson's disease, iron chelation and phlebotomy in haemochromatosis, and corticosteroids and immunosuppressants in autoimmune disease.

Ascites

Bed rest and sodium restriction are of benefit in the management of ascites but are seldom adequate alone. The supine posture improves glomerular filtration rate and so is advisable especially for a few hours after a diuretic dose. Restriction of sodium intake in diet to 2-3 grams (40-60 mEq) per day helps reduce diuretic requirement; any further reduction makes food unpalatable. Fluid intake is restricted only in those with hyponatraemia.

The aldosterone antagonist spironolactone has a weaker natriuretic effect than loop diuretics but counters the secondary hyperaldosteronism in these patients. Low doses (100 to 150 mg per day) are effective in most cases but higher doses may be required in those with marked hyperaldosteronism. Amiloride is a cheaper alternative and is free of the risk of gynaecomastia that sometimes accompanies spironolactone therapy. Simultaneous administration of the loop diuretics frusemide or torsamide increases the natriuretic effect of both drugs and reduces the risk of potassium imbalance. The goal of diuretic therapy should generally be to achieve a weight loss of 0.5 kg a day in patients without peripheral oedema and up to 1 kg a day in those with oedema.

Hyponatraemia is a common complication of diuretic therapy. Approximately 20% of patients develop azotaemia due to intravascular volume depletion. These, along with the hypokalaemia complicating frusemide therapy, contribute to the precipitation of hepatic encephalopathy.

Ascites refractory to diuretics can be managed by one of the following modalities: therapeutic paracentesis (large-volume or total paracentesis with intravenous infusion of plasma expanders like human albumin or colloids); placement of transjugular intrahepatic porto-systemic stent (TIPSS); insertion of a peritoneovenous shunt (LeVeen shunt or equivalent); or portacaval shunt. The last two methods are not in favour now.

Portal Hypertension

Portal hypertension is the most common and lethal complication of cirrhosis. It is defined as clinically significant by an increase in the portal pressure gradient above 10 mm Hg (for formation of varices) or 12 mm Hg (for variceal bleeding, ascites). Varices develop in most patients during long-term follow-up.

The Sengstaken-Blakemore triple-lumen tube and its variations have been used for emergency control of variceal bleed when endoscopic therapy is not immediately available. Endoscopic band ligation is the preferred mode of treatment for bleeding oesophageal varices; injection sclerotherapy is done if band ligation is technically difficult.

Drugs used to treat portal hypertension are usually vasoconstrictors, and include vasopressin, terlipressin, somatostatin, propranolol and other beta-blockers. Vasodilators including isosorbide 5-mononitrate cause arterial hypotension, which in turn may enhance sodium retention and aggravate renal dysfunction. Failure of medical and endoscopic treatment can be managed by surgery (which is now rarely performed) or placement of a TIPSS.

Hepatic Encephalopathy

Most precipitating events for encephalopathy are correctable with appropriate therapy. Thus, fluid, electrolyte and glucose levels must be monitored and corrected where indicated; diuretic therapy may have to be discontinued, if it contributes to the imbalance. A search should be made for a focus of infection, which in most cases is either spontaneous bacterial peritonitis or urinary or lower respiratory infection. If GI haemorrhage is present, appropriate therapy should be instituted, as this will also reduce the intestinal protein load. All medication with sedative effect should be discontinued.

Dietary protein can be started as soon as the patient is able to eat, but should be restricted initially to 0.5 g per kg body weight. Vegetable proteins are safer than animal proteins. The protein intake is increased gradually with improvement, with an aim of maintaining positive nitrogen balance. Protein overload should be avoided. Addition of the branched-chain amino acids may be beneficial especially in the protein-intolerant patient.

To reduce intestinal ammonia load, the colon should be cleansed with acidifying solutions like lactulose; tap water enema is ineffective. Ammoniagenic bacteria should be eliminated with

antibiotics; rifaximin is the current choice. The non-digestible disaccharide (lactulose) can be given orally to acidify the colon; its dose should be titrated (usually 15 g 3-6 times daily) to obtain 2 to 3 soft stools a day. Lactitol is used as an alternative.

The benzodiazepine antagonist flumazenil has been tried with some benefit in hepatic encephalopathy. Results with L-dopa and bromocriptine are less promising. Extracorporeal liver assist devices and bioartificial livers are under evaluation.

COMPLICATIONS

Functional renal failure is estimated to exist in about 15% of patients admitted to hospital with ascites and in about 50% of cirrhotics who die. The risk of developing this complication in patients with ascites is estimated at 30% and 40% at 2 and 5 years, respectively. The renal failure is secondary to alterations in systemic haemodynamics and renal perfusion; the kidneys themselves are otherwise normal. The most serious clinical type ('hepatorenal syndrome') is characterised by a rapid rise in blood urea and serum creatinine, progressive oliguria, dilutional hyponatraemia and hyperkalaemia. Most patients have tense ascites. Early institution of terlipressin and albumin infusion may help arrest this otherwise fatal development.

Spontaneous bacterial peritonitis is an infection of low-protein ascitic fluid by organisms translocated from the alimentary tract. The infection is usually monomicrobial, unlike in secondary bacterial peritonitis.

Portal vein thrombosis can complicate cirrhosis. Hepatocellular carcinoma develops in 10% to 25% of patients with liver cirrhosis depending on the cause and survival duration. The risk is much higher in patients with hepatitis B or C infection; haemochromatosis, alpha-1 antitrypsin deficiency and alcoholic cirrhosis are the other at-risk groups.

The hepatopulmonary syndrome and portopulmonary hypertension are two dreaded complications of cirrhosis for which therapy (short of liver transplantation) is presently unsatisfactory.

PROGNOSIS

It is estimated that patients with compensated cirrhosis become decompensated at the rate of approximately 10% per year. Five-year survival in compensated and decompensated cirrhosis is about 50% and 20%, respectively. Ascites is usually the first sign of decompensation. Among those with ascites, presence of tense ascites or functional renal failure carries a grave prognosis, with death usually occurring within weeks or months.

The original Child-Turcotte grading of severity of liver disease into A, B and C classes considered bilirubin and albumin levels, ascites, encephalopathy and nutrition. Pugh's modification replaced prothrombin time for nutritional status, and allocated points according to severity (**Table 4**). These systems have proved useful in determining prognosis, but consideration must also be given to other factors like age, presence of viral markers, renal function, nutritional status, continued alcohol consumption, size of varices or risk of haemorrhage, and hepatocellular carcinoma. Recently, a more accurate model for end-stage liver disease (MELD) score has been used to predict survival as well as to determine priority for liver transplantation. The MELD score is calculated using the equation: 3.8 x log (e) (bilirubin mg/dL) + 11.2 x log (e) (INR) + 9.6 log (e) (creatinine mg/dL) [INR: international normalised ratio], which is easier done by logging on to dedicated websites and entering the relevant figures. Scores range from 6 (least ill patient) to 40 (sickest patient).

Table 4: Child-Turcotte-Pugh Grading of Severity of Liver Disease

Parameters	Points		
	1	2	3
Encephalopathy (grade)	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	1 to 2	2 to 3	>3
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (seconds prolonged)	1 to 4	4 to 6	>6
Total score	CTP class		
5 to 6	A		
7 to 9	B		
10 to 15	C		

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14.10 Extra-Hepatic Portal Venous Obstruction

Sharad Shah

DEFINITION AND EPIDEMIOLOGY

Extra-hepatic portal venous obstruction (EHPVO) is blockage of the portal vein either in the lumen, in the wall or extrinsic compression from outside the portal vein. EHPVO is a form of non-cirrhotic portal hypertension (NCPH) characterised by obstruction (acute, chronic or insidious) of the extra-hepatic portal vein, with or without the involvement of intra-hepatic portal veins or splenic or superior mesenteric veins. Most commonly, the blockage occurs at the site of portal vein formation (90%). Isolated occlusion of the splenic vein or superior mesenteric vein does not constitute EHPVO. Portal hypertension in EHPVO is pre-sinusoidal and the hepatic blood flow is normal or decreased.

EHPVO is common in India and is responsible for 6% to 40% of all patients with portal hypertension in various series; this proportion is <10% in the West. Males are predominantly affected. In children, EHPVO accounts for up to 70% of cases of portal hypertension.

AETIOPATHOGENESIS

The aetiology of EHPVO differs in different age groups. Thrombosis of the portal vein is the most important mechanism causing EHPVO. However, it is debatable whether phlebosclerosis is the primary pathology with thrombosis supervening later on. The major cause of EHPVO in adults and children are shown in **Table 1**.

Table 1: Causes of Extra-Hepatic Portal Venous Obstruction (EHPVO)

Children	Adults
Idiopathic Approximately 50% of children with EHPVO	**Hypercoagulable state** Prothrombotic disorders, more often occult than overt, are more frequently detected in adult patients with EHPVO. Myeloproliferative disorders, typifid as JAK_2 mutation, deficiencies of antithrombin III, protein C and protein S, prothrombin gene mutation, factor V Leiden mutation and methylene tetrahydrofolate reductase gene mutation are examples of such disorders
Infection Neonatal umbilical sepsis and umbilical vein cannulation. Intra-abdominal sepsis, severe dehydration due to a diarrhoeal illness, abdominal surgery, Others Trauma Multiple exchange transfusions	**Intra-Abdominal Infection** Portal pyaemia, biliary infection, post-surgical sepsis, etc. (These play a role in a small proportion of adult-onset EHPVO)
Developmental anomaly Portal vein stenosis or atresia are rare causes of EHPVO. These children usually have other associated congenital anomalies	**Others** Oral contraceptives, pregnancy and abdominal surgery may also incite development of portal vein thrombosis
Hypercoagulable states It may contribute to the development of EHPVO in a few children. However, factor V Leiden and prothrombin gene G20210A mutations are uncommon in EHPVO	**Secondary involvement of portal vein** Liver diseases (cirrhosis, hepato-cellular carcinoma) and pancreatic diseases (chronic pancreatitis, trauma, tumours) are also known causes of EHPVO

CLINICAL FEATURES

EHPVO has a bimodal distribution of age of presentation, with one peak in childhood and the other in adult age group. In children, EHPVO is mostly chronic and presents with variceal bleeding. In adults, EHPVO may present either as an acute or as a chronic condition.

Children

Recurrent upper gastrointestinal (GI) bleeding from oesophageal varices presenting as haematemesis and melaena, is the most common presentation. The bleeding episodes are usually tolerated well. Some patients develop transient ascites following episodes of upper GI bleeding.

Splenomegaly is nearly universal in patients with EHPVO. A few children with EHPVO may present with a left upper abdominal lump/discomfort (due to massive splenomegaly), as the only complaint. It may be associated with a dragging feeling or mild pain in the splenic area or pain due to splenic infarcts.

Although hypersplenism is common, it is usually asymptomatic. Though, some patients may present with symptomatic anaemia or thrombocytopaenia.

About 50% of children with EHPVO show evidence of growth retardation. Reduction in portal blood flow to the liver affects growth hormone and reduced levels of insulin-like growth factor are believed to be the likely factors.

Adults

Acute portal vein thrombosis (PVT) in adults most frequently presents as acute abdominal pain. Other features in these patients include fever, ascites and intestinal ischaemia. Collaterals are not found in these patients.

In patients with chronic portal vein obstruction, recurrent upper GI bleeding from oesophageal or gastric varices is the main presenting feature. These patients can also bleed from ectopic varices located in the duodenum (presenting as melaena) or anorectal region.

Some patients develop transient transudative ascites following upper GI bleeding. Uncommon presentations of EHPVO include symptomatic hypersplenism and portal biliopathy. The latter is characterised by abnormalities of biliary ductal system due to paracholedochal collaterals compressing the bile duct from outside. The pathogenesis is not well known. It is postulated that external pressure and/or ischaemia may play a role. Though portal biliopathy is demonstrable by cholangiography in about 80% patients of EHPVO, it is rarely symptomatic in the form of biliary colic, obstructive jaundice or cholangitis.

Some patients develop liver dysfunction during long-term follow-up. Moreover, these patients are at-risk of acquiring

hepatitis B and hepatitis C virus infections through blood transfusions administered for recurrent GI bleeding.

DIAGNOSIS

The diagnosis of EHPVO is based on the presence of a typical clinical presentation (a child or young adult presenting with well-tolerated episodes of haematemesis and moderate to massive splenomegaly), normal liver function tests (LFT), demonstration of PVT and portal cavernoma on Doppler studies, and preserved liver architecture on liver biopsy to rule out compensated cirrhosis of liver.

In EHPVO, liver function tests are generally normal. However, in some patients with long-standing EHPVO, prolonged prothrombin time and reduced serum albumin levels may occur. Hypersplenism may lead to reduction in one or more blood cell lines.

Investigations for prothrombotic states, such as estimation of serum anti-thrombin III, protein C, protein S levels and the presence of factor V Leiden mutation may be useful. Overt myeloproliferative disorders can be diagnosed by bone marrow biopsy. Occult myeloproliferative disorders require more complex tests. Prothrombin gene mutation has been reported in Western populations, but not in India.

Upper GI endoscopy is used to diagnose the presence of oesophageal varices. Nearly 40% of patients also have gastric varices. Ectopic varices in the duodenum may be detected in some patients.

Most common differential diagnoses of EHPVO include other causes of portal hypertension, such as non-cirrhotic portal hypertension and liver cirrhosis. Patients with EHPVO do not have dilated venous collaterals over the anterior abdominal wall, whereas such veins can occur in intra-hepatic causes of portal hypertension. Presence of abdominal wall collaterals reliably excludes EHPVO, as does the presence of a normal portal vein at ultrasonography and Doppler studies.

It is sometimes difficult to differentiate EHPVO from well-compensated cirrhosis. The situation becomes more complex when cirrhosis is associated with PVT. The presence of dilated collaterals on anterior abdominal wall (if present) and nodularity of liver on ultrasound suggest a diagnosis of cirrhosis. Liver biopsy is often required to exclude cirrhosis. Other causes of non-cirrhotic portal hypertension like congenital hepatic fibrosis in children, veno-occlusive disease, nodular regenerative hyperplasia and partial nodular transformation of liver should be excluded.

TREATMENT

The management of EHPVO depends on the patient's age, the site of venous obstruction and clinical presentation. Acute variceal bleeding can be often easily and effectively controlled using endoscopic variceal ligation. Endoscopic variceal ligation followed by endoscopic sclerotherapy (EST) is better than EST alone in Children with EHPVO. They require fewer sessions and have fewer complications. However, evolution of gastric varices and portal hypertensive gastropathy is similar in both children and adults. Overall prognosis of patients with EHPVO is excellent, especially after variceal obliteration. Gastric varices are usually dealt with using injection of cyanoacrylate glue. In a follow-up of nearly 20 years after variceal eradication by EST only one-sixth had reccurrence of bleeding. Bleeding is unusual after 10 years have passed since initial variceal eradication. Recurrent bleeding can be prevented by producing variceal obliteration by repeated use of the above endoscopic means. Beta blockers (propranolol) have also been found to be effective in prevention of variceal rebleeding.

Shunt surgery or devascularisation surgery is indicated for patients in whom endoscopic therapy has failed. Shunt surgery is also required for patients with symptomatic portal biliopathy, symptomatic hypersplenism and in children with growth retardation. Mesenteric-left portal vein bypass may prevent growth retardation.

In elective situation, even transabdominal gastroesophageal devascularisation without transection effectively controls bleeding. Growth impairment and neurocognitive ability is of prime importance in children. For this a bypass surgery like mesenteric-left portal vein bypass (Rex shunt) gives near cure. The role of prophylactic porto-systemic shunt surgery in EHPVO is not yet conclusively studied.

The underlying prothrombotic state may need treatment in its own right. Anticoagulants are indicated in patients with acute PVT. The role of life-long anticoagulation in patients with chronic EHPVO and a demonstrable prothrombotic state is still debatable. Anticoagulation is needed in the post-operative phase after shunt surgery.

Symptomatic portal biliopathy can be managed with endoscopic biliary stenting and stone extraction. If surgical biliary-enteric anastomosis is planned for persistent symptomatic biliopathy, usually shunt surgery is also necessary to reduce portal pressure to decompress the pericholedochal venous collaterals and biliary bypass later on or at the same sitting.

Symptomatic hypersplenism should be treated using shunt surgery with or without splenectomy.

COMPLICATIONS

Presentation of EHPVO is usually by its own complications in the form of haematamesis, splenomegaly or biliopathy.

PROGNOSIS AND PREVENTION

Prevention of perinatal infection and proper care of hyper-coaguable states may prevent EHPVO.

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14.11 Non-Alcoholic Fatty Liver Disease

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INTRODUCTION

The term non-alcoholic steatohepatitis (NASH) was first introduced in 1980 to describe liver histology changes resembling alcoholic hepatitis in patients with no or insignificant alcohol intake. This condition was described as more common among women and persons with morbid obesity, diabetes mellitus or metabolic syndrome. Since then, it has been realised that NASH is a part of a wider group of conditions, now called as non-alcoholic fatty liver disease (NAFLD). NAFLD encompasses a spectrum of liver disorders characterised by macrovesicular hepatic fat accumulation alone (steatosis), or accompanied by signs of hepatocyte injury, mixed inflammatory cell infiltrate, and variable hepatic fibrosis (non-alcoholic steatohepatitis, NASH), leading to cirrhosis. Approximately 20% to 30% of adults in the general population in Western countries have non-alcoholic fatty liver disease and its prevalence increases to 70% to 90% among persons who are obese or have diabetes. It is an increasingly recognised cause of liver-related morbidity and mortality. NASH can progress to cirrhosis and end-stage liver disease and is projected to be the leading cause of liver transplantation by 2020; furthermore, emerging evidence suggests that NAFLD overall is associated with an increased cardiometabolic risk.

EPIDEMIOLOGY

The true incidence and prevalence of NAFLD are unknown. The prevalence of NAFLD has increased over the last few years. Based on imaging studies, the prevalence of NAFLD in the adult population ranges from 14% to 31%. The global epidemic of obesity and diabetes in all age groups may be partly responsible for the increase. Incidence of steatosis clearly increases with obesity. A large population-based study found that 91% of obese individuals [Body mass index (BMI) >30 kg/m^2] had evidence of steatosis on ultrasound. The prevalence of NASH is even more difficult to determine as large population-based studies are not possible, as liver biopsy is required for diagnosis of NASH.

Urbanisation and associated changes, such as sedentary life style and fat rich diet, and a higher inherited tendency for diabetes mellitus makes Indians more prone to metabolic syndrome or insulin resistance and its manifestations, such as NAFLD and NASH. In a more recent, community-based epidemiological study, 1911 inhabitants of a rural area in West Bengal were studied. The prevalence rates of NAFLD, NAFLD with elevated alanine aminotransferase, and cryptogenic cirrhosis were 8.7%, 2.3%, and 0.2%, respectively. The risk of NAFLD was the highest in those with BMI >25 kg/m^2.

Both fatty liver and NASH have been reported in all age groups, including children, with highest prevalence in those between 40 and 49 years of age. Recent studies have shown that NASH occurs with equal frequency in males and females.

AETIOPATHOGENESIS

Several mechanisms have been postulated to explain the pathogenesis of NASH. The 'multiple hit' hypotheses is currently favoured. The first 'hit' is development of hepatic macro-steatosis as a result of increased lipolysis and free fatty acids. Postulated mechanisms leading to hepatic steatosis include increased lipogenesis, decreased lipid export, and a reduction of free fatty acid oxidation with insulin resistance leading to fatty acid dysregulation. Several potential 'second hits' include oxidative stress from reactive oxygen species in the mitochondria and cytochrome P450 enzymes. Other second hits include the presence of endotoxins, cytokines, adipokines, and environmental factors. These complex interactions of the various factors lead to insulin resistance, and serum and liver iron overload and oxidative stress that lead to necroinflammation and fibrosis. NAFLD is associated with metabolic syndrome which leads to insulin resistance resulting in fat deposition in hepatocytes by inducing increased lipolysis, increased uptake of fatty acids and reduced export of very low-density lipoprotein (VLDL). Truncal or central obesity is more strongly associated with NAFLD. In severely obese people, the risk of liver disease increases progressively with the number of features of metabolic syndrome present. Family studies suggest that genetic factors may also play a role in the progression of NAFLD.

CLINICAL PRESENTATION

Most patients with NAFLD are asymptomatic. Diagnosis most often follows incidental detection of raised liver enzymes or of fatty liver on ultrasound. These abnormalities are usually picked up during evaluation for dyspepsia, malaise or fatigability, prior to medical procedures like organ donation, or routine health examination. A smaller fraction of patients experience symptoms indicative of more serious liver disease and may develop pruritus, anorexia, and nausea. The development of ascites, anasarca, variceal hemorrhage, or symptoms of hepatic encephalopathy indicates decompensated cirrhosis. Similarly, jaundice occurs late in the course of NASH and indicates advanced liver disease. No specific symptoms can distinguish NAFLD or NASH from other type of liver diseases. The diagnosis of NAFLD requires the exclusion of other specific etiologies of liver disease and excessive alcohol consumption. The majority of patients have one or more risk factors for metabolic syndrome, such as type 2 diabetes, obesity, hypertension, or hyperlipidaemia. Clinical examination is often unremarkable though nearly half the patients have mild hepatomegaly. Jaundice or signs of liver failure are absent.

DIAGNOSIS

NAFLD should be suspected as a cause of asymptomatic elevation of aminotransferases. However, it is important to remember that NAFLD can be present with normal or fluctuating aspartate aminotransferases (AST) and alanine aminotransferases (ALT). In general, ALT is higher than AST. The diagnosis of NAFLD is

strongly suggested when metabolic syndrome is present and other specific aetiologies for hepatic dysfunction have been excluded. About 30% to 50% of patients with NASH have either diabetes or glucose intolerance. A fasting lipid profile shows hypertriglyceridaemia in 20% to 80% of patients.

Ultrasound may show liver steatosis as a hyperechogenic image, that is, 'bright liver'. Radiologic techniques used to evaluate NAFLD include ultrasound, computed tomography (CT), magnetic resonance imaging, and magnetic resonance spectroscopy (MRS). However, these radiologic modalities are accurate in detecting hepatic steatosis only when there is moderate to severe steatosis. Although these modalities can detect hepatic steatosis, none is able to distinguish simple steatosis from NASH or determine the stage of hepatic fibrosis. Fibroscan (tissue elastography) is a new non-invasive modality in detecting liver fibrosis and its role in various liver diseases, including NAFLD, is still evolving.

Liver biopsy is diagnostic, but may not be routinely required. It allows semi-quantitative assessment of amount of fat deposition and of associated necro-inflammation and fibrosis. Typical histological features of NAFLD predominate in perivenular regions, i.e. zone 3 of hepatic acinus and include the presence of macrovesicular steatosis, lobular neutrophilic inflammation, presence of Mallory bodies, ballooning degeneration, lipogranuloma and pericellular fibrosis.

Non-Alcoholic Fatty Liver Disease (NAFLD) in India

NAFLD is an important cause of liver disease in India. Epidemiological studies suggest prevalence of NAFLD in around 9% to 32% of general population in India with higher prevalence in those with overweight/obesity and those with diabetes/prediabetes. Indian population has a higher body fat content and abdominal adiposity; the latter is particularly associated with insulin resistance and thus NAFLD, even if the BMI is normal. Indians also more often have atherogenic dyslipidaemia (combination of hyper-triglyceridaemia, low high-density lipoproatein (HDL)-cholesterol and high low-density lipoprotein (LDL)-cholesterol), and diabetes. These factors, along with urbanisation and associated sedentary life-style and fat-rich diet may make Indians particularly prone to metabolic syndrome, insulin resistance, and NAFLD/NASH.

In Indian patients with NAFLD, the disease is usually milder, often with either no or mild inflammation and fibrosis on liver biopsy even in those with elevated liver enzymes.

Role of NAFLD in Cryptogenic Cirrhosis and Hepato cellular Carcinoma (HCC)

NASH is associated with cryptogenic cirrhosis. Patients with NASH and fibrosis can progress to cirrhosis with the risk varying from 0% at 5 years to 12% over 8 years. It has been observed that when patients progressed to cirrhosis, inflammation and fat disappeared from their liver biopsy. A number of epidemiologic studies of cryptogenic cirrhosis have estimated that antecedent NASH constitutes a large proportion of cryptogenic cirrhosis cases. An early asymptomatic phase followed by appearance of decompensated cirrhosis is now a recognised complication of NASH. Once cirrhosis develops, patients are at high-risk of developing HCC.

TREATMENT

Currently, there are no approved therapies for NAFLD. There are many proposed agents being evaluated currently, each targeting a different step in the pathogenesis of development of hepatic steatosis or progression to steatohepatitis. The proper dosing, duration of treatment, safety, and tolerability of these treatments is still evolving (**Table 1**).

At the present time, the initial approach involves dietary modification based on the metabolic profile (obesity, diabetes, hyperlipidaemia, hypertension) and getting patients to increase

Table 1: Therapy for Non-Alcoholic Fatty Liver Disease

Treatment	Effects	Mechanism of Action	Side Effects
Insulin sensitisers			
Metformin	Enhance weight loss Improve insulin sensitivity and plasma glucose levels Reduce metabolic syndrome	Decrease production of hepatic glucose and increasing the uptake of peripheral glucose by skeletal muscle and fatty acid oxidation	Gastrointestinal (GI) intolerance
Thiazolidinediones			
Pioglitazone and Rosiglitazone (Not in use)	Improve ALT, histological steatosis and inflammation	Stimulate free fatty acid (FFA) oxidation, increase adiponectin expression	Weight gain and lower extremity oedema
Antioxidants			
Vitamin C and E	Improve ALT and steatosis	Decrease oxidative stress	No significant adverse effects
Hepatoprotective Agents			
Betaine	Improves ALT, steatosis and inflammation	Increases S-adenosylmethionine levels	
Ursodeoxycholic acid	Marginally significant benefit on various liver enzymes	Bile acid, which has various cytoprotective, anti-apoptotic and immunomodulatory properties	GI side effects: diarrhoea, motility disorders
Pentoxifylline	Improves ALT and histology	It functions by inhibiting TNF-α	Minor GI side effects
Lipid lowering Drugs			
Statins, poly unsaturated fatty acid (PUFA) and Probucol	Improves aminotransferases, steatosis and slows progression of fibrosis	Lowers elevated triglycerides and improves low HDL	Risk of hepatotoxicity reduced HDL with probocul, safety concern in patients at high cardiovascular risk
L-Carnitine	Improve steatosis, and amino-transferases	A modulator of mitochondrial FFA transport and oxidation	Well tolerated

levels of physical activity. Even small changes in body weight (0.5 to 3 kg) can achieve improvement in hepatic necro-inflammatory activity and/or radiologic resolution of hepatic steatosis and/or reversal of insulin resistance. The role of weight-reducing pharmacologic regimens, such as phentermine, sibutramine, and orlistat in NAFLD is not established. The most consistent and spectacular evidence for treatment efficacy against NASH comes from literature on obesity surgery in which highly reproducible benefits against steatosis, steatohepatitis, and hepatic fibrosis have been reported. In patients with morbid obesity, bariatric surgery may be considered.

Various other treatment modalities used for NAFLD have included treatment of risk factors like diabetes mellitus and hyperlipidaemia, and use of insulin sensitizing agents such as biguanides (metformin), thiazolidinediones (rosiglitazone, pioglitazone) and antioxidants and various hepatoprotective agents. Weight loss, thiazolidinediones (especially pioglitazone), and antioxidants have been extensively evaluated. Weight loss is safe and improves histological disease activity in NASH, but more than 50% of patients fail to achieve target weight loss. Thiazolidinediones improve steatosis and inflammation, but cause significant weight gain. Studies show conflicting results with antioxidants. Antioxidants are heterogeneous in relation to type and dose of drugs, their duration of action and implementation of life-style intervention. Other agents like pentoxifylline, telmisartan, L-carnitine and vitamin E are being evaluated.

CONCLUSION

NAFLD is a major cause of liver-related morbidity in both developed and developing countries. It is frequently associated with the presence of insulin resistance. There is increasing evidence that NAFLD can progress to cirrhosis and liver failure. Physicians should actively check for the presence of NAFLD in those who are overweight and/or diabetic. There is no established treatment for NAFLD. Treatment usually is directed toward optimising body weight and role of pharmacological therapy is under evaluation.

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14.12 Acute Liver Failure

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INTRODUCTION

The term liver failure is used when the survival of an individual is endangered as a consequence of multiple metabolic and haemodynamic disturbances resulting from severe acute or chronic liver injury. In a clinical setting, hepatic injury is usually recognised by appearance of jaundice and liver failure is recognised by occurrence of encephalopathy, ascites or coagulopathy.

Authors prefer to categorise liver failure into three distinct groups: acute liver failure (ALF), subacute hepatic failure (SHF) and chronic liver failure (CLF). ALF is defined as occurrence of hepatic encephalopathy with or without coagulopathy within 4 weeks of the onset of acute hepatitis. Occurrence of progressive ascites with or without encephalopathy after 4 weeks, but before 6 months of the onset of acute hepatic illness is termed as SHF. Occurrence of progressive ascites or encephalopathy after 6 months of recognisable or unrecognised hepatic illness is considered as CLF.

DEFINITION AND NOMENCLATURE

Trey and Davidson define ALF as occurrence of encephalopathy with or without coagulopathy within 8 weeks of onset of symptoms of acute hepatitis in an individual without any history of pre-existing liver disease. Patients who develop ALF within 7 to 10 days of the onset of icterus have significantly higher survival rates than those who develop encephalopathy later. Therefore, in Western countries, ALF is classified into hyperacute if encephalopathy develops within 10 days of onset of icterus and acute if it occurs between 10 days and 4 weeks of onset of jaundice.

Liver failure occurring more than 4 weeks after the onset of acute hepatic illness manifests with progressive ascites. In these patients, encephalopathy as a presenting feature is extremely rare. This condition, named as (SHF), behaves differently than ALF and majority do not survive beyond 6 months. The overall mortality rate is 70%; in addition, 60% of the survivors develop chronic sequelae.

AETIOLOGY OF ACUTE LIVER FAILURE

The causes of ALF are listed in **Table 1**. Geographical variations in the occurrence of common causes of ALF are well recognised and probably influence the clinical behaviour of such patients. ALF in the Eastern World, particularly in the developing world, is predominantly caused by various hepatotropic viruses (**Table 2**). Conditions like paracetamol overdose, metabolic liver diseases like Wilson's disease, acute fatty liver of pregnancy, *amanita* poisoning and drug-induced liver injury are important causes of ALF in the West, whereas these are extremely infrequent in the Eastern World (**Table 3**).

Table 1: Various Causes of Acute Liver Failure

Broad Category	Individual Aetiological Agents
Infections	Hepatotropic viruses (A-E) Cytomegalovirus Herpes simplex virus
Metabolic diseases	Wilson's disease Acute fatty liver of pregnancy Galactosaemia
Drugs	Paracetamol Rifampicin and isoniazid Sodium valproate Halothane Zidovudine Didanosine
Toxins	*Amanita phalloides* *Bacillus cereus* Akee fruit (hypoglycin)

Table 2: Causes of Acute Liver Failure in India

Author	Year	No. of Patients	Causes							
			HAV	HBV	HCV	HDV	HEV	Mixed	Non-A, Non-E	Drugs
Acharya *et al*	1999	458	4%	11%	4%	0%	23%	6%	47%	5%
Khuroo *et al*	1997	119	3%	15%	2.5%	2.5%	38%	NR	38.6%	0.8%
Jaiswal *et al*	1996	95	4%	27%	2%	5.2%	41%	4%	15%	0%

HAV = Hepatitis A virus; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HDV = Hepatitis D virus; HEV = Hepatitis E virus; NR = Not reported.

Table 3: Differences in Aetiology of Acute Liver Failure (ALF) in Various Geographical Areas

	India	USA	UK	France
Viral	95%	60%	30%	50% to 60%
Drugs	4.5%	30% to 35%	60%	15% to 20%
Other	0.5%	5%	10%	10% to 15%
Viruses	HEV, HBV, Mixed viral infection	Cryptogenic HBV: 15% HAV: 8% to 10%	NANB HBV HAV	HBV HAV
Drugs	Anti-tuberculars	Acetaminophen	Acetaminophen	Other drugs

NANB = Non-A, non-B viral hepatitis.

CLINICAL PRESENTATION AND NATURAL COURSE

Demographic and clinical profile of 423 consecutive patients with ALF admitted to AIIMS, New Delhi, during 1987 to 1993 is summarised as follows. Most of the patients (n = 334) were below 40 years of age. Females outnumbered males. Twenty-five-per cent of females were pregnant in contrast to a 3% pregnancy rate in the general population, indicating that pregnant women who develop acute viral hepatitis are more likely to develop ALF

than non-pregnant women. Most patients (88%) had a prodrome preceding the icteric illness; mean duration of the prodrome was 4.7 days. The interval between prodrome and onset of encephalopathy was similar in survivors and non-survivors indicating that rapidity of onset of encephalopathy did not influence the outcome. The survival rate using conservative and aggressive supportive therapy was 34%.

ALF and Pregnancy

Mortality is similar in pregnant and non-pregnant women, and is independent of the cause or trimester

Pregnancy *per se* should not be regarded as a poor prognostic factor

COMPLICATIONS

Complications encountered in patients with ALF may involve several organ systems, either in isolation or in combination.

Neurologic Manifestations

Neurologic complications include rather distinct, but overlapping syndrome of cerebral oedema manifesting as increased intracranial pressure (ICP) and encephalopathy. The grading of encephalopathy is depicted in **Table 4**.

Table 4: Grading of Encephalopathy in Acute Liver Failure (ALF)

I	Loss of sleep rhythm, drowsiness, confusion, hepatic flap
II	Features of grade I encephalopathy with loss of sphincter control
III	Unconsciousness, no response to oral commands, but responds to painful stimuli
IV	No response to pain, deep unconscious state

In addition to changes in mental status, signs of raised ICP include myoclonus, focal seizures, decerebrate postures, absent pupillary reflexes and hyperventilation. Papilloedema is usually absent. Lowering the ICP in patients with ALF is important because raised ICP decreases cerebral perfusion pressure and oxygenation of the brain tissue. Unlike porto-systemic shunting, which is the major cause of encephalopathy in patients with cirrhosis, encephalopathy in ALF is usually multifactorial. Ammonia, mercaptans, biological amines, short chain fatty acids, pseudo-neurotransmitters from aromatic aminoacids, gamma amino butyric acid (GABA) have been implicated in the causation of encephalopathy.

Identification of elevated ICP is important because cerebral oedema resulting in brainstem herniation is the commonest cause of death among patients with ALF.

Renal

Renal failure occurs in 30% to 70% of patients with ALF in western countries where drugs and toxins are the usual causes of ALF. In contrast, renal failure occurs in only 3% to 5% of Indian patients where hepatotropic viruses are the predominant cause of ALF. Presence of renal failure is considered to be a bad prognostic indicator. Decreased water clearance, electrolyte imbalance, increased ammonia production due to raised blood urea are sequelae of renal failure which aggravate encephalopathy and cerebral oedema in patients with ALF.

Pulmonary

Pulmonary infection is the commonest form of respiratory problem encountered in ALF. In addition, acute respiratory distress syndrome, atelectasis, aspiration and pulmonary oedema may occur.

Cardiovascular

Cardiac arrhythmias may occur due to electrolyte imbalance, hypoxaemia, acidaemia, or during placement of pulmonary artery catheter. Usually patients with ALF have a hyperdynamic circulatory state similar to septic shock. This may be caused by decreased systemic vascular resistance subsequent to a vasodilator substance which under normal conditions is cleared by liver. Candidate vasodilator substances implicated in ALF include endotoxins, nitric oxide, glucagon, substance P, vasoactive intestinal polypeptide, GABA, atrial natriuretic factor and bradykinin.

Coagulopathy

Most proteins that promote or inhibit coagulation are synthesised in the liver. Further, Kupffer's cells in the liver act as scavengers for the activated coagulation factors in the circulation. With the exception of factor VIII, the levels of all coagulation factors are reduced in patients with ALF.

The coagulation test that can be easily performed in most laboratories is prothrombin time. Almost all patients with ALF show a variable degree of prolonged prothrombin time. Prothrombin time is a good indicator for prognosis.

Other coagulation problems that may be encountered in patients with ALF are thrombocytopaenia (which may be due either to marrow suppression or hypersplenism), disseminated intravascular coagulation and fibrinolysis. Each of these conditions may cause life-threatening bleeding, such as intracranial haemorrhage and gastrointestinal (GI) bleeding.

Sepsis

Sepsis occurs in 55% to 80% of patients with ALF. Bacterial infections are the commonest cause (70% to 80%) of sepsis and fungal infection occur in 10% to 20% of these patients. The reasons for this propensity to develop sepsis include abnormal opsonisation due to reduced hepatic synthesis of proteins like fibronectin, impaired Kupffer cell function, decrease in complement synthesis and neutrophil dysfunction.

Metabolic

Three distinct metabolic complications have been documented in patients with ALF. Hypoglycaemia occurs due to decreased insulin clearance, impaired gluconeogenesis, and loss of glycogen store due to liver damage. Both acidosis and alkalosis can occur in ALF. Respiratory alkalosis can occur due to central neurogenic hyperventilation, whereas depression of respiratory centre due to raised ICP may cause respiratory acidosis. Acidosis can also result from hypoxaemia or hypotension leading to accumulation of lactate, pyruvate, citrate, acetoacetate, and free fatty acids (FFAs). Electrolyte imbalance is common in patients with ALF secondary to renal failure, dehydration, drugs, tissue damage, and acid-base imbalance.

PROGNOSIS

The assessment of prognosis soon after initial presentation is crucial in order to allow most efficient use of available therapeutic options, particularly orthotopic liver transplant (OLT) which is increasingly becoming available in the developing countries like India. Arterial ammonia concentration higher than 124 μmol/L, associated with severe hepatic encephalopathy, cerebral oedema

and high mortality. Prognostic markers in Indian patients with ALF are: age ≥40 years, clinical evidence of cerebral oedema at admission, serum bilirubin ≥15 mg/dL and prothrombin time ≥25 seconds more than the normal. More than 90% of the patients with ALF having three or more of these factors die (**Tables 5 and 6**). Anti-tuberculosis therapy (ATT) induced ALF has a poor prognosis as compared with viral hepatitis.

Table 5: King's College Prognostic Criteria in Acute Liver Failure (ALF), Predicting High Mortality

Non-Paracetamol-Induced ALF	Paracetamol-Induced ALF
Prothrombin time >100 seconds or Any three of the following Age <10 or >40 years Aetiology: non-A, non-B hepatitis Drug-induced hepatitis Icterus-encephalopathyinterval >7 days Prothrombin time >50 seconds (INR >3.5) Serum bilirubin >17.5 mg/dL	Plasma pH <7.30 or Prothrombin time >100 seconds (INR >6.5) and serum creatinine >3.4 mg/dL in patients with grade 3 to 4 encephalopathy

Table 6: Clichy Criteria (France) for Poor Prognosis in Patients with Acute Liver Failure

Factor V levels < 20% of normal in patients < 30 years of age
Factor V levels < 30% of normal in patients > 30 years of age

Causes of Death

Survival rate of patients with ALF is approximately 34%. Two-thirds of deaths occur within the first 72 hours of hospitalisation, indicating that any therapeutic intervention for such patients must be instituted soon after hospitalisation, and that early referral of such patients to advanced centres should be encouraged. The median survival time is 4 days. Cerebral oedema, sepsis, renal failure, and GI bleeding are the most important causes of death.

TREATMENT

All the patients diagnosed to have ALF should ideally be admitted to an intensive care unit. The use of aggressive monitoring, and of respiratory and cardiovascular support particularly in the presence of cerebral oedema is probably responsible for modest improvements in the survival. However, if OLT is available, early referral of such patients may reduce greater post-transplant mortality and morbidity. The essential supportive measures are listed in **Table 7**.

MANAGEMENT OF COMPLICATIONS

Cerebral Oedema

Patients with advanced grades of encephalopathy and/or with overt cerebral oedema need measures to prevent further rise in ICP and specific therapeutic intervention to decrease ICP.

Measures to prevent rise of ICP include positioning of head and trunk at 35° to 40° angle above horizontal, avoiding unnecessary motions of the head, and avoiding hypoxaemia, hypercapnoea, fluid overload and acid-base imbalance. For treating raised ICP, rapid infusion of mannitol (20%) at a dose of 100 mL is the first step; it can be repeated hourly as long as patient maintains adequate renal function. Usual recommendation is to keep the ICP below 25 mm Hg; however, it is probably more important to maintain the cerebral perfusion pressure (mean arterial pressure minus intracranial pressure) above 50 mm Hg. The placement of intra cranial transducers in patients with ALF may be associated with life-threatening bleeding and sepsis. In patients with advanced encephalopathy without overt features of cerebral oedema and intact renal function, authors use 20% mannitol at a dose of 1 g/kg body weight every 8 hourly. Hyperventilation using a ventilator and administration of corticosteroids has not been found to be useful in the treatment of cerebral oedema. Induction of barbiturate coma may be used as a rescue therapy if mannitol fails. Phenobarbital is used at an initial intravenous dose of 5 mg/kg followed by an infusion rate of 1 to 3 mg/kg per hour. However, hypotension is a major problem during such therapy and intra-arterial pressure monitoring is necessary during such therapy. Seizures might complicate advanced hepatic encephalopathy and worsen prognosis, phenytoin prophylaxis neither improves cerebral oedema nor survival.

Table 7: Supportive Therapy in Acute Liver Failure

- Hospitalisation in intensive care unit
- Detailed clinical evaluation and assessment of grade of encephalopathy, cerebral oedema and prognostic indicators
- Laboratory investigations
  - Complete blood counts, platelet count, smear for malarial parasite
  - Blood grouping
  - Electrolytes, blood urea nitrogen, creatinine
  - Serum bilirubin, transaminases, albumin, alkaline phosphatase, amylase
  - Prothrombin time, fibrin degradation products
  - Arterial blood gases, arterial ammonia
  - Urine analysis, urine output
  - Bacteriologic evaluation: blood, endotracheal aspirate in intubated patients and urine culture for bacteria and fungi
  - Serology including HBsAg, IgM anti-HBc, IgM anti-HEV, IgM anti-HAV, anti- HCV, anti-HDV
- 24-hour urine copper, serum copper, serum caeruloplasmin, anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody
- Bedside ultrasonography to rule out liver abscess, acute hepatic venous out flow tract obstruction
- Other measures
  - Central venous line insertion
  - Chest X-ray
  - Assisted ventilation in patients with cerebral oedema and grade IV encephalopathy
  - Intravenous H2 blockers, nasogastric tube placement, blood glucose, monitoring for gastrointestinal bleed, oliguria, sepsis
  - Nutritional supplement through nasogastric tube
- Optional measures
  - Placement of extradural or subdural transducers to measure ICP
  - Prophylactic broad-spectrum intravenous antibiotic and antifungal therapy
  - Dialysis, if acute renal failure supervenes

Sepsis

Sepsis, as described above, is the second major cause of death among Indian patients with ALF. Gram-negative bacteria are the major cause of sepsis in these patients. Prophylactic parenteral antibiotics using third-generation cephalosporins may reduce the incidence of sepsis.

Renal Failure

In patients with ALF developing oliguria despite maintenance of adequate central venous pressure, low dose dopamine (2 to 2.5 µg/kg/hr) may be beneficial. However, mainstay of management of renal failure in patients with ALF is haemodialysis or continuous arterio-venous haemofiltration or continuous veno-venous haemofiltration. However, these procedures are associated with problems, such as, hypotension, aggravation of cerebral oedema due to fluid overload and increased risk of bleeding. The only satisfactory treatment in patients with ALF associated with renal failure seems to be liver transplant.

Coagulopathy

Coagulopathy associated with ALF is currently not preventable. Prophylaxis use of fresh frozen plasma (FFP) and vitamin K has not been shown to prevent bleeding. However, once bleeding occurs, FFP and platelet transfusion may help.

Other Complications

Hypoglycaemia, hypokalaemia and metabolic acidosis should be looked for and treated promptly.

SPECIFIC THERAPIES

Many therapeutic measures have been tried in an attempt to improve liver function, to reduce hepatocyte necrosis, or to improve encephalopathy.

Acetylcysteine

N-acetylcysteine (NAC) is useful in patients with paracetamol overdose, probably through an increase in the concentration of hepatic glutathione which converts paracetamol to its non-toxic metabolite. However, it is most effective if given within 8 hours of the drug overdose. Even in non-paracetamol ALF patients, this drug may produce improvement in haemodynamic parameters like cardiac index and mean arterial pressure, leading to improved tissue oxygen delivery. Recent data suggests NAC is well tolerated in this group and is associated with improved non-transplanted survival, but only in those treated early in the course and with Grade I-II encephalopathy.

Antivirals

Lamivudine for hepatitis B or acyclovir for HSV related ALF, might improve outcomes, but data is scarce.

L-Ornithine L-Aspartate (LOLA)

LOLA does not improve ammonia concentration, hepatic encephalopathy or survival in ALF. Novel agents like L-ornithine phenylacetate are being investigated.

Prostaglandins

Intravenous prostaglandin E1 has been used in patients with ALF with conflicting results.

Other Forms of Therapy

For *Amanita phalloides* poisoning, infusions of penicillin and silymarin appear to be effective. Penicillin antagonises the effect of mushroom toxin, amatoxin, and silymarin blocks its hepatocellular uptake.

Liver Transplantation (LT)

Urgent LT is now the standard therapy for ALF in individuals who, on clinical and laboratory criteria, have a less than 20% chance of survival. Contraindications to LT include irreversible brain damage, uncontrolled bacteraemia, human immuno-deficiency virus infection, concurrent malignant disease and the presence of failure of any organ which would preclude a satisfactory outcome.

Auxiliary liver transplantation is another treatment option for ALF. The native liver is left *in situ*. The procedure aims to provide temporary liver support until the native liver recovers. In one such study, native liver regenerated in 68% of those surviving more than 3 months. At this stage, immunosuppression can be withdrawn in the majority of patients and the donor liver can either be removed surgically or left in place to atrophy.

In India, cadaveric LT has not been able to take off due to lack of organisational priority, severe donor shortage and lack of awareness. Living-donor liver transplant (LDLT) programme is being offered in some institutions in India.

Other Methods of Liver Support

The frequent lack of donor livers for urgent transplantation has necessitated the use of liver support or replacement therapies until a liver becomes available. Several different approaches have been tried. All of these methods involve the use of very expensive and complicated equipment and their role awaits clarification by randomised clinical trials. These include extracorporeal liver assist devices, bioartificial liver, and extracorporeal wholeorgan perfusion.

Hepatocyte Transplantation

Uncontrolled trials using infusion of human hepatocytes into the splenic artery or portal vein have shown encouraging preliminary results. The mass of hepatocytes required to provide adequate support remains unknown.

Therapies Not Useful in Acute Liver Failure

1. Lactulose
2. L-ornithine L-aspartate
3. Branched-chain amino-acids
4. FFP transfusion in absence of bleeding
5. Enteral decontamination
6. Prophylactic phenytoin
7. Prophylactic hyperventilation for raised intracranial hypertension

PREVENTION

Public health measures like availability of safe drinking water; screening of blood in blood banks; vaccination for hepatitis B and use of disposable syringes will reduce the incidence of hepatitis A, B and E viral infections, which are the major causes of ALF in our country. Empirical use of ATT should be avoided, whenever possible.

RECOMMENDED READINGS

1. Kumar R, Shalimar, Bhatia V, *et al*. Antituberculosis therapy-induced acute liver failure: magnitude, profile, prognosis, and predictors of outcome. *Hepatology* 2010; 51:1665-74.
2. Riegler JL, Lake JR. Fulminant hepatic failure. *Med Clin North Am* 1993; 77: 1057-83.

14.13 Inherited Metabolic Disorders of the Liver

P Advaitham

INTRODUCTION

Inborn errors of metabolism include a variety of disorders with varied presentations and pathophysiology. These may present as an acute life-threatening illness in the neonatal period or may manifest as chronic liver disease during adolescence and progress to liver failure, cirrhosis or hepato-cellular carcinoma. In the United States of America, 5% of liver transplants are performed for metabolic liver diseases. Although liver transplantation is life-saving for these patients, new non-transplant treatment options have become available for some of these conditions.

The presenting features of metabolic liver diseases are diverse and can range from hypoglycaemia, hyperammonaemia, psychomotor retardation, elevation of aminotransferase levels, hepatosplenomegaly, acidosis, ascites, jaundice, bleeding diathesis, coma, short stature or failure to thrive. An infant presenting with cholestasis should undergo evaluation for metabolic liver disease; as should an infant with progressive neuromuscular disease; developmental delays or regression of developmental milestones.

A history of consanguinity in parents, multiple miscarriages or early infant death may suggest metabolic derangement. History of undiagnosed liver disease, progressive neurological or muscular disease or undiagnosed developmental delay in family members should raise suspicion. Introduction of certain foods may correlate with the onset of symptoms, as in urea cycle defects, galactosaemia or fructosaemia. Since patients with metabolic liver disease often present with recurrent symptoms, it is important to investigate the patient early. Apart from screening tests (**Table 1**), liver biopsy can be a useful diagnostic tool. Serum and urine samples should always be saved and frozen for definitive studies.

Table 1: Screening Laboratory Tests for Metabolic Liver Disease

Serum electrolytes
Anion gap
Serum glucose
Serum ammonia
Serum organic and amino acid
Urine organic acid
Hepatic enzymes
Coagulation profile
Serum lactate
Urine for reducing substance
Peripheral blood smear
Evaluation for haemolysis
Serum alpha-1 antitrypsin levels
Alpha-1 antitrypsin phenotype

WILSON'S DISEASE AND HAEMOCHROMATOSIS

Refer to chapter on Wilson's disease and Haemochromatosis in Metabolism Section.

ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 antitrypsin deficiency is inherited as an autosomal-recessive disorder. The gene responsible is located on chromosome 14q31. Alpha-1 antitrypsin is synthesised and secreted predominantly by the liver. It is present in tears, duodenal fluid and saliva. Homozygous protease inhibitor phenotype ZZ (PiZZ) alpha-1 antitrypsin deficiency is the most common genetic cause of liver disease in children. In adults, it is associated with chronic liver disease and hepato-cellular carcinoma. Currently, there is no evidence that heterozygous forms, such as PiMZ, PiMS, PiSZ cause liver disease in children; their role in adults remains unclear. The hypothesis to explain liver damage include: proteolytic imbalance, abnormal immune response and inefficient over-accumulation of the mutant alpha-1 antitrypsin Z protein in liver cells.

Clinical Features

Neonatal jaundice occurs between 2 and 3 weeks of age but this may occur any time within the first 4 months of life. Jaundice usually lasts for 2 to 3 months, but may persist for up to one year. Hepatosplenomegaly is seen in 50% of symptomatic infants. Biochemical analysis shows both cholestasis and hepato-cellular damage. Liver disease may also occur in late childhood or adolescence. The affected children may present with signs of decompensated liver disease with portal hypertension. In adults, this disorder manifests clinically at some point during their lifetime in two-thirds of subjects with homozygous form of the deficiency and the rest are asymptomatic. This will present in about 40% of adult cases as cirrhosis of liver with portal hypertension including ascites and variceal bleeding. Hepato-cellular carcinoma occurs in up to 40% of cirrhotics due to this disorder.

Diagnosis

Liver biopsy shows characteristic periodic acid-Schiff (PAS) positive, diastase-resistant globules in the endoplasmic reticulum of hepatocytes. Alpha-1 antitrypsin phenotyping and serum alpha-1 antitrypsin levels are diagnostic.

Treatment

In the absence of cirrhosis of liver, alpha-1 antitrypsin deficiency is managed by supportive therapy. Avoidance of smoking and hepatotoxic agents (including alcohol) is recommended to prevent lung and liver disease, respectively.

In advanced liver disease, liver transplant is the treatment of choice. Other therapies that have been tried include synthetic androgens, such as danazol to raise the alpha-1 antitrypsin level, inhalational alpha-1 antitrypsin in cases with pulmonary disease and gene replacement therapy.

GLYCOGEN STORAGE DISEASES

In glycogen storage diseases (GSDs), enzyme deficiencies cause impaired glucose production and accumulation of abnormal

glycogen in the liver causing organ damage, leading to formation of hepatic adenomas and rarely progressing into hepato-cellular carcinoma. Clinically, three types of GSDs are common (type I, III and IV).

GSD type I (Von Gierke's) is due to deficiency of glucose-6-phosphatase which is the most common type of GSD seen clinically. It manifests as profound hypoglycaemia, hepatomegaly due to adenomas, retarded growth, hyperlipidaemia, lactic acidosis and hyperuricaemia. Liver biopsy and direct measurement of glucose-6-phosphatase activity in the liver tissue are confirmatory. Carbohydrate challenge will demonstrate the absence of any rise in blood sugar level.

Treatment is aimed at maintaining normal blood glucose, by high carbohydrate meals taken at frequent intervals. In children, frequent feeding during the day and nocturnal feedings through nasogastric tube may be required. In adults, daytime frequent feeding alone is advised. Corn starch undergoes slow degradation to glucose and steadily releases glucose into the system, hence should be the major ingredient in the diet.

GSD type III (debranching enzyme deficiency) is due to deficiency of amylo-1,6-glucosidase (debranching enzyme). The development of hepatic fibrosis and, rarely, progression into end-stage liver disease due to the direct toxic effects of abnormal form of glycogen in the liver are distinguishing features of this disorder; in addition, hypoglycaemia, growth failure, progressive muscle weakness and enlarged liver are seen. The diagnosis is made by liver histology and confirmed by direct measurement of debranching enzyme activity using ^{14}C-labelled glucose. The treatment of choice is liver transplant apart from nutritional support in the form of high-protein, low carbohydrate diet and corn starch therapy for refractory hypoglycaemia.

GSD type IV (amylopectinosis) is caused by the absence of branching enzyme β-1,4-glycosyl transferase, which results in the formation of amylopectin-like polysaccharides. Its deposition in the liver leads to hepatic fibrosis and early cirrhosis. This rare disorder presents clinically as hepato-splenomegaly, signs of liver dysfunction; failure to thrive and muscular hypotonia. The diagnosis is confirmed by demonstrating pale, basophilic deposits within the liver cells and micronodular cirrhosis with broad bands of fibrous tissue. Liver transplant is curative; however, providing nutritional support in the form of high-protein and low carbohydrate diet can control the disease.

TYROSINAEMIA

Tyrosinaemia is an autosomal recessive disorder that affects numerous organ systems, including liver, kidneys and peripheral nerves. The underlying defect is a deficiency of fumaryl-aceto-acetate hydrolase, leading to accumulation of toxic metabolites. The acute form of this disorder presents as hypoglycaemia, ascites, bleeding diathesis, anorexia, irritability and jaundice in the first 6 months of age. Serum tyrosine, methionine and alpha-foetoprotein levels are elevated. Chronic forms usually present after one year of age with hepatomegaly, enlargement of kidneys, rickets, growth retardation, cirrhosis and hepato-cellular carcinoma. Diagnosis can be confirmed by estimation of fumaryl-aceto-acetate hydrolase enzyme in the liver tissue. Dietary restriction of tyrosine and phenylalanine. NTBC [2-nitro-4-(trifluoromethyl benzoyl)-cyclohexane-1,3-dione], a potent inhibitor of hydroxyphenylpyruvate dehydrogenase, which reduces the production of toxic intermediates that damage the liver and the kidney has been shown to be useful. Liver transplantation normalises the enzyme activity and liver function.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessive, multiorgan disorder. The responsible gene is located on the long-arm of chromosome 7. Liver disease may manifest in the newborn period, and neonatal cholestasis has been identified in up to 30% of patients. Liver disease is becoming more common since the mean duration of survival of patients with CF has increased with improvements in treatment. Up to 30% of patients may have clinical or symptomatic liver disease after neonatal period. Focal biliary cirrhosis is the pathognomonic lesion; however, 5% of patients have multilobular biliary cirrhosis.

Ursodeoxycholic acid (20 to 30 mg/kg body weight) has shown improvement in cholestasis and nutritional status. Orthotopic liver transplantation (OLT) has been successfully performed for patients with portal hypertension and stable pulmonary function.

PORPHYRIA

This diverse group of metabolic derangements are due to errors in haeme synthesis. For some of these conditions, liver is the primary site of expression. Haeme synthesis occurs both in liver (15% to 20%) and bone marrow (70% to 85%). The term acute porphyria refers to the occurrence of acute neurological attacks, which are often recurrent and life-threatening. A majority of porphyrias manifest with neurological or cutaneous symptoms. Hepatic involvement is variable. In general, acute porphyrias may be associated with elevated serum levels of amino-transferases and bile acids; this abnormality worsens during acute attacks. Liver biopsy may show fatty change and iron deposition. Although the changes are minor, these patients are at an increased risk of developing hepato-cellular carcinoma.

Porphyria cutanea tarda and hepatoerythropoietic porphyria are most commonly associated with hepatic complications like enlarged liver due to fatty changes, inflammatory and granulomatous changes. Siderosis and fibrosis may lead to cirrhosis and liver failure. In porphyria cutanea tarda, the liver damage may be due to the metabolic abnormality or to additional factors, such as alcoholism and hepatitis C virus infection. In protoporphyria, protoporphyrin may have a direct toxic effect on the liver.

Increased urine porphobilinogen may suggest the diagnosis. To differentiate between different types of porphyria, urine and stool samples should be sent for porphyrin studies.

UREA CYCLE DEFECTS

Although these syndromes are not associated with liver disease, the basic genetic defect is located in the liver, and their manifestation may mimic other metabolic liver diseases. The most common defect identified is ornithine transcarbamylase deficiency.

These defects, with the exception of arginase deficiency, present as acute life-threatening events in the neonatal period. Infants are usually normal in the first 24 to 72 hours, since feeding during this period provides the initial protein load for ammonia production. Symptoms are irritability, seizures, coma, vomiting, hypertonia, lethargy and respiratory distress. Plasma ammonia reaches >3,400 µg/dL.

Blood urea nitrogen level is low. Allopurinol loading test (300 mg orally) leads to excretion of orotic acid 10 to 20 fold greater than normal. Serum ammonia level should be restored to normal. Haemodialysis is more effective than exchange transfusions. On stabilisation, introduction of low-level dietary protein (0.5 to 1g/kg) may be started. Arginase deficiency usually presents with spastic diplegia, quadriplegia or seizures.

HEREDITARY FRUCTOSAEMIA

This disorder, caused by fructose aldolase deficiency, presents clinically as chronic hepatitis or steatohepatitis. Diagnosis is made on enzyme analysis on liver biopsy. Treatment consists of removal of all fructose, sucrose, and maltose from the diet. Water-soluble vitamins should be given.

GALACTOSAEMIA

This disorder, caused by a defect of galactose-1-phosphate uridyl transferase synthesis, presents as vomiting, hepatitis, liver failure and disseminated intravascular coagulation, usually with sepsis, when the infant is first exposed to milk feeds. Diagnosis is made by measurement of enzyme levels in the infant's red blood cells. Early management consists of removal of galactose from the diet and standard treatment for liver failure and sepsis.

INHERITED DISORDERS OF BILIRUBIN METABOLISM

See chapter 2, section 14 on Clinical Approach to a Patient with Liver Disease.

NIEMANN-PICK A, B AND C DISEASES

These rare conditions are considered together because of their clinical similarities. Types A and B are associated with deficiency of sphingomyelinase in leukocytes or fibroblasts and type C with an enzymatic defect of cholesterol esterification. The genetic defect is linked to a locus on chromosome 18. All these diseases can present with neonatal hepatitis, portal hypertension and neurological disorders like ataxia. Liver disease with liver failure occurs in about 10% of cases. The overall mortality is about 67%. Demonstration of cells that stain with periodic acid-Schiff in the bone marrow aspirate helps confirm the diagnosis. The treatment is symptomatic; combined liver and bone marrow transplantation may be tried.

GAUCHER'S DISEASE

It is the common lysosomal storage disorder due to deficiency of acid β-glucosidase. The clinical presentation is massive hepatosplenomegaly but cirrhosis and portal hypertension is uncommon. Demonstration of Gaucher cells in the liver is difficult and bone marrow aspirate shows the characteristic diastase-resistant, periodic acid-Schiff positive histiocytes. The diagnosis is confirmed by estimation of enzyme levels in leukocytes. Regular infusions of the deficient enzymes have been tried with some benefit, but long-term results are not unknown. For patients with bone marrow infiltration with pancytopenia, combined liver and bone marrow transplantation has been tried.

MITOCHONDRIAL RESPIRATORY CHAIN DISORDERS

Mitochondrial respiratory chain disorders (MRCDs) as a cause of liver diseases are seen mostly in children. There is no 'gold standard' for the diagnosis of these conditions. Primary liver disease in MRCDs may present as acute liver failure, steatohepatitis, or cirrhosis of liver. Management is not specific but only supportive. Since other organ systems are also involved, the prognosis is poor.

INBORN ERRORS OF BILE ACID NUCLEUS SYNTHESIS

It may occur in conditions like 3β-hydroxy-C_{27}-steroid dehydrogenase/isomerase and δ-4-3-oxosteroid 5β deficiencies. Patients may present with neonatal liver failure, haemo-chromatosis or neonatal cholestasis. Diagnosis is made by analysis of plasma and urine bile acid profiles on fast atom bombardment mass spectroscopy. Ursodeoxycholic acid along with fat-soluble vitamins may be useful in treating these conditions.

PROPIONIC ACIDAEMIA

In this condition, there is a deficiency of mitochondrial propionyl coenzyme, a carboxylase enzyme, involving all the tissues. It presents soon after birth with episodic vomiting, coma, hypoglycaemia and acidosis, which are precipitated by protein intake or infection and can be corrected by liver transplantation.

PRIMARY OXALURIA TYPE I

This condition is due to the deficiency of alanine glyoxylate aminotransferase, which is found only in liver peroxisomes. This enzyme is used for the catabolism of oxalate, which has been either produced by the liver or consumed as food constituents (particularly leafy vegetables, rhubarb and strawberries). Oxalate can precipitate in the kidneys and is nephrotoxic.

The typical presentation of primary oxaluria is with nephrolithiasis in adults. Occasionally, it may be diagnosed in infants, based on elevated plasma oxalate level and measurement in liver biopsy material of the deficient enzyme. The ideal treatment is liver transplantation before the development of renal damage. If renal impairment has already set in, combined liver and kidney transplanstation from the same donor is useful.

RECOMMENDED READING

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14.14 Parasitic Diseases of the Liver

Samir R Shah

INTRODUCTION

Parasites are organisms, which live on or inside, and derive nourishment from another living organism. Several parasites are known to produce liver disease (**Table 1**).

Table 1: Parasitic Diseases of the Liver

Protozoal Infections	Helminthiasis
Amoebiasis	Ascariasis
Malaria	Echinococcosis
Visceral leishmaniasis	Blood and liver flukes
Cryptosporidiasis	Visceral larva migrans
	Strongyloidosis
	Capillariasis

AMOEBIC LIVER ABSCESS

Amoebic liver abscess (ALA) is an inflammatory space-occupying lesion of the liver caused by *Entamoeba histolytica*. This disease is endemic in India and is the most common form of extra-intestinal or invasive amoebiasis. The amoebiasis is extensively discussed in section 17 chapter 53.

LIVER INVOLVEMENT IN MALARIA

All the four *Plasmodium* species, viz. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*, multiply in hepatocytes during their life-cycle. *P. vivax* and *P. ovale* can persist in a dormant phase in the liver for long periods extending up to years, capable of causing recrudescence of the disease.

Pathophysiology

In the exoerythrocytic phase, the malarial parasites are confined to the hepatocytes. In uncomplicated malaria, significant hepatocyte damage is conspicuous by its absence. A persistent exoerythrocytic cycle of *P. vivax* and *P. ovale* is also not thought to produce pathological changes in the hepatocyte, except for the presence of hypnozoites. In all forms of malaria, pathological findings are similar and include sinusoidal dilatation and congestion, Kupffer cell hyperplasia, parasitised red cells and fine pigment in red cells and Kupffer cells. In severe falciparum infection, cytoadherence and sequestration of the infected erythrocytes leads to microcirculatory disturbances, which in turn lead to end-organ damage in the kidney, brain, intestines, retina and bone marrow. The resultant tissue hypoxia, lactate production and release of cytokines, such as tumour necrosis factor (TNF) and interleukin-1 is responsible for the characteristic clinical picture of the multiorgan failure. Loss of microvilli of bile canaliculi has been observed on electron microscopy; this may explain the cholestasis and conjugated hyperbilirubinaemia noted in some patients with severe *falciparum malaria*.

Clinical Presentation

Fever is the presenting complaint. Similar clinical presentation may occur in other common causes of community-acquired infections like viral fever, enteric fever and viral hepatitis. Mild jaundice during uncomplicated malaria is usually due to haemolysis. Complicated falciparum malaria may present with rapidly progressive jaundice, fever, altered sensorium, oliguria and shock. Coma in these patients is believed to be due to the involvement of the brain and not due to liver cell failure.

Diagnosis

Detection of malarial parasites on peripheral blood smear is the mainstay of diagnosis. However, multiple smears may need to be examined. In uncomplicated malaria, hyperbilirubinaemia is predominantly unconjugated in nature. Elevation of liver enzymes (AST/ALT) is mild, and much lower than the range seen in acute viral hepatitis. Enteric fever may have a similar clinical presentation, with fever, normal leucocyte count and hepato-splenomegaly; however, jaundice is uncommon. In complicated falciparum malaria, hyperbilirubinaemia is especially marked and may be predominantly conjugated.

Treatment

No specific treatment related to the liver is required either in uncomplicated or in falciparum malaria. Unconjugated hyperbilirubinaemia improves with clearance of the malarial parasites and regression of hepatosplenomegaly. In complicated falciparum malaria, treatment is directed towards the multiorgan failure with haemodynamic and respiratory support, treatment of metabolic acidosis, renal failure and hypoglycaemia; specific hepatic support is not needed. Conjugated hyperbilirubinaemia rapidly declines on clearance of parasites and improvement in renal failure.

TROPICAL SPLENOMEGALY SYNDROME

Tropical splenomegaly syndrome, also known as hyper-reactive malarial splenomegaly, is a condition that occurs in residents of areas endemic for malaria. It is postulated to be caused by repeated immunologic stimulation, and is characterised by high titres of total IgM and specific anti-malarial antibodies, hepatic sinusoidal lymphocytosis and splenomegaly.

Clinical presentation is with dragging abdominal pain due to an enlarged spleen (which is often enormous in size) and symptoms related to anaemia. Due to a prominent immunological response, malarial parasites may not be detected in the peripheral blood smear. However, most patients respond well to anti-malarial treatment with a reduction in IgM levels and splenomegaly. If untreated, the condition has a high mortality, primarily due to overwhelming sepsis.

HYDATID DISEASE OF THE LIVER

Hydatid disease is a zoonotic infection caused by larval stage of tapeworms of genus *Echinococcus*. It is characterised by the presence of medium-to-large sized cysts in the liver and other body organs. It is a public health problem in areas in Europe, Asia,

South America, Kenya and the Mediterranean region, where sheep are raised (*See chapter 59 of section Infectious Diseases*).

Clinical Presentation

Although the infection is usually acquired during childhood, most cysts are detected in third to fifth decades of life. The cysts may be asymptomatic and detected incidentally at imaging done for another reason. Symptoms are usually related to the presence of an expanding mass, pressure on surrounding structures, infection in the cyst or rupture of the cyst. Examination reveals an enlarged liver with or without palpable soft to firm masses. A thrill may be elicited over the mass. A calcified cyst may feel hard, and thus, needs to be differentiated from a liver tumour. Compression of the hepatic veins and inferior vena cava by the cyst can cause Budd-Chiari syndrome. A large cyst in the hilar area may compress the common bile duct and lead to obstructive jaundice. The cysts can rupture into the biliary tree, leading to biliary colic and cholestasis, with cholangitis; blockade of the ampulla by cyst contents can lead to acute pancreatitis. Cyst rupture into the peritoneal cavity can lead to anaphylactic shock; should the patient survive this acute catastrophe, implant of scolices on the peritoneal surface can cause extensive peritoneal cyst formation.

Diagnosis

Diagnosis can be made by detection of specific antibodies or circulating antigen. Enzyme-linked immunosorbent assay (ELISA) for IgG anti-echinococcus antibodies has a specificity of 88% to 96% with a sensitivity of 80% to 100% in patients with hepatic cysts. False positive tests can occur in persons living in endemic areas and in those with other parasitic infections. Positive tests require confirmation by arc-5 immuno-electrophoretic test, which detects antibodies against an antigen specific to the cestodes. Cross-reactions with *Taenia solium* do occur and need to be considered in regions where both the infections are a problem. A plain radiograph of abdomen may show curvilinear calcification in the liver cyst. Endocyst calcification is spotty in nature and appears as speckled calcification. Liver cysts are well seen at ultra-sonography. Cysts may appear uni- or multi-vesicular with clear fluid. Some cysts may have a hyperechoic solid pattern or may have reflective wall suggestive of calcification. Rupture of liver cyst into bile duct can be suspected on ultrasonography. Chest radiography and computed tomography (CT) can be used to concomitant cysts in other parts of the body.

Treatment

Surgery with the potential to cure patient was the standard modality of treatment till recently. It is the treatment of choice for patients with a large liver cyst, subcapsular cyst, pedunculated cysts and infected cysts. Surgery may not be possible in patients with multiple cysts, cysts that are difficult to access and in patients at extremes of age, or those with co-morbid conditions. Mebendazole (40 to 50 mg/kg/day), albendazole (10 to 15 mg/kg/day) and praziquantel have well-documented scolicidal activity. Administration of drugs in three cyclic one-month courses interspersed with drug-free intervals of 14 days each have been widely used. Recent data favour the use of uninterrupted drug therapy for 3 to 6 months. Addition of praziquantel (40 mg/kg once a week) increases the efficacy of benzimidazoles. Drug therapy is effective in small cysts (<4 cm in diameter) and cysts with thin walls. It leads to cyst disappearance in 30%, partial improvement in 30% and no response in 40%. It is recommended as primary therapy in patients at high surgical risk and as a concomitant therapy with percutaneous drainage. Benzimidazoles are hepatotoxic, can cause neutropaenia and thrombocytopaenia, and are teratogenic.

In recent years, percutaneous drainage of hepatic hydatid cysts known as PAIR (Puncture, Aspiration, Installation of scolicidal agent and Reaspiration) has gained acceptance. It is a treatment of choice in patients with liver cysts and a co-morbid condition precluding surgery, or those who refuse surgery. It is an effective procedure in uni- or multi-vesicular cyst with a few large daughter cysts. Liver puncture carries a potential risk of anaphylaxis and biliary communication of the cyst. Long-term follow-up has shown that secondary echinococcosis does not occur following percutaneous drainage.

HEPATOBILIARY ASCARIASIS

The normal habitat of the adult roundworm is the jejunum. In Indian subcontinent Ascariasis is highly endemic in Kashmir, Central and South-west India.

Clinical Presentation

Ascaris infestation is usually asymptomatic. Adult worms can enter the duodenum due to excessive load or abnormal motility, and may enter and block the ampullary orifice. They can advance further into the bile duct, hepatic ducts or cystic duct, blocking any one of these. The entry of these worms into the gall bladder or pancreatic duct is less frequent but known. Usually, the worms move out of the biliary system within a week's time. If they persist in the duct system for more than 10 days, they often die, serving as a *nidus* for the formation of bile duct calculi.

The clinical manifestations vary according to the site of involvement and include biliary colic, cholangitis, acute pancreatitis, and hepatic abscess. Ascariasis was found to be responsible for 37% of pancreatobiliary diseases in Kashmir. Due to the smaller size of their bile ductal system, children do not usually suffer from hepatobiliary ascariasis.

Diagnosis

Ultrasonography is a highly sensitive and specific method for detection of worms in the biliary tree. Endoscopy permits direct visualisation of worms in the duodenum and across the papilla. At endoscopic retrograde cholangiopancreatography, worms are seen as linear filling defects or curves and loops criss-crossing the hepatic ducts.

Treatment

Treatment of biliary ascariasis includes treatment of cholangitis by conservative means and oral administration of anti-helminthic agents to treat adult worms in the intestine. Endoscopic removal of the retained worms is performed when a patient does not respond to conservative means or when worms have not moved out of the duodenum at 3 weeks. It is successful in 90% to 100% of patients and is followed by rapid relief of symptoms. See chapter 58, section 17.

BLOOD AND LIVER FLUKES

Involvement of liver occurs in infection with *Schistosoma mansoni*, *S. japonicum*, and *S. mekongi*. Portal venous tracts are replaced by fibrous tissue resulting in peri-portal fibrosis with portal hypertension. Hepatic function is well preserved and the usual stigmata of chronic parenchymal liver disease are absent.

Clonorchis sinensis infection involves the bile ducts and causes ascending cholangitis with a risk of cholangiocarcinoma. *Fasciola hepatica* invade the liver and reside in bile ducts; clinical presentation is similar to *C. sinensis* infection, there is no association with cholangiocarcinoma. Praziquantel is the treatment of choice for all flukes, except *F. hepatica* for which bithional is recommended.

VISCERAL LEISHMANIASIS

This disease is caused by a protozoal infection with *Leishmania donovani* or related parasites *L. infantum* or *L. chagasi*. Cutaneous leishmaniasis is caused by several other species of the genus. The disease is common in Ganges and Brahmputra valleys of India. Visceral leishmaniasis is transmitted by sand fly, *Phlebotomus argentipes*, which rests in cattle sheds and bites humans at night. In the inter-epidemic period, the parasite survives in the skin of patients with post kala azar dermal leishmaniasis. The leishmaniasis is discussed extensively in infectious disease section.

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14.15 Toxic and Drug Induced Liver Injury

Abraham Koshy

INTRODUCTION

More than 1000 drugs may produce drug-induced liver injury. About half of them produce only biochemical changes but about one-third lead to clinical acute hepatitis. Antibiotics including anti-tuberculosis drugs are the commonest group of drugs that produce liver injury. In India, nearly 50% of cases of drug-induced liver injury may be due to anti-tuberculosis drugs.

To manage cases with drug-induced liver injury, one must understand mechanisms, spectrum and the approach to diagnosis, treatment and prevention of this condition.

MECHANISMS

The basic mechanism may be allergic or toxic. If less than 1% of those who consume a particular drug develop liver injury, the mechanism is likely to be allergic. If more than 10% of those who consume the drug develop liver injury, the mechanism is likely to be toxic. Examples of each are given in **Table 1**.

Table 1: Mechanisms of Drug-induced Liver Injury

Mechanism	Frequency	Example
Allergic	<1%	Rifampicin
Reactive metabolite	<1%	Indomethacin
Toxic metabolite	<1%	Halothane
Dose dependant	>10%	Methotrexate
Mitochondrial toxicity	>10%	Amiodarone
Overdose	>10%	Colchicine
Toxic	>10%	Griseofulvin

SPECTRUM

The spectrum of drug-induced liver injury can be quite varied. The liver injury may be biochemical in nature, i.e. asymptomatic elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) [AST; 1.1-6.0 times the upper limit of normal (x ULN)] or alkaline phosphatase [(ALP); (1.1-1.7 x ULN)]. Other patients may have acute hepatitis-like picture, which includes symptomatic acute hepatitis or marked elevation of transaminases (>6.0 x ULN) or alkaline phosphatase (>1.7 x ULN). Less frequent manifestations are listed in **Table 2**.

Table 2: Spectrum of Drug-Induced Liver Injury

Manifestation	Definition
Biochemical, ALT/AST	1.1-6.0 x upper limit of normal (ULN)
Acute	Symptoms like acute hepatitis and AST/ALT >6.0 x (ULN)
Acute cytolytic	
Acute cholestatic	Defined histologically or biochemically
Fulminant hepatitis	
Granulomatous hepatitis	Defined histologically
Chronic hepatitis	Elevation of transaminases for > 6 months
Steatosis	
Vascular	
Benign tumour	Defined histologically
Malignant tumour	

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase.

DIAGNOSIS

There is no reliable test for the diagnosis of drug-induced liver injury. All drugs taken during the 2-week period preceding the onset of liver injury should be suspected as the cause of liver injury. Therefore, the diagnosis depends on following the temporal relation of suspected drug intake to both the onset (<90 days) and recovery (<180 days) of liver injury; exclusion of other causes of liver injury; reappearance of liver injury on re-challenge with the same agent; and known association (previous published reports) of the suspected drug to liver injury.

A scoring system has been developed to help reach a diagnosis of drug-induced liver injury. In this system, known as the 'clinical diagnostic scale', points are given for each factor included in the scale and an overall scale calculated; a score of >9 had sensitivity of 88% and specificity of 98% for diagnosing drug-induced liver injury.

TREATMENT

Treatment essentially consists of withdrawal of all suspected drugs. N-acetylcysteine must be given for paracetamol (acetaminophen) toxicity. Corticosteroids should be used only if skin rash or other extra-hepatic manifestations are present.

If a suspect drug is considered essential, the decision to continue or withdraw the drug is based on determination of answers to the following questions: Is the drug absolutely essential? How severe is the liver damage? Can the drug dose be reduced or the drug replaced by another drug? Which is likely to be more dangerous—the underlying disease or the drug?

The liver injury should be considered severe and even an 'essential' drug should be withdrawn if the patient has hepatic encephalopathy, abnormal prothrombin time, serum bilirubin exceeding 2 mg/dL or levels of ALT or AST exceeding 3 x ULN.

If more than one drug is implicated, all the non-essential drugs should be withdrawn. Thereafter, the least implicated drug should be re-introduced the first, beginning with a lower dose and then gradually increased to the full dose, while closely monitoring the liver function tests. Thereafter, the second drug can be added in a similar manner.

Re-challenge should be avoided, unless it is considered essential to reintroduce the same drug.

PREVENTION

There is no general guidelines to prevent drug-induced hepatitis. Rifampicin and pyrazinamide should not be used for latent tuberculosis infection but rather isoniazid.

In patients with liver cirrhosis, a combination of isoniazid and rifampicin should be avoided; ethambutol and streptomycin are safer, and may be used in combination with newer fluoroquinolone.

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14.16 Liver Transplantation

Subash Gupta, Ajay Kumar

HISTORY AND TERMINOLOGY

Since the first experimental transplantation of liver in dogs in 1955 by Welch and first successful human liver transplant in 1967 by Dr Thomas Starzl in the United States of America, liver transplantation has made a considerable progress. Today, it is the sole definitive treatment for end-stage liver disease. Apart from progress in technology, improvements in critical care, anaesthesia, better understanding of liver anatomy, organ preservation and immunosuppressive therapy have improved the outcome of this surgery. From the early 1980s before the introduction of cyclosporine A (csA) to the addition of newer drugs like tacrolimus, mycophenolate, sirolimus, the 5-year survival has improved from 20% to 80%.

Liver transplantation can be from a cadaveric liver where the whole liver from a brain-dead donor is transplanted or can be from living donor where the right lobe in adults and the left lobe in children is transplanted. In 1994, India adopted the Human Transplant Act which legally accepted brain stem death facilitating cadaver organ donation. However, this has not picked up much. For this reason, living donor liver transplant is done more frequently than cadaver transplant in India.

INDICATIONS AND TIMING OF TRANSPLANT

Liver transplant is indicated in irreversible acute or chronic end-stage liver disease. Common indications for liver transplant being done in India are given in **Tables 1 and 2**.

Table 1: Indications of Liver Transplant being done in India

Indications for Adult (n = 247)	N	% of Total
Hepatitis C (HCC, 25)	95	38.5
Alcoholic liver disease	49	19.8
Hepatitis B (HCC, 8)	29	11.7
Cryptogenic cirrhosis	32	13.0
Hepato-cellular cancer	39	15.8
(non B non C)	7	
Primary sclerosing cholangitis	9	
Autoimmune/PBC	8	
Wilson's disease	4	
Miscellaneous	10	

NB: HCC figures alone as well as with Hepatitis B and Hepatitis C, and therefore, the total is more than 249.
PBC = Primary biliary cirrhosis.

Various sets of parameters have been studied in different liver diseases to decide the timing of transplant. All these criteria help in determining the timing at which patient's chances of survival are better after transplant than without transplant.

In chronic liver disease, the Child-Pugh score has been used to prognosticate in patients with liver cirrhosis. This score is based on serum bilirubin, prothrombin time, albumin and presence or absence of ascites and encephalopathy. Patients who are Child C or if they have recurrent encephalopathy, refractory ascites, spontaneous bacterial peritonitis, uncontrolled portal hypertensive bleeding are advised a liver transplant. Model for end-stage liver disease (MELD) score is used for prioritising organ allocation. This is based on bilirubin, creatinine and prothrombin time. At MELD score 15 or above transplant is indicated. In LDLT, the MELD score may be used for patient selection but will have no role in allocation as the organ is for a specific recipient.

MELD score = 0.957 log e (serum creatinine mg/dL)
+0.378 log e (serum bilirubin mg/dL)
+1.120 log e (INR)
+0.643

Table 2: Indications for Paediatric Liver Transplant

EHBA	10
PFIC	2
Wilson's disease	4
Neonatal hepatitis	3
Congenital hepatic fibrosis	2
Cryptogenic cirrhosis	2
HCC	1
CNS	1
Total	**(N) 25**

EHBA = Extra-hepatic biliary atresia; HCC = Hepato-cellular carcinoma; CNS = Crigler-Najjar syndrome; PFIC = Progressive familial intra-hepatic cholestasis.

An increasing number of patients are being transplanted for hepato-cellular cancer. MILAN criteria (single nodule of <5.0 cm or less than 3 nodules none greater than 3 cm) are widely used for selecting candidates for transplant. However of late, there has been a relaxation of the criteria as good recurrence free survival can be obtained even with a single nodule as large as 6.5 cm in diameter, the so called University of California, San Francisco (UCSF) criteria.

In acute liver failure (ALF), liver transplantation is often a treatment option. The challenge is to find the right patient where survival without transplant is unlikely.

King's college criteria are used for transplant listing in patients with ALF due to paracetamol overdose. There has been suggestion from western data that if the interval between onset of jaundice to encephalopathy is more than 1 week, then mortality is high. But there has been conflicting reports from India. As a single criterion, deterioration in prothrombin time remains the most important predictor.

CONTRAINDICATIONS

The contraindications are mainly from either decreased life expectancy from co-morbid illnesses, such as, poor cardiovascular and pulmonary reserve, renal dysfunction, extra-hepatic or hepatic malignancy with extra-hepatic spread and active sepsis. Human immuno-deficiency virus patients with

negative viral load are now considered for liver transplant. Complete portal vein thrombosis is a relative contraindication.

SURGICAL TECHNIQUE

Organ Preservation

Once a donor is identified the liver needs to be preserved so that it remains viable once arterial and portal blood flow is restored. In cadaver organs, this is achieved by perfusing cold preservation fluids such as tryptophan ketoglutarute or University of Wisconsin solution through the aorta and through the portal vein. The organ is quickly cooled to 4°C, retrieved, placed in the cold preservation fluid and then packed in ice. This can be preserved for 12 to 16 hours but is kept to minimum possible time to prevent complications like ischaemia reperfusion injury, late rejection and biliary strictures. In LDLT, the organ is retrieved and then perfused with cold fluid through the portal vein in the back table. Recipient hepatectomy is part of transplantation in the presence of coagulopathy and portal hypertension. Following this, the implantation is done by three vascular anastomosis, i.e. hepatic veins, portal vein and hepatic artery and bile duct anastomosis. The hepatic artery and bile duct anastomosis is done after reperfusing the liver. Apart from the complexity of the surgery, liver transplant operation demands management of major metabolic shifts and haemodynamic changes.

Once the operation is over, the patient is initially managed in the intensive care unit and when the patient is conscious, haemodynamically stable and is breathing properly, patient is extubated the next day. Patient is constantly monitored for sepsis, rejection, patency of various anastomoses by Doppler and renal function. Oral feeding is started by the third day and the dose of anti rejection medicines is adjusted daily according to the drug levels and the results of the blood tests.

IMMUNOSUPPRESSION

Immunosuppresive agents are required to avoid rejection. The first agent to be used were steroids. However, steroids alone are not sufficient and high doses may cause serious side-effects. Azathioprine was the next agent to be introduced but was not as effective. With the introduction of calcineurin inhibitors, such as cyclosporine, there was a marked improvement in graft survival and in many ways marked a watershed in the history of transplantation. Graft survival improved to over 70% at one year.

Concurrently, there was development of biological agents, such as OKT3 and ATG which were antibodies against T cells. Although very potent to reverse acute rejection, they were often associated with side-effects, such as fungal and viral infections and the development of lymphoproliferative disorders.

Similar to cyclosporine in many ways, tacrolimus was found to be more effective than cyclosporine in preventing acute graft rejection. Both these drugs work by inhibiting interleukin 2, and thereby, preventing proliferation of T-cells when exposed to graft. This was a major advance as they were more specific and directly inhibited graft related T-cell stimulation rather than suppression of B cell related humoral immunity.

With the introduction of mycophenolate mofetil, immuno-suppression in liver transplantation quickly changed to an initial triple combination of calcineurin inhibitors, mycophenolate mofetil/azathioprine and steroids. Most centres now use steroids for 3 to 6 months and then these are tapered off.

With the current immunosuppressive strategy, patients are living longer. However, there are side effects of long-term immunosuppression such as of diabetes, hyperlipidaemia and hypertension. Both the calcineurin inhibitors are nephrotoxic and also carry higher risk of developing malignancies.

RESULTS

Liver transplantation is a very successful operation. The results of cadaveric transplants conducted between 1968 and 1988 showed a 10-year graft and patient survival of 31% and 36% respectively. In contrast the survival of grafts and patients who were transplanted between 1988 and 2004 improved to 53% and 61%, respectively. The trend is towards better results and the projected 10-year survival now is 80%.

LIVER TRANSPLANTATION IN INDIA

It was first successfully conducted in New Delhi in 1997. Now liver transplantation is conducted routinely in India in over 14 centres. Over 90% of the transplants in the country have been conducted in two centres in Delhi. Annually about 300 transplants are now carried out in the various centres in India with a success rate of 91%.

DISEASE RECURRENCE

More than rejection or infection or the development of malignancy, the long-term results of liver transplantation is plagued by disease recurrence.

In hepatitis B, disease recurrence can be prevented by the combined use of antiviral agents and hepatitis B immunoglobulins.

The major problem is with transplants for hepatitis C with disease recurrence of over 25% at 5 years and many of these patients will need a re-transplant as therapy for hepatitis C is only partly successful.

In transplants for HCC, if the transplants are conducted within the MILAN criteria or the UCSF criteria the survival at 5 years is around 80%.

In patients who are transplanted for alcoholic liver disease, recidivism may account for late graft loss. Most centres now insist on a period of abstinence of 6 months prior to transplantation.

CONCLUSIONS

Liver transplantation is a suitable treatment for end-stage liver disease, acute liver failure and HCC. Post-transplant care is complicated by monitoring of immunosuppressive medications and their side effects. Disease recurrence, such as hepatitis C affects the long-term results.

ALCOHOLIC LIVER DISEASE

Alcoholic liver disease is discussed in chapter 8 of section 14.

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14.17 Pregnancy and Liver Disease

Ramesh Roop Rai

INTRODUCTION

Pregnant women may develop liver diseases that are aetiologically related to gestation or one of its complications. Invariably, these disorders become clinically evident during the second and third trimester or just after delivery. These diseases may be mild in presentation or may be severe, even life-threatening.

HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum occurs in 1 to 20 patients per 1,000 pregnancies; in the first trimester, usually between 4 and 10 weeks of gestation, but may occur as late as 20 weeks gestation.

The exact cause remains unknown. Multiple theories exist from psychologic predisposition, including conversion disorders to evolutionary adaptation to protect a mother and her foetus from certain potentially harmful foods. Hormone levels seem to play a role, as nausea and vomiting peak when human chorionic gonadotrophin and oestradiol levels are high. Risk factors include history of the disease, hyperthyroidism, psychiatric illness, molar pregnancy, pre-existing diabetes, multiple gestations, multiparity and high daily intake of saturated fat before pregnancy.

Symptoms include severe nausea and vomiting, at times requiring hospitalisation. Patients often present with dehydration and may show evidence of malnutrition with poor weight gain.

Although no standard diagnostic criteria exist, some commonly used include persistent vomiting with no other cause, evidence of acute starvation (usually with ketonuria), and evidence of acute weight loss. Up to half of hospitalised patients have abnormal liver enzymes. Aminotransferase levels may rise up to 200 IU/L but are generally less than 300 IU/L and alkaline phosphatase may rise to twice the normal values. Both direct and indirect bilirubin values may rise to 4 mg/dL and serum amylase and lipase may rise to 5 times normal.

Non-pharmacologic interventions include avoiding nausea inducing triggers, such as odours from perfume, smoke, cooking foods, and chemicals. Low fat, frequent, small meals may help to improve symptoms. Multivitamin use at the time of conception has also proved successful, so any patient with a history of hyperemesis in earlier pregnancies should be encouraged to start taking multivitamins prior to conception.

Vitamin B6 in a dose of 10 to 25 mg 4 times a day (QID) is the initial treatment of choice. Its use in conjunction with doxylamine (12.5 mg qid) has demonstrated great success. Promethazine 12.5 mg orally or rectally every 4 hours or diphenhydramine, 50 to 100 mg orally or rectally every 4 to 6 hours can be used in unresponsive patients. In the absence of dehydration, metoclopramide 5 to 10 mg intramuscular (IM)/orally thrice a day; promethazine 12.5 to 25 mg IM/orally/rectally every 4 hours can be added. If dehydration is present, intravenous (IV) fluids should be started, as well as either dimenhydrinate 50 mg intravenously every 4 to 6 hours, metoclopramide 5 to 10 mg intravenously thrice a day, or promethazine 12.5 to 25 mg intravenously every 4 hours. If all these agents fail, methylprednisolone 16 mg thrice a day per orally (PO)/IV for 3 days followed by a 2 week taper or ondansetron 8 mg intravenously twice a day can be added. Methyl-prednisolone has demonstrated an association with oral clefts when used in the first 10 weeks of gestation, and therefore, should be used with great caution.

Minor maternal complications can occur viz. acid-base and electrolyte disturbances. Serious complications viz. oesophageal rupture, retinal haemorrhage, pneumothorax, renal damage, and Wernicke's encephalopathy are rare. Foetal outcomes are similar to those in the general population, except in severe cases wherein mean birth weight is reportedly lower.

ACUTE FATTY LIVER OF PREGNANCY (AFLP)

The prevalence is 1 per 10,000 to 15,000 pregnancies. AFLP develops in second half of the pregnancy (27 to 40 weeks of gestation), usually close to term, but it may be diagnosed even in the post-partum period. The differential diagnosis includes fulminant viral hepatitis, drug-induced hepatic toxicity, idiopathic cholestasis of pregnancy, adult-onset Reye syndrome, and haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.

Aetiology

AFLP is in the family of microvesicular fat diseases, along with Reye syndrome and valproate toxicity. No clear geographical or racial predisposition exists. Risk factors include older maternal age, primiparity, multiple gestations, pre-eclampsia, male foetus, being underweight and a history of AFLP. Studies have revealed a higher incidence of AFLP in women with (i) genetic mutation that affects their mitochondrial fatty acid oxidation pathway, and (ii) a foetus with a long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency.

Symptoms

Symptoms develop over several days to weeks and include nausea, vomiting, anorexia, lethargy, abdominal pain, ascites, and progressive jaundice. Transient polyuria and polydipsia may occur due to transient diabetes insipidus. Acute renal failure occurs in 50% patients, hepatic encephalopathy in 60%. Approximately 50% have hypertension, proteinuria, and oedema suggestive of pre-eclampsia.

Diagnosis

In AFLP, serum aminotransferase levels are moderately elevated (typically 300 to 500 U/L), bilirubin is <5 mg/dL except in severe cases. Other typical abnormalities include hypoglycaemia, elevated ammonia levels, thrombocytopaenia, neutrophilia, coagulopathy and renal dysfunction.

Computed tomography (CT) may demonstrate diffuse low-density signals in the liver and ascites. However, ultrasonography (USG) is normal in view of microvesicular fat deposits. Liver biopsy is definitive (microvesicular steatosis), but rarely performed because of the need for prompt therapy as well as the presence of coagulopathy.

Treatment

Patient requires admission, as the disease is progressive and can have sudden deterioration. Continuous foetal monitoring should be initiated. Supportive measures are required in the form of glucose infusion, adequate hydration and blood products, wherever indicated. The primary treatment is prompt delivery of the foetus. Recovery before delivery is not seen. Patients start improving 48 to 72 hours after delivery, but those with evidence of coagulopathy, encephalopathy, or hypoglycaemia on admission, often require continued intensive care level monitoring and possible transfer to centres capable of liver transplants.

Prognosis

Liver function normalises within a week but is delayed for months in severe cases. The maternal mortality has declined from 70% to 7% to 18%. Maternal complications include post-partum haemorrhage, renal failure, hypoglycaemia, disseminated intravascular clotting, pancreatitis, and pulmonary oedema. Perinatal mortality rates have also decreased from 85% to 9% to 23%. Because of the urgent need for immediate delivery, 75% of deliveries are pre-term (average gestational age at delivery is 34 weeks).

INTRA-HEPATIC CHOLESTASIS OF PREGNANCY

Intra-hepatic cholestasis of pregnancy is a common disorder manifesting in the third trimester; symptoms resolve after delivery. The differential diagnosis includes viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, and cholelithiasis.

Aetiology

The aetiology is multifactorial, including genetic, hormonal, and exogenous factors. Intra-hepatic cholestasis of pregnancy is due to abnormal biliary transport resulting in saturation of the hepatic transport system. Recurrent familial intra-hepatic cholestasis of pregnancy has been described as a heritable defect in the multidrug resistance 3 (MDR3) gene, which encodes for a canalicular phospholipid translocator involved in bile duct secretion of phospholipids.

Risk factors include advanced maternal age, multiparity, personal or family history of the disease, and a history of cholestasis while taking oral contraceptives. Female sex hormones play an important role, as almost all cases are seen in the third trimester, when estrogen levels are rising. Exogenous progesterone is also implicated.

Symptoms

Predominant symptom is generalised pruritus that begins in the periphery, often worse on the palms and soles, and moves to the trunk and face. The pruritus progresses as pregnancy continues and resolves within 48 hours of delivery. Approximately 10% to 25% of patients develop jaundice, usually 1 to 4 weeks after the onset of pruritus. No rash is associated with intra-hepatic cholestasis of pregnancy. Constitutional symptoms and diarrhoea or steatorrhoea have been reported.

Diagnosis

Intra-hepatic cholestasis of pregnancy can be diagnosed based on clinical symptoms, bilirubin is usually < 6 mg/dL, and transaminases are elevated from a minimal rise to 20 times normal. Elevated serum bile acids, may be the first or only abnormality and is confirmatory. Bile acid levels are > 10 µmol/L and may be 100 folds normal. Laboratory abnormalities resolve within 2 to 8 weeks of delivery.

Treatment

Patients should be treated at centres capable of treating premature infants, since ICP is associated with prematurity and stillbirth. Management includes symptomatic treatment of the patient as well as close monitoring and possibly early delivery of the foetus. The medical treatment of choice is ursodeoxycholic acid (UDCA), with doses of 1 g per day. UDCA improves pruritus and liver enzymes and enables delivery to occur closer to term. Cholestyramine also reduces pruritus in total divided doses of 10 to 12 g per day, but it is less effective than UDCA and has more side-effects. Foetal mortality in patients with ICP has been recorded to be as high as 11%, and the cause of mortality is still unknown.

Prognosis

Maternal outcome is good, with symptom resolution after delivery. ICP recurs in 45% to 70% of subsequent pregnancies. Perinatal mortality is upto 3.5%. Rates of stillbirth increase after 37 weeks gestation, thus supporting active management of delivery at 37 weeks.

HAEMOLYSIS, ELEVATED LIVER ENZYMES AND LOW PLATELETS SYNDROME (HELLP)

HELLP syndrome usually presents as a complication of pre-eclampsia, but can occur independently. The HELLP syndrome affects 1 to 6 per 1,000 pregnancies and 4% to 12% of patients with severe pre-eclampsia. Pre-eclampsia is characterised by hypertension, proteinuria, and oedema with onset in the second or third trimester and affects 5% to 7% of pregnancies. Seventy percent of patients with HELLP syndrome present before delivery, and the remaining in the post-partum period.

The differential diagnosis includes hepatitis, pancreatitis, peptic ulcer, appendicitis, cholelithiasis, liver haematoma, acute fatty liver of pregnancy, immune thrombocytopaenic purpura, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, and systemic lupus erythematosus.

Risk factors

Risk factors include white, multiparous, and older patients. As most patients who develop HELLP syndrome have pre-eclampsia, it too is a risk factor.

Aetiology

The initial source of the insult is unknown, but all patients have evidence of endothelial injury with fibrin deposit that causes a microangiopathic haemolytic anaemia and platelet activation and consumption, leading to thrombocytopaenia. The fibrin deposits cause obstruction in the hepatic sinusoids, which leads to areas of haemorrhage and eventual necrosis in the liver, causing elevated liver enzymes. Haemorrhage can develop into large haematomas and cause liver capsule tears.

Symptoms

Patients with HELLP syndrome often present with right upper quadrant or epigastric pain, nausea, vomiting, malaise, and non-specific viral-like symptoms. Some patients also experience headache (30% to 60%), and fewer experience visual symptoms (17%).

Diagnosis

Physical examination findings include right upper quadrant or epigastrium tenderness and generalised oedema. Hypertension and proteinuria are common, as most of the patients have pre-eclampsia. Hypertension is absent in up to 20%, and proteinuria in up to 13%, of the patients.

Laboratory abnormalities assist in confirming the diagnosis of HELLP syndrome, but currently no standardised diagnostic laboratory criteria exists. However, commonly used laboratory values include platelet count of less than 100,000, serum aspartate aminotransferase (AST) greater than 70 U/L, and serum lactic dehydrogenase greater than 600 U/L. A peripheral blood smear may also assist in the diagnosis and often demonstrates schistocytes, burr cells and echinocytes.

Studies have demonstrated that about 50% of patients diagnosed with HELLP syndrome do not have all diagnostic criteria. Those that have all diagnostic criteria, exhibit more severe disease with increased rates of blood transfusions and disseminated intravascular coagulation (DIC).

Treatment

HELLP syndrome is progressive and can sometimes have sudden and severe advancement, eventually compromising maternal and foetal outcome. Even if the diagnosis is in doubt, good blood pressure control should be achieved. IV hydralazine or labetalol may be used to maintain systolic blood pressure less than 160 mmHg and diastolic blood pressure less than 105 mm Hg. Stable patients should be transferred to tertiary care facilities for both maternal and possible neonatal treatment. Delivery is the definitive treatment for HELLP syndrome. In patients with HELLP syndrome at less than 34 weeks gestation and with a reassuring foetal and maternal status, delivery may be delayed for a steroid course of betamethasone 12 mg IM every 24 hours for 2 doses, with delivery 24 hours after the last dose. Delivery is indicated for women with HELLP syndrome at greater than 34 weeks gestation. During labour and for 24 hours post-partum, patients should receive IV magnesium sulphate for seizure prophylaxis, usually with a 4 g loading dose, followed by 2 g per hour. If the patient is already in labour, a vaginal delivery may proceed, as long as no evidence exists of foetal distress or DIC. Any evidence of the above, multiorgan dysfunction, renal failure, or abruption should prompt immediate delivery, usually by caesarean section. Induction of labour is not indicated in these patients, as the induction process can take several hours to days and places the life of patient and the neonate in danger.

Platelets are generally transfused when the platelet count is less than 20,000/mm^3, if less than 50,000/mm^3 and cesarean delivery necessary, or with any significant bleeding. Multiple platelet transfusions are generally unnecessary without significant bleeding, as delivery eventually leads to improvement in thrombocytopaenia.

Patients should be monitored very carefully for at least 48 hours in the post-partum period for evidence of pulmonary oedema due to fluid shifts or renal or hepatic dysfunction. Laboratory abnormalities usually tend to nadir 24 hours post-partum and begin to recover 48 hours post-partum.

Prognosis

HELLP syndrome is associated with increased maternal and foetal morbidity and mortality. The risk of maternal death is approximately 1%. Multiple maternal complications are associated with HELLP syndrome, including pulmonary oedema, acute renal failure, DIC, abruptio placenta, liver haemorrhage or failure, acute respiratory distress syndrome and stroke. Patients with HELLP syndrome also require higher rates of blood transfusion.

The rate of perinatal death has been demonstrated to range from 7.4% to 20.4% and is largely dependent upon gestational age and any additional complicating factors to the pregnancy or delivery. The highest morbidity and mortality rates are associated with the earlier gestations (< 28 weeks), and studies have demonstrated that the rates are not any higher than those found at the same gestational age in women diagnosed only with pre-eclampsia. Most perinatal morbidity is due to pre-maturity with common complications, including respiratory distress syndrome, bronchopulmonary dysplasia, intra-cerebral haemorrhage and necrotising enterocolitis.

LIVER RUPTURE/HAEMATOMA

Subcapsular haematoma formation and liver capsular rupture is an uncommon complication (usually of pre-eclamsia/eclampsia and HELLP syndrome), but carries a very high maternal and perinatal mortality. The differential diagnosis includes trauma, hepatic adenoma, haemangioma, AFLP, cocaine use, and hepato-cellular carcinoma.

Initial insult in the cascade of events leading to haematoma formation is believed to be endothelial injury, which causes vasospasm. In addition to vasospasm, fibrin deposits cause vascular congestion, sinusoidal obstruction with increased pressure ultimately causing hepatic necrosis, and intra-hepatic haemorrhage. Haematomas can affect the right lobe (75%), left lobe (11%) or can be bilateral (14%).

Symptoms

Severe right upper quadrant or epigastric pain, nausea, vomiting, shoulder pain, abdominal distension with hepatomegaly, peritoneal signs, hypotension and even hypovolaemic shock may be observed.

Diagnosis

Abnormal laboratory values include severe anaemia, elevated transaminases, thrombocytopaenia, and abnormal coagulation values. Patients that are haemodynamically unstable are often diagnosed at the time of laparoscopy and/or laparotomy. Sonography, CT, magnetic resonance imaging, selective angiography, and technetium-99^m scan are helpful for haemodynamically stable patients. CT with contrast is the best imaging modality for detecting hepatic haematomas, as they can efficiently and accurately detect acute haemorrhage.

Treatment

Liver haematomas without capsule rupture require conservative management. Additional management includes blood, plasma,

and platelet transfusions as needed, close haemodynamic monitoring, often in an intensive care unit. Some patients may also be candidates for hepatic artery embolisation, which is a good option for patients with multiple intra-hepatic hematomas who are poor surgical candidates. Any sign of haemodynamic instability, continued bleeding, expanding haematoma, or infection are indications to proceed with surgery. Death may occur in 12% of the patients. Most patients who survive the event have complete resolution, with normal CT approximately 4 to 6 months later.

VIRAL HEPATITIS

The incidence of viral hepatitis A, B and C is the same in pregnancy as it is for the general population, but the incidence of hepatitis E is much higher.

In hepatitis A, presentation is similar and maternal/foetal morbidity and mortality is not increased.

All pregnant women should be screened for hepatitis B by testing for HBsAg in the first trimester. Patients who test positive should be counselled about modes of transmission, prevention of hepatitis B, neonatal concerns, and all household contacts should be immunised. No specific treatment exists for acute hepatitis B. The risk of perinatal transmission from mothers who are HBsAg positive is 10% to 20% in the absence of neonatal immunoprophylaxis. In the presence of HBeAg, the neonatal transmission risk without neonatal prophylaxis is 90%. The risk also depends upon when the infection occurred during pregnancy. The risk of perinatal transmission is greatest during the third trimester, (90% as against 10% in the second trimester). To decrease this risk, lamivudine 100 mg per day can be given from the start of the third trimester.

Chronic hepatitis C infection does not seem to alter the course of pregnancy and does not place the mother at increased risk of pre-term labour, pre-eclampsia, or gestational diabetes. Screening all pregnant women for hepatitis C is not recommended. No vaccine for hepatitis C exists and primary prevention is necessary in order to avoid infection. Treatment of hepatitis C with ribavirin and α-interferon is contraindicated in pregnancy, as ribavirin is teratogenic and α-interferon causes severe neurotoxicity under the age of 2 years. The risk of neonatal transmission is as high as 4.3% and HCV infection should not influence the method of delivery. Breastfeeding is not contraindicated.

Hepatitis E has a higher incidence, higher rate of fulminant hepatitis and higher mortality in pregnancy (up to 25% *versus* 2.8% in general population). Increased rates of abortion, stillbirths and neonatal deaths are reported. Perinatal transmission occurs, but rates are still unknown. Transmission does not differ depending on route of delivery as long as no signs of acute maternal disease are present. Post-exposure or pre-exposure anti-HEV immunoglobulins have no benefit. Although anti-HEV antibodies and HEV RNA are found in colostrum of mothers, breastfeeding is not contraindicated.

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14.18 Liver in Systemic Disease

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INTRODUCTION

Liver is frequently involved in systemic disorders which are primarily not hepatic in origin (**Table 1**). The involvement may not be clinically apparent but may change the course of the disease. Therefore, the understanding of liver involvement in systemic diseases is important for making accurate diagnosis and managing underlying disease as well as its hepatic complication.

Table 1: Systemic Diseases with Involvement of the Liver

Cardiac Diseases
Congestive hepatomegaly
Ischaemic hepatitis
Haematological Disorders
Hemolytic anaemias
Myeloproliferative and myelodysplastic disorders
Haematological malignancies
Infections
Tuberculosis
Bacteremias
Fungal infections
Human immunodeficiency virus
Pulmonary Diseases
Chronic obstructive airway disease
Interstitial lung disease
Immune System and Connective Tissue Diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Sjogren's syndrome
Amyloidosis
Sarcoidosis
Scleroderma
Endocrine and Metabolic Disorders
Diabetes mellitus
Porphyrias
Glycogen storage diseases
Thyroid disorders
Cushing's syndrome

CARDIAC DISEASES

Congestive heart failure leads to painful enlargement of liver and jaundice along with transaminasemia. Congestive hepatomegaly can be differentiated from primary liver disease by observing raised pressure in internal jugular vein. Cardiac cirrhosis can occur in long-standing congestive hepatomegaly, if the underlying cardiac disease does not improve.

Sudden reduction in blood pressure, irrespective of aetiology, can result in necrosis of hepatocytes. Clinically, this ischaemic hepatitis presents as jaundice and there is marked rise in transaminases levels. Characteristic feature of ischaemic hepatitis is rapid resolution of transaminasemia, provided hypotension is corrected.

HAEMATOLOGICAL DISORDERS

Haematological Malignancies

The liver contains multipotent cells that can differentiate into reticulo-endothelial, myeloid and erythroid cells. These can be affected by malignant disease, usually in association with systemic diseases.

Leukaemia

Liver is involved in more than 95% cases of acute lymphocytic leukaemia and nearly 75% of those with acute myeloid leukaemia. Almost all patients with chronic lymphocytic leukaemia have hepatic involvement. In myeloid leukaemia, the liver is enlarged, smooth and may show pale nodules on cut-section. Microscopically, portal tracts and sinusoids are infiltrated with myeloid cells. In lymphoid leukaemia, liver is moderately enlarged with leukaemic infiltration involving only the portal tracts and sparing of the sinusoids. Pre-sinusoidal portal hypertension may occur due to hepatic or portal involvement.

Lymphoma

Hepatic involvement occurs in about 70% of cases and implies stage IV disease. In Hodgkin's disease, hepatic involvement is seen in around half of the patients. The infiltration spreads out from the portal tracts and includes mononuclear cells and occasionally Reed-Sternberg cells. In non-Hodgkin's disease, portal zones are involved and gamma-glutamyl transpeptidase and transaminase levels are often moderately increased. Focal lesions can be seen on imaging studies. Liver biopsy with immunotyping for malignant cells may be helpful.

Multiple Myeloma

The liver may be involved in up to 50% of patients with myeloma. Portal tracts and sinusoids are filled with plasma cells. The patients may have jaundice, ascites and portal hypertension. About 10% of patients also have amyloid deposits in the space of Disse.

Haemolytic Anaemias

In sickle cell disease (SCD), liver may be involved either by sickling crisis that present with right upper quadrant pain, fever and jaundice, or with intra-hepatic cholestasis. In some patients, sickle cell crisis is precipitated by Salmonella infection or by folic acid deficiency. In 10% cases, the crisis selectively affects the liver and lasts for about 2 to 3 weeks. It is difficult to differentiate sickle crises from viral hepatitis. Hepatic histology classically shows intra-sinusoidal sickling, erythrophagocytosis by Kupffer cells and ischaemic necrosis. Bile plugs are prominent and fatty change may occur. Even asymptomatic patients with SCD commonly have raised serum transaminases and hepatomegaly. Repeated blood transfusions may lead to hepatitis B and C and iron overload.

INFECTIONS

Human Immunodeficiency Virus (HIV) Infection

With increased life-expectancy of patients infected with HIV due to the use of highly active antiretroviral therapy, liver disease has assumed greater importance in these patients as a cause of morbidity and mortality. Most HIV-infected patients with IV drug abuse have hepatitis C virus (HCV) co-infection. Though HIV infection accelerates the progression of HCV related liver disease and HCV infection increases the risk of hepatotoxicity due to antiretroviral medications, interferon based therapy for HCV appear to be as effective in HIV-infected subjects as in those without HIV infection. Severely immunosuppressed HIV-infected patients almost uniformly have abnormalities of liver enzymes. Marked liver enzyme elevation accompanied by right upper-quardrant pain, fever, jaundice, or hepatic decompensation in HIV infected person need evaluation using endoscopic retrograde cholangio-pancreatography or liver biopsy, for diagnosis of biliary tract or hepatic parenchymal diseases, respectively.

Tuberculosis

Liver involvement in tuberculosis (TB) can occur either due to granulomatous hepatitis or as a result of hepatotoxicity of anti-tuberculosis drugs. Granulomatous hepatitis most frequently presents with hepatomegaly, elevated serum alkaline phosphatase levels, fever, weight loss, and abdominal pain. A moderate or marked increase in the serum levels of alkaline phosphatase, along with normal or mildly increased serum bilirubin, is highly suggestive of granulomatous hepatitis. Histopathology of liver biopsy in these patients usually consist of granulomas (95.8%), caseation (83.3%), fatty changes (42%), portal fibrosis (20%), acid-fast bacilli in association with granulomas (9%) and mononuclear cell infiltrates. Conventional anti-tuberculosis drugs, except pyrazinamide, can be given in granulomatous hepatitis with close supervision of transaminases. Hepatotoxicity due to anti-tuberculosis drugs is a relatively common phenomenon, with almost all of the first-line drugs having significant hepatotoxicity. Clinical presentation varies from a transitory asymptomatic rise in transaminases to acute liver failure and the frequency of hepatotoxicity in different countries varies widely from 2% to 39%. Hepatotoxicity is most common in period from third week to third month from start of anti-tuberculosis drugs. Anti-tuberculosis drugs should be withheld if clinical jaundice appears or transaminases are raised more than 3 times. Reintroduction of same drugs is possible after remission of jaundice and/or transaminasemia.

PULMONARY DISEASES

Serum bilirubin, alanine transferase, γ-glutamyl transpeptidase (GGT) and alkaline phosphatase may be elevated in patients with chronic pulmonary disease or status asthmatics, and these liver abnormalities may be associated with cor-pulmonale.

IMMUNE SYSTEM AND CONNECTIVE TISSUE DISEASES

Systemic Lupus Erythematosus

Sub-clinical liver injury is seen in about 25% of patients with systemic lupus erythematosus (SLE), but may not be related to the disease itself. Liver biopsy usually shows no significant lesion; rarely, chronic hepatitis or granulomatous hepatitis may be seen. Jaundice is usually haemolytic in origin.

Rheumatoid Arthritis

In rheumatoid arthritis, elevated serum alkaline phosphatase levels may occur in up to 10% to 15% of patients and hepatomegaly in 10% of patients. However, clinical signs of liver disease are usually absent. Liver may have histological changes like fatty change, Kupffer cell hyperplasia, mild mononuclear cell infiltration of portal areas, and rare foci of hepatocyte necrosis.

Amyloidosis

Hepatic involvement is common in patients with systemic amyloidosis. Hepatomegaly is seen in 50% of cases; the liver is smooth and non-tender. Generally, liver function tests (LFT) are mildly deranged. Three patterns of hepatic amyloid deposition are seen: sinusoidal or parenchymal, periportal and mixed. Sinusoidal variety is the most common. Liver biopsy, though diagnostic in more than 95% of cases, is seldom indicated since other involved tissues may be easier and safer to biopsy. Thus, abdominal fat pad aspiration and rectal biopsy are useful alternative modalities. Hepatic involvement generally does not influence the disease prognosis or necessitate any specific management.

Sarcoidosis

Sarcoidosis is characterised by widespread granulomatous lesions involving several body organs. Liver involvement is frequent though mostly asymptomatic. Hepatomegaly is seen in 20% of patients. Overt hepatic insufficiency is rare. Liver biopsy is confirmatory in about 60% of patients, but is indicated only if another accessible tissue is not available. Histologically, small well-formed granulomas in the same stage of development are common. Rarely, asteroid bodies and Schaumann bodies are also seen. Serum immunoglobulin (Ig)G and alkaline phosphatase levels, often raised and serum angiotensin converting enzyme levels are often increased. The prognosis is usually good, except in those with widespread hepatic involvement. Corticosteroids are generally not of much help.

ENDOCRINE AND METABOLIC DISORDERS

Porphyrias

This group of diseases is caused by defects in various enzymatic steps in biosynthesis of haem. Principal clinical manifestations include photosensitivity, cutaneous lesions, neurological dysfunction, and structural liver disease. Increased urine porphobilinogen may suggest the diagnosis. In porphyria cutanea tarda, the liver damage may be due to metabolic abnormality or to additional factors; such as alcoholism and HCV infection. Phlebotomy is the first-line of therapy. In protoporphyria, protoporphyrin may have a direct toxic effect on the liver. Liver transplantation has been used successfully; however, protoporphyrin-induced damage can recur in the transplanted liver.

Diabetes Mellitus (DM)

Liver is an important site of glycogen storage and gluconeogenesis. Thus, hepatic involvement in diabetes is common. Severe, uncontrolled insulin-dependent diabetes mellitus (IDDM) can lead to significant hepatic enlargement. The liver is firm and smooth; and may have a tender edge. The enlargement is due to

glycogen deposition, fat deposition and water retention in hepatocytes secondary to acidosis. In non-insulin-dependent diabetes mellitus (NIDDM), liver may be enlarged though it is usually non-tender. Nearly 80% of diabetics with liver involvement have elevation of liver enzymes. In fact, DM and obesity are among the most common causes of non-alcoholic steato-hepatitis.

Glycogenoses

Several forms of glycogenoses with different enzymatic and structural defects are known. Most of these affect the liver except types V and VII. Hepatic forms are usually diagnosed in infancy or early childhood and are characterised by hypoglycaemia, massive hepatomegaly, poor physical growth, a tendency for increased fat deposition particularly in the cheeks, and biochemical abnormalities.

Type I (von Gierke's Disease)

This autosomal recessive condition, caused by the deficiency of glucose-6-phosphatase, affects the liver and kidney but not muscle and heart. Presentation is with massive hepatomegaly in early childhood, at age of around 2 years. The liver is enlarged, smooth and brown. Splenomegaly is not seen, as opposed to lipodioses, cirrhosis and congential hepatic fibrosis. The liver cells and nuclei are laden with glycogen and fat. Cirrhosis does not develop but occasionally, hepato-cellular adenomas and rarely carcinomas develop. Liver biopsy examination for histology, immunohistochemistry, quantitative glycogen analysis and enzyme analysis is confirmatory. Treatment is aimed at preventing hypoglycaemia; liver transplantation may be useful.

Other Forms of Glycogenoses

In Pompe's disease (type II), all organs including the liver show vacuolated cells due to lysosomal glycogen deposition. In Cori's disease (type III), serum transaminases are usually increased. Periportal fibrosis occurs but cirrhosis is rare. In Andersen's disease (type IV), cirrhosis develops which may be associated with many giant cells. The child develops hepatosplenomegaly, ascites and finally liver cell failure. In Her's disease, only liver is involved and growth retardation and hepatomegaly are the usual manifestations.

Thyroid Disease

Patients with hyperthyroidism frequently experience liver injury. Liver injury can be either cholestatic or hepato-cellular. Up to 64% of these patients show elevated serum alkaline phosphatase test (ALP) and up to 35% show elevated ALT. Interestingly, only 17% of these patients show elevated GGT and most of the increased ALP may be bone-derived. In contrast to hyperthyroidism, liver biochemistry abnormalities are less prominent in patients with hypothyroidism. However, modest elevations in serum AST and ALT have been reported in 84% and 60%, respectively, of patients with hypothyroidism. Thionamides, used for the treatment of hyperthyroidism, are also known to cause serious hepatotoxicity; rarely acute liver failure.

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14.19 Tumours of the Liver

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INTRODUCTION

Tumours of the liver arise either from the hepatocytes, supporting mesenchymal tissue or bile duct epithelium. Although metastasis from other primary tumours are the most common liver tumours, hepato-cellular carcinoma (HCC, hepatoma) is the most common primary malignant tumour and haemangioma is the most common benign tumour of the liver. Conclusive diagnosis of a focal hepatic lesion is essential because it may represent a malignancy or may be benign and carry specific risks, such as rupture, bleed or malignant transformations. Here we would be discussing the most frequently encountered and clinically most significant liver masses.

BENIGN LIVER TUMOURS

Benign focal lesions of the liver are usually found incidentally. In most cases, patients with benign hepatic lesions have no pre-existing liver disease.

HAEMANGIOMA

Haemangiomas are the most common benign solid lesions of the liver. They are congenital vascular malformations, most often found incidentally, have a female predominance (female to male ratio is 6:1) and have no major clinical implications.

Pathology

On gross examination, haemangiomas appear as a dark purple compressible spongy lesion with microscopic appearance of multiple vascular spaces of varying sizes which are lined by single layer of endothelial cells and are separated by fibrous septa. Biopsy may be associated with significant morbidity because of bleeding.

Clinical Features

In most cases, haemangiomas are small and asymptomatic. Haemangiomas larger than 4 cms in size have been referred to as giant haemangiomas. Physical examination findings are usually unremarkable. Hepatic biochemical tests are usually normal.

IMAGING

Typical ultrasonography (USG) appearance of a haemangioma is of echogenic, homogenous lesion with well defined borders. Almost all hepatic hemangiomas of > 2 cm are detected on hepatic triphasic computed tomography (CT) with typical appearance of well defined hypodense lesion on non-contrast image with serial images in triple phase, showing the lesions getting filled from periphery to the centre, with persistence of contrast in the delayed state. Findings similar to CT are seen on a T1, contrast MRI and contrast enhanced USG.

Management

As most haemangiomas are asymptomatic, rarely they enlarge in size or rupture but have no malignant potential, thus surgical intervention is rarely indicated. Surgical resection remains the main definitive treatment of symptomatic haemangiomas. Other less effective options, such as transarterial embolization had been used for symptomatic lesions, acute bleeding and consumption coagulopathy. Hepatic artery ligation, radiation therapy, radiofrequency (RF) ablation and liver transplantation are used on rare occasions for unresectable giant haemangiomas.

FOCAL NODULAR HYPERPLASIA (FNH)

FNH is a benign tumour of unclear aetiology. It is the second most common benign solid mass of liver with a female predominance (female to male ratio is 8:1).

Pathology

FNH is solitary in most cases with most of them smaller than 5 cm. Typical macroscopic appearance is of a firm nodular mass with dense central stellate scar and radiating fibrous septae and microscopically consists of normal looking hepatocytes arranged abnormally.

Clinical Features

In most cases, FNH is asymptomatic and detected incidentally. Hepatic biochemical tests and α-fetoprotein are typically normal.

Radiological Diagnosis

The characteristic central scar may be seen on imaging. The picture on triple phase CT scan, dynamic contrast enhanced MRI and contrast enhanced USG, characteristically shows early filling central arteriole with spread of contrast towards periphery of the lesion. FNH needs to be differentiated from adenoma (**Table 1**). There is no evidence of FNH progressing to malignancy.

Table 1: Differentiating Features between FNH and Hepatic Adenoma

	FNH	Adenoma
Size	Usually <5 cm	More than 5 cm
Use of oral contraceptives	No	Yes
Central scar on imaging	Yes	No
^{99}Tc Sulphur colloid scintigraphy	Hot lesion	Cold lesion
Symptoms	Usually asymptomatic	Usually symptomatic
Management	Serial observation of lesion	Surgical removal

Management

The recommended treatment for asymptomatic FNH is observation. However, if the lesion is enlarging, or is clearly symptomatic, then surgical intervention in the form of wedge resection or enucleation is generally recommended.

HEPATO-CELLULAR ADENOMA (HA)

Hepato-cellular adenoma or hepatic adenoma (HA) is a benign tumour occuring mainly in women of childbearing age and in contrast to FNH and haemangioma. HA has very strong association with oral contraceptive pills (OCPs) use. Prolonged use of OCPs (>5 years) and age over 30 years are risk factors for development of HA. Androgenic and anabolic steroids, diabetes mellitus and glycogen storage diseases type I & III are also associated with development of HA.

Pathology

HA is usually large, well-circumscribed, solitary mass and arises in an otherwise normal liver. Microscopically, cells closely resemble normal hepatocytes with absence of Kupffer cells. A percutaneous needle biopsy carries the risk of bleeding.

Clinical Features

In most series, patients present with upper abdominal pain or discomfort. Hepatic adenomas can be complicated by rupture and/or haemorrhoage. Malignant transformation is rare but does occur. Differences between HA and HCC are given in **Table 2**.

Table 2: Differentiating Features Between a Hepatic Adenoma and an HCC

	Hepatic adenoma	HCC
Predilection for (sex)	Females	Males
Cirrhosis	Absent	Present
Alanine aminotranferase	Normal	High
Use of oral contraceptives	Present	Absent
Alpha-fetoprotein	Normal	High
Portal vein thrombosis	Absent	May present

Radiological Features

USG shows a well-demarcated mass and variable echogenicity. Multiphasic contrast enhanced CT scan shows homogenous enhancement in the arterial phase and isoattenuation in relation to the normal liver on the portal venous phase. 99Tc sulfur colloid scintigraphy typically shows no uptake of colloid because of absence of Kupffer cells.

Management

Generally, surgical treatment is recommended because of the risk of rupture, haemorrhage, and malignant transformation. Surgical approaches for HA includes enucleation, resection and liver transplantation.

MALIGNANT TUMOURS OF THE LIVER

Hepato-Cellular Carcinoma

Hepato-cellular carcinoma (HCC) is the 5th most common cancer worldwide and the third leading cause of cancer-related death. In India, the incidence of HCC has been reported to be about 1.6% among prospectively followed-up cirrhotics to about 2.7% in population-based cancer registries. Risk factors for HCC are given in **Table 3**. Men are generally more susceptible than women to develop HCC. In India, HBV is the most common risk factor (50% to 60%) for HCC followed by HCV (11% to 15%) and alcohol (6% to 14%).

Clinical Features

The symptoms and signs may be those of co-existing cirrhosis or among patient with well-compensated liver disease, HCC may present with pain abdomen, abdominal mass, fever, weight loss or anorexia. HCC development may present as recent decompensation of a previously well-compensated liver disease. **Table 4** presents the frequency of symptoms and sign in a large series of 324 patients from India.

Table 3: Risk Factors for HCC

Major risk factors
- Chronic hepatitis B
- Chronic hepatitis C
- Cirrhosis
- Dietary exposure to aflatoxin B1

Minor risk factors
- Oral contraceptive steroids
- Cigarette smoking
- Hereditary haemochromatosis
- Wilson's disease
- α-1-antitrypsin deficiency
- Type 1 hereditary tyrosinemia
- Type 1 and 2 glycogen storage disease
- Hypercitrullinemia
- Ataxia telangiectasia
- Membranous obstruction of inferior vena cava

Table 4: Symptoms and Signs in Patients with HCC

Symptoms	Frequency (%)	Sign	Frequency (%)
Abdominal pain	59-95	Hepatomegaly	54-98
Weight loss	34-71	Ascites	35-61
Weakness	22-53	Splenomegaly	27-42
Abdominal swelling	28-43	Jaundice	4-35
Jaundice	5-26	Wasting	25-41
Non-specific features	25-28	Fever	11-54

Diagnosis

A number of tumour markers have been used for the diagnosis of HCC. Among these three commonly used are alpha-fetoprotein, PIVKA II or des gamma carboxyprothrombin and alpha-L-fucosidase. The alpha-fetoprotein (AFP) has been the most frequently used, a value of 400 ng/mL is used as a diagnostic level because levels below this value may be found in patients with a variety of acute and chronic benign liver diseases, such as acute and chronic hepatitis and cirrhosis. False-positive results also may occur in patients with tumours of endodermal origin and non-seminomatous germ cell tumours. However, a normal AFP level does not exclude the presence of HCC.

On USG, HCC may appear hypoechoic, hyperechoic or isoechoic to the surrounding cirrhotic liver. Although USG is sensitive in picking up HCC's, but in the presence of altered echotexture of cirrhotic liver, the sensitivity of USG is markedly reduced.

Triple phase helical CT and contrast enhanced MRI are the imaging techniques of choice. The tumour appears hypervascular during the hepatic arterial phase and relatively hypodense in the delayed phase.

Management

Symptomatic hepato-cellular carcinoma carries a grave prognosis. The main reasons for the poor outcome are the extent of tumour

burden when the patient is first seen and the frequent presence of coexisting cirrhosis and hepatic dysfunction. Treatment of HCC is difficult because you have to treat not only tumour but also the complications of cirrhosis as well as the aetiological agent of cirrhosis. Although a number of staging systems are available for staging HCC, the Barcelona Clinic Liver Cancer (BCLC) classification has emerged during recent years as the standard classification because it incorporates all the above parameters and guides therapy according to the stage (**Figure 1**). In our country, about 45% to 55% of tumours have portal vein invasion at the time of diagnosis as reported in 2 large series from tertiary care centres and a large majority of them are BCLC stage C or D.

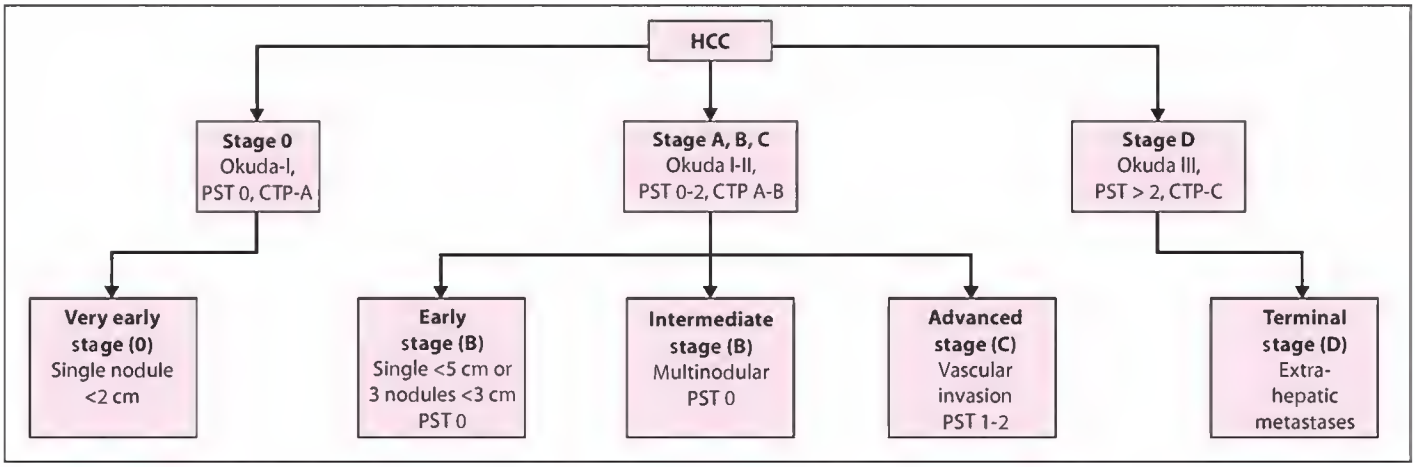


Figure 1: Barcelona Clinic Liver Cancer staging classification.

PST = Performance status; CTP = Child Turcotte Pugh classification.

Curative forms of therapy for HCC include, Liver resection (surgical removal of a part of the liver involved by the tumour), percutaneous ablative therapies [burning the tumour with either radiofrequency (RF) current (RF ablation) or with injection of 100% alcohol or with injection of 50% acetic acid] or liver transplantation. Palliative therapies include transarterial chemoembolisation or systemic chemotherapy. As mentioned earlier, BCLC staging system guides therapy as follows: Patients with very early HCC (stage 0) are optimal candidates for resection. Patients with early HCC (stage A) should be considered for radical curative therapies [resection, liver transplantation, or local ablation *via* percutaneous ethanol injection (PEI) or RF ablation]. Patients with intermediate HCC (stage B) have been found to benefit from transarterial chemoembolization (TACE). Patients with advanced HCC, defined as the presence of macroscopic vascular invasion, extra-hepatic spread, or cancer-related symptoms (ECOG performance status 1 or 2) (stage C), have only systemic chemotherapy as the option. Patients with end-stage disease (stage D) can only receive symptomatic treatment, because any form of therapy for the liver cancer is not only ineffective at this stage, but also detrimental for the already poor liver functional reserve. Recently, for patients in BCLC stage D, a new form of biological therapy, with multikinase inhibitor, sorafenib, has been shown to be associated with improved survival.

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14.20 Diseases of Gall Bladder and Biliary Tract

Rakesh Tandon

GALL BLADDER STONES

The prevalence of gall bladder stones varies widely in different parts of the world. In India, it is estimated to be around 4%, whereas in the western world it is about 10%. In certain ethnic groups like Pima Indians and Taiwan Chinese, the frequency is extremely high; about 60% of Pima Indian women develop gallstones by 25 years of age.

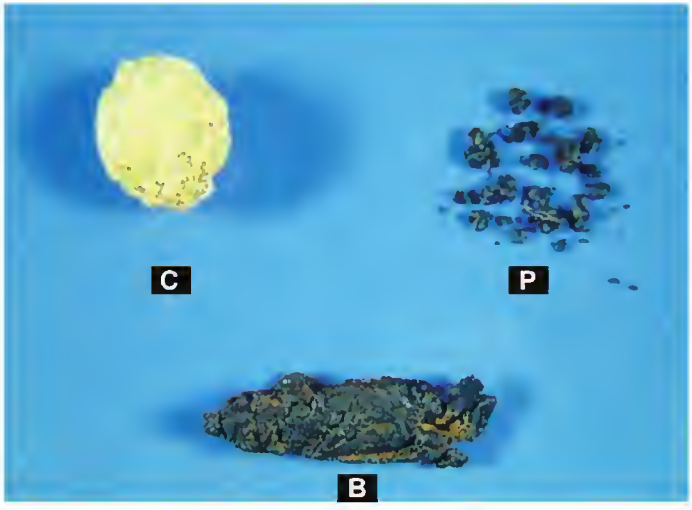
Gallstones cause substantial morbidity and mortality, although only 20% of people harbouring gallstones ever become symptomatic. The cardinal symptom of gallstones is biliary colic. It is a sharp pain appearing suddenly in the right upper or mid abdomen and is possibly caused by transient blockage of the gall bladder outlet by a stone. If the stone does not move out soon and gets lodged in the cystic duct, the patient will develop acute cholecystitis, mucocoele or pyocoele of the gall bladder. Blockage of the common bile duct by a stone results in obstructive jaundice. On the other hand, transient blockage of the ampulla of Vater by a migrating stone may induce acute pancreatitis. Finally, dyspepsia is not considered a manifestation of gallstones.

Risk Factors

At the population level, specific risk factors have been shown to predict gallstone formation. These are older age, female gender, obesity, weight loss, total parenteral nutrition, pregnancy, hypertriglyceridaemia, genetic predisposition and use of certain drugs like clofibrate, oral contraceptives, ceftriaxone and octreotide.

Types of Gallstones

By their gross appearance gallstones have been divided traditionally as cholesterol, mixed and pigment stones (**Figure 1**). The cholesterol and mixed stones contain more than 50% of their dry weight as cholesterol, and are therefore, now together referred as cholesterol gallstones. They are the predominant type and form about 80% to 90% of all gallstones in northern India. Pigment gallstones, on the other hand, contain < 20% of dry weight as cholesterol. The pathogenesis and clinical manifestations of these 2 types of pigment stones differ widely (*vide infra*).



Figures 1A to D: Photograph showing various types of gallstones: Cholesterol (C), pigment (P) and earthy brown (B).

Mechanisms of Gallstone Formation

Cholesterol which is insoluble in water is solubilised in bile by two biliary lipids, viz. bile salts and phospholipids through micelle formation. An excess of cholesterol or a deficiency of either or both of the biliary lipids in bile can result in cholesterol supersaturation and subsequent precipitation of cholesterol out of the soluble phase of bile. However, additional factors must however exist for gallstone formation since many persons have supersaturation of bile with cholesterol but only some develop gallstones. Two such factors are gall bladder hypomotility and a nucleating agent, such as mucin. Some pro-nucleating and anti-nucleating proteins have been recognised in the bile. Their excess or deficiency, respectively, promotes gallstone formation. Often a combination of these factors is operative.

The commonest cause of cholesterol supersaturation in bile is excess cholesterol secretion. Indeed, that is seen classically in obese patients with gallstones. Several hormonal, enzymatic and dietary factors influence cholesterol secretion by controlling the amount of cholesterol delivered to the liver, the amount that is synthesised in the liver through HMG CoA reductase activity and the amount that is converted into bile acids through 7-alpha hydroxylase activity and the amount that is converted into cholesterol esters by acyl cholesterol: lecithin transferase (ACAT) activity.

Genetic polymorphisms in several genes, such as Apo E, Apo B, Apo A-1, low density lipoprotein (LDL) receptor, cholesteryl ester transfer protein and LDL receptor-associated protein genes have been shown to confer susceptibility to gallstone formation. They do so by increasing the hepatic cholesterol secretion either by bringing more cholesterol to the liver or by channelling an increased proportion of cholesterol into bile. By contrast, three active bile acid transporters at the canalicular membrane, viz. bile salt excretory protein, multi-drug receptor 2 and multi-drug receptor 3 have been shown to be downregulated in cholesterol gallstone patients with certain genetic polymorphisms.

Pigment Gallstone Formation

Pigment gallstones are of two types: black-pigment stones found in the gall bladder and the earthy-brown pigment stones found in the intra-hepatic bile ducts (**Figure 1**). Black pigment stones are associated with an excess of unconjugated bilirubin in the bile. The unconjugated bilirubin gets

precipitated as an insoluble highly cross-linked polymer of bilirubin tetrapyrroles in various states of oxidation. These polymers are then bound together by mucous glycoproteins. Other biliary constituents, such as calcium carbonate may also get trapped in these stones.

Diagnosis

As 75% of gall bladder stones are radiolucent, plain film of the abdomen is of little use. The best method available today to detect gall bladder stones is abdominal ultrasonography (USG) (sensitivity > 95%; specificity 99%). Gallstones are seen as areas of echogenicity in the gall bladder with posterior acoustic shadowing (**Figure 2A**). Even stones in the common bile duct (CBD) can be seen (**Figure 2B**); CBD is identified as lying above the portal vein on ultrasound (USG) doppler. The time-honoured oral cholecystography can also be done to visualise radiolucent stones in the gall bladder. Opacification of gall bladder following oral contrast administration also indicates patency of cystic duct, an important pre-requisite for treating gallstones with oral bile acids or lithotripsy. Computed tomography (CT) helps further in knowing the density of the stones but does not detect any stones missed by other tests. For demonstrating stones in the CBD, endoscopic retrograde cholangio-pancreatography (ERCP) is the gold standard but magnetic resonance cholangiopancreatiography (MRCP) is a good non-invasive alternative. Endoscopic ultrasonography, however, appears to be the most sensitive technique for detection of these stones, and can pick up small calculi in the gall bladder as well as the bile duct .

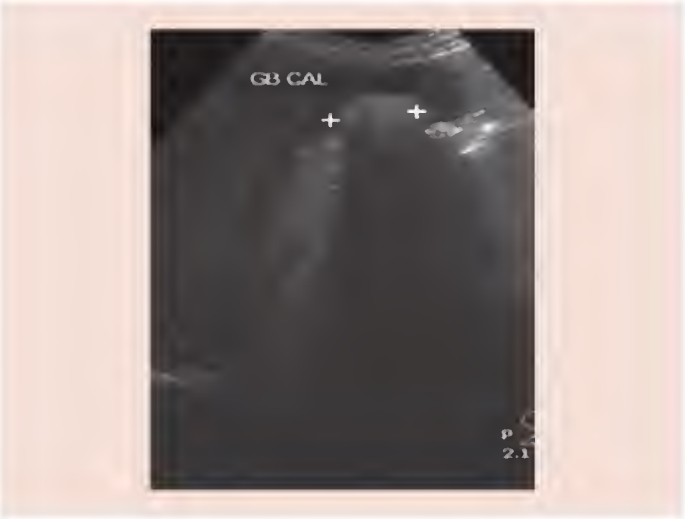


Figure 2A: A single calculus in the gall bladder seen with acoutic shadowing.

Treatment

Asymptomatic gallstones are best left alone and treated expectantly except in special circumstances such as in the case of astronauts or people residing in places that lack medical facilities. The symptomatic patients (10% to 15%) should, on the other hand, be treated effectively as they tend to have recurrence of symptoms or may develop acute cholecystitis, acute pancreatitis or other complications. Surgical removal of the diseased gall bladder (cholecystectomy) appears to be the best treatment option at present, since it provides protection against reformation of gallstones as well as development of carcinoma of the gall bladder.

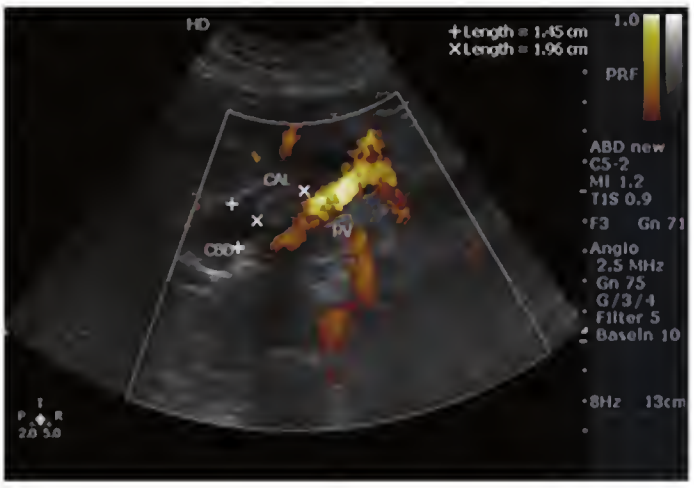


Figure 2B: Stone seen in dilated common bile duct (CBD). Below and parallel to CBD it is seen portal vein.

However, for those who are averse to surgery or those who carry a high surgical risk because of associated coronary artery disease or advanced lung disease, several non-surgical treatment options are available. Both surgical and non-surgical modes of therapy are briefly discussed below.

Surgical treatment

Cholecystectomy is curative and is relatively safe with an overall mortality of 0.1% to 0.6% and a morbidity of 10% to 30%. Both these proportions increase with age, presence of concomitant disease or when the procedure is accompanied by CBD exploration because of a suspected stone in the bile duct. Conventional cholecystectomy through laparotomy has been almost universally replaced by laparoscopic cholecystectomy. The latter has advantages of reduced post-operative pain and shorter hospital stay, as compared with conventional cholecystectomy.

In patients with a history of obstructive jaundice or with a demonstrated CBD stone, the prevailing treatment approach is to clear the CBD by performing an endoscopic sphincterotomy and basket removal of stones, and to then perform the laparoscopic cholecystectomy rather than doing a conventional surgery for both the gall bladder and CBD stones.

Non-surgical treatment

Non-surgical treatment modalities include oral bile acid therapy (OBT), extra-corporeal shock wave lithotripsy (ESWL) and contact dissolution with methyl-1-tert-butyl-1-ether (MTBE). The most popular of these and the one with which substantial experience is available is OBT with chenodeoxycholic acid (CDCA) or its 3-beta epimer ursodeoxycholic acid (UDCA). For bile acid therapy as well as ESWL, it is essential that the cystic duct is patent as established by visualisation of gall bladder on oral cholecystography. Cystic duct patency is required to allow drugs like UDCA to enter and concentrate in the gall bladder as also to let stone fragments pass out of the gall bladder. For OBT, the gallstones should not be >1.5 cm in size, should be radiolucent and preferably have a density of <100 Hounsefield units on CT. On the other hand for ESWL, the stones should be between 1 and 3 in number, 1.0 to 3.0 cm in diameter and preferably radiolucent but may have a few specks or a thin rim of calcification. Whilst OBT works slowly, ESWL is able to remove

the stones fairly fast. There are three methods of shockwave generation: underwater electrostatic spark-gap discharge, electromagnetic generation and piezo-electric generation; of these, the spark-gap lithotripsy is still the most popular and effective.

INTRA-HEPATIC BILIARY DUCTAL STONES

Intra-hepatic ductal stones, also referred to as liver stones or hepatolithiasis, are a common problem in South-east Asia including China, Korea, Japan, Thailand, Malaysia and Indonesia, where the prevalence of this condition is 5% to 10 % in contrast to 1% in the Western world. Two major aetiological factors considered have been infestation with *Clonorchis sinensis* and an intra-hepatic ductal stricture, more often in the left hepatic duct, resulting in bile stasis and bacterial infection. A bacterial enzyme, beta-glucuronidase, is believed to deconjugate bilirubin glucuronide, the water soluble form of bilirubin in the bile, resulting in the formation of free unconjugated bilirubin which is not soluble in water. This free bilirubin precipitates or combines with ionized-calcium to form calcium bilirubinate, which is the main constituent of intra-hepatic brown-pigment stones. A similar deconjugation of fatty acids occurs accounting for the presence of fatty acids in these stones. Intra-hepatic stones grow silently and may then present with recurrent pain, fever and jaundice. These may be associated with a mild rise in serum transaminases and a substantial rise in serum alkaline phosphatase. USG is the best non-invasive imaging technique to demonstrate these stones though cholangio-graphy (percutaneous or endoscopic retrograde) remains the 'gold standard'. Treatment is difficult and frustrating, and is aimed at surgical removal of the stones or of a segment of the liver which is heavily laden with intrahepatic stones. Percutaneous cholangioscopic removal of stones can be done at specialised centres. Despite complete surgical removal of such stones, recurrence rate is high and 4% of patients will develop cholangiocarcinoma.

SPHINCTER OF ODDI DYSFUNCTION

Sphincter of oddi dysfunction (SOD) is defined as a benign, non-calculous disorder with functional obstruction at the level of the SOD that causes pancreatobiliary-type pain, cholestasis and/or pancreatitis. The SOD may be a part of a generalised motility disorder of the upper gastrointestinal (GI) tract. Such cases are associated with a variable combination of abnormally high amplitude oesophageal contractions, gastroparesis, and duodenal and jejunal dysmotility.

The normal sphincter of oddi has a basal pressure of 3 to 5 mmHg with 2 to 6 contractions per minute with an amplitude of 95 to 195 mmHg. Most of the contractions proceed in an antegrade direction in normal persons and cholecystokinin administration leads to a relaxation of the sphincter of oddi.

The SOD can occur from a primary motor disturbance (dyskinesia) or a structural alteration (stenosis). The typical patients with SOD are middle-aged females who present for evaluation of recurrent right upper quadrant pain after cholecystectomy. Findings suggestive of SOD include biliary-type pain, dilatation of CBD >12 mm, delayed drainage of the CBD >45 minutes and abnormalities in serum liver function tests (LFT). Definitive diagnosis of SOD requires tests of biliary tract motility. Manometric findings in SOD include one or more of the following: elevated basal pressure >40 mmHg, more than 7 contractions per minute, retrograde progression in >50% of the contractions, and contractions of the sphincter as a response to cholecystokinin. The management of SOD is based on the Geenen-Hogan classification (**Table 1**). Group I patients mainly have sphincter of Oddi stenosis and can safely undergo endoscopic sphincterotomy without first performing SOD manometry, thus avoiding the risk of pancreatitis due to manometry. Group II patients may have stenosis or dyskinesia, and manometric findings should guide further management. Patients with elevated basal pressure may be treated with endoscopic sphincterotomy or a trial of long-acting nitrates or calcium channel blockers. Group III patients may have a non-biliary cause for pain, and therefore, common causes of abdominal pain must be ruled out.

Table 1: Geenen-Hogan Classification of Sphincter of Oddi Dysfunction

Group 1	Group 2	Group 3
Biliary pain + All of the following criteria	Biliary pain + 1 or 2 of the following criteria	Biliary pain + None of the following criteria
Delayed drainage of the common bile duct (>45 min.)		
Dilatation of the common bile duct (>12 mm) on USG		
Elevation of serum aspartate aminotransferase or alkaline phosphates to >2 times normal on 2 or more occasions		

BILIARY TRACT MALIGNANCIES

Biliary tract carcinomas are locally invasive adenocarcinomas which usually manifest as painless jaundice and biliary obstruction. These include gall bladder carcinoma, cholangio-carcinoma and intra-hepatic biliary malignancies (cholangio-cellular carcinoma) or carcinoma at the lower end of bile duct (peri-ampullary carcinoma). In the absence of treatment, most patients die of cholangitis, cachexia or hepatic failure within 3 to 6 months of diagnosis.

Gall bladder Carcinoma

Presence of gallstones has been proposed as a risk factor for cancers of the gall bladder and the extra-hepatic bile ducts. Other predisposing factors include anomalous junction of the pancreatic and biliary ductal systems, K-ras codon 12 mutation, blood groups A and AB, and *Salmonella typhi* carrier state. Gall bladder carcinoma usually presents at an advanced stage with abdominal pain and cholestatic jaundice. A hard gall bladder mass is often palpable along with hepatomegaly. Prognosis in such patients is poor. In some patients, the tumour is found incidentally after simple cholecystectomy, at gross or microscopic examination of the excised gall bladder.

Conventional surgery is being gradually replaced by aggressive extensive surgical resection procedures, such as extended cholecystectomy which includes wedge resection of the hepatic gall bladder-bed and regional lymphadenectomy. In patients with unresectable tumours, palliation may be possible through endoscopic stent placement.

Cholangiocarcinoma

Hilar cholangiocarcinomas are characterised by a slow growth rate and a low propensity to metastasise. Papillary cholangio-

carcinomas have the best survival rate but are infrequent. Pre-operative diagnosis of cholangiocarcinoma may be established by a combination of brush cytology and forceps biopsy from the bile duct lesion. The established criteria for non-resectability of cholangiocarcinoma are: bilobar extensive intra-hepatic bile duct spread, involvement of the main portal vein, bilobar involvement of hepatic arterial or portal venous branches or both, and a combination of unilobar hepatic involvement with cholangiographic evidence of extensive contralateral ductal spread.

In unresectable tumours, palliation may be possible by restoring bile flow, in order to relieve jaundice and prevent or treat complications like pruritus and sepsis. This is accomplished by endoscopic or percutaneous stenting across the obstructing lesion, or a surgical biliary enteric bypass. Combined external beam radiation and brachytherapy with intracavitary iridium seeds have been used. However, this combined therapy has not been shown to provide a definite survival advantage. Hence, the preferred mode of therapy, if feasible, is curative resection.

Cancer of the Ampulla of Vater

This tumour has a higher resectability rate and a better prognosis than other biliary cancers. This is mainly because these tumours present early with features of obstructive jaundice. USG shows a dilatation of the biliary system and/or the pancreatic duct. Diagnosis is established by an ampullary biopsy taken through a side viewing endoscope. In case the tumour is located submucosally, endoscopic USG guided fine needle aspiration may be helpful in getting the tumour tissue. The best treatment option for these patients is pancreato-duodenectomy (Whipple's procedure). If the tumour is unresectable or pre-operative biliary drainage is needed, a biliary stent can be placed across the papilla endoscopically.

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Section 15

Haematology

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15.1 Haematopoiesis

Shaji V Ramachandran, Vikram Mathews

INTRODUCTION

Healthy individuals require adequate production of blood cells on a daily basis to maintain normal function. This process needs to be tightly regulated and balanced to maintain homeostasis. Additionally, during this process, adequate haematopoietic stem cells (HSC) also have to be generated to maintain the pool of HSC. HSC and haematopoietic progenitor cells (HPC) are retained within the bone marrow by numerous ligands and cytokine gradients which are also important in regulation of differentiation and proliferation. The process of haematopoiesis is closely linked and regulated by the haematopoietic micro-environment in the bone marrow which includes mesenchymal derived stromal cells such as endothelial cells, fibroblasts, osteoblasts and adipocytes, cells of non-mesenchymal origin such as cells of the monocyte macrophage system and the extra-cellular matrix. Abnormalities at different stages in this process can result in various haematological disorders, such as aplastic anaemia, cytopaenias, leukaemia and myeloproliferative disorders. Haematopoiesis broadly consists of HSC proliferation and regulation, granulocytopoiesis, thrombopoiesis and erythropoiesis. Once HPC differentiate into mature blood elements, they leave the bone marrow by a still poorly understood mechanism.

DEFINITION

Haematopoiesis is a complex process by which HSC can both self replicate to maintain a pool of HSC and also differentiate into myeloid and lymphoid lineage committed HPC. These HPC can further terminally differentiate to produce all the cellular elements of the blood.

ONTOGENY OF HAEMATOPOIETIC TISSUES

Currently, it is believed that haematopoiesis originates as early as the third week of conception, both from the aorto-gonadal-mesonephros (AGM) region and from the extra-embryonic mesoderm in the yolk sac. Data from mice suggest that HSC arise in the AGM from a haemangioblast which can give rise to HSC and endothelial cells. In humans, HSC that arise from these regions colonise the foetal liver at 5 weeks of gestation and foetal liver haematopoiesis becomes active by 6 weeks and remains the dominant haematopoietic organ in foetal life. HSC seed the bone marrow by 8 weeks of gestation. In contrast to the foetal liver where haematopoiesis is predominantly erythroid, haematopoiesis occurring in the bone marrow is predominantly myeloid in foetal life. HSC also colonises the spleen by 12 weeks of gestation and the thymic rudiment by 8 weeks of gestation and these organs contribute to haematopoiesis in the foetal life (**Figure 1**).

During foetal life and immediately after birth a large number of HSC and HPC are found in circulation. However, within 24 to 48 hours after birth circulating progenitors disappear from the circulation. In adults, haematopoiesis shifts almost entirely into the bone marrow. *In utero* and at birth, the entire bone marrow is involved in haematopoiesis while with increasing age haematopoiesis is limited to the flat bones such as the pelvic bones, skull and ribs, the proximal ends of long bones and the vertebrae. In post-natal life the bone marrow is normally the only site of haematopoiesis, however, at times of extreme need the liver, spleen and other reticulo-endothelial tissue can contribute to extra-medullary haematopoiesis.

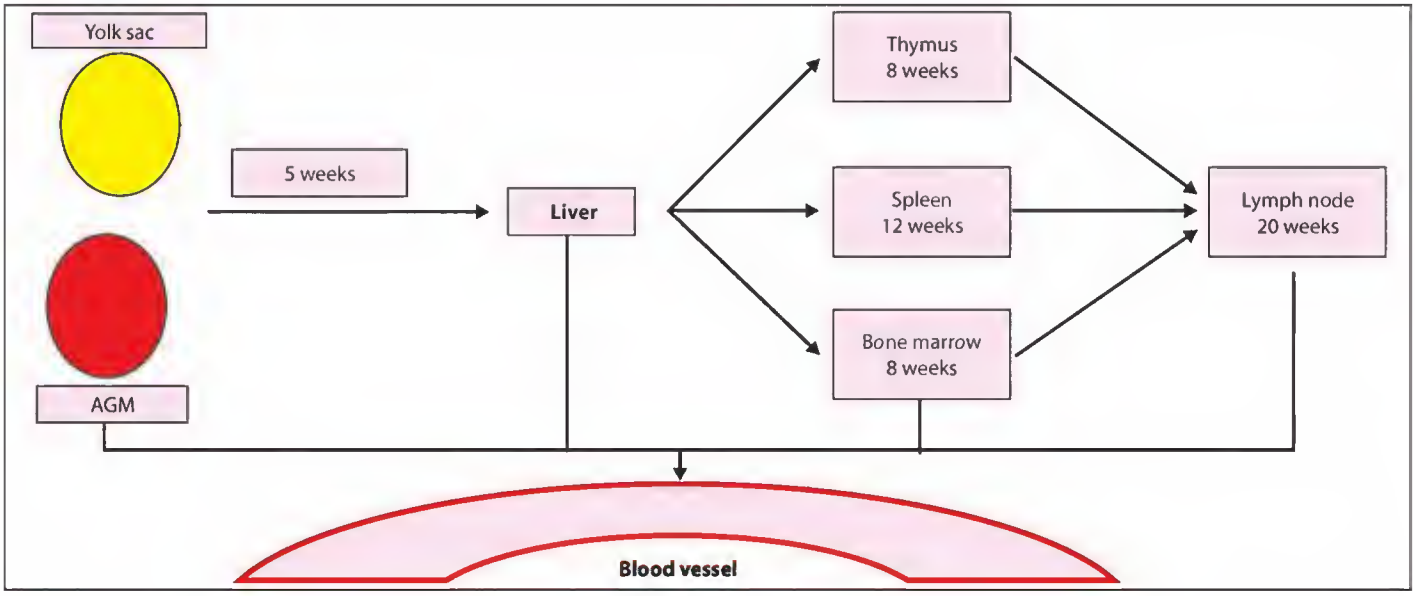


Figure 1: Ontogeny of human haematopoiesis. HSC migrate and colonise different organs. After birth they are found mainly in the bone marrow. The HSC is believed to arise from the AGM and/or extra-embryonic yolk sac at different time periods in gestation, as illustrated above.

AGM = Aorto-gonadal-mesonephros; HSC = Haematopoietic stem cell.

HAEMATOPOIETIC STEM CELLS AND STEM CELL NICHES

Haematopoietic Stem Cells

HSC has been defined functionally by their ability to reconstitute both the lymphoid and myeloid haematopoiesis when transplanted into a recipient. Immunological characteristic of HSC has been the absence of lineage specific antigens (Lin^-), in mice expression of specific antigens such as Sca1 and Thy1 and in humans expression of CD34 antigen. Another property that has been used to study stem cell populations is the ability of these cells to extrude a deoxyribonucleic acid (DNA) binding dye Hoechst 33342 which in turn is based on the property of these cells to often express drug efflux proteins. Based on this technique, a population of Lin^- and CD34 negative cells have been identified which has the capability for long-term reconstitution following a transplant, suggesting that these cells are a subset of HSC, even though they are CD34 negative.

The factors that regulate HSC proliferation and differentiation including commitment remain poorly defined. There are two major theories of HSCs renewal *versus* differentiation and these are the Stochastic model and the haematopoietic inductive microenvironment. In the Stochastic model stem cell renewal *versus* differentiation is based on probability residing within the HSCs while in the inductive micro-environment theory it is linked to probability of the extrinsic environmental signals that it is exposed to. **Figure 2** summarises the pathways of haematopoiesis starting from the HSC.

Haematopoietic Stem Cells Niche

Stem cell niche is a specific site in adult tissues where stem cells reside and undergo self renewal and produce large numbers of progeny (differentiation). The concept of a HSC niche was first proposed by Schofield in 1978 to describe the physiologically limited micro-environment in which stem cells reside. Mesenchymal stromal cell derived osteoblasts are increasingly being found to play a very important role in the HSC niche formation (*osteoblastic niche*). These osteoblastic niches have been shown to provide the structural surface on which HSC reside and also provide important signals that regulate HSC proliferation and differentiation. Thus, osteoblast cells play an important role not only in skeletal development but also in haematopoiesis. Experimental animal models have demonstrated that conditional ablation of osteoblasts leads to depletion of HSC and increasing the number of osteoblasts by the administration of parathyroid hormone has been shown to enhance HSC self renewal and engraftment. The need for physical interaction in the HSC niche probably is important to regulate the number of HSC in the stem cell pool. This physical interaction could also be important in deciding on symmetrical (proliferation) *versus* asymmetrical (differentiation). As illustrated in **Figure 3**, a daughter cell that divides with the division plane perpendicular to the niche plane has the potential to have both daughter cells remain in contact with the niche cell and retain stem cell-ness, while a cell that has its

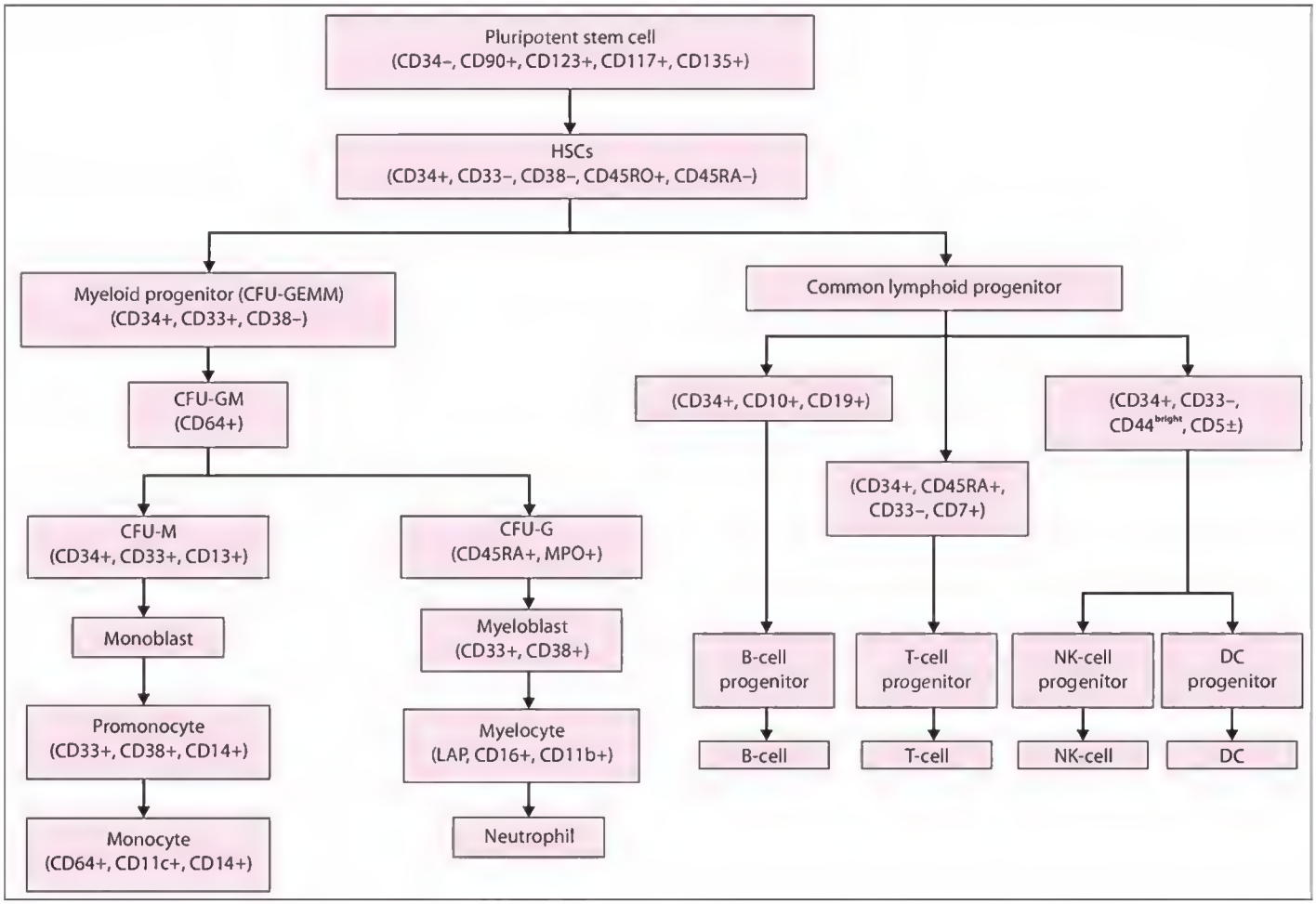


Figure 2: Model of the pathways of haematopoiesis (excluding erythropoiesis) and significant surface antigen expression at each stage.

CFU-GEMM = Colony forming unit gronulocyte/erythroid/mocrophoge/megakoryocyte; CFU-GM = Colony forming unit gronulocyte/mocrophoge; CFU-M = Colony forming unit macrophoge; CFU-G = Colony forming unit gronulocyte; MPO = Myeloperoxidose; NK Cell = Noturol killer cell; DC = Dendritic cell; LAP = Leucocyte alkaline phosphote.

division plane parallel to the niche plane will give rise to a daughter cell that will not be in contact with the niche surface and has the potential to differentiate.

The bone marrow microenvironment is very vascular with numerous sinusoidal vessels. It has been demonstrated that HSC even physiologically frequently leave the confines of the bone marrow and enter the systemic circulation (mobilisation) and also such mobilised HSC return to the bone marrow directed by various homing signals (homing). The regions adjacent to these sinusoidal vessels often house HSC and HPC and also function like a niche (*vascular niche*). The vascular niche may play an important role in mobilisation and in homing. It also appears to play a role in HSC proliferation and differentiation.

Multiple signalling and adhesion molecules are involved in the stem cell maintenance. The main signalling pathway that is involved in this process includes stem cell factor (SCF), which is a cytokine that interacts with c-kit, a receptor that is present in the stem cells and progenitors. C-kit signalling is important for promotion of cell survival, proliferation, and migration. Flt3 signalling pathway is important differentiation of cell types. Thrombopoietin (TPO) and its receptor c-Mpl constitute a pathway that is important for the cell cycle regulation of haematopoietic stem cells. Interestingly, gain of function alleles of c-kit, Flt-3 and c-Mpl it were identified as participants in leukaemia or other cancers. For example, v-kit is a constitutively active kinase that was identified in a feline sarcoma virus. In addition, point mutations or amplifications that result in constitutively active signalling have been found in several types of solid tumours and in acute myeloid leukaemia (AML). For example, Flt-3 activating mutations are found in 30% of human AML cases, and v-Mpl is a constitutively active form of the TPO receptor that was identified in a mouse myeloproliferation inducing retrovirus. Tie-2 is another tyrosine kinase receptor, bound by angiopoietin, plays an important role in steady state haematopoiesis. Tie-2/Ang signalling has been proposed to be important for maintaining quiescence within the bone marrow niche, rather than promoting expansion and proliferation. Several pathways previously known to be essential for embryogenesis also play important roles during the maintenance of HSC. These include Wnt (wingless/Int-1), Hh (hedgehog) and phosphoinositide-3 kinase signalling pathways. The pattern and level of expression of these signalling and adhesive molecules in daughter cells probably plays a role in deciding the fate of the cell.

ERYTHROPOIESIS

The mature red cell is the final product in the long process of erythropoiesis that starts from a HSC that is committed to erythroid differentiation, this process is tightly regulated. Erythroid progenitors are sparse and difficult to isolate. The first recognisable class of progenitors is the burst forming unit – erythroid (BFU-E), named for their ability to generate multi-clustered colonies of (erythroid bursts) haemoglobin containing cells. BFU-E represents the earliest progenitor cell committed exclusively to erythroid differentiation. This is a quiescent reserve of cells (only 10% to 20%) are in only cell cycle. However, once stimulated with the appropriate cytokines these

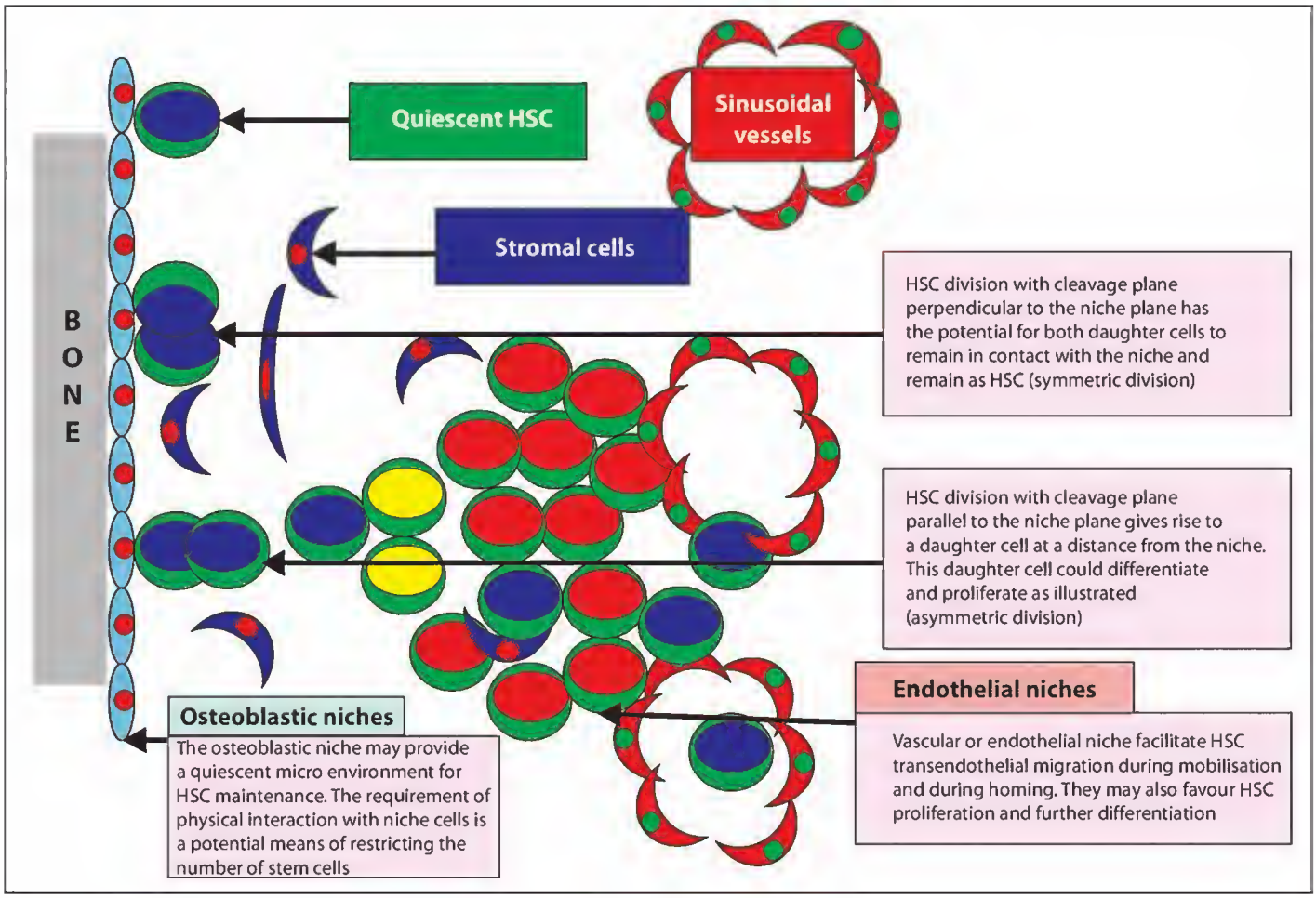


Figure 3: Haematopoietic stem cell (HSC) niches.

demonstrate significant proliferative capacity (≥30 to 40,000 colonies *in vitro*) in 2 to 4 weeks. A second more differentiated progenitor cell is the colony forming unit—erythroid (CFU-E). In contrast to BFU-E majority of these cells are in cycle, and hence, on exposure to appropriate cytokines rapidly proliferate, peaking within 7 days. It is important to understand that these cells are identified retrospectively and *in vitro* by their ability to form specific haemoglobin containing cell colonies in semisolid media (methylcellulose) with appropriate cytokines. It would not be possible with currently available techniques to identify these cells individually by their morphology and immunophenotype as being distinct from other progenitors with commitment to other lineages.

The earliest recognisable erythroid cell is the proerythroblast, it is 12 to 19 µm in diameter with a large oval nucleus which stains homogenously with indistinct nucleoli, and the cytoplasm is darkly basophilic. The basophilic normoblast follows with a diameter of 12 to 17 µm, nuclear chromatin shows coarse clumping which is often described as a cartwheel appearance, nucleoli are generally not seen. The polychromatic normoblast is about the same size as its precursor the basophilic normoblast but is distinguished by the less basophilic cytoplasm due to the increased accumulation of haemoglobin; the nucleus is also further condensed and is almost black on staining. The last nucleated erythroid precursor is the orthochromatic normoblast, this cell approaches the diameter of a reticulocyte (8 to 12 µm), the eosinophilic staining cytoplasm contains nearly the full amount of haemoglobin, the nucleus is fully condensed and pyknotic. Extrusion of the nucleus results in it becoming a reticulocyte. The reticulocyte is characterised by the presence of fine granular or reticular network of ribosomal ribonucleic acid (RNA) observed with supravital stains, such as brilliant cresyl violet or methylene blue. Reticulocytes are normally found in small numbers in the peripheral blood. Reticulocytes gradually lose their cytoplasmic RNA and mature into erythrocytes which are biconcave, relatively flat and non-nucleated disks of 7 to 8 µm in size. Normal erythrocytes survive for 100 to 120 days in the peripheral circulation.

Regulation of Erythropoiesis

The process of erythropoiesis is mainly regulated by erythropoietin (EPO) which is a cytokine produced in the kidney in the peri-tubular cells. Regulation of EPO mRNA and protein is primarily at the transcriptional level. In the setting of hypoxia, these cells are stimulated to secrete EPO by the hypoxia-inducible transcription factor (HIF); this in turn acts on cells that have EPO receptors (BFU-E, CFU-E, etc.) and promotes their survival and proliferation and this activity is thought to be the primary regulatory mechanism for maintaining the homeostasis of red cell mass. A drop in red cell numbers causes tissue hypoxia, leading to increased EPO synthesis and the survival of more CFU-E that can rapidly mature into erythrocytes. Several other cytokines have been shown to synergise with EPO to enhance erythroid differentiation, including interleukin (IL) 6, IL3 and SCF. SCF receptor, c-kit is expressed by CFU-E and BFU-E.

Lineage specific transcriptional factors are responsible for regulating the expression of erythroid genes in the course of erythroid differentiation. Two important transcription factors that are involved in the erythropoiesis are GATA-1 and EKLF (KLF1). GATA-1 forms complexes with multiple other proteins to up-regulate the expression of erythroid specific genes. Disruption of GATA-1 gene leads to block of primitive erythropoiesis resulting in embryonic lethality. FOG-1 (Friend of GATA) binds to GATA-1 and this association is required for many of the functions of GATA-1. The significance of this association is exemplified by the finding in individuals with severe congenital dyserythropoietic anaemia of GATA-1 mutations that disrupts its physical contact with FOG-1. GATA-1 also associates with CREB binding protein (CBP) which is a protein that acetylates histones suggesting that GATA-1 is involved in transcriptional activation of erythroid genes. Other proteins that are associated with GATA-1 are transcription factors stem cell leukaemia gene (SCL, TAL-1), LBD1 and LMO2. Distinct protein complexes of GATA-1 are required for activation of genes in primitive and definitive erythropoiesis.

Several members of the Kruppel-like transcriptional factor (KLF) family are known to activate erythroid specific genes. KLF1 (EKLF) is expressed in both primitive and definitive erythropoiesis. This protein associates with SWI/SNF related chromatin remodelling complex suggesting that its activity in erythroid cells may in part be related to altering the configuration of chromatin. Activation of EKLF is regulated by GATA-1 illustrating the complex transcriptional regulatory mechanisms involved in both primitive and definitive erythropoiesis. KLF2 and KLF4 are required for the expression of genes in the embryonic stage.

The continued identification of interacting transcription factors and their downstream targets will provide a better understanding of erythroid cell maturation and will facilitate the construction of increasingly complex models of the genetic regulatory networks that exist in erythroid cells. More recently micro-RNAs, small RNA molecules that target messenger RNAs in a sequence specific manner to modulate their stability or their ability to undergo translation, have been shown to play roles in erythropoiesis.

Though several studies have been carried-out to unravel the molecules and mechanisms involved in erythropoiesis, it is not yet clear how the signalling pathways, micro-RNAs and transcription factors act together in regulating erythropoiesis.

Haemoglobin synthesis

Production of haemoglobin requires the co-ordinated production of haem and globin. Haem is the prosthetic group that mediates reversible binding of oxygen by haemoglobin. Globin is the protein that surrounds and protects the haem molecule.

Haem synthesis

Haem is synthesised in a complex series of steps involving enzymes in the mitochondria and in the cytosol of the cell. The first step in haem synthesis takes place in the mitochondria, with the condensation of succinyl CoA and glycine by 5-aminolevulinic acid (ALA) synthase to form 5-ALA. This molecule is transported to the cytosol where a series of reactions produce a ring structure called coproporphyrinogen III. This molecule returns to the mitochondria where an additional reaction produces protoporphyrin IX. The enzyme ferrochelatase inserts iron into the ring structure of protoporphyrin IX to produce haem. Deranged production of haem results in a variety of anaemias (porphyrias). Iron deficiency, the world's most common cause of anaemia, impairs haem synthesis thereby producing anaemia. A number of drugs and toxins directly inhibit haem production by interfering with enzymes involved in haem biosynthesis. Lead commonly produces substantial anaemia by inhibiting haem synthesis, particularly in children.

Types of haemoglobin synthesis

Haemoglobin molecules are tetrameric proteins with two distinct types of globin chains. In humans, there are 5 different types of haemoglobins which are produced at different stages of the development. The genes that produce different types of globin chains are present as clusters in chromosomes 11 and 16 with the genes present in the order in which they are expressed during development. In adults, haemoglobin (HbA) contains two α globin and two β globin chains ($\alpha_2\beta_2$). The predominant haemoglobin produced at the embryonic stage is Hb Gower 1 and foetal stage is $\alpha_2\beta_2$ (HbF; foetal haemoglobin). **Table 1** summarises the haemoglobins seen in humans in different stages of development.

Disorders that affect the synthesis rate of the globin chains cause thalassaemias which are the most common genetic diseases in humans. There are around 400 different reported mutations that can cause α and β thalassaemia. Other types of mutations in the globin genes that affect the structure of haemoglobins (not the quantity) are broadly classified as haemoglobinopathies which include sickle cell anaemia a common genetic disease in most populations.

Table1: Normal Haemoglobin (Hb) seen at Different Stages of Development

Embryonic Hb		Foetal Hb		Adult Hb	
Gower 1	$\xi_2\varepsilon_2$	HbF	$\alpha_2\gamma_2$	HbA2	$\alpha_2\delta_2$
Gower 2	$\alpha_2\varepsilon_2$			HbA	$\alpha_2\gamma_2$
Portland	$\xi_2\gamma_2$				

A better understanding of the mechanisms regulating the activation and silencing of the embryonic, foetal and adult globin genes has important clinical implications for the treatment and cure of patients with haemoglobinopathies, particularly sickle cell disease and the thalassaemia syndromes. GATA-1 and EKLF are two major transcription factors that have been found to be playing key functions in the activation of adult globin genes responsible for the transcriptional regulation of globin genes. Recent studies have identified a key regulator protein, BCL11A, which plays a role in stage specific expression of globin genes. This protein represses foetal globin gene expression in adults. Mutations in the BCL11A gene cause increased expression of foetal haemoglobin (HbF) in normal adults and in patients with thalassaemia and sickle cell disease. Such increases HbF in these conditions could ameliorate the phenotype of these diseases and hence manipulating this proteins levels in patients with sickle cell disease and homozygous β thalassaemia has the potential to be a therapeutic option for these diseases.

GRANULOPOIESIS AND MONOCYTOPOIESIS

Granulopoiesis

The earliest identifiable cell of the myeloid lineage is the myeloblast. This cell is approximately 12 to 14 μm in diameter with a round or oval nucleus and basophilic cytoplasm. Nuclear chromatin is fine and 1 to 5 nucleoli are easily visible. The next cell in the differentiation process is the promyelocyte which is the largest cell in this differentiation series. Promyelocytes have variable nuclear morphology with less prominent nucleoli; the cytoplasm is deeply basophilic and contains variable number of peroxidase positive granules. Myelocytes are characterised by round to oval nucleoli with a characteristic nuclear indentation and coarse chromatin structure. The cytoplasm is pale pink-brown and has numerous specific granules covering the nucleus and throughout the cytoplasm except at the nuclear indentation (centrosphere), which represents the Golgi apparatus. The myelocyte is also the first cell in differentiation in which specific granules appear and the last cell that is capable of cell division during myeloid differentiation. The metamyelocyte exhibits a characteristic bean shaped nucleus, the band form a band shaped or 'S' shaped nucleus without a definite nuclear constriction and the segmented neutrophil characterised by typical nuclear segmentation. The cytoplasm in all these cells is similar to that of a myelocyte except for the absence of a centrosphere. Maturation of eosinophils and basophils follows the same morphologic steps as that of a neutrophil until the appearance of specific granules. The eosinophil exhibits a bilobed nucleus, and the basophilic cytoplasm is filled with prominent orange-red granules. Basophils exhibit less segmentation of the nucleus and the cytoplasm is filled with deeply staining blue to purple metachromatic granules. The granules often obscure the nucleus and cytoplasm which stains pink to reddish pink.

Monocytopoiesis

The earliest cell of the monocyte/macrophage series is the monoblast which can be difficult to distinguish from a myeloblast. The cell is 12-18 μm in diameter, with a round or oval nucleus which is frequently convoluted. The chromatin is fine and the nucleoli are sometimes present. The cytoplasm is basophilic and devoid of granules. The promonocyte is a large cell with an indented nucleus, exhibiting fine chromatin and a single nucleolus. The cytoplasm stains light blue. The monocyte is the largest cell with a diameter of 13-20 μm, the nucleus is large, lobulated, or bean shaped, with coarse chromatin and lacks a nucleolus. The cytoplasm has a characteristic light blue appearance. Egress of monocytes from the blood into the tissues is associated with increased cell size and larger and more lightly staining nucleus. These cells, termed macrophages or histiocytes, are phagocytic and mobile.

Lineage Commitment and Transcriptional Control of Granulopoiesis and Monocytopoiesis

The mechanisms of lineage commitment remain poorly understood. *In vitro* studies of murine embryonic stem cells reveal a coordinated expression of growth factor receptor genes during cell maturation. Certain genes are expressed constitutively during development of these cells, such as the c-kit and the α sub-units of the growth factor receptor genes. Expression of the common β sub-unit of these growth factor receptor genes (IL-3, IL-5, GM-CSF, SCF) are induced early. In contrast c-fms, G-CSFR and CD34 are induced later, at an intermediate stage of development, reflecting the initiation of myeloid commitment. At later stages, when a limited number of cytokine receptors are expressed or dominate in a progenitor cell, cytokines such as GM-CSF and G-CSF become important for neutrophil maturation, M-CSF and GM-CSF for macrophage development, IL-5 for eosinophil development and SCF, nerve growth factor and IL-3 for basophil and mast cell growth. The extent to which these growth factors and their receptor expression determine commitment remains unclear. Transcriptional factors such as PU-1 and EGR-1 play a role in macrophage development while genes such as fes and MZF-1 appear to be important in modulating granulocytic precursor proliferation.

THROMBOCYTOPOIESIS

The morphologic features of platelet forming cells are distinctly different from erythroid or leucocyte cell lineages. Distinct differentiation and morphologic changes do not occur. These processes are instead replaced by a process of polyploidisation. In this process, successive nuclear divisions without concomitant nuclear divisions lead to megakaryocytes with 1-32 nucleoli. The first identifiable cell in this lineage is the megakaryoblast, a distinctly large cell with a high nuclear/cytoplasmic ratio. The nuclear shape varies but frequently displays convolutions and deep furrows. The cytoplasm stains basophilic, does not contain granules and may exhibit fraying of the cytoplasmic membrane. Some megakaryoblasts may contain multiple nuclei. The pro-megakaryocyte exhibits a lobulated nuclear structure without nucleoli. The cytoplasm is basophilic, with azurophilic granules adjacent to the nucleus and formed platelets can be seen on the cytoplasmic surface. Mature megakaryocytes are the largest haematopoietic cell in the bone marrow. The nucleus is lobulated and exhibits coarse and clumped chromatin. Nuclear number varies from 4 to 8. Platelets can be seen in the periphery of the cytoplasm and are attached to the cell membrane. Platelets are believed to form by cytoplasmic budding from the megakaryocytes.

Regulation of Thrombocytopoiesis

Thrombopoietin (TPO) is a putative lineage specific regulator of platelet production. Data suggests the TPO production is regulated inversely by the platelet mass in the body. TPO is constitutively produced in the liver, kidney and probably the spleen and marrow as well.

LYMPHOCYTES

Lymphocytes and plasma cells are components of the immune system which also arise from HSC. Lymphocytes broadly include natural killer cells (NK cells), a component of the innate immune system, and T-cells and B-cells which are involved in adaptive immunity. Primary lymphoid organs where lymphopoiesis occurs include the bone marrow and thymus, while secondary lymphoid organs such as lymph nodes, spleen, mucosal and cutaneous associated are involved predominantly in immune sensitisation and selection.

B-Cells

B lymphocytes like all blood cells are the progeny of HSC. Once commitment to lymphoid development has occurred, a further bifurcation to T-cell and B-cell development occurs. The defining features of these commitment steps and their regulation remain poorly understood. Once committed to B-cell development there is less confusion as to precursor—progeny relationship and an orderly evolution from a precursor B-cell to a mature plasma cell occurs, antigen expression through these phases are unique and help identify the cells. This antigenic expression profile is summarised in **Table 2**.

The end result of B-cell development is generation of plasma cells that are capable of secreting immunoglobulins. These immunoglobulins are composed of heavy and light chains; these chains undergo re-arrangement of their V, D and J loci on the gene giving rise to antigen binding specificity and an immunoglobulin repertoire. These immunoglobulins are expressed on the surface of the B-cell, if the newly produced B-cell does not encounter an antigen, it undergoes apoptosis

Table 2: Antigenic Expression During the Stages of Development of T-cells and B-cells

B-cells

Antigen	Pro B-cell	Pre B-cell	Immature B-cell	Mature B-cell
CD34	+	±	–	–
CD10	–	+	±	–
CD19	+	+	+	+
CD20	–	–	+	+
CD21	–	±	+	+
CD22	–	–	±	±
CD24	±	–	±	±
CD38	+	–	–	–
CD45	±	+	+	+
Cyt Ig	–	+	+	+
SmIg	–	–	±	+

T-cells

Antigen	Prothymocyte	Early Thymocyte	Late Thymocyte	Mature T-cell
CD1	–	+	–	–
CD2	+	+	+	+
CD3	–	–	+	+ (either CD4/CD8+)
CD4	–	+	+	+
CD5	–	–	+	+
CD6	–	–	+	+
CD7	+	+	+	+
CD8	–	+	–	+ (either CD4/CD8+)
CD38	+	–	–	–
TCR	–	–	+	+

while those that encounter an antigen recognised by the re-arranged immunoglobulin molecule undergo blast transformation and proliferate.

T-Cells

These cells again arise from HSCs. They are released and home to the thymus where they must receive signals provided by the thymic stromal cells (processed antigen) for them to survive and undergo maturation into mature T-cells. Within the thymus these T-cells up-regulate CD25 (IL-2 receptor) and are now called pro-T-cells. They then go through stages of early and late pre-T-cell development and eventually mature following commitment into either CD4 positive helper T-cells or CD8 positive cytotoxic T-cells.

CONCLUSION

Haematopoiesis is a complex process involving the HSCs, osteoblasts, and components of the bone marrow micro-environment, receptors and cytokines. While attempts are made to compartmentalise the process for the sake of understanding, this does not truly represent the physiological state and does gross injustice to the complexity involved. Many of the processes and regulatory elements are poorly understood or are still in the process of being described. Abnormalities that affect this process can lead to life-threatening complications such as aplastic anaemia or myeloproliferative disorders. Additionally, better understanding of the basic science of haematopoiesis has already translated into new therapeutic tools as evidenced by the numerous cytokines that are available in the market.

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15.2 Anaemia—A Clinical Approach

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DEFINITION

Anaemia is functionally defined as an insufficient red blood cells (RBC) mass to adequately deliver oxygen to peripheral tissues. It may be due to increased RBC clearance, decreased RBC production, or both and caused by intrinsic or extrinsic causes. According to WHO, haemoglobin (Hb) of less than 13.0 g/dL in adult male, less than 12.0 g/dL in adult non-pregnant female and less than 11.0 g/dL in pregnant female should be considered as evidence of anaemia.

KINETIC CLASSIFICATION

Although, there are many classification schemes for anaemia based on aetiology, red cell morphology, etc. kinetic classification of anaemia based on reticulocyte production index (RPI) is most relevant clinically. Anaemias can be categorised as either hypoproliferative or haemolytic (hyperproliferative) and thereafter investigated appropriately.

Hypoproliferative anaemias are due to impaired RBC production and result from acquired nutritional deficiencies or systemic diseases. These are characterised by inadequate reticulocyte production (RPI <2.5) in response to anaemia.

Haemolytic anaemias (RPI >2.5) may be either congenital (membrane, enzyme or globin chain defects) or acquired (immune, microangiopathic, PNH, etc.) the former being more common in children and the latter in adults. In acute or chronic blood loss, increased RBC production occurs, provided that adequate nutrients are present.

EPIDEMIOLOGY

Nutritional deficiencies are the commonest cause of hypoproliferative anaemia in our country and affect both adults and children. Other common causes include the anaemia of acute or chronic inflammation and the anaemia of renal disease (due to low erythropoietin). Haematologic malignancies and solid tumours infiltrating the bone marrow (myelophthisis) are encountered mainly in adults. Haemoglobinopathies are more prevalent in certain geographical regions in our country like Hb-D in Punjab, Hb-E in Bihar, Bengal, Assam, North-Eastern states and Hb-S in Orissa and Maharashtra. Acquired and congenital RBC hypoplastic disorders are encountered more frequently in children. Here, we will restrict our discussion to approach of anaemia in adult patients.

CLINICAL PRESENTATION

Anaemia is not a disease, but it is a manifestation of an underlying pathology. It is never normal to be anaemic. The clinical presentations are related to anaemia itself or to the disorders causing anaemia. The signs and symptoms of anaemia will depend on how rapidly it appears, its severity, and the age of the patient. Patients with anaemia usually seek medical attention because of decreased work or exercise tolerance, shortness of breath, palpitation or fatiguability. When the haemoglobin falls below 7 g/dL, exercise capacity is markedly reduced. Older individuals with cardiovascular disease can develop angina and heart failure. Heart systolic murmurs are a common cardiac sign associated with anaemia and best heard in the pulmonary area. Pallor of skin and mucous membranes is a sign of anaemia. In the hands, the skin of the palms first becomes pale, but the creases may retain their usual pink colour until the haemoglobin concentration is less than 7 g/dL. Certain people routinely have pale-appearing skin without being anaemic. Patients with myxoedema may manifest pallor without anaemia. Skin and mucosal changes especially in nails and hairs are very common with anaemia. Thinning, loss of lustre and greying of hair may occur, the last especially with pernicious anaemia. The nails may lose their lustre, become brittle and break easily. This finding is commonly noticed in chronic iron deficiency anaemia. Headache, faintness, lack of mental concentration, tinnitus, and vertigo are common symptoms of severe anaemia.

APPROACH TO EVALUATION OF ANAEMIA

The correct diagnosis of anaemia requires a thorough history and physical examination along with complete blood cell count (CBC), reticulocyte count, and peripheral blood smear.

History and Physical Examination

A careful history and physical examination will provide clues to the potential cause as well as underlying systemic disorder (like renal failure, diabetes mellitus) or malignancy. Dietary history is very important, particularly in the young with food-fads and the elderly with anaemia. Pure vegetarian diet lacks B12 whereas insufficient green-leafy vegetables and overcooked food lacks folic acid. A detailed drug history is necessary to rule out drug induced bone marrow depression or autoimmune haemolytic anaemia. A past history of gastrectomy or ileal resection may point towards B12 deficiency anaemia. Menstrual and reproductive history is important to assess the iron status. Occupational history may be relevant in patients exposed to welding, paints and dyes resulting in exposure to lead or other potentially marrow toxic agents. A family history of anaemia, jaundice, gall stones or splenectomy may hint towards inherited haemolytic anaemia. Similarly, ethnicity of the patient helps in analysis of patients with suspected haemoglobinopathies.

On examination, pallor may be accompanied by angular cheilitis (cracking at the edges of the lips) and koilonychia (spooning of the nails) in iron deficiency anaemia and hyperpigmentation of knuckles in megaloblastic anaemia. Presence of jaundice alongwith pallor would suggest the possibility of haemolytic anaemia. Splenomegaly in adults may indicate an acquired disorder, such as autoimmune haemolytic anaemia; infections like kala-azar; venous congestion; lymphoproliferative or myeloproliferative disorder. In young adults, it may be even due to a congenital haemolytic anaemia, such as thalassaemia intermedia, hereditary spherocytosis or even congenital

dyserythropoietic anaemia. There may be exquisite tenderness over bones, especially over sternum suggesting acute leukaemia. Presence of petechiae and purpurae in addition to pallor would indicate marrow aplasia or infiltrative disease (leukaemia, lymphoma, myeloma, metastasis); these may be seen in megaloblastic anaemia also. The patients (especially pure vegetarians) presenting with neurological findings such as loss of vibration or position sense in the extremities should be investigated for early changes of megaloblastic anaemia even in absence of marked reduction of haemoglobin. Although, anaemia itself may result in systolic cardiac murmurs, the finding of an increased murmur in an anaemic patient with a prosthetic cardiac valve may be due to perivalvular leak resulting in microangiopathic change (schistocytes) on peripheral smear.

Reticulocyte Count

The reticulocyte count provides important information about the kinetics of the red cell production in response to anaemia and helps in classification and directing the initial investigations of anaemia. Reticulocyte count can be done manually using supravital stains (like brilliant cresyl blue or new methylene blue) or more accurately by automated cell counters and flow cytometers using fluorescent dyes like thiazole orange that bind to the residual ribonucleic acid present in these newly released red cells. Automated reticulocyte counting also allows the evaluation of other parameters, such as reticulocyte haemoglobin content and the proportion of immature reticulocytes (immature reticulocyte fraction). The various parameters derived from reticulocyte count are given below. RPI cut-off of 2.5 is used to differentiate hypoproliferative and hyperproliferative anaemias (**Table 1**).

Table 1: Kinetic Classification of Anaemia

Hypoproliferative anaemias (RPI <2.5) or (ARC <75000/µL)
- Anaemia of chronic disease
- Anaemia of renal disease
- Aplastic anaemia
- Pure red cell aplasia (PRCA)
- Congenital dyserythropoietic anaemia (CDA)
- Endocrine anaemias
- Marrow replacement

Maturation abnormalities (Ineffective erythropoiesis) (RPI <2.5) or (ARC <75000/µL)
- Vitamin B12 deficiency
- Iron deficiency anaemia
- Folate deficiency
- Sideroblastic anaemia
- Thalassaemia

Haemolytic anaemias (RPI >2.5) or (ARC >100,000/µL)
- Haemoglobinopathies
- Immune haemolytic anaemias
- Infectious causes of haemolysis
- Membrane abnormalities
- Metabolic abnormalities (enzymopathies)
- Mechanical haemolysis

Reticulocyte count = % reticulocytes in RBCs population

Corrected reticulocyte count = % reticulocytes × (patient Hct/45)

Reticulocyte production index = Corrected reticulocyte count × maturation time in peripheral blood in days* (Normal values of all of above 0.5-1.5%)

Absolute reticulocyte count (ARC) = % reticulocytes × RBC count/L (Normal values for ARC are from 25000 to 75000/mL; values <75000/mL indicate an inappropriately low erythropoietic response whereas an ARC >100,000/mL is indicative of hemolysis or an appropriate erythropoietic response. ARC between 75,000 and 100,000/mL require interpretation in the context of other clinical data.

*Hct = Haematocrit; *Reticulocyte maturation time = 1 day for Hct 40%; 1.5 days for Hct 30-40%; 2.0 days for Hct 20-30%; 2.5 days for Hct <20%.*

Red Cell Indices

Automated cell counters provide detailed information regarding the size, shape, and haemoglobin content of RBCs. The two parameters most useful in classifying anaemia are the mean corpuscular volume (MCV) in femtolitres (fL) and the red blood cell (RBC) distribution width (RDW). RDW reflects the variation in RBC size and shape (anisopoikilocytosis). These parameters are useful because relatively reproducible changes in the MCV and RDW are associated with certain types of anaemia (**Table 2**). Particularly when combined with the reticulocyte count, the MCV and RDW can significantly narrow the differential diagnosis (**Table 3**).

Table 2: Usefulness of the MCV and RDW in the Diagnosis of Anaemia

	Low MCV (< 80 fL)	Normal MCV (80-99 fL)	High MCV (>100 fL)
Normal RDW	Anaemia of chronic disease	Acute blood loss	Aplastic anaemia
	α- or β-thalassaemia trait	Anaemia of chronic disease	Chronic liver disease
	Haemoglobin E trait	Anaemia of renal disease	Chemotherapy/ antivirals/alcohol
Elevated RDW	Iron deficiency	Early iron, folate, or vitamin B12 deficiency	Folate or vitamin B12 deficiency
	Sickle cell-β-thalassaemia	Dimorphic anaemia (for example, iron + folate deficiency)	Immune haemolytic anaemia
		Sickle cell disease	Cytotoxic chemotherapy
		Chronic liver disease	Chronic liver disease
		Myelodysplasia	Myelodysplasia

MCV = Mean corpuscular volume; RDW = Red blood cell distribution width.

Table 3: Combining Reticulocyte Count and Red Blood Cell Parameters for Diagnosis of Anaemia

MCV, RDW	Reticulocyte Count <75,000/µL	Reticulocyte Count >100,000/µL
Low, Normal	Anaemia of chronic disease	
Normal, Normal	Anaemia of chronic disease	
High, Normal	Chemotherapy/antivirals/ alcohol, aplastic anaemia	Chronic liver disease
Low, High	Iron deficiency anaemia	Sickle cell-β thalassaemia
Normal, High	Early iron deficiency, folate, vitamin B12 deficiency	Sickle cell anaemia
	Myelodysplasia	Sickle cell disease
High, High	Folate or vitamin B12 deficiency	Immune haemolytic anaemia
	Myelodysplasia	Chronic liver disease

MCV = Mean corpuscular volume; RDW = Red blood cell distribution width.

Peripheral Blood Smear

Despite the availability of automated cell counters and sophisticated diagnostic testing, review of a well-made peripheral blood smear remains one of the most informative and rewarding diagnostic procedures. The finding of hypersegmented neutrophils suggests a megaloblastic process, and this morphologic abnormality can be seen in the blood

smear before there are significant changes in the haemoglobin or MCV. Also, only the blood smear reveals the unique morphologic changes occurring with various haemolytic disorders.

There are many commonly encountered findings in RBCs on the peripheral smear (**Table 4, Figures 1 to 4**). Microcytic, hypochromic red cells are suggestive of iron deficiency anaemia or thalassaemia; whereas macrocytic red cells with ovalocytes are suggestive of megaloblastic anaemias. Some findings reflect organ dysfunction, such as echinocytes (burr cells) in uraemia, or acanthocytes (spur cells) in severe liver disease and abetalipoproteinaemia. Target cells may be seen in cases of liver disease as well as in haemoglobinopathies, including sickle cell disease or thalassaemia. The presence of schistocytes or RBC fragmentation often reflects systemic disease, such as disseminated intravascular coagulation (DIC), thrombotic thrombocytopaenic purpura (TTP), or the haemolytic uraemic syndrome (HUS). Finding spherocytes on a smear is suggestive of autoimmune haemolytic anaemia or hereditary spherocytosis. Peripheral smear examination, especially thick blood smear, also helps in detecting haemoparasites like malaria, filaria and even leishmania. Some of the new automated cell counters have the technology to flag the sample in presence of haemoparasites based on their light scatter properties.

Table 4: Features of the Peripheral Blood Smear

RBC Morphology	Definition and Cause	Interpretation
Schistocytes	Fragmented cells; shearing force	Microangiopathic haemolytic anaemias DIC, TTP, HUS, prosthetic valves
Spherocytes	Small cells without central pallor; loss of membrane	HS, AIHA, burns, bacterial infection, G6PD
Teardrop cells	Pear-shaped erythrocytes; mechanical stress during release from bone marrow or passage through spleen	Myelophthisis (marrow replacement), thalassaemia, megaloblastic anaemia
Burr cells (Echinocytes)	Regular small projections circumferentially; shrinkage	Uraemia, PK deficiency, EDTA storage artefact
Spur cells (Acanthocytes)	Few irregular projections; abnormal lipid composition of membrane	Liver disease, Abetalipoproteinemia, Mcleod phenotype
Polychromasia	Large, bluish red blood cells; residual ribonucleic acid	Elevated reticulocyte count; haemolytic anaemia
Basophilic stippling	Many small bluish dots; clustered polyribosomes	Haemolytic anaemias, lead poisoning (lead inhibits pyrimidine 5′-nucleotidase)
Pappenheimer bodies	Several greyish, irregular inclusions; aggregates of ribosomes and ferritin	Sideroblastic and megaloblastic anaemia, haemoglobinopathies
Heinz bodies (Bite cells on routine staining)	Greyish inclusions on supravital or metachromatic stain; denatured Hb	Oxidative injury in G6PD deficiency, unstable Hb
Howell-Jolly bodies	Purplish inclusions; residual nuclear fragments	Splenectomy/splenic hypofunction

DIC = Disseminated intravascular coagulation; TTP = Thrombotic thrombocytopaenic purpura; HUS = Haemolytic uraemic syndrome; HS = Hereditary spherocytosis; AIHA = Autoimmune haemolytic anaemia; G6PD = Glucose-6-phosphate dehydrogenase; PK = Pyruvate kinase; Hb = Haemoglobin.

Bone Marrow Examination

Bone marrow aspiration and biopsy permit evaluation of cellular morphology and marrow architecture, respectively. It is generally avoided in the initial work-up of anaemia because

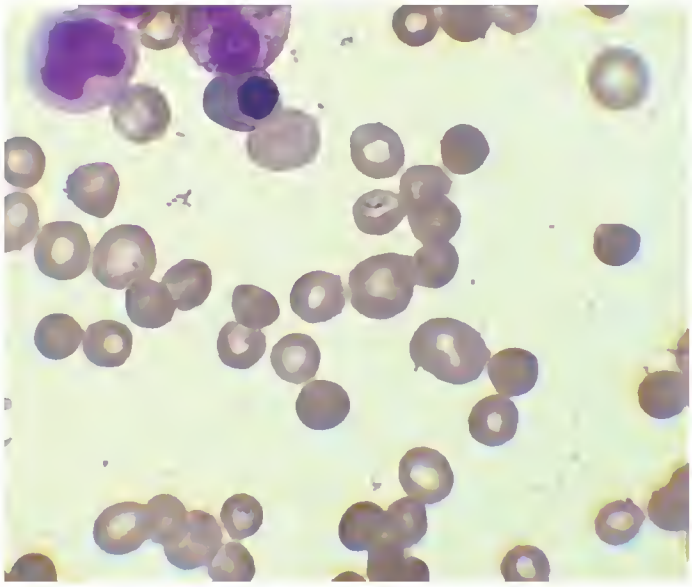


Figure 1: Peripheral smear showing spherocytes without central pallor, and nucleated RBCs.

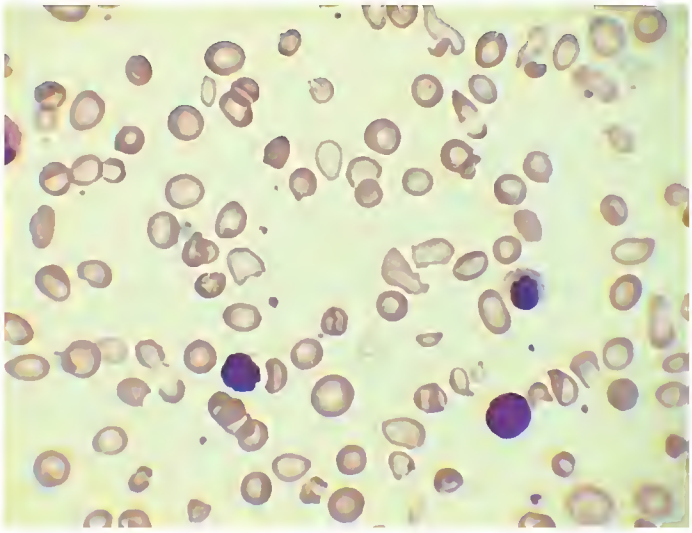


Figure 2: Peripheral smear showing fragmented RBCs with spicules (schistocytes) in a case of TTP.

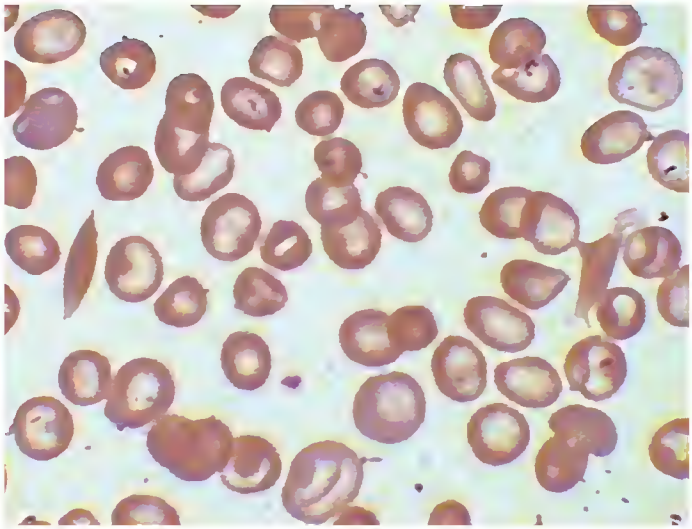


Figure 3: Peripheral smear from a patient of thalassaemia major with anisopoikilocytosis and microcytic hypochromic cells.

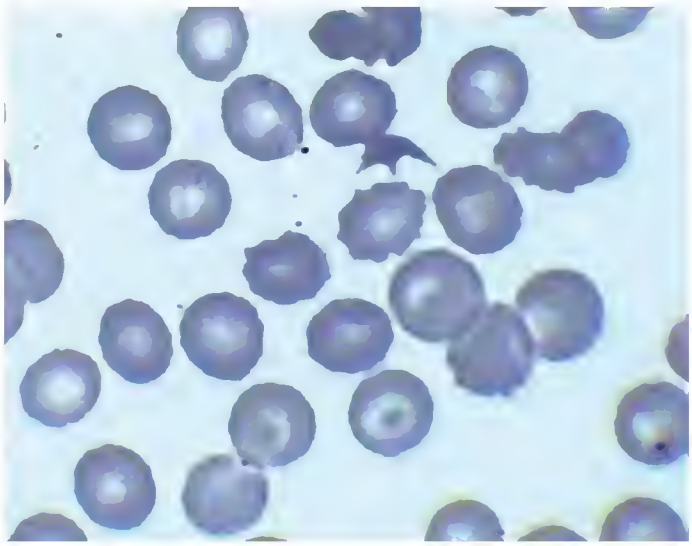


Figure 4: Peripheral smear showing sickle cells.

of the discomfort involved in the procedure and minimal additional useful information. However, it becomes necessary in cases where the possibility of myelodysplasia, leukaemia, or lymphoma is being considered. In such cases, samples of anticoagulated aspirate should be simultaneously collected for cytogenetics (heparinised tube) and flow cytometry (Heparin/EDTA) in addition to morphology and sent for the appropriate test, based on the morphology review.

Diagnostic uncertainty in the setting of hypoproliferative anaemia is an indication for bone marrow biopsy to rule out aplastic anaemia. A variety of infiltrative (myelophthisic) processes including granulomatous and metastatic deposits may be uncovered with bone marrow biopsy. Bone marrow biopsy touch preparation provides important diagnostic material especially in cases with diluted aspirate and must always accompany the bone marrow aspirate, biopsy and peripheral smear of the patient.

Other Tests in Work-up of Anaemia

Haemolytic work-up

Cation exchange Hb-HPLC (High performance liquid chromatography)/Hb Electrophoresis, sickling test, Coomb's test, test for cold agglutinins, osmotic red cell fragility and estimation of various red cell enzymes (at least G6PD screening) would be needed in suspected case of haemolytic anaemia. Raised plasma haemoglobin will indicate intravascular haemolysis.

Iron, vitamin B12, folic acid

Serum iron, iron-binding capacity, transferrin saturation, serum ferritin, marrow iron and serum transferrin receptors help in differentiating iron deficiency and anaemia due to chronic disorders. Serum vitamin B12 and folate levels may be estimated along with the metabolites like homocysteine and methylmalonic acid in suspected megaloblastic anaemia.

Urine and stool examination

Urine examination for proteins, pus cells, red cells, urobilinogen and haemosiderin can provide explanation for anaemia. Stool examination for ova, cyst and occult blood should be done in iron deficiency anaemia especially if refractory to treatment.

Other ancillary tests like upper and lower gastrointestinal endoscopy may be required in iron deficient patients to rule out bleeding ulcer or underlying gastrointestinal malignancy especially in the elderly.

TREATMENT

While it is very essential to evaluate a patient of anaemia for a definitive diagnosis, it is equally important to start any definite treatment. When anaemia is acute or so severe to threaten the patient's survival, immediate steps must be taken to guarantee oxygen delivery to tissues. Hypovolaemia can be managed with appropriate infusions of electrolytes and colloid solutions. Tissue hypoxia can be prevented by giving RBC transfusions and oxygen. If anaemia is less severe, red blood transfusion should be withheld till a proper diagnosis is made. Once the cause for anaemia is established, specific treatment should be initiated.

PREVENTION

A proper dietary guidance and balanced diet is the most important factor in preventing the occurrence of nutritional anaemias in all age groups. In addition, routine antenatal screening (e.g. Hb-HPLC, NESTROFT) and detection (DNA based) programmes should be in place to reduce the burden of thalassaemia major and other haemoglobinopathies in the society.

To conclude, a systematic approach to the evaluation of anaemia that includes a detailed history, complete blood count, and peripheral smear examination, facilitates an efficient diagnosis and minimises unnecessary testing.

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15.3 Splenomegaly—A Clinical Approach

Lalit Kumar, Anuj Kumar Bansal

INTRODUCTION

The spleen is normally not palpable. It has to be enlarged 2 to 3 times before it becomes palpable. A palpable spleen was reported in 3% of asymptomatic male, college students which was still palpable at 3 years follow-up in 30% of them and there was no evidence of lymphoid malignancies at 10-year follow-up. Higher incidence of palpable spleen without evidence of disease has been reported from some tropical countries (e.g. New Guinea); no such data is available from India. A pathologically enlarged spleen is often firm, it may have an abnormal surface and it is frequently associated with signs and symptoms of the underlying disease. When the tip of the spleen is enlarged, more than 1 to 2 cm below the costal margin, further evaluation should be considered.

CAUSES OF ENLARGED SPLEEN

Splenomegaly is often the result of some other condition and not the result of a primary pathologic state (**Table 1**). Spleen size is not always a reliable guide to splenic function because palpable spleen is not always pathologic and abnormal spleen is not always palpable. Common causes of enlarged spleen according to size of spleen are given in **Table 1**. It must be understood that the classical causes of moderate and massive splenomegaly can also cause mild splenic enlargement in the early stages.

Table 1: Causes of Splenomegaly According to Size of Spleen

Massive	Moderate	Mild
Non-malignant	**Non-malignant**	**Infections**
Tropical splenomegaly	Portal hypertension with congestive splenomegaly	*Bacterial*
Chronic malaria	Chronic haemolytic anaemias	Salmonella, tuberculosis, Sub-acute bacterial endocarditis
Kala-azar	Sarcoidosis	*Viral*
Polycythaemia vera	Essential thrombocythaemia	Infectious mononucleosis, viral hepatitis, CMV, AIDS
Gaucher's disease		*Fungal*
Thalassaemia major		Parasite: Malaria, Leishmaniasis
Malignant	**Malignant**	Megaloblastic anaemia
Chronic myeloid leukaemia	Lymphomas	SLE
Idiopathic myelofibrosis with myeloid metaplasia	Chronic myeloid leukaemia	
Hairy cell leukaemia	Chronic lymphocytic leukaemia	
Lymphomas	Acute leukaemias	
	Amyloidosis	

Note: All the diseases which cause moderate or massive splenomegaly may cause mild splenomegaly at an early stage of disease.
CMV = Cytomegalovirus; AIDS = Acquired immunodeficiency syndrome; SLE = Systemic lupus erythematosus.

CLINICAL PRESENTATION

Mild splenomegaly may be asymptomatic. The most common symptoms produced by enlarged spleen are pain and a heavy sensation in the left upper quadrant; massive splenomegaly may cause early satiety. Occasionally, patient may present with severe pain in left hypochondrium or lower left chest due to rapid or acute enlargement of spleen resulting in stretching of the spleen with stretching of the capsule, infarction or inflammation of the capsule. Enlargement of spleen can be made on palpation in supine position or right lateral decubitus position, if the spleen is mildly enlarged. Enlargement of spleen more than 8 cm beneath left subcostal margin is called as massive splenomegaly. Radiological investigations are rarely necessary to see the enlargement of spleen. If needed, presence of an enlarged spleen can be more precisely determined by ultrasonography (USG). An USG can confirm the presence of the enlarged spleen or space-occupying lesions (e.g. cyst, abscess), provide accurate dimensions and help in distinguishing between splenic enlargement and other causes of a left sub-chondral mass (e.g. kidney). Collateral blood vessels develop secondary to portal hypertension and reversal of portal vein blood flow direction may be visualised with Doppler ultrasonography. Changes in spleen structure, such as mass lesions, infarcts, inhomogeneous infiltrates and cysts, are more readily assessed by computed tomography, magnetic resonance imaging or USG. However, none of these techniques are very reliable in the detection of patchy infiltration (e.g. Hodgkin's disease).

EVALUATION

A detailed history and good physical examination coupled with complete haemogram and liver function tests can give a clue to the cause of splenomegaly in most cases. Massive splenomegaly (≥8 cm or >1000 g) occurs in few conditions, e.g. myeloproliferative disorders (e.g. chronic myelogenous leukaemia, myelofibrosis, polycythemia vera), hairy cell leukaemia, lymphomas (splenic villous lymphoma), chronic lymphocytic leukaemia, Gaucher's disease, autoimmune haemolytic anaemia and chronic malaria. Presence of pallor (anaemia) may indicate haemolysis, bone marrow infiltration and hypersplenism. Petechiae/purpura due to thrombocytopaenia is seen in conditions, e.g. bone marrow failure (e.g. leukaemia), autoimmune disorders and hypersplenism. Presence of fever or rigors is indicative of

infections such as malaria, infectious mononucleosis or bacterial endocarditis. Presence of icterus may suggest haemolytic anaemia or liver disease as possible cause of splenomegaly. Skin rash may occur in acute and chronic infective states, Systemic lupus erythematosus (SLE), infective endocarditis and rheumatoid arthritis. Cloudy cornea and cherry-red retinal spots in children may be suggestive of metabolic storage disorders, e.g. mucopolysaccharidoses. Presence of respiratory and cardiac symptoms may be secondary to congestive heart failure, severe anaemia or a new murmur may be clue to infective endocarditis as cause of mild splenomegaly. Presence of prominent veins over abdominal wall, ascites, enlarged or shrunken liver may be indicative of portal hypertension and liver pathology as possible cause of splenomegaly. History of joint pains (rheumatoid arthritis, SLE) or bone pains (e.g. leukaemia) may be an important clue to diagnosis of splenomegaly. Splenomegaly may be seen in congenital haemolytic anaemias like beta-thalassaemia, hereditary spherocytosis and sickle cell anaemia in which family history may also be present. Non-cirrhotic portal fibrosis occurs in older children and young adults. Presence of generalised lymph node enlargement may suggest lymphohaemopoietic malignancies as a possible cause of splenomegaly. Primary tumours of spleen are rare except cysts; mostly metastasis from adjacent organs, such as stomach, pancreas and kidney can spread to spleen.

LABORATORY ASSESSMENT

Blood Counts

Complete blood count with differential and peripheral blood smears is the most important test. Pancytopaenia may be present because of bone marrow infiltration. White blood cell (WBC) count may reveal atypical lymphocytes (e.g. due to viral infections), blasts (e.g. in leukaemia), neutropaenia, (e.g. due to viral infections), neutropaenia, or neutrophilia (e.g. due to infection or leukaemia). Haemoglobin concentrations, red blood cell smears and reticulocyte counts may demonstrate anaemia, abnormal erythrocyte morphology, reticulocytosis (e.g. due to haemolysis), or malarial parasites. The platelet count may be high in conditions like myeloproliferative disorders (e.g. cytomegalovirus, primary thrombocythemia, polycythemia vera), may be normal or low in congestive splenomegaly, acute leukaemia, Gaucher's disease and immune thrombocytopaenia. Thrombocytopaenia may be present due to decreased production (e.g. due to bone marrow infiltration), increased destruction (e.g. due to immunologic causes, drug reactions, or viral infections), or sequestration or hypersplenism.

Bone Marrow Examination

It is generally indicated for work-up whenever a malignant haematologic disease is suspected or disseminated infection like kala-azar or tubercular infection is suspected.

Infection Work-up

This should be done as clinically indicated. Smear or antigen test for malaria, kala-azar, cultures from blood, body fluids (for bacterial infection), viral studies (Hepatitis, human immunodeficiency virus) and antibody titers for toxoplasmosis may aid in the diagnosis of infection as cause of splenomegaly.

Evaluation for lymphohaematopoeitic disorders

In myeloproliferative disorders, there may be mild anaemia with elevation WBC count (generally 10,000 to 20,000/mm^3 in myelofibrosis and polycythaemia vera or more than 1,00,000/mm^3 in chronic myeloid leukaemia). On differential count myelocytes, metamyelocytes and basophils may be appreciated. Spleen may be enlarged in a number of lymphoproliferative disorders. Immunophenotyping from peripheral blood or bone marrow may be necessary for definite diagnosis.

Liver disease evaluation

Liver function tests may be abnormal. For portal hypertension, ultrasound and Doppler of portal venous system and endoscopy (if indicated to exclude oesophageal varices) may be considered.

Evaluation for immunological disorders

This may include erythrocyte sedimentation rate, C3, C4, antinuclear antibody, rheumatoid factor, urinalysis, blood urea nitrogen and serum creatinine.

Evaluation for haemolytic disorders

Reticulocyte count, blood smear, serum bilirubin, urinary urobilinogen, Coombs' test, osmotic fragility, haemoglobin electrophoresis and other tests for haemolytic anaemia are performed, if indicated.

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15.4 Iron Deficiency Anaemia

Subhash Varma

DEFINITION AND EPIDEMIOLOGY

Though iron is the third most abundant element yet its deficiency is the commonest nutritional deficiency and a major health problem that is estimated to afflict over two billion people globally. More than half of patients with anaemia are assumed to have iron deficiency. Between 30% and 70% population in the developing world is iron deficient. The third national family health survey (NFHS-3) estimates suggest that 56% of women and 70% of children in India have anaemia. Over half of all cases of anaemia are secondary to iron deficiency. Iron deficiency passes through a latent phase to overt iron deficiency anaemia (IDA). IDA is associated with cognitive impairment, reduced work output and is an important contributor to increased maternal and perinatal mortality.

IRON METABOLISM

Body Iron Stores

Average total human body iron is approximately 3 to 4 gm in men (50 mg/kg) and 2.3 gm (40 mg/kg) in women. Though iron is present in all cells and has several vital functions, nearly 70% of the body iron is present in haem compounds, especially haemoglobin and myoglobin; with small amounts being incorporated into enzymes that use iron in electron transfer (cytochromes, peroxidases, catalases and ribonucleotide reductase) and in enzymes containing iron-sulphur clusters (including cytochromes and aconitase). About 30% of iron, which is non-haem, is stored as ferritin or haemosiderin in the bone marrow, spleen and liver. Approximately 0.1% of body iron is in transit in the plasma, bound to the carrier protein, transferrin. The relative iron stores and their turnover are shown in **Figure 1**. Iron metabolism is discussed in details in chapter 5 of section 18.

Iron Cycle and Iron Absorption

Since most of the iron in body is recycled and normally the losses are minimal and limited to those through the epithelial cells of skin, gut and genitourinary tract, the daily loss that needs dietary replenishment is approximately 1 mg in men and post-menopausal women and up to 2 mg in menstruating women. However, it can increase several fold in those with blood loss due to any cause. Since only 10% to 15% of ingested iron is absorbed, the dietary intake has to be higher. It is generally between 12 and 15 mg in normal diet. Iron absorption from the proximal small intestine is tightly regulated and increases in patients with iron deficiency. Several factors affect iron absorption (**Table 1**). Bioavailability of ingested iron in meat containing diets is approximately two to four times compared to a vegetarian diet. Phytates and phosphates present in some foods such as leafy vegetables and tannates in tea also reduce the bioavailability of iron in vegetarian food. Vitamin C enhances the iron absorption. Ingested iron could be in organic (haem) and inorganic form. Inorganic iron is generally in ferric form that needs to be reduced to ferrous form, a function that is accomplished by the gastric acid. Consequently, achlorhydria either due to disease or drugs like proton pump inhibitors reduces iron absorption.

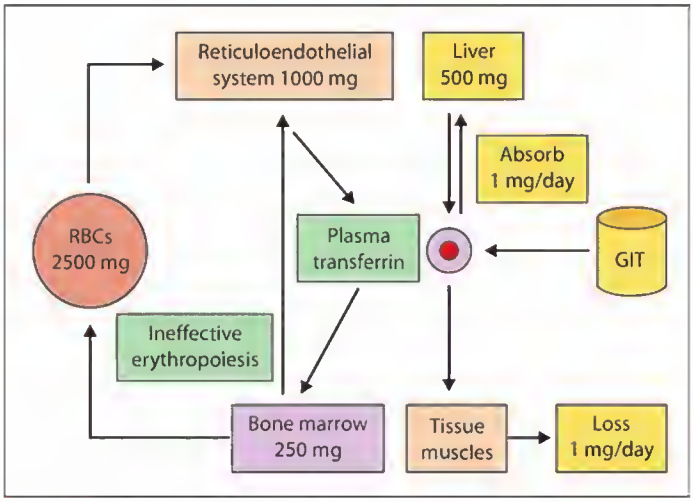


Figure 1: Iron stores and turnover.

RBCs = Red blood cells; GIT = Gastrointestinal tract.

Table 1: Factors Affecting Iron Absorption

Increased Absorption	Decreased Absorption
Dietary factors	
Increased haem-iron	Vegetarian diet
Animal protein	Achlorhydria
Vitamin C	Phytates
	Tannic acid (Tea)
	Alkali intake
Systemic factors	
Iron deficiency	Iron overload
Ineffective erythropoiesis	Inflammatory disorders
Thalassaemia, myelodysplasia	Infection
Increased erythropoiesis	
Haemorrhage (Haemolytic anaemia)	
Hypoxia	

Iron is absorbed in the duodenum and upper jejunum involving different transport mechanisms for haem and non-haem iron. Understanding of molecular mechanisms involving mucosal uptake, transfer to lamina propria, iron transport, storage and release has improved tremendously in recent years. Several key players such as diavalent metal transporter 1 (DMT1), hephaestin, ferroportin and hepcidin act in synchrony to maintain iron homeostasis. Absorbed iron is transported after binding to transferrin to the proerythroblasts for haem synthesis and some is carried to hepatocytes and reticuloendothelial cells (RE cells) for storage. The iron released from the red cells is recycled through the transferrin as well as stored in RE cells. Ferritin is the principal storage protein and ferritin levels correlate with status of body iron store, however, it is an acute phase reactant and the levels can be high in inflammatory diseases even in absence of iron

deficiency. Excess iron is also stored as haemosiderin which is water insoluble protein iron complex.

AETIOPATHOGENESIS

Iron deficiency results when demand outstrips supply and that may occur due to blood or haemoglobin loss, increased physiologic demands as in pregnancy, lactation and adolescence, decreased dietary intake or impaired absorption (**Table 2**). In a person with normal iron stores it passes through a pre-latent stage (iron store depletion) to latent stage (iron deficient erythropoiesis) and then to frank IDA (**Table 3**). With the progressive depletion of iron stores, serum iron levels fall and total iron binding capacity (TIBC) increases. When serum transferrin saturation falls to less than 16%, the supply of iron to marrow becomes sub-optimal. Initially free erythrocyte protoporphyrin levels increase and it finally results in decreased haemoglobin per cell and ultimately typical morphological changes of IDA appear. At times iron deficient erythropoiesis may result from impaired iron utilisation as in anaemia of chronic disease. Similar phenomenon occurs secondary to use of erythropoietin in chronic renal disease that is the result of impaired mobilisation of the large quantities needed for erythropoiesis.

Table 2: Causes of Iron Deficiency Anaemia

Increased Iron Requirements
Blood loss, massive haemorrhage
Gastrointestinal bleeding
- Haemorrhoids
- Duodenal or gastric ulcers or gastritis
- Nonsteroidal anti-inflammatory drugs, including aspirin
- Inflammatory bowel disease
- Diverticulosis
- Malignancy
- Arteriovenous malformation
- Varices
- Meckel's diverticulum
- Milk-induced enteropathy (infants)
- Salicylate use
- Hookworm *(Necator americanus and Ancylostoma duodenale)*
- Schistosomiasis
- Trichuriasis

Alveolar haemorrhage
Haemoglobinuria
Rapid growth in body size between 2 and 36 months of age
Menstruation, pregnancy and lactation

Inadequate Iron Supply
Poor nutritional intake

Malabsorption
- Gastric by-pass surgery for ulcers or obesity
- Achlorhydria from gastritis or drug therapy
- Severe malabsorption: coeliac disease
- Abnormal transferrin function
- Congenital atransferrinaemia
- Auto-antibodies to transferrin receptors
- Duodenal by-pass
- Drugs that increase gastric pH
- Tannins, phytates, bran
- Competing metals

Regular Blood Donation

Factitious Anaemia

Genetic Iron Deficiency Anaemia
Iron-resistant-iron deficiency anaemia
Atransferrinaemia
Acaeruloplasminaemia
Mutations in genes encoding DMT1 and glutaredoxin-5

Table 3: Stages of Iron Deficiency Anaemia

Pre-latent
Reduction in iron stores without reduced serum iron levels
Detected by a low serum ferritin measurement
Hb (N), MCV (N), iron absorption (↑), transferrin saturation (N), serum ferritin (↓), marrow iron (↓)

Latent
Iron stores are exhausted but the blood Hb level remains normal
Hb (N), MCV (N), TIBC (↑), serum ferritin (↓), transferrin saturation (↓), marrow iron (absent)

Iron deficiency anaemia
Blood Hb concentration falls below the lower limit of normal
Hb (↓), MCV (↓), TIBC (↑), serum ferritin (↓), transferrin saturation (↓), marrow iron (absent)

Hb = Haemoglobin; N = Normal; MCV = Mean corpuscular volume; TIBC = Total iron binding capacity; ↓ = Decreased; ↑ = Increased.

CLINICAL FEATURES

Patients with IDA could be incidentally diagnosed on laboratory investigations or may present with symptoms related to anaemia, the underlying cause or those peculiar to iron deficiency.

Anaemia

IDA can result in varying degree of anaemia that may be well tolerated in some persons. Severe IDA may be associated with fatigue, breathlessness, palpitations, dizziness, headache and irritability.

Growth

Iron deficiency impairs growth in infancy. In infants and pre-school children, iron deficiency anaemia affects neurological development by decreasing learning ability and altering motor functions. Iron deficiency even without overt anaemia has been linked to delayed cognitive development in children and adolescents.

Epithelial Tissue Changes

Patients with long-standing iron deficiency may develop a constellation of symptoms and signs characterised by defective structure or function of epithelial tissue. Nails, tongue and mouth are especially affected. Fingernails may become brittle, fragile, or longitudinally ridged and ultimately develop koilonychia. Soreness of tongue, mild papillary atrophy, absence of filiform papillae and angular stomatitis are the most frequent epithelial changes. Some patients may complain of dysphagia secondary to post-cricoid oesophageal web or stricture with gradual onset of dysphagia to solids but not to liquids (Paterson-Kelly syndrome/Plummer-Vinson syndrome).

Other Manifestations

IDA has been associated with impaired immune function and resultant increase in infections. Pica or craving for unusual substances like ice, clay, starch or other unusual food is a well described feature that improves on treatment with iron. Iron deficiency has also been associated with decreased work performance and exercise tolerance. Restless leg syndrome, i.e. an urge to move the legs with or without paraesthesia that worsens at rest and improves transiently with activity, has been associated with iron deficiency, especially in the elderly.

LABORATORY INVESTIGATIONS

IDA is diagnosed by the presence of biochemical indicators of iron deficiency along with characteristic blood and bone

marrow changes. Unfortunately, the classic combination of laboratory findings occurs consistently only when IDA is far advanced, when there are no complicating factors such as infection or malignant neoplasms and when there has been no previous therapy with transfusions or parenteral iron. Various tests and their limitations are listed in **Table 4**.

Table 4: Utility and Limitations of Various Investigations in Iron Deficiency

Test	Comments
Haemoglobin	Non-specific, not affected in early stages
Transferrin saturation	Low cost, widely available Marked diurnal variation in values, increased in ineffective erythropoiesis
MCV	One of the last parameters to be affected, hence low specificity
% hypochromic RBCs	Needs specialised autoanalysers, affected late
Reticulocyte Hb content	Early and sensitive sign False normal in thalassaemia and with increase in MCV
RBCs zinc protoporphyrin	Simple and precise for field surveys No additional information than % hypochromic RBCs Falsely high in lead toxicity, jaundice and haemodialysis patients
Serum ferritin	Widely available, falsely high in inflammation, liver disease, alcoholism, malignancy, chronic infection and haemophagocytic syndrome
Bone marrow iron stain	Not done routinely due to expense, discomfort and technical difficulties like high inter-observer variability
Soluble transferrin receptor	Also elevated in conditions of increased erythropoiesis, chronic haemolytic anaemias

MCV = Meon corpusculor volume; RBCs = Red blood cells.

Blood Parameters

Erythrocytes

IDA is characterised by a decrease in haemoglobin and red blood cell (RBC) counts along with decrease in the mean corpuscular volume (MCV) to less than 80 fL, mean corpuscular haemoglobin (MCH) to less than 28 pg/cell and mean corpuscular haemoglobin concentration (MCHC) to less than 30 g/dL. The content of reticulocyte haemoglobin (CHr) is an early, sensitive indicator of iron deficiency. CHr directly examines the haemoglobin endowment of the youngest circulating erythrocytes, allowing early detection of iron deficiency.

Peripheral smear

It shows characteristic findings in severe IDA. Anisocytosis is an important early sign in iron deficiency and when quantified has differential diagnostic value. An increased red cell distribution (RDW) on automated counter is indicative of anisocytosis. The red cells show microcytosis, hypochromia and poikilocytosis (**Figure 2**). Patients with parasitic diseases may show eosinophilia. Reactive thrombocytosis may be present in 50% to 70% cases, though some cases may have associated thrombocytopaenia.

Biochemical Parameters

Serum ferritin, serum iron and TIBC

Low serum ferritin invariably signifies iron deficiency. It has high negative predictive value although it lacks sensitivity and a normal value does not reliably exclude iron deficiency. In uncomplicated IDA, the serum ferritin level is less than 12 µg/L.

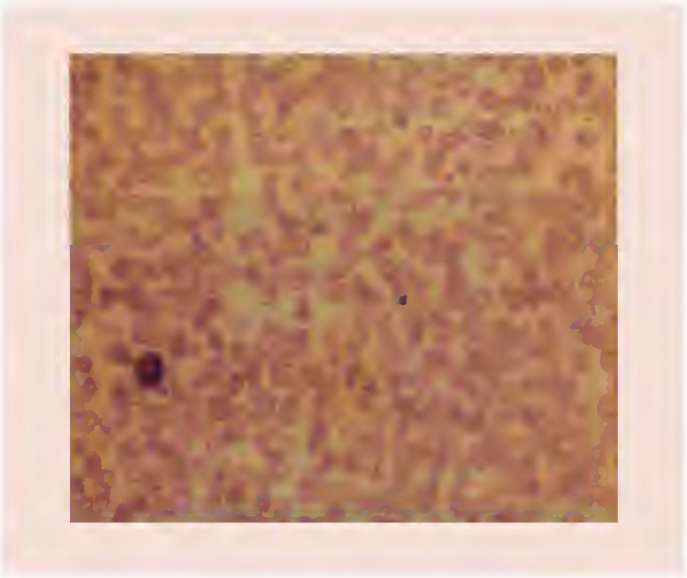


Figure 2: Peripheral smear in iron deficiency anaemia.

However, higher serum levels are the rule in the presence of a complicating infectious or inflammatory disease. Serum iron concentration (normal 30 to 160 µg/dL) is reduced in iron deficiency, and the TIBC (normal 220 to 420 µg/dL) increased. TIBC may be reduced in patients who have hypoalbuminaemia, inflammation, or both. Transferrin saturation is always reduced to less than 16% in iron deficiency.

Serum transferrin receptor (sTFR) fragments

These are measured by immunologic methods, are substantially increased in iron-deficient patients. This is useful in distinguishing iron deficiency from the anaemia of chronic disease (ACD), particularly when analysed as the ratio of sTFR to the log of the ferritin value. When the ratio of sTFR to log ferritin is greater than 1.5, iron deficiency is usually present (with or without other processes); when it is less than 1.5, the patient most likely has impaired iron use due to ACD, without frank iron deficiency.

Erythrocyte ferritin

Erythrocyte ferritin concentration is increased in thalassaemias and sideroblastic anaemias and decreased in iron deficiency. Though opinions differ, it has been suggested that basic red cell ferritin is not influenced by inflammation, and therefore could detect iron deficiency more reliably. However, this test is still not widely available.

Erythrocyte zinc protoporphyrin

Free erythrocyte protoporphyrin (FEP), mainly zinc protoporphyrin, is increased in disorders of haem synthesis, including iron deficiency, lead poisoning and sideroblastic anaemia. FEP is useful in differentiating iron deficiency from thalassaemia in which its value remains normal. This test requires small blood samples, is quite sensitive in the diagnosis of IDA and practical for large-scale screening programmes designed to identify children with either iron deficiency or lead poisoning. In addition, FEP also has a retrospective application as it helps to diagnose iron deficiency anaemia for some time even after the commencement of therapy.

Bone marrow

Hypercellularity with erythroid hyperplasia and presence of micronormoblasts is variable depending on the severity of

anaemia. These morphologic changes are not sufficiently distinctive to be of diagnostic value. However, a decrease or absence of stainable iron in marrow macrophages is characteristic finding of iron deficiency in bone marrow aspirates. Anaemias other than IDA have normal or increased iron stores.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses of IDA includes anaemia with microcytic hypochromic picture like thalassaemia minor and other haemoglobinopathies like Hb E disease, anaemia of chronic disorders and sideroblastic anaemia (**Table 5**). **Table 6** summarises laboratory tests for differentiating IDA from other microcytic hypochromic anaemias.

Table 5: Causes of Microcytic Hypochromic Anaemia

Cause	Body Iron Stores
Iron deficiency anaemia	Decreased
Disordered globin synthesis	Increased
Thalassaemia states	
Microcytic haemoglobinopathies	
Impaired iron utilisation	Increased
Anaemia of chronic disease	
Infections	
Inflammation	
Disorders of haem synthesis	Increased
Sideroblastic anaemias	
Hereditary	
Acquired	

Blood Transfusion

RBC transfusions are rarely indicated because in most instances anaemia responds well to supplementation and is well tolerated. However, elderly with cardiovascular disease and those with excessive loss may need RBC transfusion.

Iron Replacement

Both oral and parenteral forms of iron are available for therapeutic use. Most patients would benefit by oral iron which is cheap, inexpensive and easy to administer. Several salts of iron are currently marketed (**Table 7**). Ferrous sulphate is cheap, inexpensive and effective. Usual adult dose is 150-200 mg of elemental iron per day whereas children are given 3 mg/kg of elemental iron. The absorption is better when iron is taken on empty stomach. Iron absorption is inversely proportional to the level of haemoglobin. Haemoglobin in responsive patients would increase by 2 g/dL at 3 weeks. Most patients would report early subjective improvement and maximum reticulocyte response is noted between 5th to 8th day after the start of treatment. Haemoglobin would return to normal in approximately 2 months. However, the treatment should be continued for 4 to 6 months to replenish the iron stores. The maintenance dose is 60 mg of elemental iron per day.

Some patients may not tolerate oral iron and develop epigastric discomfort, nausea, vomiting, diarrhoea or constipation. In such individuals the dose may be reduced or iron may be administered with meals. Since it would decrease the iron absorption, the treatment period is likely to be prolonged. Costlier formulations and enteric coated preparations that claim

Table 6: Laboratory Investigations for Iron Deficiency Anaemia

Test	Iron Deficiency	Chronic Inflammation	Thalassaemia	Sideroblastic Anaemia
MCV	Decreased	Normal or decreased	Markedly decreased	Decreased
RDW	Increased	Increased or normal	Increased or normal	Increased or normal
Red cell morphology	Microcytic, hypochromic, pencil cells, anisocytosis	Normocytic, normochromic or microcytic, hypochromic	Microcytic, hypochromic, basophilic stippling, target cells, polychromasia	Dimorphic
Red cell count	Decreased	Decreased	Normal	Normal
Serum iron	Decreased	Decreased or normal	Normal or increased	Normal or increased
Total iron binding capacity	Increased	Decreased	Normal	Normal
Per cent saturation	Decreased	Decreased to normal	Normal or increased	Normal or increased
Ferritin	Decreased	Increased or normal	Normal	Normal
Serum transferrin receptor	Increased	Normal	Increased	Normal
Free erythrocyte protoporphyrin	Increased	Increased	Normal	Increased
Haemoglobin pattern on electrophoresis	Normal	Normal	Abnormal (Hb A_2 >3.5%)	Normal
Marrow Iron	Low or absent	Normal or increased	Normal	Ring sideroblasts seen >15%

MCV = Mean corpuscular volume; RDW = Red blood cell distribution width.

TREATMENT OF IRON DEFICIENCY

Treatment of iron deficiency requires not only the correction of anaemia but also to replenish the depleted iron stores. Though iron deficiency is easily corrected by iron administration in most cases, a thorough search for finding and treating the underlying cause of deficiency is essential. Treating hookworm infection empirically is justified in Indian context. However, more sinister causes that result in occult blood loss must be considered and investigated especially in men and non-menstruating women.

Table 7: Oral Iron Salts

Iron Preparation	Elemental Iron (%)
Ferrous sulphate	20
Exsiccated ferrous sulphate	30
Ferrous fumarate	33
Ferrous succinate	23
Ferrous gluconate	12
Ferrous carbonate	16

less side effects are available but are generally not needed in practice.

Parenteral Iron Therapy

Parenteral iron therapy is indicated only in rare instances such as intolerance of oral iron therapy despite changes in dose and time of administration, malabsorption states, excessive continued losses, noncompliance, need for acute replacement as in pregnancy or in conjunction with erythropoietin in patients with renal failure and other causes of qualitative iron deficiency. Various preparations of iron that are available include low and high molecular weight iron dextran complexes, ferric gluconate, iron sucrose and iron sorbital complex (**Table 8**). New parenteral preparation, iron ferumoxytol and iron carboxymaltose have been reported to be safe. Parenteral iron can cause serious and life-threatening reactions such as hypotension, anaphylaxis or serum sickness like illness. Hence, these must always be administered under supervision. Parenteral iron other than iron sucrose can be administered to deliver the total dose that can be calculated as under:

Total iron in mg = Weight in kg x 2.2 x 15 – patients haemoglobin in g/dL) + 1,000 for males/600 for females

The total dose is diluted in 250 to 1,000 mL normal saline. 25 mg is given as test dose over 30 seconds and if no reaction is observed over 15 minutes then the remainder is given over 4 to 6 hours. The rate of rise of haemoglobin is similar to that with oral preparations.

Table 8: Parenteral Iron Preparations

Preparation	Comments
Iron dextran	50 mg/mL, intramuscular and intravenous use Test dose required Total dose infusion possible Potentially severe side-effects
Iron sorbitol citrate	Only intramuscular use, 50 to 100 mg/day Test dose required
Iron sucrose	100 mg in 5 mL Only intravenous use. Maximum single dose 100 mg can be given as slow injection over 5 min or as infusion in 100 ml saline over 30 mins. Test dose not required, reactions very rare.
Ferric gluconate complex in sucrose (Sodium ferric gluconate)	12.5 mg in 10 mL. Slow injection over 10 mins or infusion in 100 mL saline over 1 hour Reactions very rare

IRON REFRACTORY IRON DEFICIENCY

Some patients continue to have iron deficiency despite supplementation (**Figure 3**). In some instances, it may be due to poor compliance, a wrong diagnosis or continuing losses that cannot be corrected. Iron malabsorption due to latent or overt celiac disease, autoimmune gastritis and *Helicobacter pylori* infections have been the commonest demonstrable cause of refractory IDA in adults. In addition inherited forms of IDA affecting iron uptake, transfer and release (due to increased hepcidin levels) have been described in children. A diligent search either for iron loss or iron malabsorption is often rewarding in refractory IDA.

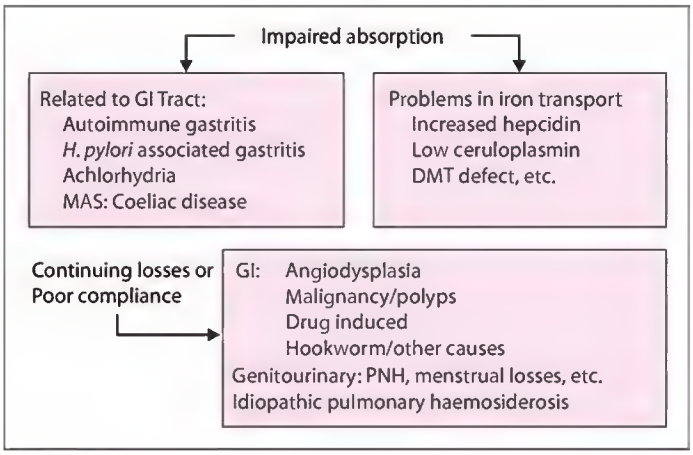


Figure 3: Iron refractory iron deficiency.

GI = Gastrointestinal; DMT = Divalent metal transporter.

CONCLUSIONS

Iron deficiency is the commonest nutritional deficiency and is responsible for more than 50% of anaemia worldwide. Iron deficiency results from an imbalance between the demand and supply of iron. It may occur secondary to decreased intake, increased requirements during pregnancy, lactation or growth spurt, inability to absorb iron from the gastrointestinal (GI) tract or increased losses from the gut, genitourinary tract or into other organs/tissues. Though easily treatable, a cause must be sought for in every case because it may be the harbinger of underlying sinister disorder, such as GI malignancy. Iron deficiency results initially in depletion of iron stores and progresses to the development of characteristic microcytic hypochromic anaemia. The diagnosis is established by biochemical parameters and it must be differentiated from other causes of hypochromic microcytic anaemia. Treatment is directed towards replacement of iron and treating the underlying cause. Oral ferrous sulphate is safe, cheap and effective in treating iron deficiency. In case of inadequate response besides looking at compliance, other reasons, such as continuing losses, co-morbidities, iron malabsorption and concomitant deficiencies should be sought.

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15.5 Megaloblastic Anaemia

Tarun Kumar Dutta

INTRODUCTION

A puzzling illness with idiopathic anaemia, debilitation, languor and finally, torpor and death was first described by Addison in 1849. In 1880, Ehrlich identified megaloblasts and proposed them as the precursors of the 'giant blood corpuscles'. These events in course of time heralded the knowledge of disease known as megaloblastic anaemia. Castle described *achylia gastrica* and demonstrated that gastric juice contains an 'intrinsic factor' (IF) that combines with an 'extrinsic factor' in meat and allows it to be absorbed.

Wills, who treated macrocytic anaemia with yeast, defined the need for folate, which was isolated and characterised in 1948.

DEFINITION

The megaloblastic anaemias are disorders caused by impaired deoxyribonucleic acid (DNA) synthesis due to deficiencies of vitamin B12 (cobalamin, i.e. Cbl) or folic acid (FA), which give rise to anaemia and macro-ovalocytic red cells (mean corpuscular volume [MCV] >100 fL) and bone marrow showing intense erythroid hyperplasia and megaloblastic changes. The megaloblast, the morphologic hallmark of the syndrome, is a product of impaired DNA formation due to deficiencies of vitamin B12 or FA.

PATHOGENESIS OF MEGALOBLASTIC ANAEMIA

Megaloblastic anaemia results from abnormal maturation of haematopoietic cells due to impaired DNA synthesis. Cbl (vitamin B12) and FA are two essential vitamins for DNA biosynthesis. Deficiency of either vitamin results in what is called as nucleo-cytoplasmic asynchrony. All proliferating cells will exhibit megaloblastosis; hence changes are evident in the buccal mucosa, tongue, small intestine, cervix, vagina and uterus. In the haematopoietic system this asynchrony results in abnormal nuclear maturation with normal cytoplasmic maturation, apoptosis, ineffective erythropoiesis, intra-medullary haemolysis, pancytopaenia and typical morphological abnormalities in the blood and marrow cells.

AETIOLOGY

Aetiology of megaloblastic anaemia is multifactorial and may result from dietary deficiency, impaired absorption and transport or impaired utilisation of these vitamins in DNA synthesis (**Table 1**). The dietary patterns vary widely across India and studies need to be conducted region-wise to find out the variable aetiology of megaloblastic anaemia.

Table 1: Causes of Cobalamin and Folic Acid Deficiencies in India

Common Causes of Cobalamin Deficiency in India

Nutritional deficiency/inadequate intake
(most important cause in India, including in strict vegans)
Malabsorption
Defective absorption of cobalamin from food
- Gastric achlorhydria
- Partial gastrectomy
- Drugs blocking gastric acid secretion

Inadequate production of intrinsic factor (IF)
- Total gastrectomy

Disorders of terminal ileum
- Tropical and coeliac sprue
- Intestinal resection
- Granulomatous diseases

Competition for cobalamin
- Bacteria (Blind loop syndrome)

Drugs
- Colchicine
- Neomycin

Uncommon Causes of Cobalamin Deficiency in India

Pernicious anaemia
Congenital absence or functional abnormality of IF
Crohn's disease
Selective cobalamin malabsorption: Imerslund-Grasbeck syndrome
Fish tapeworm infestation (*Diphyllobothrium latum*)
Transcobalamin II deficiency

Common Causes of Folic Acid Deficiency in India

Nutritional deficiency
Increased requirements
- Infancy and children
- Pregnancy
- Malignancy
- Chronic haemolytic anaemia
- Chronic exfoliative dermatitis
- Haemodialysis

Malabsorption
- Tropical and non-tropical sprue
- Drugs: Phenytoin, barbiturates

Impaired metabolism
- Inhibitors of dihydrofolate reductase

Methotrexate, pyrimethamine
Alcohol

Uncommon Causes of Folic Acid Deficiency in India

Rare enzyme defect – dihydrofolate reductase
Drugs that impair DNA synthesis
- Purine antagonists: 6-mercaptopurine, azathioprine
- Pyrimidine antagonists: 5-fluorouracil, cytosine arabinoside
- Others: Hydroxyurea, procarbazine, zidovudine, acyclovir

Metabolic disorder
- Lesch Nyhan syndrome, hereditary orotic aciduria

Megaloblastic anaemia of unknown aetiology
Refractory megaloblastic anaemia in myelodysplastic syndrome (MDS)

PREVALENCE AND CAUSATIVE FACTORS

Very few studies have been conducted to study the prevalence of megaloblastic anaemia in the general population. Analysing the western literature, it is found that dietary and pregnancy-related folate deficiencies are probably the most common causes of megaloblastic anaemias. The frequency of pernicious anaemia (PA) is 0.25-0.5 cases per 1,000 persons in their seventh decade of life. However, the frequency of PA is reported to be higher in Sweden, Denmark, and the United Kingdom (100-130 cases per 100,000 population). In a study conducted among North African population, 478 patients with megaloblastic anaemia were studied; 98% of patients had vitamin B12 deficiency. PA accounted for most of these cases, and median age at presentation was 45 years.

In a study conducted in Hong Kong on 84 consecutive Chinese patients with megaloblastic anaemia (48 males and 36 females) median age at presentation was 67 years, and vitamin B12 deficiency was found in all cases and none had folate deficiency.

Indian Scenario

A study reported that 75% of a selected urban population from India, Pune (Maharashtra) had metabolic evidence (hyperhomocysteinaemia and methylmalonic acidaemia) of Cbl deficiency, which could only partly be explained by a vegetarian diet. Folate deficiency has traditionally been linked to poverty, which (by Indian standards) afflicts ~33% of the population of India. In Delhi, a hospital-based study showed that 2.7% of all anaemia was megaloblastic anaemia.

In another study from Puducherry, megaloblastic anaemia was found in 38.4% out of 60 adult patients of macrocytic anaemia. There was a significant male preponderance in the study (65%), and majority were young. The megaloblastic anaemias observed were due to either vitamin B12 deficiency (78.3%) or combined vitamin B12 and folate deficiency (21.7%). None had lone folate deficiency. A significant proportion of non-vegetarians (73.9%) had megaloblastic anaemia.

In a study at Delhi, megaloblastic anaemia was diagnosed in 175 patients with anaemia over a period of 6 months. Assays were done on 120 patients who could be followed-up and results showed Cbl deficiency in 78 patients (65%), combined Cbl and folate deficiency in 20 patients (12%) and pure folate deficiency in 8 patients (6%). The peak incidence of megaloblastic anaemia was in the age group of 10 to 30 years (48%), with female preponderance (71%).

More and more reports from India show vitamin B12 deficiency as a predominant cause for megaloblastic anaemia in contrast to folate deficiency, which was earlier believed to be a major cause. This may be attributed to the routine FA supplementation especially among women.

Western data emphasises on PA as the major cause, but Indian data suggests nutritional deficiency of vitamin B12 and FA as major causes of megaloblastic anaemia. An attempt should always be made to find out the cause and treat accordingly.

COBALAMIN DEFICIENCY

Physiologic Considerations

Animal products (meat and dairy products) provide the only dietary source of Cbl for humans. The minimum daily requirement is 6-9 µg/day. Total body stores of Cbl are 2-5 mg, approximately one-half of which is in the liver. As a result, it takes years to develop vitamin B12 deficiency after absorption of dietary B12 ceases.

Clinical Manifestations of Cobalamin Deficiency

The classic picture of Cbl deficiency due to PA was that of a prematurely graying, mentally sluggish person with a shiny tongue (atrophic glossitis) and a shuffling broad gait. This classic picture of PA is now seen less frequently. It has been replaced by more subtle presentations. Because Cbl is required for all rapidly growing cells, including enteric mucosal cells and epithelial cells of the skin, patients with Cbl deficiency may complain of glossitis, vaginal atrophy, and malabsorption; they often have diffuse hyper-pigmentation particularly increased pigmentation over knuckles (**Figures 1 and 2**). The patient may have neuro-psychiatric problems consisting of paraesthesiae, numbness, weakness, impaired memory and personality changes. Examination reveals haematologic and neurologic abnormalities.

When the anaemia is severe, there may also be thrombocytopaenia and neutropaenia (i.e. pancytopaenia). Thrombocytopaenia occasionally may be associated with frank mucosal bleeding.



Figure 1: Diffuse pigmentation of hand and knuckle hyper-pigmentation in megaloblastic anaemia.



Figure 2: Knuckle hyper-pigmentation in a 55-year-old woman with megaloblastic anaemia due to combined vitamin B12 and folic acid deficiency.

Neurologic Abnormalities

The neurologic problems, when present, consist of the classic picture of sub-acute combined degeneration of the dorsal (posterior) and lateral spinal columns. This lesion, specific for Cbl deficiency, is due to a defect in myelin formation of unknown mechanism. The neuropathy is symmetrical and affects the legs more than the arms. It begins with paraesthesiae and ataxia associated with loss of vibration and position sense, and can progress to severe weakness, spasticity, clonus, paraplegia and even faecal and urinary incontinence.

Other neurologic abnormalities that can be seen are axonal degeneration of peripheral nerves and central nervous system symptoms including memory loss, irritability and dementia. Patients may present with Lhermitte's syndrome, a shock-like sensation that radiates to the feet during neck flexion.

Of great clinical importance, not all patients with neurologic abnormalities secondary to Cbl deficiency are either anaemic or have macrocytic red cell indices. As an example, among 141 consecutive patients with neuro-psychiatric abnormalities due to Cbl deficiency, the haematocrit was normal in 34, the mean red cell volume was normal in 25 and both tests were normal in 19.

FOLIC ACID DEFICIENCY

Physiologic Considerations of Folic Acid

Folate occurs in animal products and in leafy vegetables in the polyglutamate form. Normal daily requirements for unstressed individuals are about 200-400 μg/day; this increases to 500-800 μg/day in pregnancy and lactation.

The most common cause of folate deficiency is nutritional due to poor diet and/or alcoholism. Although folate is plentiful in liver, greens and yeast, it is easily destroyed by heat during cooking. Body stores are small (5-10 mg) and individuals on a folate deficient diet can develop megaloblastosis within 4 to 5 months.

Folate at physiologic levels enters cells by binding to a folate receptor. Once inside the cell, FA is polyglutamated, a form which is biologically active and cannot diffuse back into the plasma.

Causes of Folate Deficiency

Alcohol abuse produces a sharp fall in serum folate within 2 to 4 days by impairing its enterohepatic cycle and inhibiting its absorption. Thus, alcoholics on a low folate intake can develop megaloblastosis within 5 to 10 weeks. This period is shorter than the 4 to 5 months required in normals in part because alcoholics start with lower stores due to previous dietary habits.

Other mechanisms of folate deficiency include increased requirements in pregnancy and in patients with haemolytic anaemias and exfoliative skin disease and drug-induced interference with folate metabolism. Pregnancy and lactation increase the need for FA and the daily requirement increases from 400 μg to 800 μg.

Several drugs interfere with FA metabolism. Trimethoprim is a weak inhibitor of dihydrofolate reductase and in high dose has been implicated in megaloblastic pancytopaenia. Methotrexate can also produce folate deficiency.

Clinical Manifestations

The haematologic manifestations of folate deficiency are similar to those of Cbl deficiency but neurologic abnormalities do not occur.

Another important difference is the time required for deficiency to develop. Because Cbl stores are so large in relation to daily intake, a year of inadequate intake of absorption is required before the onset of symptoms. On the other hand, symptoms of folate deficiency can occur within a few weeks after intake is diminished.

Folate deficiency occurs in patient who abuse alcohol or other drugs and have a very poor dietary intake. Older and depressed patients who live alone and avoid cooking foods that contain folate may become deficient, as can patients with the malabsorption syndrome. Increased folate demands occur in patients with chronic severe haemolytic anaemia and pregnancy.

Hyperhomocysteinaemia

Both Cbl and FA are required for the metabolism of homocysteine to methionine. As a result, deficiencies in these vitamins can lead to elevations in plasma homocysteine levels, which is a risk factor for the development of atherosclerosis and venous thrombosis.

DIAGNOSIS OF MEGALOBLASTIC ANAEMIA

The evaluation of suspected Cbl or folate deficiency generally proceeds in two stages: Documenting the presence of the vitamin deficiency and then determining its cause (e.g. malabsorption, dietary lack or PA).

The diagnosis of deficiency can most often be established by a combination of the following; red blood cell mean corpuscular volume (MCV), evaluation of the peripheral blood smear and bone marrow examination; measurement of the serum Cbl and the red blood cell (or serum) folate concentrations and evaluation of specific metabolites (e.g. methylmalonate and homocysteine).

An elevation of the red blood cell MCV is one of the hallmarks of Cbl and folate deficiency. The degree of elevation of the MCV is often a clue as to whether a vitamin deficiency is present. The major haematologic finding is a macro-ovalocytic anaemia (**Figure 3**) (with elevated serum bilirubin and LDH levels that reflect the increased red cell breakdown due to ineffective erythropoiesis). The absolute reticulocyte count is normal or even distinctly low. The peripheral blood smear shows macro-ovalocytes, occasionally megaloblasts, and hyper-segmented neutrophils (greater than 5% of neutrophils) with 5 or more lobes or 1% with 6 or more lobes. Hypersegmentation is result of an alteration of late granulopoiesis.

When the anaemia is severe, there may also be thrombocytopaenia and neutropaenia (i.e. pancytopaenia). Bone marrow aspiration and biopsy reveal a very hypercellular marrow with megaloblastic erythroid hyperplasia and giant metamyelocytes (**Figure 4**).

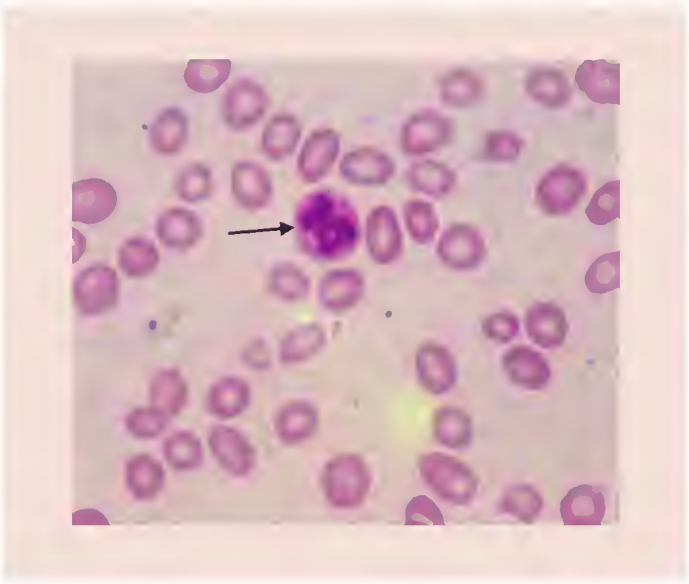


Figure 3: Peripheral smear showing macro-ovalocyte, hypersegmented neutrophil (arrow) and scanty platelets (Leishman's stain × 1000).

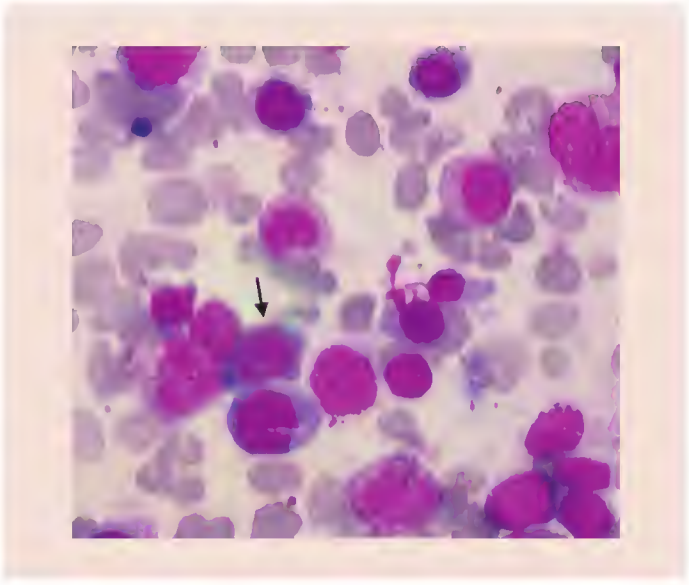


Figure 4: Bone marrow aspirate showing a colony of megaloblastic erythropoiesis with sieve-like chromatin and a giant stab form (Leishman's stain × 1000).

Cobalamin Levels

In general, however, serum Cbl levels can be interpreted, as follows:

- More than 300 pg/mL (normal result); Cbl deficiency is unlikely,
- 200 to 300 pg/mL (borderline result); Cbl deficiency possible,
- Less than 200 pg/mL (low); consistent with Cbl deficiency (specificity of 95% to 100%).

Folate Levels

The red cell folate concentration is theoretically a more reliable indicator of tissue folate adequacy, since it reflects a time-averaged value of FA availability, and is therefore not subject to the short-term fluctuations noted above. As a result, it has been suggested that the less expensive serum folate concentration should be obtained as an initial screening test and that there is no basis for the routine testing of all samples for both serum folate and red cell folate. If the serum folate concentration is more than 4 ng/mL (9.1 nanomol/L), folate deficiency is effectively ruled out.

If the Cbl and folate levels are equivocal, the next step should be evaluation of the metabolites methylmalonic acid (MMA) and total homocysteine. The measurement of the serum concentrations of the metabolities is helpful in clarifying the diagnosis in such a situation.

Measurement of Methylmalonate and Homocysteine

Serum concentrations of homocysteine and methylmalonic acid (MMA) are elevated in Cbl deficiency, due to a decreased rate of metabolism. In comparison, only homocysteine is elevated in folate deficiency, since folate does not participate in MMA metabolism. Hereditary homocysteinaemia can raise serum homocysteine levels. Serum and urinary levels of MMA are elevated in patients with methylmalonic aciduria and in patients with renal insufficiency or hypovolaemia.

If a diagnosis of Cbl and/or folate deficiency has been established through the above testing, the next step is to determine the cause of the deficiency (e.g. PA, diet, malabsorption, drugs).

The presence of anti-intrinsic factor antibodies and positive Schilling test are highly confirmatory for the diagnosis of PA.

Vitamin B12 deficiency, PA, malabsorption, blind-loop syndromes and ileal disease can be reliably and quickly diagnosed using methods other than the Schilling test. Thus, Schilling test is not commonly employed these days.

In the absence of facilities to estimate vitamin levels, a therapeutic algorithmic approach can be followed to find out cause of megaloblastic anaemia, whether due to vitamin B12 or FA deficiency (**Figure 5**).

TREATMENT

Treatment of Cobalamin Deficiency

PA is typically treated with parenteral (i.e. intramuscular) Cbl, in a dose of 1,000 µg (1 mg) every day for one week, followed by 1 mg every week for 4 weeks and then, if the underlying disorder persists, as in PA, 1 mg every month for the remaining life of the patient.

Oral Formulations

An alternative that appears to be as effective as parenteral therapy is based on the premise that there is presence of a second, lower efficiency transport system for Cbl that does not require IF or a functioning terminal ileum. Because of variability in absorption, lower doses are not completely effective in some patients with PA. The dose given in this situation (1-2 mg/day) is more than 200 times higher than the minimum daily requirement for normal subjects, and significantly higher than that available in most standard multivitamins and B12 supplements (100 µg/day). The effectiveness of this form of treatment should be monitored frequently with determinations of serum Cbl and methylmalonate concentrations.

Laboratory Monitoring

Laboratory studies should be monitored after Cbl therapy to document a haematologic and metabolic response: If the

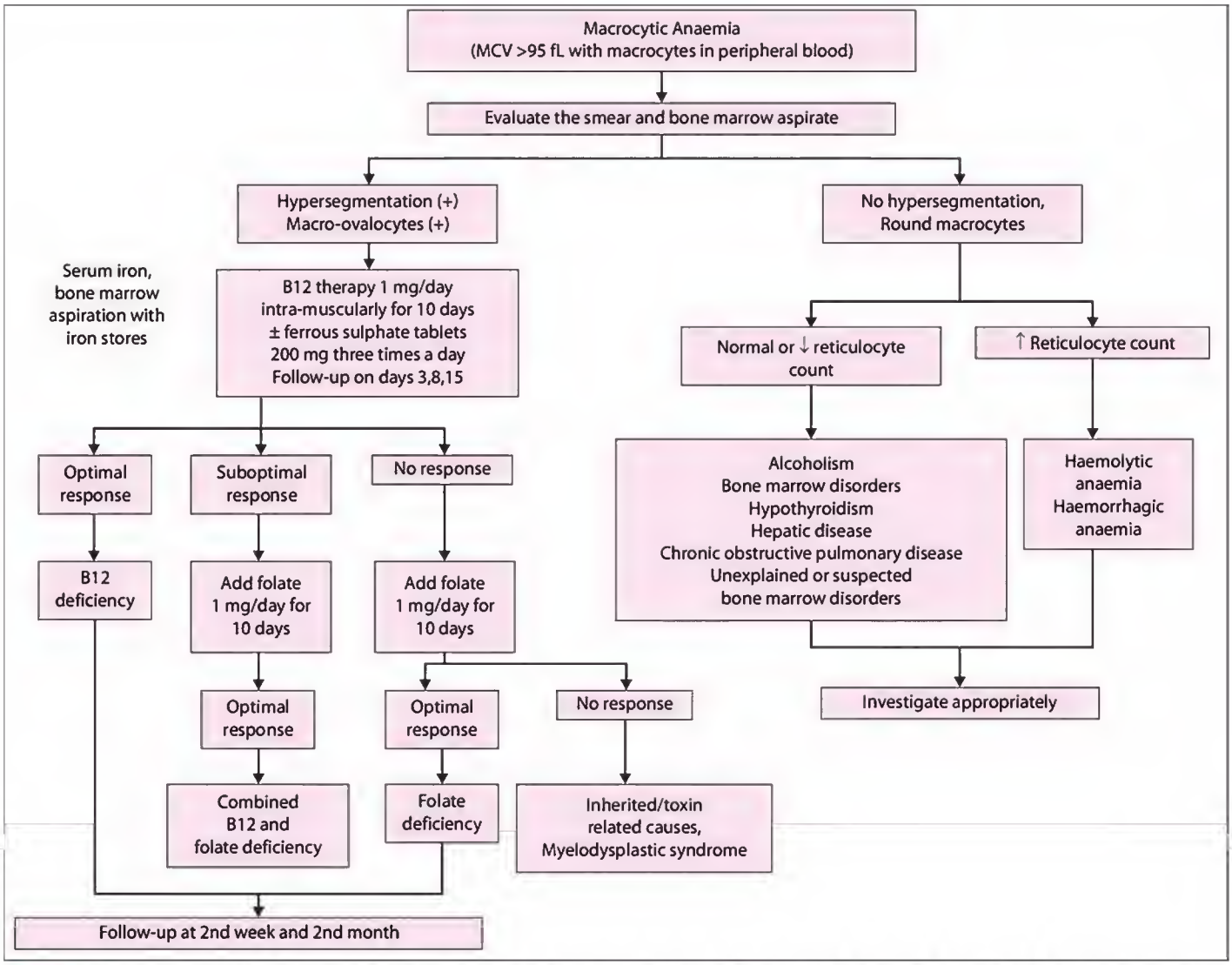


Figure 5: Algorithmic approach to find cause of macrocytic anaemia/megaloblastic anaemia (in the absence of facility for vitamin B12 or folic acid estimation).

patient is anaemic, there will be a reticulocytosis in 3 to 4 days, peaking at days 6 to 7 days, followed by a rise in haemoglobin and a fall in MCV. The haemoglobin concentration begins to rise within 10 days and usually returns to normal within 8 weeks. A delayed response suggests the presence of an additional abnormality (e.g., iron deficiency, infection, hypothyroidism, malignancy). In patients with severe anaemia, serum iron levels fall within 24 hours and the serum LDH levels begin to fall within 2 days. Hyper-segmented neutrophils disappear at 10 to 14 days. Neurologic abnormalities, if present, improve more slowly over six months; the degree of improvement is inversely related to the extent and duration of disease.

Treatment of Folate Deficiency

Folate deficiency is treated with FA (1-5 mg/day) for 1 to 4 months, or until complete haematologic recovery occurs. A dose of 1 mg/day is usually sufficient, even if malabsorption is present. These doses are in excess of those recommended for disease prevention (e.g., recommended daily allowance in normal adults, alcoholics, the elderly, prevention of neural tube defects).

Folic acid can partially reverse some of the haematologic abnormalities of Cbl deficiency, but the neurologic manifestations will progress. Thus, it is important to rule out Cbl deficiency before treating a patient of megaloblastic anaemia with FA. If initiation of treatment is urgently required, blood samples should be obtained for the appropriate assays and the patient should be treated with both FA and vitamin B12 simultaneously until the results are known.

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15.6 Hereditary Haemolytic Anaemia

MB Agarwal

Once released from marrow, red cells circulate in blood for 120 days, after which they are removed by macrophages of reticuloendothelial system (RES) in the liver, spleen and marrow. Iron is recycled via transferrin to the marrow while the pigment protoporphyrin is broken down to bilirubin which is conjugated in liver and excreted into the gut where it is converted to stercobilinogen. Most of the stercobilinogen is excreted in faeces but some of it is partially reabsorbed and excreted in urine as urobilinogen and urobilin. A small fraction of protoporphyrin is converted to carbon monoxide and excreted via the lungs. Globin chains are broken into amino acids and are reutilised for general protein synthesis in the body. Normally, there is no intravascular haemolysis. Any haemoglobin released into the plasma binds to a protein called haptoglobin and this complex of haemoglobin and haptoglobin is removed from plasma by the RES.

Haemolysis is characterised by premature removal of circulating red blood cells (RBCs) due to lysis within the circulatory system (intravascular haemolysis) or premature removal by the RES of the spleen, liver and bone marrow (extra-vascular haemolysis). Such accelerated RBC destruction is seen in various hereditary and acquired haemolytic disorders.

Normal marrow has tremendous capacity to become hyperplasic and compensate for haemolysis, and hence, anaemia occurs only when this compensation is not adequate. The erythroid hyperplasia of marrow is reflected in blood as reticulocytosis unless there is ineffective erythropoiesis as in thalassaemia major. Shortened RBC survival can be demonstrated by chromium-labelled red cell survival studies. The site of destruction can also be determined by surface counting over liver and spleen.

HEREDITARY HAEMOLYTIC ANAEMIAS

Haemolytic anaemias can be classified in various ways, e.g. inherited (hereditary) versus acquired, intra-corpuscular versus extra-corpuscular (**Table 1**) and acute versus chronic. Hereditary haemolytic anaemias are usually due to intra-corpuscular or intrinsic red cell defects. **Table 2** gives a simplified aetiological classification of hereditary haemolytic anaemias.

Table 1: Pathophysiologic Classification of Haemolytic Disorders

Intrinsic (intra-corpuscular) defects: usually hereditary
Red blood cell membrane defects
Red blood cell enzyme defects
Haemoglobinopathies
Extrinsic (extra-corpuscular) defects: usually acquired
Immune-mediated haemolysis
Physical damage to red blood cells
Toxins
Thermal injury
Mechanical disruption

Table 2: Aetiological Classification of Hereditary Haemolytic Anaemia

Membrane defects
Hereditary spherocytosis
Hereditary elliptocytosis
Hereditary stomatocytosis
Hereditary acanthocytosis
Enzyme defects (congenital non-spherocytic haemolytic anaemia)
Deficiency of glucose-6-phosphatase dehydrogenase or other enzymes in the pentose phosphate pathway
Deficiency of pyruvate kinase or other enzymes in the Embden-Meyerhof pathway
Associated with abnormalities of nucleotide metabolism
Haemoglobin defects
Thalassaemia syndrome
β-thalassaemia major
Hb-H disease
Others
Haemoglobinopathies
Sickle cell anaemia
Other abnormal haemoglobins (Hb-E, Hb-D, Hb-C, etc.)
Unstable haemoglobin disease
Others

Clinical Features

Clinical findings in a case of hereditary haemolytic anaemia include pallor, icterus (**Figure 1**), splenomegaly, haemolytic facies, ankle ulcer, pigment gall-stones, growth retardation, pathological fractures and various crises, e.g. aplastic crises due to B19 parvovirus and megaloblastic crises due to folic acid (FA) deficiency.



Figure 1: Icterus in a case of haemolytic anaemia.

Laboratory Investigations

Various laboratory investigations to be conducted for the diagnosis of hereditary haemolytic anaemias are presented in **Tables 3, 4 and 5** which can be divided into four groups as given below.

1. Those secondary to excessive red cell destruction, raised indirect serum bilirubin, increased urinary urobilinogen, decreased serum haptoglobin and haemopexin, increased serum lactic dehydrogenase, altered osmotic fragility, auto-haemolysis and shortened red cell survival as shown by chromium labelled studies.
2. Features of increased red cell production which are reticulocytosis, macrocytosis, erythroid hyperplasia of the marrow and radiological changes in the bones (skull and tubular bones).
3. Changes in red cell morphology (**Table 5**).
4. Features of intra-vascular haemolysis are haemoglobinaemia (**Figure 2**), haemoglobinuria (**Figure 3**), haemosiderinuria and methaemalbunaemia.

Table 3: Laboratory Evaluation of Red Blood Cells Production and Breakdown

Bone marrow production	↑ Reticulocyte count, ↑ BM cellularity, ^{59}Fe uptake
Red blood cell destruction	↓ Hb/PCV, ^{51}Cr RBC survival studies
Red blood cell sequestration	^{51}Cr RBC sequestration
Red blood cell breakdown	↓ Haptoglobin, ↑ bilirubin, ↑ LDH, haemoglobinaemia, methemalbumin, ↑ BM iron
Excretion	Haemosiderinuria, haemoglobinuria

BM = Bone marrow; Hb = Haemoglobin; PCV = Packed cell volume; RBC = Red blood cell; LDH = Lactate dehydrogenase.

Table 4: Urine and Serum Testing in Haemolysis

Pigment	Normal Range	Comments
Serum bilirubin	0.5 to 1.0 mg/dL	Limited significance, jaundice seen >3.0 mg/dL
Serum indirect bilirubin	<0.5 mg/dL	↑ in haemolysis, also in hereditary conjugation disorders (Crigler-Najjar syndrome, Gilbert syndrome)
Plasma haemoglobin	<10 mg/dL	Significant above 50 mg/dL, Cherry-red plasma > 150 mg/dL, binds to haptoglobin or albumin
Urine haemoglobin	Absent	Appears after haptoglobin saturation, haematuria and myoglobinuria must be excluded
Methaem albumin	Absent	Qualitative determination by electrophoresis or serum spectrophotometric measurement

Table 5: Morphological Changes in RBCs in Hereditary Haemolytic Disorders

Red Cell Abnormality	Major Diagnostic Possibilities
Permanently sickled cells	Sickle cell disease
Target cells*	Thalassaemia Hb-E, Hb-D, Hb-C disorders
Spherocytes*	Hereditary spherocytosis
Elliptocytes*	Hereditary elliptocytosis
Acanthocytes*	Hereditary acanthocytosis, Spur-cell anaemia
Basophilic stippling*	Pyrimidine 5'-nucleotidase deficiency, thalassaemia trait
Bite cells/ Blister cells	Hereditary non-spherocytic haemolytic anaemia, i.e. RBC enzymopathies (especially precipitated by drugs)

** These can also occur in various acquired conclitions which are not listed here.*

MEMBRANE DEFECTS

Hereditary Spherocytosis

Hereditary spherocytosis is the commonest hereditary haemolytic anaemias secondary to an erythrocyte membrane defect. It is due to defective structural protein (spectrin) of the red cell membrane. The greater the deficiency of spectrin, the more severe is haemolysis. There are different genetic lesions resulting in variable degree of haemolysis (**Table 6**). Hereditary spherocytosis is inherited as an autosomal dominant disorder but the phenotypic expression is variable. Very rarely, it is inherited as an autosomal recessive order.

Loss of membrane is also responsible for the spherical shape of the red cells (**Figure 4**). As the spherical cells are unable to pass through the splenic micro-circulation, these die prematurely.



Figure 2: Haemolysis showing pinkish *vs* normal plasma.

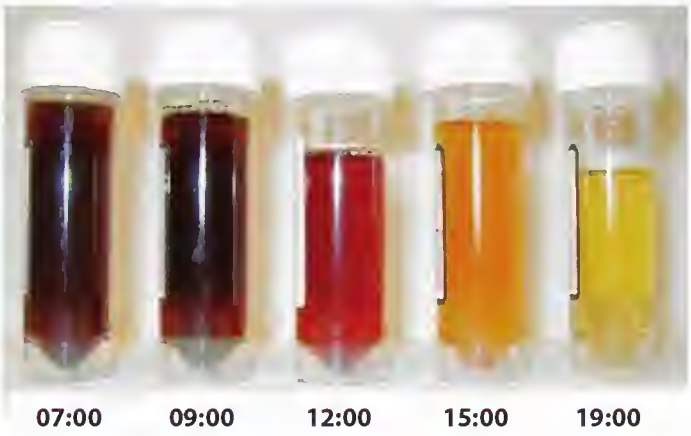


Figure 3: Haemoglobinuria.

Table 6: Heterogeneity of Hereditary Spherocytosis

Protein Defect	Haemolysis	Inheritance Pattern (Autosomal)	Frequency
Spectrin α-chain	Severe	Recessive	Rare
Spectrin β-chain	Mild-to-moderate	Dominant	Common (20 %)
Ankyrin defect	Mild-to-severe	Dominant	Common (60%)
Band 3 defect	Mild-to-moderate	Dominant	Common (20%)
Protein 4.1 defect	Mild	Dominant	Common in N. Africa
Protein 4.2 defect*	Moderate-to-severe	Recessive	Common in Japan

** = No response to splenectomy.*

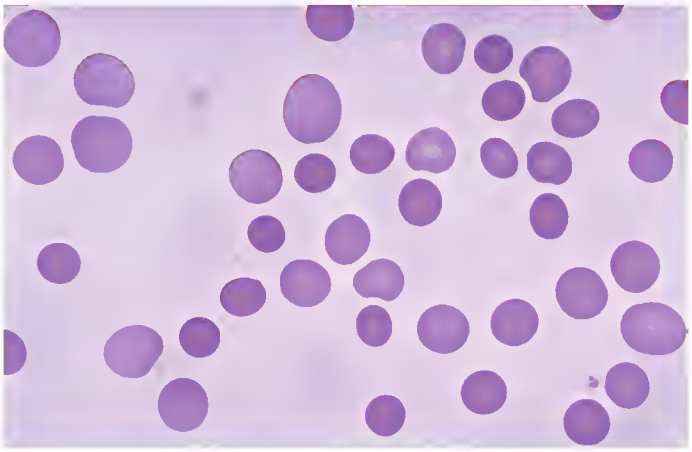


Figure 4: Hereditary spherocytosis.

Clinical Features

Clinical features include moderate anaemia, variable degree of jaundice and splenomegaly. Pigment gall-stones are common and parvovirus B19 induced aplastic crises may cause sudden increase in severity of anaemia. Multiple members from different generations of a given family may be affected. Occasionally, severity of anaemia tends to be different in different members of a given family. Reticulocyte count varies from 10% to 20%. Blood film invariably shows microspherocytes (small dense cells shown in **Figure 4**). Red cell osmotic fragility is increased (**Figure 5**). In some patients, one may need 24-hour incubation at 37°C in order to demonstrate increased osmotic fragility. Auto-haemolysis is increased and is correctable by glucose. Coombs test is negative and radio-labelled chromium studies reveal severity of haemolysis and the dominant role of spleen in the red cell destruction. The treatment is splenectomy which almost always normalises the haemoglobin, even though, microspherocytosis remains. As splenectomy in childhood increases the risk of life-threatening bacterial infections, it is avoided until the age of 5 years or more. Until then, FA should be given regularly. Pneumococcal vaccine is given prior to splenectomy and oral penicillin prophylaxis is given post-splenectomy to avoid sepsis due to encapsulated organisms. Mild cases do not need splenectomy unless gall-stones develop.

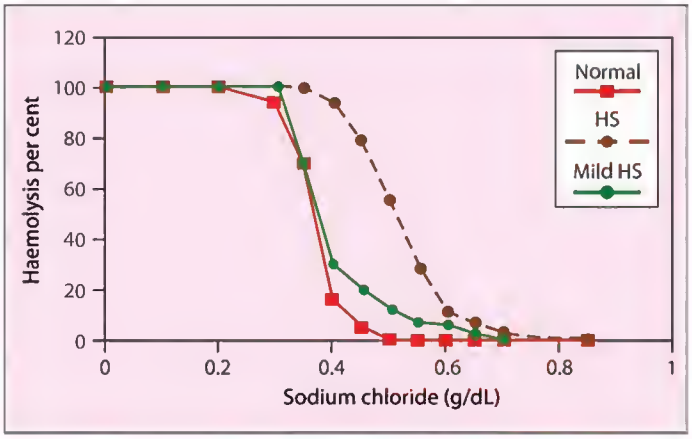


Figure 5: RBC osmotic fragility (Normal, hereditary spherocytosis and mild hereditary spherocytosis).

HS = Hereditary spherocytosis.

Hereditary Elliptocytosis (Ovalocytosis)

Hereditary elliptocytosis has clinical and laboratory features similar to that of hereditary spherocytosis except for the characteristic red cell morphology (**Figure 6**) and overall milder course. Majority of the patients can be left alone. Occasionally, splenectomy is required. Inheritance is autosomal dominant. Occasionally homozygous or doubly heterozygous cases of elliptocytosis may present with a more severe haemolytic anaemia called hereditary pyropoikilocytosis.

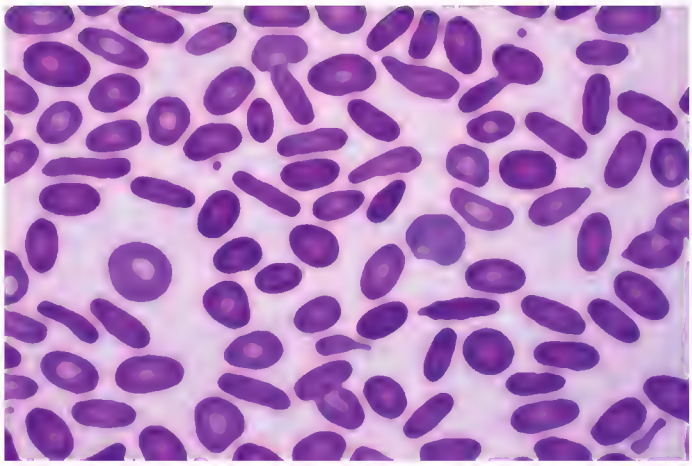


Figure 6: Hereditary elliptocytosis.

Hereditary stomatocytosis (**Figure 7**) and hereditary acanthocytosis (**Figure 8**) are rare RBC membrane disorders.

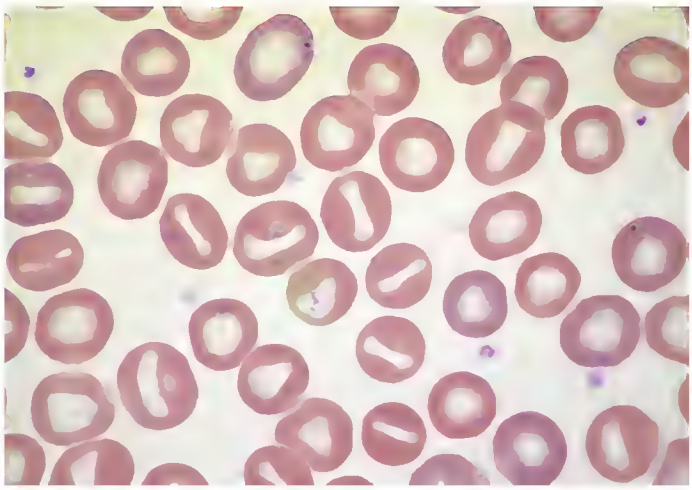


Figure 7: Hereditary stomatocytosis.

ENZYME DEFECTS

G6PD Deficiency

Glucose-6 phosphate dehydrogenase (G6PD) is an enzyme that functions to reduce nicotinamide adenine dinucleotide

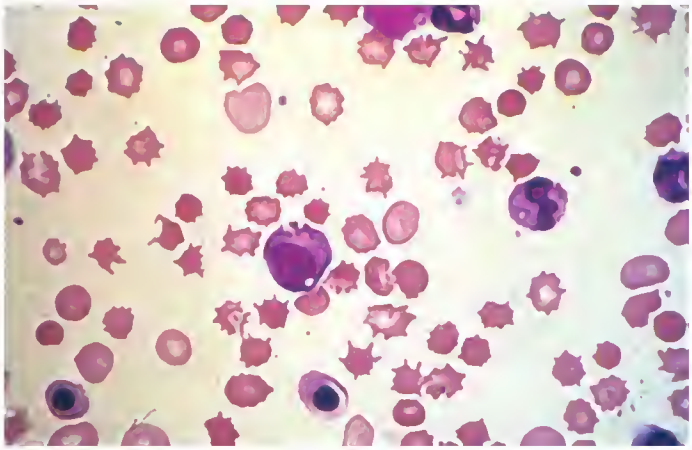


Figure 8: Hereditary acanthocytosis.

phosphate ($NADP^+$) while oxidising glucose-6 phosphate. Various genetic variants of G6PD are known (**Table 7**). The commonest of these are Type A in Africans and B in the rest of the world. In all, over 400 variants of the enzyme have been characterised which show less or more activity than normal. It has been estimated that over 200 million people are deficient in G6PD enzyme. Usually, G6PD deficiency is an asymptomatic entity. The main clinical problems are shown in **Table 8** and they are due to an acute haemolytic crises which occurs in response to an oxidant stress (drugs, infections or fava beans, **Figure 9**). Rarely, neonatal jaundice or even a congenital non-spherocytic haemolytic anaemia can occur.

Table 7: Common G6PD Variants

G6PD Variant	Haemolysis	Prevalence
G6PD A	No: Normal variant	Blacks
G6PD B	No: Normal variant	All
G6PD A-	Yes: Moderate	Blacks
G6PD ^{MED}	Yes: Severe	Whites



Figure 9: Fava beans.

The inheritance is sex-linked. Heterozygote female carriers have approximately half the normal red cell G6PD values and have an advantage of resistance to *Falciparum* malaria. Approximately 1% of Indian males are G6PD deficient. It is more common in Parsees (15%), Bhanushali (11%), Khatri (5%), Punjabi (3%), Kutchi (3%) and Muslims (2.5%). The worldwide distribution shows highest prevalence in the tropical zone chiefly West Africa, the Mediterranean, Middle East and South-East Asia. The deficiency is of variable degree. Most severely affected cases are seen in the Mediterranean countries and in orientals (**Table 7**). Rarely, severe cases also occur in Caucasians. The milder variants have mutations located at the amino-end of the gene, while the severe ones affect the carboxy-end.

Table 8: Clinical Features of G6PD Variants

Clinical Features	G6PD A	G6PD^{MED}
Drug-induced haemolysis	Common	Common
Infection-induced haemolysis	Common	Common
Favism	Non-seen	Common
Neonatal icterus	Rare	Observed
Hereditary non-spherocytic haemolytic anaemia	Not seen	Rare
Degree of anaemia	Moderate	Severe
Chronic haemolysis	Not seen	Rare

Acute haemolytic episodes have sudden onset of severe pallor, icterus and red-coloured urine. Patient may develop renal failure as well as symptoms of hypoxia. Usually, the episodes are self-limiting as the younger red cells have nearly normal G6PD activity. However, in Mediterranean type, the haemolysis may not be self-limiting. It may not be possible to make a definite diagnosis during the acute haemolysis. However, between the crises, the enzyme deficiency can be detected by one of the various screening tests or by direct enzyme assay of red cells. During crisis, the blood film may show contracted and fragmented cells, bite cells and blister cells. Reticulocyte preparation may show Heinz bodies (oxidised denatured haemoglobin, **Figure 10**), particularly if spleen has been removed.

The treatment includes stoppage of the offending drug (**Table 9**), blood transfusion, maintaining high urine output and if required, haemodialysis. If neonatal jaundice is severe, newborns may need phototherapy or even exchange transfusion.

Table 9: Drugs or Chemicals that Cause Haemolysis in Patients with G6PD Deficiency

- Analgesics
  - Acetanilide
- Antimalarials
  - Primaquine
  - Quinine
  - Chloroquine
- Fluoroquinolone
  - Norfloxacin
  - Ciprofloxacin
- Sulphonamides
  - Sulphacetamide
  - Sulphamethoxazole
  - Sulphanilamide
  - Sulphapyridine
  - Sulphasalazine
- Sulphones
  - Dapsone
  - Thiazole sulphone
- Miscellaneous
  - Acetylphenylhydrazine
  - Chloramphenicol
  - Doxorubicin
  - Methylene blue
  - Naldixic acid
  - Napthalene (moth-balls)
  - Niridazole
  - Phenylhydrazine
  - Toluidine blue
  - Trinitrotoluena
  - Vitamin K
  - Vitamin C
  - Nitrofurantoin

Other Red Cell Enzyme Deficiencies

These are listed in **Table 10**. These will not be discussed further because of their rarity.

HAEMOGLOBIN DISORDERS

Thalassaemia Syndrome

The thalassaemia syndrome consists of heterogenous group of inherited anaemias characterised by defective synthesis of one

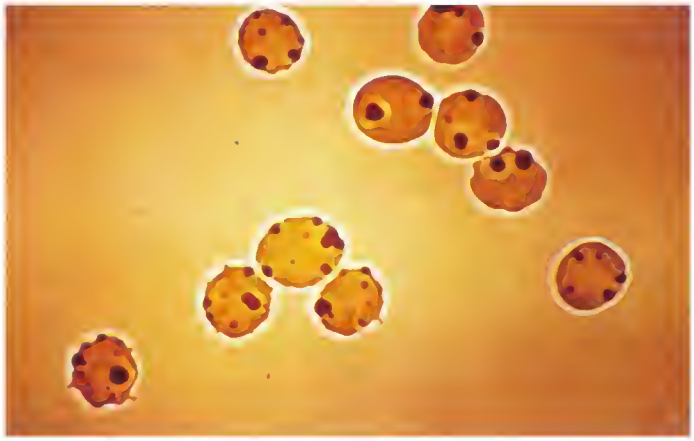


Figure 10: Heinz bodies in G6PD deficiency disorder.

Table 10: Hereditary Haemolytic Anaemias due to Rare Enzymopathies*

Associated with pentose-phosphate pathway deficiencies
Glutathione reductase
γ-glutamyl cysteine synthetase
Glutathione synthetase
Associated with Embden-Meyerhof pathway deficiencies
Pyruvate kinase
Others
Hexokinase
Glucose phosphate isomerase
Phosphofructokinase
Triose phosphate isomerase
Phosphoglycerate kinase aldolase
Associated with abnormalities of nucleotide metabolism
Adenylate kinase deficiency
Pyrimidine 5'-nucleotidase deficiency
Hyperactivity of adenosine deaminase

** Commonest of these is G6PD deficiency which is not listed here.*

or more of the globin-chain subunits of the Hb-tetramer. Taken as a group, the thalassaemia syndrome represents the most common gene disorder known to mankind. These are common in the tropical belt where *Falciparum* malaria has been endemic for Centuries (**Figure 11**). In some parts of the world, these constitute major public health problem. Thalassaemia is a Greek word which means 'the sea (water) in the blood'. Traditionally known as Cooley's anaemia, this disorder was first described in a child of Italian origin by Thomas Cooley, a paediatrician from Philadelphia. It is extremely frequent in the Mediterranean region specially amongst Italians and Greeks. Individual subtypes are named according to the nature of globin chain deficiency. β thalassaemia suggests deficiency of β globin chain, α thalassaemia suggests deficiency of α globin chain and so on. β° thalassaemia suggests total absence of β globin chain products while β^{+} thalassaemia suggests partial reduction. The genes for globin synthesis are located on chromosomes 11 and 16. The abnormalities at chromosomal level range from total deletion, rearrangement to point mutation and over 100 subtypes of molecular defects are known. The thalassaemia belt extends along the shores of the Mediterranean sea and throughout the Arabian Peninsula, Turkey, Iran, India and South-East Asia (**Figure 11**). Gene frequency ranges from 1% to 15%. In India, thalassaemia is prevalent in North-West region, i.e. Punjab, Gujarat, Maharashtra and Karnataka. It is also seen in Bengal and Assam but relatively less common in the Southern states. On an average, 3% of Indians carry the β thalassaemia gene. The highest incidence is found in Lohanas and Sindhis who have migrated from Sindh in Pakistan to many parts of India at the time of partition.

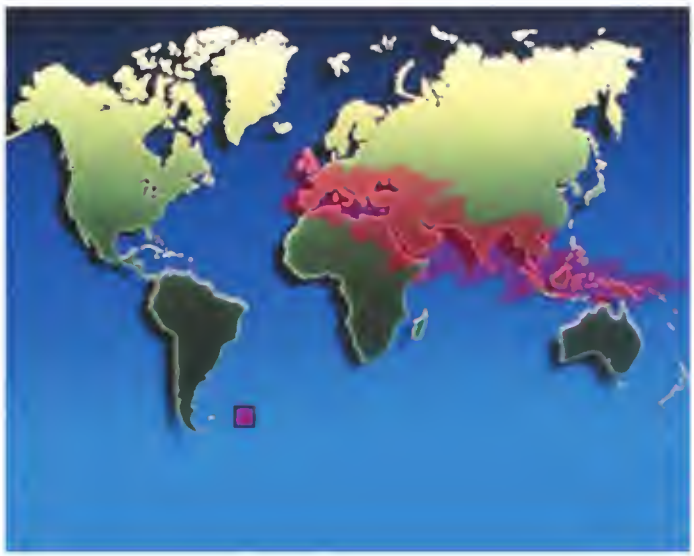


Figure 11: Geographical distribution of thalassaemia and haemoglobinopathies (Pink).

Clinically speaking, three common terms are used which connote the severity of disorder. These terms are thalassaemia major, intermedia and minor. Thalassaemia major is a severe disorder due to inheritance of two β thalassaemic genes (**Figure 12**). Child becomes anaemic within a few months of birth and the anaemia is so severe that regular transfusions are needed for survival. Thalassaemia minor, also known as thalassaemia trait or β thalassaemia heterozygous state is due to a single gene mutation together with a normal β globin gene on the other chromosome. It results in profound hypochromia and microcytosis despite minimal anaemia.

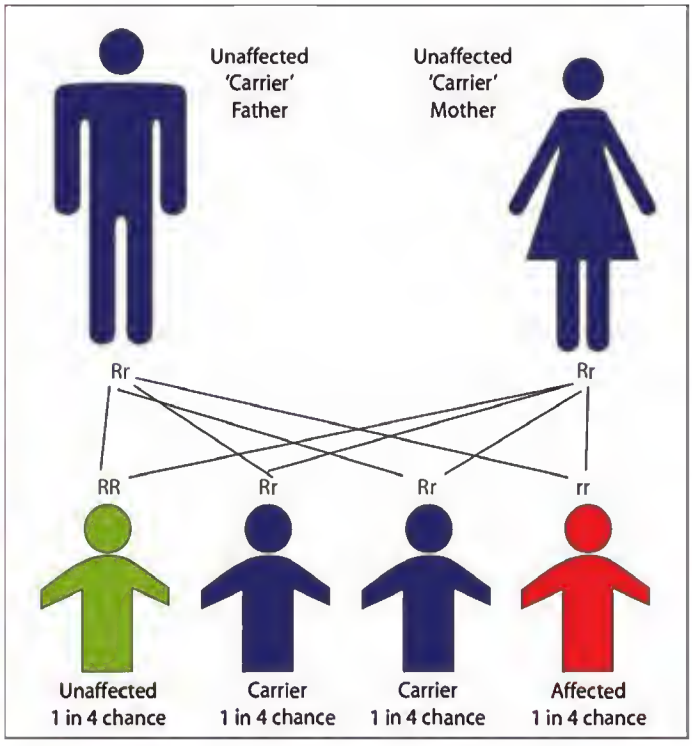


Figure 12: Inheritance of thalassaemia syndrome.

The term thalassaemia intermedia applies to a clinical phenotype where although patient is significantly anaemic, regular periodic blood transfusions are not a must for survival.

Pathophysiologically, the relative excess of the unpaired α globin chains that accumulate produce damage to the membrane of red cells leading to haemolysis. In addition, short-life of RBC precursors in the marrow results in ineffective erythropoiesis.

Clinical Features of Haemoglobin Disorders

Thalassaemia minor is often an incidental diagnosis. It does not produce many symptoms or signs as anaemia is not very significant. There are no overt signs of haemolysis or marrow expansion.

Patients with thalassaemia major develop profound anaemia within first few months of birth (anywhere from the age of 2 months to 2 years). This results in marked anorexia, failure to thrive, frequent infections and growth retardation. This also leads to production of high levels of erythropoietin which in turn causes extensive marrow expansion leading to characteristic chipmunk-facies due to frontal bossing and maxillary marrow hyperplasia. Enlarged spleen and liver lead to protuberant belly. Subsequently, patients develop massive splenomegaly, high output congestive cardiac failure, increased susceptibility to infection and even pathological fractures of long bones and vertebrae due to cortical invasion by erythroid element. Erythropoiesis may be so exuberant that masses of extra-medullary tissues may be formed in the paraspinal region, abdomen, pelvis and even in skull.

Patients of thalassaemia intermedia survive long enough without medication and develop above mentioned features to the maximum extent. Unless transfused, these patients go on to develop hypersplenism, profound increase in the blood requirement, non-healing leg ulcers and gall-stones.

Repeated transfusions in thalassaemia major and enhanced absorption of iron from the gut in thalassaemia intermedia, lead to iron overload with damage to heart, liver, pancreas and other endocrine organs including hypothalamus. Many patients die secondary to iron overload-related cardiomyopathy resulting in cardiac failure or arrhythmia. Absent or delayed puberty, retarded physical growth, diabetes mellitus, hypoparathyroidism and hypothyroidism are the other iron-related problems. Blood transfusions also lead to transmission of viruses and hence chronic liver disease secondary to hepatitis-C or B. Transmission of human immunodeficiency virus (HIV) infection may lead to acquired immune deficiency syndrome (AIDS). Development of RBCs allo-antibodies can lead to difficulty in transfusions.

With the development of modern hypertransfusion therapy and regular chelation, most of the clinical features mentioned above are largely preventable. Nonetheless, in India and many parts of the world, the clinical features mentioned above are common given the irregularity of blood transfusion and high cost of chelation therapy. An untreated child may succumb to anaemia itself during early childhood or even in infancy. Those who receive inadequate chelation, succumb between late second decade and early third decade of life. However, those receiving regular hypertransfusion and effective iron chelation can have near normal survival. Life expectancy and quality of life in thalassaemia minor do not differ from normal individuals. Thalassaemia intermedia on the other hand, has variable severity.

Investigations

Thalassaemia major leads to severe anaemia. Red cell morphology is strikingly abnormal with hypochromia, microcytosis, anisopoikilocytosis, tear drop cells and target cells. Nucleated red cells are abundant, however, reticulocyte count is low (2% to 8%). This is due to severe intra-medullary erythroid destruction. White blood cell count and platelet counts are normal unless hypersplenism develops. Marrow shows marked hypercellularity secondary to normoblastic hyperplasia. The osmotic fragility is significantly reduced, serum iron is increased and iron binding protein is fully saturated.

Normal haemoglobins in healthy adults are shown in **Table 11**. The haemoglobin profile in β° thalassaemia major reveals predominantly Hb-F which is nearly 100%. It may vary from 10% to 90% in β^+ thalassaemia. The red cell survival is diminished as seen with ^{55}Cr tagged studies. RBCs half-life ranges from 6 to 20 days. Radiological changes include striking changes in the skull and facial bones resulting in hot-cross-bun configuration of the skull, widened diploic spaces and the classic hair-on-end appearance. Compression fractures of the vertebrae and marked osteoporosis are common.

Table 11: Normal Haemoglobins in Adults

Haemoglobin Type	Globin Chains	Percentage
Hb-A	$\alpha_2\beta_2$	>95
Hb-A2	$\alpha_2\delta_2$	<3.5
Hb-F	$\alpha_2\gamma_2$	<2.0

Thalassaemia minor is a hypochromic microcytic anaemia where red cell volume distribution width (RDW) is normal and RBC counts are on higher side. Peripheral blood film, besides hypochromia and microcytosis shows target cells (**Figure 13**) and basophilic stippling (**Figure 14**). High performance liquid chromatography (HPLC) and Hb-electrophoresis shows increased HbA_2, usually 3.6% to 7.8%. α thalassaemia (Hb-H) is relatively less common in India. Hb-H disease has clinical features of thalassaemia intermedia. It is characterised by presence of a fast moving Hb-H on electrophoresis and inclusion bodies in red cells as shown in **Figure 15**.

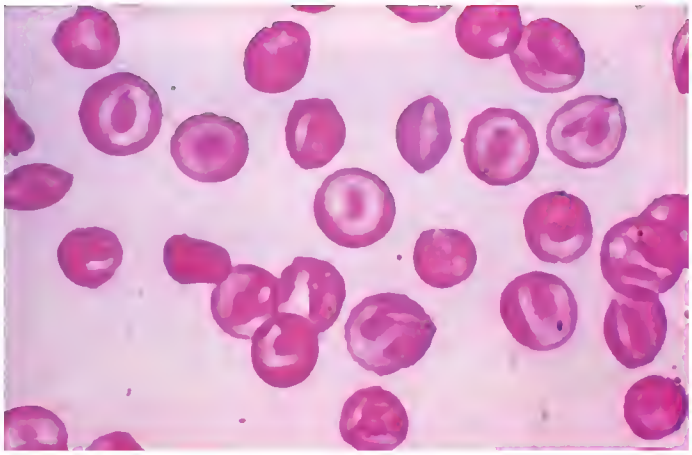


Figure 13: Target cells.

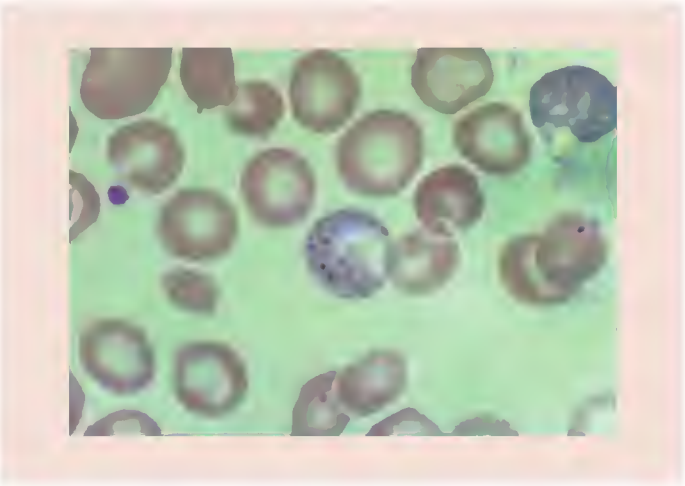


Figure 14: Basophilic stippling.

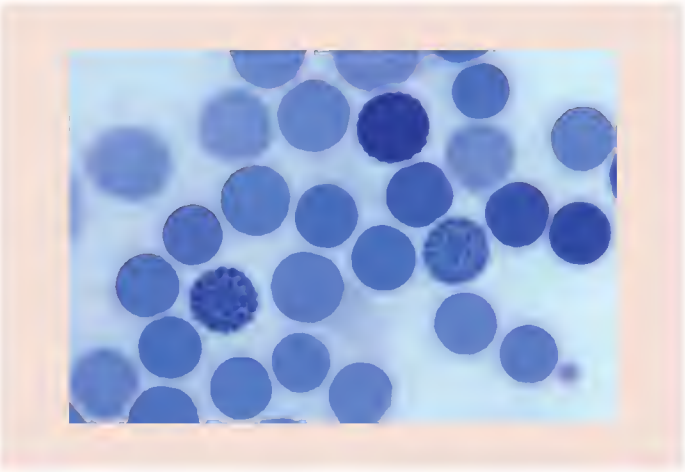


Figure 15: Inclusion bodies in a case of Hb-H disease (α thalassaemia).

Treatment

β thalassaemia major requires treatment with regular transfusions so as to maintain haemoglobin between 10 and 14 g/dL. This relieves symptoms and allows normal growth and development. However, this leads to iron overload (which is inevitable), transmission of viruses (hepatitis-B, hepatitis-C and HIV) and development of RBCs allo-antibodies. Without adequate iron chelation, such patients die during second or third decade of life due to cirrhosis of liver, endocrinopathies (specially diabetes mellitus) and cardiomyopathy. Deferoxamine given subcutaneously using an infusion pump over 8 to 10 hours a day, 5 days a week forms the standard chelation. The dose of deferoxamine is 30-50 mg/kg body weight. This has to be started once 15-20 units of blood transfusions have been given and is continued life-long. It is more effective in removing iron from liver.

Two oral iron chelators already in clinical use are: Deferiprone and Deferasirox. Deferiprone has been around for 2 decades and is superior to deferoxamine in chelating iron from the heart. It is given in the dose of 75 mg/kg per day in divided doses (usually thrice a day). Combination of deferoxamine and deferiprone has also been extensively used. Deferasirox has been recently introduced and it is given in the dose of 20-40 mg/kg per day once daily. It is whole body iron chelator and has slowly replaced the earlier compounds.

Bone marrow transplantation is an alternative. This can cure thalassaemia major provided an human leucocyte antigen-matched donor is available. Umbilical cord stem cell transplantation is another option. Alternative forms of therapy like manipulation of globin gene expression using butyrate and gene therapy are at a research stage.

Thalassaemia minor requires no treatment except genetic counselling, avoidance of inappropriate iron therapy and close monitoring during pregnancy.

Thalassaemia intermedia are most difficult form of thalassaemia to manage. Most of the patients need careful judgment regarding need of blood transfusion, iron chelation and splenectomy. Very often, the problems are complex and decisions controversial.

Prevention is possible through prenatal diagnosis. Using polymerase chain reactin (PCR) amplification of the globin gene, prenatal diagnosis can be carried out on chorionic villous sample or amniotic fluid. Sampling is done around 10th week of pregnancy and diagnosis is available within 3 to 7 days. Pre-implantation diagnosis has also been successful.

SICKLE CELL DISEASE

Sickle cell disease (SCD) is another group of hereditary haemoglobin disorder characterised by transformation of red cells into sickle shape on deoxygenation, it is produced due to single point mutation (**Figures 16 and 17**). The abnormal haemoglobin, Hb-S results from substitution of valine for glutamic acid at the 6th position of the β chain. The SCD includes sickle cell anaemia (homozygous Hb-S disease), sickle cell/β-thalassaemia, sickle cell /Hb-C disease and others. This disorder was first reported in USA in 1910 by James Herric. Typical manifestations of the disease were known to the Africans for Centuries.

Like thalassaemia, the world distribution of sickle cell gene parallels that of *Falciparum* malaria. Eight per cent of American blacks carry the gene for sickle cell trait. The SCD is inherited in an autosomal co-dominant manner.

The pathophysiology of SCD is related to the intra-cellular polymerisation of Hb-S and to the abnormal interaction that sickle erythrocytes have with the vascular endothelium. This process results in anaemia, vaso-occlusive episodes, organ damage and increased susceptibility to infection.

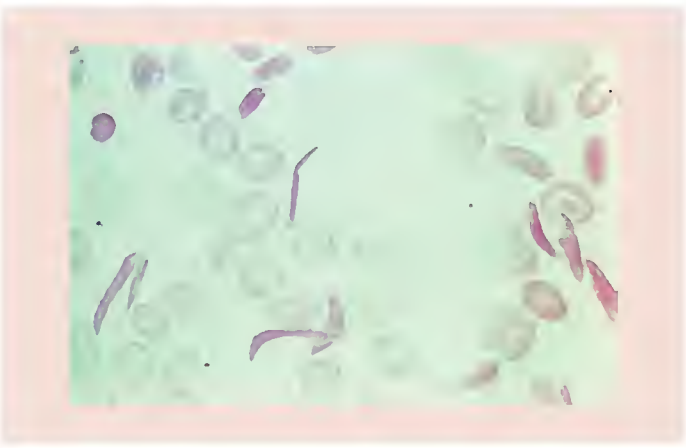


Figure 16: Sickle cells.



Figure 17: Sickle cells (Electron-microscope).

Clinical Manifestations

These include anaemia, pain, infection and damage to organ system. The whole picture is so variable that almost any symptom or sign could form a presenting feature of SCD. Ultimately, these are all related to haemolytic anaemia and vascular occlusion which in turn causes pain, organ dysfunction and organ failure. Growth failure and psycho-social problems are common. Splenic infarcts result in auto-splenectomy leading to frequent life-threatening episodes of septicaemia. Patients suffer from aplastic crisis, splenic sequestration crisis, vascular occlusion and infectious complications. Organ failure particularly related to heart and kidney are more often noted in adults while cerebral complications due to vaso-occlusion (strokes) are more often seen in children. Mortality of this disease is 10% to 20% in the first decade of life. Certain patients with SCD have very mild course or no problems at all. This is often due to the presence of high amount of Hb-F which interferes with polymerisation. The same situation can be seen if gene for a thalassaemia or hereditary persistence of Hb-F is co-inherited.

Painful crisis

Vaso-occlusion leading to pain is the commonest cause of debilitation in Hb-S disease. Acute onset of pain is referred to as a 'crisis'. Many children develop 'hand-foot' syndrome. It can also affect chest, abdomen and long bones especially in the juxta-articular position. This pain may last for 2 to 6 days.

Anaemia

Essentially a haemolytic process, anaemia of SCD can be correlated with intra-cellular polymer content. Infections especially parvovirus B19 can lead to profound drop in haemoglobin by producing red cell aplasia. This is called 'aplastic crisis' and is usually self-limited.

Another crisis known as 'megaloblastic crisis' is due to inadequate folate levels in the body. FA requirement is higher in haemolytic anaemia and this factor is responsible for severe anaemia in patients who are nutritionally weak. Haemolytic crises (rapidly accelerated haemolysis) can occur, especially, if patient has associated G6PD deficiency.

Splenic sequestration crisis is usually seen under the age of 2 years. The spleen rapidly enlarges (within hours) and most of the circulating red cell mass becomes sequestrated. This can recur and hence if severe, splenectomy is indicated. Milder cases can be managed with blood transfusions and careful observation.

Infections

Several abnormalities make these patients immune-compromised. Absent splenic function leads to infections with the encapsulated organisms, e.g. *Streptococcus pneumoniae* and *Haemophilus influenzae*. Pneumococcal infections can result in death within hours. Other immunological abnormalities are less well defined. Elderly patients are prone to get gram-negative infections due to *Escherichia coli* affecting urinary tract and this can even go into septicaemia. Osteomyelitis is common and besides *Staphylococcus aureus, Salmonella typhimurium* are the other common organisms. This is due to ability of these bacteria to flourish in partially necrosed bone.

Complications Affecting Organ Systems

Cardiovascular system

Anaemia leading to myocardial ischaemia, vaso-occlusive phenomenon causing myocardial infarction and repeated blood transfusions leading to restrictive cardiomyopathy secondary to iron overload can all occur in SCD.

Pulmonary system

Pulmonary manifestations are due to vaso-occlusion, infections or both. A typical clinical presentation called "acute chest syndrome" consists of sudden onset of chest pain and a local infiltrate on the chest radiograph which can be either due to infection or infarction. This affects 30% of patients and it can be life-threatening.

Central nervous system

Neurologic complications affect 25% of patients. These include transient ischaemic attacks, strokes and cerebral haemorrhage. Strokes are common in the first decade of life while haemorrhages occur in adults. Treatment includes red cell transfusion which may continue until the age of 5 years. This is to keep haemoglobin-S percentage below 30%. However, chronic transfusion therapy has its own hazards.

Hepato-biliary system

Gall-stones, recurrent abdominal pain due to vaso-occlusive crisis, hepatomegaly and hepatic dysfunction are all common. Like splenic sequestration crisis, patients may get hepatic sequestration crises as well.

Reproductive system

Placental infarcts can lead to intra-uterine growth retardation and low birth-weight babies. The frequency of spontaneous abortion is increased. Prophylactic transfusions do not help.

Urinary system

Kidney is a major target organ. Haematuria, hyposthenuria, abnormal acid load test, increased urinary tract infection,

hyperuricaemia and gout are all common. Renal failure is common in the elderly.

Ocular complications

Retina is an important vulnerable target for sickling. Proliferative retinopathy is commonly seen in SCD.

Orthopaedic

Besides hand-foot syndrome, patients can develop avascular necrosis of the hip. Osteomyelitis has been discussed earlier. Skin ulcers around the ankle may develop.

Treatment

This can be divided into 3 stages. General care, management of specific complications which include management of infections, blood transfusions, pain management and the newer therapeutic modalities.

General care

This includes treatment to relieve pain, prevention of dehydration, treatment of fever and psycho-social support. Dietary advice includes adequate calorie intake, adequate folic acid, vitamin-C, vitamin-E and zinc supplement.

Management of specific complications

Infections: These include prophylactic penicillin, immunisation to prevent infections and evaluation and treatment of the febrile episodes.

Pneumococcal vaccination at the age of 18 months followed by boosters every 5 years are recommended. Immunisation against *H. influenzae* is suggested by the age of 18 months. *Hepatitis-B* vaccination is also a must.

Transfusions: Transfusions are associated with 3 important problems, e.g. transmission of viral diseases, iron overload and allo-immunisation. Although, these can be used to treat each and every complications of SCD, their value has been demonstrated for only a few of them. Chronic transfusion therapy has been used with a reasoning that suppression of Hb-S would lead to decreased vaso-occlusive episodes. Even exchange-transfusions have been carried out.

Pain: This is the most frequent requirement of a patient with SCD. The guidelines include aggressive use of appropriate analgesics, ensuring fluid supplement and looking for the aetiology, especially the cause of infection.

Newer therapeutic modalities

Many chemical agents have been developed which may act as anti-sickling agents. None of them have been of any great therapeutic benefit. The most promising agent is hydroxyurea which has the ability to induce foetal haemoglobin synthesis. This has become the standard-of-care today. It decreases the number of vaso-occlusive episodes. The usual dose is 20 mg/kg per day. Extensive research, both in adults and children, has shown very satisfactory results with respect to marked freedom from painful crises, preservation of organ function and projected increase in the life-span. The drug is contraindicated during pregnancy. Co-administration of other haematopoietic agents, such as erythropoietin or butyric acid may also be useful.

Bone marrow transplantation has been carried out in patients with a total cure rate of 70% to 80%. However, only 35% of patients would have immunologically compatible donors and one must also consider the risk-benefit issue. Gene therapy may become applicable to SCD.

Prenatal diagnosis by chorionic villous biopsy is possible. Unfortunately, DNA analysis does not predict the clinical severity and many do not consider SCD as a serious enough problem for pregnancy to be terminated.

HAEMOGLOBIN-E DISORDERS

A mutation producing an amino-acid substitution β26Gu → Lys in haemoglobin molecule produces Hb-E. This mutation can be present in heterozygous, homozygous and Hb-E-β thalassaemia compound form. It is the commonest hereditary haemoglobin disorder in the eastern parts of India (Bengal and Assam). The Hb-E is characterised by mild anaemia even in homozygous individuals. However, HbE-β thalassaemia (double heterozygous state) produces severe manifestations like severe anaemia, splenomegaly and jaundice.

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15.7 Acquired Haemolytic Anaemia

Farah F Jijina

INTRODUCTION

Haemolytic anaemias may be congenital or acquired. Acquired haemolytic anaemias are generally due to extra-corpuscular (extrinsic) defects, the only exception being paroxysmal nocturnal haemoglobinuria, where the defect is intrinsic. Common clinical features of acquired haemolytic anaemia are a rapid fall of haemoglobin and increased reticulocyte counts in the absence of bleeding, repeated attacks of jaundice with unconjugated hyperbilirubinaemia, dark urine due to oxidation of urobilinogen or haemoglobinuria and splenomegaly. Features of chronic haemolysis, such as gall-stones, skeletal changes, leg ulcers, or moderate or massive splenomegaly are mainly seen in inherited haemolytic anaemia, but may be seen in acquired haemolytic anaemia if it is long standing. **Table 1** gives a simple classification of the common acquired haemolytic anaemias. For immune haemolytic anaemia, any precipitating cause should be removed and steroids or other immunosuppressives may be required. For the non-immune haemolytic anaemias, an urgent correction for treatable causes like malaria or toxic chemicals may be life-saving.

Table 1: Classification of Acquired Haemolytic Anaemias

- **Immune mechanisms**
  - Autoimmune haemolytic anaemia
    - Cold antibodies
    - Warm antibodies
    - Mixed antibodies
  - Allo-immune haemolytic anaemia
    - Haemolytic disease of the newborn
    - Incompatible blood transfusion
- **Non-immune mechanisms**
  - Mechanical
    - Macroangiopathic haemolytic anaemia
    - Microangiopathic haemolytic anaemia
    - March haemoglobinuria
  - Chemicals
  - Biological
    - Infections
  - Heat
    - Burns
  - Osmotic
  - Miscellaneous
    - Paroxysmal nocturnal haemoglobinuria

AUTOIMMUNE HAEMOLYTIC ANAEMIA (AIHA)

AIHA occurs when a patient produces pathologic antibodies that attach to, and destroy red blood cells (RBCs), causing anaemia. These are classified into two types, according to the temperature at which the antibodies are active as: (a) warm active antibodies, and (b) cold active antibodies. Occasional patients may have both types of antibodies (**Table 2**).

Warm Active Antibodies

Auto-antibodies with the greatest activity at 37°C are responsible for 70% patients of AIHA. It may be idiopathic or secondary to an underlying disorder. A small subgroup of patients with idiopathic AIHA may also develop immune thrombocytopaenia. This condition is known as Evan's syndrome and is usually associated with a higher incidence of an underlying illness, such as systemic lupus erythematosus (SLE). Many disorders may be associated with warm AIHA (**Table 3**).

Table 2: Autoimmune Haemolytic Anaemias

- **Warm active antibodies**
  - Idiopathic
  - Secondary
    - Lymphomas, CLL, SLE, APLA syndrome, drugs,
    - Haematopoietic stem cell transplantation
    - Solid organ transplantation
    - Allogeneic red blood cell transfusions
- **Cold active antibodies**
  - Cold agglutinin disease
    - Primary
    - Secondary
  - Paroxysmal cold haemoglobinuria
    - Primary
    - Secondary
- **Mixed cold and warm antibody type**

CLL = Chronic lymphocytic leukoemio; SLE = Systemic lupus erythemotosus; APLA = Antiphospholipid ontigen.

Table 3: Diseases Associated with Warm Active Antibodies

- Auto-immune disorders
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Scleroderma
  - Ulcerative colitis
- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Multiple myeloma
- Thymoma
- Waldenström macroglobulinaemia
- Teratoma
- Acquired immunodeficiency syndrome
- Drugs: Methyldopa

Pathophysiology

The antibody is usually an immunoglobulin (Ig) antibody which may or may not fix complement. It is a pan-agglutinin and reacts with the red cell Rh antigen complex. The red cells coated with the Ig are then removed from the circulation by the spleen or portions of the cell membrane may be snagged by the macrophages, the remainder of the cell escaping and resealing to produce a spherocyte.

Clinical features

The clinical presentation may vary from mild to fulminant haemolysis. Idiopathic AIHA, can occur at any age, has no racial predilection and is more common in females.

Laboratory investigations

The classical feature on peripheral smear is the presence of microspherocytes. Other non-specific features of haemolytic anaemia, such as polychromasia, macrocytosis and nucleated red cells are also present. Occasionally erythrophagocytosis and agglutination may be seen. A persistently raised reticulocyte count is a typical finding in warm AIHA, but reticulocytopaenia may be rarely seen. Possible mechanisms for reticulocytopaenia include marrow shutdown from intervening infection, malignancy, parvovirus B19 infection, depleted vitamin B12/folic acid (FA) stores, or the autoantibody being directed at antigens on the reticulocytes.

Direct anti-globulin test (also called Coombs' test)

The direct antiglobulin test (DAT) is used to determine if red cells have been coated *in vivo* with Ig, complement, or both (**Figure 1**). A positive test demonstrates *in vivo* attachment of antibodies to red cells. It is positive in 95% of warm AIHA.

Indirect anti-globulin test (or indirect Coombs' test)

In indirect Coombs' test, patient's serum suspected of containing an antibody is incubated with normal red cells, which are then washed to remove unbound globulins. Agglutination that occurs when anti-human gammaglobulin is added indicates that autoantibody was present in the patient's serum. The indirect anti-globulin test is positive in 80% of patients of warm AIHA.

Coombs' negative AIHA

In 2% to 6% of patients, who present with clinical and haematological features of AIHA, may have a negative test for

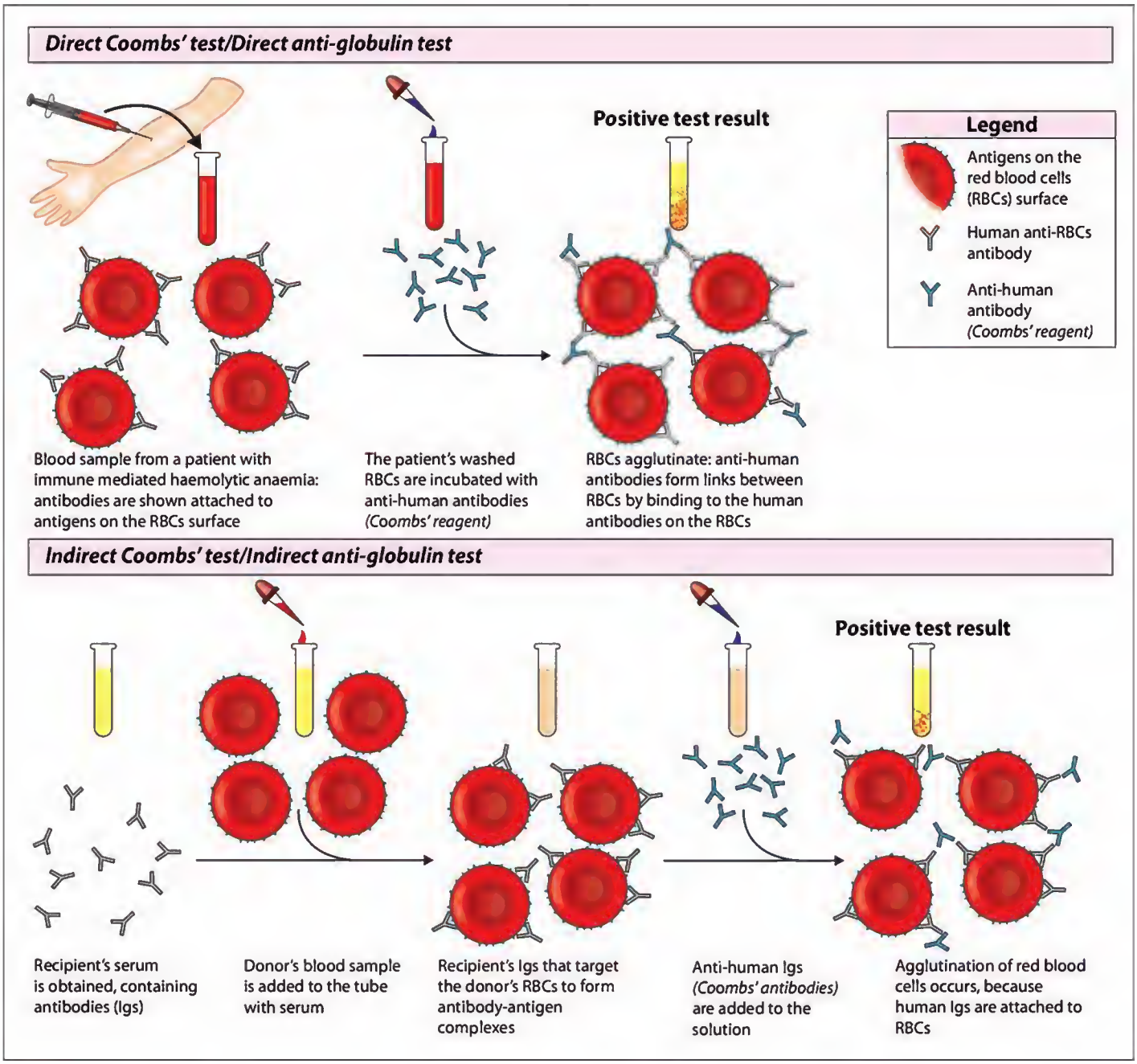


Figure 1: Direct and indirect Coombs' test.

technical reasons, presence of IgA autoantibodies or low affinity IgG autoantibodies.

Treatment

All patients of haemolytic anaemia need to be on FA supplements. In idiopathic warm AIHA, the initial treatment of choice is steroids, usually prednisolone, 1-1.5 mg/kg per day for a period of 4 to 6 weeks, followed by a gradual reduction. A response is seen within 7 days in 80% of patients, though patients often relapse on reducing the dose. Thus, only about 20% to 30% of treated patients achieve sustained complete remission. If there has been no response after 3 weeks of therapy, patient may be considered a steroid treatment failure.

Spleen is the major site of RBC sequestration and destruction and is also believed to be a major producer of IgG antibodies. Indications for splenectomy in AIHA include failure to respond to steroids or steroid dependency. About 50% to 60% of patients will respond to splenectomy; late relapses may occur.

Rituximab is a genetically engineered chimeric murine/human monoclonal anti-CD-20 antibody which targets B-cell precursors and mature B-cells. It is often used as second line therapy after steroid failure, especially when splenectomy is not possible. Rituximab has induced complete remissions in 30% to 50% patients with refractory warm AIHA. Other therapies include immunosuppressive drugs, such as azathioprine, cyclophosphamide and cyclosporine. Danazol may be useful.

Cold Active Antibodies

There are two clinical syndromes.

1. ***Cold agglutinin disease***

   This is caused by a pathologic IgM antibody directed against the red cell I antigen, is usually seen in adults and can be primary or secondary. Cold agglutinins usually attach to the red cell in the cooler peripheral circulation. As the blood proceeds back to the warmer central circulation, the antibody dissociates from the cell only to attack another unsuspecting red cell and begin the process again.

   The primary cold agglutinin disease occurs in older patients around 70 years of age. It is caused by a monoclonal IgM kappa antibody. Secondary cold agglutinin disease occurs in patients with Waldenström's macroglobulinaemia or other B-cell neoplasms and may also be seen in young patients after *Mycoplasma pneumoniae* or infectious mononucleosis. Most patients will present with features of a mild chronic haemolytic anaemia, with exacerbations in winter. Acrocyanosis can occur due to agglutinin of cells in the cooler vessels of the hands, nose, ears and feet. Few patients may have a mild hepatosplenomegaly. The peripheral smear shows agglutinin of red cells and rarely spherocytes.

   Treatment: Most patients with primary cold agglutinin disease do not require any specific treatment apart from avoiding cold temperatures. In severe cases, immunosuppressive therapy with cyclophosphamide or chlorambucil may be tried. Steroids are usually ineffective.

   Secondary cold agglutinin disease associated with infections, the course is transient and requires only supportive therapy (**Table 4**). For cold agglutinin disease associated with malignancy, effective treatment with chemotherapy is required.

2. ***Paroxysmal cold haemoglobinuria***

   In paroxysmal cold haemoglobinuria an antibody binds to the red cell at low temperature and fixes complement. When the cells are warmed, the complement cascade binds and disrupts the red cell membrane producing lysis. Patients may have a dramatic presentation with sudden onset of fever, back leg pain and haemoglobinuria after any exposure to cold. The episodes are generally self-limited. Attacks may be associated with measles, vaccinations, mumps, *M. pneumoniae*, influenza, cytomegalovirus (CMV) infections.

Table 4: Common Causes of Secondary Cold Agglutinin Disease

Neoplasms	Infections
Lymphomas	*Mycoplasma pneumoniae*
Waldenström macroglobulinaemia	Epstein-Barr virus
Chronic lymphocytic leukaemia	Cytomegalovirus
Kaposi's sarcoma	Adenovirus
Myeloma	Encephalitis
Non-haematological malignancies	Influenza viruses
	Rubella
	Varicella
	Human immunodeficiency virus (HIV)
	Mumps
Others	*Escherichia coli*
	Bacterial endocarditis
Autoimmune diseases	Syphilis
	Malaria

Drug and Chemical Induced Haemolytic Anaemia

Haemolytic anaemia may develop as a result of exposure to a variety of chemicals and drugs. There are two general mechanisms by which drugs and chemicals bring about haemolysis. The drug or chemical may directly interfere with the metabolic process of the red cell, e.g. G6PD deficiency. These aspects are covered in inherited haemolytic anaemia. Other agents can bring about oxidative denaturation of haemoglobin, leading to sequential formation of methaemoglobin, sulphaemoglobin and Heinz bodies. Certain chemicals and drugs like copper can produce haemolytic anaemia by non-oxidant mechanisms.

Drugs can also cause an immune reaction. Antibodies are formed against the drug and the red cells become damaged as a result of the drug antibody interaction or the presence of the drug may facilitate the development of red cell auto-antibodies. The most common drugs implicated now are cefotetan, ceftriaxone, and piperacillin (**Table 5**).

Haemolytic Anaemia Caused by Animal Venoms

Haemolysis may be caused by the venom of snakes, bees, wasps and spiders; however, most of these are rare. Snake venom, especially of the viper and cobra haemolyse red cells *in vitro*.

Haemolytic Anaemia Caused by Infections

Red cells may appear to be injured directly by various infections. Of these the commonest in our country is malaria. Most of the haemolytic manifestations of malaria are related to the invasion

of the erythrocyte by the organism, leading to destruction of the red cells. However, some cases of *Plasmodium falciparum* infections, may develop an acute intravascular haemolysis due to an autoimmune reaction.

Other infections that lead to haemolytic anaemia are infections by protozoa *Babesia*, trypanosomiasis, and visceral leishmaniasis. Profound fatal haemolytic anaemia can occur in clostridial sepsis with severe intravascular erythrocyte destruction.

Table 5: Drugs and Chemicals Causing Haemolytic Anaemia

Drugs and chemicals causing haemolytic anaemia by direct toxicity

- Acetylphenylhydrazine
- Arsine
- Chloramines
- Copper
- Formaldehyde
- Naphthalene
- Para-aminosalicylic acid
- Phenacetin
- Phenazopyridine
- Phenylhydrazine
- Potassium chlorate
- Resorcinol
- Sodium chlorate
- Sulphanilamide
- Sulphapyridine
- Sulphasalazine
- Sulphones

Drugs and chemicals causing haemolytic anaemia in G6PD deficiency

Analgesics
- Acetanilide

Antimalarials
- Pamaquin
- Pentaquine
- Primaquine

Nitrofurans
- Nitrofurantoin

Sulphonamides

Dapsone

Miscellaneous
- Acetylphenylhydrazine
- Methylene blue
- Nalidixic acid
- Naphthalene balls
- Phenylhydrazine
- Toluidine blue
- Trinitrotoluene

Drugs and chemicals causing haemolytic anaemia by immune mechanism

- Amidopyrine
- Cephalosporins
- Chlorpromazine
- Chlorpropamide
- Cisplatin
- Dipyrone teniposide
- Methyldopa
- Penicillin
- Piperacillin
- Quinine
- Rifampicin
- Sulphasalazine
- Stibophen
- Sulphonamides
- Teniposide
- Tetracycline

PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder brought about by a somatic mutation of the PIG – A gene situated on the X chromosome. Normal red cells are protected against complement-mediated lysis by a protein called the membrane inhibitor of reactive lysis or CD59. PNH cells are deficient in this protein.

Clinical Manifestations

The disease, usually begins insidiously, has a prolonged course and can vary from the mild to very severe. The classical presentation is characterised by attacks of intra-vascular haemolysis and nocturnal haemoglobinuria along with other symptoms of chronic haemolysis, leucopaenia and thrombocytopaenia. Haemoglobinuria is seen in 80% of PNH patients at sometime during the course of their illness and is classically nocturnal but the cause of the nocturnal occurrence is not well understood. It is hypothesised that retention of carbon dioxide in sleep causes a slight fall in plasma pH sufficient to activate the alternate pathway of complement. Exacerbations of haemolysis may be precipitated by infections or inflammations. Other features are aplastic anaemia, and intra-vascular thrombosis, especially at unusual sites in the venous circulation. The diagnosis of PNH was made in the past, by a positive Ham's acidified serum lysis test and a sucrose lysis test. However, now with the availability of monoclonal antibodies and flow cytometry, red cells and granulocytes are analysed, using monoclonal antibodies to the GPI-anchored proteins CD55 (DAF) and CD59 and these are absent in PNH cells. The latest test, not routinely available, is the fluorescein-labelled proaerolysin variant, 5-fluorescent *aer*olysin (FLAER) test.

Treatment

Most patients of classical haemolytic PNH are treated with prednisolone 1 mg/kg per day for a period of 2 to 4 weeks, to control the haemolysis. Steroids are gradually tapered depending on the response of the patient. Danazol can also be effective in some patients and is often used along with steroids. Supportive therapy is important, including the replacement of iron and FA, and the administration of red blood cell transfusions if clinically required. The latest treatment consists of eculizumab (a monoclonal antibody against complement component C5) which is very effective in controlling haemolytic episodes of classical PNH. It has been shown to decrease the need for transfusions, decrease paroxysms, decrease thrombotic complications and improve quality of life in patients with classical PNH. The disease has a median survival of 10 to 15 years. Major cause of morbidity and mortality is due to thrombosis, bleeding and infections. Haematopoietic stem cell transplantation is the only definitive treatment for PNH. Due to the inherent morbidity and mortality of transplantation, it is only indicated in severe cases of PNH, such as those with thrombotic episodes, severe haemolysis and aplastic PNH. The overall cure rates are about 50%.

RED CELL FRAGMENTATION SYNDROMES

In certain disorders, red cells may undergo premature fragmentation and lysis leading to significant intra-vascular haemolysis. These may be divided into two major groups:

1. Macroangiopathic haemolytic anaemia associated with abnormalities of the heart and great vessels. In this condition, turbulence over narrow vessels or prosthesis valves causes intra-vascular haemolysis.
2. Microangiopathic haemolytic anaemia (MAHA) develops either as a result of diffuse deposition of fibrin in the micro-vasculature or when the vessels become narrow, rough and rigid. The classical example is thrombotic thrombocytopaenic purpura (TTP). In TTP there is MAHA, thrombocytopaenia, neurologic abnormalities, renal abnormalities and fever. The haemolytic uraemic syndrome is a disorder closely related to TTP but is localised mainly to the vascular endothelium of the kidneys. The mainstay of the treatment of this symptom complex is plasma exchange and response is variable. Other modalities of treatment such as steroids, aspirin, immunosuppressive agents, and vincristine have been tried, but their efficacy is unclear (**Tables 6 and 7**).

Table 6: Causes of Macro-Angiopathic Haemolytic Anaemias

Valvular prosthesis: Synthetic, homografts, xenografts
Valvoplasties
Valvular disease
Intra-cardiac patch repairs
Coarctation of aorta

Table 7: Causes of Micro-Angiopathic Haemolytic Anaemias

Disseminated intra-vascular coagulation
Disseminated malignancies
Chemotherapy
Malignant hypertension
Vasculitis: systemic lupus erythematosus, polyarteritis nodosa
Thrombotic thrombocytopaenic purpura
Haemolytic uraemic syndrome
Giant haemangioma
Drugs like cyclosporin
HELLP syndrome

Haemolytic anaemias are a group of diverse disorders which may be hereditary or acquired. Another differentiating features to be decided is whether there is intra-vascular/extra-vascular haemolysis. History and examination of peripheral smear are very important supplemented by a battery of other tests to establish the diagnosis.

Once the diagnosis is established the treatment of precipitating factors, supportive treatment and therapy with steroids and immunosuppressive may be instituted.

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15.8 Aplastic Anaemia

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INTRODUCTION

Aplastic anaemia (AA) is defined as the presence of pancytopaenia with hypocellular marrow in which normal haemopoietic marrow is replaced by fat cells. AA is a life-threatening bone marrow failure disorder, if untreated, is associated with very high mortality.

EPIDEMIOLOGY

In Europe and USA, the incidence is about 2 to 3 per million of the population per year. It is 2- to 3-fold more common in Asia than in Europe. AA has been identified as a disease of the young and shows a biphasic age distribution between 15 and 25 years or after the age of 60 years, with a trough in middle life. It is commoner in males.

DEFINITION

Aplastic anaemia is defined as pancytopaenia with a hypocellular bone marrow without infiltration or fibrosis. To diagnose AA at least two of the following must be present: (i) haemoglobin less than 10 g/dL, (ii) platelet count less than 50,000/μL, and (iii) neutrophil count less than 1,500/μL (International Agranulocytosis and Aplastic Anaemia Study Group, 1987).

AETIOLOGY

Aetiologic classification of AA is shown in **Table 1**.

Table 1: Aetiologic Classification of Aplastic Anaemia

Hereditary
- Fanconi's anaemia
- Dyskeratosis congenita
- Shwachman-Diamond syndrome
- Other rare syndromes: reticular dysgenesis, etc.

Acquired
- Idiopathic
- Drugs
  - Cytotoxic drugs used in cancer chemotherapy, chloramphenicol phenylbutazone, indomethacin, diclofenac, chloroquine, ticlopidine, gold, hydantoins, etc.
- Paroxysmal nocturnal haemoglobinuria (PNH)
- Toxins: benzene, chlorinated hydrocarbons, organophosphates
- Viruses: Epstein-Barr virus (EBv), non-A, non-B, non-C, non-E hepatitis virus, human immunodeficiency virus
- Connective tissue disorders: eosinophilic fasciitis, immune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus.
- Pregnancy
- Iatrogenic: radiation, cytotoxic drug therapy.

PATHOGENESIS

The pathogenesis of AA remains unclear, but an immune-mediated mechanism appears to be important. There is debate about whether the primary defect is in the haemopoietic stem cell itself or is the result of environmental factors, particularly immunological attack, on the cell. There is evidence of both quantitative and qualitative stem cell defects in AA and increased apoptosis of remaining early haemopoietic progenitor cells (HPC). Not only do cytotoxic suppressor T-lymphocytes release cytokines, such as interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α), those are inhibitory to HPC, but TNF-α also upregulates Fas antigen expression on CD34+ cells, which may be one of the possible mechanisms for the reduced survival of AA marrow progenitor cells. However, the most persuasive evidence for the autoimmune pathogenesis for AA remains the clinical response to anti-lymphocyte globulin (ALG) in about two-thirds of patients.

Telomere shortening is also seen in some patients with acquired AA. These patients show increased terminal restriction fragments (TRF) loss in leucocytes compared with age-matched controls, and the extent of the loss correlates with the duration of the disease. Mutations in the genes for telomerase, telomerase ribonucleic acid (RNA) gene and telomerase reverse transcriptase (TERT) have also been described in patients of AA.

CLINICAL PRESENTATION

AA patients seek medical attention for symptoms that occur as a result of low blood counts. Symptomatic anaemia results from the decrease in red cells, bleeding symptoms secondary to thrombocytopaenia and infections result from neutropaenia.

Physical examination is generally unremarkable, except for evidence of anaemia, cutaneous or mucosal bleeds. Lymphadenopathy and splenomegaly are not the features of AA; such findings suggest an alternative diagnosis, such as leukaemia or lymphoma.

DIAGNOSIS

Investigations for the diagnosis of AA are presented in **Table 2**. Patients with AA have varying degrees of pancytopaenia. The reticulocyte count is usually less than 1.0% despite high levels of erythropoietin. Marrow aspiration and biopsy are essential to confirm the diagnosis of AA. Marrow aspirate typically contains numerous spicules with empty, fat-filled spaces and relatively few haematopoietic cells with prominence of lymphocytes, plasma cells, macrophages, and mast cells with paucity of myeloid precursor and megakaryocytes. Marrow biopsy is essential to confirm the overall hypocellularity. The assessment of disease severity is important in treatment decisions and has prognostic significance. The severity of the disease is graded according to the blood counts and bone marrow findings as summarised in **Table 3**.

DIFFERENTIAL DIAGNOSIS OF PANCYTOPAENIA

Any disease that can present with pancytopaenia may mimic AA, if only the blood counts are considered. Differential diagnosis of pancytopaenia with hypocellular bone marrow is shown in **Table 4**.

Table 2: Investigations Required for the Diagnosis of Aplastic Anaemia

Full blood count, reticulocyte count
Blood film examination
Hb-F% in children
Bone marrow aspirates and trephine biopsy, including cytogenetics
Stress cytogenetics to exclude Fanconi's anaemia, if the age is <35 years
Ham test and/or flow cytometry for phosphatidylinositol glycan (PIG)-anchored proteins (CD55 and CD59) from red blood cells or granulocyte
Urine haemosiderin if Ham test positive or PIG-anchored protein deficiency
Vitamin B12 and folate level
Liver function tests
Viral studies: hepatitis A, B, C; Epstein-Barr virus; cytomegalovirus; human immunodeficiency virus
Anti-nuclear antibody and anti-dsDNA
Chest radiograph
Abdominal ultrasound
Direct and indirect Coomb's test to rule out immune cytopaenia

Table 3: Definition of Severity of Aplastic Anaemia (AA)

Severe AA (Camitta *et al*, 1976)
Bone marrow cellularity <25%, or 25% to 50% with <30% residual haemopoietic cells
Two out of three of the following
Neutrophils <500/μL
Platelets <20,000/μL
Reticulocytes <20,000/μL
Very severe AA (Bacigalupo *et al*, 1988)
As for severe AA but neutrophils <200/μL

Table 4: Differential Diagnosis of Pancytopaenia with Hypocellular Bone Marrow

Inherited and acquired aplastic anaemia
Hypocellular myelodysplasia syndromes
Rare aleukaemic leukaemia (acute myelogenous leukaemia)
Some acute lymphoblastic leukaemias
Some lymphomas of bone marrow
PNH
Myelofibrosis
Systemic lupus erythematosus
Hairy cell leukaemia
T-cell large granular lymphocyte disease
Tuberculosis, histoplasmosis, HIV, EBV
Drugs or toxin

TREATMENT

Supportive Care

AA should be considered a medical emergency. Many patients die due to grave consequences of severe pancytopaenia. AA can be cured by immunosuppressive therapy and by bone marrow transplantation. Androgens and haematopoietic growth factors have secondary roles, other modalities are discussed as under:

1. ***Transfusion support***

   Support with red cell and platelet transfusions is essential for patients with AA to maintain a safe blood count. Blood products from close relatives (who share histocompatability antigens) should be avoided. In the presence of bleeding manifestations, platelets to be transfused irrespective of platelet count. It is recommended to give prophylactic platelet transfusions when the platelet count is less than 10,000/μL (or <20,000/μL in the presence of fever).

2. ***Haemopoietic growth factors***

   There are currently no effective and safe haemopoietic growth factors to support red cells and platelets in patients with AA. A short course of subcutaneous granulocyte colony stimulating factor (G-CSF) at a dose of 5 μg/kg per day may be considered for severe systemic infections not responding to intravenous antimicrobials. G-CSF should be stopped, if there is no response by one week.

3. ***Prevention of infection***

   The risk of infection is determined by the severity of AA. Patients with AA are at risk of bacterial and fungal infections. *Aspergillus* infections have a very high mortality in patients with severe aplastic anaemia (SAA) because of the frequent prolonged periods of severe neutropaenia.

   Most important are measures directed toward increasing general hygiene. Oro-dental hygiene is important, and sources of infection should be treated appropriately. Routine rectal examinations should be avoided. Patients with a high-risk of infection should be managed in isolation. Prophylactic antimicrobials especially in very SAA are given to help in preventing infections.

4. ***Treatment of infection***

   As for all neutropaenic patients, fever may require immediate hospitalisation and treatment before the results of bacterial investigations are available. The duration of neutropaenia, the patient's infection history and recent antibiotics influence the antibiotic choice including the early introduction of antifungal therapy. Persistent fever should be investigated aggressively with high resolution computed tomography of the chest for fungal infections.

Immunosuppressive Therapy

Anti-thymocyte globulin (ATG) and cyclosporine (CSA)

Combining ATG and CSA has considerably improved upon ATG alone. The combination of horse-ATG and CSA is current standard therapy in SAA who do not have human leucocyte antigen (HLA) matched donor.

1. *Indications:* Immunosuppressive therapy is indicated for patients who are not eligible for sibling donor bone marrow transplantation. This includes: (i) patients with transfusion dependent non-SAA, (ii) patients with SAA or very SAA who are more than 30 to 45 years of age, and (iii) patients with severe or very severe disease who lack an HLA-compatible sibling donor.
2. *Criteria for response to immunosuppressive therapy:* Response to immunosuppressive therapy is categorised as complete, partial or no response. The response criteria are summarised in **Table 5**.

   Responses should be confirmed by two or more blood counts at least 4 weeks apart. The median time to response in most of studies is about 12 weeks. The overall response rate at 3 months in patients receiving ATG and CSA is between 60% and 80%.

Table 5: Criteria for Response to Immunosuppressive Therapy in Aplastic Anaemia

	Response Criteria for SAA	Response Criteria for Non-SAA
None	Still severe	Worse or not meeting criteria below
Partial	Transfusion independent No longer meeting criteria for severe disease	Transfusion independence (if previously dependent) or doubling or normalisation of at least one cell line or increase in baseline haemoglobin of >3 g/dL (if initially <6 g/dL) neutrophils of >500/μL (if initially <500/μL platelets of >20,000/μL (if initially <20,000/μL)
Complete	Haemoglobin normal Neutrophils >1,500/μL Platelets >1.5 lacs/μL	Same criteria as for severe disease

SAA = Severe aplastic anaemia.

3. *Administration:* The ATG is a pan-antilymphocyte immunoglobulin composed of purified animal polyclonal antibodies directed against human lymphocytes. Infections, haemorrhages, and fever are not an absolute contraindication for treatment with ATG. ATG is given as a daily intravenous infusion over 6 to 8 hours. The dose is 40 mg/kg per day for 4 days for horse-ATG. The dose is 3.75 mg/kg per day for 5 days for rabbit-ATG. A test dose must be given before hand to look for severe systemic reaction or anaphylaxis. Each daily dose should be preceded by methylprednisolone. Platelet transfusions should be given to maintain a safe platelet count (ideally >30,000/μL), but should not be given concurrently with ATG administration because of the antiplatelet activity of ATG. The patient should be nursed in isolation with reverse barrier nursing. On the 5th day of ATG, prednisolone at 1 mg/kg per day is commenced to help prevent serum sickness and continued for 9 days then withdrawn over the next 5 days. Serum sickness typically occurs between day 7 and 14 from the start of ATG treatment. Oral CSA should be commenced on the last day of prednisolone (day +14) at 5 mg/kg per day, aiming to keep the trough CSA blood level between 150 and 250 μg/L for adults and between 100 and 150 μg/L for children.

4. *Results of treatment:* The combination of ATG and CSA remains the currently recommended immunosuppressive regimen for both SAA and transfusion-dependent non-severe AA (NSAA). Immunosuppressive therapy using the combination of ATG and CSA is associated with response rate of between 60% and 80% with current 5-year survival rate of around 75%. Response to ATG and CSA is delayed and response usually does not start much before 3 months. Relapse (30%) may occur after immunosuppressive therapy. For the one-third of patients who are refractory to h-ATG/CSA, repeated courses of immunosuppression have yielded response rate varying from 30% to 70%. Re-treatment with ATG/CSA in relapsed AA has resulted in response rate of 50% to 60%.

5. *CSA dependence and relapse:* CSA dependency is observed in 26% to 62% of patients, necessitating long-term maintenance of the drug. Current immunosuppressive therapy regimens including CSA dose of 5 mg/kg per day and that should be taper very slow for at least 1 year, to minimise the risk of relapse.

   After long-term follow-up some patients with AA may proceed to frank paroxysmal nocturnal haemoglobinuria (PNH), acute leukaemia and myelodysplasia (MDS). The overall risk of developing a clonal cytogenetic abnormality/MDS at 10 years is between 5% and 20%. The risk of relapse is around 30%. Relapse can be successfully rescued by an additional course of ATG.

Other immunosuppressive drugs

1. *Androgens:* Useful androgens include nandrolone decanoate, oxymetholone, danazol and stanazolol. Nandrolone decanoate administered at 400 mg intramuscularly per week is one approach. Oxymetholone (2 mg/kg per day) has been used extensively in the treatment of AA for many decades before the availability of ATG and CSA. A study from Chandigarh reported that stanazolol (1 mg/kg per day) is ineffective for SAA and very SAA in children and it induced remission in 38% of NSAA patients. In a prospective clinical trial 16 patients of AA (12 males and 4 females; 6 severe cases and 10 moderate cases) were treated with 300 mg of danazol daily for 12 weeks. All patients completed the treatment period without occurrence of severe toxicity. Three female patients achieved partial remission, whereas only 2 of the 12 male patients did so. None of the responders had shown a response to previous immunosuppressive therapy. These findings indicate that danazol is effective for a subset of AA patients, and particularly for female patients with AA refractory to immunosuppressive therapy.

   The mechanism of action by which male hormones improve haematopoietic failure states remains unclear. The haemoglobin response frequently is more impressive than improvements in granulocyte or platelet levels. Androgens, if used, should be continued for at least 3 to 6 months because responses may require prolonged treatment. Hepatotoxicity is common side-effect with androgen.

2. *Other immunosuppressive agents:* Corticosteroids have no role in the treatment of AA. The use of high dose cyclophosphamide (45 mg/kg per day for 4 days) without stem cell support is also not recommended. Other immunosuppressive agents currently under investigation include an anti-IL-2 receptor monoclonal antibody (daclizumab), mycophenolate mofetil (MMF; CellCept), FK506, and rapamycin, etc.

Bone Marrow Transplantation

HLA-identical sibling donor transplantation

Patients with severe AA, if they are less than 40 years old and have an HLA compatible sibling, should be transplanted up front. The conditioning regimen used for patients aged less than 30 years is a non-myeloablative, highly immunosuppressive regimen to help prevent graft rejection, and graft-*versus*-host disease (GvHD). Transplantation for SAA from an HLA-identical sibling donor is now very successful

with a 75% to 90% chance of long-term cure. The incidence of graft rejection has fallen from more than 30% to around 5% to 10%. GvHD remains a problem: the probability of acute GvHD grade II-IV is 18 ± 3% and chronic GvHD of any grade is 26 ± 5%. Bone marrow is preferred source of stem cells as compared to mobilised peripheral blood stem cells (PBSCs) with less incidence of chronic GvHD.

There is a significant risk of late graft failure in AA following allogeneic bone marrow transplant, which is most commonly associated with discontinuing CSA too early or low CSA blood levels. Therapeutic CSA should be continued for at least 9 months before gradually reducing the dose to zero over the following 3 months.

Matched unrelated donor (MUD)

Bone marrow transplantation may be considered when patients fulfill all the following criteria. They should have a fully matched (at DNA level for both class I and II antigens) donor, less than 40 years old, failed at least two courses of ATG and CSA and for children, at least one course, SAA, and no evidence of active infection and or acute bleeding at time of bone marrow transplant.

The long-term survival of MUD bone marrow transplant around 30% with a high incidence of graft rejection, GvHD and severe infections.

Umbilical cord blood transplantation from matched sibling donors and unrelated donor will be one of the treatment options in future.

Summary of treatment for patients with AA is shown in **Table 6**.

Table 6: Summary of Treatment in Patients with Aplastic Anaemia

Age Less than 20 years		Age 20 to 40 years		Age More than 40 years	
Sibling Donor	**No Sibling Donor**	**Sibling Donor**	**No Sibling Donor**	**Sibling Donor**	**No Sibling Donor**
First line treatment					
BMT	ATG + CSA	BMT	ATG + CSA	ATG + CSA	ATG + CSA
Second line treatment					
ATG + CSA	2nd ATG + CSA MUD transplant CB transplant	ATG + CSA	2nd ATG + CSA, MUD transplant	BMT	2nd ATG + CSA, MUD transplant

BMT = Bone marrow transplant; ATG = Anti-thymocyte globulin; CSA = Cyclosporine; MUD = Matched unrelated donor; CB = Cord blood.

MANAGEMENT OF APLASTIC ANAEMIA IN PREGNANCY

Aplastic anaemia can present in pregnancy by chance, but other possible causes need exclusion. The disease may remit spontaneously after termination or after delivery. The disease may progress or relapse during pregnancy. Around 40% cases might relapse during pregnancy. Supportive care is the mainstay of treatment in pregnancy and the platelet count should be maintained more than 20,000/μL. CSA can be used safely during pregnancy.

PROGNOSIS

Course of AA is extremely variable. The one-year mortality for patients with SAA treated with transfusion only was more than 80%. In SAA patients treated only with androgens, mortality was 58% at 2 years, 60% at 5 years and 65% at 12 years. Some patients with drug-induced AA might spontaneously recover cytopaenies within 2 weeks. Without treatment most of the SAA and very SAA patients will die in the first 6 months of the diagnosis. Main causes of morbidity and mortality are bleeding and infections before and during treatment. Bone marrow transplantation is curative for approximately 80% of patients younger than 20 years, approximately 70% of patients aged 20 to 40 years. Combined immunosuppressive therapy with ATG and CSA leads to marked improvement in at least 70% of the patients. The disease may progress over 10 years to PNH, a MDS, or AML in as many as 40% of patients who initially responded to immunosuppressive therapy.

INDIAN PERSPECTIVE

In resource poor countries due to high cost of treatment for AA algorithm for the treatment of AA is not universal. Many patients can afford best supportive treatment only (blood product supports and anti-infective therapy). The options of androgen therapy [stanazolol (menabol) and oxymethalone (anapolom)] should be given to the patients who cannot afford transplant/ immunosuppressive therapy. The response rate for androgen therapy is approximately 5% to 10%. Those who respond require life-long androgen therapy and require monitoring particularly for hepatotoxicity of the drug. Cyclosporine as a single agent can be used as immunosuppressive therapy and response in the tune of 10% to 30% can be achieved, especially in moderately SAA.

ATG is available in different preparations (ATGAM, thymoglobulin and thymogam) in India and results of 50% to 70% can be achieved when it is used with cyclosporine.

The options of allogenic bone marrow transplantation should be offered to all eligible patients since it is the only curative treatment. The cost of allogenic bone marrow transplantation is approximately Rs 8 to 10 lakhs at most of the centres.

RECOMMENDED READINGS

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15.9 Acute Leukaemia

SH Advani

INTRODUCTION

Leukaemias are abnormal proliferation of lymphoid or myeloid, immature cells of haematopoietic system, which are characterised by aberrant or arrested differentiation leukaemic cells rapidly accumulate in the bone marrow cavity, ultimately replacing most of the normal haematopoietic cells with blast cells. The signs and symptoms are commonly as a result of bone marrow failure manifesting as anaemia, haemorrhage and infection.

DEFINITION

Acute leukaemias (ALs) are defined as a malignant clonal proliferation of lymphoid or myeloid precursor cell of unknown aetiology, leading to replacement of normal haematopoiesis by blast cells comprising 20% or more of bone marrow cells and infiltration of lymph nodes, spleen, liver or other organs. For therapeutic purposes, ALs are broadly classified as acute lymphoid leukaemia (ALL) or acute myeloid leukaemia (AML).

INCIDENCE

The incidence in the West varies from 1.3 to 2.5 per 100,000 persons per year. Roughly 75% of acute leukaemia (AL) cases occur in adults. The male to female ratio is 1.3:1. The ratio in children to adults is 4:1 for ALL and 1:6 for AML. ALL has its peak incidence at less than 10 years age while AML usually occurs at a mean age of 65 years.

AETIOLOGY

The exact aetiology of AL is not known. The risk of AL is increased as a result of atomic bomb exposure. However, in majority of the cases, no single cause can be pinpointed. Genetic disorders predisposing to leukaemia include ataxia telangiectasia, Bloom's, syndrome, Down's syndrome, Klinefelter syndrome, Fanconi's anaemia and Wiskott-Aldrich syndrome, Turner's syndrome, neurofibromatosis, severe combined immuno-deficiency and Li-Fraumeni syndrome (P53 deletion). Exposure to drugs like alkylating agents, nitrosoureas and epipodophyllotoxins have also been incriminated in the pathogenesis of ALs. Environmental factors include benzene, aromatic hydrocarbons (AMLs) and ionising radiations (AML, ALL). Retroviruses have been implicated in adult T-cell lymphoma (HTLV-I) in Japan and Africa. Epstein-Barr virus (EBV) has been associated with AL. The role of high-tension voltage and microwaves is only recently being evaluated; they probably are responsible for the clustering of cases seen in closed communities. Pre-leukaemia precedes AML in as many as 25% of cases. Five per cent of Hodgkin's disease patients treated with chemotherapy and radiotherapy develop secondary AL with a peak incidence at 6 years after the treatment.

CLINICAL PRESENTATION

AL presents with a short history of a few days to months (**Table 1**). They reflect expansion of the leukaemic cells at the cost of normal cells. Pallor, easy fatiguability and dyspnoea are due to anaemia. Thrombocytopaenia causes bleeding, especially purpura and easy bruising on dependent and traumatised areas. Granulocytopaenia results in increased incidence of infection, especially of the skin, gums, perianal region, lungs and urinary tract. The symptoms occur not only because of replacement of marrow by the malignant cells but also due to feedback inhibition of normal cells, altered micro-environment and saturation of stromal niche sites. However, non-leukaemic cells remain intact as is evident from the normal repopulation of marrow space following cytotoxic chemotherapy. Infiltration of leukaemic cells into other organs leads to hepatosplenomegaly, lymphadenopathy, mediastinal masses, chloromas or granulocytic sarcomas (soft tissue masses). Central nervous system (CNS) involvement may present with headache, vomiting, papilloedema and convulsions. Testicular involvement presents with a mass lesion or pain. The expanded cell mass is directly responsible for bone pains and sternal tenderness. Overt bleeding due to disseminated intravascular coagulation (DIC) is a common feature of acute promyelocytic leukaemia (AML-M3). It may be aggravated or precipitated by the initiation of therapy. Gum hypertrophy and leukaemia cutis are characteristic of acute monocytic leukaemia (AML-M4/M5).

Table 1: Diagnosis and Evaluation of Acute Leukaemia

Symptoms
- Fatigue, malaise, dyspnoea
- Fever, weight loss, petechiae, purpura
- Bone pains or abdominal pain
- Easy bruisability, gum bleeding, epistaxis, melaena

Signs
- Anaemia and pallor
- Thrombocytopaenia, ecchymosis, purpura, mucosal bleeding
- Fever, infections: (respiratory tract infection, perirectal abscess)
- Gum hypertrophy, lymphadenopathy, hepatosplenomegaly

Investigations
- Complete blood count including peripheral blood smear examination
- Liver function tests, renal function test, serum electrolytes, calcium, phosphorus, uric acid, lactate dehydrogenase
- Chest radiography for mediastinal adenopathy, chest infection
- Bone marrow aspiration (morphology, cytochemistry, immuno-phenotyping and cytogenetic studies, molecular studies)
- Cerebrospinal fluid examination for central nervous system involvement

INVESTIGATIONS

Total white blood cell (WBC) counts can be as high as 100,000/mm^3 or more. However, it is normal or low in nearly one-half of the cases. Haemoglobin level and platelet count are usually decreased at presentation. Bone marrow examination is essential for the diagnosis, and also to confirm complete remission and relapse following treatment. In addition to morphological evaluation, the cells are also subject to

cytochemistry, electron microscopy, immunophenotyping, cytogenetics and molecular studies. Rapid turnover of cells causes elevated serum lactate dehydrogenase, uric acid and alkaline phosphatase. Coagulation tests may show evidence of DIC, especially in AML-M3. Cerebrospinal fluid (CSF) examination is mandatory in all patients of ALL to evaluate CNS involvement at presentation and follow-up. If therapy is commenced without adequate precautions like hydration, allopurinol and diuresis then tumour lysis syndrome may be precipitated; this is characterised by hyperkalaemia, lactic acidosis, and hyperphosphataemia. Radiograph of the chest may show a mediastinal mass in T-cell ALL.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of AL includes other neoplastic haematopoietic diseases like lymphomas, myelodysplastic syndrome (MDS) and multiple myeloma. Other haematological disorders, like aplastic anaemia, severe megaloblastic anaemia (due to folate or B12 deficiency), viral infections (like EBV), disseminated tuberculosis, or myelophthisic anaemia (infiltration of bone marrow by other carcinoma) can present with similar picture. Careful morphologic examination and immunophenotype of the cells will exclude all other haematopoietic malignant disorders.

CLASSIFICATION

Morphology

The French-American-British (FAB) classification for AL is shown in **Tables 2 and 3**. For AML, the FAB classification was widely used. However, the new World Health Organization (WHO) classification is now gaining acceptance (**Table 4**).

Table 4: WHO Classification of Acute Myeloid Leukaemia (AML)

I. AML with recurrent cytogenetic translocations
- AML with t(8;21) (q22;q22) AML1/CBF alpha/ETO
- Acute promyelocytic leukaemia
- AML with t(15;17) (q22;q12) and variants PML/RAR alpha
- AML with abnormal bone marrow eosinophils inv (16) (p13;q22) t (16;16) (p13;q22) CBF beta/MYH1
- AML with 11q23 MLL abnormalities

II. AML with multilineage dysplasia
- With prior MDS
- Without prior MDS

III. AML with myelodysplastic syndrome, therapy related
- Alkylating agent-related
- Epipodophyllotoxin-related

IV. AML not otherwise categorised
- AML minimally differentiated
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukaemia
- Acute monocytic leukaemia
- Acute erythroid leukaemia
- Acute megakaryocytic leukaemia
- Acute basophilic leukaemia
- Acute panmyelosis with myelofibrosis

Table 2: French-American-British (FAB) Classification of Acute Lymphoid Leukaemia (ALL)

Cytologic features	ALL-L1	ALL-L2	ALL-L3
Cell size	Small	Large heterogeneous	Medium to large and homogeneous
Cytoplasmic amount	Scanty	Variable, often moderate	Moderately abundant
Nucleoli	Not visible or inconspicuous	One or more, often large	One or more, often prominent
Nuclear shape	Regular, occasional clefting or indentation	Irregular clefting and indentation common	Irregular, oval to round
Nuclear chromatin	Homogeneous	Variable, heterogeneous	Finely stippled and homogeneous

Table 3: French-American-British (FAB) Classification of Acute Myeloid Leukaemia (AML)

Subtype	FAB Type	Frequency (%)	Morphology	MPO	SB	NSE
Minimally differentiated leukaemia	M0	5	No azurophil granules	–	–	–
Acute myeloblastic leukaemia (AML) without maturation	M1	15	Few azurophilic granules or Auer rods	±	±	–
AML with differentiation with maturation	M2	25	Some maturation beyond promyelocytes; Auer rods	++	++	–
Acute promyelocytic leukaemia (APL)	M3	5	Hypergranular promyelocytes; Auer rods	+++	+++	–
Acute myelomonocytic leukaemia (AMML)	M4	25	≥ 20% monocytes; monocytoid cells in blood	++	++	++
Acute monocytic leukaemia (AMOL)	M5	5	Monoblastic (M5A) promonocytic (M5B)	±	–	+++
Acute erythroleukaemia	M6	5	Predominance of erythroblasts; dyserythropoiesis	–	–	–
Acute megakaryocytic leukaemia	M7	10	'Dry' aspirate; biopsy with blasts and dysplastic	–	–	–

MPO = Myeloperoxidase; SB = Sudan black; NSE = Non-specific esterase.

According to this new classification, presence of more than 20% blasts in the bone marrow is diagnostic of AL. The changes are easily summarised, the leukaemias with consistent cytogenetic abnormalities and these that are MDS related were taken into separate groups, the rest of the old FAB classification was put under the 'AML not otherwise categorised' entry. In general, ALL blasts are smaller (10 to 15 mm), have a thin rim of cytoplasm and are Tdt-positive (**Figure 1**). AML blasts are larger (12 to 20 mm), and have discrete nuclear chromatin, multiple nucleoli and Auer rods (**Figures 2 and 3**). They are Sudan black and myeloperoxidase positive. Morphology and cytochemistry are sufficient to allow an accurate subtyping in most cases.

Immunophenotyping

The recent development of highly specific monoclonal antibodies to differentiate antigens as well as advances in flow cytometry has made immunophenotyping readily available. Immuophenotyping is useful in defining lineage (B-cell *versus* T-cell) and stages of differentiation of ALL, identifying characteristic

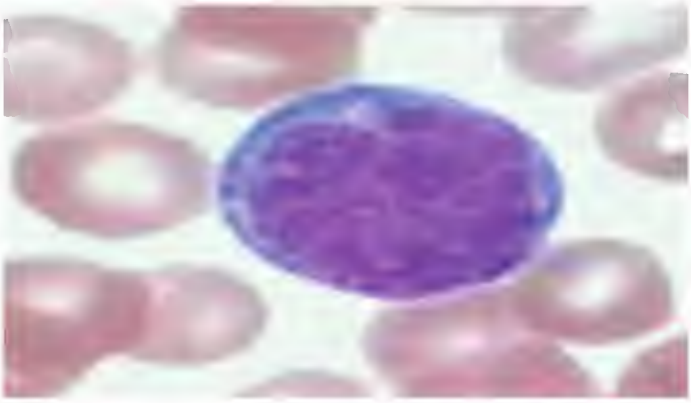


Figure 1: Lymphoblasts—bone marrow.

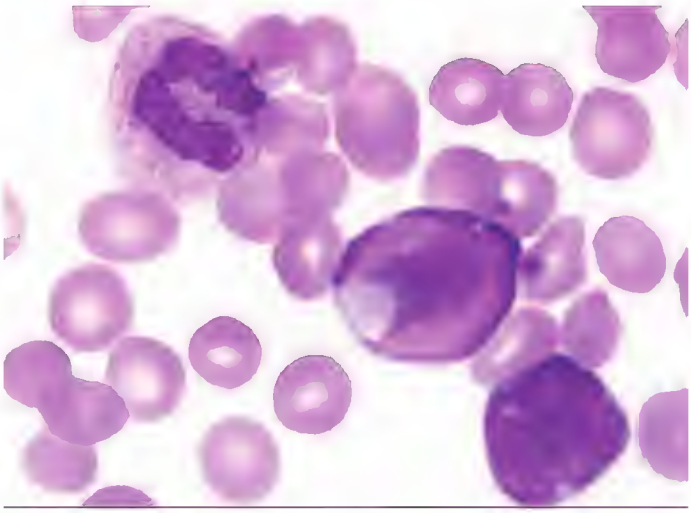


Figure 2: Myeloblast—bone marrow.

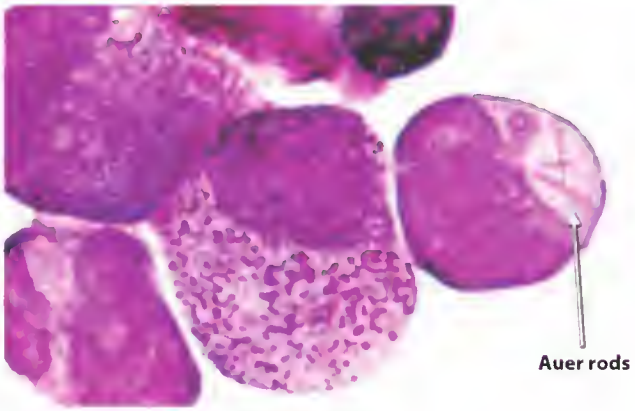


Figure 3: AML-M2 Auer rods.

features of AML, aiding in lineage determination in AL that are morphologically undifferentiated, diagnosing rare entities, such as AML-M6, AML-M7 or minimally differentiated AML M0, recognising mixed lineage or biphenotypic AL (ALL with myeloid markers or AML with lymphoid markers), and distinguishing AL from other haematopoietic and non-haematopoietic disorders. Groups of monoclonal antibodies that recognise the same antigens have been identified and are designated as cluster group of differentiation. The most useful and commonly used antibodies for the study of AL are listed in **Tables 5 and 6**. Reactivity with one antigen is not sufficient, but when used in combination these antibodies can help determine the cell lineage.

Table 5: Immunophenotyping in Acute Leukaemia

Subtype	Cluster designation of monoclonal antibodies
Acute lymphoblastic leukaemia	
T-cell	CD1, CD2, CD3, CDS, CD4, CD8, CD7
B-cell	CD10±, CDI9, CD20, CD22, S Ig+
Pre B	CD9, CD10, CDI9, clg M, HLA-DR
CALLA	CD10
Acute myeloid leukaemia	
M1, M2, M3	CD11, CDI3, CD33
M4, M5	CD11, CDI3, CDI4, CDI5, CD33
M6	Glycoprotein, spectrin
M7	CD41 (glycoprotein IIb/IIIa)/CD43 (glycoprotein Ib) S

Ig = Immunoglobulin; HLA = Human leucocyte antigen; CALLA = Common acute lymphoid leukaemia antigen.

Table 6: Co-relation of ALL Subtypes with Surface Markers

Pre B-cell	CD10+, CD19+, CD20+, CD21+, HLA DR+	Presence of CD10 (common ALL antigen) connotes a favourable prognosis
Mature B-cell	CD19+, CD20+, CD21+, slg +	Correlates with L3 leukaemia - Burkitt's leukaemia, needs intensified therapy
T-cell	CD3+, CD5+, CD7+	Associated with older age, high initial WBC count, mediastinal mass and higher risk of CNS disease

ALL = Acute lymphoid leukaemia; CALLA = Common acute lymphoid leukaemia antigen; WBC = White blood cell; CNS = Central nervous system.

Molecular Studies

Three major techniques of molecular analysis are currently used to diagnose and monitor AL, namely, Southern blot analysis, the polymerase chain reaction (PCR) and fluorescent *in situ* hybridisation (FISH). These methods enable the demonstration and characterisation of genetic abnormalities inherent in leukaemic cells. Southern blot analysis is currently the most sensitive method for the detection of minimal residual disease after treatment. The chromosomal abnormalities and oncogenes associated with various acute leukaemias are shown in **Table 7**.

THERAPY

The goal of therapy in AL is eradication of the leukaemia along with the restoration of normal haematopoiesis. At presentation the tumour load is 10^{11} to 10^{12} cells; chemotherapy can reduce it by 3 to 5 logs. Hence, the patient still has 10^{8} leukaemic cells when the marrow examination shows complete remission (**Figure 4**). Therefore, to achieve a long-term cure, the patient needs further treatment. The initial high-dose chemotherapy given to reduce the leukaemic cells below the levels of morphologic detection is called induction. This is followed by another course of chemotherapy meant to further attenuate the leukaemic burden consolidation or early intensification. Low-dose oral therapy given for 18 months to 2 years is called maintenance therapy. High-dose therapy given more than 6 months after induction is termed late intensification. The state-of-the-art treatment of AL is summarised in **Table 8**. Each mode of therapy has a specific aim and the drugs are selected accordingly.

Table 7: Non-Random Chromosomal Abnormalities and Oncogenes Associated with Acute Leukaemia

Disease	Chromosomal rearrangement	Involved gene	Comments
Acute lymphoblastic leukaemia (ALL)			
Early-B precursor	t(4;1l)	MLL	High-risk associated with infantile leukaemia
Common ALL	t(9;22)	BCR-ABL	High-risk
Pre-B	t(1;19)	IGH-IL3	High-risk
B ALL	t(8;14)	IGH-MYC	Needs short duration intensive therapy
Acute myeloid leukaemia (AML)			
AML M1	t(12;21)	TEL-AML1	Good prognosis
AML M2	t(8;21)		
AML M3	t(15;17)	PML-RARα	
AML M4	inv 16		
AML M5	t(9;11), 11q23		
AML M6	del(7q) and del (5q)		Poor chemotherapy response
AML M7	t(12; 21), trisomy 21		Poor chemotherapy response

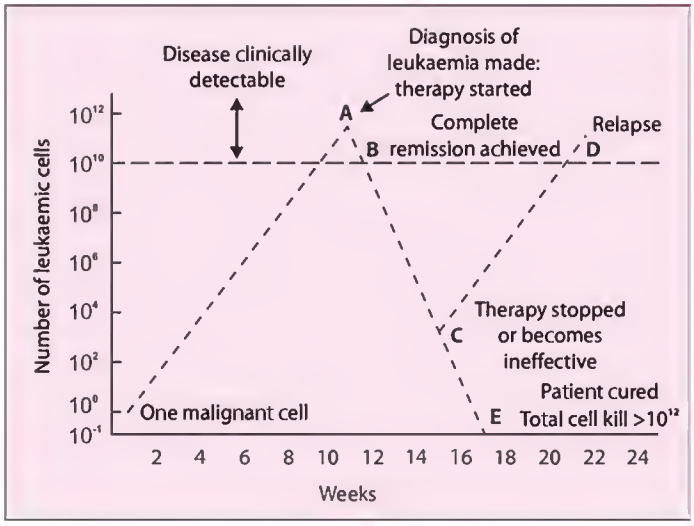


Figure 4: Cell turnover in acute leukaemia diagnosis and treatment.

Table 8: State-of-the-Art Treatment Protocol for Adult Acute Leukaemia

Acute myelogenous leukaemia

Anthracycline and cytarabine-based induction regimens
Intensive post-remission therapy: either bone marrow transplant or high-dose cytarabine is required for prolonged remission
Maintenance therapy is not generally indicated with the exception of acute promyelocytic leukaemia

Acute promyelocytic leukaemia

Retinoic acid and anthracycline and cytarabine-based treatment
Management of disseminated intravascular coagulation
Administration of cryoprecipitate or fresh frozen plasma to maintain fibrinogen >100 mg/dL;
Platelet transfusions to maintain platelet count >50,000/μL
Bone marrow transplant, high-dose cytarabine therapy are reserved for relapsed disease

Acute lymphoblastic leukaemias

Four or five drug induction regimens using anthracyclines, cyclophosphamide, and/or asparaginase in addition to vincristine and prednisone
Intensive consolidation therapy based on cytarabine combined with anthracyclines, epidophyllotoxins, or antimetabolites
Protracted maintenance therapy (approximately 2 years) based on oral methotrexate combined with mercaptopurine
Prophylactic intrathecal chemotherapy (with or without cranial radiotherapy) for central nervous system prophylaxis

Supportive care is extremely important in the treatment of AL. The major portion of therapy-related morbidity and mortality can be averted by meticulous attention to these aspects. Adequate hydration, allopurinol and low-dose steroid therapy for the first 48 hours are important to prevent tumour lysis, especially when the cell count is high. All chemotherapies are myelotoxic. Hence, supportive care includes blood and platelet transfusions and antibiotics whenever indicated. Platelet transfusion should be given whenever there is overt bleeding or the platelet count falls below 10,000/mm^3. It needs to be replaced every 24 to 48 hours. Keeping the haemoglobin as near normal as possible clearly reduces morbidity and improves the ability of the patient to combat septicaemia. Infections and haemorrhage are the primary cause of death in patients with leukaemia. Untreated infection in the neutropaenic host can be fatal. All febrile episodes in a neutropaenic patient are considered to be due to infection unless proved otherwise, even in negative blood, urine and cultures. Common regimen for the treatment of febrile neutropaenia includes antipseudomonal penicillin or cephalosporin coupled with an aminoglycoside. Patients with central venous catheter may require early institution of vancomycin. The use of granulocyte transfusions is still controversial. All patients should be given prophylaxis for *Pneumocystis carinii* and fungal infections.

ACUTE LYMPHOBLASTIC LEUKAEMIA

Combination chemotherapy remains the primary therapeutic modality with evolving indications for limited radiation therapy. Current treatment for ALL is divided into four phases as described below.

Remission Induction

Although prednisolone and vincristine are capable of producing remission in approximately 80% of patients, it is now clear that it is inadequate. The addition of a third agent, either L-asparaginase, daunorubicin raises the induction remission rate to 90% and significantly prolongs remission. However, addition of a fourth induction agent, usually an anthracycline, improves remission duration even in patients with poor-risk factors.

Central Nervous System Prophylaxis

The concept of CNS prevention therapy is based on the assumption that undetectable CNS leukaemia is present at the

time of diagnosis. In high-risk patients cranial irradiation and intrathecal methotrexate prevent CNS relapse. However, long-term ALL survivors have adverse effects of CNS irradiation on neurological and intellectual functions. The combination of intrathecal and moderate-dose intravenous methotrexate, maintenance triple intrathecal therapy (methotrexate, cytarabine and hydrocortisone) and high-dose intravenous methotrexate alone appear to provide equivalent protection to that offered by cranial irradiation.

Consolidation

The cranial prophylaxis is followed by another dose of chemotherapy meant to decrease the leukaemic burden to the minimum. The drugs used for consolidation are a combination of drugs used for induction and maintenance therapy.

Maintenance

Methotrexate and 6-mercaptopurine are the two drugs most frequently administered. This therapy is continued for 2 years in order to eradicate the dormant leukaemic cells. The dosage of these drugs should be adjusted to maintain the total leucocyte count between 1,000/mm^3 and 3,000/mm^3. The most commonly used intensive therapy protocol for children with ALL in India is shown in **Table 9**.

This protocol is being used in major centres across the country. This protocol has been designed along with National Cancer Institute (NCI), USA. Analysis of the results over the last decade revealed 70% to 75% patients have hepatosplenomegaly or lymphadenopathy or both. Two-third of patients have C-ALL, while 18% to 20% have T-ALL.

Complete response was achieved in 92% patients at the end of induction.

Table 9: MCP-841 Protocol Used for Childhood Acute Lymphoblastic Leukaemia

Induction-I (Month 1 and Month 3)		
L-asparaginase	6000 units/m^2	Days 2,4,6,8,10,12,14,16,18,20
Vincristine	1.4 mg/m^2	Days 1, 8, 15, 22, 28
Daunomycin	30 mg/m^2	Days 8, 15, 28
Prednisolone	40 mg/m^2	Days 1 to 28
IT methotrexate	12 mg	Days 1, 8, 15, 22, 28
Induction-2 (Month 2)		
Cyclophosphamide	750 mg/m^2	Day 1, 15
6-mercaptopurine	75 mg/m^2	Days 1 to 7, 15 to 22
IT methotrexate	12 mg	Days 1, 8, 15, 22
Cranial radiotherapy	1200 cGy	Days 5 to 15
Consolidation (Month 4)		
Vincristine	1.4 mg/m^2	Days 1, 15
Cyclophosphamide	750 mg/m^2	Day 1
Daunomycin	30 mg/m^2	Day 15
Cytosar	100 mg/m^2	Days 1, 2, 3 and 15, 16, 17
6-mercaptopurine	75 mg/m^2	Days 1 to 8, and 15 to 22
Maintenance (3 Monthly Cycle x 6 Cycles)		
L-asparaginase	6000 units/m^2	Days 1, 3, 5, 7
Vincristine	1.4 mg/m^2	Day 1
Daunomycin	30 mg/m^2	Day 1
Prednisolone	40 mg/m^2	Days 1 to 7
6-mercaptopurine	75 mg/m^2	Days 15 to 90 (5 days per week)
Methotrexate	15 mg/m^2	Days 15, 22, 29...90 (once per week)

IT = Intrathecal.

Relapse was seen in 25% to 30% of patients. Most relapses were seen during maintenance and within first few months of completion of therapy. For the entire series, overall survival, disease-free survival and event-free survival are 55.7%, 55.5% and 51.9%, respectively.

ACUTE MYELOID LEUKAEMIA

Advances in the treatment of adult AML have resulted in substantially improved complete remission rates.

While the chemotherapy has remained the same over last two decades, progress in the treatment is attributed to the following: application of high-dose therapy (cytarabine) in first remission with rescue bone marrow transplant, identification of the major histocompatibility complex leading to successful application of bone marrow transplant and recognition of the importance of infection and the development of prophylaxis for prevention of Gram-negative infection, fungal infection and *cytomegalovirus* infection. Treatment should be sufficiently aggressive to achieve complete remission because partial remission offers no substantial survival benefit. Approximately 60% to 70% of adults with AML can be expected to attain remission status following appropriate induction therapy. More than 15% of adults with AML (about 25% of those who attain complete remission) can be expected to survive 3 or more years and may be cured. Remission rates in adult AML are inversely related to age, with an expected remission rate of greater than 65% for those younger than 60 years of age. Other adverse prognostic factors include CNS involvement with leukaemia, systemic infection at diagnosis, elevated WBC count (>100,000/mm^3), secondary AML, and history of myelodysplastic syndrome. Cytogenetic abnormalities which indicate a good prognosis include t(8;21), inv(16), and t(15;17). Normal cytogenetics portends average-risk AML. Patients with AML that is characterised by deletions of the long arms or monosomies of chromosomes 5 or 7; by translocations or inversions of chromosome 3, t(6;9), t(9;22); or by abnormalities of chromosome 11q23 have particularly poor prognosis with chemotherapy. For practical purposes, antileukaemic therapy is similar for all subtypes. Factors that predict for shorter response durations with chemotherapy (high initial WBC count, monocytic morphology and age) may also result in shorter remission duration following transplantation.

Induction Therapy

Induction therapy is the mainstay of treatment. It consists of a combination of cytarabine (100-200 mg/m^2 per day for 7 days) and an anthracycline (daunorubicin 40-50 mg/m^2 per day for 3 days); the addition of a third agent (thioguanine or etoposide) may improve the results. The overall complete remission rate is 65% after a single course of therapy. About 5% patients are currently refractory to therapy and 5% succumb to infection and haemorrhage during remission induction. AML arising from myelodysplasia or secondary to previous cytotoxic chemotherapy has a lower rate of remission than *de novo* AML. Supportive care during remission induction treatment should routinely include red blood cell and platelet transfusions when appropriate. Empiric broad-spectrum antimicrobial therapy is an absolute necessity for febrile patients who are profoundly neutropaenic (absolute neutrophil count <500/mm^3). Careful

construction in personal hygiene, dental care, and recognition of early signs of infection are appropriate in all patients. White blood cell transfusions can be beneficial in selected patients with aplastic marrow and serious infections that do not respond to antibiotics.

Achievement of remission is defined as a normal peripheral blood cell count, normocellular marrow with less than 5% blasts in the marrow and no signs or symptoms of the disease. In addition, there are no signs or symptoms of CNS leukaemia or other extra-medullary infiltration.

Post-Remission Therapy

Post-remission therapy is designed to eliminate clonogenic cells which remain in bone marrow and are detectable as minimal residual disease. Further therapy options to eradicate minimal residual therapy are intensive treatment with high-dose cytarabine-containing combinations and myeloablative therapy, followed by allogenic or autologous bone marrow transplant. The duration of consolidation therapy ranges from one cycle to four or more cycles. High dose cytarabine-based chemotherapy can be complicated by severe gastro-intestinal, neurologic or pulmonary toxic effects. Patients in the good-risk group have a reasonable chance of cure with intensive consolidation, and it may be reasonable to defer transplantation in that group until early first relapse. Poor-risk factors include deletion of 5q and 7q, trisomy 8, t(6;9), t(9;22), and a history of myelodysplasia or antecedent haematologic disorder. The poor-risk group is unlikely to be cured with consolidation chemotherapy and allogeneic bone marrow transplant in first complete remission is a reasonable option for patients with an human leucocyte antigen (HLA)-identical sibling donor. Allogeneic bone marrow transplant offers the best anti-leukaemic therapy as cure.

The 5-year survival with chemotherapy alone is 30% to 40%. Chemotherapy alone is able to prolong survival without achieving cure in a majority of the patients with AML. Allogeneic bone marrow transplant provides cure for up to 50% of AML patients. The application of modern immunotherapy in the course of treatment may be beneficial in the near future.

Therapy for Recurrent AML

Treatment with new agents under clinical evaluation are particularly appropriate in patients with recurrent AML and should be considered whenever possible. There are a number of newer agents with activity in recurrent AML, including amsacrine, mitoxantrone, diaziquone, high-dose cytarabine, homoharringtonine, idarubicin, and etoposide; some of these agents are being tested in combination regimens. A study with mitoxantrone and cytarabine was successful in 50% to 60% of patients who experienced relapse after initially obtaining a complete remission. Gemtuzumab ozogamicin anti-CD33 antibody has shown some response in relapsed patients. However, it leads to prolonged myelosuppression. Allogeneic stem-cell transplantation in early first relapse or in second complete remission provides a disease-free survival rate of approximately 30%.

Allogeneic stem-cell transplantation can salvage some patients whose disease fails to go into remission with intensive chemotherapy. Autologous bone marrow transplant has no survival benefit.

ACUTE PROMYELOCYTIC LEUKAEMIA

The large lysosomal granules seen in APL have high probability of severe haemorrhagic complications and DIC during early induction therapy. Aggressive transfusion support with fresh frozen plasma, cryoprecipitate and platelets is often necessary. Remission induction of APML with all-transretinoic acid (ATRA) alone or in combination with cytotoxic agents, is used. ATRA induction appears to normalise the coagulopathy more quickly than does conventional induction therapy, but it can be associated with the development of hyperleucocytosis and acute respiratory distress syndrome, 'ATRA syndrome'. Prompt recognition of the syndrome and aggressive administration of steroids can prevent severe respiratory distress. It is now well recognised that oral administration of ATRA (45/m^2/day) can induce remission in 70% to 90% of patients with APL. Coagulopathy is occasionally a problem in patients undergoing induction with ATRA plus chemotherapy. This coagulopathy can lead to catastrophic intracranial bleeding, but can be well-controlled by replacement of clotting factors. The use of heparin for control of DIC remains controversial.

Arsenic trioxide has become standard treatment for relapse of APL. As O_3 is also used as induction therapy in India.

BONE MARROW TRANSPLANT

Allogeneic Bone Marrow Transplantation

Allogeneic bone marrow transplant results in the lowest incidence of leukaemic relapse. The use of bone marrow transplant as primary post-remission therapy is limited by the need for a HLA matched sibling donor and the increased mortality from bone marrow transplant of patients who are older than 50 years of age. Good-risk factors include young age, t(8;21), inv(16) and t(15;17) associated with APL.

For patients planned for transplant, transfusion of blood products from potential donors should be avoided. Histocompatibility testing should be done at the earliest possible time. Most studies demonstrate that the rate of leukaemic relapse is decreased following bone marrow transplant in first remission compared with chemotherapy alone. Factors that predict for shorter response durations with chemotherapy may also result in shorter remission duration following transplantation. Bone marrow transplant has yielded a high rate of complete response in patients for whom initial induction therapy failed and autologous bone marrow transplantation may produce long-term leukaemia-free survival in approximately one-third of patients in either first relapse or second complete remission. The use of bone marrow or stem-cell transplantation as post-remission therapy has a curative role in ALs. High doses of chemotherapy with or without total body radiation are used in an effort to maximise leukaemia cell kill. Haematopoiesis is restored by the infusion of HLA-matched stem cells harvested from an HLA-compatible donor (sibling, parents) thereby rescuing the patient from the consequences of bone marrow failure. Because of differences in HLA composition, the graft may reject the host cells resulting in graft-*versus*-host disease (GvHD).

This complication may increase the risk of infection and represents a major source of morbidity and mortality in transplant patients. Allogeneic bone marrow transplant in first

complete response using HLA-compatible related donors resulted in a 5-year, disease-free survival in approximately 45% to 50%, with relapse rates ranging only from 10% to 20%. However, a significant number of patients succumb to such complications as GvHD, infection, or interstitial pneumonitis affecting the overall survival of the group as a whole. The transplant-related complications increases with age, and it is not advisable to offer allogeneic bone marrow transplant of patients older than the age of 50 to 55 years. As the median age of patients with AML is approximately 65 years, it is clear that most patients with this disease are not eligible for this form of therapy. In addition, only approximately 30% of eligible patients have an HLA-compatible donor. Despite meeting the minimum requirements of age and availability of a donor, a significant number of patients still fail to undergo transplantation.

Autologous Bone Marrow Transplantation

Majority of patients do not have an acceptable HLA-matched donor and cannot undergo allogeneic bone marrow transplant. In an attempt to allow such patients to undergo high-dose therapy with curative intent, the use of the patient's own bone marrow obtained while in CR as a source of haematopoietic reconstitution. Such an approach was thought to provide the anti-leukaemic benefits associated with high-dose conditioning regimens yet avoid the toxic complications. However, one major disadvantage is the potential contamination of the autologous graft by residual leukaemia cells. The inability of currently available laboratory techniques to reliably detect minimal residual disease and predict outcome based on its presence represents a major problem in leukaemia therapy. Hence, there is a concern that despite the high-dose conditioning designed to eradicate residual leukaemia cells in the body, patients will ultimately relapse because undetectable leukaemia cells will be reinfused with the graft. Results from these trials have generally reported a disease-free survival of approximately 40% to 50%. Relapse rates (50% to 60%) are higher than allogeneic bone marrow transplant, but as expected the toxicities are less. In studies that have used either immunologic or pharmacologic methods to purge bone marrow there has been a profound suppression of normal bone marrow progenitors resulting in delayed engraftment and generally shown a decrease in the duration of neutropaenia and a prolonged period of haematologic recovery. Therefore, studies using newer more sensitive techniques, such as PCR or multiparameter flow cytometry, will continue to address the issue of graft contamination by minimal residual disease.

PROGNOSIS

Survival in ALL has improved from 1% in 1965 to 50% in the mid 70s and up to 70% in the mid 80s and currently up to 90%. A variety of prognostic factors have been identified in AL (**Table 10**). Improvement in supportive care, mainly in preventing and treatment of infections has helped to decrease the leukaemic fatality-rate.

Less than one-third of the patients with AML who are treated with the current intensive chemotherapy are permanently cured. Of those who have an HLA-matched sibling donor and have a bone marrow transplant in the first remission more than 50% will be cured. In early relapse or second chemotherapy-induced remission, only a small fraction of patients can be salvaged by bone marrow transplant. The results of bone marrow transplant are equivocal.

Table 10: Prognostic Features in Acute Adult Leukaemia

Acute Lymphoblastic Leukaemia

- White blood cell count: High count associated with poor prognosis
- Leukaemic cell immunophenotype: T-cell has a favourable prognosis, pre-B cell has an intermediate prognosis, whereas mature B-cell has a poor prognosis with standard regimens
- Age: Older age associated with worse prognosis
- Philadelphia chromosome: Positive disease has a worse prognosis
- Time to complete response: Patients requiring > 4 to 5 weeks to achieve a complete response have a lower likelihood of being cured

Acute Myeloid Leukaemia

- Age: Older age is associated with a reduced incidence of complete response
- Antecedent haematologic disorder or secondary acute myelogenous leukaemia
- These subgroups have a lower incidence of complete response and a reduced overall survival
- Cytogenetics: The t(15;17), t(8;21), and inv(16) denote good prognostic subgroups; abnormalities of chromosome 5 or 7, trisomy 8, and t(9;11) denote poor prognostic subgroups

RELAPSED ACUTE LEUKAEMIA

Relapse is defined as the recurrence of evident leukaemia. The bone marrow is the most common site of relapse. It is either due to residual disease or the emergence of drug resistance. The multidrug resistant gene may have a significant role to play in refractory and relapsed leukaemias. Early bone marrow relapse occurring during treatment or within six months after cessation of therapy has a poor prognosis unless salvaged by allogeneic bone marrow transplant. Where there is no compatible donor, aggressive chemotherapy is employed using infusions of high-dose methotrexate and cytarabine. CNS relapse is an extra-medullary relapse occurring in 3% to 8% of patients within 18 to 24 months after the start of front-line treatment. Local therapy to the meninges by intrathecal chemotherapy combined with systemic chemotherapy together with CNS irradiation in previously non-irradiated patients will cure 40%. Testicular relapse usually manifests itself 4 to 6 months after cessation of maintenance thereby. A single involved testis should be removed and in bilateral involvement local radiation with 20 cGy should be applied. Systemic chemotherapy should include maintenance therapy for at least one year. Combined relapse most frequently involves the bone marrow and CNS. The prognosis is extremely unfavourable and transplantation is the only chance of cure.

RECOMMENDED READINGS

1. Gilliland GR. Acute leukaemia. In: DeVita, *et al*, editors; *Cancer: Principles and Practice of Oncology*; 7th Ed. Philadelphia: Lippincott Williams and Wilkins; 2005: pp 2077-88.
2. Scheinberg, Maslak P, Weiss. *Management of Acute Leukaemias: Principles and Practice of Oncology*; 7th Ed. Philadelphia: Lippincott Williams and Wilkins; 2005: pp 2088-115.

15.10 Chronic Myeloid Leukaemia and Other Myeloproliferative Disorders

Tapan Kumar Saikia

INTRODUCTION

In recent years, our understanding of myeloproliferative conditions has improved significantly. Therefore, in the 4th edition (2008) of World Health Organization (WHO) classification of myeloid neoplastic pathologies, the nomenclature of myeloproliferative disorders (MPDs) has been changed to myeloproliferative neoplasms (MPNs) to accurately reflect the neoplastic nature of these diseases. William Dameshek in 1951 brought the concept of 4 pathological conditions of chronic myelogenous leukaemia (CML), essential thrombocythaemia (ET), polycythaemia vera (PV) and primary myelofibrosis (PMF) as related ones. Since then, significant advances have occurred in understanding the biology and the management of these. Additionally, new entities have been included. The diagnosis of these disorders has serious implications for our country. This is due to paucity of diagnostic and therapeutic facilities.

Definition

MPNs are clonal myeloproliferation (i.e. peripheral blood granulocytosis, thrombocytosis or erythrocytosis) that is devoid of dyserythropoiesis, granulocytic dysplasia or monocytosis.

CLASSIFICATION

Currently, the WHO classification is accepted internationally. This is a dynamic classification based on amalgamation of newer biological information to already known parameters. The WHO 2008 classification is comprehensive and includes histology and genetic information (**Table 1**). The classification also provides scope for further investigation of relatively ill-understood categories.

Some important changes in the current classification and diagnosis of MPNs include: (a) the nomenclature (MPDs to MPNs), (b) diagnostic algorithms for PV, ET, and PMF need information regarding JAK2V617F and similar activating mechanism along with additional clinical, laboratory, and histologic parameters even in absence of JAK2V617F or simliar mutations, (c) reduction of threshold of platelet counts to more than or equal to 450 x 10^9/L for ET, (d) some cases previously diagnosed as chronic eosinophilic leukaemia (CEL) could now be categorised as myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDFGRB, or FGFR1, and (e) systemic mastocytosis as an MPN.

EPIDEMIOLOGY

All MPNs are uncommon disorders, with an incidence of 0.2-3 (average 0.5) per 100,000 persons per year. Nevertheless, it appears that the exact incidence is under-reported in registries as diagnosis has remained a challenge, especially of PV, ET and PMF. The average age is 60 years, but may occur at any age, CML being not uncommon in children and young adults. There is slight male preponderance for MPNs except for ET.

AETIOLOGY

Exact aetiologies of MPNs remain unknown. Radiation may play a role in some cases. Congenital or familial cases have been reported. Much molecular work needs to be done in this field. Aetiopathogenesis and maintenance of MPNs appear to be dependent on the molecular abnormalities like bcr-abl chimeric oncogene in CML and JAK2 and possibly TET2 mutations in other types.

Table 1: The 2008 World Health Organization Classification for Myeloid Neoplasms

Acute myeloid leukaemia (AML)
Myelodysplastic syndrome (MDS)
Myeloproliferative neoplasms (MPNs)
Chronic myelogenous (myeloid) leukaemia (CML)
Polycythaemia vera (PV)
Essential thrombocythaemia (ET)
Primary myelofibrosis (PMF)
Chronic neutrophilic leukaemia (CNL)
Chronic eosinophilic leukaemia (CEL), not otherwise classified
Hypereosinophilic syndrome (HES)
Mast cell disease (MCD)
MPNs, unclassifiable
MDS/MPNs
Chronic myelomonocytic leukaemia (CMML)
Juvenile myelomonocytic leukaemia (JMML)
Atypical chronic myeloid leukaemia (ACML)
MDS/MPN, unclassifiable
Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
Myeloid neoplasms associated with PDGFRA rearrangement
Myeloid neoplasms associated with PDGFRB rearrangement
Myeloid neoplasms associated with FGR1 rearrangement (8p11 myeloproliferative syndrome)

CHRONIC MYELOGENOUS (MYELOID) LEUKAEMIA

CML is characterised by the presence of an abnormal chromosome known as Philadelphia chromosome (Ph) resulting from reciprocal translocation of a part of the long arms of chromosomes 9 and 22. At the molecular level, the abl gene from chromosome 9 is translocated to bcr in chromosome 22; likewise, part of bcr gets translocated to chromosome 9, resulting in bcr-abl chimeric oncogene and finally translated to bcr-abl chimeric protein. This brings about increased proliferation, reduced apoptosis and loss of adhesion of immature cells in marrow stroma. White blood counts rise to a high level with appearance of immature cells; platelet counts may also rise in many cases.

Clinical features include: asymptomatic cases detected on routine blood examination, weight loss, low-grade fever, malaise, and left hypochondrial pain caused by splenomegaly. Median age is 55 to 60 years in Western countries and about 40 years in many Asian countries. There is slight male preponderance. Clinically and haematologically 3 distinct phases of the disease are defined—chronic, accelerated and blastic. **Table 2** shows

the investigations required for the diagnosis of CML. It cannot be over emphasised that a cytogenetic and/or molecular diagnosis is of prime importance in diagnosing CML accurately as morphological features of other MPNs can overlap those of CML.

Table 2: Diagnosis of Chronic Myelogenous Leukaemia

Chronic Phase or Any Phase at Presentation
Blood: Leucocytosis with immature cells at various stages of maturation, thrombocytosis in some.
Absent or reduced leucocyte alkaline phosphatase (LAP) score
Marrow aspirate and trephine biopsy: Morphology suggestive of myeloid hyperplasia with a shift to the left
Cytogenetics: Conventional karyotyping for presence of t (9;22) and/or FISH for bcr-abl
Molecular: RQ-PCR for bcr-abl level
Accelerated phase: Blasts 10% to 19% in blood or marrow, basophils ≥ 20%, platelets <100 x 10^9/L
Blastic phase: Blasts ≥ 20% in blood or marrow

FISH = Fluorescent in situ hybridisation; RQ-PCR = Quantitative.

Treatment

Chronic phase (CML-CP)

Before the advent of biological agents (also known as targeted therapy) and tyrosine kinase inhibitors (TKIs), patients were treated with oral busulfan, hydroxyurea, interferon-alpha and allogeneic haematopoietic stem cell transplantation (HSCT). While oral cytotoxic drugs like busulfan or hydroxyurea had no significant impact on the natural history of the disease, interferon-alpha could produce meaningful cytogenetic responses in 15% to 20% of patients and many became long-term survivors. However, interferon had significant constitutional side-effects.

HSCT remains the only proven curative modality for CML. It brings about leukaemia cell eradication with cytotoxic therapy and graft *versus* leukaemia (GVL) effect. A long-term survival of more than 15 years has been reported in more than 50% patients. Others have died due to treatment-related mortality (TRM) or relapse. Some (10%) survivors live with significant chronic GVHD. In young patients it can be the treatment of choice as first-line therapy (<20 years) or in those resistant to TKIs. The cost is usually one time (unless prolonged chronic GVHD occurs) and less expensive than imatinib which needs to be taken for an indefinite period. This is regardless of the less expensive imatinib available in India. The timing for a best outcome following transplant is within the first year of the diagnosis.

Discovery of imatinib mesylate (2-phenylaminopyrimidine derivative) and its clinical use since 1998 has completely changed our approach for the management of CML-CP. Imatinib is a small molecule with activity on p210 bcr-abl protein by competitively inhibiting phosphorylation on the ATP binding site of the protein. It is an oral preparation with 98% bioavailability and a long half-life (14 to 18 hours), taken as single daily dose of 400 mg. Higher doses of 600 mg or 800 mg are not to be used routinely but can be used for inadequate responders. Imatinib is the first generation TKI. The results of the IRIS trial at 5-year follow-up have shown complete cytogenetic response of 69% at 12 months and 87% cumulative at 5-year, event free survival of 83%, and estimated overall survival of 89% with 7% progressing to accelerated or blastic phases. About 60% patients are continuing to receive the drug at 8-year follow-up. Currently, imatinib is standard of care for all newly diagnosed patients with CML.

It has a favourable toxicity profile. Grades 3-4 side-effects of cytopaenia (neutropaenia 17%, anaemia 4%, thrombocytopaenia 9%), elevated liver enzymes 5%, skin rash, muscle cramps, upper gastrointestinal symptoms, oedema, fatigue, occurring in only 1% to 2% cases. Hepatotoxicity if develops early and is severe, the drug is usually discontinued. However, grades 1-2 toxicities occur in 40% to 60% of the patients.

Second generation TKIs like dasatinib (~300 times more potent than imatinib), a dual kinase inhibitor (abl and src), nilotinib (~30 times more potent than imatinib), bosutinib and INNO4 have been developed and are undergoing clinical trials at various phases. Dasatinib at 100 mg daily and nilotinib at 400 mg twice daily were initially approved for use in imatinib intolerant and resistant cases. They have recently been approved for first-line therapy. Efforts are on to develop many other TKIs which could be better than currently available ones. **Table 3** shows the details of currently available TKIs.

Table 3: Tyrosine Kinase Inhibitors for Treatment of CML

Names (potency)	Mechanisms	Current Use
Imatinib (x 1)	Inhibits bcr-abl, PDGFR, others	CP, AP, BP
Dasatinib (x 300)	Inhibits bcr-abl, src	IM-resistant/ intolerant, AP, BP, CP
Nilotinib (x 30)	Inhibits bcr-abl	IM-resistant/ intolerant, AP, CP.

CP = Chronic phase; AP = Accelerated phase; BP = Blastic phase; IM = Imatinib.

Accelerated phase

As disease progression is associated with accumulation of additional genetic and molecular abnormalities, management becomes increasingly difficult. Imatinib in a 600 mg daily dose can produce haematological response in ~60% of patients with major cytogenetic responses in a fraction; overall survival at 3 years is reported as 60%. Second generation TKIs also produce significant responses. If feasible, younger patients should receive allogeneic HSCT.

Blastic phase

It is extremely difficult to achieve durable responses in blastic phase patients. Any form of therapy that includes any TKIs produces 30% to 50% remissions with median survival of 3 to 10 months. Only an allogeneic HSCT may achieve long-term survival in 10% to 20% of patients.

POLYCYTHAEMIA VERA (PV)

It is defined by an elevated red cell mass in the absence of conditions that induce secondary erythrocytosis, such as hypoxia or inappropriate erythropoietin production. As it is a clonal stem cell disorder, it is often accompanied by increased platelets and granulocytes. PV is associated with acquired point mutations of the JAK2 tyrosine kinase in more than 90% of cases. JAK2 is an intracellular signalling molecule and its constitutive expression leads to excess production of various blood cells in

the marrow. The diagnostic criteria for PV are given in **Table 4**. In the absence of availability of facilities to study JAK2, one can reasonably diagnose PV with splenomegaly, raised PCV (red cell mass), subnormal erythropoietin level and marrow biopsies.

Table 4: Diagnostic Criteria for Polycythaemia Vera

Major Criteria
Hb >18.5 g/dL (men), >16.5 g/dL (women) or Hb/Hct >99th percentile of reference range for age, sex or altitude of residence or Hb >17 g/dL (men), >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency or elevated red cell mass more than 25% above mean normal predicted values
Presence of JAK2V617F or similar mutation
Minor Criteria
Bone marrow trilineage myeloproliferation
Subnormal serum erythropoietin level
Endogenous erythroid colony growth

Hb = Hoemoglobin; Hct = Hoemotocrit.

Clinical features include splenomegaly, facial or conjunctival a plethora, hypertension, hepatomegaly, cutaneous ulcers and gouty features. It is a chronic disease with a median survival of 10 years or more. Disease progression leads to massive hepatosplenomegaly, marrow fibrosis in the majority and transformation into acute leukaemia in 20% to 25% cases.

Management includes cases: (i) phlebotomies for all to maintain a haematocrit levels at less than 45% in men and more than 42% in women, (ii) use of low-dose aspirin 100 mg daily in all reduces the incidence of thrombosis and risk of cardiovascular deaths, (iii) cytotoxic drugs like hydroxyurea are usually reserved for high-risk patients with risk of vascular events, older than 60 years of age and lowering platelet count and reducing the spleen size.

ESSENTIAL THROMBOCYTHAEMIA (ET)

Diagnostic criteria for ET are given in **Table 5**. Reactive thrombocytosis, which is a very common phenomenon, should be carefully ruled out by looking for a primary focus of other illnesses. JAK2 mutations occur in 30% to 50% of cases and are of mixed clonality. Clinically, many patients are asymptomatic or may develop vasomotor, thrombotic, or haemorrhagic manifestations. Splenomegaly occurs in ~25% cases. It is about 2.5 times more common in males. Most patients live more than 10 years after the diagnosis.

Table 5: Diagnostic Criteria for Essential Thrombocythaemia

Platelet count ≥450 x 10^9/L
Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid proliferation
Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm
Demonstration of JAK2V617F or other clonal marker or no evidence of reactive thrombocytosis

Management modalities include, close observation and starting treatment when platelets rise more than 1,000 x 10^9/L with hydroxyurea, anagrelide and interferon-alpha with an aim to lower platelet counts. Some may require early intervention. Aspirin is also used commonly to prevent thrombosis. Heparin, warfarin or thrombolytic agents are used in the presence of thrombosis.

PRIMARY MYELOFIBROSIS (PMF)

It is the least common type of the major MPNs and carries a poor prognosis with a median survival of 3.5 to 5.5 years. JAK2 mutations are detected in ~50% of cases. Diagnostic criteria are given in **Table 6**. Reactive myelofibrosis may occur in some chronic infections including tuberculosis. Splenomegaly is the most common presenting feature. Anaemia develops with disease progression. Constitutional symptoms are caused by cytokine release. Extramedullary haematopoiesis causes massive splenomegaly leading to hypersplenism and typical morphological features of red cells in peripheral blood. Marrow aspirates are often a dry tap and trephine biopsies are mandatory for the diagnosis.

Table 6: Diagnostic Criteria for Primary Myelofibrosis

Major Criteria
Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis, or in its absence increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis
Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
Demonstration of JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis
Minor Criteria
Leucoerythroblastosis
Increased serum LDH
Anaemia
Palpable splenomegaly

Management includes, close observation in earlier stages with reservation of hydroxyurea for later stages. Interferon-alpha may ameliorate some features for a certain period. Blood transfusions become the most important supportive care once significant anaemia sets in. Attempts are onto develop new molecules like pomalidomide, a thalidomide analogue that may offer meaningful palliation. Allogeneic stem cell transplantation remains a curative therapy in selected patients.

Management of Rare MPNs

No standard of care has emerged for these uncommon conditions. Most patients remain under observation and managed symptomatically. Nevertheless, certain conditions like hypereosinophilic leukaemia with PDGFRA and PDGFRB rearrangements and certain types of systemic mastocytosis can be treated effectively with low-dose imatinib.

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15.11 Myelodysplastic Syndromes

Rajat Kumar, Seema Tyagi

DEFINITION

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders characterised by ineffective haematopoiesis, leading to one or more cytopaenias, marrow dysplasia, and a tendency for leukaemic progression. The overall disease incidence is about 4 per 100,000 population but this rises to more than 30 per 100,000 in those over 70 years of age. As the longevity increases in India, MDS is being diagnosed more frequently.

CLINICAL FEATURES

The clinical features of MDS relate to the presence and severity of cytopaenias and are non-specific. MDS is common in the elderly. A detailed history and examination should be done to consider the differential diagnosis and exclude other causes of cytopaenias with reversible causes (**Table 1**).

Table 1: Clinical Evaluation and Investigations

History	Comments
Prior exposure to chemotherapy/radiation Family history of MDS/AML Recurrent infections or bleeding/bruising	Prior chemotherapy/radiation may predispose to MDS
	Ongoing cytotoxic therapy may be a cause of reversible cytopaenia with dysplasia in BM and is not MDS
Examination	
Pallor/infection/bruising Splenomegaly	
Baseline Investigations	
Full blood count Macrocytosis, cytopaenia(s) Occasionally,neutrophilia, monocytosis, thrombocytosis if additional myeloproliferative component	Dysplasia is better detected on aspirate and cellularity on bone marrow biopsy
Blood film examination	
Assay of serum ferritin, vitamin B12 and folate levels	
Bone marrow aspirate	
Bone marrow trephine biopsy	
Bone marrow cytogenetic analysis	Bone marrow cytogenetics are normal in about 50% of MDS patients.
Exclude reactive or other causes of dysplasia or secondary cytopaenias by relevant investigations: Megaloblastic anaemia HIV infection, Hepatitis B and C Cirrhosis with hypersplenism Alcoholism	Clinical assessment will determine the extent of investigations
Undiagnosed haemoglobinopathies or low grade haemolytic anaemias with erythroid dysplasia	
Severe intercurrent illness tuberculosis, kala-azar	Facilities for BM cytogenetics are lacking in many Indian centres

DIAGNOSIS

The diagnosis of MDS is usually suspected because of persistent unexplained peripheral blood cytopaenias. The bone marrow aspirate examination may show a single or multi-lineage dysplasia (**Figures 1 to 3**). The laboratory work-up is shown in **Table 1**. The "minimal" morphologic criteria in bone marrow for the diagnosis of MDS are: in the appropriate clinical setting, at least 10% of the cells of at least one myeloid BM lineage (erythroid, granulocytic, megakaryocytic) must show unequivocal dysplasia for the lineage to be considered as dysplastic in a cellular marrow. If a patient with clinical and other laboratory features consistent with MDS has inconclusive morphologic features, a presumptive diagnosis of MDS can be made if a specific clonal chromosomal abnormality is present. However, cytogenetic studies are normal in approximately 40% to 50% cases at diagnosis.

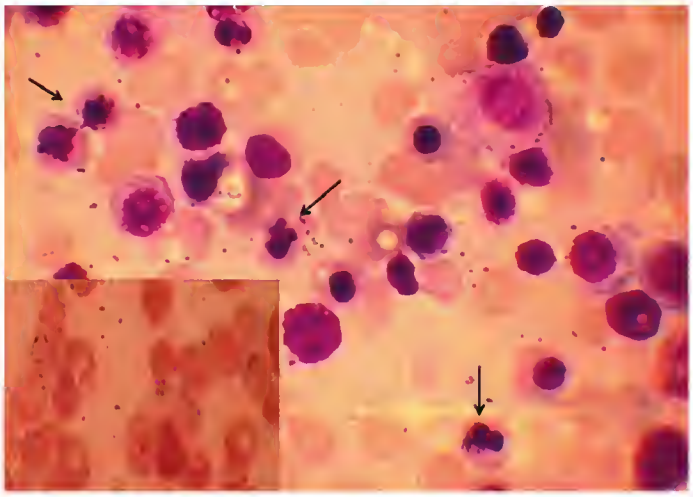


Figure 1: Bone marrow smear shows erythroid hyperplasia with dyserythropoiesis (Giemsa x 1000). Inset picture shows ring sideroblasts (Perl's stain x 1000).

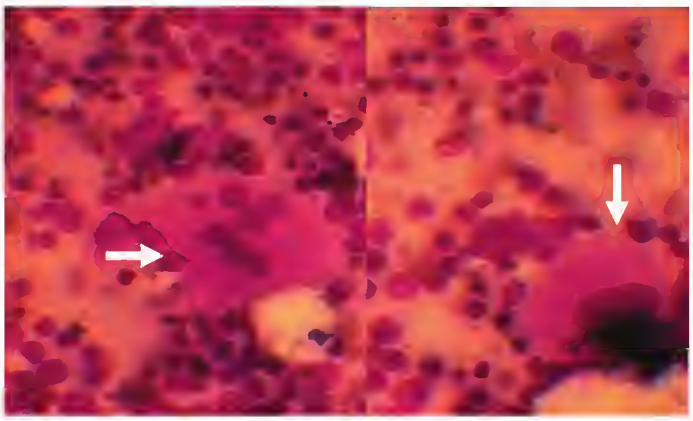


Figure 2: Bone marrow aspirate smear shows a cellular marrow with dysmegakaryopoiesis (Giemsa x 400).

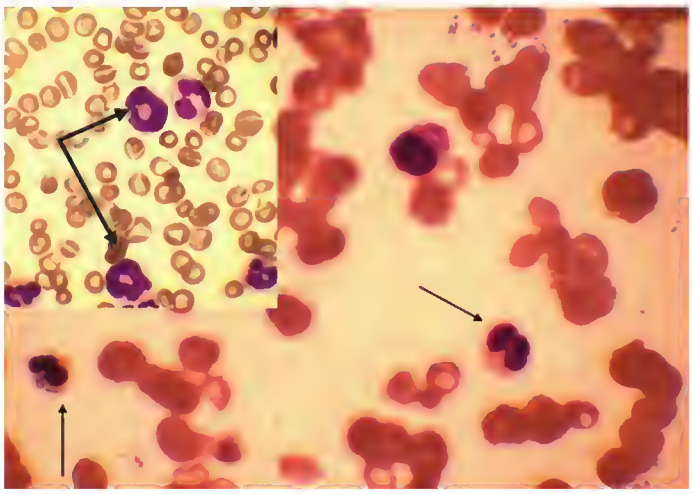


Figure 3: Peripheral smear shows dysplastic neutrophil and erythroid cell (thin arrows). Inset picture shows two ring neutrophils (thick arrows) (Giemsa x1000).

CLASSIFICATION

The MDS were initially classified as per the French-American-British (FAB) classification. This was revised by the WHO in 2001. The latest revision by the WHO was made in 2008 by lowering the threshold of bone marrow blasts from 30% to 20% for the diagnosis of acute myeloid leukaemia (AML) (**Table 2**). Paediatric MDS has been considered a different entity.

AETIOPATHOGENESIS AND BIOLOGY

Prior chemotherapy/radiotherapy predisposes to MDS, but most patients have no such history. The pathological processes responsible are: (a) augmented apoptosis, leading to ineffective haematopoiesis and peripheral cytopaenias, (b) accumulated genetic lesions causing tendency for transformation to AML, (c) chromosomal abnormalities, mostly deletions and monosomy, leading to loss of tumour suppressor genes, and (d) immune dysregulation of bone marrow micro-environment causing disruption of signal transduction pathways. There is an overlap and evolution between MDS, aplastic anaemia, paroxysmal nocturnal haemoglobinuria (PNH) and AML.

TREATMENT

Till recently, MDS had a dismal prognosis, but recent advances in therapy are improving the outcomes. The only curative treatment for MDS is bone marrow transplantation, but the majority of patients are not eligible on account of age and co-morbid conditions. Their prognostication is based on the International Prognostic Scoring System (IPSS) (**Table 3**). A more recent WHO based Prognostic Scoring System (WPSS) is more dynamic and includes transfusion requirement as a prognostic factor. The National Comprehensive Cancer Network (NCCN) guidelines are very useful in considering the appropriate therapy for patients with MDS, subdividing treatment based on IPSS risk (**Table 4**).

Table 2: World Health Organization's Revised 2008 Classification of Myelodysplastic Syndrome

Disease	Blood Findings	Bone Marrow Findings
Refractory cytopaenia with unilineage dysplasia (RCUD): (refractory anaemia [RA]; refractory neutropaenia [RN]; refractory thrombocytopaenia [RT])	Unicytopaenia or bicytopaenia (occasional) No or rare blasts (<1%)	(a) Unilineage dysplasia: ≥10% of the cells in one myeloid lineage (b) <5% blasts (c) <15% of erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anaemia, No blasts	(a) ≥15% of erythroid precursors are ring sideroblasts (b) Erythroid dysplasia only <5% blasts
Refractory cytopaenia with multilineage dysplasia (RCMD)	Cytopaenia(s) No or rare blasts (<1%) No Auer rods <1 × 10^9/L monocytes	(a) Dysplasia in 10% of the cells in 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) (b) <5% blasts in marrow (c) No Auer rods (d) ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopaenia(s) <5% blasts No Auer rods <1 × 10^9/L monocytes	(a) Unilineage or multilineage dysplasia (b) 5% to 9% blasts (c) No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopaenia(s) 5 to 19% blasts Auer rods ± <1 × 10^9/L monocytes	(a) Unilineage or multilineage dysplasia (b) 10% to 19% blasts (c) Auer rods ±
Myelodysplastic syndrome—unclassified (MDS-U)	Cytopaenias <1% blasts	(a) Unequivocal dysplasia in less than 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS (b) <5% blasts
MDS associated with isolated del (5q)	Anaemia, usually normal or increased platelet count No or rare blasts (<1%)	(a) Normal to increased megakaryocytes with hypolobated nuclei (b) <5% blasts (c) Isolated del (5q) cytogenetic abnormality (d) No Auer rods

Table 3: International Prognostic Scoring System (IPSS) for *De Novo* Myelodysplastic Syndromes

Scoring and survival in *De novo* MDS

	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blast %	<5	5 to 10	—	11 to 20	20 to 30
Karyotype	Good	Intermediate	Poor	—	—
Cytopaenia	0/1	2/3	—	—	—

Karyotype: *Good = Normal, –Y, del (5q), del (20q); Intermediate = Other abnormolities; Poor = Complex (> 3 abnormolities) or chromosome 7 anomolies. [This excludes karyotype t(8;21), inv 16 and t(15;17) which are considered AML and not MDS].*
Cytopaenias: *Haemoglobin concentrotion <10g/dL, neutrophils < 1800/μL and plotelets <100,000/μL.*

Risk Categories	Overall Score	Median Survival (Years) in Absence of Therapy
Low	0	5.7
Intermediate - 1 (Int-1)	0.5 to 1.0	3.5
Intermediate - 2 (Int-2)	1.5 to 2.0	1.1
High	>2.5	0.4

Table 4: Summary of Medical Management of Myelodysplastic Syndromes

All Patients		Best Supportive Therapy	
Patient Characteristics		**First-line Treatment**	**Second-line Treatment**
IPSS: Low, Int-1	Anaemia	Lenalidomide	Other treatment/BMT
	Del 5q	EPO/DBO ± G-CSF	AZA/DEC or Other/BMT
	S EPO < 500 mU/mL	ATG/CSA	
	S EPO >500 mU/mL	AZA/DEC	ATG/Other
	Thrombocytopaenia/Neutropaenia		
IPSS: High, Int-2	Transplant candidate	BMT	
	No Donor	AZA/DEC/Chemotherapy	
	Comorbid	Supportive care	
Selected Patients	High serum ferritin + (a) BMT candidate or (b) expected long survival	Iron chelation	

Int = Intermediate; BMT = Bone marrow transplantation; EPO = Erythropoietin; DBO = Darbepoietin; G-CSF = Granulocyte-colony stimuloting foctor; AZA = Azocytidine; DEC = Decitobine; ATG = Anti-thymocyte globulin; CSA = Cyclosporine A.

Supportive Care Alone

For most patients with MDS, observation and supportive care is appropriate. Blood transfusions for symptomatic anaemia should be given.

Erythropoiesis Stimulating Agents: Erythropoietin and Darbepoietin

Relief of anaemia with erythropoiesis stimulating agents (ESAs) + granulocyte-colony stimulating factor (G-CSF) is effective in about 25% of mainly low-risk MDS patients. If there is no response in 8 weeks, this should be stopped. Predictors of response are low or nil requirement of blood transfusions and relatively low levels of serum erythropoietin for the degree of anaemia.

Iron Chelation

Recently, a number of guidelines have recommended iron chelation in patients with transfusional iron overload, but this is not universally accepted. Effective iron chelation is known to improve survival in patients with thalassaemia, but the survival benefit is usually associated with 10 years of iron chelation. Since most newly diagnosed patients with MDS are older than 70 years, it is unclear whether they will survive long enough to achieve any benefit from expensive iron chelation. It seems reasonable to use iron chelation in chronically transfused patients who are expected to live for many years.

Lenalidomide

Lenalidomide, an oral immunomodulatory agent, has been approved for the management of MDS classified as low risk or intermediate-1 risk and with a deletion 5q cytogenetic abnormality. The recommended dose is 10 mg per day continuously. Cytopaenias are common and are particularly pronounced in MDS with deletion 5q, but the majority of cytopaenias occur in the first 8 weeks of the treatment. The major benefit is independence from transfusion.

Immunosuppression in Myelodysplastic Syndrome

The present guidelines for the treatment of MDS recommend use of immunosuppressive therapy for a subset of patients likely to respond. Most studies have shown responses between 30% and 50% in selected patients with anti-thymocyte globulin (ATG). Cyclosporine used alone leads to responses in 30% selected patients.

The predictors of response and survival reported are: (a) younger age, (b) low IPSS score, (c) presence of HLA-DR15, (d) shorter duration of red cell transfusion dependence, (e) marrow hypocellularity, and (f) presence of PNH clone.

DNA-Hypomethylating Agents

The United States-Federal Drug Authority (US-FDA) approved the use of DNA-hypomethylating agents, 5-azacytidine (AZA)

in 2004 and decitabine in 2006 for use in all subtypes of MDS. These drugs are not curative. In Phase III multicentre trial, patients with higher-risk of MDS were randomly assigned to receive AZA at 75 mg/m^2 per day for 7 days every 28 days or conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy). After a median follow-up of 21.1 months, median overall survival was 24.5 months for the AZA group *versus* 15.0 months for the conventional care group. The drug should be given for 4–6 cycles before determining whether benefit has occurred. The response rates to decitabine are similar to those observed with AZA.

Bone Marrow Transplantation

The only curative treatment for MDS is allogeneic haematopoietic stem cell transplantation (HSCT). All patients who are considered as eligible for HSCT should be referred to a transplant centre as soon as a diagnosis is made. Younger patients would get myeloablative conditioning, while older ones are given reduced intensity conditioning.

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15.12 Chronic Lymphocytic Leukaemia

M Mahapatra, Renu Saxena

Chronic lymphocytic leukaemia (CLL) is a clonal, proliferative disorder of monoclonal B-lymphocytes which is characterised by accumulation of mature looking lymphocytes in the blood, lymph nodes, spleen, bone marrow and other organs. It is not rare in Asians and in India, it forms about 17% of new cases of haematological malignancy. The disease is rare in young people, but the incidence rises in the fourth decade of life and continues to rise exponentially with median age at diagnosis being 70 years.

PATHOPHYSIOLOGY

CLL is a disease of slow accumulation of tumour cells due to disrupted or defective apoptosis. CLL cells overexpress several anti-apoptotic proteins including bcl-2, mcl-1, bak and XIAP and have diminished expression of pro-apoptotic proteins like bax. This leads to monoclonal accumulation of neoplastic B-cells. Recently, it has been shown that micro-RNAs (miRs) may be involved in the pathogenesis and progression of CLL, e.g. miR15 and miR16 at 13q14; miR16 normally regulates expression of bcl-2. Also, silencing of genes by methylation occurs in CLL in a gene-specific manner that is greater than that observed in normal B-cells, providing support for the importance of epigenetic silencing of genes in CLL.

There are two subsets of CLL: (i) leukaemias whose cell of origin has successfully traversed the germinal centre, resulting in the mutated immunoglobulin heavy chain variable region genes (IgVH) phenotype, and (ii) leukaemias that are derived from naïve B-cells with the unmutated (germline) IgVH sequence. Approximately 60% of patients with CLL have cells with mutated IgVH genes (less than 98% identity to germline), whereas the remaining patients have cells exhibiting unmutated IgVH (98% or greater sequence identity with germline) resulting in inferior survival in the latter group.

CLINICAL FEATURES

Although most patients with CLL are elderly, around 25% to 30% patients in India are less than 55 years. Twenty-five per cent of patients may be asymptomatic and diagnosed only on routine blood testing. Common manifestations include: fatigue, malaise and reduced exercise tolerance. Generalised lymphadenopathy and splenomegaly may be noted on physical examination. Less common manifestations are enlargement of tonsils, abdominal masses due to mesenteric or retroperitoneal lymphadenopathy, and skin infiltration. Patients can also present with features of anaemia, which may be related to marrow replacement or more rarely, to autoimmune haemolysis or aplasia. Patients with CLL are prone to repeated infections, such as pneumonia and herpes zoster.

LABORATORY DIAGNOSIS

Diagnostic Criteria

The diagnosis of CLL, as defined by the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) 2008, requires the presence of at least 5000/μL B-lymphocytes in the peripheral blood. The clonality of the circulating B-lymphocytes needs to be confirmed by flow cytometry. In the absence of lymphadenopathy or organomegaly (as defined by physical examination or computed tomographs), cytopaenias, or disease-related symptoms, the presence of less than 5000/μL B-lymphocytes is defined as 'monoclonal B-lymphocytosis' (MBL). MBL may progress to frank CLL at a rate of 1% to 2% per year. The definition of small lymphocytic lymphoma (SLL) requires the presence of lymphadenopathy and/or splenomegaly with less than 5000/μL B-lymphocytes in blood.

Peripheral Blood and Bone Marrow

A complete blood count, review of the peripheral smear, and immunophenotyping are required for diagnosis and prognosis in CLL. On peripheral smear examination, the lymphocytes appear mature with a 'soccer ball' chromatin pattern. There are increased 'smudge cells' or 'basket cells' as a result of the fragility of the CLL cells (**Figure 1**). Those patients with ≥30% smudge cells are more likely to have mutated IgVH and have a better prognosis than with more than 30% smudge cells. Some cases have increased large cells, atypical cells or prolymphocytes (<55%), with more open chromatin and prominent 'punched-out' nucleoli. If ≥55% of the cells are prolymphocytes, it is diagnosed as prolymphocytic leukaemia.

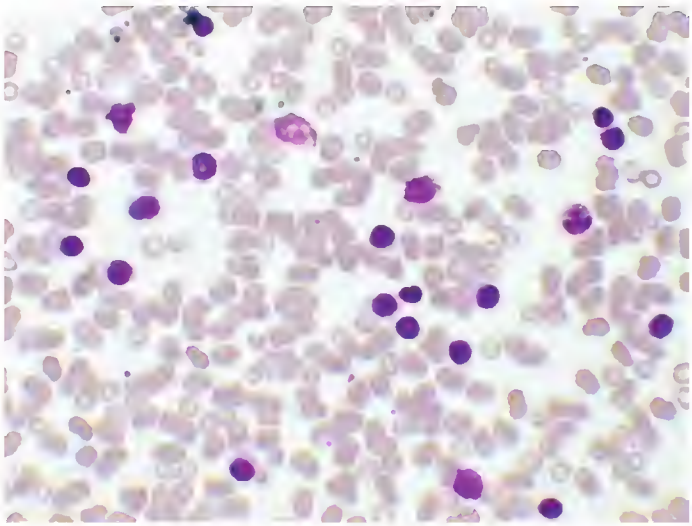


Figure 1: Chronic lymphocytic leukaemia. Peripheral smear showing leucocytosis with mature lymphocytes and degenerated basket cells.

In addition to lymphocytosis, anaemia, (with spherocytic RBC as shown in **Figure 2**) neutropaenia and thrombocytopaenia can develop as a consequence of bone marrow infiltration or chemotherapy. Hypogammaglobulinaemia is common in CLL and becomes more frequent and marked as the disease progresses.

The bone marrow aspirate in patients with CLL characteristically shows greater than 30% lymphoid cells. The bone marrow biopsy shows nodular, interstitial, mixed or diffuse infiltrate of CLL

cells. Although bone marrow examination provides important information about marrow reserve, pattern of infiltration, etc. it is not mandatory for the diagnosis if peripheral blood lymphocytes are consistent with CLL on morphology and immunophenotyping. It may be useful under the following circumstances:

1. To assess normal marrow reserve and to establish the cause of anaemia and thrombocytopaenia.
2. To rule out paratrabecular localisation or cyclin D1 staining in atypical cases.
3. To assess the pattern of marrow infiltration, which is of prognostic value.
4. To assess response following chemotherapy—minimal residual disease (MRD)—negative marrow following chemotherapy predicts a prolonged remission.

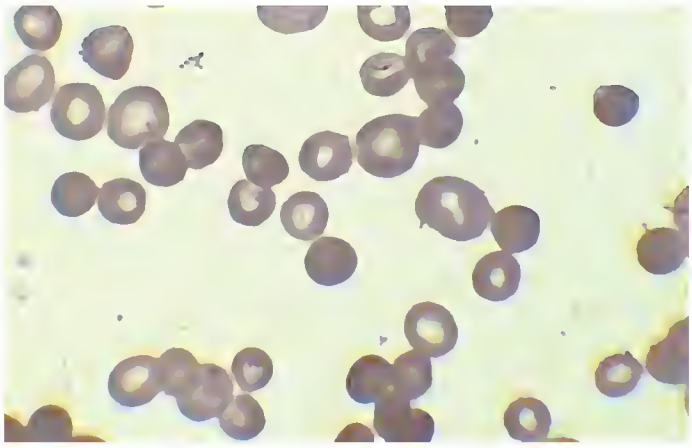


Figure 2: Peripheral smear showing spherocytic red blood cells in patients with CLL.

Immunophenotype

It is of vital importance to differentiate correctly CLL from other condition which mimic like CLL. This is to properly & effectively use new and effective treatment for CLL (**Table 1**). Flow cytometry, or immunophenotyping is now the standard approach to establish the diagnosis of CLL. CLL cells have a relatively consistent immunophenotype, which differentiates CLL from mantle cell lymphoma, hairy cell leukaemia, follicular centre cell lymphoma, splenic lymphoma with villous lymphocytes, and other indolent B-cell malignancies.

Table 1: Diseases that can Mimic Chronic Lymphocytic Leukaemia

Malignant Causes	
B-Cell	
	Monoclonal B-cell lymphocytosis
	Prolymphocytic leukaemia
	Mantle cell lymphoma
	Follicular lymphomas
	Splenic lymphoma with villous lymphocytes
	Hairy cell leukaemia
	Waldenström macroglobulinaemia
T-Cell	
	Polygranular lymphocytic leukaemia
Benign Causes	
Bacterial (e.g. tuberculosis)	
Viral (e.g. infectious mononucleosis)	

CLL cells express B-cell markers, including dim sIg, CD19, dim CD20 and CD23, as well as the pan T-cell marker CD5. Kappa or lambda restriction is always present, establishing the presence of a clonal B-cell population. In contrast, presence of CD10, FMC7, or CD79b (all typically absent on CLL cells) or bright expression of CD11c, CD20, or CD25 (all typically dim on CLL cells) suggests an alternative low-grade B-cell lymphoproliferative malignancy. Expression of CD5 without CD23 suggests mantle cell lymphoma. CLL is always a B-cell neoplasm and the World Health Organization nomenclature reclassified the entity formerly known as T-CLL as T-prolymphocytic leukaemia. Repeating immunophenotyping after the initial diagnosis is not required unless there is a suspicion of transformation to a more aggressive histology or for presence of minimal residual disease following treatment.

Surrogate Markers for IgVH Mutational Status

Both CD38 and ZAP-70 have been evaluated as surrogate markers for IgVH mutational status, as these can be measured readily by flow cytometry. CLL patients with more than 30% CD38+ cells had unmutated IgVH and a worse prognosis than those with less than 30% CD38+ cells. However, there is disagreement about the number of cells that are required to define positivity, with values ranging from 5% to 30%. ZAP-70 is a member of the Syk-ZAP-70 protein kinase family and is expressed in T-cells and natural killer cells. B-cells may also express ZAP-70, particularly when activated. Gene expression studies in CLL have shown that cells with unmutated IgVH have increased expression of ZAP-70 (>20% cells positive), whereas those with mutations have low levels. ZAP-70 positivity also correlates moderately with CD38 positivity and the presence of poor-risk cytogenetics, i.e. del 11q22–q23, del 17p13, and trisomy 12. Moreover, unlike CD38, the ZAP-70 status appears stable over time. The major obstacle in the routine use of ZAP-70 is the variability in the assay as a result of the sensitivity of different antibodies and differences in protocols for sample preparation and analysis.

Cytogenetics

Conventional metaphase cytogenetics can identify chromosomal aberrations in only 20% to 50% of cases, because of the low *in vitro* mitotic activity of CLL cells. Abnormalities noted in descending frequency of occurrence include trisomy 12, deletions at 13q14, structural aberrations of 14q32, and deletions of 11q, 17p, and 6q. Interphase cytogenetics by fluorescence *in situ* hybridisation (FISH) improves the sensitivity of detecting abnormal cytogenetics (80% cases) with 13q14 deletion being the most common. The two microRNA genes, associated with the good prognostic group 13q14 deletion, are miR-15 and miR-16.

STAGING

On the basis of clinical features and bone marrow involvement, CLL can be staged according to Rai and Binet staging system (**Table 2**). Both staging system have important role in predicting the median survival and for treatment planning.

PROGNOSTIC FACTORS

Patients in low and intermediate groups may have an indolent course spanning over decades or may progress rapidly with shortened survival. Recently, few other prognostic factors have been identified in patients with CLL (**Table 3**).

Table 2: Rai and Binet Staging of Chronic Lymphocytic Leukaemia

Rai Staging

Stage	Modified Stage	Description
0	Low risk	Lymphocytosis
I	Intermediate risk	Lymphocytosis + Lymphadenopathy
II	Intermediate risk	Lymphocytosis + Splenomegaly ± Lymphadenopathy
III	High risk	Lymphocytosis + Anaemia ± Splenomegaly or Lymphadenopathy
IV	High risk	Lymphocytosis + Thrombocytopaenia ± Anaemia ± Splenomegaly ± Lymphadenopathy

Binet Staging

Stage	Blood Counts	Involved Areas
A	Haemoglobin: >10.0 g/dL and platelets: >100 x 10^9/L	<3
B	Haemoglobin: >10.0 g/dL and platelets: >100 x 10^9/L	>3
C	Haemoglobin: <10.0 g/dL and platelets: <100 x 10^9/L or Both	Any number

Note: For Roi staging: Anoemio = hoemoglobin <11 g/dL; thrombocytopoenio = plotelets <100 x 10^9/L; lymphocytosis = >15 x 10^9/L.

For Binet staging following constitute one oreo each: Cervicol lymph nodes (LN), oxillory LN, inguinol LN, spleen, liver.

Table 3: Prognostic Factors in Chronic Lymphocytic Leukaemia that Predict an Unfavourable Outcome

Routine Markers

- Advanced Rai and Binet clinical stage
- Lymphocytic doubling time less than 12 months
- Elevated lactic dehydrogenase
- Elevated β2 microglobulin level
- Elevated thymidine kinase
- Elevated soluble CD23
- Atypical morphology or CLL/PLL
- Diffuse pattern of bone marrow infiltration
- Fludarabine resistance

Newer Markers

- Del(11q) and del(17p) using interphase FISH
- Unmutated immunoglobulin heavy chain variable region genes (IgVH genes)
- VH3.21 gene usage independent of IgVH
- ZAP-70 (≥20% positive)
- CD38 (≥30% positive)

TREATMENT

It is estimated that one-third of patients with CLL never require therapy; one-third need treatment at diagnosis; and one-third have disease progression over years and require treatment at some point. The indications for treatment and the type of treatment will vary according to patient's age and condition. The International workshop on CLL guidelines provides objective criteria for starting treatment in patients with CLL (**Table 4**).

Table 4: International Workshop Guidelines on Chronic Lymphocytic Leukaemia for Initiation of Treatment

- Evidence of progressive marrow failure as manifest by worsening anaemia and/or thrombocytopaenia
- Massive (>6 cm below left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (>10 cm in the largest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a period of 2 months or lymphocyte doubling time of <6 months
- Autoimmune anaemia and/or thrombocytopaenia poorly responsive to corticosteroids or other standard therapy
- Presence of a minimum of any one of the following disease-related symptoms: unintended weight loss of ≥10% body weight within 6 months, significant fatigue (ECOG performance status ≥2), fever of >100.5°F or 38.0°C for 2 or more weeks without infection, night sweats >1 month without infection

Common initial treatments in India include chlorambucil, cyclophosphamide, chlorambucil/prednisolone, fludarabine, fludarabine/cyclophosphamide (FC) or fludarabine/cyclophosphamide/rituximab (FCR). The choice of treatment depends on the aggressiveness of the disease, patient's age and cost of therapy. Although more aggressive chemotherapies may improve the depth and duration of remission, no randomised trials could show that this translates into improved survival. Recently, a large randomised trial has demonstrated that FCR improves overall survival, compared to FC, in previously untreated patients with advanced CLL.

Chemotherapeutic Agents

Chlorambucil

Oral chlorambucil in a dose of 0.1 to 0.4 mg/kg per day has served as initial, front-line therapy for CLL for several decades and is still considered appropriate by many specialists, particularly in a frail or medically unfit patient. The advantages of single agent chlorambucil or cyclophosphamide are related to their toxicity profiles, low cost and convenience in use, however, they are associated with very low complete response rate. Combination of chlorambucil and prednisolone (20 to 80 mg per day) given for 15 days and repeated every month for a maximum of 6 months, leads to a better response rate, but with no survival advantage.

Fludarabine

Fludarabine, a purine analogue inhibits the synthesis of DNA, RNA and proteins and also activates apoptosis. Fludarabine as a single agent therapy has been shown to achieve higher response rate and progression-free survival when compared to chlorambucil. It is administered in the dose of 25 mg/m^2 for 5 consecutive days and repeated every 4 to 6 weeks for 4 to 6 cycles. Myelosuppression, immunosuppression, autoimmune haemolytic anaemia, hearing loss, renal failure and skin rash can be observed as the adverse effects. Phase 2 trials showed that FC produces increase response rates and progression free survival in patients with CLL.

Bendamustine

Single agent bendamustine has shown improved responses when compared with chlorambucil. Complete responses are reported in 31% of bendamustine recipients *versus* 2% with chlorambucil.

Monoclonal antibodies

Rituximab (monoclonal anti-CD20 antibody) as a single agent in high-doses or in combination with fludarabine and cyclophosphamide can achieve high response rates in patients with CLL. Alemtuzumab is a recombinant DNA-derived humanised monoclonal antibody (Campath-1H) that is directed against the CD52, protein present on the surface of mature B- and T-lymphocytes. It is used as second-line therapy for CLL patients who have failed fludarabine therapy. Immunosuppression and infusional reactions are common adverse effects.

Haematopoietic Stem Cell Transplantation (HSCT)

Autologous stem cell transplantation (Auto-SCT) may prolong progression-free survival in patients with CLL and low-risk features. However, it does not appear to be curative in CLL and its use is rapidly declining with advent of modern immunochemotherapy. Allogeneic stem cell transplantation (Allo-SCT) remains a unique modality because of its graft-*versus*-CLL effect and can be effective in otherwise refractory disease. However, its role in CLL is less defined, except for young patients with high-risk features, because of the high treatment related mortality. Recently, with the development of reduced intensity conditioning regimens, a good number of patients of CLL are managed with Allo-SCT.

COMPLICATIONS IN CHRONIC LYMPHOCYTIC LEUKAEMIA

Infections

Infection remains a potentially lethal complication of CLL. Though its pathogenesis is multifactorial, hypogammaglobulinaemia is the major defect. Patients treated with purine analogues develop infections with opportunistic pathogens like *Pneumocystis jirovecii, Aspergillus* and *Candida.* Antifungal and co-trimoxazole prophylaxis should be given to all patients on treatment. Use of prophylactic gammaglobulin reduces infection-related morbidity (not mortality), but is very expensive.

Autoimmune Phenomenon

Autoimmune haemolytic anaemia (AIHA)

CLL patients can have dysregulated immunity leading to formation of immunogloublin (Ig)G antibodies against surface red blood cell antigen. This results in haemolytic anaemia. AIHA occurs in 10% patients of CLL. Prednisolone at the dose of 1 mg/kg per day is the treatment of choice.

Pure red cell aplasia (PRCA)

PRCA in CLL is characterised by severe anaemia, reticulocytopaenia and depleted red cell precursors in the bone marrow. Control of CLL is necessary for the resolution of PRCA. Additional treatment with corticosteroids may be required.

Autoimmune thrombocytopaenia

Autoimmune thrombocytopaenia or secondary ITP may be observed in patients of CLL.

Richter Transformation

A Richter transformation occurs when CLL transforms into another lymphoid malignancy, such as prolymphocytic leukaemia, diffuse large cell lymphoma, Hodgkin's disease, multiple myeloma or acute leukaemia. *Richter syndrome* refers to the development of a diffuse large B-cell lymphoma or its immunoblastic variant in a patient with CLL.

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15.13 Lymphoid Neoplasms

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Lymphoid neoplasms consist of cancers grouped together because they arise from the cells of the immune system. However, they are clinically heterogeneous and distinction between different entities and accurate diagnosis is essential for prognostication and treatment. The previous classifications have mainly relied on the morphological features of the lymphomas and some have also taken clinical behaviour into consideration. The identification of Reed-Sternberg (RS) cell separated Hodgkin's lymphoma from non-Hodgkin's lymphoma (NHL). The presence of lymphoid blasts in the peripheral blood distinguishes acute lymphoblastic leukaemia (ALL) from chronic lymphocytic leukaemia (CLL) and other chronic lympho-proliferative disorders which show mature lymphoid cells in the peripheral blood. The current WHO classification relies on morphological, immunophenotypic, genetic and clinical features to subtype lymphomas (**Table 1**).

HODGKIN'S LYMPHOMA

Hodgkin's disease or lymphoma is characterised by pleomorphic lymphocyte infiltrate interspersed by malignant multinuclear giant cells (RS cells). After a long controversy regarding the cell of origin of the pathological RS cells, now it has been accepted that Hodgkin's-RS cells are clonal lymphoma cells derived from B-cells, hence the term Hodgkin's lymphoma is preferred over the Hodgkin's disease. The majority of patients in developing countries are associated with Epstein-Barr virus (EBV) in the RS cells (as compared to 33% positivity in USA). Chronic stimulation due to EBV infection is postulated to result in pleomorphic infiltration; some of the cells undergo a clonal malignant transformation subsequently. Hodgkin's lymphoma is different from other cancers. The malignant RS cells form only a fraction of the enlarged lymphoid tissue. Rarely Hodgkin's lymphoma can be familial.

History and Physical Examination

There is a bimodal age distribution with one peak in mid to late twenties and the other one in late adulthood. The usual presentation is with painless lymphadenopathy, commonly in cervical region (76%). These have a characteristic rubbery feel. Other areas of involvement include lymphoid tissue in the mediastinum (60%), abdomen and groin, axilla, and spleen (20% to 25% each). Less common sites include liver, bone marrow, extra-nodal soft tissue, lungs, bone, pleura, pericardium and Waldeyer's ring; bony involvement is characterised by sclerosis. Constitutional symptoms (commonly termed as B symptoms) indicate systemic disease.

These include unexplained weight loss (>10% of body weight over 6 months), unexplained fever (>38°C for >3 days) and drenching night sweats. Symptoms like pruritus, pain in enlarged lymph nodes after consuming alcohol and Pel-Ebstein fever (alternating febrile and afebrile periods lasting for several days) are uncommon. As many as 47% of cases are wrongly treated with anti-tubercular drugs before the correct diagnosis is achieved stressing the importance of biopsy and confirmation of diagnosis.

Table 1: WHO Staging of Non-Hodgkin's Lymphoid Neoplasms

Precursor B- and T-Cell Neoplasms
Precursor B-lymphoblastic leukaemia/lymphoma
Precursor T-lymphoblastic leukaemia/lymphoma

Mature B-Cell Neoplasms
Chronic lymphocytic leukaemia/small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinaemia
Splenic marginal zone B-cell lymphoma
Hairy cell leukaemia
Plasma cell neoplasms
- Plasma cell myeloma
- Plasmacytoma
- Monoclonal immunoglobulin deposition diseases
- Heavy chain diseases

Extra-nodal marginal zone B-cell lymphoma (MALT lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Burkitt lymphoma/leukaemia
Lymphomatoid granulomatosis

Mature T- and NK-Cell Neoplasms
T-cell prolymphocytic leukaemia
T-cell large granular lymphocytic leukaemia
Aggressive NK-cell leukaemia
Adult T-cell leukaemia/lymphoma
Extra-nodal NK-T-cell lymphoma, nasal type
Enteropathy type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Sub-cutaneous panniculitis like T-cell lymphoma
Blastic NK-cell lymphoma
Mycosis fungoides/Sezary syndrome
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis
- Borderline lesions

Angioimmunoblastic T-cell lymphoma
Peripheral T-cell lymphoma, unspecified
Anaplastic large cell lymphoma

Immunodeficiency Associated Lymphoproliferative Disorders
Lymphoproliferative diseases associated with primary immune disorders
Human immunodeficiency virus-related lymphomas
Post-transplant lymphoproliferative disorders
Methotrexate-associated lymphoproliferative disorders

WHO classification of Hodgkin's lymphoma identifies 2 classes

1. Classical Hodgkin's lymphoma (CHL): CHL is further subdivided into 4 subtypes:
   (a) Nodular sclerosis (NS)
   (b) Mixed cellularity (MC)
   (c) Lymphocyte-rich
   (d) Lymphocyte-depleted
2. Nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL)

Diagnosis of Hodgkin's lymphoma requires demonstration of typical RS cells in the biopsy. Fine needle aspiration cytology (FNAC) can be misleading in patients with suspected lymphoma. RS cells are large multi-nucleated giant cells with a clear halo around prominent nucleoli (caterpillar or owl-eye appearance), which are scattered amidst a background rich in lymphocytes, histiocytes, eosinophils and plasma cells, effacing the normal lymphoid architecture. Based on the relative preponderance of these cells as well as the degree of sclerosis or fibrosis, various subtypes of Hodgkin's lymphoma are identified. Immuno-phenotyping suggests positivity for CD15 and CD30 in CHL and for CD45 in NLPHL, along with other B-cell markers.

Nodular sclerosis is the most common subtype in the Western population. Developing countries like India have mixed cellularity as the commonest histology (66% to 74%). Patients with lymphocyte predominant type tend to have localised disease and no symptoms. They also have increased risk of a second malignancy, and therefore, they are cured by less intensive therapy. As a general rule, however, histological type does not influence treatment decisions in classical Hodgkin's lymphoma with NLPHL being the exception where early stages may require only observation or radiotherapy alone.

Staging

The common perception is that Hodgkin' lymphoma spreads to contiguous areas through lymphatics. The Ann Arbor staging system is based on this concept (**Table 2**). The diagnostic and staging work-up is shown in **Table 3**. Originally a staging laparotomy and splenectomy was considered mandatory for staging. With the availability of better imaging modalities, staging laparotomy has hardly any role in the present era.

The advent of positron emission tomography in staging and prognostication of Hodgkin's lymphoma has now given birth to the philosophy of response based escalation or de-escalation of treatment. PET based staging and response evaluation tailored treatment also allows for identification of high-risk group patients, poor responders and non-responders to chemotherapy and subsequent appropriate escalation of treatment to improve cure rates. This prevents unnecessary over-treatment and long-term treatment related complications. In addition to staging, other prognostic factors like mediastinal involvement, 'X' disease, lactate dehydrogenase levels are important prognostic factors which determine the aggressiveness of the therapy. The adverse prognostic factors for early stage disease include higher age, elevated erythrocyte sedimentation rate, large mediastinal man, not Nodular lymphocyte-predominant Hodgkin's lymphoma or nodular sclerosis an histology and more than 4 involved nodal regions. Adverse prognostic factors for the advance disease are presented in **Table 4**.

Table 2: Ann Arbor Staging for Lymphoma

Stage	Description
I	Involvement of a single lymph node region or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) or localised involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Bone marrow and liver involvement are always stage IV

Designation of Alphabetical Suffixes in Lymphoma Staging

A	No symptoms
B	Fever (temperature, >38°C), drenching night sweats, unexplained loss of >10% body weight within the preceding 6 months.
X	Bulky disease (a widening of the mediastinum by more than one-third or the presence of a nodal mass with a maximal dimension >10 cm).
E	Involvement of a single extra-nodal site that is contiguous or proximal to the known nodal site.

Table 3: Diagnostic and Staging Work-up in Lymphoma

Mandatory Procedures

History: Fever, weight loss and night sweats
Physical examination: Measurement of all palpable lymph node with biopsy of doubtful nodes
Tissue excision biopsy for immunohistochemistry and further cytogenetic/molecular studies if needed (not FNAC)
Complete blood count and biochemistry (including LDH)
Chest radiograph
Computed tomography (CT) of thorax, abdomen and pelvis
Bone marrow biopsy and aspiration

Optional Procedures

Post-nasal space/Neck CT if cervical nodes are involved
Liver biopsy
Radioisotope bone scan if stage IV
Pleural cytology if there is pleural effusion
PET scan (accepted staging procedure in Hodgkin's and for response evaluation in NHL)
Lymphangiography and Gallium scan (decreasing use after PET scan availability)
Staging laparotomy with splenectomy (not done at present time)
Bone scan and skeletal survey
MRI (if suspicion of CNS disease/parameningeal or intracranial extension of disease)
Lumbar puncture and CSF examination (if suspicion of CNS disease/testicular involvement/parameningeal or intracranial extension of disease)

FNAC = Fine needle aspiration cytology; LDH = Lactate dehydrogenase; PET = Positron emission tomography; NHL = Non-Hodgkin's lymphoma; CNS = Central nervous system; MRI = Magnetic resonance imaging; CSF = Cerebrospinal fluid.

Treatment

Chemotherapy

Various chemotherapeutic regimen are listed in **Table 5**. ABVD regimen is associated with less myelotoxicity, less incidence of secondary leukaemias and infertility; and has been established as the standard chemotherapeutic regimen in patients with Hodgkin's lymphoma. The stage of the disease and the

Table 4: Prognostic Factors Predicting Unfavourable Outcomes in Advanced Stage (Stage IIB and above) Hodgkin's Lymphoma

Serum albumin <4 g/dL
Haemoglobin <10.5 g/dL
Male gender
Stage IV disease
Age >45 years
White blood cell count >15,000/mm^3
Lymphocyte count <600/mm^3 or <8% of white blood cell count

Table 5: Chemotherapy Regimens

ABVD[1]	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
MOPP[1]	Mechlorethamine, Vincristine, Prednisone, Procarbazine
COPP[1]	Cyclophosphamide, Vincristine, Prednisone, Procarbazine
BEACOPP	Bleomycin, Aetoposide, Doxorubicin, Mechlorethamine,
Escalated BEACOPP[1]	Vincristine, Prednisone, Procarbazine (G-CSF support)
Stanford V[1]	Mechlorethamine, Vincristine, Prednisone, Procarbazine Doxorubicin, Bleomycin, Vinblastine, Aetoposide
CHOP[2]	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHEOP[2]	Cyclophosphamide, Doxorubicin, Aetoposide, Vincristine, Prednisone
DHAP[1,2]	Dexamethasone, High-dose Cytosine Arabinoside, Cisplatin
MINE[2]	Mitoxantrone, I-posphamide with Mesna and Aetoposide
ESHAP[2]	Aetoposide, Methyl prednisolone, High-dose Cytosine Arabinoside, Cisplatin
ICE[1,2,3]	Ifosfamide with Mesna, Carboplatin, Aetoposide
GDP[1,2]	Gemcitabine, Cisplatin and Dexamethasone
BEAM[3]/ miniBEAM[1,2]	BCNU, Aetoposide, Cytosine Arabinoside, Melphalan
BEAC[3]	BCNU, Aetoposide, Cytosine Arabinoside, Cyclophosphamide
LACE[3]	Lomustin, Cytosine Arabinoside, Cyclophosphamide, Aetoposide
FC[4]	Fludarabine , Cyclophosphamide
FN[4]	Fludarabine, Mitoxantrone

1. *Chemotherapeutic regimens for Hodgkin's lymphoma*
2. *Chemotherapeutic regimens for Non-Hodgkin's lymphoma*
3. *Chemotherapeutic conditioning regimens for pre-haematopoietic stem cell transplant*
4. *Chemotherapeutic regimens for chronic lymphocytic leukaemia.*

prognostic factors decide the number of cycles required and the necessity of radiotherapy.

Radiotherapy

Radiotherapy was the mainstay of treatment in Hodgkin's lymphoma. For supra-diaphragmatic disease, *Mantle field* radiation was used. The mantle field comprises of submandibular, cervical, supra-clavicular, infra-clavicular, axillary, mediastinal, subcarinal and hilar lymph nodes. Para-aortic (involving para-aortic lymph nodes up to L4-5 - *Inverted 'Y' field*, splenic and pelvic field radiation was used for infra-diaphragmatic disease. These extensive radiation fields were associated with higher incidence of radiation toxicities which has led to the development of smaller radiation portals. In involved field radiation (IFRT) that is commonly used in the present era of combined modality treatment, the field encompasses the involved lymph node regions (e.g. upper cervical and supraclavicular lymph nodes in one field).

Combined modality therapy

Combined modality therapy including radiotherapy and chemotherapy is now the standard treatment for almost all advanced stage Hodgkin's lymphoma and for selected patients with early stage disease. Advantages of such a strategy include early effective treatment of systemic disease, delay in induction of irreversible loss of bone marrow function and potential to use smaller radiotherapy field.

Treatment of relapses

The relapse rate of Hodgkin's lymphoma varies from approximately 20% for the early stage favourable, 30% for the early stage unfavourable, and over 50% for the advanced Hodgkin's lymphoma with multiple poor prognostic factors. A large number of these patients can be salvaged with second-line chemotherapy regimens (**Table 6**).

High-dose chemotherapy followed by autologous haematopoietic stem cell transplant (Bone marrow transplant) has been used extensively in patients with relapsed and refractory Hodgkin's lymphoma, the rationale being based on a steep dose-response relationship.

Table 6: Treatment Strategies in Patients with Hodgkin's Lymphoma Based on Stage of Disease

Stage	Treatment
Early stage favourable	Chemotherapy (2 ABVD) and involved field RT
Early stage unfavourable	Chemotherapy (6-8 cycles) + involved field RT
Advanced stage	Chemotherapy (8 cycles) with or without consolidating local RT (20-30 Gy)/RT to X disease

RT = Radiotherapy.

NON-HODGKIN'S LYMPHOMA

NHL is a group of lymphoid malignancies resulting from the clonal expansion of B- or T-lymphocytes (**Table 1**).

Aetiology and Pathogenesis

The cause in most cases of NHL is unknown. Various factors associated with the development of NHL are shown in **Table 7**.

Table 7: Aetiologic Factors Implicated in the Development of Non-Hodgkin's Lymphoma

Immunodeficiency: SCID, hypogammaglobulinaemia, ataxia telangiectasia, Wiskott-Aldrich syndrome
Infections: EBV, HTLV-I, HIV, HHV-8, HCV, *Helicobacter pylori*, *Chlamydia psittaci*
Herbicides: 2, 4-dichlorophenoxy acetic acid
Diet: Meat, fat
Previous treatment for Hodgkin's disease

SCID = Severe combined immunodeficiency; EBV = Epstein-Barr virus; HTLV = Human T-cell lymphotropic virus; HIV = Human immunodeficiency virus; HHV = Human herpes virus.

It is now accepted that the incidence of certain lymphomas increases in immunodeficient subjects, e.g. HIV associated or congenital immunodeficiency syndromes. The increased incidence of lymphomas in immunodeficient individuals is associated with infectious agents, e.g. Kaposi's sarcoma and primary effusion lymphoma with human herpes virus-8, primary central nervous system (CNS) lymphoma and post-transplant lymphomas with EBV. The association of certain subtypes of lymphomas with bacterial infections is also now established and includes mucosa-associated lymphoid tissue lymphoma with *Helicobacter pylori*, primary cutaneous lymphoma with *Borrelia burgdorferi*, and ocular adnexal lymphoma with *Chlamydia psittaci*.

Lymphoid neoplasms are also associated with specific cytogenetic abnormalities and oncogene rearrangements which place normally silent genes next to promoter regions of immunoglobulin (Ig) or T-cell receptor (TCR) which activates the gene and initiates oncogenesis. These are summarised in **Table 8**.

Classification

The 1995 classification of NHL, provided by the WHO is commonly followed (**Table 1**).

History and Physical Examination

Clinically, most patients present with lymph node enlargement with or without hepatosplenomegaly. Extra-lymphatic presentations are common in the regions of head and neck, gastrointestinal tract, skin, bone marrow and rarely in the bone, testis, liver and lungs. The presence of B symptoms is known to have an adverse prognosis in patients.

Table 8: Cytogenetic and Molecular Abnormalities Associated with Non-Hodgkin's Lymphoma

t(8;14) (q23;q32)	c-MYC/IgH	Burkitt lymphoma
t(2;8) (p12;q23)	c-MYC/Igκ	Burkitt lymphoma
t(8;22) (q23;q11)	c-MYC/Igλ	Burkitt lymphoma
t(11;14) (q13;q32)	BCL1(CCND1)/ IgH	Mantle cell lymphoma, plasma cell myeloma
t(14;18) (q32;q21)	BCL2/IgH	Follicular lymphoma, diffuse large B-cell lymphoma
t(3;14) (q27;q32) and t(V;3q27)	BCL6/IgH, variable/BCL6	Large B-cell lymphoma, follicular lymphoma
t(14;18) (q32;q21)	MALT1/IgH	MALT lymphoma (gastric, pulmonary)
t(3;14) (p14;q32)	FOXP1/IgH	MALT lymphoma (ocular adnexal, thyroid)
t(1;14) (p22;q32)	BCL10/IgH	MALT lymphoma (pulmonary)
t(9;14) (p13;q32)	PAX5(BSAP)/ IgH	Lymphoplasmacytic lymphoma, plasma cell myeloma
inv(14) (q11;q32) or t(14;14) (q11;q32)	TCRÎ±/TCL1	T-prolymphocytic leukaemia
t(X;14) (q28;q11)	TCRÎ±/MTCP1	T-prolymphocytic leukaemia
t(11;18) (q21;q21)	AP12/MLT	MALT lymphoma
t(2;5) (p23;q35)	NPM/ALK	ALCL (70% to 80%)
t(1;2) (q25;p23)	TPM3/ALK	ALCL (10% to 20%)

Laboratory Evaluation

Laboratory studies are shown in **Table 3**. Immunophenotyping and flowcytometry studies on biopsy sample are valuable for sub-classification of NHL, prognostication and treatment planning (use of monoclonal antibody, e.g. rituximab-anti-CD20 antibody). Cerebrospinal (CSF) studies are necessary to rule out CNS involvement in selected cases. Imaging studies include chest radiography, computed tomography of chest and abdomen. Positron emission tomography has emerged a valuable non-invasive, bio-imaging technique for accurate staging and re-staging of lymphomas.

Staging System

The anatomic staging system used is the Ann Arbor staging (**Table 2**).

Prognostic Factors

The prognostic factors also determine the risk of relapse in patients with lymphoma and the International prognostic index (IPI) predicts the response and survival rates with standard chemotherapy (**Table 9**).

Table 9: Non-Hodgkin's Lymphoma-International Prognostic Index (IPI) and Follicular Lymphoma-IPI and Treatment Outcomes

Score	Complete Response (%)	5-Year Survival (%)
International prognostic index		
0,1	35	73
2	27	51
3	22	43
4,5	16	26
Follicular lymphoma international prognostic index		
0,1	36	90
2	37	77
3,4,5	27	52

Treatment

Each individual patient has to be subtyped and treatment planned according to type of NHL, age, performance score, co-morbidities, etc. This is essential as the disease specific treatment can achieve high cure rates in some types of NHL, e.g. cure rates above 90% in paediatric patients with Burkitt's lymphoma with appropriate chemotherapy protocol.

Low-grade NHL

The indolent histological subtypes of NHL include follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, and small lymphocytic lymphoma. More than 80% of patients present with advanced stage disease with bone marrow involvement. However, even in advanced stage, most patients are asymptomatic. Although chemotherapy produces responses in most patients, the disease-free survival and overall survival may not be altered by chemotherapy. The median survival is 7 to 8 years. Chemotherapy regimens may include cyclophosphamide, vincristine and prednisolone or anthracycline based regimen like cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). The newer purine analogue fludarabine alone or in combination with cyclophosphamide or mitoxantrone is associated with higher response rates and longer disease-free survival and is one of the first-line chemotherapy regimens at present.

The current standard of care in CD 20 positive NHL is chemo-immunotherapy. Rituximab is a chimeric monoclonal antibody (MoAb) directed against the B-cell-specific antigen CD20 expressed on NHL. It induces apoptosis and use with chemotherapy has reported better outcomes. Maintenance

with rituximab has also shown to improve relapse-free interval and overall survival in follicular NHL. The drug is usually well tolerated except for infusional reactions in few patients. In elderly patients with localised disease it may be worthwhile to defer chemotherapy till the symptoms develop. The use of radio-immunotherapy with Yttrium 90 (^{90}Y) or Iodine 131 (^{131}I) conjugated anti CD20 antibodies, though effective in relapsed and refractory settings, is limited in India mainly due to lack of availability. High-dose chemotherapy with autologous bone marrow transplant may be considered in patients with relapsed diseases particularly in young patients.

High-grade NHL

Diffuse large B-cell lymphoma constitutes more than 50% of the adult high grade NHL. CHOP chemotherapy cyclophosphamide regimen is a commonly used and most extensively studied in patients with high grade NHL. The patients with early stages (IA, IB IIA) and low IPI scores have good long-term survival. This regimen produces complete response in 45% to 55% of patients and cure approximately in 30% to 35%.

Mantle cell lymphoma, anaplastic large cell lymphoma, Burkitt's lymphoma, peripheral T-cell lymphoma, etc. constitute the other group of high grade or aggressive NHL. These lymphomas have poorer cure rates with standard CHOP regime and require more aggressive therapy. Addition of rituximab may be helpful. Other more aggressive regimens are associated with toxicity but no additional survival benefit.

Radiotherapy

Radiotherapy has limited role in the treatment of low grade lymphoma and is used rarely for symptom control in chemo-refractory patients. A select group of patients with high grade lymphomas and 'X' disease, specified extra-lymphatic sites like bone, primary CNS lymphoma, etc. patients may be treated with involved field radiotherapy (whole brain radiotherapy in case of CNS lymphoma).

Treatment of relapsed NHL

As the cure rates and survival of NHL patients have improved steadily in the last 4 decades, relapsed disease is now treated aggressively with salvage regimens with an attempt to cure the disease. The chemotherapy regimens for relapsed disease include DHAP, ESHAP, MINE, ICE, etc. (**Table 5**).

Autologous haematopoietic stem cell transplantation is standard of care for all eligible patients below 65 years of age after achieving disease control with second-line salvage chemotherapy. The conditioning regimens are similar to those for Hodgkin's lymphoma.

ONCOLOGIC EMERGENCIES ASSOCIATED WITH LYMPHOMA

Superior venacaval obstruction syndrome and tumour lysis syndrome are the two common emergencies seen and are discussed in the Chapter "Oncological Emergencies".

CONCLUSIONS

The classification of lymphomas have improved as also the staging with non-invasive diagnostic modalities. Chemotherapy and chemotherapy with biologicals have become the mainstay of treatment and radiotherapy is less preferred mode of treatment in developing countries like India due to cost constraints.

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15.14 Plasma Cell Dyscrasias

Pankaj Manubhai Shah

INTRODUCTION

Plasma cells and plasmacytoid lymphocytes are the most mature cells of B-lymphocyte origin and may secrete immunoglobulins (Igs). Plasma cell dyscrasias (PCD) are a group of disorders characterised by uncontrolled proliferation and accumulation of a single clone of immunoglobulin (Ig) secreting cells (plasma cell) and secretion of a structurally homogeneous Ig or its polypeptide chains. Multiple myeloma, Waldenstrom's macroglobulinaemia, primary amyloidosis, heavy chain diseases and monoclonal gammopathy of undetermined significance (MGUS) are traditionally included in this group. Amyloidosis has been discussed separately.

IMMUNOGLOBULIN SYNTHESIS AND STRUCTURE

Ig is synthesised and incorporated into the outer membrane of resting B-lymphocytes. Presentation of an antigen to B-cell results in cell proliferation and subsequently differentiation into a clone of plasma cells, synthesising large amount of antibody specific for the antigen and secretion of the antibody into the extra-cellular fluid. Different antigenic stimuli give rise to antigenically different types of Igs, producing diffuse gamma globulin band on electrophoresis. Basic structure of Ig consists of 2 heavy (H) polypeptide chains and 2 light (L) polypeptide chains of the same type.

IgG, IgA, IgM, IgE and IgD are 5 major types of Igs, each defined by type of heavy chain they possess. The light chain of molecule may be kappa or lambda. IgM is the first Ig produced during primary immune response. IgM is also known as macroglobulin due to its pentameric structure and large size. IgM efficiently binds complement and is restricted to intra-vascular space. IgG is the major Ig in the serum. It is normally produced during secondary immune response. It consists of 4 isotypic subclasses (IgG 1 to 4). It is the only Ig transported across the placenta providing passive immunity to the newborn. IgA is the main antibody in saliva, tears and secretions of gastrointestinal and respiratory tract and serves as the first-line of local defense against environmental agents. IgD is thought to act as a cell surface receptor that binds antigen and triggers B-cell proliferation and differentiation. IgE serum levels can be elevated during parasitic infections or in atopic individuals. IgG makes up the largest proportion of Ig in adult plasma, followed by IgA and IgM. The distribution of these proteins in normal serum is parallel to the observed distribution of monoclonal protein (M protein) types in PCD.

Abnormal Synthesis of Immunoglobulins

Ig production and secretion becomes abnormal when an abnormally large monoclonal population of plasmacytes or lymphocytes cells develops from a single precursor cell. This clone produces identical molecules or identical fragments of Ig. As the secreted Ig is homogeneous, the electrophoretic band is discrete and homogeneous. The M protein spike or band is formed which is commonly referred as a paraprotein. The presence of this paraprotein is the most characteristic feature of PCD. The production of normal Igs may be reduced and the normal antibody responses to antigens may be blunted. In normal Ig synthesis, there is a balance between the heavy and the light chains. There is an imbalance between the heavy and the light chains' synthesis in PCD. In myeloma, the most common abnormality is the excess production of light chains over heavy chains. These excess light chains pass into the extra-cellular fluid and are eliminated in urine as Bence-Jones protein. In 11% of myeloma only light chains are secreted. This type of myeloma is referred to as "Bence-Jones myeloma". In heavy chain disease, the neoplastic cells secrete only fragments of intact molecules of the heavy chains. Very rarely neoplastic plasma cells may not secrete paraprotein.

Detection of Monoclonal Proteins

Clinical presentation of PCD is highly variable and related to the sites of infiltration by neoplastic cells and biochemical properties of the protein being overproduced. Frequently, patients are asymptomatic and the diagnosis is suggested by detection of abnormal protein by laboratory profile. The most important means of detecting PCD is electrophoretic measurement of Ig in both serum and urine. The serum electrophoresis with cellulose acetate membrane is satisfactory for screening purpose. The M protein is usually seen as a dense and discrete band on the cellulose acetate membrane. High-resolution agarose gel electrophoresis is more sensitive for the detection of small M proteins. Immuno-electrophoresis or immunofixation with agarose gel or both should be used to confirm the presence of the M protein and to distinguish the Ig class and its light chain type. Radial immunodiffusion is useful for quantitative assessment of Ig. Bence-Jones proteins are made up of light chains, which cross the glomerular filter. Bence-Jones proteins precipitate at 40-60°C, dissolve at 100°C and reprecipitate on cooling. Routine urine examination does not detect presence of Bence-Jones protein. Immunoelectrophoresis or immunofixation of 24-hour urine specimen reliably detects Bence-Jones protein. The detection of a monoclonal urinary light chain peak in the presence of a large amount of protein including albumin raises the possibility of primary amyloidosis or amyloidosis secondary to myeloma.

AETIOLOGY

The aetiology of PCD is not completely understood. The predisposing factors include radiation exposure, chronic antigenic stimulation and environmental exposure to benzene at work place.

MULTIPLE MYELOMA (MYELOMATOSIS, PLASMA CELL MYELOMA OR KAHLER'S DISEASE)

Multiple myeloma is a malignancy arising from the plasma cell. Myeloma may arise unicentrically or multicentrically from the

bone marrow, or as a localised tumour in other sites. It constitutes 10% of haematological malignancy. Majority of cases are seen above the age of 50 years and male to female ratio is 3:2.

Clinical Features and Complications

Multiple myeloma can remain asymptomatic for many years and 20% of cases may be detected by routine laboratory work-up. In symptomatic patients, clinical consequences result from the abnormal accumulation of myeloma cells within the marrow, causing disruption of normal bone marrow function, reflected by anaemia, destruction and invasion of bone surrounding the bone marrow cavity (**Figures 1 and 2**), production and release of M protein from myeloma into the blood stream and/or into the urine, reduction of normal immune function reflected by reduced level of normal Igs and increased susceptibility to infection.

Skeletal System

Skeletal manifestations result from diffuse or focal areas of osteolysis in anatomic relation to an expanding mass of plasma cells. The patients may present with localised area of bone pain and/or swelling in conjunction with marked tenderness; back pain is common. Severe intractable discomfort may represent pathologic fracture. Compression fractures of vertebra are common and can cause the patient to lose height. In 15% of patients, firm plasma cell tumour arising from underlying bone destruction may be palpated on the skull, sternum, clavicle and ribs. Multiple 'punched-out lytic-lesions' are the most frequent radiographic abnormalities (Figure 1). There is a little osteoblastic activity or periosteal reaction unlike the situation in other metastatic lesions of bones. Occasionally only diffuse osteoporosis is seen, which on microradiography may reveal extensive bone destruction. Isotope bone scan may be normal, as there is minimal osteoblastic activity. Computed tomography (CT) and magnetic resonance imaging (MRI) may detect abnormality when routine radiograph is normal in symptomatic patients.

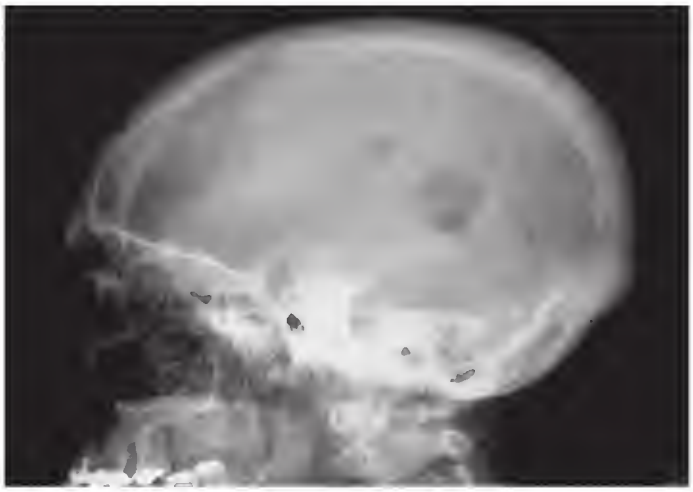


Figure 1: Radiograph of the skull showing multiple punched-out lytic lesions in multiple myeloma.

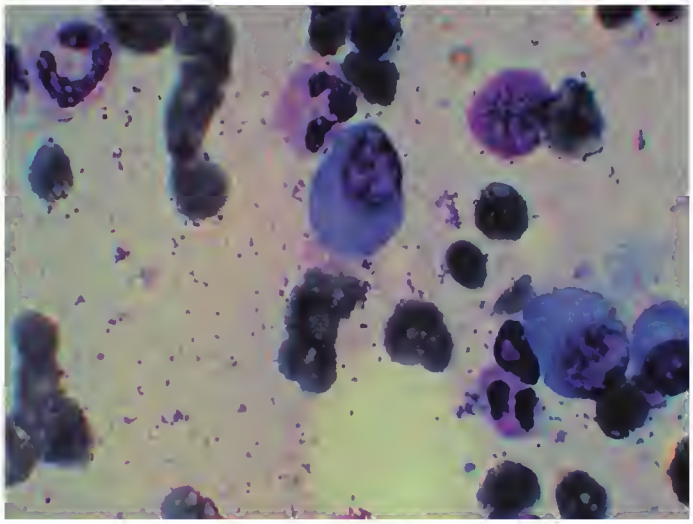


Figure 2: Bone marrow slide showing plasmacytosis. (Haematoxylin and eosin) in multiple myeloma.

Hypercalcaemia

Hypercalcaemia and hypercalciuria due to mobilisation of calcium from bone may accompany myelomatous bone disease. Serum calcium is elevated in one-fourth of patients on presentation. It causes nausea, polyuria, constipation and confusion. It is often precipitated by enforced bed rest and dehydration.

Haematological Manifestations

Normocytic normochromic anaemia is frequent. The peripheral blood smear shows marked rouleaux formation that reflects high globulins. Progressive anaemia, neutropaenia and thrombocytopaenia are suggestive of infiltration of marrow by plasma cells. The M protein may specifically interact with clotting factors leading to acquired clotting abnormalities; it can also coat platelets and interfere with function of platelets. Neutropaenia and inhibition of normal B-cell function leads to the development of bacterial infection. When large number of plasma cells appear in peripheral blood, it is known as plasma cell leukaemia. Bone marrow aspiration shows presence of increased number of plasma cells that may show morphologic abnormalities. Some plasma cells show multinucleation and cytoplasmic vacuoles. When bone marrow aspiration is normal, aspiration from radiological abnormal area should be attempted.

Renal Manifestations

Proteinuria, Bence-Jones proteinuria and elevated serum creatinine levels suggest renal involvement in myeloma. Major causes of renal damage are 'myeloma kidney' and hypercalcaemia. Myeloma kidney is characterised by the presence of large, waxy, laminated casts in the distal and collecting tubules. The casts are composed of mainly precipitated monoclonal light chains. The extent of cast formation correlates directly with the severity of renal insufficiency. Hypercalcaemia and hyperuricaemia are major and treatable causes of renal insufficiency. Amyloidosis and deposition of monoclonal light chains in the renal glomeruli may produce nephrotic syndrome and renal insufficiency. Acquired Fanconi's syndrome may develop due to deposition of light chains in proximal tubule.

Infections

Recurrent bacterial infections are major cause of illness in patients with myeloma due to marked depression of normal immunoglobulin production. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common pathogens. Herpes zoster could be seen more commonly in patients with myeloma complicated by renal failure.

Neurological Manifestations

Vertebral lesions due to plasma cell proliferation lead to radiculopathy/cord compression. Serum protein abnormality may lead to amyloid infiltration of nerves and neuropathy. Intra-cranial plasmacytoma usually represents extension of myelomatous lesions of skull.

Hyperviscosity

High paraprotein levels, particularly IgM, occasionally cause hyperviscosity. Clinical features of hyperviscosity include bruising, epistaxis, hazy vision, headache, gastrointestinal bleeding, sleepiness and variety of ischaemic neurological symptoms.

Diagnostic Procedures and Tests

Tests should be performed to confirm diagnosis, detect complications, assist in the staging of disease and establish baseline value for monitoring the progress. Investigations include complete blood count, serum creatinine, serum electrolytes, serum calcium, serum albumin, serum and urine electrophoresis and immunofixation, bone marrow aspirate and biopsy, complete skeletal survey (plain radiographs of bony skeleton), beta-2 microglobulin and biopsy of solitary or extra-medullary lesion.

Differential Diagnosis

The differential diagnosis of multiple myeloma includes multiple bony secondaries from carcinoma of prostate, breast, thyroid and other organs. Eosinophilic granuloma may also produce multiple lytic lesions in the skull. Biopsy may be required to confirm the diagnosis.

Course and Prognosis

The disease runs a chronic course extending over few years. Most patients succumb to their disease within 36 to 48 months. Various measures to predict prognosis are described. The staging system of Durie and Salmon which is based on haemoglobin, serum calcium and M protein concentration, as well as characteristics of bone survey, classifies patients into three stages which correlates with myeloma cell mass (**Table 1**). Recently, a new staging system has been developed by International myeloma working group after analysing 10,750 untreated symptomatic patients from all over the world. Serum beta-2 microglobulin, serum albumin, platelet count, serum creatinine and age are important prognostic factors. Based on these observations, a combination of beta-2 microglobulin and serum albumin provided the simplest, most powerful and reproducible three stage international staging system.

It is increasingly being appreciated that genetic abnormalities that induce myeloma are the major drivers of disease course and prognosis. These abnormalities can be detected with tests like metaphase cytogenetics and fluorescent *in situ* hybridisation (FISH). Genetic abnormalities like deletion 17, t(14;16) confer a much worse prognosis than that by a hyperdiploid karyotype, t(6;14), t(11;14) and t(4;14). In future, we may see a staging system based predominantly on underlying genetic abnormalities.

Table 1: Staging System for Multiple Myeloma

Dories-Salmon Staging System

Stage	Criteria	Estimated Tumour Burden	Median Survival (in Months)
I	All of the following:		
	Haemoglobin: >10 g/dL	<0.6 x10^{12} cells/m^2 (low)	61 for IA
	Serum calcium: <12 mg/dL		
	Bone radiograph: Normal or solitary lesion		
	Low M-component production		
	IgG level <5 g/dL		
	IgA level <3 g/dL		
	Urine light chain <4 g/24 hour		
II	Fitting neither I nor III	0.6 to 1.20 x 10^{12} cells/m^2 (intermediate)	55
III	One or more of the following:		
	Haemoglobin: <8.5 g/dL	>1.20 x10^{12} cells/m^2 (high)	15 to 30
	Serum calcium: >12 mg/dL		
	Advanced lytic bone lesions		
	High M-component production		
	IgG level >7 g/dL		
	IgA level >5 g/dL		
	Urine light chains >12 g/24 hour		

Sub-classification based on serum creatinine levels: A <2 mg/dL, B >2 mg/dL

International Staging System	Stage (% of Patients)	Median Survival (in Months)
β_2M <3.5 mg/L, alb ≤3.5 g/dL	I (28%)	62
β_2M <3.5 mg/L, alb <3.5 g/dL, *or*	II (39%)	44
β_2M = 3.5 mg/L to 5.5 mg/L		
β_2M >5.5 mg/L	III (33%)	29

Management

The indications for treatment are symptomatic disease, usually due to the presence of hypercalcaemia, renal impairment, anaemia or bony disease. Asymptomatic patients do not require active treatment. However close clinical follow-up, physical examination and measurement of serum and urinary paraprotein every 3 months should be carried-out. Up to 10% of asymptomatic multiple myeloma cases can enter a symptomatic phase every year.

Symptomatic patients need treatment directed control of myeloma activity and to correct complications of myeloma. Supportive care extended to patients during work-up and treatment can lead to significant reduction in initial mortality and morbidity in these patients. Common complications and their treatments are summarised in **Table 2**.

Table 2: Treatment of Complications in Multiple Myeloma

Complication	Therapeutic Options
Bone disease	Bisphosphonates-pamidronic or zolendronic acid in all with bone disease including osteopaenia Monitor renal function Radiation to bony lesions refractory to analgesics or causing cord compression Surgical intervention to treat pathologic fracture Pain control with narcotic analgesics avoid non-steroidal anti-inflammatory drugs (NSAIDs)
Anaemia	Packed cell transfusion Erythropoietin is controversial
Hypocalcaemia	Intravenous fluids and corticosteroids Biphosphonate for severe hypercalcaemia
Infections	Vaccination against *Streptococcus pneumoniae*, *Haemophilus influenzae* and influenza Intravenous immunoglobulin therapy for recurrent life-threatening infection associated with hypogammaglobulinaemia *Pneumocystis jiroveci* prophylaxis with trimethoprim and sulphamethoxazole for patients on high-dose steroids
Renal failure	Correct dehydration, hyperuriasemia and hypercalcaemia. Avoid NSAIDs, and intravenous contrast
Hyperviscosity	Plasmapheresis for symptomatic patient Therapy with a regimen containing high-dose dexamethasone

The choice of initial chemotherapy depends upon need for stem cells harvest after high-dose chemotherapy. Currently practiced chemotherapy regimens are summarised in Table 3. All regimens can prolong survival but none are curative. Patients are initially divided into those who are eligible for high-dose chemotherapy with stem cell rescue and those who are not. Use of melphalan, cyclophosphamide and nitrosourea should be avoided as initial induction therapy in patients planned for high-dose chemotherapy with stem cell rescue, as these drugs damage stem cells, which would be difficult to collect later for transplantation. The options in these patients include 'non-stem cell toxic' drugs like thalidomide, lenalidomide, bortezomib alone or in combination with dexamethasone or VAD. Patients not eligible for high-dose chemotherapy are treated with combination of melphalan, prednisolone with or without thalidomide. Drugs, like lenalidomide and bortezomib, are characterised by high response rates even in patients with "high-risk cytogenetics".

High-dose chemotherapy with hematopoietic stem cell rescue helps in prolonging survival compared to conventional therapy by approximately one year by autologous approaches. There is no survival benefit for early *versus* late transplant. There is also a role for two back-to-back (tandem) transplants in select cases. For maintenance, low-dose thalidomide or alternate day prednisolone is used.

Therapy for relapse cases depends on the timing of relapse, age, prior therapy and clinical status. Options include repeat primary conventional therapy, high-dose therapy with stem cell support, high-dose cyclophosphamide, thalidomide, bortezomib, arsenic trioxide and high-dose steroids.

Treatment of Localised Myeloma

Local irradiation gives pain relief and helps to clear lesion. Isolated extra-medullary plasmacytoma occurring in the tonsils, nasopharynx and paranasal sinuses also disappear after adequate radiotherapy. Rarely surgery may be required followed by radiotherapy.

Variant Forms of Myeloma

Smouldering myeloma

Biologically these patients have very indolent course. The M protein level is more than or equal to 3 g/dL and marrow contains more than or equal to 10% plasma cells. They have no anaemia, renal insufficiency or bony lesions. These patients do not require treatment till the disease progresses.

Plasma cell leukaemia

These patients have more than 20% plasma cells in peripheral smear and have poor response to therapy. Haematopoietic stem cell transplantation may be tried, but relapses are common.

Non-secretory myeloma

In 1% cases of myeloma, plasma cells may produce abnormal protein but do not secrete in plasma. Immune peroxides staining may detect M protein in plasma cells.

POEMS syndrome/osteosclerotic myeloma

These patients have single or multiple osteosclerotic lesions on radiography and have polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. Local irradiation of sclerotic area is the treatment of choice.

Waldenstrom's macroglobulinaemia

In this condition there is proliferation of plasmacytoid lymphocytes secreting IgM protein. Patients often have lymphadenopathy and hepatosplenomegaly but no bony lesions. The most common symptoms are fatigue and manifestations of hyperviscosity (headache, epistaxis and visual disturbances); although characteristics are seen in 5% of patients. Treatment is same as for low grade lymphomas.

Heavy chain disease

These are rare group of lymphoplasmacytoid malignancies producing only various types of heavy chain molecules, which include gamma (γ), alpha (α) and mu (μ). Gamma heavy chain disease is characterised by lymphadenopathy, fever anaemia

Table 3: Chemotherapy Regimen Used in the Treatment of Myeloma

Regimen	Usual Dose	Response Rate	Comment
Pulse dexamethasone	Dexamethasone 40 mg orally day 1 to 4, 9 to 12 and 17 to 20 Repeat every 4 to 5 weeks	45% 25% to 35% in relapsed cases	Helpful in patient with initial aggressive disease, renal failure or impending spinal cord compression
Dexamethasone and thalidomide	Dexamethasone 40 mg orally day 1 to 4, 9 to 12 and 17 to 20 Thalidomide 200 mg orally day 1 to 28, Repeat every 4 weeks	65% to 70% 50% in relapsed cases	Currently used frontline therapy. Useful in relapsed cases. Neuropathy and DVT are potential side-effects
Thalidomide	200 to 400 mg/day orally	35% 25% to 45% response rate in relapse cases	Low-dose useful as maintenance therapy Lenalidomide causes fatigue, thrombosis, skin rash and leucopaenia
Lenalidomide and dexamethasone	Lenalidomide and high-dose dexamethasone	70% first-line therapy	
	Lenalidomide and low-dose dexamethasone	80% first-line therapy	Low-dose dexamethasone has lesser steroid induced toxicities
Melphalan and prednisolone	Melphalan 8 to 10 mg orally on day 1 to 7 Prednisolone 60 mg orally day 1 to 7 Repeat every 6 weeks	50% to 55%	Well tolerated; widely used; slow to act; not good in renal insufficiency
Melphalan prednisolone and thalidomide	Melphalan 4 mg/m^2 day 1 to 7 Prednisolone 40 mg/m^2 day 1 to 7 Thalidomide 100 mg orally day 1 to 28	80%	Recommended in elderly with myeloma
Bortezomib	1.3 mg/m^2 on day 1, 4, 8 and 11 every 28 days	70% 25% in relapsed cases	Produces neuropathy

and malaise. Some cases develop oedema of glottis and palate due to lymphatic obstruction. Disease runs progressive downhill course. Alpha heavy chain disease is the most common amongst heavy chain diseases and is characterised by infiltration of lamina propria of small intestine by lymphoplasmacytoid cells which secret incomplete alpha chains. Chronic diarrhoea, malabsorption and weight loss are major symptoms. Extensive lymphadenopathy in midline, such as paraaortic and mesenteric group, can be demonstrated. Usually alpha heavy chain disease is progressive and foatal. Mu heavy chain disease is characterised by the demonstration of mu chain fragment in the serum. The patient may present with chronic lymphatic leukaemia or lymphoma.

Monoclonal gammopathy of undetermined significance

Patients with MGUS have an M protein in the serum without findings of multiple myeloma, macroglobulinaemia, amyloidosis, or lymphoma and with fewer than 10% plasma cells in the bone marrow. These patients are asymptomatic and should not be treated. They must, however, be followed carefully with protein electrophoresis, bone marrow biopsy and skeletal survey since about 2% per year will progress to develop one of the symptomatic B-cell neoplasm and may then require therapy.

RECOMMENDED READINGS

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15.15 Bleeding Disorders

Kanjaksha Ghosh

INTRODUCTION

Approach to a bleeding patient must follow the classical approach in medicine, i.e. taking history, physical examination and finally deciding about the order and priority of laboratory investigations which will assist in the diagnosis, prognosis and management.

CAUSES OF BLEEDING

Bleeding takes place because of defective/deficient coagulation factors, defective or deficient platelet function or platelet count, diseases of the blood vessels, and combination of all these factors. These defects or deficiencies can arise either due to a genetic cause or due to acquired causes. Acquired causes could again be diverse in nature and may involve traumatic, inflammatory (infective), neoplastic, and drug-induced processes (**Table 1**).

Table 1: Causes of Bleeding in a Patient

Inherited Bleeding Disorders

Deficiency of coagulation factors, i.e. Haemophilia A, B, von Willebrand disease, etc.

Defective platelet number and/or function, i.e. Glanzmann's thromboasthenia, Bernard-Soulier syndrome, etc.

Defective blood vessel wall, i.e. Hereditary haemorrhagic telangiectasia, Marfan syndrome, Pseudoxanthoma elasticum, etc.

Acquired Disorders Causing Systemic Bleeding

Disseminated intravascular coagulation, i.e. snake-bite, septicaemia, malignancy, obstetric accidents, etc.

Deficiency of coagulation factors due to:

- Lack of production/secretion
  - Acquired von Willebrand disease due to hypothyroidism, chronic/acute liver disease.
- Development of antibody to coagulation factors
  - Autoimmune disorders
  - Lymphoreticular malignancies
  - Drugs: penicillin, factor VIII inhibitor, INH, factor XIII inhibitors, heparin-induced thrombocytopaenia and other drug-induced thrombocytopaenia
  - Miscellaneous: old age, post-partum
- Absorption/utilisation of coagulation factors, amyloidosis causing factor X deficiency.

Drugs and vitamin deficiency

- Aspirin, clopidogrel by knocking down platelet function
- Heparin, hirudin, argatroban, oral anticoagulants, etc.
- Vitamin K deficiency, vitamin C deficiency
- Drugs causing marrow aplasia, thrombocytopaenia

Vasculitic disorders of uncertain aetiology

Disorders involving high molecular weight or its clearing activity (ADAMTS-13)

Generally, in congenital disorders of blood coagulation, patient is usually healthy but his disease is a consequence of bleeding (anaemia, haemarthrosis, epistaxis, gum bleeding, genitourinary, gastrointestinal bleeding, etc.). Occasionally bleeding could be trivial in the form of purpura, petechiae, ecchymoses or may be life-threatening like intracerebral bleed, severe bleeding in the lungs, gastrointestinal and genitourinary tract, retroperitoneal or retro-pharyngeal bleed, which can quickly obstruct the major airway.

CLINICAL PATTERNS OF BLEEDING

Severe coagulation factor deficiency as in haemophilia tends to produce joint bleeding (haemarthrosis), intra-muscular bleeds and deeper tissue bleeds, whereas platelet defects/deficiencies tend to produce mucocutaneous bleeding. von Willebrand disease (vWD), where there is low levels of circulating factor VIII and platelet dysfunction due to absence of von Willebrand factor (vWF) produces a clinical picture that is a combination of platelet defect (mucocutaneous bleed) as well as severe factor VIII deficiency (haemarthrosis).

HISTORY

Taking a patient's past history of bleeding particularly with reference to spontaneous bleeding, minor traumatic bleeding, bleeding during falling of deciduous teeth, severe post-operative bleeding, and minor bleeding requiring transfusion; all point to a congenital bleeding tendency. Present history can be elicited taking the points from **Table 2**.

Table 2: History of Bleeding Disorders

Abnormal bruising
Abnormal bleeding from cuts and abrasions
Nasal bleeding
Menorrhagia
Haemarthroses
Bleeding after dental extraction
Bleeding during childbirth
Bleeding during surgery
Previous history of anaemia and transfusion
Drug history
Family history

Drawing a pedigree is an important exercise to find out whether the bleeding disorder is X-linked or autosomal, recessive or dominant in inheritance. Inheritance pattern gives a fair clue to the nature of the defects, which lead to bleeding.

As wound healing and blood coagulation are closely related, congenital defects like afibrinogenaemia/dysfibrinogenaemia and factor XIII deficiency may be associated with delayed wound healing, umbilical cord bleeding or central nervous system (CNS) bleeding following delivery. About 25% to 30% of haemophilia are due to new mutations, hence may not have a family history. Bleeding tendency in other members of a family points to an inherited defect. Sometimes this history may not be straightforward, but exploring the nature of early and unusual deaths in the family may reveal that the cause was excessive bleeding.

Physical examination in the patients may show haemarthrosis, chronic synovitis, muscle haematoma or Volkman's ischaemic contracture due to compartment syndrome following a bleed, compressive neuropathy, petechiae, purpura, ecchymoses, nasal bleeding, gum bleed, bleeding from urogenital, gastrointestinal tract, etc. Sometimes hereditary disorders of connective tissues can give rise to bleeding diathesis and physical examination in these patients may reveal marfanoid habitus, subluxation of lens, pseudo-xanthoma and cardiac murmurs of aortic regurgitation. Ophthalmoscopic examination in these patients may show angioid streaks.

Hereditary platelet defects may sometimes be associated with oculocutaneous albinism, ataxia and oculocutaneous telangiectasia. Severe epistaxis, haemoptysis may occur in patients with hereditary haemorrhagic telangiectasia. In these patients telangiectatic blood vessels may be seen in the palm, nasal septum or tongue. Similar lesions when present in the lungs may produce continuous murmurs and may be imaged using magnetic resonance imaging/high definition computed tomography.

Acquired cause of bleeding involves chronic diseases involving liver, kidneys, obstructive jaundice, acute liver failure, use of anticoagulants or aspirin-like drugs. Haematological disorders like aplastic anaemia, myelodysplastic syndrome (MDS), acute leukaemias (especially acute promyelocytic leukaemia) may be associated with bleeding.

Disseminated intravascular coagulation (DIC) is an important cause of acute bleeding due to diverse insults (physical injury like burns, septicaemia, snake bite, malignancies) that leads to systemic activation of blood coagulation and consumption of coagulation factors. Often this kind of bleeding is associated with multi-organ failure. Causes of DIC and their management have been discussed elsewhere.

Drugs are very important cause of bleeding. Anticoagulants and antiplatelet drugs like aspirin, clopidogrel causing bleeding is easily understood but many drugs can lead to thrombocytopaenia, aplastic anaemia or may cause development of antibodies to coagulation factors resulting in bleeding. Hence, taking history of drugs is an extremely important aspect in the assessment of bleeding disorders. Autoimmune disorders and various vasculitides can cause bleeding tendency either by producing severe thrombocytopaenia, inhibitors to coagulation factors, immune complexes or leucocytoclastic vasculitis or by a combination of all the causes.

Generally, antiphospholipid antibodies associated with systemic lupus erythematosus or occurring *de novo* can cause thrombotic tendency but occasionally it may lead to severe hypoprothrombinaemia causing severe bleeding.

PHYSICAL EXAMINATION

Look for signs of systemic diseases, anaemia, hepatosplenomegaly, and lymphadenopathy, etc. Examine the joints for haemarthrosis, chronic arthritis, muscle contractures, pseudocysts, etc. from the previous bleed. Assess bleeding sites like palate, fundi, size of cutaneous bleeds, e.g. petechiae (pinhead); purpura (~1 cm); bruises and ecchymoses (measure them).

LABORATORY EVALUATION

The first step is to do screening tests as described in **Table 3**. Depending on the defects found in screening tests proceed for correction studies, i.e. see whether mixing normal and patient's plasma in equal proportion corrects the test abnormality. If abnormality is corrected then the patient has deficiency of one or more factors, if not then the presence of an inhibitor to blood coagulation (heparin, antibody, fibrin degradation predict) is indicated. When a factor deficiency is indicated on a screening test and correction studies, relevant factor assays can establish severity of the deficiency. It is to be noted that screening coagulation test (e.g. activated partial thromboplastin time) may be normal in moderate and mild factor deficiency; hence if the patient has strong bleeding history then even if screening coagulation is normal, more detailed investigations are indicated. Factor XIII deficiency, vWF assay and platelet function tests are indicated in the context of relevant clinical presentations. Finally if a patient who has bleeding diathesis and cause is not found out, referral to a specialised coagulation laboratory should be strongly considered. DIC is a very common problem in medical, surgical and gynaecological set-up. Apart from screening coagulation studies which in addition to providing the severity of coagulation disturbances also suggest a rational order of blood components to be replaced, D-dimer assay confirms systemic generation of thrombin and cross-linking of fibrin monomer to dimers or the presence of a big thrombus. In post-operative patients, D-dimer may be weakly positive.

Table 3: Screening Tests for Assessing Bleeding Disorders

Test	Abnormality Detected
Complete blood count including smear exam	Anaemia, pancytopaenia, leukaemia severe thrombocytopaenia, microangiopathy
Platelet count	Thrombocytopaenia
Prothrombin time	Prolonged in deficiency of fibrinogen, prothrombin, factors V, VIII and X, liver disease, oral anticoagulants, isolated deficiency of above-mentioned clotting factors.
Activated partial thromboplastin time	Defects in intrinsic and common pathways. Prolonged in deficiency of factors involved in intrinsic and common pathways of blood coagulation, i.e. haemophilias, von Willebrand disease. Circulating Inhibitors to coagulation like heparin, antibodies to coagulation factors and antiphospholipid antibodies.
Thrombin time	Prolonged in heparin therapy, hypofibrinogenaemia, high levels of FDP in DIC (confirmed by D-dimer assay).

FDP = Fibrin degradation product; DIC = Disseminated intravascular coagulation.

MANAGEMENT

Management of a bleeding patient depends on understanding the cause of bleeding. A patient who is bleeding severely may need supportive therapy in the form of blood transfusion. If non-blood product treatment stops the bleeding, they are to be used first, i.e. DDAVP (Desmopressin) for moderate vWD, moderate and mild haemophiliac patients. Relevant factor concentrates

(plasma-derived and recombinant) for the given factor deficiency, FEIBA (Factor VIII inhibitor bypass activity) or recombinant activated factor VII for a patient with inhibitor who is bleeding should be considered. High levels of heparin in blood causing bleeding can be controlled by protamine sulphate injection. Offending drugs need to be stopped immediately.

Various blood components can be replaced depending on the need of that particular product e.g., platelet concentrates for low platelets or functional defects in platelets, cryoprecipitate to replace factor VIII, vWF and fibrinogen. Fresh frozen plasma for chronic liver disease and for other factor deficiency. No intramuscular injection or non-steroidal anti-inflammatory drugs should be given to a patient with congenital bleeding disorder.

Over anticoagulated (oral) patients who are bleeding can be managed by stopping oral anticoagulation and depending on availability of small dose (1 mg) of vitamin K may be added and if it does not stop bleeding then prothrombin complex/ recombinant activated factor VII/FEIBA and if they are not available then fresh frozen plasma may be used.

RECOMMENDED READINGS

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15.16 Platelet Disorders

SK Bichile

PHYSIOLOGICAL CONSIDERATIONS

Platelets are the smallest component of the blood cells in the peripheral blood. On peripheral blood film from normal uncoagulated blood stained with Ramonavsky stain they appear as anucleate, granular structures of about 2 µm diameter, distributed throughout the film and some of them forming platelet clumps.

They originate from megakaryocytes in the bone marrow. The microstructure of platelet, as revealed by electron microscopy, is complex. Major function of platelets is to form platelet plug at the site of injury. Platelet plug is formed within seconds of injury and it plays crucial role in achieving haemostasis.

Platelet counts are done by using electronic cell counters (manual methods are less accurate). Normal range of platelet count is 1.5 to 4 lakhs/mm^3 (150 to 400 x 10^3/µL). Life span of platelets *in vivo* is estimated to be 9 to 12 days. Old platelets or damaged platelets are phagocytosed in the spleen by macrophages of phagocytic system. The number of platelets in circulation is maintained fairly constant. The major regulator of platelets production is a colony stimulating factor called thrombopoietin.

CLASSIFICATION OF PLATELET DISORDERS

Disorders of platelets are broadly of three types, i.e. thrombocytopaenia (low platelet count), thrombocytosis (high platelet count) and thromboasthenia (normal platelet count with defective function).

THROMBOCYTOPAENIAS

Basically thrombocytopaenia is produced by one of the three mechanisms, i.e. reduced platelet production, excessive peripheral destruction and increased platelet sequestration in spleen. Thrombocytopaenia can occur as an isolated phenomenon or along with suppression of other formed elements of blood (bicytopaenia or pancytopaenia). **Table 1** enumerates causes of thrombocytopaenia.

Clinical Manifestations

Typical clinical manifestation of thrombocytopaenia is skin (dry) and mucous membrane (wet) purpura. The bleeding occurs spontaneously or after trivial trauma. Bleeding gums, epistaxis, menorrhagia and gastrointestinal bleeding are commonly encountered. Severe thrombocytopaenia can lead to life-threatening bleeding such as intracranial bleeding. Severity of bleeding is dependent on the platelet count (**Table 2**).

Clinical and Laboratory Evaluation

Clinical evaluation of thrombocytopaenia should include information on duration of bleeding manifestations, presence or absence of fever, high-risk behaviour, joint pains, symptoms suggesting systemic illness and history of all or any drug. Physical examination should record presence of pallor, lymph node enlargement, hepatosplenomegaly, malar rash, examination of joints and fundoscopy. Laboratory evaluation should include full blood count, peripheral blood film examination for abnormal cells and platelet morphology, prothrombin time, partial thromboplastin time, screening test for human immunodeficiency virus (HIV), test for antinuclear antibodies and bone marrow examination.

Table 1: Causes of Thrombocytopaenia

- **Acquired Thrombocytopaenia**
  - Increased destruction
    - Immune mechanism
      - Idiopathic thrombocytopaenic purpura
      - Drug induced
      - Systemic lupus erythematosus
      - Lymphoproliferative disorders
      - HIV-1 associated
      - Mononucleosis
      - Sarcoidosis
      - Autoimmune thyroiditis
      - Isoimmune thrombocytopaenia
        - Congenital
        - Post-blood transfusion
    - Non-immune mechanism
      - Disseminated intravascular coagulation
      - Thrombotic thrombocytopaenic purpura
      - Haemolytic uraemic syndrome
      - Bacterial infections
      - Massive blood transfusion
      - Thrombocytopaenia of pregnancy
  - Reduced production
    - Vitamin B12 and/or folic acid deficiency
    - Viral infections
    - Hypoplastic/aplastic anaemia
    - Bone marrow infiltration
    - Paroxysmal nocturnal haemoglobinuria
    - Thrombopoietin deficiency
  - Increased sequestration
    - Hypersplenism
    - Hypothermic anaesthesia
- **Hereditary Thrombocytopaenia**
  - Wiskott-Aldrich syndrome
  - May-Hegglin anomaly
  - Bernard-Soulier syndrome

Table 2: Severity of Thrombocytopaenia and Clinical Manifestations

Platelet Count (x 10^3/µL)*	Clinical Manifestation**
>100	Asymptomatic
50 to 100	Haemorrhage after injury
20 to 50	Skin purpura
<20	Spontaneous bleed from mucous membrane, intracranial bleeding

** Pseudothrombocytopaenia is false low platelet count (platelets are not counted accurately); it is suspected when there is no bleeding despite very low platelet count.*

*** Presence of fever or coagulation factor deficiency adversely affects severity.*

Immune Thrombocytopaenic Purpura

Immune thrombocytopaenic purpura occurs due to excessive destruction of platelets by reticuloendothelial system due to autoantibodies or immune complex deposition on platelet membrane. They are broadly classified in two categories: idiopathic thrombocytopaenic purpura (ITP) in which no known aetiological factor is found, and secondary immune thrombocytopaenia seen in systemic lupus erythematosus, lymphoproliferative disorders, drugs and infections.

Idiopathic Thrombocytopaenic Purpura

Pathophysiology of ITP is summarised in **Figure 1**.

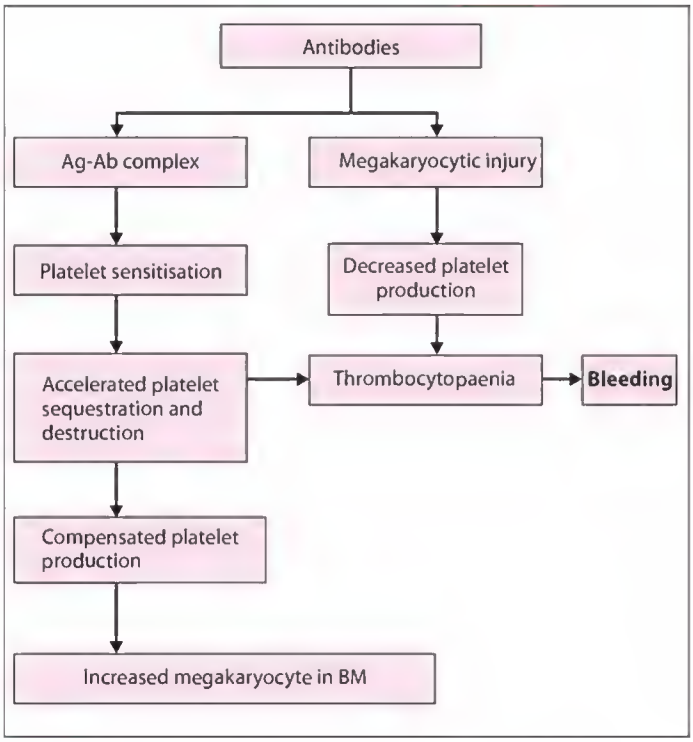


Figure 1: Pathophysiology of idiopathic thrombocytopaenic purpura.

Typically ITP presents with purpuric lesions (red, flat haemorrhages of pin-head size which do not blanch on pressure) or ecchymosis (large purple lesions) on skin and mucous membrane, no symptoms suggestive of systemic illness, absence of lymph node enlargement and absence of hepatosplenomegaly. Bleeding gums, epistaxis, menorrhagia and haematuria are common manifestations. Sometimes bleeding can occur in intracranial site which may be fatal. Clinically ITP is of two types, i.e. acute ITP and chronic ITP. These types differ as regards their clinical characteristics, prognosis and therapeutic strategies (**Table 3**).

Laboratory features

Thrombocytopaenia, large platelets in peripheral blood film, normal total and differential white blood cell count, normal screening coagulation tests and bone marrow aspiration revealing normal or increased megakaryocytes are typical laboratory features of ITP. There can be anaemia proportional to blood loss. In some patients Coombs' test is positive (Evans syndrome). Diagnosis of ITP is by exclusion of causes that produce secondary immune thrombocytopaenia. Decision to skip bone marrow examination in children should be taken in consultation with haematologists.

Table 3: Clinical Characteristics of Acute and Chronic Idiopathic Thrombocytopaenic Purpura (ITP)

	Acute ITP	Chronic ITP
Occurrence	Common in children	Common in adults
Sex	None	Female preponderance
Antecedent infection	1 to 3 weeks prior	Unusual
Bleeding onset	Abrupt	Insidious
Platelet count	<20,000/mm^3	30/mm^3 to 80,000/mm^3
Duration	Usually 2 to 6 weeks	Months to years
Spontaneous remission	80% (6 to 12 months)	Uncommon
Initial treatment approaches	Palliative Keep patient trouble-free Avoid splenectomy	Oral prednisolone High recurrence rate Often require other drugs and splenectomy

Treatment

Although treatment modalities available are similar, different treatment strategies are adopted for ITP in children and ITP in adults. Commonly used initial therapies are described below:

Prednisolone: Prednisolone can be administered orally in an initial dose of 1 to 2 mg/kg daily for 2 to 4 weeks and then gradually tapered over 8 to 12 weeks or more. Oral prednisolone can be effective but it is frequently associated with unacceptable side-effects.

Intravenous immunoglobulin: Immunoglobulins can be administered intravenously in a dose of 400 mg/kg per day for 5 days or 1000 mg/kg for 2 days can be done. Both regimens are equally effective in raising platelet count especially when rapid increase in platelet count is required, e.g. life-threatening bleeding or before surgery. The disadvantages are high-cost and need for repeated administration.

Intravenous anti-D: It can be used as an alternative to intravenous immunoglobulin and has an advantage of lower cost. It can result in an increase in platelet count after 48 hours. Patients have to be monitored for drop in haemoglobin.

Platelet transfusion: It is not required or recommended for initial therapy except in severe life-threatening bleeding. Platelet transfusion must be preceded by a single dose of intravenous immunoglobulin.

Childhood ITP is usually a self-limiting disorder. Patients with mild thrombocytopaenia (no bleeding or minor purpura) are kept under observation. Majority of these patients recover spontaneously over few weeks. The indications to initiate therapy in childhood ITP are platelet count less than 20,000/mm^3 and/or bleeding from multiple sites, impending intracranial or life-threatening bleeding and thrombocytopaenia persisting for more than 6 months.

ITP in adults is insidious in onset and often a chronic disease. It rarely remits spontaneously; however these generally do not have bleeding manifestation if platelet count is between 20,000 to 30,000/mm^3. The natural course of adult ITP varies with periods of exacerbations of thrombocytopaenia and bleeding episodes. Therefore, treatment options are highly individualised and subjective. Patients with mild thrombocytopaenia are kept

under observation without any drug therapy. Those in whom platelet count is less than 20,000/mm^3 and/or have bleeding are given oral prednisolone (1 mg/kg/day). Adult patients require prednisolone for longer periods. Decision of maintenance dose administered is decided by side-effects of chronic steroid administration *versus* its effectivity to maintain target platelet count of 20,000 to 30,000/mm^3.

In patients with chronic and recurrent bleeding manifestations the choice of therapy revolves between off and on steroids, intravenous immunoglobulins, intravenous anti-D, methyl-prednisolone, danazol, immunosuppressive therapy and splenectomy. Other modalities available for such patients are intravenous vincristine, oral dapsone, cyclosporine, interferon-alpha and anti-CD20 antibodies.

Thrombotic Thrombocytopaenic Purpura and Haemolytic Uraemic Syndrome

TTP and haemolytic uraemic syndrome (HUS) are characterised by microangiopathic thrombosis. In TTP the thrombotic process is diffuse whereas in HUS thrombotic process is localised in kidneys.

TTP is a syndrome characterised by pentad of haemolytic anaemia, thrombocytopaenia, fluctuating neurological symptoms, fever and renal dysfunction. It occurs due to disseminated thrombotic occlusion of micro-circulation (terminal arterioles and capillaries). The thrombi are composed of platelets, von Willebrand factor and fibrin is only in small amount.

TTP can occur in previously healthy individuals or associated with disorders such as HIV, *Escherichia coli*, antineoplastic drugs, collagen vascular disease, malignancies and bone marrow transplantation.

TTP is a clinical diagnosis and it requires to be differentiated from HUS. HUS typically occurs in children, associated with localised thrombosis in kidney and often preceded by infection. Clinically HUS is characterised by anaemia, renal failure, abdominal pain and absence of neurological manifestations.

Treatment

TTP carries a high-risk of mortality unless promptly treated. The main modality of treatment is plasma exchange or therapeutic plasma pheresis after which patients respond dramatically and laboratory abnormalities disappear. Plasma exchange of a single plasma volume is done daily up to 10 days. Antiplatelet drugs and corticosteroids are of unproven benefit.

THROMBOCYTOSIS

Thrombocytosis refers to high platelets count (platelet count of 5 to 10 lakhs/mm^3). The term thrombocythaemia is used for a clonal disorder of multipotent stem cells in which platelets count generally, higher than 10 lakhs/mm^3.

Aetiology of thrombocytosis is given in **Table 4**.

Table 4: Causes of Thrombocytosis

Primary Thrombocytosis
Chronic myeloid leukaemia
Myeloproliferative disorders
Polycythaemia vera
Essential thrombocythaemia
Myelofibrosis
Secondary or Reactive Thrombocytosis
Blood loss
Infections
Neoplasms
Post-splenectomy

The differentiation between reactive thrombocytosis and essential thrombocythaemia (ET) is important. In essential thrombocythaemia symptoms are frequent due to disturbances in the micro-circulation. Common clinical features of essential thrombocythaemia are erythromelalgia (red and congested extremities which are warm), central nervous system (headache, giddiness, ringing in ears) and splenomegaly.

Diagnosis of essential thrombocythaemia is by excluding causes of reactive thrombocytosis and myeloproliferative disorders. Treatment of essential thrombocythaemia includes oral anagralide 0.5 mg thrice a day, which effectively controls increased platelet count but it is expensive. Other treatment which has been used is busulfan, hydroxyurea or radioactive phosphorus.

PLATELET FUNCTION DISORDERS

Platelet function disorders are suspected in individuals with history of purpura and having normal platelet counts, absence of platelet clumps in peripheral blood film and prolonged bleeding time. Diagnosis is confirmed by platelet aggregation studies. Platelet function disorders are of two broad types: hereditary and acquired (**Table 5**).

Hereditary platelet disorders present at early age with easy bruisability, bleeding gums, epistaxis, menorrhagia and post-operative bleeding.

Table 5: Causes of Thromboasthenia

Acquired Thromboasthenia
Uraemia
Paraproteinaemia
Drugs: acetyl salicylic acid, ticlopidine, nonsteroidal anti-inflammatory drugs, clopidogrel, tricyclic antidepressants
Myeloproliferative disorders
Hereditary Thromboasthenia
Glanzmann's thromboasthenia
Bernard-Soulier syndrome
Storage pool disorders

Treatment of thromboasthenia includes supportive measures such as local pressure, application of local agents, e.g. fibrin glue, and antifibrinolytic agents (tranexamic acid, epsilon amino caproic acid). Use of 1-desamino-8D-arginine vasopressin (DDAVP) has been shown to shorten the bleeding time. Intravenous administration of recombinant factor VII has been shown to be effective in Glanzmann's thromboasthenia. Patients with severe disease have been successfully treated with allogenic bone marrow transplantation.

RECOMMENDED READING

1. Greer JP, Rodgers GM, Foerster J, *et al*, editors. *Wintrobe's Clinical Haematology;* 11th edition. Philadelphia: Lippincott Williams and Wilkins; 2004.

15.17 Disorders of Coagulation

Jina Bhattacharyya

INTRODUCTION

Disorder of coagulation results because of a defect in any of the processes of coagulation. To know about the defects and the resulting disorders we must have a basic understanding of the steps of coagulation.

MECHANISM OF COAGULATION

The process of coagulation or haemostasis involves a series of proteolytic enzymatic reactions. The reactions that govern haemostasis may be divided into 5 distinct phases:

1. Initiation of coagulation
2. Propagation of α-thrombin formation
3. Termination of the procoagulant response
4. Elimination of the fibrin clot
5. Tissue repair and regenerations

The essential features of the haemostatic response are speed, amplifications, regulations and localisation. The response to injury must be rapid. Initiation of coagulation occurs whenever the vascular milieu is perturbed and antithrombotic nature of the endothelium turns to prothrombotic. The membrane surface and tissue factors are exposed, setting the stage for next phase of coagulation.

There is rapid burst of α-thrombin which activates platelets, pro-cofactors V and VIII, the zymogen factors VII and XI and also factor XIII (F XIII). This cleaves fibrinogen to fibrin clot which is stabilised by F XIII. The activated thrombin activable fibrinolysis inhibitor (TAFIa) protects the fibrin clot from proteolysis. Thus, the propagation phase stops blood loss by forming a stable clot. The termination phase limits the coagulation process and prevents excessive clot formation through plasmin dependent process. The enzyme plasmin cleaves fibrin clot to produce soluble fibrin peptide. This whole process of solubilisation and removal of fibrin clot is coordinated with processes of tissue repair and regeneration.

All these steps of coagulation must occur rapidly and in a precise choreographed manner and must be located at the site of injury. This localisation is controlled at several levels. Unperturbed endothelial cells actively inhibit coagulation; the surface of undamaged cells is not conducive to the assembly and function of procoagulant protein complexes.

There are two distinct procoagulant pathways. The primary or extrinsic [tissue factor (TF)] pathway consists of the intrinsic and extrinsic tenase complexes and prothrombinase complex whereas accessory or intrinsic pathway is composed of F XII – high molecular weight kininogen (HMWK) – Prekallikrein complexes. Both pathways lead to activation of F IX and converge at the intrinsic tenase complex. Finally, prothrombinase complex is formed with generation of α-thrombin. Classical coagulation tests differentiate between the two pathways; activated partial thromboplastin time (APTT) initiates coagulation through accessory pathway and prothrombin time through primary pathway. The procoagulant response is triggered upon by the interaction of activated factor VIIa (F VIIa) and TF when TF is expressed as a result of vascular perturbation. The resulted extrinsic tenase complex activates F IX and F X; F IX combines with F VIIa to form the intrinsic tenase complex to accelerate activated factor X (F Xa) generation. The burst of F Xa overcomes the inhibition and initiates maximal levels of prothrombinase complex activity which in turn leads to burst of α-thrombin generation and propagation of the procoagulant response (**Figure 1**).

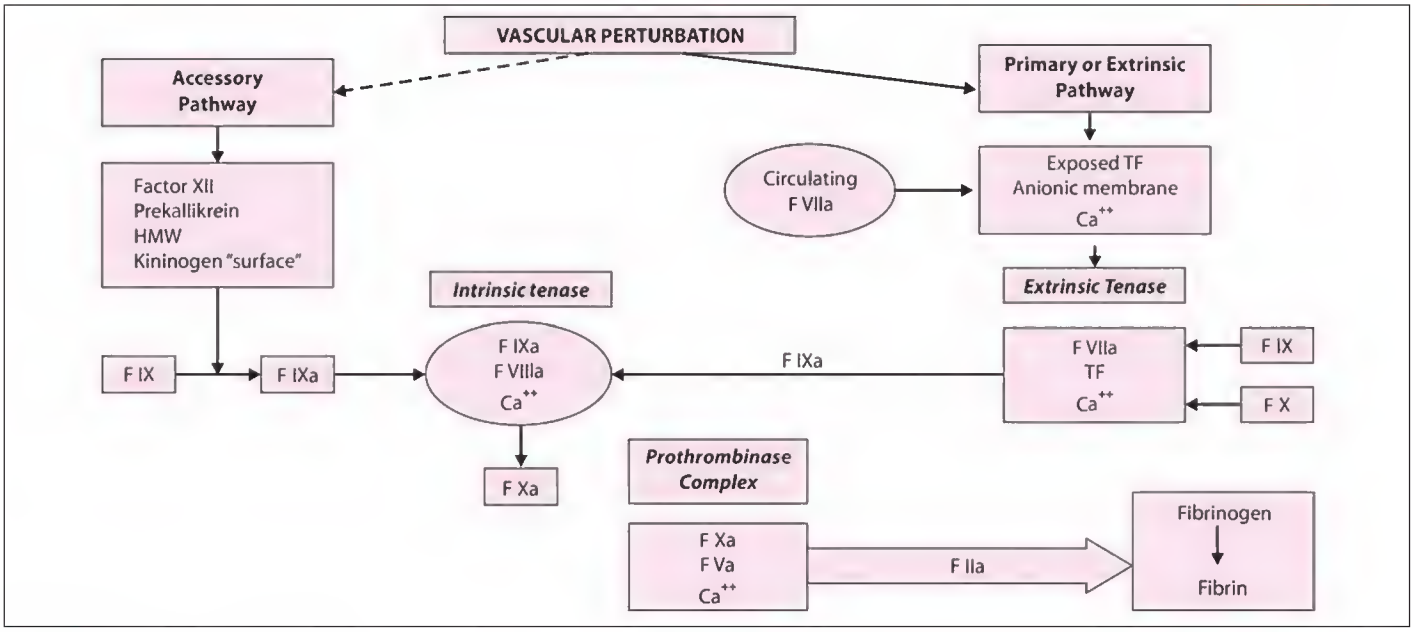


Figure 1: Basic pathways of coagulation.

HMW = High molecular weight; TF = Tissue factor.

The role of intrinsic or accessory pathway is not clearly defined and it appears that this pathway is not essential for haemostasis, because it has been seen that persons deficient in the factors needed in accessory pathway do not have any bleeding manifestation even after surgical challenge.

INHERITED DISORDERS OF COAGULATION

Disorders of coagulation may be inherited or acquired. Inherited disorders of coagulation usually result from a deficiency or abnormality of a single plasma protein. **Table 1** shows different types of inherited disorders of coagulation. Haemophilia A and von Willebrand disease (vWD) are the two most common inherited coagulation disorders. Diagnosis of these disorders is based on clinical pointers as to the pattern of bleeding and laboratory tests as shown in **Table 2**. Immunologic assays available for coagulation factor are expressed as positive or negative for cross reactive material (CRM). A CRM positivity means the disorder is qualitative and CRM negativity means it is a quantitative disorder.

Table 1: Inherited Disorders of Coagulation

X-linked Recessive Traits
- Haemophilia A
- Haemophilia B (i.e. CRM^+ and CRM^- variants; haemophilia B_m, B Leyden, etc.)

Autosomal Recessive Traits
- von Willebrand disease
- Dysfibrinogenaemias

Combined Abnormalities
- Associated with factor VIII deficiency (i.e. factor V deficiency, haemophilia B, factor XI deficiency, factor VII deficiency, von Willebrand disease, dysfibrinogenaemias, platelet dysfunction)
- Involving vitamin K-dependent factors (i.e. factors II, VII, IX, and X; factors IX and XII; others)

Miscellaneous
- Prekallikrein deficiency
- High molecular weight kininogen deficiency
- Deficiency of physiologic inhibitors [i.e. α_2-antiplasmin, abnormal α_1-antitrypsin (antithrombin Pittsburgh)]

Haemophilia A and B are X-linked with bleeding manifestation in male homozygote, vWD is autosomal dominant and the rest of the disorders are autosomal recessive where bleeding manifestation occur in homozygotes or complex heterozygotes.

Table 2: Basic Diagnostic Evaluation of Coagulation Disorders

Clinical pointers like mucosal bleed versus bleeding into joints and muscles, delayed bleeding, family history, age of onset, sex, etc.

Screening coagulation test including platelet count and morphology, bleeding time, prothrombin time, activated partial thromboplastin time and factor XIII assay

Correction studies of prolonged coagulation times, with pooled normal plasma, absorbed and aged plasma and/or factor deficient plasma

Factor assays to confirm the deficiency and establish its severity—functional/antigenic.

The treatment of these disorders is replacement for each bleeding episode. The dose depends on the level of haemostasis required based on the severity of bleeding. The activity of various coagulations factor are expressed in units, defined as the activity present in 1 mL of fresh plasma from a normal donor. Thus, the concentration of all coagulation factors in normal pooled plasma is 1 IU/mL or 100 mg/dL or 100% activity; in the blood bank the level is 80 IU/dL because of dilution with anticoagulants. Common inherited disorders will be discussed briefly here.

HAEMOPHILIA

It can be haemophilia A (deficiency of factor VIII) or haemophilia B (deficiency of IX). Haemophilia A is more common; the incidence of the disease can be as high as 1 in 10,000 person. In India, the estimated prevalence of Haemophilia A is ~50,000 and 1,300 new cases are born per year. It is inherited as X- linked recessive disorder. However, in one-third of the patients there is a lack of family history which suggests that one-third would result from spontaneous mutation. The molecular defect can be a point mutation, deletion or inversions. Approximately 5% of patients with haemophilia A have deletions in the F VIII gene; 40% severe haemophilias are secondary to major inversion of section of the tip of long arm of X chromosome (intron 22 inversion). Haemophilia in females is rarely seen; most common form is seen in a minority of heterozygous female where X chromosome inactivation occurs at an early stage of embryogenesis and the second form is seen in homozygous female as a result of mating between a haemophilic male and a heterozygous female.

Patients with haemophilia have prolonged and excessive bleeding with minor trauma. Bleeding into joints and soft tissues is the hallmark of the disease. The severity and frequency of the bleeding episodes depend upon the factor level. Based on severity a consensus committee has classified haemophilia into 3 categories as shown in **Table 3**. Earliest manifestations of the disease are subcutaneous haematomas when the child starts crawling and as the child starts walking bleeding into joint starts appearing. Haemarthrosis is the most common, most painful and most physically, economically and psychologically disabling manifestation of these disorders. It results from bleeding into the joint cavity or its epiphysis or diaphysis from the synovial vessels. The retained blood results in chronic inflammation. Recurrent haemarthrosis leads to progressive thickening of the synovium resulting in chronic proliferative synovitis. In the terminal stage, chronic haemophilic arthritis sets in which is a form of fibrous or bony ankylosis of the joints. The knee joint is the most commonly affected joint and most often is permanently crippled. Besides bleeding into joints, a patient can have subcutaneous and intramuscular haematomas, which may compress vital structures. Psoas and retroperitoneal haematomas, gastrointestinal and genitourinary bleeding and intracranial bleeding, are different forms of bleeding episodes.

Table 3: Severity of Haemophilia and Clinical Manifestations

Severe	Factors VIII or IX level is less than 1% Spontaneous joint and soft tissue bleeding several times every month.
Moderate	Factors VIII or IX level is 1% to 5% Spontaneous bleeding is uncommon but occurs after minor trauma or surgery.
Mild	Factors VIII or IX level is 5% to 30% Bleeding occurs only after significant trauma or surgery.

Replacement of the deficient factor is the principal treatment. The objective is to achieve a haemostatic level. This depends on severity of bleeding and availability of factor concentrate. Dose can be calculated on the basis of body weight or plasma volume. One unit of factor per kilogram would raise F VIII level by 2% and F IX level by 1%. **Table 4** shows replacement doses for different bleeding episodes. Factor can be replaced on demand, at the onset or premonition of bleed or as regular prophylaxis 2 to 3 times a week to maintain factor level of more than or equal to 1%. The goal of the treatment is to maintain a normal life. The patient and family members should be counselled about the disease, its implications and its management. They should be able to recognise the onset of bleeding early and be aware of its management.

VON WILLEBRAND DISEASE

It is the most common bleeding disorder affecting 1% of population. The name derived from von Willebrand who had recognised the disease in 1926 amongst the inhabitants of Aland Islands. It is a very heterogeneous disorder and multiple variants have been recognised. However, all of these variants are either due to insufficient amounts of von Willebrand factor (vWF) or defective function of this protein. Broadly, the disease is divided into 2 parts: quantitative which can be partial or severe deficiency and qualitative deficiency. However, as per the revised classification the diseases are sub-grouped into 3 variants as shown in **Table 5**. Type 1 vWD accounts for 70% of all cases.

Table 4: Replacement Therapy in Haemophilia A and Haemophilia B

Disorder	Therapeutic Product	Minor bleeding (i.e. uncomplicated haemarthroses; haematomas in noncritical areas; haematuria; dressing changes; arthrocentesis; removal of sutures and drains)		Major bleeding (haematomas in critical locations; traumatic injuries; multiple tooth extractions; major surgical procedures)	
		Loading Dose	Maintenance Dose	Loading Dose	Maintenance Dose
Haemophilia A (factor VIII deficiency)	Cryoprecipitate	Not required	1.25 to 1.75 bags/10 kg every 12 h for 1 to 3 days	3.5 bags/10 kg	1.75 bags/10 kg every 8 h for 1 to 2 days; every 12 h thereafter
	Purified factor VIII	Not required	10 to 15 IU/kg every 12 h for 2 to 4 days	30 to 40 IU/kg	30 to 40 IU/kg every 12 h
Haemophilia B (factor IX deficiency)	Prothrombin complex	20 to 30 IU/kg	15 IU/kg every 24 h for 2 to 4 days	40 to 60 IU/kg	20 to 25 IU/kg every 24 h
	Purified factor IX	20 to 30 IU/kg	15 IU/kg every 24 h for 2 to 4 days	60 to 70 IU/kg	20 to 40 IU/kg every 24 h for 2 to 4 days

The replacement therapy requires a large quantity of factor concentrate which is very costly. It becomes very difficult for the patients and families to bear the cost, especially in India. Due to lack of treatment, therefore, many patients in India become crippled.

Anti-fibrinolytic agents like tranexamic acid and ε-epsilon amino-caproic acid (EACA) are used mostly in mucosal bleeds and also bleeding into central nervous system. These agents bind fibrinogen and thus, inhibit fibrinolysis. These should not be used in patients with haematuria.

Desmopressin (DDAVP; 1-desamino-1-D-arginine vasopressin) is used for mild bleeding episodes and mild haemophiliacs. It acts by increasing the release of stored factor VIII from endothelial cells. Hence, it is not useful for severe haemophiliacs. It is given as slow intravenous infusion or subcutaneous or intranasal route.

Additional measures include ice cold compression, analgesics, fibrin sealants, rest and physiotherapy. Physiotherapy is an important element of management and patient and family members must know its importance to have a normal quality of life. For complications like chronic haemophilic arthropathies, and pseudotumour, surgical management may be required.

Carrier detection helps in prevention of the disease by genetic counselling and antenatal diagnosis. Daughters of men with haemophilia and mothers with an affected son and another haemophiliac male relative are obligate carriers. Other females in the family from the same lineage are possible carriers. Carriers have reduced or low normal factor VIII/IX coagulant activity.

Table 5: Revised Classification of von Willebrand Disease

Revised type	Features
1	Partial deficiency of von Willebrand factor (vWF)
2	Qualitative vWF defects
2A	vWF variants with loss of high molecular weight multimers and decreased vWF-dependent platelet adhesion
2B	vWF variants with loss of high molecular weight multimers caused by increased affinity for platelet glycoprotein Ib
2M	vWF variants with decreased vWF-dependent platelet adhesion not associated with the loss of high molecular weight multimers
2N	vWF variants with decreased binding affinity for factor VIII
3	Severe deficiency of vWF

The basic defect is a deficiency or abnormality of vWF function. vWF is synthesised in the endothelial cells and megakaryocytes. It is required for normal platelet adhesion and it also acts as a carrier for factor VIII in the plasma. Whenever, vWF is deficient or aberrant, abnormalities in the early stages of primary haemostasis or F VIII deficiency result. Bleeding manifestations are heterogeneous. In mild forms, the manifestations may be skin and mucosal bleed due to defective primary haemostasis whereas in severe forms, haemarthrosis and dissecting intramuscular haematomas are seen. Epistaxis, easy bruisability, menorrhagia are amongst the different spectrum of disease manifestations.

Diagnosis of the disease may require repeated observations over a prolonged period of time. Both vWF and F VIII are acute phase reactants and increase in stress, pregnancy, trauma, oestrogen therapy, etc. Screening tests include bleeding time, platelet count, PFA-100, partial thromoboplastin time (PTT). Bleeding time is increased but may be normal; however, prolonged bleeding time adds to the diagnosis. Bleeding time is not recommended to monitor disease response to treatment. Plasma level of F VIII varies greatly from as low as ~3 µ/dL in patients with Type 3 vWD to normal levels in patients with mild type. vWF immunoassay is a quantitative measure of vWF. In patients with blood group O, the level is 25% lower. Ristocetin cofactor activity assay (vWF: RCo) is the most sensitive and specific assay for the diagnosis of vWD. Multimeric analysis is done to further characterise the disease.

Majority of the patients with vWD are mild, hence seldom need factor replacement. The goal of therapy is to stop active bleeding and prevent excessive bleeding during procedures, surgery and trauma.

DDAVP (Desmopressin) is the mainstay of treatment for mild forms of vWD. It raises the levels of vWF and F VIII by 2 to 4-fold over baseline. Response to treatment is variable between patients, and therefore, it is essential that therapeutic response is documented for each patient by a test dose at the time of diagnosis or before elective treatment or surgical prophylaxis.

DDAVP unresponsive patients need transfusion support; cryoprecipitate which can be obtained from the blood bank gives 80 to 100 units of factors per bag. Alternatively, intermediate purity F VIII concentrate with preservation of vWF multimers can be used.

Limited studies in India have reported a prevalence of approximately 10% of vWD among the cases with inherited bleeding disorders. In contrast to the Western countries Type 3 vWD has been shown to be more common; in a recent Indian Council of Medical Research study of vWD in Western India, it has been shown that Type 3 vWD is prevalent in ~ 60% of the cases. This may be because of low awareness and under-diagnosis of the mild cases.

OTHER INHERITED COAGULATION DISORDERS

Other inherited coagulation disorders like deficiencies of factor II, VII, IX, XI are rare and more commonly seen in populations that have consanguineous marriages. Afibrinogenaemia, dysfibrinogenaemia and factor XIII deficiency are also rare. Classically, in factor XIII deficiency there is history of bleeding from the umbilical stump, and spontaneous bleeding into the central nervous system is common. **Table 6** shows replacement therapy for this group of deficiency disorders. Inherited deficiency of multiple coagulation factors is very rare and only a few cases are reported. Congenital vitamin K-dependent coagulation factor deficiency (VKCFD) is one such form and has received increasing interest lately.

Table 6: Replacement Therapy in Other Inherited Coagulation Disorders

Disorder	Therapeutic product	Loading dose	Maintenance dose
von Willebrand disease	Hymate-P Cryoprecipitate	40 to 60 IU/kg Not required	40 to 50 IU/kg every 12 to 24 h;up to 7 days 1 bag/10 kg daily
Fibrinogen deficiency	Cryoprecipitate Purified fibrinogen	1 to 2 bags/10 kg 50 to 100 mg/kg	1 bag/10 kg every other day 20 mg/kg every other day
Prothrombin deficiency	Fresh frozen plasma	15 mL/kg	5 to 10 mL/kg daily
Dysprothrombinaemia	Purified prothrombin complex	20 IU/kg	10 IU/kg daily
Factor V deficiency	Fresh frozen plasma	20 mL/kg	10 mL/kg every 12 to 24 h
Factor VII deficiency	Fresh frozen plasma Purified prothrombin complex	20 mL/kg 30 IU/kg	5 mL/kg every 6 to 24 h 10 to 20 IU/kg every 6 to 24 h
Factor X deficiency	Fresh frozen plasma Purified prothrombin complex	15 to 20 mL/kg 15 IU/kg	5 to 10 mL/kg daily 10 IU/kg daily
Factor XI deficiency	Fresh frozen plasma	15 to 20 mL/kg	5 mL/kg every 12 to 24 h
Factor XIII deficiency	Fresh frozen plasma	5 mL/kg every 1 to 2 weeks	Not usually required

ACQUIRED COAGULATION DISORDERS

The acquired coagulation defects are usually characterised by multiple coagulation factor deficiencies, unlike congenital coagulation disorders which are because of a single factor deficiency. Acquired ones are usually associated with thrombocytopaenia, platelet functional defect and/ or vascular abnormalities. **Table 7** shows different forms of acquired coagulation disorders.

COAGULOPATHY DUE TO LIVER DISEASE

Liver disease can impair coagulation as a result of both biosynthetic and clearance dysfunction of liver. **Table 8** shows abnormalities of haemostasis and coagulation associated with liver disease. Even though numerous haemostatic abnormalities are associated with liver disease, majority of the patients do not bleed spontaneously. Most common bleeding manifestation is gastrointestinal haemorrhage and most commonly this originates from oesophageal varices, peptic ulcer, gastritis, etc. All patients with coagulation and liver disease do not require haemostatic correction. Patients with prolonged prothrombin thrombin time and high fibrin degradation products (FDPs) have a high-risk of bleeding.

Vitamin K supplementation can produce some improvement in coagulation abnormalities in ~30% of the patients. Replacement with fresh frozen plasma (FFP) is recommended only to patients with active bleeding and as surgical prophylaxis. Recombinant F VIIa may be used for hepatic coagulopathy. For

Table 7: Acquired Coagulation Disorders

Deficiencies of vitamin K-dependent coagulation factors

- Haemorrhagic disease of the newborn (vitamin K deficiency bleeding)
- Biliary obstruction (gallstone, strictures, fistulas)
- Malabsorption of vitamin K (sprue, idiopathic steatorrhoea, coeliac disease, ulcerative colitis, regional enteritis, gastrocolic fistulas, *Ascaris* infestation)
- Nutritional deficiency
- Drugs
  1. Pharmacologic antagonists of vitamin K (coumarins, indandiones, others)
  2. Those that alter gut flora (broad-spectrum antibiotics, sulphonamides)
  3. Miscellaneous (cholestyramine)

Liver Disease

Accelerated destruction of coagulation factors

- Disseminated intravascular coagulation
- Fibrinolysis (liver disease, thrombolytic agents, tumours, after surgery)

Inhibitors of coagulation

- Specific inhibitors (antibodies)
- Antiphospholipid-protein antibodies
- Miscellaneous (antithrombins, paraproteinemias)

Miscellaneous

- After massive transfusion
- After extracorporeal circulation
- Drugs (antibiotics, antineoplastic agents, others)
- Miscellaneous (polycythaemia vera, congenital heart disease, amyloidosis, nephrotic syndrome, Sheehan syndrome, Gaucher's disease, leukaemia, others)

Table 8: Abnormalities of Haemostasis and Coagulation in Liver Disease

Deficient biosynthesis

- Of fibrinogen; prothrombin; coagulation factors V, VII, IX, X, XI, XII, XIII; prekallikrein; high molecular weight kininogen
- Of antiplasmins, antithrombin, proteins C and S

Aberrant biosynthesis

- Of abnormal fibrinogen, factor V
- Of abnormal inhibitory analogue of prothrombin factors VII, IX, and X

Deficient clearance

- Of haemostatic 'products' [e.g. fibrin monomers, fibrin(ogen) degradation products, platelet factor-3]
- Of activated coagulation factors (IXa, Xa, XIa)
- Of plasminogen activators

Accelerated destruction of coagulation factors

- Disseminated intravascular coagulation
- Abnormal fibrinolysis

Thrombocytopaenia

- Hypersplenism (portal hypertension)
- Folic acid deficiency
- Chronic ethanol intoxication
- Disseminated intravascular coagulation

Platelet dysfunction

- Acute and chronic ethanol intoxication
- Effects of products of fibrinogen degradation
- Uraemia

Miscellaneous

- Inhibition of coagulation by products of fibrinogen degradation
- Loss or consumption of coagulation factors in ascitic fluid

thrombocytopaenia synthetic thrombopoietin or thrombopoietin mimetic agents are nowadays available, but yet unproven in controlled trials.

Disseminated Intravascular Coagulation

A consensus definition of disseminated intravascular coagulation (DIC) has been proposed:

'It is an acquired syndrome characterised by intravascular activation of coagulation with loss of localisation arising from different causes. It can originate from and cause damage to the microvasculature which if sufficiently severe can cause organ dysfunction.'

The pathophysiology of DIC is complex. The trigger acts on processes involved in normal haemostasis; thrombin is persistently generated and fibrin is formed in the circulating blood. Thus, fibrinogen and other coagulation factors are consumed. The fibrinolytic mechanism is activated and large numbr of FDP are generated.

The major clinical features of DIC are abrupt onset serious bleeding, shock out of proportion to blood loss, acute renal failure, and thromboembolic manifestations. There is a marked heterogeneity in clinical manifestations; it has been shown that DIC due to obstetric disorders manifests as bleeding in almost all whereas DIC due to sepsis are mostly associated with organ dysfunction.

Laboratory tests should be interpreted carefully as levels of many coagulation factors remain elevated in many of the conditions associated with DIC. Basic blood examination would show schistocytes on peripheral blood smear in ~50% of the cases which is suggestive of DIC. D-dimer is one of the important tests; level of more than 2,000 ng/mL is consistent with DIC, but is NOT specific.

The aim of replacement therapy in DIC is to replenish fibrinogen and is achieved by using cryoprecipitate which contain fibrinogen of ~250 mg per bag. Bleeding patients with platelet count of less than 50,000/cu mm should be given platelet transfusion; due to associated platelet function defect, DIC patients required a higher platelet count, for adequate haemostasis. Anti-fibrinolytic agents like EACA and tranexamic acid should be used carefully and only in selected cases where fibrinogenolysis, hypofibrinogenaemia, and adequate renal function is clearly documented. Heparin therapy has favourable result in patients with chronic DIC manifesting mainly with thrombosis, but is avoided in acute DIC with active bleeding.

ACQUIRED HAEMOPHILIA

Acquired haemophilia is seen as a result of autoantibodies to factor VIII in non-haemophilia persons. It can arise spontaneously or secondary to various diseases as shown in **Table 9**. In elderly persons it is most often idiopathic. The disease manifestations are like congenital haemophilia except that haemarthrosis is an uncommon presentation. Antibodies to F VIII that arise during pregnancy may cross the placenta. Prolonged APTT which does not correct on mixing with normal pooled plasma gives clue to the diagnosis which can be confirmed by factor

assay and inhibitor assays. Treatment includes replacement therapy with large doses of recombinant factor VIII concentrate, steroids, cytotoxic agents, intravenous immunoglobulin (IVIG), recombinant F VIIa and rituximab (monoclonal antibody to CD20).

Table 9: Different Causes of Acquired Haemophilia

Alloantibodies in haemophilia A
Autoantibodies in non-haemophilia patients
Autoimmune disease
Systemic lupus erythematosus
Rheumatoid arthritis
Dermatologic conditions
Psoriasis
Pemphigus vulgaris
Pregnancy (peripartum)
Malignancy
Lymphoproliferative disorders
Plasma cell dyscrasias
Non-haematologic
Medications: penicillin, sulpha antibiotics, chloramphenicol, phenytoin
Idiopathic

ACQUIRED DEFICIENCY OF SINGLE COAGULATION FACTOR

This is an uncommon phenomenon. Isolated F X deficiency is seen in patients with primary amyloidosis. Likewise, hypoprothrombinemia has been seen to be associated with lupus anticoagulant. In nephritic syndrome, deficiencies of prothrombin, F IX and F XII, plasminogen and antithrombin have been reported due to loss in urine. F XIII deficiency has been associated with inflammatory bowel disease.

CONCLUSION

Coagulation disorders are seen commonly in clinical practice. History of the pattern of bleeding, age of onset, family history and clinical examination (haematomas, haemarthrosis, joint deformity, petechia, ecchymosis, evidence of underlying clinical condition, etc.) are of utmost importance while evaluating such patients. Short screening is the first line of laboratory evaluation on the basis of which confirmatory tests are planned. Principal treatment of this disorder is replacement of the deficient factor. Most of the factors are commercially available; however cost is a concern especially in India. Transfusion transmitted infection, inhibitor formation and thrombosis are the major concerns of replacement therapy. Therefore, mild haemophilia and mild vWD should be treated with DDAVP or antifibrinolytic agents to avoid unnecessary exposure to factor concentrates or blood or animal products. Factor concentrates used for replacement should preferably be recombinant or otherwise be virus inactivated. Awareness amongst patients and family members and measures for carrier detection would go a long way for the prevention of common inherited disorders.

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15.18 Hypercoagulable Disorders

Mammen Chandy

PHYSIOLOGY OF HAEMOSTASIS AND ITS REGULATION

There are three integral components of haemostasis—blood vessel wall, platelets and coagulation cascade, which lays down the fibrin clot. Haemostasis is always linked to fibrinolysis since the clot must be removed within the lumen of the vessel and blood flow restored. There is a finely tuned regulatory mechanism to balance the need to arrest haemorrhage and also prevent thrombosis.

The key initiator of coagulation is tissue factor VIIa which generates a small amount of thrombin through factors X and V and this then augments the process by activating factors XI, IX and VIII. More thrombin is generated, fibrinogen is converted to fibrin and this is stabilised by factor XIII. Tissue factor pathway inhibitor (TFPI) blocks the tissue factor/VIIa complex while antithrombin III (ATM) inhibits coagulation by blocking the action of thrombin and factor X while protein C and its co-factor protein S act by breaking down activated Factors VIII and V. Platelets are important in primary haemostasis as they play an important role in arterial thrombosis and atherosclerosis (**Figure 1**). The endothelial cell is not just the part of a conduit but it has important procoagulant and anticoagulant functions (**Figure 2**). Once a clot has been formed the intraluminal portion is broken down by plasmin which is formed by the action of activators on plasminogen within the clot, while any free plasmin is inactivated (**Figure 3**).

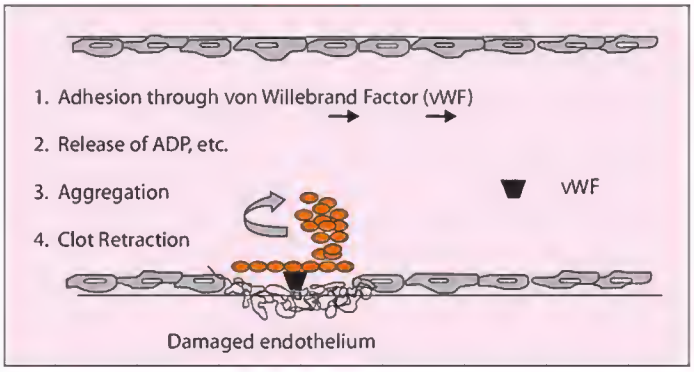


Figure 1: Role of platelets in haemostasis.

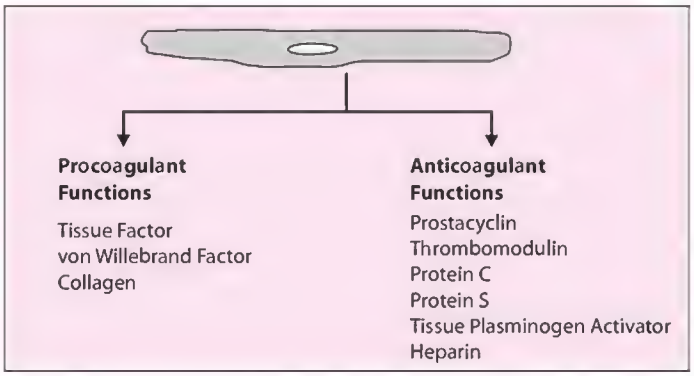


Figure 2: Endothelial cell in haemostasis.

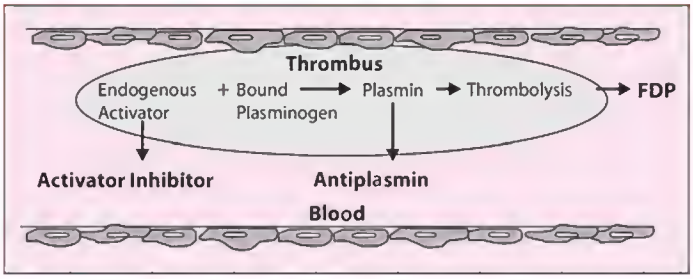


Figure 3: Normal fibrinolysis within a thrombus.

PATHOGENESIS OF THROMBOSIS

It is evident that any change in this finely balanced system can result in either thrombosis or haemorrhage; Rudolf Virchow was the first to suggest that there are three underlying precipitating factors in the pathogenesis of thrombosis: stasis, damage to the vessel wall and change in the composition of blood. Today the pathogenesis can be understood in terms of genetic risk factors and acquired factors and in a given patient these two could be operating together resulting in thrombosis (**Tables 1 and 2**).

Table 1: Acquired Causes of Thrombosis

Lupus anticoagulant syndrome
Malignancy
Drugs: oestrogen, prothrombin complex concentrates, heparin
L-asparaginase
Nephrotic syndrome
HUS, TTP
Paroxysmal nocturnal haemoglobinuria (PNH)
Myeloproliferative disorders: Polycythaemia, essential thrombocythaemia
Vascular damage due to diabetes, hypertension, atherosclerosis
Hyperlipidaemia
Congestive cardiac failure, hyperviscosity
Immobilisation

HUS = Haemolytic-uraemic syndrome; TTP = Thrombotic thrombocytopaenic purpura.

Table 2: Hereditary Causes of Thrombosis

Resistance to activated protein C-Factor V Leiden
AT III deficiency
Protein C deficiency
Protein S deficiency
Prothrombin gene mutations
Disorders of fibrinolysis
Dysfibrinogenaemia
Homocystinuria homozygous and due to methylene tetrahydrofolate reductase mutations
Sickle cell anaemia

Fifteen per cent of patients less than 45 years of age with venous thrombosis may have an inherited thrombotic disorder. Clinical features and diagnosis of venous and arterial thromboembolism are discussed in different sections of this book.

THROMBOPHILIA

This is a term used when an individual has a predisposition to thrombosis which can be inherited or acquired. Table 2 lists the hereditary causes and the probability of finding a genetic predisposition in patients with deep venous thrombosis (DVT). Deficiencies of AT III, protein C and protein S are rare with a frequency of less than 0.5% in the population. AT III deficiency is autosomal dominant and there is a high-risk of thrombosis. Homozygous protein C is very severe and presents as purpura fulminans. Acquired deficiencies of these anticoagulant proteins can occur in patients on L-asparaginase, those with nephrotic syndrome and vitamin K deficiency. The most common genetic cause for thrombosis among Caucasians is factor V Leiden where the mutation makes FV resistant to proteolytic cleavage by protein C. Mutations in the methylene tetrahydrofolate reductase gene are present in 20% of the population and this may produce a mild increase in the tendency to clot because of raised homocysteine levels. Clinical indications of a hereditary thrombotic disorder include: thrombosis occurring at an early age, family history of thrombosis, thrombosis at an unusual site, recurrent thrombosis, thrombosis while on anticoagulants and warfarin-induced skin necrosis.

Thrombophilia in Developing Countries

Data on thrombophilia from the developing world is scarce because of inadequate laboratory facilities for documentation and the denominator is different in published studies. There are no large epidemiological studies in the general population. However, it appears that in comparison with the incidence of DVT (48 per 100,000 admissions) and pulmonary embolism (23 per 100,000 admissions) in patients admitted to a hospital in the West, in India the incidence is much lower, DVT—7 per 100,000 and pulmonary embolism—6 per 100,000.

In a study done in the UK, the incidence of thrombophilia in patients attending an anticoagulant clinic was significantly lower in Asians when compared to Caucasians but in Asians with thrombosis there was a higher chance of finding a genetic cause.

Investigating the Underlying Cause in a Patient with Thrombosis

Detailed investigations are best avoided in the acute post-thrombotic phase since heparin therapy reduces AT III levels and oral anticoagulants reduce protein C and protein S levels. The algorithm showing the timing of different tests is given in **Table 3**.

Family members of the index patient should be studied. Management guidelines of hereditary thrombophilia are given in **Table 4**.

Antiphospholipid Antibodies and Lupus Anticoagulant

Antiphospholipid antibodies are acquired antibodies present in the circulation, seen commonly, but not exclusively, in patients with systemic lupus erythematosus. These antibodies are associated with the antiphospholipid syndrome, the clinical manifestations, diagnostic criteria, laboratory diagnosis and management of which are discussed in the chapter on 'Antiphospholipid Syndrome' (see chapter 10 of section 24).

Table 3: Investigation of a Patient with a Thrombotic Disorder

Step I tests: Initiate anticoagulation after sending blood for Step I tests
- Full blood count
- Blood film for schistocytes
- Haemoglobin
- White cell count
- Platelet count
- Prothrombin time
- Activated partial thromboplastin time
- Thrombin time
- Fibrinogen estimation

Step II tests: Can be done in the acute phase while on anticoagulants
- Sickle preparation
- Anticardiolipin antibody
- Lupus anticoagulant
- ANA, dsDNA
- Tests for paroxysmal nocturnal haemoglobinuria—Ham's test, sucrose lysis, urine haemosiderin, flow cytometry for CD55, CD59

Step III tests#: Can be done while on anticoagulants since they are DNA-based
- Factor V Leiden
- Prothrombin gene 20210 mutation
- Methylene tetrahydrofolate reductase mutation

Step IV tests#: To be done after stopping anticoagulants
- Antithrombin III#
- Protein C*
- Protein S*

*#can be done while on coumarin; *can be done while on heparin.*
ANA = Antinuclear antibody; dsDNA = Double stranded deoxyribonucleic acid.

Table 4: Management Guidelines for Patients with Hereditary Thrombophilia

High risk: Indefinite anticoagulation
- Two or more spontaneous thromboses
- One spontaneous thrombosis in the case of antithrombin deficiency or the antiphospholipid antibody syndrome
- One spontaneous life-threatening thrombosis (e.g., near-fatal pulmonary embolism; cerebral, mesenteric or portal vein thrombosis)
- One spontaneous thrombosis at an unusual site (e.g., mesenteric or cerebral vein)
- One spontaneous thrombosis in the presence of more than a single genetic defect predisposing to a thromboembolic event

Moderate risk: Vigorous prophylaxis during high-risk situations
- One thrombosis with a prothrombotic stimulus
- Asymptomatic family member

ANTITHROMBOTIC DRUGS

Broadly, these may be grouped as those used for preventing the formation of a clot (anticoagulants and antiplatelet drugs) and those used for clot lysis (thrombolytic agents).

Anticoagulants

Heparin

Unfractionated heparin is a mixture of heparins with molecular weights ranging from 3,000 to 30,000 Da. Only 30% of the administered dose contains AT III–binding sequences and

therefore the effects are variable. The activity is low compared to the purified low molecular weight heparin (LMWH). Heparin forms a complex with AT III which inactivates thrombin, factors Xa and IXa. Heparin also inhibits platelet aggregation.

Heparin may be administered as intravenous bolus, infusion, or subcutaneous. Heparin therapy is best monitored by checking the partial thromboplastin time (PTT), which should be kept at 1.5-2 times the normal level. Adverse side effects include bleeding tendencies in up to one-third of cases, allergic reactions, thrombocytopaenia, osteoporosis and hyperkalaemia. Thrombocytopaenia due to heparin can be associated with thrombosis Heparin-induced thrombocytopaenia/thrombosis (HITT) with life-threatening venous and arterial thrombosis and this is managed with direct thrombin inhibitors like hirudin. Heparin does not cross the placenta, and therefore, there is no risk of foetal haemorrhage or foetal malformation. Overdose of heparin is treated by withdrawal of further doses, fresh frozen plasma, and the specific antidote, protamine sulphate, which neutralises heparin at a ratio of 1 mg/100 units.

Low molecular weight heparin

LMWH (molecular weight 3,000 to 7,000 Da) has lower ability to inhibit thrombin, but 2 to 4 times greater ability to inhibit factor Xa than unfractionated heparin. LMWH also stimulates the release of an endogenous tissue factor pathway inhibitor (TFPI), enhancing the anticoagulant potential.

LMWH has higher bioavailability on subcutaneous injection and its half-life is greater, so that single or twice daily injections are sufficient. The antithrombotic effect manifests even without prolonging the PTT and therefore, *in vitro* tests are not essential to monitor the anticoagulant effect. LMWH is effective in the prophylaxis of DVT and pulmonary embolism. The dose is dependent on the preparation used (enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily for therapy and 40 mg daily for prophylaxis). LMWH should not be used in renal failure and protamine is not effective as an antidote.

Newer Anticoagulants

Pentasaccharides

Fondaparinux exerts its anticoagulant effect solely via antithrombin-III mediated neutralisation of factor Xa and is devoid of IIa inhibition. It does not bind to platelet factor 4 and therefore should not produce Heparin-induced thrombocytopaenia/thrombosis (HIT/HITT). It is given as a single daily subcutaneous dose of 2.5 mg.

Hirudin

Hirudin is 10 times as potent than heparin. It does not produce thrombocytopaenia and can be used to treat HITT. Lepirudin is a synthetic analogue.

Oral Anticoagulant Drugs

Coumarins are the most commonly used oral anticoagulants which act by blocking vitamin K-dependent gamma carboxylation of coagulation factors II, VII, IX and X and the anticoagulant proteins C and S. Different coumarins and their dosing pattern is given in **Table 5**. It is usual to start heparin or a similar drug for immediate action and to simultaneously introduce the oral anticoagulant. After 4 to 5 days heparin is withdrawn and anticoagulation is maintained with the oral drugs indefinitely or for specified periods depending upon the clinical indications.

Table 5: Common Oral Anticoagulants

Name of Drug	Dose	Remarks
Warfarin	4 to 5 mg per day for 5 days followed by reduced doses based on required INR	72 hours half-life
Acenocoumarol	1 to 8 mg per day	24 hours half-life
Dicoumarol	25 to 200 mg per day	Slow and erratic absorption
Indanediones (phenindione)	50 to 100 mg per day	Rarely used, does not cause alopaecia but can cause agranulocytosis

INR = International normalised ratio.

Adverse Effects

Haemorrhage related mostly to the dose and concomitant administration of interacting drugs is the most common side effect and this risk is increased in older patients. These drugs cross the placenta and may lead to foetal malformations and foetal haemorrhage. Monitoring the level of anticoagulation is done by the prothrombin time with a target international normalised ratio (INR) ranging from 1.5 to 3.5 depending on the risk of thrombosis. The following drugs potentiate the action of coumarins: acetaminophen, allopurinol, antibiotics, clofibrate, tolbutamide, isoniazid, phenytoin and the following drugs reduce the action by stimulating cytochrome P450: barbiturates, carbamazepine, digitalis, alcohol, prednisolone, oral contraceptives, haloperidol. The specific antidote is vitamin K_1 at a dose of 1 mg intravenously. If immediate reversal of the bleeding tendency is desired fresh frozen plasma should be given. The indications and contraindications for the use of anticoagulation are given in **Table 6**. Dabigatran is a new oral anticoagulant which can be administered for prophylaxis of DVT without PT monitoring.

ANTIPLATELET DRUGS

Aspirin, dipyridamole, ticlopidine and clopidogrel are the main drugs used for inhibiting platelet aggregation. Among these, aspirin is the most widely used on account of its safety and low cost.

Table 6: Use of Anticoagulation

Indications
- Deep venous thrombosis
- Pulmonary embolism
- Myocardial infarction
- Unstable angina
- Acute peripheral arterial occlusion and embolism
- Mitral stenosis with atrial fibrillation
- Transient ischaemic attacks
- Mechanical prosthetic cardiac valves

Contraindications
- Recent neurosurgery or eye surgery
- Pre-existing bleeding disorders, e.g. chronic liver disease, haemophilia
- Peptic ulcer
- Recent intracerebral haemorrhage
- Uncontrolled hypertension

Note: Anticoagulation is initiated with heparin because of the rapid onset of action and because an occasional patient with protein C deficiency may develop skin necrosis if coumarins are given without heparin. Loading doses of coumarins are no longer given: start with 4 to 5 mg of coumarin, check PT in 3 days and when desired INR is reached, stop heparin.

Aspirin

At a dose of 75 mg per day it blocks the formation of thromboxane A_2 (TxA_2), preventing aggregation of platelets. The action on the platelet is irreversible and platelets remain non-functional for the whole life-span of 5 to 7 days. In larger doses (over 1 g/day) aspirin also inhibits the production of prostacyclin which normally inhibits platelet aggregation and induces vasodilatation, hence low dose aspirin is preferred for prevention of thrombosis. Adverse effects include gastric erosions and gastrointestinal bleeding. Maximal inhibition of platelet aggregation is seen in 3 to 5 days, a larger dose of 325 mg daily for 2 days may be started if rapid onset of action is required.

Dipyridamole

This drug acts by increasing the cellular concentration of cyclic adenosine monophosphate (AMP) and thereby inhibits platelet function. In cases of intolerance to aspirin, dipyridamole is a suitable alternative. The dose is 100 to 300 mg per day as oral tablets.

Ticlopidine and Clopidogrel

These are thienopyridines which inhibits platelet function by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. It takes 2 to 3 days for full action to be established. The action persists for a few days even after stopping the drug. Ticlopidine has a higher risk (0.8%) of agranulocytosis and therefore, clopidogrel is preferred and the daily dose is 75 mg once.

DRUGS USED FOR THROMBOLYSIS

These are fibrinolytic agents which activate the endogenous plasminogen system or which have intrinsic fibrinolytic properties, streptokinase, urokinase and recombinant tissue plasminogen activator are examples. These are mainly used in the management of coronary artery thrombosis, pulmonary embolism, peripheral vascular occlusions and selected cases of non-haemorrhagic cerebral infarcts.

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15.19 Transfusion Medicine

Neelam Marwaha

Transfusion medicine today is a multi-faceted discipline. Its scope extends from collection of blood units to preparation and standardisation of blood components, blood serology, testing for transfusion transmitted diseases, to direct patient care services based on aphaeresis technology for therapeutic plasma exchange, cytoreduction and cellular therapies. Historically, the discovery of ABO blood groups by Karl Landsteiner in 1900 laid the foundation of clinical practice of blood transfusion.

BLOOD GROUP SYSTEMS

Thirty blood group systems are presently recognised, though all are not clinically significant. The clinical importance depends upon: (i) frequency with which alloantibodies occur in response to red cell antigens, (ii) characteristics of the alloantibodies such as immunoglobulin (Ig) class; IgG or IgM, subclasses of IgG, (iii) thermal range of the antibody, and (iv) its ability to fix complement.

ABO Blood Group System

The ABO blood group system is most significant for transfusion. This is because of regular presence of naturally occurring reciprocal alloantibodies in individuals who had no exposure to that antigen (**Table 1**).

Table 1: ABO Red Cell Antigens and Alloantibodies

Group	Antigen on red cells	Alloantibodies in plasma
A	A	Anti B
B	B	Anti A
O	H	Anti A, Anti B
AB	A,B	None

Hence, transfusion of ABO incompatible blood leads to an acute haemolytic transfusion reaction (HTR). These antibodies are IgM in nature, fix complement and cause intravascular haemolysis. Group 'O' red cells have neither A nor B antigen and can, thus, be transfused to 'A' or 'B' individuals. Therefore, 'O' individuals are referred to as universal donors. The antigen present on 'O' group red cells is the 'H' substance which is the precursor of A and B antigens. Absence of 'H' substance leads to a rare blood group termed that is the Bombay blood group, designated as (Oh). These individuals have anti A, anti B and anti H antibodies, and thus can receive blood only from individuals with Bombay blood group. Transfusion of 'O' group red cells will lead to haemolysis due to presence of anti-H. Individuals with AB phenotype do not have ABO alloantibodies and are, thus, universal recipients.

ABO grouping consists of testing the red cells with anti-A and anti-B sera (cell or forward grouping) and testing the serum with A and B red cells (serum or reverse grouping). The two serve as a check on each other. In neonates and infants up to 4 months of age, no serum grouping is necessary since antibodies appear later. When the results of red cell grouping do not match with serum grouping, the individual has an ABO discrepancy which needs resolution before proceeding for transfusion.

The Rh System

The Rh system is next in importance for transfusion. About 49 antigens are known but D antigen is most immunogenic. Transfusion of D positive red cells to D negative recipient leads to alloimmunisation in 90% of the recipients. It is the most common cause of haemolytic disease of newborn (HDN) in Rh D negative mothers carrying an Rh D positive foetus. Presence of D antigen connotes Rh positive blood group while absence of D antigen leads to Rh negative phenotype. However, there are four other clinically significant antigens in the Rh system; C, c, E and e. Alloantibodies to these may appear in multiply transfused patients. Antibodies to Rh antigens appear only after exposure to the antigens, are usually IgG and lead to delayed HTRs due to extravascular haemolysis.

Other Clinically Significant Blood Group Systems

Kell, kidd and duffy systems

Kell antigen (K) is next in order of immunogenicity after ABO and Rh antigens. Anti-kell alloantibodies complicate the management in patients on regular transfusion therapy, such as thalassaemics. Two Kidd antigens, Jk^a and Jk^b are well characterised. Antibodies to these antigens disappear rapidly in alloimmunised patients, hence on subsequent transfusion with Kidd antigen positive red cells, there is anamnestic response and delayed HTR. Fy^a and Fy^b are the clinically significant Duffy antigens. The alloantibodies are IgG, cause delayed HTRs and can also cause HDN as they cross the placenta. The Duffy protein is also the receptor for *P. vivax* and Duffy negative inviduals are resistant to *P. vivax* infection. This phenotype is most common in black races.

MNS system

The important antigens are M,N,S,s and U. Anti-M and N may occur naturally, are IgM in nature and have been associated with acute HTR. Anti S, s and U usually occur following red cell transfusions and are IgG. Anti-U antibodies are problematic since it is difficult to find U negative donors.

Lewis and P systems

The Lewis system antigens are Le^a and Le^b. They are adsorbed onto red cells from plasma. Antibodies may form in Le (a-b-) individuals, are IgM in nature and can cause acute HTRs. P_1 negative individuals may contain naturally occurring IgM alloantibodies. In paroxysmal cold haemoglobinuria, the biphasic Donath Landsteiner autoantibody is directed towards P antigens. These also form receptors for many pathogens including *Escherichia coli* and parvovirus B19.

The I/i antigens and antibodies

Cold agglutinins which arise in lymphoproliferative disorders and cold agglutinin disease, usually have 'I' specificity, an antigen

found on adult red cells. Cold agglutinins which appear post-infection as in *Mycoplasma pneumoniae* or infectious mononucleosis have 'i' specificity, an antigen found on cord blood red cells.

PRE-TRANSFUSION TESTING

It commences with request for transfusion where the requisition form should have relevant clinical details,informed consent, number of blood units required and signature of the physician. This is followed by identification check of the patient's sample and requisition form in the transfusion services. Recipient's ABO and Rh(D) grouping and repeat donor unit blood grouping are performed. Hereafter, depending upon the facilities available, an antibody screen is performed on recipient's serum/plasma for any irregular antibodies. If antibody screen is positive, the alloantibody is identified and donor units typed for the corresponding antigen to find an antigen negative unit. Cross-match is then put-up with antigen negative donor red cells and recipient's serum. In case of non-availability of antibody screening and identification technology, the donor red cells are cross-matched with recipient's serum. In case of incompatibility, cross-match is repeated with other group specific units until compatible units are found. Cross-match is performed in the saline phase which detects IgM antibodies and in the antiglobulin or Coombs' phase which detects IgG antibodies. During urgent requisitions, only saline cross-match is performed by many transfusion services and this may fail to detect clinically significant IgG antibodies.

BLOOD COMPONENTS

Donor blood is collected in citrate phosphate dextrose adenine (CPDA-1) as anticoagulant preservative solution either as 350 mL or 450 mL volume. This unit is referred to as whole blood and has a haematocrit of 30% to 40%. It is stored at 4°C. At this temperature platelets rapidly lose their viability, granulocytes disintegrate and labile coagulation factors (F VIII) decline rapidly. Separation of whole blood into components helps to preserve functions and optimises blood usage. The components are prepared within 6 to 8 hours of whole blood donation. The various components which can be prepared are as follows:

Packed Red Blood Cells (PRBCs)

Haematocrit is 65% to 75% and volume almost half of whole blood. Shelf-life in CPDA-1 is 35 days, but can be increased to 42 days in additive solutions.

Platelets

These are platelet rich plasma, random donor platelet (RDP) concentrates, pooled buffy coat platelet concentrates and aphaeresis platelets. Aphaeresis platelets also known as single donor platelet (SDP) are equivalent to 5 to 6 RDPs. Platelets are stored at +22°C and have a shelf-life of 5 days.

Fresh Frozen Plasma (FFP)

It contains all coagulation factors and plasma proteins. Its shelf-life is one year at temperatures below –30°C.

Cryoprecipitate

It is prepared from FFP and is rich in F VIII, von Willebrand factor (vWF), fibrinogen and F XIII. Its shelf-life is one year at temperatures below -30°C.

Granulocytes

These can be obtained from buffy coat or granulocytaphaeresis. The former has granulocyte count less than 1×10^9 and can only be used in neonates. Aphaeresis product has 1×10^{10} granulocytes.

INDICATIONS FOR TRANSFUSION

Whole Blood

Whole blood, fresh or stored has no appropriate indication except perhaps in an acutely bleeding patient, especially trauma. However, in developing countries due to limited or no availability of blood components, whole blood continues to be used. No medication other than normal saline should be added to the intravenous line to avoid haemolysis.

Packed Red Cells

They are indicated in patients with symptomatic anaemia. In chronic anaemias, volume overload can be avoided. One unit raises haemoglobin (Hb) by 1 g/dL or haematocrit by 3%. In treatable anaemias like iron/B12/folate deficiency, transfusions are to be avoided unless there is evidence of severe oxygen deficit. There is no absolute transfusion trigger, but transfusion is recommended when the Hb is less than 6 g/dL and between 6 to 10 g/dL, as per the clinical situation. In older patients and those with cardiac disease, a higher threshold of 10 g/dL is recommended.

PRBCs can be modified to reduce adverse events. These can be plasma reduced by adding additive solutions and washed to remove plasma in patients with allergic reactions. Once washed the shelf-life reduces to 24 hours. These are irradiated for prevention of transfusion-associated graft *versus* host disease (TA-GvHD) in susceptible patients. Leucofilters remove 99.9% white blood cells and decrease the risk of alloimmunisation and febrile non-haemolytic transfusion reactions. For rare blood groups, PRBCs can be frozen up to 10 years.

Platelets

Platelet transfusions are given prophylactically or therapeutically. For prophylaxis, the rationale is to prevent bleed when the platelet count reaches certain thresholds. The maximum numbers of prophylactic platelet transfusions are given in haemato-oncology patients on intensive chemo-radiotherapy. The transfusion thresholds are as follows:

- 5,000/µL for stable chronic thrombocytopaenic patients, e.g. aplastic anaemia.
- 10,000/µL for stable acute leukaemia patients
- 20,000/µL for patients with fever, sepsis
- 50,000/µL for invasive procedures
- 1,00,000/µL for brain/eye surgery

One unit of RDP raises platelet count by 5,000 to 10,000/µL. One aphaeresis unit raises platelet count by 30,000 to 60,000/µL. Therapeutic platelet transfusions are given in actively bleeding thrombocytopaenic patients. The threshold is 50,000/µL. Platelet transfusions are contraindicated in thrombotic thrombocytopaenic purpura (TTP), while in idiopathic thrombocytopaenic purpura, platelets may be given in life-threatening bleeds or just prior to splenectomy. Dosage in adults is one RDP unit/10 kg. Irradiated platelets are issued for immunosuppressed patients to prevent TA-GvHD.

Fresh Frozen Plasma

Appropriate indications are coagulation disorders like disseminated intravascular coagulation (DIC), liver disease,

congenital bleeding disorders where factor concentrates are unavailable and reversal of warfarin therapy. The dose is 10 to 15 mL/kg body weight. One unit of FFP causes an increment of coagulation factors by 8% to 10%. Therapy should be monitored by prothrombin time ratio, if it falls below 1.5 times normal FFP transfusions should be stopped.

Cryoprecipitate

In the developing countries it serves as a source of F VIII in haemophilia A, where F VIII concentrates are scarce. One unit contains 80 IU of F VIII. It is a good source of fibrinogen and is often used in DIC when fibrinogen level falls below 100 mg/dL. One bag of cryoprecipitate increases fibrinogen level by 10 mg/dL.

FFP and cryoprecipitate should be thawed immediately prior to use and transfused within 6 hours of thawing.

TRANSFUSION-ASSOCIATED ADVERSE EVENTS

Adverse events are classified as acute if they occur within 24 hours of transfusion or delayed. They may also be classified based on aetiopathogenesis. **Tables 2 and 3** depict the adverse events, their pathogenesis and salient clinical features.

Metabolic and haemostatic abnormalities can occur during massive transfusion (MT). MT is usually required in patients with trauma, obstetric haemorrhage, liver transplant or massive gastrointestinal bleeds. It is defined as replacement of whole blood volume within 24 hours or loss of 150 mL blood per hour. In neonates double volume exchange transfusion and transfusion for major surgeries constitutes MT. Metabolic complications like hyperkalaemia, acidosis and citrate toxicity leading to hypocalcaemia may occur. Hypothermia and dilutional coagulopathy and thrombocytopaenia may also develop. In such situations blood warmers, FFP, cryoprecipitate and platelet transfusions are of tremendous value.

HAEMOVIGILANCE

It is a surveillance system aimed to detect and analyse all serious adverse effects of blood transfusion in order to rectify their cause and prevent their occurrence. It may be through legislation as it happened in France or voluntary as exemplified by the UK [United Kingdom Serious Hazards of Transfusion (SHOT Project)]. However, confidentiality of patients, donors and reporting clinicians needs to be maintained. Haemovigilance

Table 2: Acute Adverse Events

Adverse Event	Pathogenesis	Clinical Features
Haemolytic transfusion reactions	Immune Preformed complement fixing alloantibodies in recipient Non-immune mechanical/osmotic/thermal damage to RBCs	Fever, chills, flank pain, hypotension, DIC, renal failure, haemoglobinuria
Febrile non-haemolytic transfusion reactions (FNHTRs)	Alloantibodies to WBCs in recipient Cytokine accumulation in cellular blood components	Fever (rise >1°C) chills, rigours
Urticarial reactions	IgE antibodies	Pruritis, rash
Anaphylaxis	Antibodies to donor plasma proteins	Hypotension, respiratory distress
Transfusion related acute lung injury (TRALI)	Anti HLA/neutrophil antibodies in donor plasma chemokine/bioactive lipids in cellular components	Respiratory distress, hypoxia, bilateral non-cardiogenic pulmonary oedema
Transfusion-associated circulatory overload (TACO)	Rapid large volume transfusion in elderly and neonatal patients	Respiratory distress, hypertension, increased levels of beta natriuretic peptide
Transfusion-associated bacterial sepsis	Bacterial contamination due to skin flora, asymptomatic donor bacteraemia More often seen with platelet concentrates due to higher storage temperature (22 °C)	Fever, chills, hypotension, shock

DIC = Disseminated intravascular coagulation; RBCs = Red blood cells; WBCs = White blood cells; Ig = Immunoglobulin; HLA = Human leucocyte antigen.

Table 3: Delayed Adverse Events

Adverse Event	Pathogenesis	Symptoms
Haemolytic transfusion reactions	IgG type of alloantibodies in previously sensitised patients	Unconjugated hyperbilirubinaemia, fall in Hb
Post-transfusion purpura	Antiplatelet HPA1 antibodies, destroy allogeneic and autologous platelets	Purpura within 7 to 10 days of transfusion
Iron overload	Regular transfusion therapy with inadequate iron chelation. Each unit contains 200 mg of iron, appears after 100 RBCs units	Cardiac, hepatic, endocrine dysfunction
Transfusion transmitted viral infections	Window period transmission (pre-seroconversion phase)	HIV, hepatitis B, C, parvovirus B19, CMV in susceptible recipients
Transfusion transmitted malaria	Merozoites in donor erythrocytes (asymptomatic)	Malaria symptoms within 7 to 14 days
Transfusion-associated graft versus host disease (TA-GvHD)	Recognition of host antigens as foreign by donor T-lymphocytes	Skin, gastrointestinal and hepatic symptoms, pancytopaenia
Transfusion related immuno-modulation (TRIM)	Increased cytokine stimulation by donor leucocytes, still not completely understood	Increased renal allograft survival but infection and tumour recurrence
Prion's disease	Asymptomatic infected individuals	vCJD

Ig = Immunoglobulin; Hb = Haemoglobin; RBCs = Red blood cells; HIV = Human immunodeficiency virus; CMV = Cytomegalovirus; vCJD = Variant Creutzfeldt-Jakob disease.

data is of enormous value for improving transfusion practices. Some of the initiatives taken are universal leucodepletion to prevent alloimmunisation, febrile non-haemolytic transfusion reactions and cytomegalovirus transmission, irradiation to prevent TA-GvHD, methods to reduce bacterial contamination, avoiding use of plasma components from parous females to avoid transfusion related acute lung injury and methods to check mismatched blood/component transfusions.

HOSPITAL TRANSFUSION COMMITTEE

Hospital Transfusion Committee should be constituted in all health care facilities to evaluate all aspects of transfusion in the hospital and to ensure compliance with various national/international guidelines on good transfusion practices. Members should comprise major clinical users of blood and the consultant in-charge of the blood transfusion services.

THERAPEUTIC PLASMA EXCHANGE

Therapeutic plasma exchange constitutes an extra-corporeal blood purification technique designed to remove high molecular weight substances from plasma, implicated in disease causation in the patient, using aphaeresis technology. The most commonly removed macromolecules are immunoglobulins/immune complexes and low density lipoproteins (hyperlipidaemia). Therapeutic plasma exchange is the standard first-line therapy in certain neurological disorders (Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy), haematological disorders (TTP, hyperviscosity syndrome) and autoimmune disorders (Goodpasture's syndrome). Therapeutic cytapheresis helps in reducing cellular load prior to chemotherapy in leukaemic patients with hyperleucocytosis. Therapeutic thrombocyte apheresis provides symptomatic relief in extreme thrombocytosis.

RECOMMENDED READINGS

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15.20 Haematopoietic Stem Cell Transplantation

Velu Nair

INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is a life-saving procedure for a number of malignant and non-malignant diseases which were considered incurable in the past. The term bone marrow transplantation is used synonymously with HSCT. Technically HSCT is the correct nomenclature as stem cells can be sourced from the bone marrow for bone marrow transplantation, from peripheral blood stem cell (PBSC) for peripheral blood stem cell transplant (PBSCT) and umbilical cord blood for cord blood transplant. Stem cells are immunophenotypically labelled as CD34+ cells. In allogeneic (allo) HSCT, the stem cells are harvested from an human leucocyte antigen (HLA) matched donor, either related or unrelated. In autologous (auto) transplants, the patients own stem cells are harvested. In HSCT, the diseased marrow is ablated using chemotherapy or/and radiotherapy which is referred to as 'conditioning' followed by stem cell rescue. There is high incidence of relapse in auto-HSCTs because it is difficult to achieve 100% ablation of the malignant clone. The relapse rates are lower in allo-HSCT due to the added immunological effect of 'graft *versus* tumour' or '*versus* leukaemia (GvL)' effect which is lacking in auto-HSCT. Complications encountered during HSCT are graft-rejection, graft *versus* host disease (GvHD), veno-occlusive disease (VOD), infections and haemorrhagic episodes.

HISTORICAL BACKGROUND

The first use of bone marrow in the present context of HSCT was done by Schrezenmeier in 1937. Following the Hiroshima and Nagasaki disaster in 1945, radiation biologists, Jacobson and Lorenz pioneered the mice model demonstrating effect of radiation on bone marrow and spleen. They also showed that infusion of spleen cells prevented bone marrow aplasia. 1954 was the benchmark year when Lorenz elegantly demonstrated using chromosomal markers, that the new cells produced by the recovering marrow following infusion of splenic cells contained the same chromosomal marker as that of donor spleen. This stimulated further experimental work in the field of stem cell biology and HSCT.

E. Donnell Thomas, in a series of carefully planned experiments in dogs, for the first time defined the radiation doses, marrow harvesting procedures, regimen for GvHD prophylaxis and supportive care required for HSCT for which he was awarded the Nobel Prize in 1990. However, it was another Nobel laureate, Jean Daussett who discovered the HLA system which revolutionised the field of HSCT and the first HLA identical sibling transplant was done in the Netherlands in an infant with severe combined immune deficiency disease. In the 1970s, the Centre for International Blood and Marrow Transplant Research (CIBMTR) and the European Group for Blood and Marrow Transplantation (EBMT) was set up. The 1980s saw the entry of new drugs, such as ciclosporine for GvHD prophylaxis, newer generation of antivirals, antifungals and antibiotics which helped reduce transplant related morbidity and mortality due to infections. In the 1990s, discovery of PBSC and Cord blood stem cells was a landmark in establishing stem cell sources other than the bone marrow. In India more than 3,000 transplants (auto- and allo-HSCTs) have been performed at various centres, the first being done in Tata Memorial Hospital, Mumbai in 1983.

INDICATIONS FOR HAEMATOPOIETIC STEM CELL TRANSPLANTATIONS

The indications have been rapidly expanding over the years (**Table 1**). HSCT is indicated for all refractory or high-risk

Table 1: Indications for Allo- and Auto-Haematopoietic Stem Cell Transplantation (HSCT)

Indications for Allogeneic HSCT

- Malignancy
  - Acute myeloid leukaemia
  - Acute lymphoblastic leukaemia
  - Chronic myeloid leukaemia
  - Chronic lymphocytic leukaemia
  - Myelodysplasia
  - Hodgkin's disease
  - Non-Hodgkin's lymphoma
  - Multiple myeloma
- Immunodeficiency
  - Severe combined immunodeficiency
  - Wiscott-Aldrich syndrome
  - Adenosine deaminase deficiency
  - X-linked lymphoproliferative syndrome
  - Cartilage hair hypoplasia
- Defective haemopoiesis
  - Aplastic anaemia
  - Acquired severe aplastic anaemia
  - Congenital aplastic anaemia (Fanconi's anaemia)
  - Post-radiation Injury
  - Thalassaemia major
  - Sickle cell disease
  - Kostmann syndrome
  - Chronic granulomatous disease
  - Chediak-Higashi syndrome
  - Adhesion molecule deficiencies
  - Platelet disorders
  - Glanzmann thromboasthenia
  - Bernard-Soulier syndrome
  - Metabolic storage disease
  - Osteopetrosis
  - Familial haemophagocytic syndrome

Indications for Autologous HSCT

- Lymphoma and Hodgkin's disease
- Multiple myeloma
- Acute myeloid leukaemia, Acute lymphoblastic leukaemia
- Chronic myeloid leukaemia
- Neuroblastoma
- Breast cancer, germ cell tumour
- Autoimmune disorders
- Scleroderma, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus

haematological malignancies, various genetic disorders and for bone marrow failure syndromes. In addition, it is also being offered of late for autoimmune disease.

Autologous Haematopoietic Stem Cell Transplantation

This is useful in myeloma, lymphoma, acute and chronic leukemias and solid tumours (breast, neuroblastoma and lung neoplasms). Bone marrow or PBSC is harvested from the patient itself, while the disease is in remission. This graft is then cryopreserved at –80 °C (freezers) or at –180 °C (liquid nitrogen). The harvested graft is stored in a cryoprotectant bag after mixing with dimethyl sulphoxide which is a cryoprotectant. Following this marrow is myeloablated with high dose chemotherapy and/or radiotherapy followed by reinfusion of the cryopreserved bone marrow or PBSC.

Allogeneic Haematopoietic Stem Cell Transplantation

Allo-HSCT involves stem cells being sourced from a related or unrelated donor [matched unrelated donor (MUD)]. The chances of finding a related donor (ideally a sibling) is 25% to 30% while it increases to 50% to 70% in case of MUD transplants where a donor is sought from a web-based registry. Earlier allo-HSCTs were myeloablative but of late, non-myeloablative transplants are being done increasingly in older patients. This is the treatment of choice for all high-risk/refractory haematological malignancies, several genetic disorders (thalassaemia major, Diamond Blackfan syndrome, etc.) and also for bone marrow failure syndromes (severe aplastic anaemia).

SOURCE OF HAEMATOPOIETIC STEM CELLS

Bone Marrow

In bone marrow transplantation, the haematopoietic stem cells (HSCs) are collected from the pelvic bone (posterior iliac spine) of the donor using bone marrow harvest needles under general anaesthesia.

Peripheral Blood Stem Cells (PBSCs)

PBSCs represent the richest source of stem cells and engraftment has been noted to be earlier compared to bone marrow or cord blood. As the lymphocyte content is higher in PBSC the incidence of GvHD (especially chronic GvHD) is higher in PBSCT compared to bone marrow transplantation or cord blood transplant. The advantages and disadvantages of PBSCT are listed in **Table 2**.

Table 2: The Advantages and Disadvantages of Peripheral Blood Stem Cell Transplantation

	Advantages	Disadvantages
Recipient	Faster neutrophil recovery Faster platelet recovery Faster immunologic recovery Less intravenous antibiotics Shorter hospitalisation Lower cost More GvL (?)	Higher incidence of chronic GvHD
Donor	No general anaesthesia No marrow harvest No hospitalisation	Venepuncture or central line Side-effect from growth stimulating factors and citrate used for PBSC harvest

Umbilical Cord Blood

Cord blood has a higher concentration of HSCs than in adult blood. They are naïve and less immunogenic, thereby causing less GvHD. They bear an immature phenotype and lack perforin expression. Cytotoxic cells seem to comprise mostly of a NK cell subset. Newer techniques using *ex vivo* expansion of cord blood units or the use of two cord blood units from different donors are being explored to allow cord blood transplants to be used in adults.

Engraftment

It takes 2 to 3 weeks for stem cells to re-grow (engraft) in the bone marrow. Haematopoietic growth factors, such as G-cerebrospinal fluid (G-CSF) and GM- CSF are used post transplant to enhance engraftment. The engraftment is monitored by chimerism studies. The presence of deoxy-ribonucleic acid (DNA) pattern of the donor type in the blood and bone marrow cells of the recipient confirms engraftment. Reconstitution of the immune system takes several months pre-disposing these patients to infections. Factors affecting engraftment are depicted in **Table 3**.

Table 3: Factors Affecting Marrow Engraftment

Haematological
- Stem cell dose
  - $>10^6$ CD34+ cells/kg associated with better engraftment
- Stem cells quality
  - Previous chemotherapy decreases, take
- Normal recipient environment
  - No fibrosis; no splenomegaly
  - Adequate intensity of preparative regimen

Immunological
- Donor/recipient human leucocyte antigen compatibility
- Increasing incompatibility decreases the chance of 'take'
- Recipient sensitisation to donor through transfusion strongly increases rejection risk
- Recipient immunosuppression
- Low-intensity preparative regimen increases rejection risk

STEPS INVOLVED IN HAEMATOPOIETIC STEM CELL TRANSPLANTATION

The various steps involved in allo-HSCT are described as under and depicted in **Figure 1**.

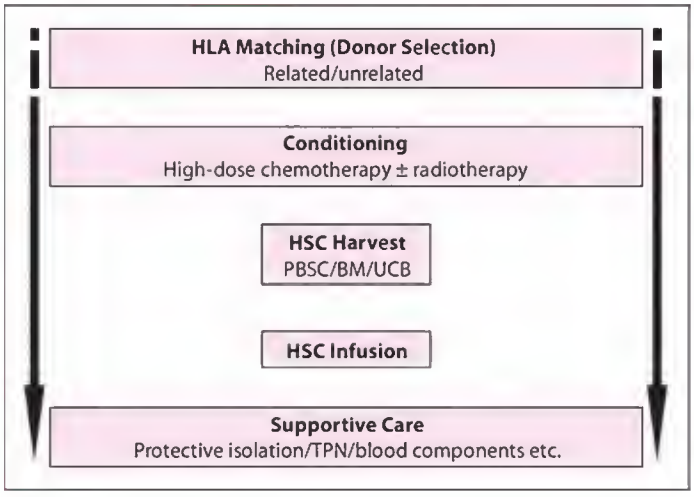


Figure 1: Steps involved in allo-HSCT.

HLA = Human leucocyte antigen; HSC = Haematopoietic stem cell; PBSC = Peripheral blood stem cell; BM = Bone marrow; UCB = Umbilical cord blood; TPN = Total parenteral nutrition.

Donor Selection and HLA Matching

The outcome of allo-HSCT is dictated by a set of immune response genes clustered together as the HLA system which is

analogous to the major histocompatibility complex (MHC) in animals. Ideally a sibling donor with matched major HLA loci stands the best chance for a successful HSCT. However, minor histocompatibility loci are not matched and this can lead to GvHD and graft-rejection. Initially, HLA was done by serology and later by molecular typing using sequence specific primers (SSP) which is a low resolution DNA based typing for HLA using polymerase chain reaction (PCR) technology. HLA loci A, B and DR are done for all related transplants and in addition HLA C, DP and DQ are also done for unrelated transplants.

Establishing a venous access

Since a long-term venous access is required for several weeks, a double or triple lumen central sialistic flexible catheter can be used, double lumen being preferred. This is introduced through a subcutaneous tunnel in the pectoral region and then inserted into the internal jugular or subclavian vein as shown in **Figure 2**. There are dedicated lines for blood component infusion, intravenous drugs and parenteral nutrition. Blood sampling is also done using these lines. Meticulous care of these central lines is required to prevent catheter sepsis.



Figure 2: Double lumen Hickman catheter.

Conditioning

Myeloablative: Conditioning or preparatory regimens containing high dose chemotherapy ± radiotherapy are used to ablate the abnormal clone of cells and create space in the bone marrow for engraftment of the new graft. It also suppresses the patient's immune system to prevent rejection of the new graft. Immunosuppression is achieved by irradiating lymphoid system ± cyclophosphamide (Cy) or combining fludarabine, Cy ± anti-thymocyte globulin (ATG). Myeloablation is achieved using busulfan (Bu) or melphalan. Total body irradiation achieves both; immunosuppression and myeloablation. In auto-HSCTs the main aim of conditioning is to achieve specific anti-tumour effect.

Non-myeloablative: Reduced intensity conditioning, using lower doses of chemotherapy and radiation, is an evolving approach of treatment which is less intensive and less toxic, minimising the risk of regimen related toxicity and transplant related mortality (TRM). The tumour kill is achieved by preparatory regimen and also by the GvL.

Graft *Versus* Host Disease Prophylaxis

For GvHD prophylaxis various protocols using combinations of immunosuppressive drugs are in use. A combination of cyclosporine A (CSA) with methotrexate (MTX) is a commonly used protocol. Intravenous (IV) CSA is administered beginning day 3 and continued till mucositis settles and oral fluids are tolerated, following which oral CSA is started (usually double the dose of IV-CSA). CSA levels are done weekly, targeting a level of 250 ng/mL. In cases of CSA intolerance, mycophenolate mofetil/tacrolimus can be given.

Stem Cells Harvest and Infusion

A target cell dose of total nucleated cells of 3 or more x 10^8 cells/kg or CD34 (stem cells) of 3 or more x 10^6 cells/kg is harvested followed by infusion into the patient either directly, if done within 48 hours (stored at 4°C) or following cryopreservation when infusion is done later than 48 hours.

Supportive Care

Success of a transplant programme relies heavily on an efficient support system, which includes blood bank for blood component support, good microbiological laboratory, molecular laboratory for HLA typing and well-trained transplant team of medical and nursing staff. In tropical conditions, protective isolation is important because of high-risk of infections when neutropenia occurs following myeloablation. However, in many centres in the West, HSCT has been successfully done without isolation. The nutritional status is often poor because of the underlying disease, occurrence of GvHD, sepsis and psychosocial issues like depression. Parenteral nutrition is resorted to, once the patient develops mucositis and is unable to take oral feeds.

ABO INCOMPATIBILITY

Unlike solid organ transplantation, HSCT can be performed despite ABO incompatibility. Major ABO incompatibility consists of the presence of ABO antibodies in the recipient directed against ABO antigens of the donor, e.g. O group recipient and A, B or AB donor. This can cause delayed erythroid engraftment and rarely red cell aplasia which is minimised by depleting donor red cells from the graft. In addition the ABO antibodies in the recipient can be neutralised by infusing donor specific fresh frozen plasma (FFP) and by plasmapheresis to reduce the antibody titre to less than 1:16. Minor ABO incompatibility is the presence of ABO antigens on recipient's red cells which are lacking in the donor, who has antibodies against the recipient's red cells, e.g. group O donor into group A, B or AB recipient. It is referred to as major and minor or 'bidirectional incompatibility' if group A donor and group B recipient or vice-versa is transplanted (**Table 4**).

Table 4: Selection of Blood Components in ABO Incompatible Allo-Haematopoietic Stem Cell Transplantation

	Recipient / Donor	Major ABO Incompatibility	Minor ABO Incompatibility	Mixed Major + Minor ABO Incompatibility	Rh^+ / Rh^-	Rh^- / Rh^+
Pre-transplant regimen	Red cells	Recipients type	Recipients type	Recipients type	Rh^+	Rh^-
	Platelets	Recipients type	Recipients type	Recipients type	Rh^+	Rh^-
	Fresh frozen plasma	Recipients type	Recipients type	Recipients type	Rh^+	Rh^-
Post-transplant regimen	Red cells	Recipients type/ Group O	Donor type/ Group O	Group O	Rh^-	Rh^+
< 8 weeks or until DAT is negative	Platelets	Donor type	Recipients type	Group AB	Rh^-	Rh^+
	FFP	Donor type	Recipients type	Group AB	—	—
Post-transplant regimen	Red cells	Donor type	Donor type	Donor type	Rh^-	Rh^+
	Platelets	Donor type	Donor type	Donor type	Rh^-	Rh^+
> 8 weeks or once DAT is negative	FFP	Group AB +ve for 12 weeks	Group AB +ve for 12 weeks	Group AB +ve for 12 weeks	—	—

Blood Component Support

Haemolysis of donor red blood cells (RBCs) by isoagglutinins in the recipient can cause immediate haemolysis. Formation of isoagglutinins by donor lymphocytes against recipient's ABO antigens can produce haemolysis after engraftment in ABO mismatched transplants as lifespan of residual recipient RBCs following allo-HSCT is about 40 days, whereas, circulating recipient's IgG and IgM antibodies have a half-life of approximately 20 days and 6 days respectively.

COMPLICATIONS

The first 100 days of post-HSCT is referred to as the early post-transplant period. Considerable morbidity and mortality is noted during this period, especially in allo-HSCT. These early complications are often related to the conditioning regimen, metabolic, fluid and electrolyte disturbances, microbial infections secondary to the neutropaenic state, haemorrhagic episodes secondary to underlying thrombocytopaenia, hepatic veno-occlusive disease (VOD) and acute GvHD. Some of the complications, listed in **Table 5**, will be discussed in more detail.

Infections

The HSCT recipient is immunocompromised both for humoral and cell-mediated immunity. There are 3 phases for opportunistic infections to occur in a transplant patient.

Pre-engraftment phase (2-4 weeks post-HSCT)

Febrile neutropaenia is commonly due to Gram-positive and negative bacteria followed by *Candida* and *Aspergillus* fungal infections. Herpes simplex virus (HSV) viral reactivation is known to occur during this period.

Early post-engraftment phase (< 100 day post-HSCT)

During this phase, viral [CMV (cytomegalovirus), HSV] and fungal infections are common, besides bacterial infections.

Late post-engraftment phase (> 100 day post-HSCT)

During this period infection with encapsulated bacteria, fungi and viruses are known to occur. This phase technically is a late complication of HSCT. However, for the convenience, it has been included under the category of infection.

Hepatic Veno-Occlusive Disease

VOD is a clinical syndrome, presenting with elevated levels of bilirubin, hepatomegaly and fluid retention. There is now a greater appreciation of obstruction in the hepatic venus sinuses, hence it is also referred to as sinusoidal obstruction syndrome. In VOD, endothelial damage due to the intensive conditioning leads to a local hyper-coagulable state with initiation of a 'cytokine storm' interleukin (IL)-1, tumour necrosis factor (TNF) which is responsible for hepatocyte necrosis. Signs of severe VOD include renal failure, thrombocytopaenia unresponsive to platelet transfusion and hepatic encephalopathy. VOD occurs in the first 20 days post-HSCT and 30% to 50% of patients undergoing HSCT develop VOD of varying severity and approximately 5% of these are life-threatening.

Table 5: Early Post-Transplant Complications

- **Infections**
  - Bacterial
  - Viral
  - Fungal
  - Protozoal
- **Gastrointestinal**
  - Nausea, vomiting
  - Mucositis, oesophagitis and gastroduodenitis
  - Diarrhoea and typhilitis
  - Pancreatitis and cholecystitis
- **Hepatic veno-occlusive disease**
- **Interstitial pneumonitis**
- **Renal and urinary tract complications**
  - Acute renal failure
  - Haemolytic uraemic syndrome
  - Acute tumour lysis syndrome
  - Haemorrhagic cystitis
- **Cardiovascular complications**
  - Pericarditis
  - Endocarditis
  - Hypertension
- **Metabolic complications**
  - Syndrome of inappropriate antidiuretic hormone secretion
  - Fluid and electrolyte imbalance
- **Neurological complications**
  - Encephalopathy
  - Seizures
  - Central nervous system haemorrhage
  - Thrombotic thrombocytopaenic purpura
- **Graft-*versus*-host disease (GvHD)**
  - Acute GvHD
  - Chronic GvHD

Prophylaxis has been attempted using low-molecular-weight heparin (LMWH), AT-III concentrates, prostaglandin E2,

pentoxyfilline, and ursodeoxycholic acid. Of these, though, ursodeoxycholic acid and LMWH have shown some benefit, besides supportive care there is no specific therapy for managing VOD. Prostaglandin-E, tPA and AT-III concentrates have been tried with mixed results. Liver transplantation has been carried out successfully but is clearly an unlikely option for the majority of cases. Defibrotide, an adenosine receptor agonist with antithrombotic and fibrinolytic properties, is being used with good results improving survival.

Pulmonary Complications

The pulmonary complications commonly encountered in HSCT are elaborated in **Table 6**.

Table 6: Causes of Pulmonary Complications of Post-Haematopoietic Stem Cell Transplantation

Infection
Bacterial
Viral
Fungal
Protozoal
Pulmonary oedema
Fluid overload
Cardiac dysfunction
Acute respiratory distress syndrome (ARDS)
Sepsis
Drug toxicity (e.g. cyclosporine A (CSA) and cytosine arabinoside)
Idiopathic (toxic)
Pulmonary embolism
Pulmonary graft-*versus*-host disease

Haemorrhagic Cystitis

This is characterised by frequency, dysuria and haematuria soon after administration of Cy. When severe it can pose a serious therapeutic challenge. This occurs primarily due to damage brought about by acrolein (a metabolite of Cy) to the uroepithelium of the urinary bladder. Prevention of haemorrhagic cystitis secondary to use of high dose Cy is done by administering continuous infusion of MESNA (2-mercaptoethanesulfonic acid sodium salt) starting 12 hours prior to and continuing 12 hours following cessation of Cy along with hydration.

Graft *Versus* Host Disease

GvHD is an inflammatory condition, unique to allo-HSCT, wherein, the donor immune cells attack the recipient's tissues. It is mainly, mediated by T-cells, when they react to foreign peptides presented on the MHC of the host.

Acute graft versus host disease

It typically appears in the first 3 months after allo-HSCT. Billinghan in 1966 defined the essential elements for the occurrence of acute GvHD.

1. The graft must contain immunologically competent cells.
2. The recipient must express tissue antigens that are not present in the transplant donor.
3. The recipient must be unable to mount an effective response to destroy the transplanted T-lymphocytes.

It is known that these immunocompetent cells are T-lymphocytes. However, there is no clear evidence as to which specific subsets are involved in acute GvHD. The CD8+ lymphocytes act against class-I HLA antigens and CD4+ against class-II HLA antigens. GvHD is understood to be a multi-step process. Step one causes tissue damage in the recipient which is cytokine (IL-1, IL-6 and TNF-α) mediated. Skin (**Figure 3**), gut and liver ducts are the target organs as they exhibit an increase expression of HLA molecules, adhesion molecules and other products with pro-coagulant activity. The next step involves activation of individual T-cells and expression of IL-2 receptors and production of interferon-gamma (IFN-γ) and IL-2. Activated T-lymphocytes undergo clonal proliferation and



Figure 3: Acute skin graft-*versus*-host disease (grade IV) in a patient with chronic myelogenous leukaemia after allo-HSCT.

differentiation, elaborating IL-2 which stimulates mononuclear cells which in turn secretes IL-1, TNF-α and IFN-γ producing a cytokine storm. In addition the lymphocytes also have a cytolytic action.

Glucksberg's scale is used to stage acute GvHD. The clinical grading of acute GvHD is shown in **Tables 7 and 8**.

Chronic graft versus host disease

Chronic GvHD is a late complication which occurs 100 days post-HSCT with clinical manifestations closely mimicking autoimmune disease, such as skin dyspigmentation, xerosis, erythema, scleroderma (**Figure 4**), lichen planus, xerostomia, ocular keratitis, jaundice, pulmonary obstruction/restrictive defects. Corticosteroids such as prednisone is the standard treatment for chronic GvHD with other drugs, such as mycophenolate mofetil (MMF), CSA, tacrolimus and thalidomide being used singly or in combination.

Table 7: Acute Graft *Versus* Host Disease Grading

Stage	Skin: Maculopapular Rash	Liver: Bilirubin	Intestinal Tract: Diarrhoea
+	< 25% of body surface	2 to 3 mg/dL (34 to 50 μ/L)	>500 mL/24h
++	25% to 50% body surface	3 to 6 mg/dL (51 to 102 μ/L)	>1000 mL/24h
+++	Generalised erythroderma	6 to 15 mg/dL (103 to 255 μ/L)	>1500 mL/24h
++++	Generalised erythroderma with bullae and desquamation	>15 mg/dL (>255 μ/L)	Severe abdominal pain with or without ileus



Figure 4: Scleroderma like skin chronic oral lesions due to chronic GvHD in a patient with allo-HSCT for CML.

Table 8: Clinical Grading of Acute Graft *Versus* Host Disease

Grade	Degree of Organ Involvement
I	+ to ++ skin rash; no gut or liver involvement; no decrease in clinical performance
II	+ to +++ skin rash; + gut or liver involvement (or both); mild decrease in clinical performance
III	++ to +++ skin rash; ++ to +++ gut or liver involvement (or both); marked decrease in clinical performance
IV	Similar to grade III and profound decrease in clinical performance

HSCT PROGRAMME IN INDIA

The institutes running HSCT programme in India are outlined in **Table 9**. Many more transplant centres are expected to open all over India as there is a lot of scope for this procedure considering the patient load of various haematological disorders.

There is no functional donor registry in India, while this is well-established in Europe, North America and Japan. These registries improve the chances of finding a fully matched, unrelated, HLA donor to 60% to 80%, whereas, it is only 25% to 30%, when siblings form the donor pool.

Table 9: Haematopoietic Stem Cell Transplantations (HSCTs) done in Various Centres Across India

Centres (period for which HSCT data is available)	No. HSCT	Allo-HSCT	Auto-HSCT
Christian Medical College, Vellore (1986-Dec 2009)	1002	767	235
AIIMS, New Delhi (1992-Dec 2009)	458	126	332
Tata Memorial Centre, Mumbai (1983-Jun 2010)	439	249	190
Sahyadri Speciality Hospital, Pune (1999-Mar 2010)	314	216	98
Apollo Cancer Hospital, Chennai (1995-Dec 2009)	249	151	98
Jaslok Hospital and Research Centre, Mumbai (2000-May 2010)	224	79	145
Army Hospital, Delhi (1998-Jun 2010)	207	137	70
Gujarat Cancer and Research Institute (1999-Jun 2010)	112	44	68
Narayana Hrudayalaya, Bangalore (2004-Jun 2010)	80	67	13
Rajiv Gandhi Cancer Centre, New Delhi (2001-Dec 2009)	72	16	56
PGIMER, Chandigarh (2003-May 2010)	45	18	27
SGPGIMS, Lucknow (1999-Dec 2009)	34	24	10
Prince Aly Khan Hospital, Mumbai (2007-Jun 2010)	32	01	31
Manipal, Bangalore (2004-Dec 2009)	28	8	20

FUTURE PROSPECTS IN HSCT

HSCT has revolutionised the treatment of many, hitherto, incurable diseases. However, because of significant peri and post-transplant morbidity and mortality (5% to 30%) further research and trials are required to refine and optimise conditioning regimens and supportive care. Stem cell manipulation and T-cell depletion to improve transplant outcomes and minimise incidence of GvHD is another area of research. Gene therapy using

haematopoietic stem cells is an exciting prospect. Adult stem cells and mesenchymal stem cells have been used in various trials for treatment of type 2 diabetes mellitus, neurodegenerative, heart and peripheral vascular diseases exploiting the potential of stem cell plasticity (or trans-differentiation).

Other developing areas which would help improve transplant outcomes and minimise complications are given below:

1. Non-myeloablative and cord blood transplantation
2. Matching for minor HLA antigens
3. *Ex vivo* expansion of HSCs
4. New immunosuppressive agents and monoclonal antibodies to minimise GvHD risk
5. Improving GVL without worsening of GvHD
6. Positive selection of CD34 cells and negative selection of allo-reactive T-cells responsible for GvHD

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Section 16

HIV and AIDS

Section Editors: Alaka Deshpande and B.B. Rewari

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16.1 Epidemiology

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INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) was first recognised among men who have sex with men (MSM) in the United States in 1981. The causative agent, human immunodeficiency virus (HIV) was discovered in 1983 by Luc Montagnier and Francoise Barre-Sinoussi at the Pasteur Institute, Paris, France and were awarded the 2008 Nobel Prize in Medicine for this discovery.

Molecular studies have revealed that HIV originated from the cross-species transmission to man of the simian immunodeficiency virus (SIV), which naturally infects non-human primates in Africa and has very close genetic similarity to HIV. The HIV viruses are broadly classified into HIV 1 and HIV 2 and it is further subdivided into groups and subtypes (**Table 1**).

Table 1: The Classification of HIV

Type	Group	Subtype (clades)	Distribution
HIV 1	M (major)	A1, A2, A3, A4, B, C, D, F1, F2, G, H, J, and K	Global Subtype C prevalent in India most
	O (outlier)		Limited to equatorial West Africa
	N (non-major and non-outlier)		Limited to equatorial West Africa
HIV 2			Limited to West Africa

The major routes for HIV transmission are:

1. Unprotected sexual intercourse with an HIV-infected partner.
2. Exposure to HIV-infected blood and blood products (e.g. blood transfusion, sharing of infected needles, needle-stick injuries, etc.).
3. Peri-partum (vertical) transmission from an HIV-infected mother to her child.

GLOBAL AIDS SCENARIO

HIV infection has evolved to become the greatest pandemic in human history. Since the beginning of the epidemic, almost 60 million people have been infected and 25 million people have died of HIV-related causes. Sub-Saharan Africa and Asia are the regions most affected by the HIV epidemic. India accounts for roughly half of Asia's HIV prevalence. **Table 2** shows the summary of United Nations AIDS global report for the year 2009.

BURDEN OF HIV EPIDEMIC IN INDIA

The first cases of HIV infection in India were documented in 1986 among female sex workers (FSWs) in Chennai, Tamil Nadu. Subsequently, cases of HIV infection have been reported from every state. The HIV epidemic in India has followed the 'type 4 pattern', where new infections occur first among the most vulnerable populations (such as FSW and injecting drug users [IDU]), then spread to 'bridge' populations (clients of sex workers and sexual partners of drug users) and then finally enter the general population. **Table 3** summarises the AIDS epidemic in India.

Table 2: Global Summary of the AIDS Epidemic

Number of people living with HIV in 2009	Total	33.3 million (31.4-35.3 million)
	Adults	30.8 million (29.2-33.6 million)
	Women	15.9 million (14.8-17.2 million)
	Children under 15 years	2.5 million (1.6-3.4 million)
People newly infected with HIV in 2009	Total	2.6 million (2.3-2.8 million)
	Adults	2.2 million (2.0-2.4 million)
	Children under 15 years	370 000 (230 000-510 000)
AIDS-related deaths in 2009	Total	1.8 million (1.6-2.1 million)
	Adults	1.6 million (1.4-1.8 million)
	Children under 15 years	260 000 (150 000 – 360 000)

Table 3: Summary of AIDS Epidemic in India

Number of people living with HIV infection	Total	2.40 million (1.9-3.0 million)
	Males	61%
	Females	39%
	Children	3.5%
Prevalence among adults	Overall	0.31%
	Males	0.44%
	Females	0.23%

These estimates are derived from sentinel surveillance (unlinked, anonymous HIV testing of consecutively collected samples from designated sites across the country for different target populations) conducted annually and is complemented by population-based surveys (e.g. National Family Health Survey).

A critical review of the HIV epidemic in India reveals the following trends:

- Young adults (15-49 years) account for 89% of the burden of HIV infection.
- The male to female ratio is 3:2.
- The states of Andhra Pradesh, Maharashtra, Karnataka, West Bengal, Tamil Nadu, Gujarat and Uttar Pradesh together account for 80% of the burden in India (**Figure 1**). The prevalence is <1% the north-eastern states of Nagaland and Manipur.
- India has a 'concentrated epidemic', the prevalence being significantly higher among various high-risk groups (MSM, IDU, FSW and STD clinic attendees) than among antenatal clinic (ANC) attendees (**Figure 2**).
- There is considerable variability in the spread of HIV infection in the country. At the district level, 87 districts had HIV prevalence <1% among ANC attendees and 47 had <5% prevalence among FSW in 2007. Several of these districts are in moderate and low prevalence states like Bihar, Chhattisgarh, West Bengal, Gujarat, etc.

- The predominant mode of transmission is heterosexual exposure (**Figure 3**), while it is injecting drug use in north-eastern states.
- HIV prevalence has been stable from 2002 to 2007 (**Figure 4**).
- HIV prevalence among women attending antenatal clinic (ANC) has declined from 2000 to 2007 (**Figure 5**), indicating a decrease in the incidence of new infections.

National Response to the HIV Epidemic

The first phase of the National AIDS Control Program (NACP) was launched in 1992 and the third phase (NACP-III) in 2007. The overall goal of NACP-III is to halt and reverse the HIV epidemic in India over the next 5 years. Since <99% of the population in the country is free from HIV infection, NACP-III places the highest priority on preventive efforts, and also seeks to integrate prevention with care, support and treatment. Populations that have the highest risk of exposure to HIV (FSW, MSM, IDU) will receive the highest priority in the prevention and comprehensive management. All infected persons will have access to treatment.

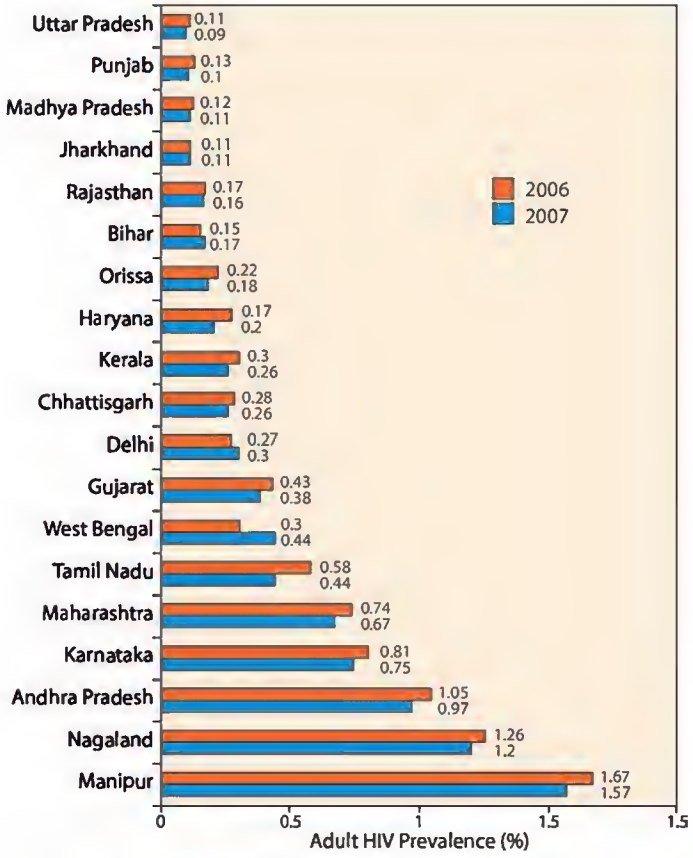


Figure 1: State-wise estimated adult HIV prevalence, 2006-2007.
Source: NACO.

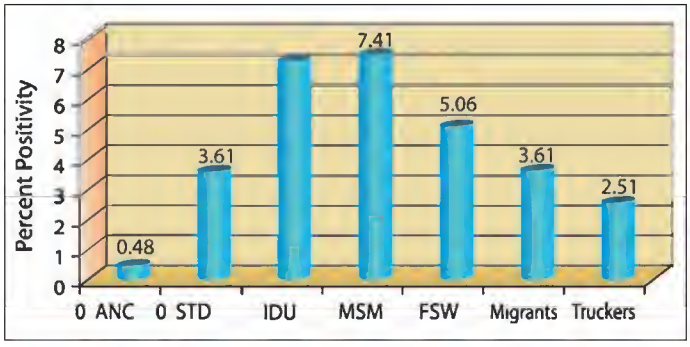


Figure 2: HIV prevalence among various population groups, India, 2007.
Source: NACO.

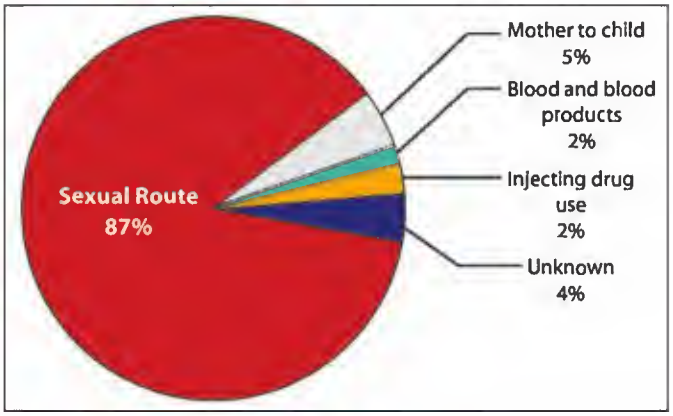


Figure 3: Routes of transmission
Source: NACO.

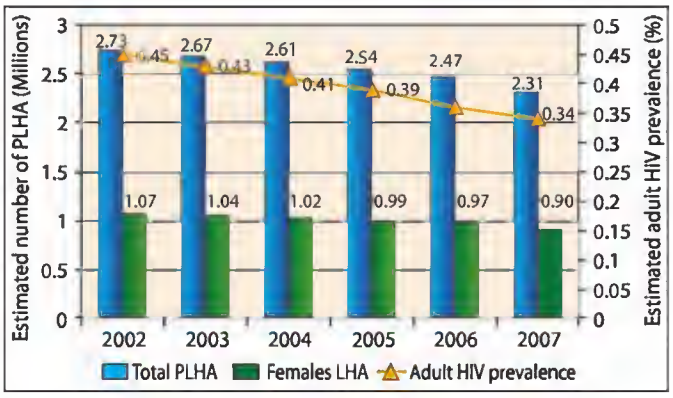


Figure 4: Trends of HIV prevalence and number of PLHA, India, 2002-2007.
Source: NACO.

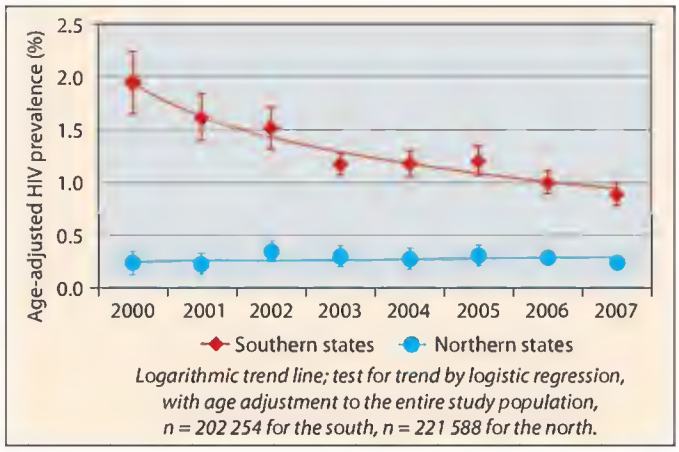


Figure 5: Age-adjusted HIV prevalence among antenatal attendees aged 15-24 from 2000 to 2007 in high-prevalence southern states (Andhra Pradesh, Karnataka, Maharashtra and Tamil Nadu) and northern states of India.
Source: AIDS Epidemic Update, 2009. UNAIDS.

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16.2 Virology, Immunology and Diagnosis

V Ravi, Anita Desai

More than a quarter of a century has passed since the discovery of human immunodeficiency virus (HIV), which is the causative agent of acquired immune deficiency syndrome (AIDS). While HIV-1 is responsible for majority of the infections, HIV-2 occurs in a small minority of HIV infections in some countries including India.

CLASSIFICATION OF HIV

Human immunodeficiency viruses (HIVs) belong to the family *Retroviridae* and subfamily *Lentivirinae*. This subfamily has two types HIV-1 and HIV-2. **Table 1** shows the subgroups.

Table 1: Subgroups of HIV

	Subgroups		
HIV	HIV-1	M major (clades A—K)	
		N new	
		O outlier	
	HIV-2	clades A—H	

Both differ in geographical distribution, biological and molecular characteristics as well as the extent of transmissibility. These subtypes have envelope gene sequences that vary by 20-50% or more between subtypes. The subtypes also differ in geographical distribution, biological characteristics and major modes of transmission. HIV-1 subtypes O and N are more distantly related genetically to all other HIV-1 subtypes but less so compared to HIV-2. Studies of HIV-2 genomes showed that there is a remarkably close relationship between HIV-2 and SIV strains that infect sooteymagabey monkeys (SIVsm). HIV-2 has also been reported from other countries other than Western Africa and has been subclassified into clades A-H.

HIV STRUCTURE

As depicted in **Figure 1**, HIV is an enveloped positive stranded RNA virus that measures 120 nm in diameter and consists of a lipid bilayer with uniformly arranged 72 spikes or knobs of glycoprotein – gp 120 and gp 41 (HIV-1)/gp 36 (HIV-2). The virion gp120 located on the virus surface contains the binding site for cellular receptor(s). The two plus stranded RNA molecules are embedded in a protein capsid (p24) together with certain viral enzymes (viral RNA-dependent DNA polymerase (Pol, also called the reverse transcriptase, RT (p66, p51) and nucleocapsid proteins (p9, p7). The capsid (p24) is surrounded by a matrix layer (p17) that in turn is enclosed in lipid bi-layer, the envelope.

Genome Organisation

The genome of HIV-1 measures about 9.8kb while that of HIV-2 measures 10.3 kb (**Figure 2**). Long terminal repeats (LTRs) of

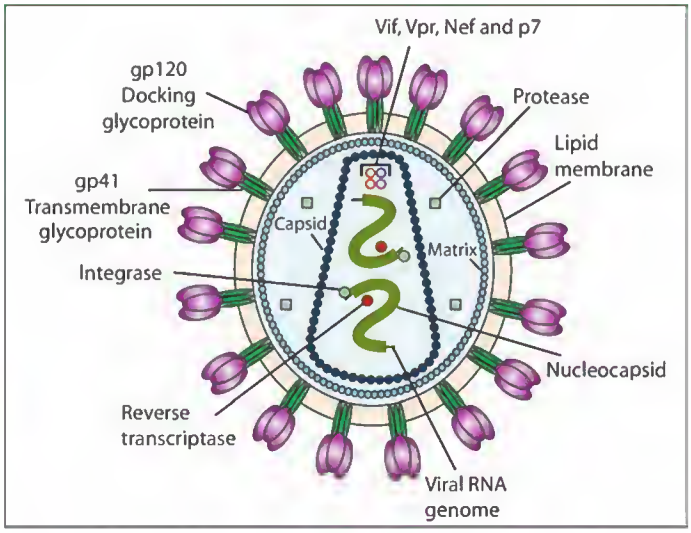


Figure 1: A diagram depicting the structure of human immunodeficiency virus.

nucleotides flank the structural and regulatory genes. Both HIV-1 and HIV-2 have similar genetic organisations encoded in a single positive-stranded RNA. The accessory gene vpu is unique for HIV-1 and is replaced by vpx in HIV-2. The primary transcript of HIV is a full length viral mRNA, which is translated into the gag and pol proteins. The *gag* gene codes for the proteins p24, p17, p9 and p7. The *pol* gene codes for the reverse transcriptase (RT), the protease (PR), and the integrase (IN) proteins. The *envelope* gene codes for the gp120 and gp41 proteins which are made from a precursor gp160. One of the regulatory proteins is *Tat*, a transactivating protein, which along with certain cellular proteins, interacts with an RNA loop structure formed in the 3' portion of the viral LTR and upregulates HIV replication. The other viral regulatory proteins include, *Rev* (Regulation of viral protein expression), which is needed for the synthesis of viral proteins, *Nef* (Negative factor), whose actual function remains unclear is believed to downregulate viral expression. The accessory HIV viral gene products and *vif, vpr, vpu/vpx* appear to influence events such as assembly and budding, as well as infectivity involved in the production of infectious viruses.

REPLICATION OF HIV

HIV enters the body when an individual comes in contact with infected blood, semen and/or vaginal secretions. The CD4 receptor is the principal target site for HIV, however specific chemokine receptors appear to serve as important secondary cellular receptors for HIV. HIV-1 strains have been divided into T-tropic (preferring to replicate in T-lymphocytes) and M-tropic (macrophages) viruses. The chemokine receptor usage is different for each of these viruses, with T-tropic viruses making use of CD4 and CXCR4 (or fusin, the receptor for SDF-1), and M-tropic viruses making use of CD4 and CCR5 (receptor for

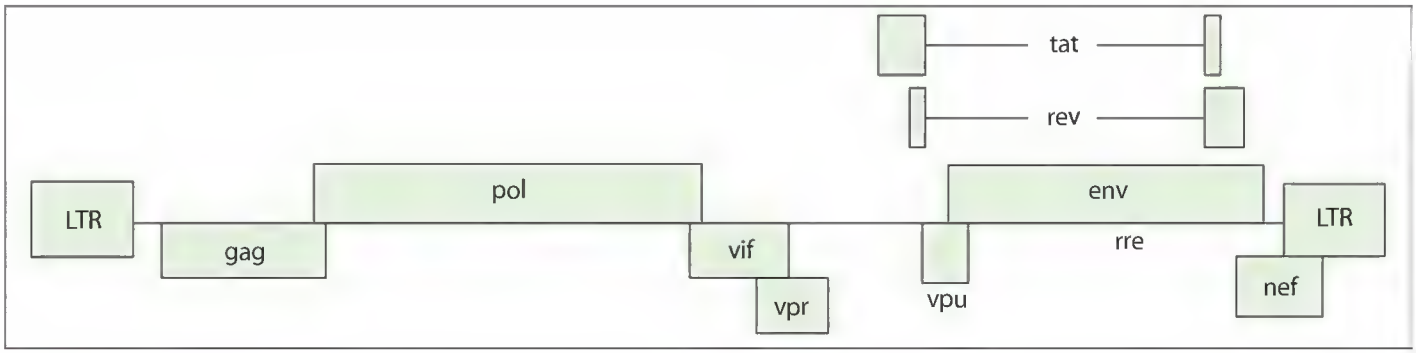


Figure 2: A diagram depicting the genome of HIV and the genes encoded in a single positive-stranded RNA.
Note that both HIV-1 and HIV-2 have similar genetic organisations except the accessory gene vpu is unique for HIV-1 and is replaced by vpx in HIV-2.

RANTES). After attachment of CD4, gp120 is displaced leading to uncovering of domains on the envelope gp41 needed for virus cell fusion. Gp41 is involved in infectivity as well as syncytium formation.

Shortly after the viral capsid enters the cell, an enzyme called *reverse transcriptase* liberates the single-stranded RNA genome from the attached viral proteins and copies it into a complementary DNA (cDNA). The cDNA and its complement form a double-stranded viral DNA which is then transported into the cell nucleus where it is integrated into the host cell's genome by the enzyme called integrase. During viral replication, the integrated DNA provirus is transcribed into mRNA, which is then spliced into smaller pieces. These small pieces are exported from the nucleus into the cytoplasm, where they are translated into the proteins. The final step of the viral cycle, assembly of new HIV-1 virion, begins at the plasma membrane of the host cell where the various structural components then assemble to produce a mature HIV virion. This cleavage step can be inhibited by protease inhibitors. The mature virus is then able to infect another cell. Schematic representation of HIV replication is depicted in **Figure 3**.

IMMUNOLOGY OF HIV INFECTION

The principal impact of HIV infection on the immune system is destruction of the CD4 T-lymphocytes. During primary infection, HIV and HIV-infected cells reach the lymph nodes and other lymphoid tissues. The virus rapidly disseminates during this early phase of HIV infection. As a result, there is a significant fall in CD4 cells and viral levels may be as high as 10^6-10^7 viral copies/ml. The next stage is downregulation of viraemia. This coincides with a robust, intense immune response by the host (**Figure 4**). Both effective cellular immune response mediated by HIV specific cytotoxic T-lymphocytes (CTLs) and humoral response mediated by complement fixing and neutralising HIV specific antibodies comes into play. As a result, the viraemia drops and CD4 levels bounce back to values slightly lower than the normal levels. However, active and continuous virus replication continues in the lymph nodes and lymphoid organs. There is a gradual reduction in the number of CD4 cells with a steady increase in viral load during the long asymptomatic stage. Humoral immunity is intact during the asymptomatic stage and specific antibodies are produced against different viral proteins, but the antibodies are not protective and unable to interfere with cell to cell transmission. This period on average lasts for 8-10 years. The advanced stage of HIV infection is characterised by increase in all the virological parameters (virus load, p24 antigen, etc.) in both peripheral blood and lymph nodes. Lymphoid tissue is totally destroyed and replaced by fibrous tissue. Consequently, there is profound immune suppression and a variety of opportunistic infections set in, which may prove fatal. The CD4 count at this stage is usually less than 200 cells/μl and progressively declines.

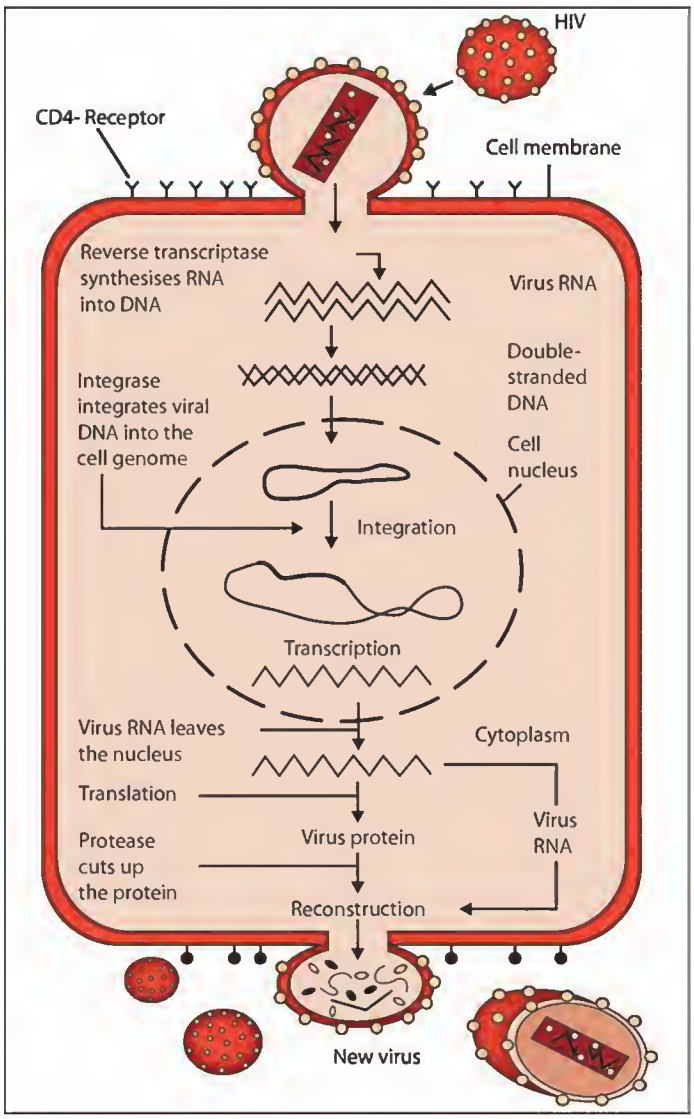


Figure 3: A schematic representation of the various steps in the replication of HIV.

LABORATORY DIAGNOSIS OF HIV INFECTION

Diagnosis of HIV infection can be achieved by the detection of: (a) antibodies in blood and body fluids; (b) antigen in blood and body fluids; (c) viral nucleic acid by polymerase chain reaction (PCR); and (d) virus isolation from blood and tissues. World over, the diagnosis of HIV infection is largely based on the detection of antibodies to HIV in the patient's serum sample. According to NACO, a three-tiered strategy is adopted for diagnosis of HIV infection in clinical settings. Initially, a sample is tested by an ELISA/rapid test. If it is found reactive it is subjected to second and third ELISA/rapid assay using different antigen or principle of testing. If the entire three tests are reactive, the samples are considered positive for antibodies against HIV. Samples that are negative in the first and second levels of testing are considered negative while samples that are positive in the two tests and negative in the third are considered equivocal and subjected to western blot for confirmation.

Detection of HIV Specific Antibodies

Immunoassays for the detection of a serological response to HIV-1 infection were developed in a series of stages, called generations. The first generation assays were very sensitive but not specific and the technology was improved by using recombinant and synthetic peptides as antigens (2nd and 3rd generation kits). More recently, 4th generation ELISA tests have been developed that detect both antibody and p24 antigen simultaneously. The different HIV-1 antibody detection tests available currently are ELISA, rapid immunoassays such as HIV spot tests, immuno Combs' tests, dot blot immunoassays and agglutination assay (Capillus). Antibodies to HIV-2 in clinical samples were detected by ELISA with synthetic gp36 (TM portion of the HIV-2 envelope) antigens.

Detection of Viral Antigen in Blood and Body Fluids

The p24 antigen assay detects the viral capsid (core) p24 protein in blood which is detected earlier than HIV antibody during acute infection. The most commonly used HIV p24 antigen test procedure is a basic antibody-sandwich ELISA. This test has limited diagnostic potential because antigenaemia is restricted to two stages of HIV infection: early in the illness during the latter half of the window period and late in the illness (end-stages) when immune collapse has set in.

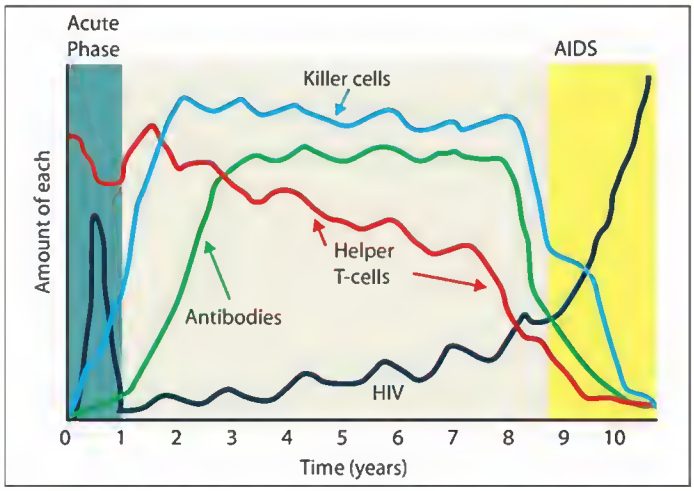


Figure 4: Immune events in relation to natural course of HIV infection.

Detection of Viral Nucleic Acid

Detection of HIV nucleic acid in plasma/serum is used in clinical practice for diagnosis of HIV infection in children aged less than 18 months (early infant diagnosis or EID) and estimation of viral loads. The detection of HIV nucleic acid can be achieved by either polymerase chain reaction (PCR), nucleic acid sequence based amplification (NASBA) or branched DNA (bDNA) technique. However, the most widely used test is the polymerase chain reaction (PCR). For EID, the NACO recommends the use of a HIV DNA PCR using dried blood spot specimens.

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16.3 Pathophysiology and Clinical Features

UL Wagholikar

INTRODUCTION

'Human immunodeficiency virus' (HIV) is a human-specific retrovirus. Types HIV-1 and HIV-2 are identified by their unshared antigens.

Figure 1 depicts viral genes. **Table 1** summarises gene encoded products and their actions. Viral components, *proteins*, RNA, enzymes and structural proteins and *glycoproteins* are indicated by letters 'p' and 'gp' and allotted numbers, as per molecular weight in 'micro-daltons'. Together, they determine viral characters. Components are antigenic to man. Antibody responses to them differ from antigen to antigen, person-to-person and time-to-time (in a person). Some antigens resemble human components (e.g. p17 and thymosin, gp120 and neuroleukin, etc.). Anti-HIV antibodies may cross react with host tissues to cause autoimmune lesions in HIV disease.

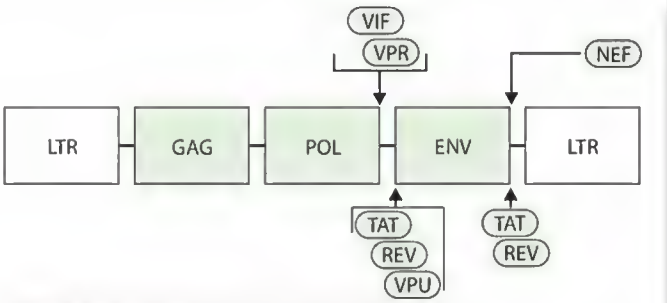


Figure 1: Human immunodeficiency virus genes.

INVASION OF TARGET CELLS

'CD4' molecules on cells and 'gp120' molecules on HIV have affinity for each other. A chance contact leads to firm bondage and lays the foundation for cell invasion. T-helper lymphocytes (including immature, mature and derived cells), monocytes, macrophages, dendritic cells (DCs) [in epidermis (Langerhans cells), mucosal surfaces of alimentary and genital tracts, lymphoid depots and tissues], epithelial cells lining mucosae of the said tracts and microglial cells of the central nervous system (CNS) carry CD4 molecules. HIV targets them for replication.

Just establishment of 'gp120↔CD4' bond does not ensure successful cell-invasion, gp120 must also bind with one or more cytokines on the surfaces of target cells, which act as co-receptors. Two co-receptors, essential for HIV, are CCR5 and CXCR4. Due to minute differences in gp120 molecules, strains

Table 1: HIV Genes, Products Encoded by Them and Actions of the Products

Gene	Products encoded by it	Action of the product
LTR	Transcription control factors	Initiates transcription process
GAG	GAG protein p55, a complex macromolecular poly protein, which is cleaved by 'protease', into smaller proteins, listed below:	p6 participates in terminal stages of building the viral particle p24 and p17 are used to form proteinous membranes around the core
	Core proteins (p6 and p24) Matrix protein (p17) and Nucleocapsid proteins (p7 and p9)	 p7 and p9 bind RNA to p24 to form nucleocapsid
POL	RNA (p31), Enzyme protease (p10), POL protein (p150), which is cleaved by 'protease' into 3 enzyme molecules:	p31 is the template for synthesis of proviral DNA p10 cleaves p55, p15, p150 and gp160 into smaller fragments, as mentioned in middle column
	Reverse Transcriptase (p64), Integrase (p32) and Ribonuclease H (p66/51)	p64 catalyses manufacture of proviral DNA p32 brings about integration of proviral DNA into cell genome p66/51 hydrolyses (remnant) RNA (p31) after synthesis of proviral DNA
ENV	ENV antigen p92 is formed first. It is glycosylated to gp160, which is further cleaved by 'protease' into 2 separate glycoproteins gp41 and gp120	gp120 selects the target cell and binds to it gp41 brings about fusion of viral envelop with target cell and manoeuvres viral entry into it
TAT	Transcriptional activator protein (p13/14)	Enhances (1000 times) transcriptional activity
REV	Regulator of gene expression protein (p19)	Regulates gene expression of virus
VIF	Viral infectivity factor (p23)	Overcomes inhibition from the host cell
NEF	Negative effector protein (p27)	Enhances viral infectivity
VPR	Viral protein R (p15)	Facilitates infection of macrophages
VPU	Viral protein U (p16)	Influences virus release from cell

First four genes are common to all retroviruses. Last 6 are HIV specific regulatory genes.

of HIV differ in their affinity to them. Other co-receptors (CCR2b, CCR3, STRL33 and GPR15) have also been identified.

After binding with CD4, the configuration of gp120 is changed. New sites are opened on it for binding with co-receptors. After "CD4↔gp120↔CCR5/CXC4" binding, gp41 also undergoes changes. It emerges on the surface, by the side of gp120. Now, gp41 can establish contact with the target cell membrane. Molecules of 'fusion' peptides (FPs) are inserted on the exposed ends of gp41. FPs cause fusion of viral envelope with the cell membrane. An opening is thus created. Viral genome then enters the target. This opening is sealed after viral entry. Only one virus can infect a cell. The infected cell cannot get rid of HIV.

FACTORS INFLUENCING REPLICATION

Interplay, between regulatory factors of the virus and of the host cell, determines when, in which cell and how much the virus replicates.

Virulence, mutations and tropism of HIV are significant viral factors. HIV-1 is more virulent than HIV-2. Group M is most virulent. Infections by more virulent strains are more prevalent and progress at a faster pace. Arguably, differences in virulence are related to efficiency of replication. HIV-1 (M) is the most common isolate all over the world. Clade B is the most common in USA and Europe, Clade E in Thailand. Clade C is emerging as the fastest spreading subtype in India, Ethiopia and South Africa. Isolates from different cases of HIV infection (even when of same type, group or clade) are seldom identical, on account of mutations. Mutations are clustered in POL, ENV and regulatory genes. Some mutations favour viral replication. Some act the other way (**Table 2**).

Table 2: Effects of HIV Mutations

Gene	Nature of mutation	Effect on virus
POL	Enzyme deficient mutant	Poor replication of virus → Diminished virulence
	Enzyme altered mutant	Replication, even in presence of ART drugs → Drug resistant virus
ENV	gp120 defective mutant	Poor binding with CD4 → Diminished virulence
	gp120 variant mutant	No effect of anti-gp120 antibodies → Immune escape of virus
VIF	p23 negative mutant	Cannot overcome effect of APOBEC 3G → Non-replicating impotent virus
TAT	p13/14 deficient mutant	Poor transcriptional activity → Diminished virulence
REV	p19 deficient mutant	Poor capacity to express genetic properties → Diminished virulence
NEF	p27 deficient mutant	Poor infective capacity → Diminished virulence
VPR	p15 deficient mutant	Incapability to target macrophages → Diminished virulence
VPU	p16 deficient mutant	Defect in release of virus from cell → Diminished virulence

Mutations 1 to 4 have been encountered, 5 to 10 are (to the best of author's knowledge) theoretical possibilities (as of today).

APOBEC 3G: apolipoprotein B mRNA-editing, enzyme catalytic, polypeptide-like 3G.

Cells have an inherent mechanism of protecting themselves against any viral invasion. They produce 'APOBEC 3G', a factor which inhibits viral replication. Its effect is counter-acted by p23, encoded by the gene VIF. By corollary, 'VIF negative' mutants will be impotent.

Strains which bind only with CXCR4 are called X4 strains. CXCR4 is present only on T-lymphocytes. Thus, X4 strain is 'T tropic'. Strains with affinity for CCR5 are R5 strains. Since, CCR5 co-receptors are predominant on macrophages and monocytes (MM series), R5 strain is 'M tropic'. Strains with affinity for both receptors are 'dual tropic'.

Besides MM series, CCR5 is present on DCs and T-lymphocytes also. So, M tropic strain has a wider range of target cells. Usually, in the early phase of infection, M tropic strains predominate in viral isolates from patients. In the later phases, T tropic strains predominate. It is likely that M tropic virus, with many targets at the portal of entry, establishes infection with greater ease and success. Later, it mutates to T tropism and switches on to the most susceptible target.

T tropic strains, with 'syncytium inducing' (SI) capacity on targets, are more devastating.

Other retroviruses can replicate only in cells capable of multiplication. But HIV has the capacity, *albeit* limited, of replication, even in terminally differentiated non-dividing macrophages. Viral protein R (p15) makes this possible.

Activation status, co-receptor profile and nature are significant cell related factors.

In targeted cells, proviral deoxyribonucleic acid (DNA) (free/integrated) remains transcriptionally inactive (latent) if the cell is in a resting state. Activation of the cell initiates viral replication. In a HIV patient, presence/acquisition of any sexually transmitted diseases (STDs) enhances HIV replication. Cytokines from inflammatory lesions of STD trigger activation of virus-infected cells. Lesions of tuberculosis (TB) and other viral infections (HBV/ HCV/EBV/CMV) also have a similar effect. Any such infection converts latent into active virus. Some cytokines, e.g. IL-10, also exert a minor anti-HIV influence.

In an individual, co-receptor production (quality and quantity) is genetically controlled. Co-receptor produced in excess, may be shed by the cell. Co-receptors floating in the micro-environment around a cell can hinder meeting of gp120 and cell-bound co-receptor and protect it partially. Delta-32 chromosomal mutation causes a homozygous defect in the gene responsible for expression of CCR5 in about 1% of population in Western European Caucasians and their American descendents. M tropic HIV-1 cannot replicate in them. In individuals with a heterozygous defect, the virus cannot replicate rampantly; in them the disease progresses slowly.

Replication is not equally efficient in all cells. T-helper cells and MM series are the principle targets. T-helper and T-memory cells are more easily infected by HIV. In the replication cycle, all target cells may not synthesise viral components in the proper proportion. Deficient production of any component will adversely affect replication. Viral proteins and

nucleoproteins, synthesised in excess, accumulate in the cell in cytotoxic proportion.

EFFECTS OF VIRUS ON CELLS

Interactions between HIV and the host cell are summarised in **Table 3**.

Table 3: Interactions between HIV and Host Cells

Peaceful co-existence of cell and virus
- When virus is non-replicating, the infected cell is unharmed
- Latent virus retains its viability. It can start replicating at opportune time

Pathogenetic virus-cell relationship
- When virus replicates, host cell is always damaged
- Cell may be killed by direct or indirect effects of the virus
  - Direct cell death of infected cells: due to enormous replication of virus
    - By 'fragmentation' of cell due to excess 'budding'
    - By 'lysis' of cell due to cytotoxic protein components of virus
    - By 'causing fusion' of cells (only by 'X4' strains of HIV)
    - (It is also called syncitium inducing (SI) effect of virus)
  - Indirect cell death of infected as well as non-infected cells:
    - Due to apoptosis
    - Due to IgM and IgG antibodies and cytotoxic lymphocytes
- When viral replication is not sufficient to kill the cell, it causes dysfunction
  - Functional damage
    - Reduced normal function
    - Abnormal function

CD4+ T Lymphocytes

Infected cells suffer most and by various mechanisms. Even non-infected cells suffer 'accelerated apoptotic death' (AAD), induced by excess, prolonged activation. Molecular basis of AAD is not clear. Non-infected cells, carrying viral antigens on the surface, are sequestered by anti-viral IgM/IgG antibodies and killed by cytotoxic lymphocyte (CTL) T-cells. Cells with lesser viral loads may not die; these get functionally impaired. Deficient antigen-induced proliferation and cell-mediated immune (CMI) response are the major defects.

In active phase of infection, CD4+ loss can be up to 2 million cells per day. Sometime loss of non-infected cells can be more than that of infected cells. In the initial phases of infection, enormous loss does not reflect as an immediate, proportionate drop in their blood count, due to compensatory proliferation of precursor cells. CD4+ counts start dropping, when the virus kills lymphoid precursor cells and replenishment of lost cells becomes increasingly inadequate. Not all research workers accept this as a satisfactory and complete explanation of drop in count.

Cells of MM Series and DCs

They are comparatively resistant to cytopathic effects of HIV because the extent of budding and fragmentation is low in them and because toxic products of viral replication are enclosed in vacuoles. Besides, M tropic virus does not express 'SI' effect. DCs, by carrying virus on their surfaces, minimise contact between their cytoplasm and viral chemicals. Loss of these cells is far less than that of CD4+ T-cells. Monocyte counts of blood do not drop.

Viral replication in these cells is less profound but not less significant. Migratory monocytes transport HIV to many organs, including CNS. Tissue macrophages establish viral reservoirs in gonads, kidneys, genital mucosa, etc. In transmucosal (rectal/vaginal/oral) infections, DCs get infected first. They carry the virus on the surfaces of their processes, migrate and present it to susceptible cells in the regional lymph nodes. Cell-to-cell transfer is a more efficient mechanism of cellular infection than random contact between the free virus and receptors on cell.

When CD4+ T counts drop, MM series and DCs act as virus supplying factories.

These infected cells show significant functional defects. Their microbicidal activity is reduced, response to chemotactic agents is decreased and capacity to present antigens to T-cells is poor. Secretion of useful IL-1 is reduced. They produce harmful IL-6.

B-cells

These are not infected, but are functionally affected by viral replication in other cells. IL-6 and gp 41 molecules instigate proliferation of B-cells and synthesis of abnormal immuno-globulins (IG) in excess quantity (hypergamma-globulinaemia). Abnormal Igs form immune-complexes (ICX) with other microbial antigens. Circulating ICXs can initiate type III allergic lesions.

CD8+ Lymphocytes

These also, are 'indirectly' damaged. In the initial phases of infection, these produce CTLs, which minimise viral replication by killing infected CD4 lymphocytes and also by producing cytokines which inhibit viral replication. As infection prolongs, the number of CTLs tends to fall, due to AAD. In terminal phases, CD8+ cells get exhausted.

Adaptive Immune Response of the Host

In an immunologically normal adult, immune response, as in other infections, would be expected in HIV infection too. Immune control of any viral replication is achieved through virus specific CD4+ T-cells, antibody dependent cellular toxicity and by CTLs. But, in HIV infection CD4+ T-cells, themselves, are the viral targets. Due to the vagaries of HIV antigens, the magnitude and pattern of antibody response can be unreliable. Antibody levels may be high, but viral neutralisation, not proportionately so. Moreover, mutant strains can escape immune damage. CTLs are the body's major effective measure of inhibiting HIV replication. Efficiency of their action determines the future course of events. Initially, in HIV infection, they are variably successful but later on they fail. As infection continues, CTL counts fall, due to AAD. On exhaustion of CD8+ cells, CTL response gets suppressed (immuno suppression). Other reasons for lack of effective immune control of viral replications are magnitude of HIV reservoirs in body, functional defects in immunocompetent cells, lifestyle (intravenous drug abuse) of patient and his genetic make-up.

Balance of forces 'producing and killing HIV' sets a level of viral load in body. Higher the 'set point', worse is the prognosis. When CTL response declines, the 'set point' gets raised. Disease progresses faster. ART, aiming at lowering the load, has to be life-long.

PROGRESS AND CLINICAL STAGES OF DISEASE

Lymphocytes, MM series and DCs constitute the backbone of CMI. HIV affects almost all. The immune apparatus and function show the most obvious primary clinico-pathologic manifestations. Others which bear the primary brunt are the gastrointestinal tract (GIT) and CNS.

Pathogenesis of Immunodeficiency

Incubation period

After transmucosal (and also parenteral) transmission, HIV reaches and establishes in T-cell areas of lymph nodes. Mucosal and nodal changes and early viral replication are clinically silent. Viral release into circulation increases slowly. Viral antigens appear in blood. HIV infection clinically manifests in 3 to 6 weeks post-exposure in up to 90% cases.

Acute retroviral syndrome (ARVS)

Increasing viraemia makes the infection manifest as 'flu like' episode, called ARVS (sore throat, myalgia, fever, rash, fatigue, enlarged nodes, diarrhoea and vomiting). Proportionate to the viral load in blood, there is a downward spike in CD4 count. With virus dissemination to all lymph depots, the infection becomes multi-systemic and permanent.

Due to the host's immune response, viral replication is restrained. Symptoms abate in 2 to 4 weeks. CD4 count gets corrected. Patient is sero-converted. He may be diagnosable, also by virus/its components in blood. After recovery, the patient goes through a variable period of clinical latency. Two types of 'latent' phases are possible.

Virus non-productive latent (VNPL) phase

Persons with a strong immune response take care of total viral replication while the virus lurks in reservoirs, in peaceful co-existence, awaiting an opportunity to reactivate. This can continue for months to years. The patient is sero-positive, has no viral load in blood and has a normal immune profile. Cases in VNPL phase are clinically healthy and symptom-free. They may even be non-infective to sex partners but are not safe blood donors.

Virus low-productive subdued (VLPS) phase

If the initial immune response is not strong enough to restrain viral replication completely, virus is produced in minute amount, but not sufficient to produce continuous clinical manifestations. The virus keeps on infecting new CD4+ T-cells. Its replication steadily increases without causing a drop in their count. A period of apparent inaction continues over a variable period, depending upon the magnitude of viral replication. Patient is sero-positive. His viral load depends on the 'set point'. CD4 count, usually normal, shows a trend of gradual annual decline (25 to 60 cells per year).

Cases in VLPS phase are not totally symptom-free. They may have mild/moderate episodes of symptoms due to GIT lesions (see below). In between the episodes, they do not appear seriously ill. There may be 'non-alarming' weight loss. Their infectivity is proportional to viral load.

Persistent generalised lymph adenopathy (PGLA)

Some cases in VLPS phase have PGLA. Enlarged nodes show non-specific polyclonal hyperplasia of 'B' and 'T' cell areas. Abnormal antibodies and their effects may appear. Some cases may have few, mild symptoms (fever, rash, fatigue). Constitutional symptoms indicate that the next stage is imminent very soon.

Stage of Immunodeficiency (SIMD)

Viral replication continued over a long period, plays havoc with the immune apparatus. CD4+ T-cells play the role of an 'orchestra conductor' for humoral immunity as well as CMI. Dysfunction of humoral immunity is *indirect* due to influences on B-cells. Dysfunction of CMI is the direct result of loss of T-lymphocytes. Progressive, relentless loss and dysfunction of almost all subsets of immunocompetent T-cells are the major events. Lymph nodes, thymus, bone marrow, lymphoid depots in tissues and gastrointestinal tract get depleted of T-cells. They show structural disorganisation and atrophy. CD4 and CD8 cell counts in blood drop. SIMD invites opportunistic pathogens and activates the pre-existing latent ones.

CD4 count in peripheral blood is used as an indicator of immune function. It is however not a perfect guide. 2% of the total pool of CD4 cells is in blood; rest is in tissues. Even a minute change in the distribution can bring about a vast change in the count. In some studies, CD4 percentage was a better marker than CD4 count. As of today, CD4 count is used and has served as a useful practical guide.

Time required for progress from infection to SIMD is variable. It depends on the summation of dynamics of viral replication and the host's anti-HIV immune response. It can be prolonged by ART regime. Usually, the period cannot be predicted with certainty, except in cases in VLPS, showing decline of CD4 count at a steady rate. SIMD is reached in 2 to 5 years in 'rapid progressors'. 'Slow progressors' take more than 10 years. 8 to 10 years is the period required for majority of the cases. Hallmarks of SIMD are increasing viral load, increasing titer of viral components in blood and CD4 count below 300/mL. An ill-understood group consists of patients in whom CD4 counts are below 300/mL and yet who show no manifestations of immunodeficiency. Co-existing STD/TB/(enlisted) viral infections accelerate the onset of SIMD. SIMD aggravates these diseases. A vicious cycle is thus established.

Possible Co-Morbidities Associated with HIV

These are immune complex lesions, autoimmune lesions and hypergammaglobulinaemia.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Development of opportunistic infections (OIs) due to immuno-deficiency, and/or tumours in HIV infection defines the status as AIDS. AIDS defining OIs and tumours are enlisted in **Table 4**.

Pathogenesis of GIT Lesions

It is claimed (but not unanimously accepted) that GIT houses 40% to 65% of total immune cells of th body. Immune cells of GIT (all subsets of T-cells, B-cells and plasma cells, DCs and antigen identifying and processing clusters of T-cells and DCs) are organised into Peyer's patches and lymphoid follicles. They are also scattered in the lamina propria and in between the lining epithelial cells. Specialised (micro-folded) epithelial cells also act as 'immune cells'; they can take-up and transfer antigens and some pathogens to DCs. Epithelial cells bear CD4 receptors and possess the capacity to synthesise viral components and cytokines. Histology of gut mucosa is similar

Table 4: AIDS Defining Lesions in HIV Infection

Type of lesion	Disease	Distribution
Protozoal and Helminthic infections	Cryptosporidiosis/Isosporiasis	Enteritis
	Pneumocystosis	Pneumonia/Disseminated
	Toxoplasmosis	Pneumonia/CNS
Fungal infections	Candidiasis	Oesophageal/Tracheal/Pulmonary
	Cryptococcosis	CNS
	Coccidioidomycosis	Disseminated
	Histoplasmosis	Disseminated
Bacterial infections	Atypical Mycobacteriosis	Disseminated/Extrapulmonary
	Mycobacterium tuberculosis	Pulmonary/Extrapulmonary
	Nocardiosis	Pulmonary/Meningeal/Disseminated
	Salmonellosis	Pneumonia/CNS/Disseminated
Viral infections	CMV disease	Pulmonary/Intestinal/Retinal/CNS
	Herpes simplex disease	Localised/Disseminated
	Varicella-zoster disease	Localised/Disseminated
	JC polyomavirus disease	Progressive multi-focal leucoencephalopathy
Tumours	Kaposi's sarcoma	Anywhere
	B-cell non-Hodgkin's lymphoma	Anywhere
	Primary lymphoma of brain	Brain
	Invasive cancer of cervix	Uterus

to that of a tissue harbouring low-grade inflammation. It reflects ongoing contact and conflict with intestinal flora.

Mucosal T-memory cells are perpetually in a state of activation. Mucosal CD4+ cells are both CCR5+ and CXCR4+. They constitute 80% of the co-receptor positive population of the total body. For these reasons, the GIT is highly susceptible to HIV.

Studies on Macaque monkeys and simian immunodeficiency virus (SIV) have shown that the kinetics of destruction of immune cells of GIT was same as in other parts of the body. Depletion of intestinal CD4+ cells was noticeable within days after infection. It was same, regardless of route of the infection. It continued throughout the course of the infection. By the time SIMD was reached, the mucosa, almost totally depleted of immunocompetent cells, was markedly thinned out. There was also direct HIV driven mucosal inflammation, a lesion called 'HIV enteropathy'.

Intestinal disease manifests with episodic diarrhoea, dehydration and anorexia. All patients do not exhibit these manifestations. When present, they may not be proportionate to the severity of the lesions. Other factors, contributory to GIT dysfunction include: fat malabsorption, bacterial overgrowth, bile salt excess and reaction to drugs. The patient is markedly emaciated.

Pathogenesis of CNS Lesions

This is the third primary feature of HIV disease, even when HIV cannot cross the blood-brain barrier (BBB) and target neurones. Infected monocytes carry HIV across the BBB. A pre-existing inflammatory focus in brain attracts HIV infested macrophages and facilitates CNS infection. M tropic strain is the main invader. CNS macrophages and microglial cells pick-up HIV and suffer.

About 10% of patients have short meningitic episodes at sero-conversion. Serious disorder, 'dementia' (insidious onset, progressive course, impaired memory and concentration, apathy, social withdrawal, slow movements, ataxia, etc.) is seen late, when patients are approaching SIMD. Incidence (80% to 90%, prior to ART) is now declining.

Virus and antibodies are present in cerebrospinal fluid (CSF). Damage is indirect, probably caused by soluble neurotoxic components (gp41 and gp120) of virus and toxic chemicals produced by infected microglia. Excess entry of calcium ions into neurones, triggered by toxic chemicals, is the postulated mechanism. The lesion is slowly destructive (focal glial necrosis) accompanied by reparative gliosis. The brain shows cerebral atrophy, widening of sulci and ventricles, microglial nodules, perivascular infiltrates and giant cell encephalitis. Clinical severity is out of proportion to the magnitude and extent of lesions. The major factor responsible for functional loss of brain is invisible: 'synaptodendritic injury (chemical injury that disrupts neuronal network function)'.

PAEDIATRIC HIV AND AIDS

About 2% of cases of AIDS occur in children. 90% of them are due to materno-foetal transmission (MFT), intrauterine (trans-placental), intranatal (by fluids in birth canal) or postnatal (by breast milk). Intranatal transmission is the most common. By any mode, MFT is directly proportional to the viral load in the mother. Its incidence (24% to 65%, as per earlier reports) has been brought down by ART regimes for HIV positive pregnant women.

Pathophysiology of paediatric HIV/AIDS is essentially the same as in adults. Transplacental transmission can cause intrauterine death or congenital HIV, which reaches SIMD before infancy is over. In neonatal disease, most children are about a year old at presentation. Over recent years, the trend is shifting to older age. Failure to thrive, fever, lymphadenopathy and respiratory and neurological manifestations are the most common presentations. In patients younger than 15 months, demonstration of virus (its component) is needed to establish the diagnosis.

Some differences between paediatric and adult lesions are prominent. All lesions described in adults occur in paediatric disease, but with different frequency. Following lesions, rare in adults, are more frequent and prominent in the paediatric group: thymic lesions, systemic lymphoreticular disorder (SLD), pulmonary lymphoid hyperplasia (PLH) and arteriopathy (APT).

Moreover, secondary infections in children are more often by pathogenic than by opportunistic microbes.

Thymic lesions: They include precocious involution, dysinvolution and thymitis. They occur in different combinations. SLD is similar to PGLA in adults, but it affects not only lymph nodes but also lymphoid depots in parenchymal organs. There is polyclonal hyperplasia of both B- and T-cell domains. There is hypergammaglobulinaemia. Cytomorphologically, lesions are on the borderline of malignancy. Many cases have accompanying B-cell lymphomas in other organs. The name PLH is self explanatory. Hyperplasia can be focal (nodular) or diffuse and extensive. This 'associated' lesion is probably EBV induced. Frequently, it is accompanied by desquamative interstitial giant cell pneumonitis. APT lesions (luminal narrowing due to disruption and calcification of elastic lamina and fibrosis of intima and media) are seen in small and medium sized arteries in multiple organs. Pathogenesis and significance of APT remain undetermined.

Stringent blood bank enforcements have reduced the incidence of parenteral transmission.

WHAT WE DO NOT KNOW

T-lymphocytes are very versatile. Their 'homeostatic control', in health/disease, is very efficient. Despite enormous daily turnover, their 'number' and 'proportion of subsets' in blood/tissues are constant. In other infections there are outbursts of increase in number, but homeostatic control brings the counts back to normal, once the antigen is cleared from the body. Their progressive depletion is the unique theme in HIV infection. Mechanisms of loss of lymphocytes in HIV disease are well understood. What is not equally well understood (and accepted) is: the reason why the destroyed cells are not replenished at the same rate, despite the remarkable capacity of CD4+ cells to self-replicate. Mechanism of progressive T-cell depletion is under shroud.

Further, in HIV infection, depletion of the CD4 pool is accompanied by activation of all the cellular elements of the immune system. In other infections, activation of immunocytes leads to heightening of their performance, which is favourable to the host. Paradoxically, in HIV infection, activation leads to reduced function of CD4+, CD8+, CTL and natural killer cells, increased AAD of even non-infected immunocompetent cells and elevated production of pro-inflammatory cytokines. Weak CTL response allows ongoing viral replication. Ongoing viral replication escalates the level of activation of immunocompetent cells.

It is conceptually acceptable that the level of immune activation (if it could be measured in numerical figures) would be a more accurate predictor of disease progress than the CD4 count. We do not know the cause and mechanism of HIV-induced widespread, progressive immune activation.

The two enigmas are better appreciated by an appraisal of the striking features of natural disease in monkeys. 'Sooty mangabeys' monkeys (SMM) are natural hosts to SIV. The magnitude and mechanisms of death of SMM CD4+ cells by SIV are identical to those of human CD4+ cells by HIV. And yet, there are fundamental differences between monkey disease and human disease. In infected SMM, CD4+ counts remain normal and there is no immune activation. SIV infected SMM do not get immunodepleted. Obviously, up its sleeve, HIV has secrets, we do not know.

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16.4 Antiretroviral Therapy

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INTRODUCTION

The advent of antiretroviral drugs in the early 1990s began a revolution in the management of HIV infection. Results from various trials involving different drug combinations showing their efficacy opened the opportunities to reduce the morbidity and mortality due to HIV/AIDS. The combination of at least three antiretroviral drugs from different groups is the current standard of care and is commonly referred to as highly active antiretroviral therapy (HAART) or simply as combination antiretroviral therapy (cART). There is enough epidemiological and clinical evidence that effective combinations of antiretroviral drugs inhibit the replication of HIV and reduce viraemia to undetectable levels. Treatment slows down the disease progression, improves the quality of life and increases the longevity. Success achieved by antiretroviral therapy (ART) has now transformed the common perception about HIV infection from being a 'virtual death sentence' to a 'chronic manageable illness'.

GOALS OF ANTIRETROVIRAL THERAPY

The primary goals of ART are maximal and durable reduction in plasma viral levels and restoration of immunological functions. The reduction in viral load also leads to reduced transmissibility. However, as yet there is no therapy to eradicate HIV from the body.

Antiretroviral (ARV) drugs can also be used to reduce the risk of vertical transmission. The ARVs can be used after exposure to HIV too, as in cases of accidental needle stick injury, and in cases of sexual assault and rape. It is called post-exposure prophylaxis (PEP).

Till date 26 antiretroviral agents have been approved by US-FDA, of which 19 are currently available in India. Considering the lifelong management, one has to sequence the drug therapy in view of easy and repeated viral mutability. Therefore, the management of HIV is becoming increasingly complex in view of long-term toxicity, drug-to-drug interaction and drug resistance. In addition, monitoring facilities such as CD4 counts, viral load estimation and drug resistance assay have become necessary for follow-up.

PRINCIPLES OF ANTIRETROVIRAL THERAPY

A continuous high level of replication of HIV takes place in the body right from the early stages of infection. At least one billion viral particles are produced and destroyed each day. The antiretroviral drugs act on various stages of replication of HIV in the body and interrupt the process of viral replication. Theoretically, these drugs can act at the following steps in viral replication. Most commonly used drugs target the virus mainly by inhibiting the enzymes reverse transcriptase (RT) inhibitors and protease inhibitors (PIs). **Table 1** lists the classes of various ARV drugs. **Figures 1A and B** depict the therapy targets.

Table 1: Classes of ARV Drugs

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)	Fusion inhibitors (FIs)
Nevirapine (NVP)	Saquinavir (SQV)	Enfuvirtide (ENF)
Delavirdine (DLV)	Indinavir (IDV)	
	Amprenavir (APV)	
	Nelfinavir (NFV)	
Efavirenz (EFV)	Fosamprenavir (FPV)	*CCR5 co-receptor antagonists*
Etravirine	Lopinavir (LPV)	Maraviroc (MVC)
	Ritonavir (RTV)	
	Atazanavir (ATV)	*HIV integrase strand transfer inhibitors*
	Tipranavir (TPV)	
	Darunavir (DRV)	Raltegravir (RAR)

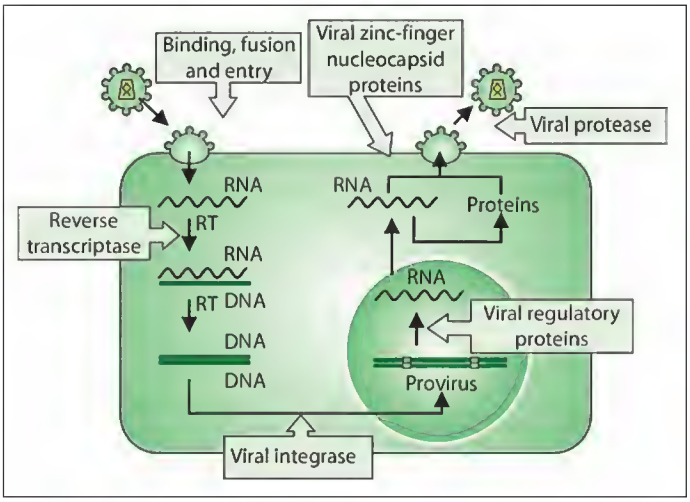


Figure 1A: Therapy targets.

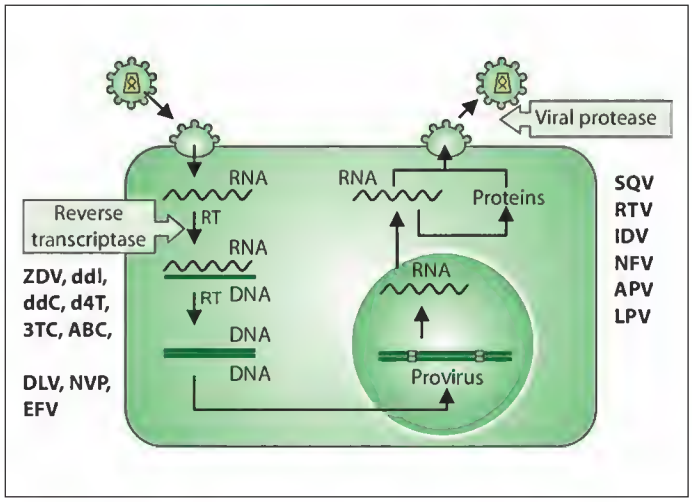


Figure 1B: Antiretroviral drugs.

Based on the scientific evidence, therapy guidelines have been developed by various international agencies such as WHO, DHHS, BHIVA, IAS (**Tables 2 to 4**). They define the optimum time, parameters and drugs to initiate and sequence treatment. Since, the drug therapy is lifelong, the selection of patients for therapy is based on clinical, immunological and viral parameters. Patients' preparedness for such a prolonged therapy and monitoring ensures their adherence. Oppurtunistic infections (OIs), if any, should be treated first. Patients should undergo therapy counselling. Along with detailed clinical evaluation, co-morbid conditions such as hepatitis B virus (HBV), hepatitis C virus (HCV) need to be evaluated for proper selection of ARVs considering the efficacy and drug interactions.

Table 2: Indications to Start Antiretroviral Therapy

WHO guidelines

Clinical	CD4 count available
Stage I or II	ART if CD4 <350/mm^3
Stage III and IV	ART regardless of CD4

Source: http://AIDSinfo.nih.gov, HIV Med 2008; 9: 563.
Guidelines by National AIDS Control Organisation and Department of Health and Human Services have been formulated with minor variations from WHO guidelines.

Table 3: Antiretroviral Therapy

WHO guidelines (Dec 2009)
Any one regimen to be initiated

Regimen
AZT+ 3TC +EFV
AZT+ 3TC +NVP
TDF+ 3TC +EFV
TDF +3TC + NVP
AZT to be avoided in patients with anaemia (Hb <8gm/dl)

DHHS guidelines (Dec 2009)

Preferred regimens	Alternative regimens	Acceptable regimens
EFV + TDF/FTC	EFV + (ABC/ZDV)/3TC	EFV + ddI + (3TC/FTC)
ATV/r + TDF/FTC	NVP + ZDV/3TC	ATV + (ABC/ZDV)/3TC
DRV/r + TDF/FTC	ATV/r + (ABC/ZDV)/3TC	
RAL + TDF/FTC	LPV/r + (ABC/ZDV)/3TC or TDF/FTC	
LPV/r + ZDV/3TC	SQV/r + TDF/FTC	

Source: Guidelines by National AIDS Control Organisation and Department of Health and Human Services have been formulated with minor variations from WHO guidelines.

Table 4: Treatment in Specific Situations

HIV and Tuberculosis (start Efavirenz-based regimen)

Pulmonary and extrapulmonary TB and HIV: Start ART for all patients irrespective of CD4 count (start TB treatment first and when it is tolerated start ART and within the first 8 weeks)

HIV and Pregnancy (Efavirenz not to be prescribed in first trimester)

a. WHO stages I and II: start ART at CD4 <350 cells/mm^3
b. WHO stages III and IV: start ART irrespective of CD4 count

MONITORING OF THERAPY

Frequent and regular follow-up especially during the initial months of the treatment is very important in order to ensure timely diagnosis and management of adverse events, to work with the patient on adherence issues and to diagnose any clinical manifestations like OIs and immune reconstitution inflammatory syndrome (IRIS). Generally, morbidity and mortality on ART occurs in the first 3 to 6 months of initiation of therapy. Once the patient is stable on ART, a quarterly review is recommended.

Regular CD4 count (and plasma viral load if possible) is desirable every 6 months. Clinical assessment and adherence monitoring should be done initially at 2 weeks and then regularly on a monthly basis.

ANTIRETROVIRAL DRUG TOXICITY

Antiretroviral drugs have a broad range of toxicities, ranging from low-grade intolerance which may be self-limiting to life-threatening side-effects (**Table 5**). Differentiating between complications of HIV disease and ART toxicity is very important. Considerations should also include intercurrent illness (e.g. hepatitis A, malaria, etc.) or reactions to medications other than ARVs, e.g. isoniazid-induced hepatitis or rash induced by cotrimoxazole. However, most of the toxicity/effects can be adequately co-managed with good clinical monitoring at all the levels of the health care system. As a general principle, mild toxicity does not require discontinuation of ART or substitution. Symptomatic treatment may be given. Moderate or severe toxicities may require substitution with a drug of the same ARV class but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilised and the toxicity is resolved.

Treatment Failure: When to Change and What to Change

It is now well known, that even with good adherence levels, resistance occurs to ARV drugs over a period of time due to viral mutation and this requires change of ARV drugs. The virological failure appears first followed by immunological failure which finally leads to clinical failure. It is desirable to switch the entire regimen from first to second line as soon as virological failure is detected. Table 6 shows the guidelines for resource limited settings.

SPECIAL SITUATIONS

HIV Infection and Pregnancy

In case of pregnant women, an additional goal of ART is to prevent transmission of HIV infection from the mother to the child. It is recommended that all those pregnant women who have CD4 counts less than 350 cells/mm^3 should be initiated on ART. Some important considerations before initiating ARV therapy are:

- Zidovudine should be included in the regimen unless there is severe toxicity or anaemia.
- Efavirenz-based regimen should be avoided in the first trimester, because of teratogenic effects.
- It is recommended to closely monitor liver function tests if NVP containing ART is initiated in women with CD4 count >250.

The recent guidelines for usage of antiretroviral drugs for prevention of mother-to-child transmission (PMTCT) are available on WHO website http://www.who.int/hiv/pub/mtct/advice/en/index.html

Table 5: Toxicity of Commonly Used Antiretroviral Drugs

Occurrence	Zidovudine	Stavudine	Nevirapine	Efavirenz	Protease inhibitors
Short-term	Nausea, vomiting, diarrhoea	Nausea, vomiting	Hypersensitivity rash, Hepatotoxicity	Rash, hepatotoxicity, drowsiness, dizziness, confusion, vivid dreams	Abdominal pain, Abnormal stools or bowel movements, diarrhoea, nausea
Medium-term	Bone marrow suppression, anaemia, hyperpigmentation, Lactic acidosis	Lactic acidosis, Peripheral neuritis, Pancreatitis		Dyslipidaemia	Weakness/tiredness, Headache, Hyperglycaemia, Hypertriglyceridaemia, Hyperuricaemia
Long-term	Lipodystrophy	Lipodystrophy, Dyslipidaemia			Lipodystrophy

Table 6: Defining Antiretroviral Failure

Clinical failure	New or recurrent WHO Stage-IV condition, after at least 6 months of ART
Immunological failure	Fall of CD4 count to pre-therapy baseline (or below); or 50% fall from the on-treatment peak value (if known); or Persistent CD4 levels below 100 cells/mm^3
Virological failure	Plasma viral load >5,000 copies/ml

HIV/Tuberculosis Co-Infection

Initiation of treatment for active TB should always be on priority followed by initiation of ARV therapy as per the guidelines and should be started as soon as the patient is stabilised on ATT. In HIV-infected patients with TB who are not currently on ART, and who are provided rifampicin-based anti-TB treatment, initiate ART directly with EFV. No lead in dose is required for EFV. Nevirapine or PIs should not be administered along with rifampicin because of the enzyme inducing effect of rifampicin which renders NVP levels subtherapeutical. EFV blood levels are also decreased in presence of rifampicin, but remain at therapeutic levels. It is recommended to use the standard dose of EFV (usually 600 mg/day) in patients receiving EFV and rifampicin or use rifabutin if patient is on LPV/r based ART. Details on initiation guidelines have already been discussed.

HIV and Hepatitis B, C Co-Infection

Liver-related morbidity and mortality is very common in patients on ART. The common cause for liver related deaths is co-infection with hepatitis viruses. It is recommended that all HIV-infected patients should be screened for HBsAg, anti-HBcAb (if possible), HCV-RNA and HCV genotype at the baseline. It should be ensured that additional baseline investigations like LFTs, PT, serum proteins, HbeAg and HBV-DNA are also done.

1. HIV+HBV:
   - If treatment is not indicated for either infection, monitor the patient.
   - If treatment is indicated for HIV, then initiate with TDF+3TC/FTC-based regimen along with EFV.
   - If treatment is indicated only for HBV, pegylated interferon is recommended.
2. HCV treatment:

   HCV infection increases the risk of developing hepatic-toxicity with antiretroviral treatment. With regards to treatment, chronic HCV should be treated first if the patient does not qualify for anti-HIV treatment. Patients who qualify for anti-HIV treatment should be first initiated on ART and when the CD4 rises to more than 350 cells/mm^3, anti-HCV treatment may be considered. The treatment of choice for HCV is pegylated interferon and ribavirin. If the patient is also on anti-HCV treatment, care should be taken not to administer a regimen that has AZT or Didanosine (ddI) as they are contraindicated with ribavirin.

RECOMMENDED READINGS

1. Bartlett JG, Gallant JE. *Medical Management of HIV infection.* John Hopkins University School of Medicine, Maryland, USA. 2009. http://www.hopkins-aids.edu
2. National Guidelines on Second line ART for Adults and Adolescents (Draft). (October 2008). National AIDS Control Organisation, Ministry of health and Family Welfare, Government of India. Available at: www.nacoonline.org
3. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Available at: http://www.who.int/hiv/pub/mtct/advice/en/index.html
4. UNAIDS report on the Global AIDS Epidemic. December 2009.

16.5 Drug Resistance

Alaka Deshpande

INTRODUCTION

Self survival and replication for propagation are the two main goals of every living organism. To achieve them, all organisms follow Darwinian model of continuous selection of the 'fittest'. Under adverse circumstances, including drug pressures which pose a threat to their survival, the microbes mutate and select those mutants which can survive in the presence of drugs.

HIV drug resistance can be broadly defined as any change that improves viral replication and survival in the presence of the inhibitors. It can appropriately be termed as 'altered drug susceptibility'. It is an altered phenotype resulting from a change in viral genotype.

HIV lacks the proofreading mechanism; therefore while replicating, the reverse transcription of viral RNA into DNA is error prone introducing on an average one mutation for each transcription. Some commonly used terms are defined here:

Gene

It is a unit of genetic information. Genes are encoded in the DNA.

DNA

It is a polymeric nucleic acid macromolecule composed of:

(a) Deoxyribose sugar

(b) Nitrogen containing two purine bases, namely adenine and guanine and two pyrimidine bases, namely thymine and cytosine

(c) A phosphate group

Nucleotides

They are composed of a base, phosphate and a sugar moiety which polymerise into long polynucleotide chains.

Codon

It is a code that relates specific amino acids to a combination of three adjacent bases along with mRNA.

Polymorphism

Variations in nucleotide sequence may produce different amino acid changes in the primary protein structure without producing a functional change.

Mutation

It is a change in nucleotide sequence resulting in functional change.

Primary/major resistance mutations

These are directly responsible for conferring drug resistance. They inhibit the drug action. In case of the Protease inhibitors (PIs), the terms are interchanged.

Secondary/minor mutations

These mutations include:

(a) Compensatory mutation, which aid in restoring the rate of viral replication despite presence of resistant mutation.

(b) Mutations that contribute to resistance in presence of primary mutations.

DETECTION OF RESISTANCE

Genotypic Assay

The various genes such as RT gene, Prot gene are sequenced. The observed mutations are compared with algorithms of large data base of Stanford, aNRS and IAS.

Phenotypic Assay

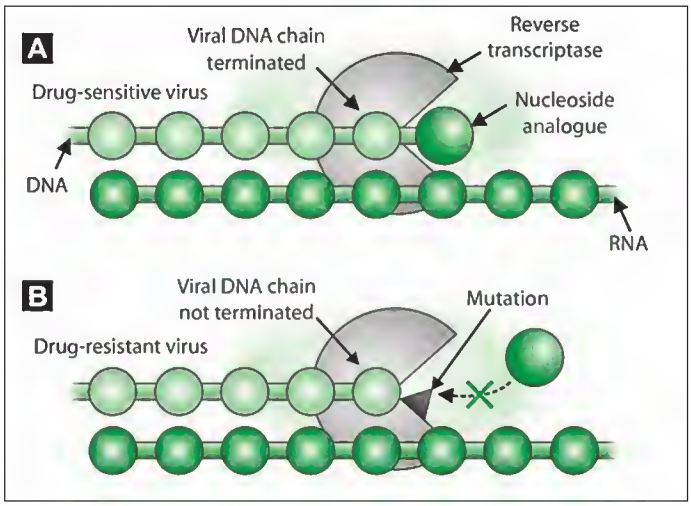
Phenotypic resistance of HIV is an *in vitro* test. HIV-1 isolates are cultured in the presence of serial dilutions of inhibitor drugs. The concentrations which are required to inhibit virus replication by 50%, i.e. Ic 50 or 90%, i.e. Ic 90, are the most commonly used methods. The process is expensive, cumbersome and time consuming.

MECHANISMS OF DRUG RESISTANCE

Two distinct mechanisms are involved in HIV resistance to NRTI drugs:

(a) Impairment of the Incorporation of the Analogue into DNA

Figures 1A and B shows the development of resistance by the incorporation of a nucleoside analogue into drug-sensitive viruses results in the termination of the viral DNA chain. Mutations in drug-resistant viruses prevent the incorporation of the nucleoside analogue into the growing viral DNA chain.



Figures 1A and B: Resistance by interference with the incorporation of nucleoside analogue.

(b) Pyrophosphorolysis

It is a removal of the analogue from the prematurely terminated DNA chain. **Figure 2** shows the mechanism of ATP-mediated excision of the nucleoside analogue.

ATP in drug-sensitive viruses does not have access to a reverse transcriptase that has formed a complex with a nucleoside analogue. Mutations that cause resistance to nucleoside analogues, referred to as thymidine analogue mutations (TAMs) allow ATP to bind reverse transcriptase near the 3' end of viral DNA terminated by the incorporation of a nucleoside analogue. ATP then excises the analogue from viral DNA, allowing reverse transcription to proceed normally.

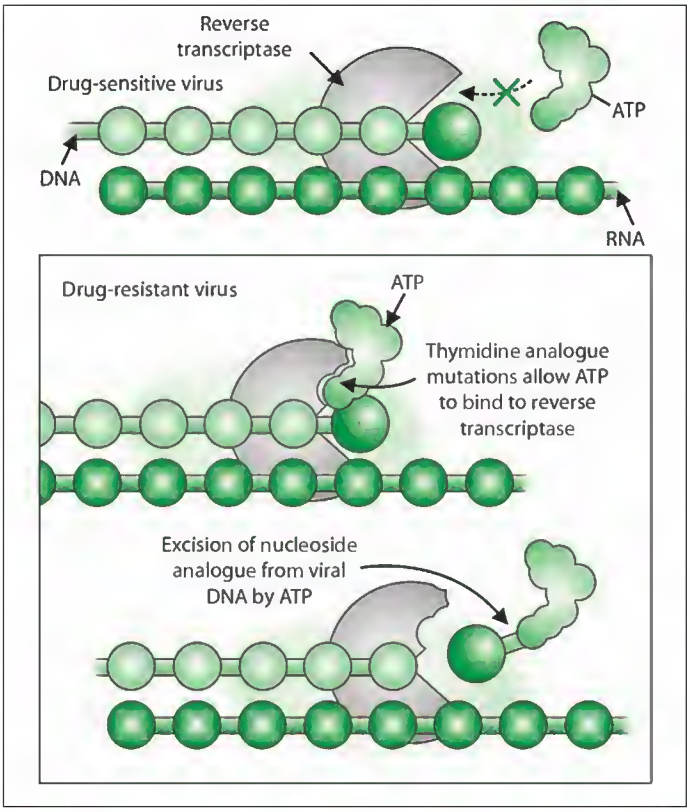


Figure 2: Resistance by ATP-mediated excision of the nucleoside analogue.

Thymidine Analogue Mutations

Mutations at positions 41, 67, 70, 210, 215 and 219 are referred to as TAMs because they are most often selected by ZDV and Stav containing regimens. These mutations occur gradually and their order of emergence can vary. TAMs promote ATP or pyrophosphate mediated removal of nucleoside analogue from 3' end of terminated DNA strand.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Figure 3 shows non-nucleoside reverse transcriptase inhibitors (NNRTIs) have a strong affinity for a pocket next to the active site of reverse transcriptase. In drug-sensitive viruses, NNRTIs bind this pocket and block the polymerisation of DNA by reverse transcriptase. In drug-resistant viruses, mutations prevent the binding of NNRTIs, allowing DNA polymerisation to proceed normally.

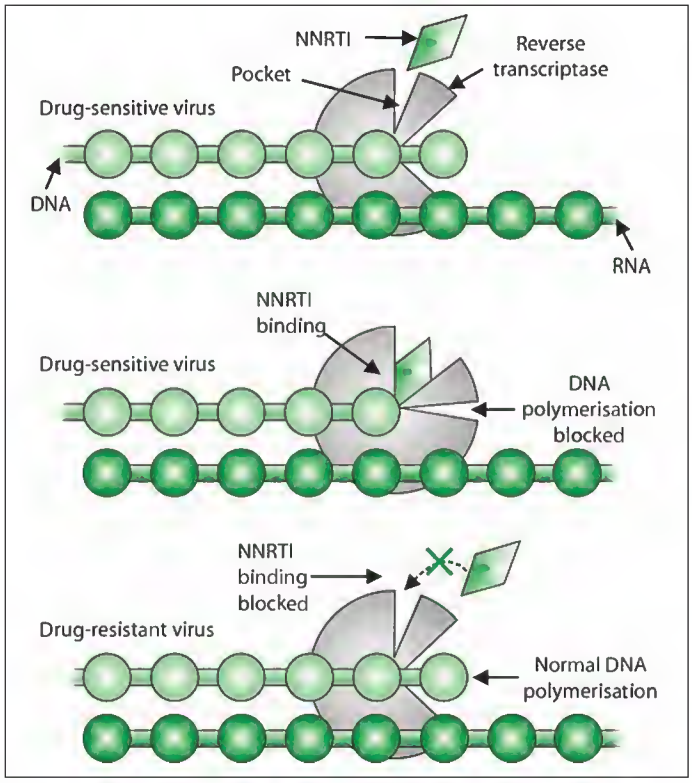


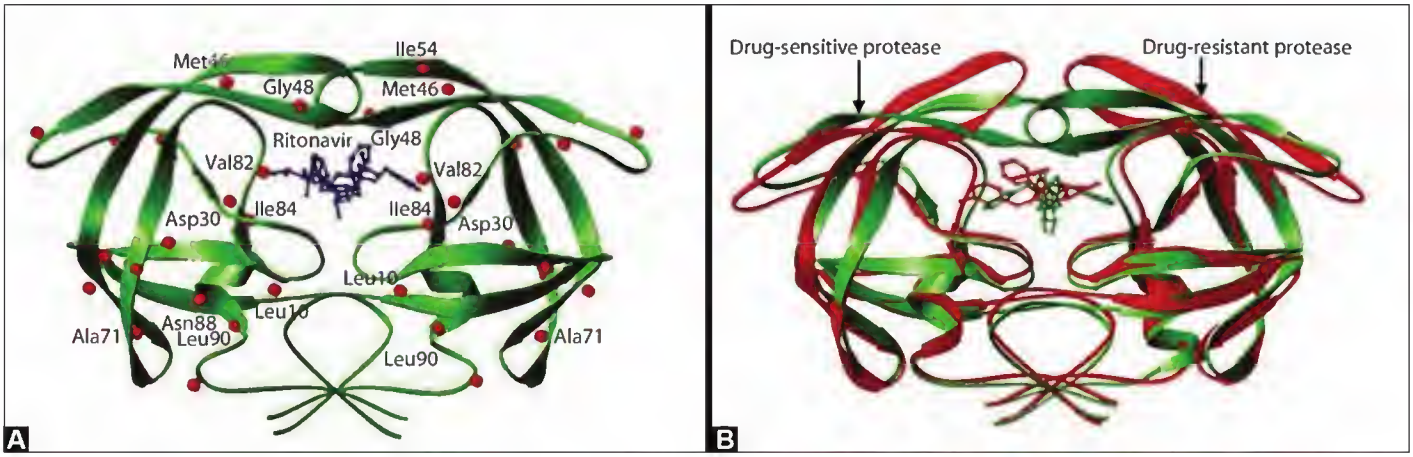
Figure 3: Mechanism of action of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Protease Inhibitors (PIs)

The three-dimensional structure of wild type HIV-1 is shown below (**Figures 4A and B**). The PIs bind to certain sites and block the protease activity.

Fusion Inhibitors

The fusion inhibitors destabilise the process of binding to hydrophobic region HR1, thus blocking the infectivity of HIV-1.



Figures 4A and B: Mechanism of action of protease inhibitors.

Viral resistance to fusion inhibitors results from mutations located in a stretch of 10 amino acids in HR1.

Convention for Describing Drug Resistant Mutation

Based on the amino acid sequences of RT and Protease, a standard numbering system has been developed in reference to wild type virus (mainly subtype B). For example, a change in genotype from ATG to GTG at codon 184 would be reported as a change from methionine to valine at residue 184 or as M184V. The resistant mutations to different drugs are shown in **Tables 1 and 2**.

Table 1: Resistant Mutants to Various Drugs

ARV	**NsRTI/NtRTI**	ARV	**NNRTI**
AZT	41L, 67N, 70R, 210W, 215Y/F, 219Q/E	NPV	100I, 103N, 106A/M, 108I,
		NVP	181C/I, 188C/L/H, 190A
d4T	41L, 67N, 70R, 210W, 215Y/F, 219Q/E	EFV	100I, 103N, 106M, 108I, 181I/C, 188L, 190S/A, 225H
3TC	65R, 184V/I		
FTC	65R, 184V/I		
ddI	65R, 74V		
ABC	65R, 74V, 115F, 184V		
TDF	65R, 70E		

The various factors which are responsible for drug resistant mutations are:

- Gastrointestinal intolerance
- Episodic compliance failure
- Poor adherence
- Drug toxicity
- High pill burden
- Drug interactions
- Irrational combinations
- Inadequate duration of therapy
- Infection with resistant strain

CONCLUSION

The effective pathway of therapy involves the following rational combination of therapy, adequate duration of treatment and adherence counselling. The therapy may be started only after the patients' preparedness for long-term antiretroviral therapy. The monitoring of therapy with the help of viral load is desirable. The viral load is suppressed to be less than 400 copies/mL in 16 to 24 weeks after successful therapy. The time when the viral load again starts rising after the initial viral suppression, indicates virological failure. This is the time viral resistance may be suspected.

Ideally, the genotypic assays should be performed before initiation of ARV therapy. Based on the viral drug susceptibility, the ARV may be selected.

Table 2: Resistant Mutants to Protease Inhibitors and Fusion Inhibitors

Drug	Major	Minor mutation
Protease inhibitors		
IDV and IDV/r	46I/L, 82A/F/T, 84V	10I/F/I/R/V, 20M/R, 24I, 32I, 36I, 54V, 71V/T, 73S/A, 76V, 77I, 90M
NFV	30N, 90M	10F/I, 36I, 46I/L, 71V/T, 77I, 82A/F/T/S, 84V, 88D/S
SQV and SQV/r	48V, 90M	10I/R/V, 24I, 54L/V, 62V, 71V/T, 73S, 77I, 82A/F/T/S, 84V
FPV and FPV/r	50V, 84V	10F/I/R/V, 32I, 46I/L, 47V, 54L/V/M, 73S, 76V, 82A/F/T/S, 90M
LPV/r	32I, 47V/A, 84A/F/T/S	10F/I/R/V, 20M/R/V, 24I, 33F, 46I/L, 50V, 53L, 54V/L/A/M/T/S, 63P, 71V/T, 73S, 76V, 84V, 90M
TPV/r	33F, 82L/T, 84V	10V, 13V, 20M/R/V, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 83D
DRV/r	50V, 54M/L, 76V, 84V	11I, 32I, 33F, 47V, 50V, 54L/M, 74P, 76V, 84V, 89V
ATV and ATV/r	50L, 84V, 88S	10I/F/V/C, 16E, 20R/M/I/T/V, 24I, 32I, 33I/F/V, 36I/L/V, 46I/L, 48V, 53L/Y, 54L/V/M/ T/A, 60E, 62V, 64I/M/V, 71V/I/T/L, 73C/S/T/A, 82A/T/F/I, 85V, 90M, 93L/M
Fusion inhibitors: gp41 mutations		
ENF		36D/S, 37V, 38A/M/E, 39R, 40H, 42T, 43D

Source: www.iasusa.org/http://hivdb.stanford.edu.

16.6 Non-Opportunistic Infections

Anil Kumar Tripathi, Shailendra P Verma

The presentation of HIV disease is mainly due to opportunistic infections (OIs) which become evident with advancing immunodeficiency. The present description will include variety of manifestations in HIV/AIDS patients which are not due to OI or malignancy.

ACUTE HIV SYNDROME

This acute clinical syndrome develops in about 50% to 90% persons after 3 to 6 weeks of primary infection with HIV. This phase corresponds with seroconversion phase of HIV infection. Acute burst of HIV viraemia leads to destruction and dysfunction of CD4+ T-cells. There is rise in CD8+ T-cells leading to reversal of CD4+/CD8+ ratio. Symptoms and their incidence in acute HIV syndrome are given in **Table 1**.

Table 1: Clinical Manifestations of Acute HIV Syndrome

Symptoms	Incidence (%)
Fever	96
Lymphadenopathy	74
Pharyngitis	70
Rash	70
Myalgias or arthralgias	54
Diarrhoea	32
Headache	32
Nausea/Vomiting	27
Hepatosplenomegaly	14
Weight loss	13
Thrush	12
Neurological manifestations	12

Maculopapular rashes which are painless, non-pruritic and erythematous are the usual lesions found on trunk, face and occasionally in extremities. Vesiculopapular rashes, oro-pharyngeal ulcers and penile ulcers can also occur in acute HIV syndrome. Neurological manifestations can be aseptic meningitis, encephalitis, myelopathy, Guillain-Barrè syndrome or peripheral neuropathy. Most symptoms of acute infection resolve after 2 to 4 weeks spontaneously with the development of antibodies to HIV virus.

Persons should be tested for HIV p24 antigen and HIV RNA levels by PCR which can detect infection in around 10 days and 7 days, respectively. Those who are negative should again be tested for HIV by ELISA after 3 months and 6 months of clinical presentation. No definitive recommendation about the use of ART are available. However, treatment in acute viraemia is recommended to curb the dissemination of the virus to various organs.

CARDIOVASCULAR MANIFESTATIONS

Prevalence of cardiac involvement in HIV disease varies from 5% to 50% but symptomatic involvement occurs in 5% to 7% of patients only. Most common clinically significant cardiac abnormality due to direct HIV infection is HIV-associated dilated cardiomyopathy. There is evidence of myocarditis and HIV has been isolated from myocardial cells. Diagnosis can be supported by chest radiograph and electrocardiogram and confirmed by echocardiography and elevated serum NTproBNP. CD4+ count in these patients is generally >200/cumm. HIV associated cardiomyopathy has poor prognosis.

Other findings on echocardiography may be diastolic dysfunction, pericardial effusion, right ventricular hypertrophy, pulmonary arterial hypertension and non-bacterial thrombotic endocarditis.

GASTROINTESTINAL MANIFESTATIONS

Manifestations of gastrointestinal tract can be due to HIV itself or drugs used in the treatment. Aphthous ulcers are generally found in posterior oropharynx and oesophagus. Ulcers produce dysphagia and severe odynophagia due to ulcerative oesophagitis. These lesions can be present in cases of severe immunodeficiency or during seroconversion. Several studies have demonstrated HIV infected inflammatory cells in the base of these lesions suggesting aetiological role of HIV. Endoscopically one or multiple ulcers of variable depth with normal intervening mucosa may be present, as seen in CMV infection. Short-term steroids or thalidomides are effective. Relapse rate of these ulcers is high. Other gastric problems are generally rare.

AIDS Enteropathy

Direct involvement of intestine by HIV can cause AIDS enteropathy or HIV enteropathy. Features include villous blunting, low mitotic figures and decrease in villous-crypt ratio. Patients usually present with chronic diarrhoea and weight loss. Stool studies, sigmoidoscopy and/or upper gastrointestinal endoscopy should be done to rule out other aetiologies. Tests of malabsorption are deranged. Treatment includes non-specific management like dietary fibre supplementation, antimotility agents, octreotide and oral rehydration solution.

HEPATOBILIARY MANIFESTATIONS

Direct involvement of liver parenchyma by HIV is not documented, and most common cause of hepatic involvement is co-infection with hepatitis B, C and antiretroviral therapy.

In India hepatitis B coinfection is present in 2% to 9 % cases and hepatitis C in 2% to 3%. Intravenous drug users may have HCV co-infection in up to 50% to 90%.

Drugs like nevirapine, protease inhibitors (atazanavir) can cause severe acute hepatitis or hepatic failure and their use should be properly monitored. Lactic acidosis syndrome occurs due to impaired mitochondrial DNA synthesis by NRTI'S such as AZT, ddI, and stavudine. It has high mortality and the only curative treatment is liver transplantation.

AIDS cholangiopathy is a syndrome resembling sclerosing cholangitis with papillary stenosis. Diagnosis is made by ERCP and papillotomy can relieve obstruction.

NEUROLOGICAL MANIFESTATIONS

Neurological diseases due to direct HIV infection occur throughout the course of infection and may be due to basic pathology like inflammation, demyelination or degeneration.

AIDS-Dementia Complex (HIV Encephalopathy)

It is an AIDS defining illness and usually occurs at CD4+ counts >200/cumm. If untreated, 15% to 20% of HIV patients will develop this entity. AIDS-dementia complex (ADC) or HIV encephalopathy (HIVE) is the term used to describe the advanced neurological involvement. HIV infects macrophages and glial cells in central nervous system. Release of various cytokines/neurotoxins such as interleukin (IL)-1β, tumour necrosis factor-α, IL-6 and TGF-β may be responsible for involvement of neuronal cells.

HIV encephalopathy is a slowly progressive subcortical dementia. Typical complaints are forgetfulness, poor concentration, slowing of reasoning, lack of energy drive, mild depression and emotional blunting. Patients look apathetic and slow and become socially withdrawn. Sexual dysfunction is common. Signs of HIV encephalopathy include impaired gait, slowing of rapidly alternating movements, tremor, brisk deep tendon reflexes, positive Babinski sign, slowed gaze saccades, sphincter impairment including incontinence and frontal release signs. Neuropsychological findings such as slowing of psychomotor speed, impaired short-term memory and mental flexibility, problem with recalling events in correct order, disorientation to time, place and person and finally mutism can occur.

MRI is preferred imaging modality. It reveals patchy or diffuse, hyperintense and relatively symmetrical lesions of white matter suggestive of leucoencephalopathy. Cerebrospinal fluid examination should be done to exclude alternative diagnosis. A systematic mental status examination is an important part of the examination. Quantitative neuropsychological tests can be done to see progressive decline in neurological functions. Metabolic disorders, depression and anxiety should be ruled out.

Antiretroviral therapy should be optimised. Highly CNS penetrant drugs should best be used from the list of lamivudine, zidovudine, nevirapine and indinavir. Outlook for prolonged independent life is guarded.

HIV Myelopathy

Myelopathy is present in 20% patients with AIDS. Vacuolar myelopathy is pathologically similar to subacute combined degeneration of cord. The histological hallmark are vacuoles and lipid laden macrophages most prominent is cervical and thoracic spinal cord. It is characterised by insidious onset of leg weakness and gait abnormalities. Vague leg discomfort and paraesthesias are main sensory symptoms. Bladder and bowel dysfunction is also common. Posterior columns of cord can also be separately involved producing pure sensory myelopathy and pure sensory ataxia. MRI of spinal cord is usually normal. Treatment of myelopathy with ART is not much rewarding.

Peripheral Neuropathy

It can present like acute inflammatory demyelinating polyneuropathy resembling GB syndrome. Chronic inflammatory demyelinating polyneuropathy (CIDP) with relapsing and remitting course has also been documented. Distal sensory neuropathy is most common type of neuropathy which can be due to HIV itself or nucleoside analogue drugs. Mononeuritis multiplex can also be present. Pregabalin, carbamazepine, gabapentin, tricyclic antidepressant and analgesics can provide symptomatic improvement.

HAEMATOLOGICAL MANIFESTATIONS

Anaemia is the most common haematological finding. Normocyctic normochronic anaemia is found in HIV-associated bone marrow suppression. Reticulocyte count is inappropriately low. Drugs like zidovudine is the other main culprit. It can block erythroid maturation earlier than other components of bone marrow. Mean corpuscular volume of RBC is increased. HIV-induced anaemia may respond well to ART therapy. Erythropoietin is also effective if its levels are less than that expected for severity of anaemia. Zidovudine should be replaced.

Neutropaenia is mostly mild but sometimes it can be severe. The cause of neutropaenia can be a direct effect or therapy-induced. Presence of neutropaenia generally indicates advanced disease. G-CSF or GM-CSF can be of use in increasing counts of neutrophils regardless of the cause. Myelosuppressive drugs should be removed.

Thrombocytopaenia can be due to decreased platelet survival probably by immunological mechanism and decreased platelet production due to infection of megakaryocytes with HIV. Treatment should be initiated in patients having platelet count <20000/cumm. IVIG and Anti Rh(D) are equally effective but sustained responses are few. Prednisolone 0.5-1.0 mg/kg is used cautiously. Splenectomy may be needed in relapsed/refractory cases.

Persistent generalised lymphadenopathy is an early clinical presentation of body response to HIV infection. The condition is defined as lymph node enlargement of 2 or more extrainguinal sites of size >1 cm for at least more than 3 months without obvious cause. Histologically follicular hyperplasia of lymph nodes is present.

RENAL MANIFESTATIONS

HIV-associated nephropathy (HIV-AN) is a true direct complication of HIV infection occurring in 2% to 10% of HIV infected individuals. Clinical presentations of HIV-AN consist of heavy proteinuria (90% have nephritic range), rapid deterioration of renal function, normal size of kidneys, no or minimal increase in blood pressure. End stage renal disease commonly occurs in 6 to 12 months. Kidney biopsy is diagnostic. Histology is similar to that of idiopathic focal segmental glomerulosclerosis (80%) and mesangial proliferation in 10% to 15% cases. HIV-AN also exhibits sclerosis of the whole glomerular tuft which is distinctly known as collapsing glomerulopathy. Majority of patients have CD4+ T-cell counts <200/cumm. ACE inhibitors and prednisolone with tapering dose have been effective in preventing progression of the disease. IgA nephropathy can also occur in HIV patients.

Acute tubular necrosis can result from nephrotoxic drugs, hypovolaemia, shock and sepsis. Drugs like pentamidine, amphotericin, adefovir, tenofovir, NSAIDs and radiocontrast

agents can cause acute tubular necrosis. Patient should be closely monitored and dose adjustments or stoppage of drug should be considered once renal dysfunction develops.

RHEUMATOLOGICAL MANIFESTATIONS

Rheumatological manifestations include Reiter's syndrome, non-specific reactive arthritis and septic arthritis. Myopathy, vasculitis and diffuse infiltrative lymphocytosis syndrome can also occur. Myopathy occurs in 1% to 2% of all HIV patients and can appear at any stage of the disease. Myopathy can be drug-induced, inflammatory or non-inflammatory. Drug notorious for causing myopathy is zidovudine probably due to mitochondrial toxicity. Inflammatory myopathy indistinguishable from idiopathic polymyositis can also be seen. Zidovudine should be replaced first, if no improvement, immunosuppressive drugs should be started.

Vasculitis should be considered in the setting of unexplained multi-system disease, unexplained myopathy or arthritis, unexplained organ ischaemia and in presence of mononeuritis multiplex.

DILS is presumably of autoimmune origin. Dryness of mouth, eyes and massive enlargement of parotids are common. Histopathological study of salivary gland shows infiltrating lymphocytes which are CD8+ cells.

METABOLIC MANIFESTATIONS

Hyperglycaemia can occur due to various drugs used in HIV disease treatment. Protease inhibitors, pentamidine and didanosine are main culprits. Hypercholesterolaemia is usually seen with protease inhibitors and efavirenz. In HAART era, HDL Cholesterol levels are reduced, total and LDL cholesterol levels are increased with concomitant severe hypertriglyceridaemia. HMG COA reductase inhibitors (statins) with diet modification and exercises should be used to treat these conditions. Lipohypertrophy and lipoatrophy can occur with PI's in long-term use. Mitochondrial toxicity is the probable mechanism.

HIV-Associated Wasting

It is an AIDS defining illness. Centers for Disease Control and Prevention (CDC) definition of HIV-associated wasting is a weight loss of $\geq$10% associated with intermittent or constant fever and chronic diarrhoea or fatigue lasting >30 days in the absence of a defined cause other than HIV infection. Dietary assessment and weight monitoring should be done. Key to prevention and management of HIV wasting is aggressive management of infection.

ENDOCRINE DISORDERS

Hypogonadism is common in HIV patients. Patients present with decreased libido, impotence, gynaecomastia or amenorrhoea. Production of GnRH is decreased or its release is abnormal. Diagnosis is made by low or normal levels of FSH and LH in response to GnRH. MRI of brain should be done to see pituitary gland. Management includes hormone replacement therapy. Hypothyroidism, hyperthyroidism and adrenal dysfunction are rare. Less than 5% of patients with AIDS have adrenal insufficiency.

PULMONARY MANIFESTATIONS

Most of the pulmonary manifestations are due to opportunistic infections and should be ruled out before attributing it to HIV disease. Lymphocytic interstitial pneumonia, non-specific interstitial pneumonia and increased incidence of pulmonary hypertension is seen as the non-OI manifestations of HIV disease.

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16.7 Opportunistic Infections

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Opportunistic infection (OI) is a disease caused by microbial agent(s) in hosts with defects in humoral and cell mediated immunity. Immunocompromised secondary to human immunodeficiency virus (HIV) infection, use of immunomodulatory agents (including steroids and anticancer drugs) are emerging predisposing factors to OI.

Opportunistic infections (OIs) may serve as indicators of underlying HIV infection. Mortality among HIV-infected individuals is due to improper awareness and consequent poor clinical management of OIs. HIV load increases in the presence of ongoing OIs, thus accelerating progression to clinical acquired immunodeficiency syndrome (AIDS). Changes in the CD4 lymphocyte count occur with the institution of highly active antiretroviral therapy (HAART) which in turn results in changes in OI epidemiology, clinical presentation and treatment outcomes. As HAART results in reconstitution of the immune system – certain OIs respond to HAART alone. However, the ensuing immune mediated inflammatory response may present as a paradoxical worsening of disease. It is, therefore, essential to be able to recognise and treat OIs prior to the institution of antiretroviral agents. OIs play a role in the clinical staging of HIV infection. OIs may present as indolent chronic infections (pyrexia of unknown origin), reactivation of latent infections, or as acute medical emergencies. They may affect single or multiple organ systems.

The incidence of OIs range from 10.7 to 69.7 /100 patient years. Among 28 OIs—tuberculosis (65%), candidiasis (57.5%) and diarrhoeal diseases (40%) are the most common OIs found in Indian patients (**Table 1**) [National AIDS Control Organisation (NACO), 2007] while OIs due to infection with *Rhodococcus equi, Blastomyces, Coccidioides, Bartonella* and Human Herpes Virus 8 have not been described in India. Various OI are seen to increase and organism with poor penetration and infectivity seem to become pathogenic. **Table 2** lists various OI with falling CD4 count.

Table 2: Correlation of OIs with CD4 Lymphocyte Count

CD4 cell count (/mm^3)	Infectious conditions
>500	Candida vaginitis
200 to 500	Pneumococcal pneumonia Pulmonary tuberculosis Herpes zoster Oropharyngeal candidiasis Cryptosporidiosis Self-limited Kaposi's sarcoma Oral hairy leukoplakia
<200	*Pneumocystis jiroveci* pneumonia Disseminated histoplasmosis Miliary/extrapulmonary TB Progressive multifocal leucoencephalopathy
<100	Disseminated herpes simplex Toxoplasmosis Cryptococcosis Cryptosporidiosis Microsporidiosis Candida oesophagitis
<50	Disseminated cytomegalovirus (CMV) *Mycobacterium avium* complex

TUBERCULOSIS (TB)

Tables 3 and 4 show the salient features of Koch's and the difference in tuberculosis in HIV positive patient and a normal immunocompetent patient.

Table 1: Common Opportunistic Infections (OIs) seen in India

Bacterial	Viral	Fungal	Parasitic	Other illnesses
Tuberculosis	Herpes simplex virus infection	Candidiasis	Cryptosporidiosis	Non-Hodgkin's lymphoma
Bacterial respiratory infections	Oral leukoplakia	Cryptococcosis	Microsporidiosis	Invasive cervical cancer
Bacterial enteric infection	Varicella zoster	*Pneumocystis carinii jiroveci* pneumonia	Isosporiasis	
	Cytomegalovirus infection	Penicilliosis	Giardiasis	
	Human papilloma virus infections		Strongyloidiasis Toxoplasmosis	

Epidemiology

Table 3: Epidemiology of Tuberculosis in HIV-infected and Immunocompetent Individuals

	Immunocompetent individuals	HIV-infected individuals
Risk of reactivation of latent tuberculosis	10% (lifetime)	10% per annum 50% (lifetime)
Disease recurrence after treatment	2-3%	14%

Clinical Features

Table 4: Differences between TB Infection in HIV-infected and Immunocompetent Patient

	Immuno-competent	Immunocompromised
Sputum AFB	Multibacillary disease—sputum positive	Paucibacillary disease—usually sputum negative
Pulmonary radiography	Upper lobe cavitatory lesions	Bilateral interstitial infiltrates usually lower zone Predominant extrapulmonary involvement – pleural effusion and hilar adenopathy
Extrapulmonary disease	10 to 20% of TB infection	40 to 80% of TB burden

Treatment

Antituberculosis therapy (ATT) must be administered according to the directly observed treatment-shortcourse (DOTS) regimen.

Institution of HAART is recommended 10-14 days after institution of ATT in patients with CD4 counts less than 200 cells/mm^3. In patients with CD4 counts over 200 cells/mm^3 HAART may be commenced 2-8 weeks after the institution of ATT. As rifampicin is known to enhance the metabolism of protease inhibitors and nevirapine, efavirenz based antiretroviral therapy (ART) is recommended while patients are on rifampin.

OROGENITAL CANDIDIASIS

Clinical features and management are shown in **Table 5**.

Table 5: Clinical Features and Management

Site of disease	Clinical features	Treatment
Oral	Cotton-like sensation in mouth	Clotrimazole troche 10 mg five times/day for 7-14 days Oral Fluconazole 100-200 mg once daily for 7-14 days
Oesophageal	Odynophagia with oesophageal ulcers	Tab Fluconazole 200 mg once daily for 14-21 days.
Vaginal	Curdy white pruritic vaginal discharge adhering to erythematous base	Tab Fluconazole 150 mg stat Tab Fluconazole 150 mg x 3 doses

DIARRHOEAL DISEASE

Epidemiology

The common infective organism which are usually responsible for diarrhoea in patients are depicted in **Table 6**.

Table 6: Common Pathogens Associated with Diarrhoea in HIV-infected Individuals

Infectious agent	Small intestinal pathogen	Large intestinal pathogen
Bacteria	*Mycobacterium avium intercellulare* *Salmonella* spp	*E. coli* *Campylobacter* spp *Aeromonas* spp *C. difficile*
Virus	Rotavirus Norovirus	Adenovirus *Herpes simplex virus* Cytomegalovirus
Protozoa	Cryptosporidium Cyclospora *Giardia lamblia* *Isospora belli* Microsporidiosis	*Entamoeba histolytica*

Clinical Features

Four distinct clinical syndromes exist:

- Small bowel diarrhoea—watery, large volume associated with bloating and weight loss.
- Large bowel involvement—frequent, small volume, painful stools.
- Anorectal involvement—associated with tenesmus, dyschezia and urgency.
- Disseminated infection—with fever is seen in Salmonellosis, atypical mycobacteria or CMV.

Treatment

Treatment of chronic diarrhoea is outlined in **Table 7**.

Table 7: Definitive Therapy of Chronic Diarrhoea

Organism	Drugs
Salmonella	Oral double strength Cotrimoxazole (800 mg sulphamethoxazole/160 mg trimethoprim) once daily for 10 to 14 days
Shigella	Oral Cotrimoxazole double strength tablet for five days
Giardia lamblia	Oral Metronidazole 200 mg thrice daily for a week
Entamoeba histolytica	Oral Metronidazole 400 mg thrice daily for a week
Cryptosporidium	HAART
Cyclospora	Oral double strength Cotrimoxazole every 6 hours for 10 days then twice a week indefinitely
Isospora belli	Single double strength Cotrimoxazole tablet four times a day for 10 days followed by thrice daily for 3 weeks
Microsporidiosis	Oral Itraconazole 400 mg once daily and Albendazole 400 mg once daily

CRYPTOCOCCOSIS

Cryptococcus neoformans is an encapsulated yeast-like fungus which produces meningitis, pneumonia, cutaneous abscesses among individuals with CD4 count <100 per mm^3.

Clinical Features

Cryptococcal meningitis begins as a subacute onset of fever, headache and malaise with seizures or altered mentation. Stiff neck, photophobia, and vomiting are seen in 25% patients. Symptoms suggesting disseminated disease such as cough, dyspnoea, and skin rash may be present.

Diagnosis

The gold standard for diagnosis of cryptococcal infection is a positive cerebrospinal fluid (CSF) culture. CSF India ink staining demonstrates the organism in 75% of patients. CSF and serum cryptococcal antigen have sensitivity and specificity ranging from 93 to 100%.

Treatment

The treatment of choice is amphotericin B 0.7 to 1 mg/kg/day, usually combined with flucytosine 100 mg/kg/day, for two weeks, followed by fluconazole 400 mg once daily for 8 weeks. Maintenance fluconazole 200 mg/day is recommended till patients begin HAART and maintain CD4 counts >200/mm^3 for more than 6 months.

Repeated therapeutic lumbar punctures may be required if CSF opening pressures are >250 mm CSF draining 20-30 mL CSF so as to decrease CSF pressures by 50%.

If new symptoms or signs develop after 2 weeks of treatment, repeat diagnostic lumbar puncture may be required to exclude coinfection with tuberculosis.

CYTOMEGALOVIRUS

Clinical Features and Diagnosis

Table 8 shows the clinical features of cytomegalovirus while **Table 9** charts the other common opportunistic infections.

Table 8: Clinical Disease Produced by Cytomegalovirus

Organ affected	Clinical features	Diagnosis
Retina infiltrates	Flashes, blurred central vision	Fundoscopy reveals perivascular fluffy yellow-white retinal and focal necrotising retinitis with or without intraretinal haemorrhage
Gastrointestinal tract	Fever and odynophagia with lower oesophageal ulcers Abdominal pain, diarrhoea (large bowel type), weight loss	Endoscopic visualisation of mucosal ulcers or erosions and histological evidence of tissue destruction with presence of viral inclusion bodies
Lung	Fever, cough and dyspnoea	Positive CMV culture of bronchoalveolar lavage fluid or histopathologic cytopathologic effect
CMV encephalitis	Delirium, confusion and focal deficits	MRI brain or spinal cord is useful in excluding other OIs
Myeloradiculoneuropathy	Ascending flaccid paralysis with bowel and bladder involvement	Positive CMV PCR from CSF is highly suggestive of CMV

Table 9: Other Opportunistic Infections

Disease	Pathogen	Clinical features	Diagnosis	Management
Pneumocystis jiroveci pneumonia	*Pneumocystis jiroveci*	Fever, cough dyspnoea with diffuse dry rales in individuals with CD4 count <100 cells/ microlitre	Demonstration of the organism in pulmonary secretions by immunofluorescence or methenamine silver staining	2 double strength tablets of Cotrimoxazole (800 mg sulphamethoxazole/160 mg trimethoprim) every 8 hours for 21 days PaO_2 <70 mm of Hg and alveoloarterial gradient greater than 35 mm Hg mandates steroids
Progressive multifocal leucoencephalopathy	JC virus	Subacute onset altered mentalstatus, motor deficits, limb ataxia, gait ataxia and visual symptoms	Asymmetric periventricular white matter foci of demyelination without oedema or mass effect sparing the optic nerves and spinal cord – confirmation by brain biopsy	HAART
Toxoplasmosis	*Toxoplasma gondii*	Encephalitis in individuals with CD4 count <50 cells/ microlitre	Identification of ring-enhancing intracranial mass lesions and detection of the organism on biopsy. Positive CMV IgG is suggestive. Therapeutic response in 2 weeks is confirmatory	Pyrimethamine (200 mg loading dose orally followed by 75 mg/ day) plus sulphadiazine (6 to 8 g/day orally in four divided doses)
Oral hairy leukoplakia	Epstein-Barr virus	Adherent white patches on lateral tongue and mouth	Clinical	Topical tretinoin or podophyllin
Herpes zoster	*Varicella zoster*	Grape-like clusters of clear fluid-filled blisters on red skin	Tzanck preparation showing multinucleate giant cells	800 mg oral Acyclovir 5 times a day for 7-20 days
Penicilliosis Histoplasmosis	*Penicillium marneffi Histoplasma capsulatum*	Fever, lymphadenopathy hepatosplenomegaly molluscum like skin lesions	Histopathology – yeast like organisms. Fungal culture from blood, bone marrow, lymph nodes confirmatory	Amphotericin B 0.6 mg/kg/day for 2 weeks followed by oral Itraconazole 200 mg twice daily for 10 weeks.

Table 10: Common Immune Reconstitution Inflammatory Syndrome (IRIS)

Disease	Clinical manifestations	Treatment
Tuberculosis Usually occurs in 10-180 days of institution of HAART	Fever, malaise, weight loss Worsening respiratory symptoms Increase in size of lymph nodes New pleural effusion Resurgence of fever with pulmonary symptoms Increase in size of tuberculomata	Continuation of ART unless life-threatening IRIS or localised symptoms threaten to cause permanent sequelae Prednisolone 1 mg/kg/day tapered over 14 days (adjunct) Appropriate antimicrobial therapy for the opportunistic agent
Cryptococcosis	Fever, increased headache, nuchal pain, eye pain	
Cytomegalovirus	Immune recovery vitritis – Uveitis, vitreous inflammation with or without cystoid macular oedema, epiretinal membrane or retinal neovascularisation	

Treatment

Oral Valganciclovir is recommended for CMV retinitis (900 mg twice daily for 3 weeks as induction followed by 900 mg once daily as maintenance – till CD4 count >100 cells/microlitre for 6 months while on ART). In patients with vision threatening disease, gastrointestinal, neurologic and pulmonary disease, intravenous ganciclovir 5 mg/kg every 12 hours for 21 days followed by the oral preparation (1,000 mg capsules thrice daily) for maintenance is recommended.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) (Table 10)

IRIS refers to inflammatory reactions occurring at the site of pre-existing infection owing to reconstitution of the immune system in HIV-infected individuals following the initiation of HAART. Up to 30% of individuals responding to HAART manifest IRIS.

It may be possible to avoid IRIS by treating identified OIs that have an effective antimicrobial therapy for one to two months prior to initiation of HAART thereby reducing the microbial burden when ART is initiated.

PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS

Primary chemoprophylaxis against OIs is recommended in all HIV-infected individuals who have WHO Stage III disease or Stage II disease with a CD4 count less than 200 cells/mm^3.

Primary prophylaxis may be ceased once the CD4 count is over 200 cells/mm^3 for over 6 months (**Table 11**).

Secondary prophylaxis may be discontinued when the CD4 count is above 100 cells/mm^3 for more than 6 months while patient is on HAART (**Table 12**).

Table 11: Primary Prophylaxis of OIs

Agent	CD4 count/ mm^3	Drug	Comments
Pneumocystis jiroveci	CD4 <200	Cotrimoxazole double strength tablet once daily	Cotrimoxazole is useful in the prevention of Toxoplasmosis, certain bacterial pneumonia, Nocardiosis and Isosporiasis
Mycobacterium avium intercellulare	CD4 <50	Azithromycin 1.2 g once a week	

Table 12: Secondary Prophylaxis of OIs

Agent	Drug
Cytomegalovirus	Valganciclovir 900 mg once daily
Cryptococcosis	Fluconazole 100 to 200 mg orally daily
Candidiasis	

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16.8 Non-Pharmacologic Interventions and Prevention

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INTRODUCTION

Human immunodeficiency virus (HIV) has a long incubation period and florid disease takes a long time before becoming clinically manifest. This, therefore, provides a unique window period to prevent its progression, and in case of disease, to reduce its morbidity. This chapter deals with interventions in asymptomatic and symptomatic PLWHAs (Persons Living With HIV/AIDS). Many alternative therapies (like yoga) have been occasionally reported as useful. Counselling is a useful tool right from the stage when the tests are being planned to crisis situations. Nutritional support is another well recognised intervention. Periodic screening and monitoring will assist in early detection and treatment of infections and malignancies. There are effective preventive vaccines for many infections which can be used in PLWHAs. HIV vaccine development is advancing. Many vaccines are being studied for their potential therapeutic efficacy (delaying progress) even when primary prevention is not possible.

The interventions in HIV disease can be grossly classified as follows:

1. Interventions for general public.
2. Interventions for vulnerable groups.
3. General interventions amongst PLWHAs.
4. Specific interventions at certain stages.

INTERVENTIONS FOR GENERAL PUBLIC

These include IEC (Information, Education and Communication) strategies, e.g. general education, sex education and health awareness programmes, etc. They aim at generating knowledge which leads to healthy attitudes, improved behaviour translating to better practices. The behaviour change must be regularly re-inforced with repeated attempts. Health issues and safe sex education at various levels have been found to be useful. IEC also generates healthy attitudes in infected persons, special categories, i.e. intravenous drug users (IVDUs), men having sex with men (MSM) and commercial sex-workers (CSWs). Across cultures this is the most commonly tried intervention and adjudged the most acceptable.

ABC OF HIV PREVENTION

A- Abstinence, B- Being faithful with an uninfected partner and C- Condom use, proper and consistent has been the cornerstone of prevention of sexual transmission of HIV. Such a strategy has been found to be useful and successful but the first practice is hard to follow and in the second, the HIV status of the partner has to be known, which at times is difficult. While effective use of condom is possible and quite useful.

INTERVENTIONS FOR SPECIAL GROUPS

Interventions in this category can be divided into two main groups: (1) those practicing high-risk sexual behaviour and (2) those indulging in IV drug use.

Reducing Sexual Transmission

The high-risk sexual behaviour includes: (a) male homosexuality with multiple partners, (b) multi-partner sex, (c) sex with casual (non-regular) sex partners. In heterosexual practice (sex between opposite sexes), the risk is graded differently as unprotected anal intercourse, unprotected vaginal intercourse, unprotected oral sex and as protected sex using condoms. The strategies aim at shifting a person from practices of higher risk to safer practices. Condom promotion plays a major role in all these modalities.

Syndromic Approach to Sexually Transmitted Infections (STIs) Management

Refer to chapter 16 of section 10.

Reducing Transmission by IV Drug Use

Intravenous drug users have been recognised as a vulnerable group from the early days of the epidemic. Sharing syringes used for IV injection particularly was an efficient mode of transmission in many populations. Recreational drug use is illegal in many countries and unacceptable in many cultures. Even non-injectable drug use makes people vulnerable by modifying their level of judgement and taking away inhibitions leading to unsafe sex behaviours. IVDUs have been targeted in many activities across the globe. *Supply reduction, demand reduction and harm reduction* are three major strategies in this group. Supply reduction prevents illegal trafficking, confiscation and destruction of drug supplies and supply lines. Demand reduction is practiced in many educational institutions. Proper IEC programmes on the risks of drug use are acceptable to all societies and all ages. Rehabilitation and detoxification clinics modify use pattern by scientific methods like counselling, methadone or buprenorphine substitution, etc. These will gradually reduce dependency and promote adherence to counselling and healthy lifestyles. Walk in centres with facilities for sterilisation or sterile injections are beneficial. Community-based rehabilitation packages including promotion of safer sex practices are needed for IVDUs. There is evidence from multicentric studies that these significantly reduce HIV transmission.

Reducing Transmission Among MSM

Men having sex with men (male homosexuals) have been recognised as vulnerable from the early days of the epidemic. Many of them have problems like having sex with many partners (regular and non-regular) at any point in time, having STIs, propensity for anal intercourse, habituation to injecting/other drug use, having sex with female partners. Poly-drug use, partner violence, depression and other psychosocial issues are also important. Specialised sex education packages, condom promotion, integrated STI care, context specific counselling, etc. are strategies found successful for them.

Reducing Transmission by Blood and Blood Products

All health establishments handle emergencies where blood is required. Proper screening, donor selection, storage and

delivery are vital. Quality of screening is ensured. Licensing of blood banks and avoidance of all unauthorised blood collections are needed across the globe. Recruitment of voluntary low risk donors is encouraged and all professional donors excluded. Supply of non-human blood components, component transfusion, autologous transfusion, etc. are important strategies.

Reducing Transmission in Health Care Settings

It is dealt in chapter 9 of section 17.

Targeted Intervention Approach of NACO (India)

National AIDS Control Organisation (NACO), Ministry of Health and Family Welfare, Government of India has adopted targeted intervention as a regular strategy. It envisages comprehensive and integrated approach to marginalised and vulnerable populations like CSWs, MSMs, IVDUs, migrant labourers, street children, prisoners, etc. There are around 900 projects run by Non-Governmental Organisations (NGOs) and other agencies across the country. They perform need assessment, counselling, education, peer group activities, behaviour change communication monitoring and care and support activities. They are run with financial assistance and scrutinised by the state AIDS control societies.

Voluntary Counselling and Testing (VCT)

One major activity aimed at making the above facilities available to the public at low cost includes Voluntary Counselling and Confidential Testing Centres in all states. The services of male and female counsellor for pre-/post-test counselling and laboratory technician for serological testing is available. These centres have become Integrated Counselling and Testing Centres (ICTCs). These will act as the portal of entry for people with high-risk behaviour to enter the care set-up voluntarily and confidentially.

GENERAL INTERVENTIONS AMONGST HIV INFECTED PERSONS

Lifestyle Changes

Avoidance of high-risk behaviour and change to safer sex and safer injection practices are the most important issues for PLWHAs at all stages. The usage of condoms and sterile needles must be insisted. Avoidance of both needle-sharing and dangerous sex practices (multi-partner sex, unprotected sex) do help. Even among well educated people, there is a wrong belief that if both partners are infected, there is no need for protected sex. Protected sex at any stage will help in preventing first or subsequent infection with various subtypes of HIV and more importantly other sexually transmitted pathogens. It is well known that any infection (including common infections and self-limited infections) like herpes or candida can activate immunologic cells and increase the viral load. Therefore, PLWHA must clearly avoid contact with other infectious diseases patients, pets and other animals, untreated animal products, etc.

Use of habit forming drugs like alcohol, psychedelic drugs, etc. can lead to chronic systemic ailments, hampering the health status. The person should be cautious when working or travelling to high-risk environments including endemic areas. They should take only boiled water and well washed vegetables to avoid gastrointestinal infections.

Regular exercise must be promoted. All lifestyle risk factors like smoking, sedentary lifestyle, high intake of fatty foods, etc. should be curtailed. Interventions like counselling, yoga, etc. can create a good mental make-up for the affected individuals.

Nutrition plays a major role. Improvement in nutritional status of all family members of PLWHA gets reflected in the survival. High calorie, high protein diet rich in micronutrients must be encouraged. Early screening for diabetes, metabolic syndrome and other such ailments are to be done systematically.

Specific Interventions at Certain Stages

Crisis situations can occur any time in human life. Issues related to marriage, contraception, conception, childbirth, breast feeding, death, etc. might make the services of a well trained counsellor absolutely essential.

PREVENTION OF MOTHER TO CHILD TRANSMISSION

HIV affects women of the childbearing age and hence pregnancies associated with HIV infection are bound to happen. Proper contraceptive counselling in PLWHAs can prevent a large number of avoidable pregnancies and thus help reduce the number of infected children being born. In many instances antenatal screening is the first time a woman is found to be infected. Apart from the psychological support needed for the expectant mother, proper use of antiretrovirals (ARVs) can ensure a significant reduction in vertical transmission. The use of ARV drugs before labour, reduction in the time spent in labour (by elective caesarian section), and avoidance of breastfeeding has all been shown to be effective. Exclusive formula or breast feeding is superior to mixed feeding. Routine screening of antenatal women (with informed consent and counselling) is fast becoming the standard practice. Infected persons are given full care and further counselling regarding child rearing and infection control practices in children. All vaccines must be given to the newborn as in any other child.

EMERGING AVENUES IN PREVENTIVE INTERVENTION

HIV Vaccines

Even though a vaccine is the most sought after preventive intervention in any disease, HIV vaccine development must overcome many obstacles like variations in antigen configurations, rapidity of new mutant evolution, sanctuaries of virus persistence in the body and the difficulty in immunologically active cells being part of the disease process. However under the International AIDS Vaccine Initiative (IAVI), many countries (including India) are enthusiastic about vaccines. Many candidate materials have been tried as prophylactic and therapeutic vaccines. DNA vaccines (either alone or with adjuvants), live vector based vaccines, subunit vaccines, peptide vaccines, VLP (virus like particle) vaccines, fusion competent vaccines, Tat toxoid vaccines, inactivated vaccines are all being tried. Many of them act through cytotoxic T-cell (CTL) production or by inducing neutralising antibodies. There are many ethical and psychological issues involved in any vaccine trial and hence an easy solution is not likely to evolve soon. A prophylactic vaccine is not going to prevent HIV infections in everybody and the importance of all other preventive strategies should not be underestimated. According to a model developed by IAVI, a 30% effective vaccine given to 20% of the risk population could reduce new infections by just

17%. There have been several advanced-phased HIV vaccine trials to date that have been conducted in developed and developing countries. Phase 3 trials involve thousands of high-risk volunteers to test the effectiveness of an HIV vaccine on HIV seroincidence. Phase 2B trials involve a smaller number of volunteers and can determine a preliminary assessment of efficacy. They can guide future vaccine efforts, but are not enough for licensing or release of a vaccine. Currently, there is no licensed preventive (in HIV-negative participants) or therapeutic (in HIV-positive participants) HIV vaccine. Despite the recent encouraging progress from the Thai RV144 trial, we remain a long way from an affordable, effective vaccine against HIV.

Microbicides

Microbicides are chemicals that work in the vagina by different mechanisms. They are materials that can be used by a woman without depending on the partner to protect herself. Some of them are foaming agents, acidifying gels, entry inhibitors or vaginal defense enhancers. The initial euphoria associated with the introduction of vaginal microbicides has given way to a more realistic approach that looks at the side effects and actual statistically proven effectiveness. Many agents are being discarded and newer ones are being studied. A detailed evaluation of microbicides is not within the purview of this book.

Male Circumcision

Many reports have highlighted the decreased risk of HIV transmission if the male partner is circumcised. The inner part of the foreskin has a higher number of Langerhans' cells with receptors for HIV. The skin over the penis is different in circumcised man which reduces trauma during penetrative sex. Many models have shown a possible reduction of 10% to 20% new infections in communities where at least 10% males are circumcised every year. The reduction in male infection rate will lead in future to a similar fall in female infection rate as well. However, male circumcision is to be considered alongwith proper and consistent condom use as the most important intervention.

CONCLUSION

With the current level of knowledge about HIV disease and the modalities available for countering the replication and transmission of the virus, it is now possible to do many preventive interventions at different stages of the disease and the epidemic. Even when ARV drugs are changing the scenario of survival in PLWHAs, this epidemic is still not under control. A few best practices from countries like Thailand, Uganda and Senegal could be extrapolated to other parts of the world and newer observations from other countries must be identified and disseminated. Changes in knowledge, attitudes, behaviour and practices are to be addressed in larger scale.

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Section 17

Infectious Diseases

Section Editors: Shyam Sundar and Subhasish Kamal Guha

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17.1 Basic Considerations of Infections

Subhasish Kamal Guha

The infectious diseases continue to pose a major public health challenge for the developing nations. However, the morbidity and mortality due to infectious diseases has declined among developed nations because of improvements in sanitation, overall living conditions, availability of safe drinking water, and access to many anti-microbials and vaccines.

EPIDEMIOLOGY OF INFECTIOUS DISEASES IN INDIA

A number of infectious diseases are prevalent in India. With successful implementation of immunisation of infant and children, there has been considerable decline in the incidence of diseases like measles, diphtheria, whooping cough, etc. However, certain diseases continue to be endemic in various states of India. Some of the infectious diseases are localised to certain states or districts. Kala-azar is endemic in Bihar, Jharkhand, Eastern Uttar Pradesh and West Bengal. *Penicillium marneffei* is similarly observed in Manipur and Nagaland among people living with HIV/AIDS. Kyasanur Forest disease, endemic in Shimoga, North and South Kannada and Chikamagaloor districts of Karnataka is another example of localised disease.

Certain infectious diseases, although prevalent throughout the country, seem to have increased incidence in certain states, e.g. hydatid disease in Andhra Pradesh and Tamilnadu, lymphatic filariasis in Uttar Pradesh, Bihar, Jharkhand, Andhra Pradesh, Orissa, Tamilnadu, Kerala and Gujarat. It may be mentioned here that lymphatic filariasis is distinctly uncommon in North and Northeastern states. Malaria is a major public health problem across the country. But malaria in forests, forested foothills and hills, forest fringe areas and development project sites is a matter of concern. Fifteen major cities including the four metropolitan ones contribute to the bulk of urban malaria. Dengue and dengue haemorrhagic fever (DHF) has caused epidemics during 2005-2006 in Delhi, West Bengal, Rajasthan, Kerala and Punjab. Chikungunya is reported from Maharashtra, Karnataka, Andhra Pradesh, Gujarat, Tamilnadu, Madhya Pradesh, Delhi, Kerala, and Rajasthan. Although Japanese encephalitis is endemic in the states of Bihar, Haryana, Karnataka, Kerala, Maharashtra, Manipur, Tamilnadu and West Bengal, most of the recent outbreaks have occurred in Assam and Uttar Pradesh. Leptospirosis, endemic throughout the country, caused epidemic in Orissa in 1994 following the super cyclone and outbreaks during the monsoon of 2000 in Gujarat, Kerala, Maharashtra, and Andaman & Nicobar Islands.

Outbreak of Bubonic plague occurred in Beed, Maharashtra in 1994 followed by an outbreak of pneumonic plague in Surat, Gujarat. In 2002, the last report of pneumonic plague came from Hat Koti village of Shimla district of Himachal Pradesh. Rabies is endemic all over India except Lakshadweep and Andaman and Nicobar islands. India is the highest tuberculosis burden country of the world.

The HIV epidemic is also fuelling the spread of tuberculosis. The 'high prevalent' states for HIV include Maharashtra, Tamilnadu, Andhra Pradesh, Karnataka, Manipur and Nagaland. HIV/AIDS is an emerging health and social problems of the entire country. The incidence of leprosy is on the decline. The six states/union territories that are still having high prevalence include Bihar, Chhattisgarh, Jharkhand, West Bengal, Chandigarh and Dadra & Nagar Haveli.

HOST FACTORS IN INFECTION

Age, immunisation, prior illness, nutritional status, pregnancy, immune status, co-morbid diseases—all have impact on the risk of infection following exposure to potential pathogens. Hospitalisation also increases the risk of acquiring infection through contact with pathogens, through breach of skin (intravenous devices or surgical incisions) or mucosa (catheter or endotracheal tubes), by introduction of foreign bodies, through alteration of the natural flora with antibiotics, and by immunosuppressive therapy.

Both innate and adaptive or specific immunity play important roles in determining the outcome of host-microbial interactions and have been discussed in the Immunology Section of this book.

MICROORGANISM-HOST INTERACTION

Impact of Infection on the Body

Infection has many effects on the host. These can be acute, chronic, allergic, and toxigenic.

Acute effects are fever, protein catabolism, negative nitrogen balance, acute-phase protein response, hypoalbuminaemia, low serum iron, anaemia, neutrophilia, inflammation, convulsion, confusion, shock, haemorrhage, haemolytic anaemia, intra-vascular coagulation, organ failure involving kidneys, liver, lung, heart, brain, and necrosis of skin.

Chronic effects of infection can be loss of weight, muscle wasting, malnutrition, growth retardation in children, anaemia, tissue destruction, etc. Post-infective syndromes may include lactose intolerance, malabsorption, fatigue, depression, etc.

Allergic (immune-mediated) manifestations of infection include rash, arthritis, pericarditis, encephalitis, peripheral neuropathy, haemolytic anaemia, and glomerulonephritis.

Toxin-mediated effects include erythematous rash in streptococcal infection, multisystem disturbances in staphylococcal toxic shock syndrome, diarrhoea due to toxins, organ dysfunction (e.g. diphtheria) and neurological manifestations (e.g. tetanus, botulism and diphtheria).

In addition, certain viruses (oncogenic) are implicated in the aetiology of malignancies.

PATHOLOGY OF INFECTION

Diseases due to an infectious agent are the outcome of interaction between the microorganism and the host defence mechanism. Depending on this interaction, infection may vary from sub-clinical or asymptomatic infection on one hand to severe, fulminant disease culminating in death on the other. Factors like number and virulence of the organisms, anatomical and physiological effects produced by it and the ability of the host's defence mechanism—all play important role in the outcome of host-microorganism interaction. Certain genetic factors are also significantly involved in the response to infection.

Organisms act either directly and/or indirectly through their toxins. The effects of infection may be generalised but can also be site-specific, e.g. poliomyelitis virus in anterior horn cells.

EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Declaration by WHO of global eradication of smallpox on 8th May, 1980, was a landmark in the battle against infectious diseases. Guinea worm disease has also been eradicated from most of the world except for few countries in Africa. It is expected that diseases like poliomyelitis, neonatal tetanus, leprosy, onchocerciasis and Chagas' disease will soon join the list.

Some of the infectious diseases, once largely controlled by public health measures, have come back with vengeance in recent years. These re-emerging infections include malaria, dengue, chikungunya, plague, cholera, yellow fever with spread to new geographical areas.

Additionally, a number of new infectious agents have emerged in the last 2 to 3 decades causing outbreaks or epidemic in various countries with rapid spread across the globe. Some of the examples are severe acute respiratory syndrome (corona virus), diarrhoeal diseases (*Vibrio cholerae* O139, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Escherichia coli* O157-H7, *Campylobacter jejuni/coli*, and *Shigella* spp.), Ebola and Nipah haemorrhagic fever, pulmonary Hanta virus, Monkey pox, HIV/AIDS, Avian (H5N1) and Swine (H1N1) flu, etc.

Factors responsible for spread of new, re-emerging or drug resistant infections include changes in human demographics and behaviour, impact of new technologies and industries, economic development and changes in land use, increased international travel and commerce, microbial adaptation and change, and the breakdown of public health measures.

Some of these diseases like plague, dengue, chikungunya, cholera, Nipah virus, avian and swine flu have recently caused outbreaks in India raising public health concerns.

Anti-microbial drug resistance is also a pervasive health problem. multidrug-resistant (MDR) and extensively drug-resistant tuberculosis (XDR TB), methicillin and vancomycin resistant *Staphylococcus aureus* (MRSA and VRSA), vancomycin resistant Enterococcus (VRE), multidrug resistant *Plasmodium falciparum* malaria, penicillin resistant pneumococcus and penicillin and tetracycline resistant gonococcus are all major problems of anti-microbial therapy.

FUTURE DIRECTIONS

The genetic constitution of many microorganisms allows them to undergo rapid evolution and to develop mutations that offer them survival benefit. Changes in environment and the host can predispose new populations to some infections. The deliberate release of deadly spores of *Bacillus anthracis* via the US Postal Service was an eye-opener to everyone about the reality of bioterrorism. We have also witnessed recently the scare in public minds, media, politicians and even health care delivery system when swine flu epidemic broke out in India. The battle between the emerging anti-microbial resistance and new, potent, costly anti-microbial is destined to continue. A well-coordinated team approach involving physicians, microbiologist, intensive care specialists and public health managers is the need of the hour for the war against infection.

RECOMMENDED READINGS

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17.2 Laboratory Diagnosis of Infections

Camilla Rodrigues

There are several advantages in making a specific diagnosis of an infectious disease. In addition to better patient care with appropriate therapy, considerable financial expense is spared and preventive measures can be initiated.

SPECIMEN COLLECTION AND TRANSPORT

This is the first vital step. It is important to protect the sample from contamination by normal flora as with stool and urine specimens. Also for isolation of anaerobes, maintenance of the redox potential with transport media as Stuart's medium along with rapid transport to the laboratory is essential. The stage of an illness determines what sample is required and whether or not the microorganisms will be isolated, e.g. *Salmonella typhi* is recovered maximally from blood cultures in the first week of typhoid fever but from stool and urine only in subsequent weeks. For tuberculosis where irregular shedding of *Mycobacterium tuberculosis* occurs, successive samples need to be tested.

IDENTIFICATION OF INFECTIOUS AGENTS

To identify microorganisms five different approaches may be adopted namely microscopy, culture, serology, antigen detection and molecular methods.

Microscopy

Direct microscopy

Examination of coverslip preparations helps in the immediate diagnosis of cholera, amoebiasis, giardiasis and helminthic infestations. Various staining procedures can be employed like Gram's stain, acid fast staining for Mycobacteria; Wright's stain to detect malarial parasites and microfilaria in blood smears and silver stains are for the identification of fungi and *Pneumocystis*. India ink is useful in negative staining to detect capsular organisms, e.g. *Cryptococcus* in CSF.

Culture

Blood culture

This is indicated in all infections where bacteraemia is the hallmark, e.g. in infective endocarditis, where ideally three blood samples should be drawn at least half an hour apart. If cultures are persistently negative, supplemental media for nutritionally dependent *Streptococci* can be used. Blood culture is also helpful in other acute febrile illnesses, such as typhoid, meningitis, bacterial pneumonia, osteomyelitis and in fever of unknown origin.

Although recovery of bacteria from blood during episodes of sepsis is not difficult, certain concepts need to be understood. Adequate skin preparation prior to venepuncture is of utmost importance. In addition, a minimum of 30 to 40 ml of blood should be cultured. Increasing the volume collected for culture is regarded as an essential component in enhancing isolation of microorganisms. The culture medium should include an anticoagulant and ideally an anti-complement and anti-phagocytic substance to reduce the intra-cellular killing of microorganisms by neutrophils following injection of the blood into the culture medium.

There is data to substantiate that two or three blood culture sets are adequate for detecting common pathogens. The recovery in the first culture is 80%, 88% in two cultures and 99% in all three cultures.

Timing

Optimally at the onset of a shaking chill but in less urgent situations spaced at intervals of ½ to 1 hour. Ratio of blood to broth ideally should be 1:5 to 1:10. Organisms as *Brucella*, *Legionella*, some fungi, mycobacteria should be incubated for longer than the traditional 5 days.

Automated blood culture systems

The continuous monitoring blood culture systems are modular with a single computer controlling the incubator units. Culture vials are incubated in individual cells and monitored at intervals of 10 to 15 minutes for evidence of microbial growth. Three such systems, the BACTEC blood culture system (BD Diagnostic Systems), the BacT/alert (Biomerieux) and the TREK-ESP culture systems (TREK Diagnostic systems) are available in India. Multiple studies have shown that the bottles need to be incubated for only 5 days.

Sputum culture

Sputum samples may contain large number of bacteria indigenous to the oral cavity. Early morning samples are advisable since they contain pooled overnight secretions likely to contain pathogenic organisms. When sputum production is not possible, induction with heated or ultrasonic nebulised saline may be effective. More invasive methods include transtracheal aspiration, bronchoscopy and bronchoalveolar lavage.

Urine culture

Collection of urine should be performed to minimise contamination by organisms from the urethra. Thus, adequate cleaning prior to the collection of mid-stream specimen of urine is vital. Urine samples should reach the laboratory within 30 minutes. Dip slides should be used if delay is anticipated in the samples reaching the laboratory. The presence of more than 100,000 colonies/ml signifies true infection.

Gastrointestinal culture

Gastric aspirates for culture is used for the diagnosis of tuberculosis in children. Endoscopic biopsies are used to detect *Helicobacter pylori*. Stool samples are cultured on special media to prevent the colonic flora from overgrowing the pathogen.

TB culture techniques

Culture of mycobacteria is a much more sensitive test than smear examination and allows for biochemical identification

of the species considerably enhancing the specificity. Agar based media allow detection of colonies in 10 to 12 days, whereas the most commonly used Lowenstein-Jensen medium (L-J) usually takes 18 to 24 days; because of the slow doubling time of *M. tuberculosis*.

Automated liquid culture methods

The mycobacterial growth indicator tube (MGIT) 960: The test employs a new state of the art fluorescent technology that enables positive results in 7 to 10 days. This dispenses with the need for radioisotope labelled substrates required for BACTEC 460 TB. It is based on oxygen quenching of mycobacteria with a fluorescent embedded dye.

Automated organism identification and anti-microbial susceptibility testing: There are fully automated instruments available today for rapid and accurate identification as well as susceptibility testing by minimum inhibitory concentration (MIC). The basis of identification system reactivity is usually based on pH or enzyme profiles but can also be carbon sourced and visual detection of growth.

Importantly, dialogue between the clinician and microbiologist is necessary if one is to tell whether organisms identified by the laboratory represent contaminants, commensals or true pathogens.

Serology

Isolation of the offending agent is the mainstay in the diagnosis of disease. If this is not possible and the organism is either fastidious or hazardous to grow or takes long to cultivate, serology is resorted to. This detects either (1) the specific or non-specific immune responses of the host, or (2) the presence of the antigen in the host.

Specific IgG and IgM antibodies can be detected using immunological techniques against an increasing range of viruses, e.g. hepatitis (A-G), HIV, rubella, measles, Epstein Barr, CMV, herpes simplex, etc. IgM antibodies are indicative of recent infection. The secondary response on re-exposure to the same antigen is predominantly IgG driven. There are various types of serological reactions, such as precipitation, agglutination, complement fixation, immunofluorescence, ELISA, Western blot, etc.

Widal test

Whilst interpreting this commonly used agglutination test certain provisos need to be kept in mind. The majority of patients develop a four-fold rise against the somatic O antigen of the typhoid bacillus; H agglutinins are more subject to non-specific variations. Early anti-microbial therapy may dampen the immunologic response and false positives can occur in an anamnestic response during an unrelated fever.

Enzyme-linked immunosorbent assay (ELISA)

ELISA assay has been used extensively to detect either antigen or antibody and has been described as specific, sensitive, simple, inexpensive and reproducible. The indicator in this technique is an enzyme which catalyses a chemical reaction in a substrate. Various enzyme-substrate combinations have been used. The end product of the enzyme reaction can be quantitatively measured spectrophotometrically, fluorometrically, or by other means. It has proven to be as sensitive as radioimmunoassay (RIA) in detecting small quantities of antigen. These techniques are being extensively utilised in diagnosis of toxoplasma, rubella, cytomegalovirus and herpes simplex infections (TORCH), hepatitis and HIV infections.

Immunofluorescence antibody (IFA)

Immunofluorescence staining has long been used in rapid viral diagnosis. The method is based on tagging an antibody with fluorescein isothiocyanate and demonstrating the antibody-virus complex or viral antigens within or on the surface of the cells by examining the preparation microscopically with UV illumination. A number of procedures have been described, including the direct and indirect or anti-complementary IFAs. As the IFA test is performed microscopically it requires approximately 10^5 infectious particles to be visualised.

DETECTION OF MICROBIAL ANTIGENS/PRODUCTS

Today assays are available for rapid detection of bacterial antigens in various body fluids. These are also useful when smear is negative, prior antibiotics have been initiated and culture is negative. Also rapid antigen methods have the advantage that since they are antigen based detection systems, they can be used in the initial stages of the illness and one does not have to wait for specific antibody production. The turn around time is faster in these assays – ranging from 10 minutes to a couple of hours. The common methods encompass latex agglutination, counter current immunoelectrophoresis (CIEP), immunochromatographic assays (ICT)/lateral flow formats, ELISA, direct immunofluorescence, etc.

A. Cerebrospinal Fluid (CSF)

i. Latex agglutination

Latex agglutination techniques are used to demonstrate the soluble polysaccharide antigens of *Neisseria meningitidis*, *Haemophilus influenzae* type B and *Streptococcus pneumoniae* in patients of acute pyogenic meningitis.

In neonatal meningitis the latex agglutination method can be used for detection of *E. coli* and Group B *Streptococci*. These tests offer good specificity more than 98% but the sensitivity varies with each bacterium tested. For *N. meningitidis* A, C, Y, W135, and *N. meningitidis* B/*E. coli* K1 it is 71% and 65% respectively. For *S. pneumoniae* it is 88% and for *Haemophilus influenzae* and Group B *Streptococci*, it is 67%. This assay can also be used for serum after appropriate treatment with EDTA.

ii. Cryptococcus neoformans

Latex agglutination and ELISA are the preferred tests for detection of cryptococcal antigen. They can be used for diagnosis as well as therapeutic monitoring. The latex agglutination methods have a sensitivity of approximately 93% and specificity from 93% to100% and are equivalent to ELISA in detecting antigen. *Trichosporon beigelii*, *Capnocytophaga* spps. and *Stomatococcus* have been shown to produce a cross reacting polysaccharide antigen. Treatment with pronase B reduces the false positive in serum tests in certain rheumatological disorders.

B. Serum

i. Plasmodium species

Rapid diagnostic tests (RDTs) for malaria have an ability to detect more than 100 parasites/mL of blood. These qualitative

tests are rapid, simple, easy to perform and interpret. The stability of the kit in high environmental temperature and humidity in tropics should be taken into account. As they cannot quantitate, they are not useful for prognostication. RDTs have decreased sensitivity at lower levels of parasitaemia yielding false negative results in non-immune patients with low levels of parasitaemia.

There are 3 types of antigens that are used in detection namely pLDH (*parasite* Lactate dehydrogenase), Hrp II (histidine rich protein) and *parasite* aldolase:

(a) pLDH : This enzyme is located in the glycolytic pathway of the malaria parasite produced by both sexual and asexual stages of the parasite.

Though microscopy is considered the 'gold standard' method for diagnosis of malaria, it requires up to 60 minutes time from specimen collection to reporting of result. Detection of parasite specific lactate dehydrogenase (pLDH) are available in a lateral flow format that have high sensitivity and specificity in high endemic regions and are a useful adjunct to microscopy.

(b) Hrp II: Water soluble protein produced by asexual stage and young gametocytes of *P. falciparum*. Hrp II is generally more sensitive than pLDH but has a disadvantage that the antigen persists at detectable levels for more than 28 days after treatment.

(c) *Plasmodium* aldolase, an enzyme of the glycolytic pathway produced by all four species, has been recently developed.

ii. Dengue

Dengue enzyme immunoassay (EIA) NS1 antigen: Detection of the NS1 antigen is valuable as it allows for detection of infection prior to seroconversion and can be detected in serum from day 1 after onset of fever up to day 9. This antigen is a marker of early acute active infection and early diagnosis of dengue allows for earlier implementation of supportive therapy and monitoring. This reduces the risk of complications, such as dengue haemorrhagic fever, or dengue shock syndrome. After day 9, once NS1 antibodies are produced this antigen is no longer detected. Cross reactivity across the flavivirus group may occur.

iii. Aspergillus

Enzyme immunoassay (EIA) for galactomannan antigen assays: Galactomannan is a heteropolysaccharide present in the cell wall of most *Aspergillus* and *Penicillium* spp. and its production is proportional to the fungal load in tissues. Though strictly not a rapid assay, the decision to offer galactomannan testing depends on resources, institutional index of invasive aspergillosis and the hospital case mix. A high unremitting level of galactomannan despite antifungal therapy is associated with an unfavourable prognosis.

This test is best performed before the initiation of antifungal therapy as otherwise sensitivity is diminished. It is also advised that twice-weekly tests be performed to enhance sensitivity. The clinical specificity is around 90% but can be lower in infants due to ingestion of dietary galactomannans. False positive results may be seen in patients on piperacillin-tazobactam. The early latex agglutination tests were specific but not very sensitive (detection limit 25 ng/ml). Sandwich ELISA techniques have enhanced the sensitivity to 1ng/ml.

β-D-glucan: 1,3-β-D-glucan antigen is present in the cell wall of most fungi including *Pneumocystis jirovecii* (except *Cryptococcus* spp. and Zygomycetes). The EIA assay utilises serum for antigen detection. False positive results are seen in haemodialysis, cardiopulmonary bypass and patients on immunoglobulin products. Environmental contamination may compromise specificity. The cut off of 60 pg/ml is under consideration.

C. Urine

In patients with community-acquired pneumonia, antigen testing is useful in patients on treatment to establish the aetiological agent.

S. pneumoniae

A rapid immunochromatographic (ICT) assay for the detection of the *S. pneumoniae* antigen in urine of patients with pneumonia, and in the CSF of patients with meningitis is available. Urinary antigens of *Pneumococci* are detected and their sensitivity surpasses that of Gram stain. The clinical sensitivity and specificity is 86% and 94% respectively. Similarly for detection of *Legionella pneumophila* serogroup I antigen in urine, an *in vitro* rapid ICT assay is available that has a clinical sensitivity and specificity of >95%.

Histoplasma antigen detection in serum, urine and CSF is a useful indicator of systemic infection. ELISA tests can be performed on urine, CSF, serum and bronchoalveolar lavage fluid. The sensitivity is approximately 92% in urine specimens and 82% in serum specimens from patients with disseminated disease. The test has low sensitivity in self limited disease and chronic pulmonary histoplasmosis. This test is not readily available in India due to low prevalence of the disease.

D. Stool

i. Clostridium difficile antigen

Clostridium difficile associated diarrhoea (CDAD) is a cause of infectious diarrhoea mostly in hospitals. By enzyme immunoassays (EIA) toxin A and B can be detected with a specificity approaching 100%. Direct testing of stool sample extracts for toxin presence using a variety of immunoassay techniques has largely replaced the culture method. As strains which only produce either toxin A or B have been reported as pathogenic, methods which detect both are preferable.

ii. Helicobacter pylori

Antigen assays are available for detection with sensitivity of 96% and specificity of 95%. The *H. pylori* Sp HpSA antigen assay (Meridian diagnostics) detects faecal excretion of *H. pylori* antigens and is a useful non-invasive test for diagnosis and follow-up to ascertain complete eradication and outcome of successful therapy.

iii. Rotavirus and adenovirus

Rotavirus and adenovirus antigens can be demonstrated by latex agglutination tests. Ready to use homogenous ICT systems are also available incorporating monoclonal antibodies to specific viral antigens. The advantage is that if these assays flag positive, needless antibiotics can be avoided.

iv. Cryptosporidial antigen

Stool samples in human disease provide for high numbers of oocysts and relatively simple preparation and processing. Non-invasive, acid-fast staining techniques are used widely in clinical laboratories.

E. Throat/Nasopharyngeal Samples/Sputum

Bronchoalveolar lavage (BAL)

Viruses can be detected directly from patient specimens and by culture isolation/confirmation. Respiratory Viral Screen DFA Kits utilises fluorescein-labelled monoclonal antibodies to detect and identify in patient specimens, and to screen for the presence of influenza A, influenza B, adenovirus, and respiratory syncytial virus (RSV) in patient specimens and culture confirmation, and to screen for parainfluenza 1, 2 and 3 following amplification in culture.

Rapid antigen detection methods also include sophisticated methods as gas liquid chromatography (GLC) and high performance liquid chromatography (HPLC). It is used today in the rapid identification of mycobacteria.

MOLECULAR METHODS

Advances in molecular medicine have provided the research and diagnostic laboratory with tools that are revolutionising its function. Molecular methods of diagnosis offer the answer to microorganisms with growth characteristics that are slow (mycobacteria), difficult (viruses, chlamydia) or fastidious (mycoplasma). Another advantage is the ability to detect low pathogen numbers as in meningitis and can be employed in monitoring response to treatment (viral load assays for Hepatitis B, Hepatitis C and HIV).

Nucleic Acid Probes

Nucleic acid hybridisation is a powerful and widely used technique which exploits the ability of complementary sequence in single-stranded (ss) DNA or RNA to pair with each other to form a duplex. The single strand nucleic acid probes used for hybridisation should be complementary to the amplified sequence or the region of interest on the gene to be identified. *In situ* hybridization is used to detect and locate specific DNA/RNA sequence(s) in tissues or chromosomes by making use of radioactive or fluorescent labelled DNA/RNA probes complementary to the required sequence. However in paucibacillary states like tuberculous meningitis and pleural effusion the number of bacilli is too low to be picked-up by this technology. This technique is commercially available for the identification of *M. tuberculosis* complex, *M. avium*, *M. intracellulare*, *M. kansasii* and *M. gordonae*. Nucleic acid probes form a useful adjunct to automated cultures for confirmatory identification.

Nucleic Acid Amplification

These tests can be divided into three groups: (a) target amplification; (b) signal amplification; (c) probe amplification

(a) Target amplification

Polymerase chain reaction (PCR): PCR is an *in vitro* method for amplifying specific DNA sequence.

Real-time PCR: This technology offers rapid PCR with simultaneous amplicon detection. A fluorescent signal is used for real-time monitoring of PCR amplicon production.

Transcription mediated amplification (TMA): TMA uses a species sequence of ribosomal RNA (rRNA) as the target for reverse transcriptase. The advantage of this technology being that the dead cells have no transcription machinery hence only viable cells are picked-up and amplified.

Nucleic acid sequence based amplification (NASBA): NASBA is also like TMA as isothermal amplification wherein RNA is transcribed into cDNA and then RNA copies are synthesised using RNA polymerase.

(b) Signal amplification

This is an alternative to enzymatic duplication of target nucleic acid to increase the signal generated from a hybridised probe molecule. Commonly used technologies include branched DNA (bDNA) and hybrid capture assays.

(c) Probe amplification

The end product of the reaction is an amplified version of the original components used to detect the target and include the ligase chain reaction (LCR), Q-beta replicase and cycling probe technology. In LCR, a phenotypic change in the organism, such as virulence or drug resistance, can be detected.

Emerging technologies: DNA micro array technology, i.e. biochip, DNA chip, gene array, etc. have the potential to assess and visualise thousands of nucleic acids simultaneously. The solid platform contains genetic material arrayed in a pre-determined fashion. When the chip is probed with cDNA (from RNA of the clinical sample) hybridisation can be detected.

Thus, significant developments have occurred in the past two decades in the diagnostic arena. The large scale global use of antibiotics with consequent anti-microbial resistance in pathogens and opportunistic microorganisms stress the importance of rapid, accurate, comprehensive and up-to-date microbiology diagnostics. Physicians must continue to apply traditional microbiology with newer molecular testing to the understanding and application of clinical medicine.

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17.3 Syndromic Approach to Infectious Diseases

Rajeev Soman

Infectious diseases cut across the usual boundaries established by medical specialists and various combinations of organ involvement occur in particular infectious diseases. Combining clues from the history, physical examination and laboratory can help to establish the pattern of organ involvement. This pattern or syndrome determines the differential diagnosis. The principle of parsimony in medicine is to explain the observed signs and symptoms on the basis of a single unifying diagnosis. By combining several findings that are nonspecific when present alone, a diagnosis can be arrived at. However, this can be difficult when all the characteristics of a disease have not developed at that point in time.

FEVER AND RASH

Patients with fever and rash require immediate attention. The need for cardiorespiratory support, specific anti-microbial therapy or for isolation precautions has to be ascertained. Patients with viral and bacterial illnesses allow droplet or airborne spread of the pathogen. Hence, health care workers should use standard precautions including avoidance of intimate contact with secretions.

Causes of fever and rash can be life-threatening or trivial, and the extensive differential diagnosis tests the clinical acumen of the most experienced clinician (**Tables 1 and 2**). A thorough history is crucial; details of recent travel, exposure to an animal or human source of infection, or specific ingestion might furnish an important clue to help discover the cause. The patient with fever may receive an antibiotic or nonsteroidal anti-inflammatory drug (NSAID) and subsequently develop a rash, or the rash may be a late appearing manifestation or a unique interaction between the microbe and the antibiotic. The specifics of the rash on physical examination are also frequently helpful. It is often necessary to treat these patients empirically before the results of cultures and other investigations are available; thus, it is helpful to reduce the differential diagnosis to a few major possibilities.

It is most convenient to categorise patients with fever and rash according to the type of rash. Although there is some overlap, most of the causes of fever with rash can be grouped according to the specifics of the eruption. A petechial eruption is generally the most threatening, as several rapidly fatal diseases are associated with a petechial rash.

Common causes of acute febrile illness include upper and lower respiratory tract infections, gastroenteritis, genitourinary infections, soft tissue infections, bacteraemia, malaria, typhoid, meningitis or viral exanthems in children.

Chronic febrile states could result from infections like tuberculosis, infective endocarditis, abscesses (abdominal, liver, prostatic, renal or perinephric), cholanigitis, pyelonephritis, bacteraemia, brucellosis and toxoplasmosis. Non-infectious causes like collagen vascular diseases—systemic lupus erythematosus (SLE), rheumatoid arthritis, Still's diseases, temporal arteritis, polyarteritis nodosa (PAN) and Wegener's granulomatosis. Inflammatory bowel disease, sarcoidosis, myxoma, pulmonary thromboembolism and drug fevers are other non-infective causes.

Fever with headache, neck stiffness, mental changes and confusion: It suggests a meningo-encephalitic process and the differential diagnosis should be accordingly considered.

Fever with conjunctival suffusion and haemorrhages: Possible differential diagnosis include leptospirosis, infective endocarditis, trichinosis.

Fever with eye pain and sinus involvement. It could be attributed to orbital cellulitis (*Streptococci*, *Staphylococci*, *Moraxella*, Pseudomonas, anaerobes), Mucormycosis, *Aspergillus*, *cavernous* sinus thrombosis, Wegener's granulomatosis and lymphoma.

Table 1: Fever and Petechial Rash

Infectious (specific treatment available)	Infectious (specific treatment not available)	Non-infectious
Meningococcaemia	Enteroviral	Thrombocytopaenia
Gonococcaemia	Rubella	Allergy
Endocarditis	Dengue	Henoch-Schönlein purpura
Purpura fulminans due to Group A *Streptococci*, *Streptococcus pneumoniae*, *Meningococci*	Atypical measles	Hypersensitivity vasculitis
	EBV0	Acute rheumatic fever, SLE, hyperglobulinaemia, amyloidosis, scurvy
Acinetobacter	Yellow fever	
Rickettsiosis		
Trichinosis		
CMV, HBV		

Table 2: Different Types of Rashes Based on Their Infective Potential

Maculopapular Rash

Infectious (specific treatment available)	Infectious (specific treatment not available)	Non-infectious
Meningococcaemia	Enteroviral infection	Drugs
Mycoplasma	HHV-6	Erythema multiforme
Chlamydia	Parvovirus B19 (fifth disease)	Erythema marginatum
Typhoid		Dermatomyositis
Secondary syphilis	Rubeola	SLE
Leptospirosis	Rubella	JRA
Scarlet fever	Adenovirus	Sweet's syndrome
Lyme disease	EBV	Kawasaki disease
Rickettsiosis	HIV (primary)	Serum sickness
Trichinosis		
Toxoplasmosis		

Contd...

Contd...

Vesico-bullous Rash

Infectious (specific treatment available)	Infectious (specific treatment not available)	Non-infectious
Staphylococcaemia	Enteroviral infection	Toxic epidermal necrolysis (TEN)
Gonococcaemia	Parvovirus B19	Plant dermatitis
Rickettsial pox	HIV	Eczema vaccinatum
Varicella-Zoster		Erythema multiforme bullosum
Herpes simplex virus		Pyoderma gangrenosum
Mycoplasma		Pustular psoriasis
Folliculitis		
Staphylococcal infection		
Pseudomonas		
Candida		
Vibrio vulnificus		

Erythematous Rash

Infectious (specific treatment available)	Infectious (specific treatment not available)	Non-infectious
Streptococcal infection	Enteroviral infection	TEN
Staphylococcal infection		Kawasaki disease
Ehrlichiosis		Eczema
S. viridans		Psoriasis pityriasis rubra
C. haemolyticum		Lymphoma
Kawasaki disease		Sézary syndrome vasodilation

Annular Erythema

Infectious (specific treatment available)
Erythema multiforme, mycoplasma, HSV
Erythema marginatum of rheumatic fever
Erythema chronicum migrans of lyme disease

Urticarial Rash

Infectious (specific treatment available)	Infectious (specific treatment not available)	Non-infectious
Mycoplasma	Adenovirus	Drugs
Lyme disease	Enteroviral	Serum sickness
Trichinosis	EBV*	Vasculitis
Strongyloidosis	Hepatitis B	Malignancy
Schistosomiasis	HIV	Idiopathic
Echinococcal cyst leakage	HSV**	

Nodular Rash

Infectious (specific treatment available)	Non-infectious
Erythema nodosum leprosum (ENL)	Weber Christian disease
Candida, cryptococci, histoplasma, Sporotrichosis	Sweet's syndrome
TB, Nocardia, melioidosis, *Staphylococci, Yersinia*	

** EBV = Epstein-Barr virus; **HSV = Herpes simplex virus.*

Fever with neck pain: Possible causes could be tuberculous lymph node abscess or spinal epidural abscess, septic jugular phlebitis, thyroiditis, temporal arteritis and Kikuchi disease.

Fever with throat pain, trismus, dysphonia, stridor: This symptom complex requires immediate attention and early institution of therapy. Aetiologies could be tetanus, Ludwig's angina, botulism, retro-pharyngeal/tonsillar/peritonsillar abscess, epiglottitis and diphtheria.

Fever with acute breathlessness and cough suggests a pneumonitic process.

Fever with chest pain, murmur, rub, plop indicates pericarditis, myocarditis, endocarditis, atrial myxoma, etc.

Fever with diarrhoea or dysentery: In many cases, a specific diagnosis is neither available nor necessary to guide treatment. Information obtained from history, stool examination and the severity of dehydration can be helpful for planning treatment.

Non-inflammatory diarrhoea: The causative organisms could be enterotoxigenic *E. Coli (ETEC)*, *Vibrio*, *Bacillus cereus*, *Staphylococci*, *Salmonella*, *Clostridium perfringens*, Rotavirus, Norwalk virus, *Giardia*, *Cryptosporidium*.

Diarrhoea peristing for more than 15 days and weight loss: It could be caused by *Giardia*, *Cryptosporidium*, bacterial overgrowth syndrome, etc.

Diarrhoea could also be a manifestation of systemic infection viz. malaria, legionella, listeria, measles, viral hepatitis, toxic shock syndrome, etc.

Fever with abdominal pain and dysentery: It could be caused by *Shigella*, *Salmonella*, enteroinvasive *E. Coli (EIEC)*, *C. difficile*, *Campylobacter*, *Yersinia*, *Tuberculosis (TB)*, *E. histolytica*, *Strongyloides*.

Bloody diarrhoea, especially if without fecal leucocytes, suggests enterohemorrhagic (Shiga toxin-producing) *E. coli* 0157 or amoebiasis (where leucocytes are destroyed by the parasite).

Persistent abdominal pain and fever or an appendicitis-like syndrome suggests *Yersinia enterocolitica*.

An outbreak involving many persons suggests: *S. aureus*, *B. cereus*, (incubation period <6 hours), *C. perfringens*, *Vibrio*, *Salmonella*, *Campylobacter*, *Shigella* or EIEC, ETEC infection. Rotavirus, Norwalk virus.

Fever with jaundice: It is commonly encountered in biliary sepsis, systemic sepsis, *Salmonella*, *Leptospira*, malaria, yellow fever, disseminated herpes simplex virus (HSV), cytomegalovirus (CMV), granulomatous hepatitis, haemolytic crisis in G6PD deficiency, cirrhosis with septicaemia, *Yersinia*, pasturella infections.

Fever with flank pain, urinary symptoms or urinary abnormalities: It can be witnessed in pyelonephritis, perinephric abscess, renal TB, prostatitis or systemic conditions like infective endocarditis and leptospirosis. Non-infective conditions like renal cell carcinoma can also present in this way.

Fever with joint involvement: It is commonly seen with rheumatic fever, septic arthritis, TB, syphilis, *Brucella*, LGV, Lyme, Whipple's disease, acute RA, SLE, JRA, haemarthrosis and acute gout.

Fever with lymphadenopathy: The various causes of fever with regional lymphadenopathy are tabulated (**Table 3**).

Table 3: Causes of Fever with Lymphadenopathy

Cervical
- Throat infection with adenovirus, enterovirus, *Streptococcus, C. diphtheriae*
- Tuberculosis (TB)
- Rubella, HSV, CMV*, EBV,
- Toxoplasmosis
- Kikuchi disease

Axillary, epitrochlear
- TB, Brucella, tularemia, CSD*
- EBV
- Filaria
- Hodgkin's disease

Mediastinal, hilar, paratracheal
- TB
- EBV, CMV*
- Histoplasmosis, cryptococcosis, coccidioidomycosis
- *Pneumocystis carinii (jiroveci)* pneumonia (PCP)
- Sarcoidosis, lymphoma

Abdominal
- TB
- Lymphoma, carcinoma

Inguinal
- Chancroid, LGV, syphilis, gonorrhoea, granuloma inguinale, HSV
- Filariasis
- TB, plague, tularemia, CSD*
- Toxoplasmosis

Generalised
- TB
- HIV, viral hepatitis
- Syphilis, LGV*
- Rickettsia
- Histoplasmosis
- Lymphoma, leukaemia

**LGV = Lymphagranulama venereum; *CSD = Cat-scratch disease; *CMV = Cytamegalovirus.*

Soft Tissue Infections

An array of terms have been used leading to confusion. These are based on the pattern of tissue involved, the pathological process and the etiologic microorganisms (**Table 4**).

Undifferentiated fever syndromes (where there are no localising features): It could be seen with malaria, sepsis, bacteraemia and endovascular infections.

Fulminant infectious disease syndromes: Aggressive and often empiric treatment is needed in infections due to *P. falciparum*, *Meningococci*, *Streptococci*. Delay contributes to fatality even in intra-abdominal abscess (specially splenic), miliary tuberculosis and disseminated fungal infection.

Pattern of fever: Some points to keep in mind are:

- Intermittent fever in abscess, miliary tuberculosis, lymphoma.
- Sustained fever in typhoid, typhus.
- Fever at regular intervals in non-falciparum malaria, cyclic neutropaenia.
- Periodic fever in lymphoma (Pel-Ebstein), rat-bite fever, cholangitis, UTI.
- Sweats, chills, weight-loss are not diagnostic of any particular disease.
- Relative bradycardia in typhoid, *Legionella*, psittacosis, *Leptospira*, *Brucella*, neoplasm, factitious.

Table 4: Categories of Soft Tissue Infections and Common Organisms Involved

Name	Tissues Involve	Organisation
Meleney's synergistic gangrene	Post-surgical, slowly expanding indolent ulceration that involves superficial fascia	*S. aureus* + microaerophilic *Streptococci*
Clostridial cellulitis	Gas in tissues, but fascia and muscle spared	*Cl. perfringens*
Non-clostridial anaerobic cellulitis	Usually in diabetics, foul odour, gas in tissues	*Cl. perfringens*
Necrotising fasciitis	Progressive destruction of fascia and fat, may spare the skin initially, pain, fever, toxicity	
	Type 1 post-surgical, DM, PVD, breach in continuity of mucosa or skin, e.g. Ludwig's, Fournier's	aerobic + anaerobic
	Type 2 younger patient, after trauma, skin is portal of entry, no other co-morbid condition	Group A *Streptococci*
Myonecrosis	Bronze, black skin, haemorrhagic bullae, gas in tissues, haemolysis, severe systemic toxicity	Clostridia
	Post-traumatic, post surgical, colonic carcinoma, leukaemia, chemotherapy, radiotherapy	

FEVER IN THE IMMUNOCOMPROMISED HOST

Infections are difficult to evaluate as the usual symptoms, signs, and radiologic, serologic and haematologic alterations may not develop. The law of parsimony does not hold good and co-infections, and multiple, sequential infections occur. Non-infectious mimics can also occur. However, the current diagnostic tests are not rapid, sensitive or specific enough to identify or exclude a microbial cause. On the other hand, prompt treatment is needed.

Fever in the Elderly

The signs of infection are more general than focal and so need careful evaluation.

CONCLUSION

The syndromic approach to infectious diseases is helpful. Integrating the findings about the nature of the infection, the setting in which it has developed and the host characteristics can help to predict the likely organism and its susceptibility to anti-microbial agents. Those entities that have a specific treatment and will have grave consequences if left untreated, have to be given a greater emphasis and should not be missed.

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17.4 Anti-Microbial Therapy—An Overview

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INTRODUCTION

The anti-microbial agents kill or attenuate the growth of micro organisms. These include anti-bacterials, anti-fungals, anti-virals, anti-protozoal, and anthelmintic agents that may have been obtained either from a natural, semi-synthetic or a synthetic source. The modern day anti-microbial agents have made a giant leap forward from the infancy period of 1930s and 40s when sulphonamide and penicillin were the only 'miracle' anti-bacterials available. This medical achievement is shadowed in the present circumstances of 'irrational' use of anti-microbials resulting in development of antibiotic resistance and a dark possibility of non-availability of antibiotics to treat infections with multi-drug resistant organisms.

PHARMACOLOGY OF ANTI-MICROBIALS

Pharmacokinetics

The processes of absorption, distribution, metabolism, and excretion ultimately determine the drug concentration achieved in the blood and tissues after the drug administration. The knowledge of these pharmacokinetic parameters helps to ascertain the dosing as well as selection of a given anti-microbial for a particular infection. The selected drug has to be able to reach the site of infection to be effective, e.g. levofloxacin achieves high concentration in urine and is thus very effective in urinary tract infections.

The absorption of a drug and its movement across membranes is determined by its lipid solubility, size and the charge. In addition, the membrane transporters, like the P-glycoprotein, can selectively efflux some drugs out of the cell and reduce the drug absorption. The anti-microbials that are either poorly absorbed or are excreted in bile and are eliminated through gut may disturb the normal gastrointestinal flora, e.g. ampicillin causes diarrhoea more frequently than amoxicillin because it is incompletely absorbed.

The anti-microbial drug concentration in plasma and extracellular fluid (ECF) tends to be similar provided the capillaries allow free diffusion of the drug. The surface area to volume ratio of the ECF also determines the drug concentration achieved in the ECF. Thus, peritoneal fluid rapidly equilibrates with the plasma levels of the drug in contrast to a fluid-filled cyst. The capillaries supplying the central nervous system (CNS), posterior chamber of the eye and prostate are non-fenestrated. Thus, concentration of anti-bacterials in these specialised tissues cannot be predicted from the knowledge of plasma concentrations. However, when there is inflammation, as in the case of meningitis, the tight junctions in the cerebral capillaries open and allow marked penetration of even the polar drugs.

The access of anti-microbials is also physically difficult in avascular sites and in the case of cardiac vegetations as there is collection of fibrin. The penetration is also poor in the case of bacterial and fungal 'biofilm' on prosthetic devices like the artificial heart valves, artificial hip, long dwelling intravascular catheters.

The intracellular penetration of drug depends on lipid solubility. Lipid-soluble drugs like rifampicin, quinolones, and macrolides achieve high intracellular concentrations. The pH of the tissue also affects drug diffusion, e.g. prostatic tissue has a lower pH than plasma. Thus, weakly basic drugs like macrolides and quinolones accumulate in the prostatic fluid. Since, these drugs ionise at the acidic pH they fail to back diffuse into the prostatic capillaries.

It is important to have knowledge of drug kinetics in children, elderly, pregnancy, renal failure, and hepatic failure. These physiological and pathological states can profoundly affect selection of anti-microbials. For instance, aminoglycosides are eliminated by the kidneys and hence their dose should be reduced in renal failure.

Pharmacodynamics

It refers to the quantitative relationship between anti-microbial drug concentrations in serum and tissues, *in vitro* susceptibility and microbial response at the site of infection. Many factors affect the relationship between drug concentration and anti-microbial effect *in vitro*. The *in vitro* testing of bacterial susceptibility to various anti-microbials and determination of the minimal inhibitory concentration (MIC) provides good information regarding anti-microbial drug selection. MIC is a measure of the anti-microbial concentration required to inhibit the growth of the bacteria.

Anti-bacterials have relatively little bactericidal effect on bacteria in the stationary phase of growth as compared to the exponential phase of growth. The anti-microbial may be bactericidal, i.e. reduces bacterial numbers like aminoglycosides, cephalsporins, rifampin, or bacteristatic, i.e. inhibit bacterial growth like tetracyclines, erythromycin, chloramphenicol. The bactericidal agents act best on rapidly dividing bacteria. The bactericidal agents are generally preferred in an immunocompromised patient and in the treatment of serious infections like meningitis and endocarditis.

The bactericidal anti-microbials may exhibit either concentration-dependent killing (e.g. aminoglycosides and quinolones) or time-dependent killing (β-lactams and vancomycin). In the former, the rate and the extent of anti-bacterial activity is proportional to the anti-microbial concentration, whereas in the latter it is determined by the length of time the drug concentration was above the MIC. The drugs that have concentration-dependent killing also have post antibiotic effect (PAE). The PAE is the length of time for which the bacterial growth is inhibited after concentration of the anti-microbial falls below the MIC. There are several mechanisms by which the drug may exhibit PAE. Since, aminoglycosides have a

long PAE, once daily dosing produces good bactericidal effect. Also, this regimen is associated with less side-effects.

Any change in the milieu in which microbes grow will influence their growth rate and this will influence the action of anti-microbials. Important factors influencing the growth of microbes include temperature, pH, pO_2 and the type and concentration of nutrients.

In addition to their effect on microbial growths, pH and pO_2 can influence anti-microbials directly, e.g. macrolides are ineffective below the pH of 7 as in an abscess cavity. Oxygen is critical to the bactericidal effect of aminoglycosides because they enter bacteria via an oxygen-dependent transport system.

Anti-Microbial Therapy

The anti-microbials are used prophylactically either to prevent infection or to suppress the early infection from progressing further. Anti-microbials are generally administered to prevent wound infections following surgery, dental procedures, prosthetic implants and in immunocompromised patients to prevent emergence of opportunistic infections, e.g. in HIV-AIDS and neutropaenic patients or on immunosuppressive drugs. Post-exposure prophylaxis is used to prevent development of disease in a healthy person who has been exposed to specific microorganisms. The example of latter is use of rifampin to prevent meningococcal meningitis, anti-retrovirals for HIV exposure and oseltamivir for influenza.

The anti-microbial therapy is sometimes begun empirically without isolating the infecting organism. In this case, the appropriate specimens should be obtained for laboratory diagnosis of the pathogen prior to start of the anti-microbial therapy. The initial anti-microbial therapy is directed at the most likely pathogen involved and is later modified in accordance with the patient's clinical condition and the laboratory report. The selection of anti-microbials should also be guided by the various factors like the age, pregnancy, immune status, hepatic and renal function, malnutrition source of infection (e.g. hospital or community) and site of infection in the host (e.g. meningitis, endocarditis, urinary tract infection).

It is preferable to use single and specific anti-microbial agent with narrow spectrum of activity as it diminishes the alteration of normal flora and thus limits the overgrowth of resistant nosocomial organisms (e.g. *Candida albicans*, *Enterococci*, *Clostridium difficile*). However, combination anti-microbial therapy has to be used in certain conditions to prevent emergence of resistant mutants or to enhance the microbial killing, e.g. in tuberculosis, leprosy, malaria, pseudomonas infection, AIDS.

Anti-Microbial Drug Resistance

Microbial resistance is of two types: intrinsic and acquired. Intrinsic resistance means that the bacterial species is inherently resistant to the effect of the anti-bacterial drug, e.g. *Streptococci* and anaerobes, both lack the respiratory quinones required for energy-dependent uptake of aminoglycosides. Acquired resistance means that bacterial species has acquired a mechanism of resistance since the introduction of antibacterial drugs into clinical medicine, e.g. growing proportion of gonococci that produce penicillinase.

The production of drug inactivating enzymes (e.g. production of beta-lactamase by *Gonococci*) is a common mechanism of resistance in the case of aminoglycosides, β-lactams, macrolides and chloramphenicol. Another mechanism is alteration in the target site of the drug, e.g. resistance to quinolones. Alternatively, the organism can develop mechanisms to prevent access of drug to the target site, e.g. *Pseudomonas* has become resistant to aminoglycosides, β-lactams and quinolones because of reduced permeability of their outer membranes.

The acquisition of resistance can occur either by mutation or by transfer of genetic information between bacteria on plasmids. Plasmids can transfer complex mechanism of resistance including the active efflux pumps that render some bacteria resistant to tetracyclines.

The anti-microbial drugs are grouped based on their pharmacological structure but for a clinician it is worthwhile to remember them based on their clinical use as given in **Table 1**.

Table 1: Anti-Microbials Used Against Common Infections

Anti-bacterial and anti-tubercular drugs
Anti-leprotic drugs
Anti-fungal drugs
Anti-viral drugs
Anti-malarial drugs
Anti-amoebic and other anti-protozoal drugs
Anthelmintic drugs

The details of these anti-microbial, anti-protozoal, anti-fungal and anti-viral drugs are discussed in their respective chapters. Here the description is given of the commonly or routinely used antibiotics.

BETA-LACTAM ANTIBIOTICS

The antibiotics included in this group are penicillins, cephalosporins, carbapenems, and monobactams. These share a common structure as well as mechanism of action. These agents act by inhibiting the cell wall formation in the bacteria which predisposes the bacteria to lysis. The bacteria resistant to these drugs may produce β-lactamase enzyme to destroy the β-lactam antibiotics. The 'extended spectrum β-lactamases' (ESBLs) can target penicillins, cephalosporins and also carbapenems. These enzymes are usually produced by the plasmids.

Penicillins are combined with β-lactamase inhibitors like clavulanic acid, sulbactam, and tazobactam to enhance their activity by preventing their hydrolysis.

Penicillins

Penicillins are amongst the most effective and least toxic anti-microbials available. They are excreted by the kidney and hence dose should be adjusted in renal failure.

Acid-labile penicillins

They are hydrolysed by gastric acid and hence are ineffective orally. These agents are active against most Gram-positive and Gram-negative aerobic cocci that do not produce β-lactamase and against many anaerobes including anaerobic cocci, *Clostridium*, *Spirochaetes*, and *Actinomyces*.

Aqueous penicillin G (benzyl penicillin or crystalline penicillin) is given IM or IV in divided doses. Procaine penicillin G is given IM in the dose of 500,000 to 1,000,000 U/day. Benzathine penicillin G, administered IM provides detectable blood levels for 4 weeks. Its use is limited to prophylaxis of rheumatic fever and treatment of syphilis.

Hypersensitivity is the most common reaction producing fever, eosinophilia, serum sickness or anaphylaxis. Hence skin testing should be performed before penicillin is administered.

Extended spectrum penicillins

They provide coverage against many aerobic gram-negative bacilli and many anaerobes.

Ampicillin is active against many of the *Enterobacteriaceae* and against *H. influenzae* and *Neisseria* spp. It is hydrolysed by β-lactamase and is therefore inactive against most strains of *Staphylococci, Pseudomonas, Enterobacter* and *Klebsiella*.

Usual dose—0.5 g PO q 6 h for mild infections 1 to 2 g IM or IV q 4 to 6 h for moderate or severe infection.

Amoxicillin has identical spectrum as that of ampicillin. Gastrointestinal absorption is better than ampicillin, hence is associated with less diarrhoea than with ampicillin, but it is also less effective in the treatment of shigellosis.

Carboxy- and ureido-penicillins

These are also known as anti-pseudomonal penicillins. Both of these are susceptible to destruction by β-lactamases. Carboxypenicillins (carbenicillin, ticarcillin) are indicated for treatment of infection due to *Pseudomonas aeruginosa* and indole positive Proteus spp. However, not all isolates may be sensitive to carbenicillins. Carbenicillin indanyl sodium is an acid stable, orally active indanyl ester of carbenicillin. It is rapidly converted to carbenicillin by ester hydrolysis and achieves good concentration in urine. Thus, it is indicated in urinary tract infection with sensitive bacteria. The ureido-penicillins (azlocillin, mezlocillin, piperacillin) have superior activity against *Pseudomonas aeruginosa* and are also useful in the treatment of infections with *Klebsiella*. These agents are combined with a β-lactamase inhibitor and are indicated in serious gram-negative infections especially in neutropaenic and immunocompromised patients and in burns. The concurrent use of an aminoglycoside like gentamicin makes the combination synergistic.

The adverse effects include phlebitis and hypokalaemia. Prolongation of bleeding time due to inhibition of platelet aggregation has been reported with all anti-pseudomonal penicillins but is less severe with ureido-penicillins. Carbenicillin is inactive orally and is available as a sodium salt. Thus, the risk of volume overload should be remembered when using high doses of carbenicillin.

Beta-lactamase resistant or semisynthetic penicillins

They are produced by modification of 6-aminopenicillanic acid nucleus and are indicated for the treatment of infections caused by beta-lactamase producing *Staphylococci*. The drugs in this group are oxacillin, dicloxacillin and nafcillin. *Staphylococci* resistant to any one semisynthetic penicillin are also resistant to other semisynthetic penicillins and cephalosporins.

Cephalosporins

The cephalosporins are grouped into four generations. The Gram-positive activity decreases and Gram-negative activity of cephalosporin increases from 1st to 4th generation. These agents are not effective in enterococcal infections. Most of the cephalosporins are excreted by kidney; hence dose adjustment is required in renal failure.

Hypersensitivity reactions can occur and some penicillin allergic patients are also allergic to cephalosporins. Thrombophlebitis, sterile abscess (after IM injection), diarrhoea, coagulopathy (seen with cefamandole, cefoperazone, cefotetan and moxalactam) and disulfiram-like reaction (cefoperazone) are some other adverse effects associated with cephalosporins.

First-generation cephalosporins

The cephalosporins in this group are cephalothin, cephapirin, cefazolin, cefadroxil, cephalexin and cephaloridine.

The anti-bacterial spectrum includes beta-lactamase producing Gram-positive cocci (*Staphylococci, Pneumococci, Streptococci*) and Gram-negative bacilli (*E. coli, Proteus*) that cause most community-acquired infections including *Klebsiella* spp. However, *Enterobacter* spp. and *P. aeruginosa* are typically resistant as are methicillin-resistant *Staphylococci*. None of these achieve sufficient concentration in CSF. The dose for cephalexin is 250 to 500 mg PO q 6 h and for cefadroxil is 1 to 2 g/day PO in 1 to 2 doses.

These are well absorbed orally and are used primarily in treatment of community-acquired respiratory tract and urinary tract infections. However, they are not used for serious infections. Cefazolin is used in the dose of 0.5 to 2 g IM or IV q 8 h.

Second-generation cephalosporins

The drugs in this group are cefamandole, cefoxitin, cefuroxime, cefaclor.

These agents offer wider coverage against gram-negative bacilli than the first-generation cephalosporins. Their main use would appear to be in the Gram-negative infections, especially those caused by beta-lactamase producing organisms including *H. influenzae*. However, they are less active than first-generation cephalosporins against the Gram-positive cocci and are inactive against anaerobes and *Pseudomonas aeruginosa*.

Dose of cefuroxime is 0.75 to 1.5 g IV q 8 h, up to 3 g q 8 h in meningitis. Cefuroxime enters CSF in sufficient concentration. It is also used in surgical prophylaxis. The dose of cefuroxime axetil (well absorbed by mouth) is 250 to 500 mg PO q 12 h. It is effective for treatment of otitis media, urinary tract infections (UTI), respiratory tract infection, but equally effective and less expensive drugs are available for these conditions.

Cefaclor—dose is 250 to 500 mg PO q 8 h. Spectrum of activity is similar to cephalexin but with enhanced activity against *H. influenzae* including beta-lactamase producing strains.

Third-generation cephalosporins

These are cefotaxime, ceftizoxime, ceftriaxone, ceftazidime, cefoperazone, moxalactam, ceftibuten. In general these agents are more active against most Gram-negative bacilli and less active against Gram-positive cocci especially *S. aureus* than the first- and second-generation agents. The anti-pseudomonal

activity is variable but reaches its peak in ceftazidime and cefoperazone. None are effective against *Enterococci*. Most of them are capable of inducing β-lactamase production in Gram-negative bacilli. These drugs are the drugs of choice for Gram-negative bacillary meningitis. They may also be useful for treatment of other Gram-negative bacillary infections but widespread use may lead to the emergence of resistant flora and superinfection with *Enterococci*. These agents should not be used for surgical prophylaxis because of increased cost and decreased activity against Gram-positive organisms. The dosages are: cefotaxime 1 to 2 g IV q 6 to 12 h, ceftizoxime 0.5 to 2 g IV q 8 to 12 h and ceftriaxone 1 to 2 g IV q 12 to 24 h.

Ceftriaxone does not require dose adjustment in mild to moderate renal failure because of dual hepatic and renal excretion. Cefotaxime and Ceftizoxime dose should be reduced in renal failure.

Ceftazidime (1 to 2 g IV q 8 to 12 h) has the best activity against *P. aeruginosa* amongst all the cephalosporins. It is less active against Gram-positive organisms compared to other third-generation cephalosporins. Its activity against other Gram-negative rods is equivalent to Cefotaxime.

Cefoperazone (1 to 2 g IV q 8 to 12 h) is less active than other third-generation agents against most Gram-negative pathogens. Cefoperazone does not penetrate the CSF as well as other third generation cephalosporins and is not recommended for treatment of meningitis. Dose adjustment is not required in renal failure because of hepatic excretion. Dose reduction may be required in hepatic insufficiency.

Ceftibuten (400 to 800 mg PO) is recently introduced oral third-generation cephalosporin. The anti-bacterial spectrum is limited to *Streptococci, H. influenzae* and most *Enterobacteriaceae*.

Cefixime is the oral third-generation cephalosporin (200 mg bd), is active against *Enterobacteriaceae, Salmonella, Shigella, H. influenzae, S. pyogenes, S. pneumoniae, Moraxella, E. coli, Proteus* and *N. gonorrhoeae*, and is resistant to many beta-lactamases. It does not act on *S. aureus* and *Pseudomonas*.

Fourth-generation cephalosporins

Cefepime and cefpirome are resistant to hydrolysis by several β-lactamases and are more active against the Gram-negative bacteria.

Several cephalosporins, e.g. ceftibiprole with activity against MRSA are in development. These agents are able to inhibit pbp2a in *Staphylococci*.

Aztreonam

Aztreonam is a monobactam, a monocyclic beta-lactam antibiotic with activity exclusively against gram-negative bacilli, including most strains of *P. aeruginosa* and *Serratia. It is administered intravenously and eliminated by kidneys by tubular secretion.* Aztreonam may be administered to patients allergic to penicillin or cephalosporin (with the exception of ceftazidime) as it lacks cross-sensitivity with other β-lactam drugs.

Carbapenem

It includes imipenem, meropenem, doripenem and ertapenem. These drugs have a β-lactam structure but are neither penicillins nor cephalosporins. They also have a low susceptibility to β-lactamases. Imipenem is rapidly degraded by renal dehydropeptidase I. Thus, it is administered with cilastatin which inhibits this enzyme and increases the duration of action of imipenem. It is a broad spectrum antibiotic with activity against most Gram-positive cocci (except *Enterococcus faecium* and methicillin-resistant *Staphylococci*), Gram-negative bacilli (excluding *P. maltophilia* and some *P. cepacia*) and anaerobes. Some strains of *P. aeruginosa* have become resistant to imipenem. The indications for its use are infections with highly resistant organisms and as empirical therapy for serious mixed aerobic/anaerobic infections when the potential toxicity of alternative anti-microbial combination is unacceptable. In addition to hypersensitivity reactions and gastrointestinal upset like nausea and vomiting, imipenem in high doses may also cause seizures, especially in those patients who have a concomitant renal insufficiency.

The anti-microbial spectrum of meropenem is similar to that of imipenem. Since, meropenem is not inactivated by renal dehydropeptidase, it does not require to be combined with cilastatin. It is also less likely to cause seizures than imipenem. Ertapenem has a long plasma half-life and thus once-daily dosing is possible. It is also less active against *Pseudomonas* and *Acinetobacter* species.

MACROLIDES

These are bacteriostatic agents which act by inhibition of ribosomal protein synthesis. This group includes erythromycin, azithromycin, clarithromycin, roxithromycin and spiramycin.

Their anti-bacterial spectrum includes *Moraxella, H. influenzae, Legionella, Mycoplasma, Campylobacter* and *Chlamydia*. Erythromycin is also active against some Gram-positive cocci. Clarithromycin and azithromycin are effective in Mycobacterium avium complex (MAC) infection. The adverse effects are mainly due to gastrointestinal irritation. This is less with clarithromycin and azithromycin as compared to erythromycin. There is risk of hepatitis with erythromycin estolate, especially in adults. Drug interactions like rise in the plasma levels of digoxin, theophylline, anti-coagulants, and cisapride is seen with erythromycin.

The indication for use are respiratory tract infections, skin and soft tissue infections, sexually transmitted diseases and *H. pylori* infection. Azithromycin and clarithromycin are also useful in MAC infection.

TETRACYCLINES

These are bacteriostatic agents and act by inhibiting ribosomal protein synthesis. They are well absorbed orally. Doxycycline is well absorbed orally. It is preferred in renal insufficiency because it is excreted by liver. The clinical uses of tetracyclines are treatment of non-gonococcal urethritis, rocky-mountain spotted fever, chronic bronchitis, and acne. They may be used in infections caused by rickettsiae, *Chlamydia, Nocardia, Actinomyces, Plasmodium falciparum, Campylobacter jejuni*, and *H. pylori*. Resistance is widespread among *Staphylococci* and Gram-negative bacilli. Demeclocycline is used to treat syndrome of inappropriate antidiuretic hormone secretion (SIADH). The gastrointestinal upset and photosensitivity are common adverse effects. The use of outdated tetracyclines damage kidney and cause Fanconi's syndrome. They damage the growing bones and teeth and hence are contraindicated in pregnant, lactating mothers and children.

CHLORAMPHENICOL

It is a bacteriostatic agent and acts by reversibly inhibiting ribosomal protein synthesis.

It is active against wide variety of Gram-negative and Gram-positive organisms including anaerobes. It can be used orally or intravenously. Intramuscular absorption is not reliable. It penetrates into all body compartments including CSF. It is metabolised in liver, hence dose adjustment is required in hepatic insufficiency.

Its use is associated with idiosyncratic aplastic anaemia, dose-related reversible bone marrow suppression, gray baby syndrome in infants and peripheral neuritis.

Chloramphenicol was earlier the drug of choice for typhoid fever. It may be used for the treatment of meningococcal meningitis and *H. influenzae* infection and anaerobic infections, e.g. empyema, brain abscess and rickettsial infection.

FLUOROQUINOLONES

These inhibit DNA gyrase in a wide variety of bacteria and are well absorbed orally.

Older fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin) have a spectrum of activity that includes Gram-negative rods and some atypical bacteria. The newer fluoroquinolones (levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, gemifloxacin) have improved activity against *Staphylococci* and *Streptococci*. However, gatifloxacin has recently been withdrawn from the market due to toxicity. *In vitro* activity against anaerobes has been demonstrated with clinafloxacin and gatifloxacin. Ofloxacin, ciprofloxacin, levofloxacin and sparfloxacin are also effective against *Mycobacterium tuberculosis*. The older fluoroquinolones also have activity against atypical mycobacteria. Among the fluoroquinolones, ciprofloxacin has the best anti-pseudomonal activity. In the process of developing a fluoroquinolone with enhanced Gram-positive activity the newer quinolones have lost some activity against *P. aeruginosa*.

The adverse reactions seen with fluoroquinolones are hypotension, tachycardia, QTc interval prolongation, headache, dizziness, sleep disturbances, seizures, confusion, rash, photosensitivity, urticaria, transient elevation of transaminases, cholestatic jaundice, arthropathy, tendinitis, tendon rupture, azotaemia, crystalluria, haematuria, interstitial nephritis, and renal failure.

The newer fluoroquinolones with their expanded Gram-positive activity and excellent activity against the atypical pneumonia pathogens have quickly become the drugs of choice for community-acquired pneumonia.

Dose

Ciprofloxacin	–	250 to 750 mg q 12 h
Ofloxacin	–	200 to 400 mg q 12 h
Moxifloxacin	–	400 mg od
Norfloxacin	–	400 to 800 mg q 12 h
Gemifloxacin	–	320 mg od
Sparfloxacin	–	400 mg PO on day one and 200 mg PO q 24 h on subsequent days
Levofloxacin	–	500 mg orally q 24 h

VANCOMYCIN

It is a glycopeptide which acts by inhibition of cell wall synthesis.

It is bactericidal against only Gram-positive organisms. It is used to treat infections caused by methicillin-resistant *Staphylococci*, as a substitute to penicillins and cephalosporins when patient is allergic to either of them, and enterococcal endocarditis. Oral vancomycin is used to treat *C. difficile*-induced colitis.

Vancomycin may give rise to red-man syndrome characterised by tingling, flushing of face, neck and upper torso, sometimes with hypertension, deafness, and skin rash. *Nephrotoxicity* is not seen with currently available preparations (chromatographically purified).

Dose

500 mg to 1 gm IV q 12 h given in a drip form not faster than 1 gm/hr.

TEICOPLANIN

Teicoplanin is a glycopeptide with activity similar to vancomycin. The half-life is longer allowing once a day dosing. The combination of teicoplanin and rifampin is antagonistic. Teicoplanin resistance is well described in *Enterococci*. *S. aureus* isolates, resistant to teicoplanin have been described and they can be cross resistant to vancomycin.

Indications are similar to vancomycin and dose is 200 to 400 mg IV q 24 h.

Oritavancin, dalbavancin, telavancin are newer glycopeptides having activity against vancomycin-resistant *Enterococci* and being rapidly bactericidal. These are highly protein bound and have very long elimination half-life.

LIPOPEPTIDES

Daptomycin is a cyclic lipopeptide. It binds to the cell membrane and then forms complexes in a calcium-dependent manner which ultimately causes disruption of the cell membrane and cell lysis.

It is used in the treatment of complicated skin and skin structure infections involving *Staphylococci*, *Enterococci* and some *Streptococci*. It can be used in combination when infection with a gram-negative or anaerobic organism is suspected.

The adverse effect of daptomycin is myositis and myopathy leading to elevation of CPK level.

Dose

A dose of 4 mg/kg over a period of 30 mins. By IV infusion in 0.9% sodium chloride solution once a day for 7 to 14 days. If creatinine clearance is less than 30 ml/min, then give once in 48 hrs.

STREPTOGRAMINS

Quinupristin/dalfopristin is a combination of two naturally occurring compounds isolated from *Streptomyces pristinaespiralis*. They act by inhibiting protein synthesis. The anti-bacterial spectrum of activity is similar to vancomycin. It may cause venous irritation, arthralgias, myalgias and conjugated hyperbilirubinaemia. It is used for the treatment of vancomycin-resistant *E. faecium* and treatment of glycopeptide intermediate-resistant *S. aureus* (GISA). Dose (quinupristin/dalfopristin)

(30 to 70 mix) 7.5 mg/kg 8 h by IV route. No dose adjustment required for renal or hepatic insufficiency.

OXAZOLIDINONES

Linezolid, eperezolid are synthetic anti-microbials and act by inhibiting protein synthesis. Anti-microbial spectrum is similar to vancomycin. These compounds also have activity against gram-negative anaerobes and mycobacteria. Adverse reactions are skin rash and increase in transaminases.

Dose

The recommended dose is 600 mg twice daily. Indications are similar to quinupristin/dalfopristin in treatment of vancomycin-resistant *Enterococci* (VRE) and GISA.

AMINOGLYCOSIDES

They bind to the bacterial ribosomes and inhibit protein synthesis. Gentamicin, tobramycin, amikacin, netilmicin, kanamycin and streptomycin are the currently used aminoglycosides.

The aminoglycosides are active against Gram-negative organisms including *E. coli, Klebsiella, Aerobacter, Salmonella, Shigella, Vibrio, M. tuberculosis,* atypical mycobacteria, *Neisseria* and *Brucella*. They are also effective against *Staphylococci*.

Nephrotoxicity is usually reversible but acute renal failure with azotaemia may occur. Ototoxicity occurs with prolonged use (more than 14 days) of aminoglycosides and with concurrent use of other ototoxic agent. Neuromuscular blockade is a rare complication.

They are used in urinary tract infections, along with penicillin in treatment of streptococcal endocarditis, bacteraemia in immunocompromised patients and other serious infections caused by gram-negative bacilli (especially *Pseudomonas*). Streptomycin is used in plague, tularaemia, brucellosis, and tuberculosis.

Dose

Gentamicin and tobramycin (3 to 5 mg/kg/day), netilmicin (4 to 6 mg/kg/day) and amikacin and kanamycin (15 mg/kg/day).

It is advisable to give aminoglycosides as single dose because the efficacy is related to peak-levels and side-effects are also less with single dose.

SULPHONAMIDES AND TRIMETHOPRIM

The fixed dose combination of trimethoprim and sulphamethoxazole in the ratio of 1:5 is bactericidal. The use of these two drugs causes sequential block in the folinic acid synthesis by the bacteria. In *in vitro* studies it is highly effective against *S. aureus, Streptococci, C. diphtheriae, E. coli, Salmonella, Shigella, H. influenzae, K. pneumoniae, Proteus* and *V. cholerae*. It is somewhat less effective against *N. gonorrhoeae, N. meningitidis, C. welchii* and *B. pertusis*. It is useful in urinary tract infection due to *E. coli* and *Proteus, Pneumocystis carinii* infection and prophylaxis in HIV patients, acute and chronic bronchitis, chancroid, gonorrhoea, shigellosis, typhoid fever. The adverse reactions include glossitis, stomatitis, anaemia, leucopaenia, thrombocytopaenia and megaloblastic marrow changes.

METRONIDAZOLE

Metronidazole is active against most Gram-negative anaerobic bacteria including *B. fragilis* and many *Clostridium* spp. Many anaerobic *Streptococci* however are resistant to this agent. Metronidazole is also active against several protozoa (*Trichomonas vaginalis, Giardia lamblia, Entamoeba histolytica* and *Dracunculus medinensis*).

The side-effects with metronidazole are nausea, dry mouth, metallic taste, disulfiram-like effect, peripheral neuropathy, encephalopathy, ataxia, seizures and teratogenicity.

It is useful in anaerobic infections like pelvic inflammatory disease, lung abscess, intra-abdominal infection, pseudomembranous colitis, amoebiasis, and giardiasis.

Dose

400 to 800 mg q 8 h.

CLINDAMYCIN

It is semisynthetic derivative of lincomycin. It is bacteriostatic at low concentration and bactericidal at high concentration. It is well absorbed orally. It probably acts by interfering with protein synthesis.

It inhibits growth of many gram-positive organisms especially *Staphylococci* (including those producing penicillinase), pneumococci, certain *Streptococci* and *C. diphtheriae, B. anthracis* is moderately sensitive.

The adverse reactions observed are nausea, vomiting, abdominal pain, diarrhoea. Rarely may it cause pseudomembranous colitis and monilial superinfection.

It is useful in acute and chronic osteomyelitis, anaerobic infections like empyema, brain abscess and in staphylococcal, pneumococcal and streptococcal infections not responding to penicillin or erythromycin.

Dose

150 to 450 mg four times a day.

ANTI-MYCOBACTERIAL DRUGS

These include the first line anti-tubercular agents like isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin; the second line agents like thiacetazone, para-aminosalicylic acid, ethionamide, cycloserine, kanamycin, amikacin, capreomycin, ciprofloxacin, ofloxacin, moxifloxacin. The drugs like clarithromycin, azithromycin, and rifabutin are more active against the nontubercular mycobacteria. The treatment of tuberculosis is complicated by the development of multi-drug resistant (MDR) and extremely drug resistant (XDR) strains.

ANTI-LEPROTIC DRUGS

These include dapsone, clofazimine, rifampin, ethionamide, ofloxacin, minocycline, and clarithromycin. The multi-drug therapy is preferred for all cases of leprosy.

ANTI-VIRAL AGENTS

These include anti-herpes agents like the idoxuridine, acyclovir, valacyclovir, famciclovir, foscarnet, trifluridine, vidarabine; anti-influenza agents like the amantadine, rimantadine, oseltamivir; and others like lamivudine for hepatitis B.

The anti-retroviral agents include the nucleoside reverse transcriptase inhibitors (NRTIs) like zidovudine, didanosine, lamivudine, stavudine; non-nucleoside reverse transcriptase inhibitors (NNRTIs) like nevirapine, efavirenz; protease

inhibitors like saquinavir, indinavir, ritonavir, nelfinavir; integrase inhibitors like raltegravir; and fusion inhibitor like enfuvirtide.

ANTI-FUNGALS

The systemic mycoses are usually treated with amphotericin B, flucytosine, ketoconazole, fluconazole, itraconazole, voriconazole and echinocandins like the caspofungin, amidulafungin, and micafungin.The superficial fungal infections may be treated with oral drugs like griseofulvin and terbinafine and also topically with nystatin, miconazole, clotrimazole, and topical terbinafine. The systemic fungal infections may be difficult to treat especially in the immunocompromised or neutropaenic patients.

CONCLUSIONS

In conclusion one has to remember to use antibiotics with a definite indication. Use antibiotics in adequate dosage and for adequate length of time so that it eradicates infection as well as precludes the occurrence of drug resistance. It is important to remember the excretion of drugs so that the dose is properly adjusted based on the clinical condition like age, i.e. childhood and old age, but associated disorders like renal impairment, cardiovascular disorders, and also always consider the possibility of drug allergy so that the anti-microbials serve purpose effectively well and to the benefit of the patient simultaneously avoiding drug resistance.

RECOMMENDED READINGS

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17.5 Infections in the Immunocompromised Host

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INTRODUCTION

The dysfunction of immune system in the body can occur due to infections, use of specific drugs and certain disease states like malignancy, diabetes, etc. Such situations are being increasingly encountered because of the spread of the HIV/AIDS epidemic, success with organ transplants and also with immunosuppressive and cancer chemotherapy medications. Infections *per se* contribute to significant morbidity and mortality; however, infections in the immunocompromised states can prove to be devastating. Three decades back, the commonest infecting organisms were bacteria (76.1%) followed by serious opportunistic viral and fungal infections (10.7%) and oppurtunistic pneumonias were the leading cause of death. Despite advent of efficacious antibiotics and improvement in health care standards, this spectrum has only changed towards a slightly greater preponderance of viral and fungal infections. Indian data is however, lacking.

This chapter discusses the basic considerations of infections in the immunocompromised patients (ICP) only as far as they differ from that in immunocompetent individuals. ICP are more susceptible to infection and disease, have a greater tendency to develop persistent infection and multiple infections, and may exhibit unusual clinical manifestations.

AETIOPATHOGENESIS

The failure of immune system may be witnessed in malnutrition (<75% of ideal body weight), alcoholism, extremes of ages, uncontrolled diabetes, uraemia, HIV infection, leukaemias/lymphomas, congenital/primary immunodeficiency disorders, hypogammaglobulinaemia, malignancies, and use of corticosteroids, monoclonal antibodies, immunosuppressive or cancer chemotherapeutic agents, post-splenectomy and post-irradiation states. Viral infections like Epstein-Barr virus, measles and varicella can also be associated with transient immunosuppression. Corticosteroids exert multiple effects on both immune response and the inflammatory response by decreasing concentration and activity of lymphocytes, monocytes and basophils in vascular circulation and redistribution to lymphoid compartment. Absolute neutrophil count, however, increases as these cells become restricted to vascular compartment and are unable to migrate to areas of inflammation. Corticosteroids also inhibit interleukins, especially IL-1 and IL-2 (IL-1 stimulates production of prostaglandins and IL-2 promotes further T-cell proliferation). Cyclosporin and tacrolimus are calcineurin inhibitors which are commonly used as immunosuppressives and interfere with cytokine transcription in response to T-cell receptor signalling. Cyclosporine decreases IL-2, while tacrolimus decreases IL-1, IL-2, interferon-gamma, IL-2 receptors and T-cell proliferation. RNA and DNA synthesis inhibitors like azathioprine and mycophenolate mofetil block proliferation of T and B cells during clonal expansion and cause leucopaenia.

The common infections associated with specific defects in immunity are given in **Table 1**. Candidiasis remains the commonest fungal infection in ICPs but *Pneumocystis jirovecii*, aspergillosis, zygomycosis, cryptococcosis, histoplasmosis, and coccidioidomycosis increasingly pose a major problem. Less common fungal pathogens include—*Sporothrix schenckii*, *Penicillium marneffei*, *Paracoccidioides brasiliensis*, *Fusarium* spp., *Trichosporon beigelii*, *Pseudallescheria boydii*.

Table 1: Diseases Resulting from Immune Deficiency or Component Defect of the Immune System

Component (deficiency/defect)	Disease	Pathogens
Phagocytes (Abnormal NADPH Oxidase Degranulation defect)	Chronic granulomatous disease	*Staphylococcus aureus*, *Pseudomonas* spp., *Escherichia coli*, *Aspergillus* spp.
Complement (C1, C2, C4 deficiency C5-9)	Deficiency of classical pathway	Encapsulated bacteria: *Streptococcus pneumoniae* Severe Neisserial infections, meningococcal meningitis
Cytokines (IL-12 deficiency)	Mutations in *B1* chain *or* IL receptors	*Salmonella* spp. *Mycobacteria* spp. Recurrent opportunistic infection with bacteria and viruses (i.e. atypical mycobacteria)
MHC I/II (Bare lymphocyte syndrome)	Defective CMI	Opportunistic infections (e.g. *Candida, Cryptococcus neoformans*)
T cells (DiGeorge syndrome, AIDS, hyper IgM syndrome)	Defective CMI: Thymic failure, CD4 deficiency	Intracellular pathogens (e.g. Mycobacteria) *Pneumocystis carinii* Invasive fungal infections (e.g. *Candida albicans*), Pyogenic bacterial infection, *Cryptosporidium parvum*
B cells (X linked agammaglo-bulinaemia)	B cell dysfunction or low antibody production	*Haemophilus influenzae* *Streptococcus pneumoniae*
T/B cells (Adenosine deaminase deficiency)	Complete dysfunction of humoral and cellular immune respone	Recurrent infections with opportunistic pathogens (e.g. *Pneumocystis jirovecii*, Mycobacteria, Herpes, pyogenic bacteria
Splenectomy patients	Loss of phagocytic activity	*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*
Desferrioxamine therapy	Acts as sider-ophore (act like growth hormone)	*Rhizopus oryzae*

ICP infected with *Mycobacterium tuberculosis* also have increased risk of tuberculosis reactivation. These patients are also at increased risk of serious influenza-associated complications.

CLINICAL FEATURES

Fever along with system-specific signs and symptoms may or may not be observed in ICP and the signs of inflammation or infection may be absent. The infectious complications are usually insidious in onset as the inflammatory response is muted. Besides, there are greater chances that the patients develop bacteraemia, fungaemia and multi-organ dysfunction rather than system-specific signs or symptoms. This is attributable to the inability of the body's defences to localise the infection. Hypothermia, tachypnoea, tachycardia, depressed sensorium, hypotension, and evidence of vital organ dysfunction may be present. Interestingly, clinical presentations caused by the same aetiological agent can vary depending upon the underlying immunosuppressive state, viz. CMV causes retinitis in HIV and pneumonitis in transplant recipients while BK virus causes nephropathy in renal transplantation and haemorrhagic cystitis in haematopoietic stem cell transplants.

INVESTIGATIONS

A careful clinical history followed by thorough examination is the key to identification of the cause of infection. It is important to identify the portal of entry as these are the common sites of defence breach leading to infection and gives a clue to the aetiological agent. Therefore, cultures from all possible sites are important (blood, urine, sputum, stool, catheter sites, catheter tips, nail scrapings, skin lesions), since empirical antibiotics need to be started without any delay, as infections in an ICP can be rapidly fatal. Bacterial, fungal and anaerobic cultures may be warranted. Complete blood counts are essential to see for the leucocyte response to infections and to identify or monitor neutropaenic states. Blood biochemistry and oxygen saturation help identify vital organ dysfunctions. Staining of aspiration or biopsy of skin lesions may be helpful to identify meningococcal/gonococcal or fungal aetiologies. Sputum examination or tracheal aspirate/bronchoalveolar lavage fluid examination may be helpful in suspected cases of pneumonia. Imaging studies and echocardiography need to be individualised as per situation. Cerebrospinal fluid (CSF) examination is helpful in suspected meningitis. Specific antigen detection kits or polymerase chain reaction (PCR) may be utilised for CMV, *Aspergillus*, herpes and mycobacterial diseases. In the ICP, although there is a greater risk of tuberculosis reactivation, tuberculin skin testing is falsely negative and newer assays (T-cell interferon-gamma release and QuantiFERON-TB Gold) can improve diagnostic yield.

The infectious causes of fever can be confirmed microbiologically in only 30% to 50% patients. The various pathogenic organisms commonly infecting the neutropenic cancer patients are enumerated in **Table 2**. Even though the organism may not be isolated in up to two-third of patients but most of them respond to empirical antibiotic therapy suggesting the cause to be infectious only.

MANAGEMENT

Empirical antibiotic and anti-fungal therapy needs to be initiated at the earliest in the ICP depending upon the likely pathogen, pending culture reports. In neutropaenic patients (post-chemotherapy), broad-spectrum antibiotics covering both gram-positive and gram-negative organisms need to be administered while anti-fungal agent is required if the immunosuppression is prolonged (**Table 3**). Granulocyte-colony-stimulating factor may be needed for persistent neutropaenia. A high index of suspicion for fungal and anaerobic infections is required especially in patients with sepsis, uncontrolled diabetes, on cancer chemotherapy, having prolonged intravenous catheters or receiving broad spectrum antibiotics. Management of specific infections and underlying immunocompromised states has been dealt in respective chapters.

Table 2: Common Infections in Neutropaenic Cancer Patients

Gram-positive aerobic: Coagulase negative *Staphylococci*, *Streptococcus viridans*, *Staphylococcus aureus*, other *Streptococci*, *Enterococcus* spp., *Corynebacterium* spp., *Bacillus* spp., *Listeria monocytogenes*

Gram-negative aerobic: *Escherichia coli*, *Klebsiella* spp. *Pseudomonas* spp. Other Enterobacteriaceae (*Proteus*, *Enterobacter*, *Serratia*, *Citrobacter* spp.) *Legionella*

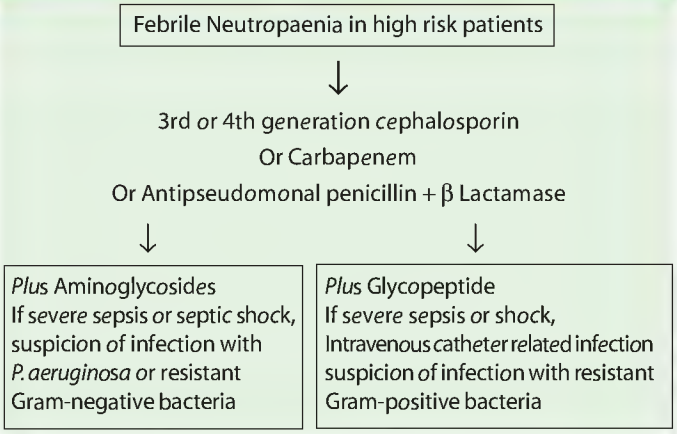
Anaerobic: *Bacteroides* spp., *Clostridium* spp., *Fusobacterium* spp., *Propionibacterium* spp.

Fungal: *Candida* spp., *Aspergillus* spp., Others (*Fusarium*, *Pseudallescheria boydii*, *Scedosporium*, *Rhizopus*, *Mucor*)

Viral: Herpes simplex virus, varicella-zoster virus, respiratory viruses (influenzae, RSV)

Parasitic infection: *Strongyloides stercoralis*, *Leishmania*, etc.

Table 3: Empirical Antibiotic Therapy for High Risk Febrile Neutropaenia Patients



PREVENTION

Apart from the routine measures of sticking to aseptic precautions, meticulous care of indwelling devices and intravascular catheters, personal hygiene practices; primary or secondary prophylactic antibiotic use should be employed. Primary prophylaxis is indicated in patients at high risk of infection, e.g. in severely neutropaenic patients (absolute neutrophil count <500/mm^3). Secondary prophylaxis is considered following the treatment of an infectious episode during the subsequent phase of treatment, e.g. use of co-trimoxazole in HIV patients with CD4 counts <250/mm^3. Vaccination in the ICP is also recommended, viz. vaccination for hepatitis B in uraemia and influenza vaccination in HIV-infected, solid-organ and haematopoietic stem-cell transplant recipients, haemodialysis patients; and is discussed in appropriate sections of the book.

RECOMMENDED READING

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17.6 Hospital Acquired Infections/ Nosocomial Infections

A Shobhana

DEFINITION

The term nosocomial infection has been replaced by 'hospital acquired infection' (HAI) and has been expanded to 'health care associated infections' (HCAI), which includes infections acquired in institutions other than acute-care facilities (e.g. nursing homes) during hospitalisation but not identified until after discharge and through outpatient care such as day surgery, dialysis, or those on home parenteral therapy. It is defined as a disease condition resulting from the presence of an infectious agent or its toxin which was not present or incubating at the time of admission to hospital. Usually the infection becomes evident 48 hours or more after admission.

The common sites of infection are respiratory tract, blood stream, urinary tract, and surgical site.

The Burden

The worldwide nosocomial infection rate ranges from 6% to 15%. In Asia it ranges from 4% to 48% of which 45% to 65% are lower respiratory tract infections. Highest prevalence occurs in intensive care units (ICUs), in acute surgical and orthopaedic wards. In a surveillance conducted in 12 ICUs in India, the rate of HCAI was 4.9% and 9.6 per 1000 ICU days. The commonest organisms were *Pseudomonas* spp, *Acinetobacter* spp, *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *Enterobacteriaceae*, *Candida* spp, *Enterococci and Stenotrophomonas.*

Common Sources of Infection

Causative organisms may be present on the skin, nose, mouth, gastrointestinal tract, or vagina of the patient. They may be acquired from external sources like health care personnel, visitors, hospital equipments, medical devices, or the health care environment. Most infections are of bacterial aetiology, though fungal and viral infections may occur in immunosuppressed patients and those already on broad-spectrum antibiotics.

Modes of Transmission

The mode of transmission usually is either cross-infection via unclean hands of hospital personnel, auto-inoculation (e.g. aspiration), droplet infection or through contaminated materials (e.g. contaminated intravenous fluids).

HOSPITAL ACQUIRED PNEUMONIA (HAP)

Definitions

Pneumonia occurring 48 hours or more after admission and which was not incubating at the time of admission is HAP. Intubation and mechanical ventilation (MV) is associated with 20-fold increase in the risk of developing pneumonia. Ventilator associated pneumonia (VAP) is pneumonia in a person who has a device to assist respiration through an endotracheal tube or tracheostomy tube for a period of at least 48 hours before the onset of infection. VAP represents 80% of episodes of HAP. Mortality in VAP due to *Pseudomonas* and *Staphylococcus* is very high. Health care associated pneumonia (HCAP) is defined as pneumonia in any patient with at least one of the following risk factors:

1. Hospitalisation in an acute care hospital for ≥2 days within the last 90 days.
2. Residence in a nursing home or long-term care facility within the last 90 days.
3. Received outpatient intravenous antibiotics or chemotherapy or home wound care in last 30 days.
4. Attended a hospital clinic or haemodialysis clinic in the last 30 days.
5. Has a family member with known multi-drug resistant pathogens.

Causative Organisms

HCAP may be early onset, that is within 4 days of hospitalisation or late onset, beyond 4 days. The organisms causing early infections are *Moraxella catarrhalis, Haemophilus influenzae* and *S. pneumoniae;* whereas Gram-negative bacteria or *S. aureus* are associated with the late HCAP. Viruses may cause early and late infections while yeasts, fungi, *Legionella and Pneumocystis carinii* are typically late pathogens. Late onset pathogens often are multi-drug resistant (MDR). Over 80% of nosocomial pneumonias are caused by Gram-negative bacteria. Now *Acinetobacter* is the organism which is of great concern.

In India, 38% of HAP are caused by *Acinetobacter, Pseudomonas* spp (20%), *Klebsiella pneumoniae* (23%) and MRSA (5%). Forty-eight percent of VAP and 2.3% HAP are caused by MDR organisms (**Table 1**), while 7.3% are polymicrobial. In most ICUs, MRSA although present is not as big a problem as in the western world. (**Table 2**) outlines the various risk factors for HAP and VAP

Table 1: Risk Factors for Multidrug Resistant (MDR) Infections

Regular dialysis
Immunosuppression
Heart disease
Renal failure
Hepatic failure
High incidence of antibiotic resistance in the community
Presence of a family member with MDR organism

Table 2: Risk Factors for HAP and VAP

Males
Elderly age
Pre-existing diseases—pulmonary, diabetes, dialysis
Immunosuppression
Presence of intubation
Enteral feeding
Mechanical ventilation
Supine position
APACHE II score >15
Previous use of antibiotic for >2 weeks
Multi-organ failure
Reintubation due to failed weaning
Use of paralytics, sedative
Length of ICU stay

Diagnosis of HCAP or VAP is made in the presence of progressive radiographic infiltrates or pleural effusion and at least 2 of the 4 clinical signs of infection—fever >38°C, purulent secretions, leucocytosis or leucopaenia, decreasing oxygenation.

Management

1. Identification of pulmonary infection is the first step.
2. Appropriate cultures are required. Semi-quantitative or quantitative cultures of lower respiratory tract should be performed if HAP or VAP is suspected. Endotracheal aspirates, bronchoalveolar lavage (BAL), protected specimen brush (PSB) are required to isolate organisms. A quantitative endotracheal culture or non-bronchoscopic BAL is more relevant in the Indian set-up. Recent start or change of antibiotics in the preceding 24 to 72 hours may give rise to false negative reports.
3. A broad-spectrum antibiotic should be started at the earliest in all clinically unstable patients regardless of culture reports as delay is associated with increased mortality. Choice of empirical antibiotic is guided by the local data on risk factors, local prevalence of organisms, and resistance patterns. Broad spectrum antibiotics covering Gram-negative and Gram-positive organisms are usually started. A re-evaluation is done at 48 to 72 hours. Once culture-sensitivity reports are available de-escalation may be done.

A clinical pulmonary infection score (CPIS), based on temperature, total leucocyte count, chest radiographic findings, respiratory secretions, endotracheal aspirate cultures and oxygenation status has been developed to predict presence of VAP. If CPIS is less than, 6 both at baseline and at 72 hours, most clinicians would safely allow stopping antibiotics.

BLOOD STREAM INFECTION (BSI)

Epidemiology

Primary blood stream infections are identified by growth of pathogenic bacteria or fungi (that are not related to another site of infection) from one or more blood cultures. Skin contaminants like coagulase negative *Staphylococcus* or *Diphtheroids* are considered causative of BSI, if more than one blood culture is positive along with presence of systemic signs and symptoms of infection like fever, chills, and hypotension. An alternative focus of infection should be absent.

Catheter associated blood stream infections (CABSI) is said to be present if fever occurs during and up to 48 hours after removal of central venous catheter or arterial catheter but diagnosis does not require growth of same organism from the blood and the catheter.

Catheter related blood stream infection (CRBSI)

Diagnosis of CRBSI requires growth of same organism quantitative or semiquantitative from the blood as well as the catheter.

CRBSI is seen in 5% patients with indwelling vascular uncoated catheter and almost 2 to 5 infections per 1000 catheter days. All lines arterial or central venous are risky. The incidence of CRBSI increases with the duration of catheterisation, number of ports, and number of manipulations. Mortality may be almost 8% in *S. aureus* bacteraemia. Fever, hypotension, purulence at exit site, blocked lumen, all may herald CRBSI. BSI due to short peripheral intravenous catheters is very low but phlebitis is very common.

In a report from north India, incidence of CRBSI was 19.4%, organisms causing nosocomial BSIs were *Pseudomonas* (33.3% episodes), and *Acinetobacter, Escherichia coli, Candida spp, coagulase-negative Staphylococci* and *S. aureus*.

Diagnosis

BSI are identified by the growth of pathogenic bacteria or fungi (that are not related to another site of infection) from one or more blood cultures drawn from peripheral veins. Atleast two sets of blood cultures must be drawn in each instance. Three sets may be needed to establish continuous bacteraemia.

Different methods of diagnosing CRBSI have been described. Some require removal of the catheter (qualitative, semi-quantitative and quantitative cultures) while some can be done while retaining the catheter in place (qualitative or quantitative blood cultures from catheter). The best method is to obtain paired blood cultures, one from the central catheter and another from the peripheral venous blood and the differential time to culture positivity is noted. If central line sample shows positivity 2 hours earlier than the peripheral culture, it is a CRBSI.

Management

Catheter should be removed if CRBSI is suspected, if there is purulence at the insertion site or the patient is haemodynamically unstable, has organ dysfunction, fungal sepsis or MDR organisms and once the diagnosis is confirmed. Routine replacement over a guidewire is not recommended. Empirical antibiotics should be started in seriously ill patients according to the local microbiological flora and this may require a change according to the culture sensitivity reports. Duration of antibiotics is tailored according to the causative organism and by the presence or absence of any complication. Fungal sepsis should be considered in patients at risk like in those with prior antibiotic exposure, parenteral nutrition, abdominal surgeries, and immunocompromised host.

SURGICAL SITE INFECTION (SSI)

Epidemiology

In India, incidence of post-operative infections in hospitals varies from 10% to 25%. Wound infection affects nearly 20% of post-operative cases **Table 3**. These occur due to close contact of medical and paramedical staff with the patient at various stages of treatment. In a north Indian hospital, incidence of wound infection in post-operative elective surgeries ranged from 11% to 70% due to *S. aureus* and 30% due to *E. coli*.

Table 3: Factors Determining Nosocomial Wound Infection

Factors related to surgical procedures: Pre-operative shaving-1 day before operation, type of surgery, anaesthesia, wound drains, tissue damage, blood loss
Host factors: Age, immunity, diabetes, nutrition, obesity, antibiotic exposures

Diagnosis and Management

Signs of wound infection are local redness, swelling, wound discharge, fever and in severe cases shock and organ dysfunction. Appropriate cultures from wound, drain and blood should be sent and empirical antibiotics started. Prevention of SSI includes treating infections harboured by the host before surgery, good antiseptic precautions, and antibiotic prophylaxis within 1 hour of surgery, hair clipping rather

removal and optimum post-operative care including good glycaemic control.

URINARY TRACT INFECTIONS (UTI)

UTIs in hospital are mostly due to urological manipulation or the presence of indwelling catheters. Risk for UTI is high in females, diabetics, the elderly, in the peripartum period and is proportional to the duration of catheterisation.

Catheter-Associated Urinary Tract Infections (CAUTI)

A diagnosis of CAUTIs is confirmed when a patient meets one of the two criteria. The first is when a patient with a urinary catheter has one or more of the following symptoms with no other recognised cause: fever (temperature >38°C), urgency or suprapubic tenderness with a culture-positive urine showing more than 10^5 colony-forming units per ml, with no more than two microorganisms isolated. The second criterion is when a patient with a urinary catheter has at least two of the following criteria with no other recognised cause: positive dipstick analysis for leucocyte esterase or nitrate, pyuria (>10 leucocytes per mL of urine), organisms seen on gram-stain or physician diagnosis of urinary tract infection. In a report from north India, 24% of nosocomial infections were due to UTIs and all had indwelling catheters. Commonest isolated pathogen is *E. coli*, others include *Enterococci*, *Pseudomonas*, *Klebsiella*, *Enterobacter*, *S. epidermidis*, *S. aureus*, and *Serratia*.

To prevent UTIs, indwelling catheters are to be used only when necessary, sterile techniques are to be used during catheterisation, closed system of drainage is to be used, samples must be taken aseptically and irrigation is to be avoided. Asymptomatic bacteriuria in catheterised patients is not to be treated.

TRACHEOBRONCHITIS

It is a very common problem, characterised by at least 2 of the 4, namely fever, cough, new or increased sputum production, rhonchi, or wheezing and at least one of the following: positive culture obtained by deep tracheal aspirate or bronchoscopy or positive antigen on respiratory secretions but without radiographic evidence of pneumonia.

SINUSITIS

This entity is often overlooked in febrile patients especially when nasogastric or nasotracheal tubes are present. Apart from imaging, aspiration of affected sinus is necessary to diagnose the causative organism.

CLOSTRIDIUM DIFFICILE ASSOCIATED DIARRHOEA (CDAD)

In hospitalised patients *C. difficile* is one of the most important causes of diarrhoea. Illness ranges from mild watery stool to life-threatening colitis and toxic megacolon.

The identifiable risk factors for this include previous antibiotic treatment, chemotherapeutics, immunosuppressives, surgery, exposure to gastric acid suppressants, low immunity and advanced age. Metronidazole and oral vancomycin are the drugs of choice.

PREVENTION AND CONTROL OF NOSOCOMIAL INFECTIONS

A hospital infection control committee comprising of a senior microbiologist, intensivist, physician and surgeon is essential to prevent and control HAI. A central sterile supply department (CSSD) should be involved in dealing with sterile equipment and stores. Periodic surveillance of infections is important. Microorganisms, sensitivity patterns, antibiotic use, outcomes, all must be audited. Antibiotic policy should be formulated and revised regularly for effective therapy.

STRATEGIES TO BE ADOPTED TO COMBAT HCAI

1. Environmental factors:
   - Adequate bed-space ratio
   - Identifying infected zones
   - Proper disposal of biomedical wastes in protocol containers
   - Ensure food hygiene
   - Routine checking of potable, dialysis water
   - Ventilation strategies for operating theatres, isolation areas for infected or immunocompromised cases
2. Specific standard precautions for all patients in health care settings as recommended by Centers for Disease Control and Prevention:
   - Hand hygiene with alcohol based hand rubs is to be performed after examining each patient, before and after every procedure or handling patient's body fluids. In suspected *C. difficile* infection hands are to be washed with soap and water.
   - Respiratory and cough etiquettes are to be followed.
   - Mask, eye protection or face shield is to be worn for procedures which might involve splashes.
   - N95 or higher masks for diseases transmitted by respiratory aerosols like tuberculosis, some viruses.
   - Gloves are to be used where recommended. Masks and gowns are to be worn while handling patients infected with *Acinetobacter*, MRSA or MDR pathogens.
   - Appropriate handling of soiled linen and equipment and disinfection of environmental surfaces.
   - Used needles are not to be bent, broken by hand or recapped.
   - For patient resuscitation, a mouthpiece, resuscitation bag are needed to prevent contact with oral secretions.
   - For injected medications, single dose vials are preferable to multiple dose vials.

CONCLUSION

With the better availability of technology, India also faces the problems of HAI with its attendant emergence of MDR pathogens. As a consequence of these the outcome in the form of patient survival and cost of therapy is worrying. Strict infection control policies and judicious use of antibiotic will be the cornerstone of combating these problems.

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4. Mehta VD, Rosenthal Y, Mehta M, Chakravarthy SK, Todi N, *et al*. Device-associated nosocomial infection rates in intensive care units of seven Indian cities. Findings of the International Nosocomial Infection Control Consortium (INICC). *Hospital Infect* 2007; 67: 168-74.

17.7 Prevention of Health Care Associated Infections

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INTRODUCTION

The health care personnel/professionals/workers (HCP/W) are at constant risk of acquiring infections from patients, specimens, contaminated equipment/articles and the hospital environment during routine activities. Three elements are required for transmission of infectious agents in a health care setting. These include the reservoir/source of infectious microorganism; a susceptible host with a portal of entry optimal for the agent and mode of transmission advantageous to the agent. The reservoirs of infectious agents include patients, health care workers, and visitors carrying the agent/s. The susceptibility of the host is determined by a complex interaction between the host factors on one hand and the virulence of infectious agent, and timely administration of care and appropriate prophylaxis on the other hand. The portal of entry of infectious agent has to be ideal, only then the infectious agent will be able to enter the host, colonise, establish itself and cause infection.

MODES OF TRANSMISSION OF INFECTIOUS AGENTS

Infectious agents in healthcare settings can be transmitted by various routes including contact (direct and indirect), droplet, and airborne and other less common routes.

Contact Transmission

There are two types of contact transmission: direct and indirect. *Direct contact transmission* is the most common and important mode of transmission of healthcare associated infections. Such transmission involves direct body-to-body contact with the transfer of microorganisms during routine care of patients. Examples are: percutaneous exposure due to needle sticks or cuts from other sharp instruments, etc. Muco-cutaneous exposure occurs through contact of the mucous membrane of the eyes, nose or mouth, or contact of the skin with the blood of infected patients.

Indirect contact transmission is the transmission of pathogens by contact with blood/body fluid contaminated objects such as dressings, needles, surfaces and instruments.

Droplet Transmission

Droplets are primarily generated by patients during coughing, sneezing and talking, and during the performance of certain procedures such as suctioning and bronchoscopy. Here, the pathogen (bacteria, viruses, fungi and parasites) in the droplet travel directly from mucosal surface of patient to the mucosal surface of HCW. The area of defined risk for such transmission is approximately ≤3 feet around the patient based on epidemiological and simulated studies.

Airborne Transmission

Aerosolisation means the formation of aerosols and droplets when blood or another body fluid is mechanically disturbed. Small particles (<5 µm) can remain suspended in air and can be dispersed widely by air currents. *Mycobacterium tuberculosis* is an example of a typical microorganism transmitted by this airborne route. Many viral infections like severe acute respiratory syndrome (SARS), avian influenza, H1N1 influenza are also transmitted through this route in addition to the direct contact route.

Oral-Faecal Transmission

Enteric pathogens spread in various ways, including through the ingestion of contaminated food; through direct person-to-person contact; and through contact with infectious waste, usually faeces.

Other Sources of Infections

Transmission of infection from other sources like contaminated water, contaminated fluids, fomites, etc., can also occur. In addition, the vector borne infection can also be transmitted in a healthcare facility like anywhere else through different vectors.

TRANSMISSIBLE INFECTIONS

HCW are at occupational risk for a number of infections that include air-borne infections such as tuberculosis, varicella, measles, influenza; blood-borne infections such as HIV, hepatitis B virus, hepatitis C virus, Ebola, Lhasa viruses; faeco-oral transmission such as *Salmonella*, hepatitis A virus, and through direct contact (herpes simplex virus, *Sarcoptes scabiei*).

RISK OF OCCUPATIONALLY ACQUIRED INFECTIONS IN HCWs

Rate of infection following needle stick/percutaneous exposure/cuts from other sharps with blood or body fluids and other potentially infectious materials (OPIM):

- HIV – 0.3%
- HBV – 6% to 30%
- HCV – 2% to 9%

Factors affecting transmission of blood borne viruses:

- Amount of blood in the exposure;
- Amount of virus in patient's blood;
- Duration of contact;
- Stage of disease (e.g. HIV-infection stage) of the patient;
- Type of exposure (abrasion, penetration, injection);
- Whether post-exposure prophylaxis (PEP) taken in time (within 2 hrs) or not; and
- In case of HBV whether the HCW is immunised or not and whether the source material is positive for HBsAg/HBe antigen.

FACTORS DETERMINING THE RATE OF TRANSMISSION OF INFECTIONS TO HCWs

Blood Borne Viruses

- Frequency of occupational exposure (contact with blood or body fluids, accidental needle stick/sharp instrument injuries).

- Occupational area in the hospital: Such as gynaecology, obstetrics departments, haemodialysis unit, pathology/microbiology, surgery, surgical intensive care, emergency room, blood bank, clinical laboratory, intravenous teams, dentistry; oral surgery, etc.
- Working with 'at risk' populations [injecting drug users (IDUs), multiply transfused, commercial sex workers (CSWs), dialysis patients].
- Practice of standard work precautions.
- HBV immunisation status.
- Source of infectivity (HBeAg-positive, HIV-positive, HCV positive).

Respiratory emerging pathogens have a higher transmission potential compared to those pathogens transmitted through faeco-oral route.

PREVENTION OF HEALTH CARE ASSOCIATED INFECTIONS IN HCWs

HCWs need to protect themselves from highly transmissible airborne/droplet infections including emerging viral respiratory infections and tuberculosis; blood borne viral and bacterial infections acquired through accidental mucocutaneous exposure; food and water borne infections; infections acquired from the environment and vector borne diseases in the health care setting.

Immunisation of HCWs

Centers for Disease Control (CDC) strongly recommends that all the HCWs must be immunised against vaccine preventable diseases as per the National Immunisation Schedules of the countries. Briefly, these include HBV, MMR, BCG (TB), varicella, influenza, DPT, polio and enteric fever. Vaccines for diseases like HAV, meningococcal, pneumococcal disease outbreaks and so many emerging infections like H1N1, etc. are given under defined special circumstances, e.g. outbreak of a disease which may adversely affect HCWs providing care (high morbidity and mortality). In certain situations hyperimmune gamma globulins are administered to provide instant protection as in cases of tetanus, diphtheria, pneumococcal disease and following needle stick injury in a non-vaccinated HCW with HBV-positive blood.

Prevention of Air Borne Infections

Engineering controls

To minimise exposure to air borne biological agents, health care facilities should use isolation rooms, negative pressure ventilation, air filtration and disinfection.

The routine practices and droplet/contact precautions required to prevent transmission of airborne/droplet infections like wearing mask (1/N95 respirator as the case warrants), eye and face protection, hand hygiene, respiratory hygiene, proper cleaning and disinfection of equipment need to be followed.

Hand hygiene

All persons entering the facility should practice good hand hygiene; alcohol-based hand rub should be available at the entrances and exits of the facility, residential units and at point-of-care in the resident's room.

Respiratory hygiene (respiratory cough etiquette)

Patients should be taught how to perform respiratory hygiene practices (coughing into sleeve, using tissues, wearing a mask).

Contact precautions

HCW should wear gloves when entering the room of a patient suspected to have H1N1 or similar infection. Gowns should be worn as per routine practices. HCW should use alcohol-based hand rubs or soap and water after removing gown and gloves, and after leaving the patient's room.

Droplet precautions/respiratory protection

HCW should wear a mask1 (droplet precautions) or N95 respirator (respiratory protection) when within 2 metres of a case with H1N1. The choice between a mask1 and N95 respirator should be based on the following:

A mask1 should be worn: If within 2 metres of a patient. An N95 respirator should be worn: If conducting an aerosol-generating medical procedure. HCW should also wear eye or face protection (i.e. goggles, safety glasses, or face shield).

Cleaning and disinfection of equipment

Equipment and environmental surfaces should be cleaned and disinfected daily.

Prevention of Blood Borne Infections

Risk reduction by prevention of exposure to infected blood/OPIM remains the mainstay to prevent occupational exposure and subsequent infection. All HCWs must follow standard work precautions at all the times while providing healthcare services; follow the correct protocols for sterilisation and disinfection; safe disposal of waste; educate themselves about post-exposure management and prophylaxis and take immunisation against HBV, etc. All the patients and all specimens should be considered potentially infectious and blood and body fluid precautions must be practiced at all times while giving care to patients.

Standard work precautions include:

- Hand washing;
- Use of personal protective equipment (barrier precautions) as indicated. Barrier precautions include use of latex or vinyl gloves, gown/apron, protective eyewear or mask and protective foot cover;
- Safe handling of sharps;
- Careful handling of hollow bore needle to prevent deep injuries;
- No recapping, bending of the needles. Dispose needles immediately. Do not leave used needles on trolley or bed. Use safe autodestruct-retract needles;
- Never pass used sharps from one person to another directly, place the sharp on the trolley to be picked up by the surgeon;
- Use forceps instead of fingers for guiding sutures; and
- Follow correct protocols of biomedical waste management/disposal and sharps disposal (plastic sharps container with 1% fresh bleach).

However, the success of standard work precautions is limited.

Management of Occupational Exposure to HIV

Most exposures do not result in infection. Every exposure is assessed (mild, moderate, severe) taking into account factors as given below and a prudent decision on PEP is made.

- Amount of blood in the exposure;
- Amount of virus in patient's blood;
- Duration of contact;
- Stage of disease (HIV-infection stage) of the patient; and
- Type of exposure (abrasion, penetration, injection).

The need for HIV PEP has to be evaluated based on types of exposure and status of source material as described in **Table 1**.

Determination of HIV, HBV and HCV status of source material; evaluation of source

- If the HIV/HBV status of the source patient is known, and confirmed negative for HIV and HBV, there is no need for prophylaxis for HIV and/or HBV.
- If the status of the patient is unknown, and neither the patient nor his/her blood is available for testing, then the choice of whether to use PEP and what regimen will depend on the severity of the wound, and how much is known about the individual's (source patient's) risk history.
- If the status of the patient is unknown, and the patient is available to be counselled and gives consent for testing, this should be done.
- If the patient is known to be HIV positive, and evaluation of risk is in order, the two key factors to consider are whether the patient is anti-retroviral (ARV) drug naïve, or whether s/he has been exposed to ARV medications; and whether the patient is likely to have a high viral load—as determined by testing if available, or by clinical signs and symptoms.
- In the case of a high risk exposure from a source patient who has been exposed to or is taking ARV medications, consult an expert to choose PEP regimen taking into consideration the possibility of drug resistance.

A decision to administer PEP for HIV and prophylaxis against HBV is taken after ascertaining the above facts and appropriate prophylaxis is given.

Management of exposure

The situation is treated as an emergency.

Immediate steps after exposure:

- Do not panic, allow site to bleed under running tap water, do not squeeze the area;
- Do not use bleach, alcohol, betadine, or iodine on the cut/needle stick, etc., which may be caustic and may cause inflammation;
- Wash cuts with plenty of soap and running tap water;
- Flush splashes into nose, mouth, skin with water. Irrigate eyes with clean water or saline;
- Report the incident to the designated officer in-charge (EMO);
- Counselling and medical management;
- Administer PEP as required (depending upon the infection status of source blood) and
- Collect 3 to 5 ml blood specimen from HCW immediately and test for HIV, HBV and HCV to ensure that the HCW is not already infected.

Take first dose of PEP within 2 hours if status of blood/body fluid is known to be positive or unknown. The various regimens for PEP and drugs to be used are given in **Table 2**.

HIV, HBV and HCV testing of the exposed HCW

The blood is collected at zero hour and tested for the above markers. This is done to know the pre-exposure status of the HCP as far as these infections are concerned. If the HCP is already positive for HIV, then PEP is not recommended. In such a case the HCP should access the ART services like any other HIV infected individual. In case the HCW is positive for HBV and negative for HIV, then PEP should be given after evaluation of the severity of exposure. The guidelines for HBV prophylaxis are given in **Table 3**.

Irrespective of whether the HCW decides to take PEP or not, the testing for HIV has to be undertaken at zero hour, 6 weeks, 12 weeks, and 6 months after exposure to ensure that HIV transmission has been prevented.

In case the source blood is found to be positive for HBV and HCW is found to be negative for the same, appropriate prophylaxis for HBV should be administered.

Table 1: Evaluation of Need for PEP Based on Exposure and Status of Source

Exposure	Status of Source Material			HIV Status Negative
	HIV+ and low risk	HIV+ and high risk	HIV status unknown	
Mucous membrane/non-intact skin; small volume (drops)	Consider 2-drug PEP	2-drug PEP	Consider 2-drug PEP	No PEP is required if the source blood is confirmed HIV and HBV negative
Mucous membrane/non-intact skin; large volume (major blood splash)	2-drug PEP	3-drug PEP	Consider 2-drug PEP	
Percutaneous exposure: not severe solid needle, superficial	2-drug PEP	3-drug PEP	Consider 2-drug PEP	
Percutaneous exposure: severe large bore hollow needle, deep injury, visible blood in device, needle in patient artery/vein/blood injected	3-drug PEP	3-drug PEP	2-drug PEP Consider	

Table 2: PEP Regimen (Basic and Advanced)

Medication	Dosage of drugs for PEP	
	Basic regimen (2-drug)	**Advanced Regimen (3-drug regimen)**
Zidovudine (AZT) (or Stavudine (d4T) + Lamivudine (3TC)	300 mg twice a day 150 mg twice a day	300 mg twice a day + (150 mg twice a day) **+ Protease Inhibitors** **1st choice** Lopinavir/ritonavir (LPV/r) 800/200 mg once daily with meals **2nd choice** Nelfinavir (NLF) 1250 mg twice a day or **3rd choice** EFV 600 mg at Bed time

Table 3: HBV Post-Exposure Prophylaxis

Exposed person	Treatment according to the status of source material		
	HBsAg-positive	**HBsAg-negative**	**Source not tested or unknown**
Unvaccinated	HBIG x 1*, initiate HBV vaccine	Initiate HBV vaccine	Initiate HBV vaccine
Previously vaccinated, known responder	Test exposed for HBsAb. If adequate no treatment. If inadequate, HB vaccine booster	No treatment	No treatment
Previously vaccinated, known non-responder	HBIG x 2 or HBIG x 1 plus 1 dose HB vaccine	No treatment	If source high risk for Hep B, treat as if source is positive
Response unknown	Test exposed for HBsAb. If adequate no treatment. If inadequate HBIG x 1*, initiate HBV vaccine	No treatment	Test exposed for HBsAb. If adequate, no treatment. If adequate, HBV vaccine booster

** HBIG dose 0.06 mL/kg IM.*

If the source is found to be positive for HCV and HCW is found to be negative for HCV, then refer the HCP to the designated hospital team for further care.

Management of Exposure to Hepatitis C Virus

There is no vaccination at this time, and no recommended chemoprophylaxis. For HCW exposed to Hepatitis C virus, follow-up care by the designated team is recommended.

CONCLUSION

The risk of health care associated infections is an unavoidable part of care-giving activities. However, the risk can be minimised by taking required immunisations; diligently following infection control practices and following standard work precautions while rendering service to patients.

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17.8 Hospital Infection Control

Rohini Kelkar

DEFINITION AND EPIDEMIOLOGY

Hospital acquired infection can be defined as 'An infection occurring in a patient in a hospital in whom the infection was not present or incubating at the time of admission'. Hospital acquired infections (HAIs) or nosocomial infections are a significant cause of mortality and morbidity amongst hospitalised patients and compromise patient safety. Early studies in the 1980s from the US have reported that HAIs account for 14% of all adverse events. A World Health Organisation prevalence study showed an average of 8.7% of hospital patients had nosocomial infections with 10% prevalence in the South-East Asian region.

Despite progress in medical care, infections continue to develop in hospitalised patients due to factors, like increasing numbers of immunocompromised patients, invasive medical procedures, overcrowding leading to transmission of drug-resistant bacteria coupled with poor infection control procedures.

HAIs may be endemic or epidemic. Epidemic infections occur during outbreaks. Definitions have been developed for site-specific infections, e.g. urinary tract infection (UTI), surgical site infection (SSI), bloodstream infection (BSI), catheter related BSI and nosocomial pneumonia. These definitions can be utilised to identify the risk factors and take corrective measures in each organisation so as to reduce HAIs to acceptable limits.

AETIOPATHOGENESIS

HAIs are caused by many different microorganisms ranging from pathogenic bacteria like methicillin resistant *Staphylococcus aureus* to commensals like coagulase negative *Staphylococci* causing line associated infections. *Legionella* species found in water can cause nosocomial outbreaks of pneumonia through inhalation of contaminated aerosols. Viruses like hepatitis B and C can be transmitted through contaminated injections, transfusions, etc. Many parasites and fungi are opportunistic organisms and can cause infections during severe immunosuppression and extended antibiotic treatment. *Aspergillus* spores present in dust can cause nosocomial infections during hospital renovation and construction activities.

The reservoirs of infection may be endogenous, for example, Gram-negative bacteria present in the gut can cause surgical site infections after abdominal surgery. Exogenous infections are due to cross-transmission through direct contact as in the case of hands or body fluids; air-borne as in the case of droplets or dust; through carriers or through contaminated objects, like equipment, hands of health care workers or environmental sources like water, fluids and food.

DIAGNOSIS

By definition, HAIs are infections that occur more than 48 hours after admission. There are two important components to the diagnosis: (a) a simple timely and effective surveillance system that can monitor HAIs, and (b) standardised microbiology services to provide timely diagnosis of infections, monitor data and provide management guidelines through the performance of anti-microbial susceptibility testing using internationally recognised methods, reports of resistance patterns and accurate identification of aetiologic agents.

PREVENTION AND CONTROL

Hospital Infection Control Programme

Prevention of HAIs is the responsibility of every health care provider. Important components of the programme include:

1. Infection Control Committee which recommends the policies and practices.
2. Infection Control Team which includes an infection control nurse and a doctor.

The infection control committee should have representation from all relevant specialities and should perform the following:

1. Compile an infection control manual of recommended instructions and practices for patient care in hospital settings.
2. Review the activities for prevention of HAIs.
3. Review epidemiological surveillance data and plan appropriate interventions.
4. Ensure health care worker training on infection control.
5. Review investigation of outbreaks.

Important inputs are required from the hospital management, physicians, the nursing department, microbiologist, sterilisation services, food services and laundry, housekeeping and engineering departments.

Standards of Hygiene

In dealing with patients it is of utmost importance to maintain high standards of hygiene for all procedures.

Hand hygiene

Hand washing is the single most important measure for preventing the spread of infection. Hands should be washed before significant contact with any patient and after all activities likely to cause contamination.

Hand antisepsis is with antiseptics like chlorhexidine gluconate 2% w/v, povidone iodine or triclosan, if the hands are soiled or with 4% w/v chlorhexidine gluconate before surgery or any invasive procedures.

The hand wash procedure, duration and agent used are all critical.

Hand-rubs are useful for lowering the microbial counts on the skin, but cannot be used in the presence of organic soil.

Universal precautions

These are devised by the Centers for Disease Control and Prevention to protect health care workers from transmissible blood borne pathogens. These apply to blood, body fluids and any body fluid visibly contaminated with blood. These do not apply to secretions and excretions unless they contain visible blood.

These precautions include good hygienic practices particularly hand washing, the use of protective barriers like gloves, gowns, masks and eye shields, appropriate handling and disposal of sharps and other infectious wastes and the use of aseptic techniques.

These are recommended during the handling of blood, e.g. during blood collection and in laboratories, while handling body fluids and while handling non-intact skin and mucous membranes. Any spillage of blood and or body fluids should also be treated immediately with a solution of sodium hypochlorite (10,000 ppm available chlorine).

Isolation

Isolation of patients in a separate room or an isolated area is required only for patients with epidemiologically significant and highly contagious infections like pneumonia due to methicillin resistant *Staphylococcus aureus* or multiple drug resistant-tuberculosis and during outbreaks with viruses like acute respiratory syndrome.

Physical Environment

The physical environment of the hospital has to be designed taking into account the physical requirements that are fundamental to infection control.

Patient care areas should be adequately ventilated. Operating rooms are designed to minimise the risk of infection. Ideally, these have air handling systems that provide filtered air. The temperature, humidity and air changes per hour are all controlled as to minimise bacteria multiplication. Special environmental control measures are required during construction activities. This also includes control and monitoring of hospital water, food hygiene, laundry services, especially care of contaminated linen and biomedical waste.

Sterility of Instruments and Equipment

All instruments used for patient procedures must be thoroughly cleaned and decontaminated/sterilised depending on the use, e.g. surgical instruments must be sterilised to make them free from all forms of microbial life including bacterial spores.

Heat labile instruments like fibreoptics used for endoscopy or bronchoscopy should be decontaminated with an approved high level chemical disinfectant.

Adequate quality controls are essential for sterilisation and disinfection procedures.

In general single use items should not be reprocessed except in situations of non-availability, high cost or if the item has crossed the expiry date. Injection needles should not be reused/reprocessed.

Surveillance of Nosocomial/Health Care Associated Infection

This includes monitoring of hospital-acquired infections. Surveillance helps to track infection trends, i.e. the prevalent microorganisms, anti-microbial susceptibility patterns and multi-drug resistant organisms.

Outbreak Investigation

An unusual increase of cases of HAI indicates an outbreak, which requires prompt identification followed by investigation and the institution of appropriate control measures.

Occupational Health and Safety

Health care workers are at risk of acquiring infections through occupational exposures or may transmit infections to patients or other employees. Immunisation and specific post exposure policies for blood borne pathogens must be implemented.

Antibiotic Policy

In countries like India, where anti-microbials are sold across the counter, it is essential to control and rationalise the use of anti-microbials. Moreover, it is this 'misuse' that is responsible for the high levels of drug resistant microorganisms. Each facility should have a policy that outlines the rational use of anti-microbials in different clinical situations. Emphasis must be placed on preventive measures rather than concentrating on only therapeutics.

Biomedical Wastes

Disposal of hospital wastes has become an important component of infection control. The process involves several steps as given below:

1. Identification of different categories of hospital wastes
2. Segregation of wastes at the point of generation
3. Collection in appropriate containers, e.g. all sharp (needles etc.) must be collected in puncture-proof containers
4. Transportation
5. Storage
6. Treatment
7. Disposal

This is the 'cradle to grave' concept of waste management. Presently, there is a legal requirement to manage hospital wastes in India. The Biomedical Waste Management and Handling Rules Act came into force on 1998. In exercise of the powers conferred by section 6, 8 and 25 of EP Act, 1986. The central government notified these rules. For violating the rules the board can provide imprisonment which may extend up to 5 years with fine.

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17.9 Staphylococcal Infections

Rita Sood

Association between cluster-forming cocci and abscesses was first observed by a Scottish surgeon, Alexander Ogston. He coined the name *'Staphylococcus'* for the organism (*Staphyle*, bunch of grapes; *kokkos*, berry) to distinguish it from chain-forming *Streptococci*. More than 30 species of *Staphylococci* can infect humans. However, most infections are caused by *Staphylococcus aureus*, the most virulent species and an important cause of morbidity and mortality in humans. It is distinguishable from other *Staphylococci* by its ability to produce coagulase, an enzyme that converts fibrinogen to fibrin. The other less virulent species of *Staphylococci* are grouped together as *coagulase negative Staphylococci* (CoNS).

STAPHYLOCOCCUS AUREUS INFECTIONS

S. aureus forms part of normal human flora, colonising the anterior nares, axilla, perineum, oropharynx, vagina and toe-webs. 25% to 50% of healthy persons may be carriers and this is relevant to the epidemiology, as source of most infections is endogeneous. Factors predisposing to *S. aureus* colonisation are shown in **Table 1**.

Table 1: Factors Predisposing to *S. aureus* Colonisation

Insulin-dependent diabetes
HIV-infection
IV drug abuse
Chronic haemodialysis
Skin diseases, e.g. eczema

S. aureus may also be acquired from other people or from environment as from hands of hospital personnel or through aerosols contaminated by respiratory or nasal secretions.

Pathogenesis

S. aureus has a capacity to induce abscess formation. A breach in the skin or mucosal barrier is necessary for initiation of a staphylococcal infection. After colonisation, the organisms replicate at the initial site of infection, elaborating enzymes which facilitate their survival and local spread across tissue surfaces. *S. aureus* also has a capacity for intracellular survival and to induce cellular changes which contribute to systemic manifestations of the disease. The predisposing factors for occurrence of staphylococcal diseases are shown in **Table 2**.

The primary host response to *S. aureus* infection is the recruitment of neutrophils. The staphylococcal cell wall as well as staphylococcal toxin can initiate an inflammatory response that can lead to sepsis.

Clinical Manifestations

S. aureus usually causes localised infections resulting in abscess formation. However, bacteraemia and haematogenous spread may occur, the severity of which is determined by the host response. Constitutional symptoms may result from both, localised or systemic infections (**Table 3**).

Table 2: Factors Predisposing to Staphylococcal Infections

Breach in Skin	**Impaired Leucocyte Function**
Wounds—traumatic, surgical	Quantitative
Burns	Neutropaenia
Skin diseases, e.g. eczema	Qualitative
Minor abrasions	Chronic granulomatous disease
Injections, e.g. insulin	Job's syndrome
Intravenous access, e.g. catheters	Chediak-Higashi syndrome
Breach in Mucous Membrane	
Viral infections, e.g. influenza	
Presence of Foreign Materials	
Intravenous catheters	
Arterio-venous shunts	
Prosthetic cardiac valves	
Orthopaedic prostheses	

Table 3: Common Illnesses Caused by *S. aureus*

Localised Infections

Skin and Soft-tissue Infections	**Pleuro-pulmonary Infections**
Folliculitis	Nosocomial pneumonia
Furuncle	Aspiration pneumonia
Carbuncle	Post viral (e.g. influenza) pneumonia
Cellulitis	Septic pulmonary emboli
Impetigo	Empyema
Surgical wound infections	Pyopneumothorax
Acute paronychia	**Musculoskeletal Infections**
Mastitis, breast abscess	Osteomyelitis
Umbilical infections in new born	Septic arthritis
Stye or hordeolum externa	Pyomyositis
Urinary Tract Infections (rare)	Psoas abscess
Post-surgery	**Toxin-mediated Illness**
Renal cortical abscess	Food poisoning
Peri-nephric abscess	Toxic shock syndrome
Bacteraemia and Septicaemia	Staphylococcal scalded skin syndrome
Sepsis, septic shock	
Metastatic foci of infections (kidney, bones, joints, lungs)	
Infective endocarditis	
Device-related infections	
Injection drug use related infections	

Localised Infections

Skin, appendages and soft tissue infections

Most infections arise in relation to hair follicles and result in localised pus collection. The affected area may be red,

swollen and painful. Common predisposing factors are minor trauma, insect bites, injections and poor personal hygiene. *Folliculitis* is a superficial infection of hair follicle. When this infection becomes more extensive and deep seated, it presents as a boil or *furuncle*. When several adjacent hair follicles are involved, they coalesce and may involve deeper layer of subcutaneous tissue and result in large indurated mass with multiple draining sinuses called *carbuncle*. These may occur in poorly controlled diabetics. *Staphylococcus* can result in mastitis or breast abscesses in 1% to 3% of breast-feeding women.

Pleuropulmonary infections

Staphylococcal pneumonia can occur as a result of aspiration of oro-pharyngeal flora, commonly in a patient with pre-existing lung disease, e.g. bronchiectasis, or due to metastatic seeding of a previously healthy lung. *S. aureus* is a cause of serious pulmonary infections in newborns and infants. In adults, nosocomial *S. aureus* pneumonia is often a complication of intubation and ventilation. Patients with right-sided endocarditis can present with septic pulmonary emboli. Staphylococcal pneumonias can be complicated by pneumatoceles, empyema and pyopneumothorax.

Musculoskeletal infections

S. aureus is the most common cause of bone and joint infections, both haematogenous and due to contiguous spread from adjacent soft tissue infections. Commonly involved joints include knees, shoulders, hips and phalanges. Pre-existing joint diseases, like osteoarthritis and rheumatoid arthritis are the predisposing factors. Increasing use of joint aspirations is contributing to higher incidence of septic arthritis.

Haematogenous osteomyelitis involves long bones more commonly in children whereas in adults, vertebrae are the commoner site. These infections are more common in patients with endocarditis, intravenous drug users, diabetics and those undergoing haemodialysis.

Pyomyositis is an acute inflammation of skeletal muscles seen only in tropics and sub-tropics. It presents as fever, swelling and pain overlying the involved muscle. The infection is almost always caused by *S. aureus* and gluteal and quadriceps are the common muscles involved.

Bacteremia, Septicaemia and Infective Endocarditis

S. aureus bacteraemia may be complicated by sepsis, endocarditis, vasculitis or metastatic seeding of infection. Commonly seeded tissue sites are bones, kidneys, joints and lungs. Immunocompromised states particularly diabetes, HIV infection and renal insufficiency increase the risk of bacteraemia and its complications. The presence of *S. aureus* in the urine suggests haematogenous dissemination. In patients with severe burns, staphylococcal sepsis is a leading cause of shock and death.

The overall incidence of *S. aureus* endocarditis has increased over the last few years. Intravenous drug abuse, diabetes mellitus, chronic haemodialysis and immunosuppression are predisposing factors and increase mortality. Acute right-sided endocarditis is most often seen in intravenous drug users. Prosthetic device infections are usually caused by *Staphylococcus aureus*.

Toxin-Mediated Illness

Staphylococcal food poisoning

Food poisoning due to *S. aureus* is caused by the ingestion of staphylococcal enterotoxin, preformed in the contaminated food. It is characterised by severe vomiting, nausea, abdominal cramps and diarrhoea and occurs within 1 to 6 hours of ingestion of food. Symptoms generally resolve within few hours and treatment is supportive.

Toxic shock syndrome (TSS)

It is characterised by high fever, erythematous rash, desquamation, diarrhoea, mental confusion, hypotension and multi-organ failure. It is caused by toxins secreted by *S. aureus* bacteria growing under conditions in which there is little or no oxygen. TSS was originally described in menstruating women using tampons. TSS is caused by enterotoxin or TSS toxin-1 (TSST-1). As the syndrome is caused by toxin, the mainstay of treatment is supportive measures along with antibiotics.

Staphylococcal scalded skin syndrome (SSSS)

SSSS mostly affects newborns and children. It is characterised by sudden onset of extensive erythema followed by bullous desquamation of large areas of skin. It is caused by epidermolytic toxins of *S. aureus*.

COAGULASE-NEGATIVE INFECTIONS

The coagulase-negative *Staphylococci* (CoNS) form large part of skin flora and are among the most common causes of prosthetic-device infections. *S. epidermidis* is the commonest, others being *S. hominis, S. haemolyticus* and *S. saprophyticus*.

Pathogenesis

S. epidermidis has a capacity to produce an exopolysaccharide (a bioflim, slime) which facilitates the adherence of this organism to plastic material and also their resistance to phagocytosis, other host-defences and to anti-microbial action. Majority of these infections are acquired in the hospital. Generally, the signs of localised infection are subtle, the rate of disease progression is slow, and systemic findings are limited. In the community, *S. saprophyticus* is an important pathogen causing urinary tract infections in sexually active young women whereas *S. epidermidis* is the organism associated with hospital-acquired infections.

Diagnosis

In cases of minor skin infections, staphylococcal infections are commonly diagnosed by their appearance without the need for laboratory testing. More serious infections require culture of samples of blood or infected fluids.

Laboratory diagnosis

S. aureus can be easily identified in the laboratory by Gram's stain and microscopic examination of the infected tissue. The organism can be seen as clumps of Gram-positive cocci. The diagnosis can be confirmed by cultures of infected material and blood. The isolation of *S. aureus* from blood culture is almost always indicative of bacteraemia. The laboratory diagnosis of CoNS is more difficult than *S. aureus* infections because of difficulty in interpretation. Only about 10% to 25% of blood cultures positive for CoNS reflect true bacteraemia. Multiple positive cultures of the same strain from separate

cultures, growth of the strain within 48 hours and bacterial growth in both aerobic and anaerobic cultures is likely to suggest true bacteraemia. Repeated cultures should always be taken.

Serology is not useful for the diagnosis of staphylococcal infections.

TREATMENT

General Principles

Localised skin infections can be treated with an antibiotic ointment or oral antibiotics. Serious infections warrant intravenous antibiotics supplemented by drainage with or without surgical excision. In almost all cases of infections with *S. aureus*, the prosthetic device removal is needed. In infections due to CoNS, sometimes an initial attempt at medical therapy without removal of device may be warranted.

Choice of Anti-microbials

The choice of antibiotic depends on prevailing susceptibility patterns and the severity of infection. Almost all *Staphylococci* produce beta-lactamase, and hence, penicillin use is not recommended. Semisynthetic penicillinase-resistant penicillins (SPRPs) like flucloxacillin or cloxacillin are important agents for community-acquired infections. Alternatively, first generation cephalosporins, macrolides and related agents like clindamycin can be used.

Multi-drug resistant strains of both *S. aureus* and CoNS are now prevalent. These methicillin-resistant strains of *Staphylococci* (MRSA) are usually resistant to other antibiotics and are associated with nosocomial infections. MRSA prevalence is increasing in the community setting and is associated with recent antibiotic use, sharing contaminated items, having active skin diseases, poor hygiene and living in crowded settings. HIV positive patients have been found to be at increased risk of infections with community acquired MRSA. The transmission of MRSA is largely from people with active MRSA skin infections. MRSA almost always spreads by physical contact and not through the air. Vancomycin and teicoplanin are the only agents with reliable activity against MRSA. New agents include linezolid and quinupristin/dalfopristin. Although, imipenem has excellent activity against methicillin sensitive *Staphylococci* but not against MRSA. Recently, vancomycin-resistant strains of *S. aureus* have been identified—vancomycin-intermediate resistance *S. aureus* and vancomycin resistant *S. aureus*. For minor skin and soft tissue infections in adults, tetracyclines could be useful. Parenteral vancomycin or teicoplanin are recommended in infections where risk of bacteraemia is high. Linezolid though bacteriostatic has an added benefit of being available and efficacious as an oral agent and can be useful in infections which are not deep-seated. Daptomycin is a new parenteral bactericidal agent with anti-staphylococcal activity and has been approved in USA for treatment of bactaeremias. Combinations of anti-staphylococcal antibiotics are sometimes used to enhance bactericidal activity (e.g. endocarditis). The agents used include rifampicin, gentamicin and fusidic acid, in combination with vancomycin. Therapy for toxin-mediated illnesses is entirely supportive with some role of antibiotics in TSS and SSSS.

Duration of Treatment

A 10 to 14 day treatment with antibiotics is recommended for uncomplicated infections and 4 to 8 weeks for complicated infections. Untreated *S. aureus* sepsis carries 80% mortality. Factors associated with increased risk of complications include persistently positive blood cultures 3 to 4 days after institution of therapy, community acquired infection, a removable focus of infection which is not removed and embolic manifestations.

PREVENTION

Simple measures like hand washing and appropriate isolation procedures can prevent spread of *S. aureus* infections. Regular hospital associated infection monitoring, antibiotic sensitivity surveillance and formulation of an antibiotic policy is helpful to reduce MRSA prevalence. Use of topical anti-microbial agents like mupirocin to eliminate nasal colonisation with *S. aureus* helps prevent infections in dialysis patients, but is not recommended routinely. A capsular polysaccharide-protein conjugate vaccine is under investigation.

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17.10 Streptococcal Infections

Abhay Narain Rai

INTRODUCTION

Streptococcus is a genus of coccus, or sphere-like, Gram-positive, chained (the cells divide along a single plane, so *Streptococci* occur in pairs or in chains) bacteria. The name has been derived from Greek 'στεπτος' streptos, meaning easily bent or twisted, like a chain (twisted chain).

CLASSIFICATION

Streptococcus bacteria are divided into eighteen alphabetwise groups, called Lancefield groups. American bacteriologist Ms Rebecca Craighill Lancefield developed this method of classifying *Streptococci* in 1933 based on the antigens, found in the cell wall of the *Streptococcus* bacteria. Several types of *Streptococcus* do not react to Lancefield grouping, and must be classified using haemolysis.

The type of haemolytic reaction displayed on blood agar has long been used to classify the *Streptococci*. Beta-haemolysis is associated with complete lysis of red cells surrounding the colony, whereas alpha-haemolysis is a partial or 'green' haemolysis associated with reduction of red cell haemoglobin. Non-haemolytic colonies have been termed gamma-haemolytic. Group A *Streptococci* are nearly always beta-haemolytic; related Group B can manifest alpha, beta or gamma haemolysis. Most strains of *S. pneumoniae* are alpha-haemolytic but can cause ß-haemolysis during anaerobic incubation. Most of the oral *Streptococci* and *Enterococci* are non-haemolytic. The group viridans *Streptococcus* is either non-haemolytic or breaks down only partially, causing the green stain responsible for the name 'viridans'.

Group A *Streptococcus*, Group B *Streptococcus*, viridans *Streptococcus* and *S. pneumoniae* are the types most commonly of medical concern. Group A *Streptococcus* (GAS), or *S. pyogenes*, is one of the most common pathogens in humans.

Epidemiological data from developing countries for streptococcal infections is poor. On a global scale, GAS is an important cause of morbidity and mortality. In India, beta-haemolytic *Streptococci* causes up to 20% of acute respiratory tract infections and invasive streptococcal infection among hospital inmates has been reported as 2.4 per thousand (culture positive).

DISEASES

Acute *Streptococcus pyogenes* infections may present as pharyngitis (strep. throat), scarlet fever (rash), impetigo (infection of the superficial layers of the skin) or cellulitis (infection of the deep layers of the skin). Invasive, toxic infections can result in necrotizing fasciitis, myositis and streptococcal toxic shock syndrome (TSS). Patients may also develop immune-mediated post-streptococcal sequelae, such as acute rheumatic fever and acute glomerulonephritis, following acute infections caused by *Streptococcus pyogenes*. GAS infections may also cause pneumonia, meningitis, tonsillitis, septic arthritis.

Pharyngitis

Streptococcal pharyngitis presents as sore throat, pain on swallowing, fever, swollen and tender lymph nodes in the neck, and fatigue. The tonsils are swollen and often covered with pus. Cough, hoarseness, and running nose are not the symptoms of streptococcal pharyngitis, but indicate viral upper respiratory infections. When a red rash and fever accompany streptococcal sore throat, it is called scarlet fever. The two major complications of streptococcal pharyngitis are rheumatic fever and post-streptococcal glomerulonephritis.

Diagnosis

Streptococcal rapid antigen test—used to distinguish intermediate probability of *Streptococcus*.

Throat culture—used to confirm a negative rapid antigen test.

Antistreptolysin O titre (ASO titre)—confirms diagnosis, but not helpful in acute disease.

Meningitis

Bacterial meningitis is a serious infection of the CSF. It is most commonly caused by one of three types of bacteria: *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. Meningitis caused by *Streptococcus pneumoniae* is called pneumococcal meningitis. The bacteria are spread by direct close contact with the discharges from the nose or throat of an infected person. Common symptoms are high fever, headache, and stiff neck. Other symptoms can include nausea, vomiting, photophobia, confusion, and drowsiness. Advanced bacterial meningitis can lead to brain damage, coma, and death. Survivors can suffer long-term complications, including hearing loss, mental retardation, paralysis and seizures.

Impetigo

Impetigo is a skin infection caused by bacteria. Usually the cause is staphylococcal but sometimes *Streptococcus* can cause it—the non-bullous type. It is most common in children between the ages of two and six. It usually starts when bacteria get into a break in the skin, such as a cut, scratch or insect bite. Impetigo generally appears as honey-coloured scabs formed from dried serum, and is often found on the arms, legs, or face. It could be bullous (mostly by *Staphylococcus*) or non-bullous (caused by both of them). One potential complication of impetigo is glomerulonephritis. Impetigo is contagious, mostly from direct contact but sometimes from fornites, towels, toys, clothing or household items. Once it starts, impetigo often spreads to other parts of the body.

Cellulitis (Figure 1)

Unlike impetigo, which is a very superficial skin infection, cellulitis refers to an infection also involving the skin's deeper



Figure 1: Upper limb cellulitis.

layers: the dermis and subcutaneous tissue. The main bacteria involved in cellulitis are *Streptococcus* and *Staphylococcus*. Cellulitis may occur anywhere on the body, but the leg is the most common site of the infection. Diabetics are more susceptible to cellulitis than the general population because of impairment of the immune system.

Necrotising Fasciitis

It is a rare infection of the deeper layers of skin and subcutaneous tissues (**Figure 2**), easily spreading across the fascial plane within the subcutaneous tissue. The infection begins locally, at a site of trauma, which may be severe (such as the result of surgery), minor, or even non-apparent. Patients usually complain of intense pain that may seem in excess given the external appearance of the skin. With progression of the disease, tissue becomes swollen, often within hours. Diarrhoea and vomiting are also common symptoms. In the early stages, signs of inflammation may not be apparent if the bacteria are deep within the tissue. If they are *not* deep, signs of inflammation, such as redness and swollen or hot skin, show very quickly. Skin colour may progress to violet, and blisters may form, with subsequent necrosis (death) of the subcutaneous tissues. Patients with necrotising fasciitis typically have a fever and appear very ill. Mortality rates have been noted as high as 73% if left untreated.



Figure 2: Necrotising fasciitis.

TREATMENT

GAS infections can be treated with many different antibiotics. Penicillin G (2 to 4 mU IV q4h) and clindamycin (600 to 900 mg g8h) are recommended. Supportive care in an intensive care unit may also be needed for severely ill. For persons with necrotising fasciitis, early and aggressive surgery is often needed to remove damaged tissue and stop disease spread. Early treatment reduces risk of death from invasive group A streptococcal disease. However, even the best medical care does not prevent death in every case.

Group B Streptococcus (GBS), or *S. agalactiae*, is frequently found in the urogenital tracts and rectums of women of childbearing age. Complications may arise in women with compromised immune systems, but it is more commonly significant when transmitted to babies during childbirth. A GBS infection of a newborn can cause life-threatening infections like meningitis or sepsis. Group B *Streptococcus* can also cause serious diseases in pregnant women, the elderly, and adults with other illnesses.

Streptococcus viridans is often responsible for dental infections and the formation of plaque. This type of bacteria, along with Group C, F, G and particularly D, can cause endocarditis, especially when the valves of the heart are previously damaged.

Streptococcus pneumoniae, or *Pneumococcus*, is the most common cause of invasive bacterial infection of children and the elderly. It is a normal inhabitant of the human upper respiratory tract. The bacterium can cause pneumonia, usually of the lobar type, paranasal sinusitis and otitis media, or meningitis, which is usually secondary to one of the former infections. It also causes osteomyelitis, septic arthritis, endocarditis, peritonitis, cellulitis and brain abscesses.

PREVENTION

Infections caused by streptococcal bacteria can be prevented or reduced in most cases by ensuring high standards of personal hygiene. The most helpful practice to prevent the likelihood of acquiring streptococcal diseases and reducing their spread to others is by good handwashing and prevent generation of aerosols from infected persons.

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17.11 Pneumococcal Infections

DP Bhadoria, Koushik Dutta

Streptococcus pneumoniae (nicknamed pneumococcus) is the most common cause of community-acquired pneumonia and acute otitis media worldwide. Its growth in liquid media resembles *Streptococci*. Hence, it used to be called '*Diplococci*' which is no longer used now.

MICROBIOLOGY

Pneumococci are catalase negative, Gram-positive, round-shaped (coccus) capsulated bacteria growing in chains. They produce α-haemolytic toxin called pneumolysin that breaks down haemoglobin and is related to disease manifestations. The colonies are uniformly dissolved by bile salts. More than 98% isolates are susceptible to optochin.

A polysaccharide capsule is present in all but a few conjunctivitis causing strains, prevents phagocytosis and is an important virulence factor. Capsule swelling following antibody binding produces the fascinating 'quellung reaction'. Ninety serotypes have been identified based on capsule antigen. Serotyping is important since vaccines are used to produce antibodies to specific capsular polysaccharides.

β-lactam antibiotics inhibit the peptidoglycan to teichoic acid cross-linking by transpeptidase and carboxypeptidase enzymes in bacterial cell wall. A unique cell-wall polysaccharide consisting of teichoic acid with a phosphorylcholine residue is present in all strains. The exposed choline residues provide attachment to virulence factors like pneumococcal surface protein A (PspA) and pneumococcal surface adhesin A (PsaA).

EPIDEMIOLOGY

Pneumococci colonise the nasopharynx in 5% to 10% of healthy adults and 20% to 40% of children where they persist ordinarily for 4 to 6 weeks, sometimes up to 6 months. The *Pneumococci* are transmitted mainly through droplets, the transmission is increased in closed communities (school children, recruits in army, nursing homes, etc.), and in close contacts (crowding and poor ventilation). Individuals with complement deficiency, HIV infection, agammaglobulinaemia and splenectomy tend to have severe infection. Bacteraemia, usually secondary to pneumonia, is common in extremes of ages below 2 years and above 65 years.

PATHOGENESIS: HOST-PATHOGEN INTERACTIONS

Bacterial surface adhesins help in nasopharyngeal colonisation. Mucociliary clearance, glottal and cough reflexes prevent further spread. Viral infections, smoking, alcoholism, chronic lung diseases and heart failure compromise the defence resulting in easy spread to anatomically contiguous structures (Eustachian tube, nasal sinuses or the airways). Pneumococcal cell-wall constituents and antibody-antigen reactions activate complements and release cytokines [interleukin (IL)-1β, tumour necrosis factor (TNF)-α and IL-6] resulting in influx of polymorphonuclear (PMN) leucocytes. The capsule prevents phagocytosis and promotes invasion. Uncapsulated *Pneuomococci* seldom cause invasive disease. Pneumolysin damages membranes. An IgA1 protease dampens mucosal immunity.

Specific anticapsular antibody formed a few weeks after colonisation offers best protection. Compromised IgG synthesis, defective phagocytosis and absence of spleen predispose to overwhelming infection.

SPECIFIC INFECTIONS CAUSED BY *S. PNEUMONIAE*

Apart from pneumonia, *Pneumococci* commonly cause acute otitis media, sinusitis, acute tracheobronchitis, empyema and meningitis. Pneumococcal infections are listed in **Table 1**. Airway infections are caused by direct spread from primary site of colonisation whereas remote sites can be invaded via the haematogenous route.

Table 1: Adult Infections Caused by *S. pneumoniae*

Site of Infection	Disease Caused
Common infections	
Upper respiratory tract	Acute suppurative otitis media, acute sinusitis, tracheobronchitis
Lungs	Pneumonia (usually lobar)
Pleura	Empyema (often with pneumonia)
Central nervous system	Acute pyogenic meningitis, brain abscess
Heart and pericardium	Endocarditis (acute/subacute), pericarditis
Unidentified focus	Bacteraemia (primary)/sepsis
Less common infections	
Bone and soft tissue	Septic arthritis, osteomyelitis, cellulitis
Uterus	Endometritis
Abdomen	Peritonitis (spontaneous)

Acute Otitis Media and Sinusitis

Diagnosis

Acute suppurative otitis media (ASOM), manifesting as ear ache, aural pressure and fever is commonest in infants and children. Erythema, decreased mobility, even bulging of the tympanic membrane may be seen. If untreated, the tympanic membrane may rupture leading to otorrhoea.

Maxillary sinusitis presents with unilateral pain over the sinus which may refer to the upper incisor and canine teeth. Purulent nasal discharge, local pain, tenderness, and rarely, erythema are observed. Acute pain and pressure over the high lateral wall of the nose radiating to the orbit suggests acute ethmoiditis. Pain of frontal and sphenoid sinusitis is felt in the forehead and vertex regions, respectively. The hallmark of acute sinusitis radiologically is soft-tissue density without bone destruction. Although more sensitive than clinical examination routine radiographs are not cost-effective and are not usually recommended.

Pneumonia

Diagnosis

The symptom-triad of pneumococcal pneumonia is fever, cough with purulent rusty sputum/haemoptysis and dyspnoea. Pleuritic chest pain indicates pleural inflammation and if persistent suggests empyema. Elderly patients may present with insidious and vague symptoms like fever, fatigue, confusion with minimal cough. Lobar pneumonia causes diminished chest excursion and impaired percussion note, bronchial breath sounds and/or crackles on the affected side. Pleural effusion causes dull percussion note with loss of breath sounds and vocal fremitus (**Figure 1**).



Figure 1: Chest radiograph shows right upper and middle-lobe consolidation and non-homogeneous opacities in the left lower zone, in a case of pneumonia caused by *Streptococcus pneumoniae*. The patient also had empyema which necessitated tube thoracostomy.

Chest radiograph confirms pneumonia. Gram staining of properly obtained sputum sample (<10 epithelial cells and >25 neutrophils/high-power field) shows Gram-positive *Diplococci* in 80% to 90% of cases. Sputum and blood cultures are positive in 50% to 60% and 15% to 25% of cases, respectively. Rational antibiotic therapy mandates prior attempt to isolate the organism. Pneumococcal urinary antigen assay is a rapid method to augment the diagnostic yield.

Empyema, the most common complication, occurs in almost 2% to 3% of cases. The appearance of confusion should also raise concern about meningitis. Meningitis and pneumonia in the same patient is often associated with infective endocarditis (Austrian triad). Pneumococcal endocarditis causes rapid destruction of the heart valves.

Patients with severe pneumonia (**Table 2**) often require intensive care unit (ICU) admission.

Meningitis

Diagnosis

S. pneumoniae is the most common cause of pyogenic meningitis in adults. Rapid onset of fever, headache, meningismus (neck stiffness and positive Kernig's sign) and altered mental status is typical. Lumbar puncture should be done early after ruling out optic-disk oedema, stroke and coagulopathy. Typical cerebrospinal fluid (CSF) findings include pleocytosis (500 to 5,000 cells/μL) with predominant polymorphs, an elevated protein level (0.100 0.5 g/dL), and a decrease in glucose content (< 50% of the corresponding blood glucose) with Gram-positive cocci in 80% to 90% of cases. Empiric therapy may be started immediately after drawing two blood cultures (positive in 50%), if lumbar puncture is delayed.

Table 2: Criteria for Severe Pneumococcal Pneumonia

Patients who fulfil two of the following criteria at admission
Respiratory rate ≥30/min
Partial pressure of oxygen (PaO_2/FiO_2) ≤250
Bilateral pneumonia or multilobar pneumonia
Systolic blood pressure (BP) <90 mm Hg and/or diastolic BP <60 mm Hg
Patients who develop one of the following features during admission
Need for mechanical ventilation
Increase in the size of infiltrates by ≥50% within 48 hours
Septic shock or the need for vasopressors for ≥4 hours
Urine output < 80 mL in 4 hours or serum creatinine >2 mg/dL in the absence of chronic renal failure

Seizures, cerebral oedema or hydrocephalus develop in 64% to 75% of patients. Systemic complications like septic shock or disseminated intravascular coagulation are seen in 38% to 45% patients.

TREATMENT

Beta-lactams are the mainstay of anti-pneumococcal therapy. They prevent cell-wall synthesis by blocking endo-, trans- and carboxypeptidases. Oral amoxycillin (20 to 40 mg/kg/day) for 10 days (with/without clavulanate), newer macrolides, newer fluoroquinolones, or first generation cephalosporins are commonly used antibiotics for ASOM and pneumonia. Intravenous penicillin G 4 million units q4h, amoxycillin 1g q4h or an injectable cephalosporin may be used for serious or resistant infections. Penicillins still fare better than macrolides, at least in pneumococcal pneumonia, despite some *in vitro* resistance. Failure of treatment with β-lactams, macrolides and trimethoprim/sulphamethoxazole has been reported in meningitis and otitis media caused by drug-resistant *Pneumococci;* but not for drug-resistant pneumococcal pneumonia. Susceptibility testing is essential in cases of meningitis. Antibiotics for sinusitis are reserved for patients not responding to decongestants in two weeks. Patients with severe pneumococcal pneumonia are usually treated with a combination of penicillins with macrolides (e.g. azithromycin) or newer fluoroquinolones (e.g. levofloxacin or moxifloxacin) or clindamycin. If high antibiotic resistance is suspected, empiric therapy may be started with a third generation cephalosporin combined with a newer quinolone or vancomycin (to which pneumococci are invariably sensitive *in vitro*). In case of severe penicillin/cephalosporin allergy a carbapenem may be used.

If acute pyogenic meningitis is suspected, intravenous antibiotics should be started as soon as possible with ceftriaxone 2 g twice daily plus vancomycin 15 mg/kg twice daily and dexamethasone. The treatment is modified when culture reports are available (**Table 3**). Treatment is continued for a minimum of 10 to 14 days. If a patient with a penicillin-resistant organism is slow to respond

clinically, repeat lumbar puncture may be indicated to assess bacteriologic response. Treatment failures have been reported with ceftriaxone or cefotaxime for some strains with higher penicillin resistance (MICs ≥2 µg/dL).

Table 3: Choice of Antibiotics in Pneumococcal Meningitis According to the Susceptibility Reports

Minimum Inhibitory Concentrations (MIC)	Antibiotic Therapy
Penicillin <0.1 µg/ml	Penicillin G, 4 million units intravenously daily every 4 hourly, or ceftriaxone, 2 gm intra-venously every 12 hourly
Ceftriaxone or cefotaxime ≤0.5 µg/ml	Ceftriaxone 2 g intravenously every 12 hourly, or, Cefotaxime 2 g intravenously every 6 to 8 hourly
Ceftriaxone ≥1 µg/ml	Ceftriaxone, 2 g intravenously every 12 hourly plus vancomycin, 30 mg/kg/day intravenously in two divided doses

In pneumococcal endocarditis, urgent empirical therapy should start with intravenous β-lactams (usually ceftriaxone or cefotaxime), combined with vancomycin if antibiotic resistance is prevalent in the community, which should be continued for 4 weeks.

Adjunctive Management

For ASOM and sinusitis nasal decongestants may be used. Myringotomy may relieve severe otalgia and prevent complications like mastoiditis. Recurrent infections require long-term antibiotic prophylaxis. Failure of oral therapy may require hospitalisation for intravenous antibiotics, insertion of ventilating tubes or surgical drainage of sinus.

Patients with complicated pneumococcal parapneumonic pleural effusion (pleural fluid glucose less than 50 mg/dL, Gram-stain or culture positivity or turbid/purulent pleural fluid) require tube thoracostomy.

Patients with sepsis and multi-organ dysfunction are managed according to the Surviving Sepsis Campaign Guidelines with early intensive therapy, low-dose glucocorticoids, low tidal volume ventilation, intensive glycaemic control and drotrecogin-alpha [recombinant human activated protein C (rhAPC)]. The landmark PROWESS study showed a better survival benefit of rhAPC infusion in community-acquired pneumonia related sepsis than abdominal sepsis.

The administration of dexamethasone along with antibiotic in adults with bacterial meningitis reduces mortality by 60% and all unfavourable outcomes by 50%. Adults with acute pyogenic meningitis should receive 10 mg of dexamethasone intravenously immediately before the first dose of appropriate antibiotic and then every 6 hourly for 4 days. The use of high-dose steroids in patients with severe sepsis and septic shock, however, worsens the outcome. Its role in meningitis caused by penicillin-resistant organisms is unclear as its anti-inflammatory activity may reduce penetration of some drugs into the CSF. Such patients should be carefully monitored for treatment failure. Almost two-thirds of the patients with pneumococcal meningitis required mechanical ventilation.

Prevention

The commonly used pneumococcal polysaccharide vaccine includes 25 µg each of 23 purified capsular polysaccharide antigens from serotypes causing 85% to 90% of invasive disease. This adjuvant-free, phenol/thiomersal preserved vaccine has been shown to have an overall efficacy of 50% to 70% in adults. Vaccination protects against invasive disease including meningitis but does not prevent local infections including pneumonia. Antibody level gradually declines and there is no anamnestic response. So it is prudent to offer revaccination to people more than 65 years old and splenectomised patients, more than 5 years after the previous vaccination. Unfortunately, some of the high risk groups for whom the vaccine is recommended benefit poorly from the vaccine. These include debilitated elderly or people with chronic lung disease or people with lymphoma or HIV/AIDS.

For children less than 2 years, an alterantive seven-valent pneumococcal conjugate vaccine is recommended. Widespread use of the vaccine resulted in reduced disease in unvaccinated children and adults and also due to herd immunity. The overall incidence of antibiotic resistance has also decreased. However, infections by other (replacement) serotypes are on the rise along with the prevalence of antibiotic resistance among those strains.

Conjugate vaccines with more than 8 serotypes are showing promising results in trials. Current indications of pneumococcal vaccination are summarised in **Table 4.**

Table 4: Current Indications for Pneumococcal Vaccination

Immunocompetent adults ≥65 years of age

Immunocompetent adults aged 19 to 64 years with:
- Cerebrospinal fluid leaks
- Chronic cardiovascular disease
- Chronic pulmonary disease
- Alcoholism
- Cochlear implants
- Residence in chronic care facilities

Groups of adults aged >19 years and <65 years with impaired immunity
- Those with immunocompromising diseases like HIV infection, lymphoma, multiple myeloma
- Those on immunosuppressive chemotherapy (including corticosteroids) and post-organ or bone-marrow transplantation
- Those with splenectomy or asplenia
- Patients of chronic renal disease, chronic liver disease, diabetes mellitus

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17.12 Meningococcal Infections

RK Singal, Vivek Pal Singh

INTRODUCTION

Neisseria meningitidis has been recognised as a cause of serious disease for centuries. Description of an illness resembling meningococcal disease dates back to the 16th century. Vieusseux first described meningococcal disease in 1805. However, Anton Weichselaum first isolated *N. meningitidis* as the causative agent of meningococcal disease in 1887.

Approximately 10% of the general population are carriers of *N. meningitidis*. In rare instances, *Meningococci* can overcome the body's natural defence mechanisms and cause life-threatening infections—meningococcal meningitis and fulminant meningococcaemia, which can often coexist.

AETIOPATHOGENESIS

N.meningitidis is Gram-negative, aerobic, bean-shaped *Diplococci*, best isolated on chocolate agar and exclusively found in humans. Based on antigenicity of capsular polysa-ccharides *Meningococci* are divided into 13 subtypes: A, B, C, D, E, H, I, K, L, W-135, X, Y, Z. Of these five, serogroups (A, B, C, Y, and W-135) are known to cause epidemics and outbreaks accounting for more than 90% of cases.

Meningococci have the ability to exchange genetic material responsible for the capsular production and thereby can switch from serogroup B to C and *vice versa*. This switch mechanism may become an important part of meningococcal virulence with the widespread use of serogroup specific vaccines.

Humans are the only natural reservoirs of *N. meningitidis*. Spread is by direct contact or droplet infection. The incubation period averages 3 to 4 days (range 1 to 10 days), during which the person is infective. Asymptomatic nasopharyngeal carriage of *N. meningitidis* is seen in 5% to 10% of adults. Most of these strains are nonpathogenic. Colonisation of the nasopharynx by *N. meningitidis* may be transient, intermittent or long-term and the prevalence may increase in the presence of concomitant respiratory tract infection, overcrowded living conditions and smoking. Colonisation induces an immunological response to *N. meningitidis*, so that by young adulthood majority of people have measurable antibodies to the pathogenic serogroups of *N. meningitidis* (A, B, C, Y and W-135). In some people, meningococci penetrate the mucosa and gain access to the blood stream, where they may be killed by bactericidal antibodies, complement or phagocytic cells or may multiply and initiate bacteremic phase. The bacteria may seed the meninges, joints or pericardium or may multiply in the bloodstream causing meningococcaemia. Disease occurs most commonly in persons who are sero-negative and have newly acquired *N. meningitidis*. Meningococcal cell wall lipoligosaccharide (LOS) is responsible for the inflammatory cascade in meningococcaemia. In addition, *Meningococci* can invade the vascular endothelium, which produces molecules with procoagulant and adhesive properties for leucocytes. Both platelets and leucocytes contribute to the formation of microthrombi and vascular injury. Thrombosis of small to mid-sized arteries produces peripheral necrosis and gangrene necessitating digit or limb amputation.

EPIDEMIOLOGY

Meningococcal disease occurs globally and is a major cause of epidemics in sub-Saharan Africa (the meningitic belt – a region extending from Ethiopia in the east to Senegal in the west). The disease is endemic in temperate climate, but the majority of cases occur during winter and early spring. The incidence is highest amongst infants in whom protective antibodies have not yet developed. It drops after infancy and then increases during adolescence and early adulthood.

Serogroups A, B and C account for most cases of meningococcal disease worldwide, with serogroups B and C causing the majority of cases in Europe and America and serogroups A and C in Asia and Africa. The Islamic Haj pilgrimage to Mecca has historically been associated with outbreaks of *N. meningitidis* serogroup A. In India, meningococcal disease is endemic in Delhi and sporadic cases occur in Haryana, Uttar Pradesh, Rajasthan, Sikkim, Gujarat, West Bengal and Orissa. Serogroups A and C account for most cases in India. However, sporadic group B meningococcal infection has been reported in Delhi.

Those who lack or have a deficiency of antibody-dependent, complement-mediated immune lysis are most susceptible to invasive meningococcal disease. Various risk factors for invasive meningococcal disease are summarised in **Table 1**.

Table 1: Risk Factors for Invasive Meningococcal Infections

Children 6 months to 4 years
Complement deficiency
Functional/anatomic asplenia
Concurrent upper respiratory tract infection
Tobacco smoking
Immunodeficiency states (HIV, drugs)
Chronic diseases (SLE, cirrhosis, multiple myeloma)

CLINICAL FEATURES

The clinical spectrum of invasive meningococcal disease includes pyogenic meningitis, meningitis with or without meningococcaemia. Meningeal infection occurs in about 50% of patients and is similar to other forms of acute purulent meningitis. Patients present with sudden onset of fever, vomiting, photophobia, headache, neck stiffness and altered mental status. Infants usually have a slower onset of the disease with non-specific signs and without neck stiffness. *N. meningitidis* can be isolated from the bloodstream in approximately 75% of the patients, but meningococcal sepsis, also known as meningococcaemia, occurs in only 5% to 20% of patients. Meningococcaemia is characterised by the abrupt onset of fever and a petechial, purpuric or ecchymotic rash (**Figure 1**), which may progress to purpura fulminans. Meningococcaemia is often

associated with hypotension and acute adrenal haemorrhage (Waterhouse-Friedrichsen syndrome) and multi-organ failure. Up to one-third of patients present with meningitis without signs of sepsis. However, absence of meningeal signs in a patient with meningococcaemia is a poor prognostic sign. It suggests that the bacteria have multiplied so rapidly in the blood that meningeal seeding and inflammation could not occur. Neurological complications include generalised and focal seizures in up to 40% of cases. The complications of invasive meningococcal infection are summarised in **Table 2**.



Figure 1: Characteristic skin rash in a patient with meningococcaemia.

Table 2: Complications of Meningococcal Meningitis and Fulminant Meningococcaemia

Seizures
Cerebral venous thrombosis
Subdural empyema
Hydrocephalus
Hemiparesis
Deafness
Cranial nerve palsies
Mental retardation
Loss of digits/limb
Shock
Disseminated intravascular coagulation (DIC)
Multi-organ failure

Chronic meningococcaemia is a rare syndrome of prolonged, intermittent fever, rash, arthralgias, headache and splenomegaly that lasts for weeks to months. Untreated or when treated with steroids, chronic meningococcaemia may evolve into meningitis, fulminant meningococcaemia or endocarditis.

Meningococcal disease may have varied systemic manifestations. Apart from meningitis and meningococcaemia, arthritis occurs in 10% of patients. Early onset arthritis reflects a direct invasion of the joint by Meningococci, whereas late onset arthritis reflects immune complex deposition. Primary meningococcal pneumonia occurs in 5% to 15% of patients and is often due to serogroup Y. Systemic or extra-meningeal manifestations are uncommon during the course of both meningococcal meningitis and sepsis and usually occur within the first seven days of the disease.

DIFFERENTIAL DIAGNOSIS

Cutaneous differential diagnosis of acute meningococcaemia includes acute viral syndromes particularly dengue haemorrhagic fever, leptospirosis, acute hypersensitive vasculitides, septic vasculitis due to acute bacteraemia or endocarditis, toxic shock syndrome, purpura fulminans or rocky mountain spotted fever.

Chronic meningococcaemia may resemble chronic gonococcaemia, Henoch-Schönlein purpura, rat-bite fever, sweet syndrome, erythema multiforme and subacute bacterial endocarditis.

DIAGNOSIS

The gold standard for the laboratory diagnosis of meningococcal disease is bacteriologic culture, but its sensitivity may be low in patients pre-treated with antibiotics. Gram staining of cerebrospinal fluid (CSF) is still an important method of rapid and accurate diagnosis of *N. meningitidis*. Gram staining of peripheral blood buffy coat may reveal Gram-negative *Diplococci* in fulminant meningococcaemia. Non-culture methods such as direct antigen detection using latex agglutination in serum or urine can provide a rapid, group specific diagnosis but false negative results are common, especially in cases of serogroups B disease.

Since *Meningococci* are fastidious and fragile, isolation rates can be increased, if the clinical specimen is examined as soon as possible after collection. In case delay is anticipated, the sample may be incubated at 35°C in a 5% carbondioxide atmosphere or may be inoculated aseptically into a recently developed biphasic medium (trans-isolate medium) to enhance the recovery of the causative organism.

Needle aspirates or skin biopsy specimens from patients with meningococcal sepsis tested using gram stain and culture yielded a 56% to 80% sensitivity based on few studies. A study comprising of adult cases with fulminant meningococcaemia observed four variables at the time of admission indicating a fatal outcome.

1. Plasma fibrinogen levels less than 1.5g/L (sole adverse prognostic factor)
2. Factor V concentration of 0.2 or less
3. Platelet count less than 80×10^9/L
4. CSF leucocyte count 20×10^6/L or less

TREATMENT

Meningococcal disease can kill more rapidly than any other infection. Patients with either meningococcaemia or meningococcal meningitis should be hospitalised immediately. Many a times meningitis due to *N. meningitidis* may be impossible to differentiate from other causes of pyogenic meningitis, prompt antibiotic therapy with a third generation cephalosporin-ceftriaxone (2 g IV every 12 hourly) or cefotaxime (2 g IV every 4 hourly) should be initiated. Due to high prevalence of penicillin-resistant *Streptococcus pneumoniae*, empirical treatment of meningitis in infants or elderly should be a combination of vancomycin plus ceftriaxone or cefotaxime. In established cases of meningococcal meningitis penicillin G in a dose of 18 to 24 million units (4 million units IV 4 hourly) per day is the first line of therapy. Antibiotic therapy is essential for at least one week.

N. meningitidis has been relatively slow to acquire resistance to penicillin. However, invasive Meningococcal disease strains with

decreased susceptibility to penicillin have been reported worldwide including from India. Invasive meningococcal disease with decreased susceptibility to penicillin has been found to be strongly associated with serogroup Y and W-135 strains. In a study, resistance to quinolones was reported at 100% for levofloxacin, 84.6% for ofloxacin and 65.4% for ciprofloxacin. However, all isolates were susceptible to third-generation cephalosporins, azithromycin and rifampicin. Meropenem (1 g IV 8 hourly) and chloramphenicol (75 to 100 mg/kg dL) are alternatives in penicillin allergic individuals. Dexamethasone 10 mg IV 20 minutes before the first antibiotic dose and then every 6 hourly for 4 days, is recommended in every case of purulent meningitis. Activated protein C in a dose of 24 mg/kg per hour (2 g every 4 hour) as a continuous intravenous infusion for 96 hours is approved for use in patients with early severe sepsis with multi-organ failure (APACHE II score <25).

Early microsurgical arteriolysis is a reliable method to reduce the devastating amputations found in patients with meningococcal sepsis. This approach significantly improves the functional outcome in severely ischaemic limbs in meningococcal-induced sepsis in children.

PROGNOSIS

Timely treatment with appropriate antibiotics results in a good outcome in patients with meningococcal disease.

Extremes of age, shock, coma or focal neurological deficits, absence of meningeal signs, confluent rash and leucopaenia are associated with a poor prognosis.

The fatality rate in untreated cases is up to 90%. The sequelae such as deafness, seizures or mental retardation are seen in 3% to 4% of survivors, mostly children.

PREVENTION

Chemoprophylaxis

Once a case of meningococcal disease is identified, the patient's close contacts should be treated with an effective anti-microbial agent so as to eradicate potential colonisation by *N. meningitidis*. Close contacts who have previously received meningococcal vaccine should still be given chemoprophylaxis as vaccines do not confer 100% protection and immunity wanes with time.

Chemoprophylaxis is advocated for close contacts who have been directly exposed to the patient's oral secretions within one week before the onset of patient's symptoms until 24 hours after appropriate anti-microbial therapy has been initiated. Rifampicin 600 mg bid for 2 days, ciprofloxacin 500 mg orally once or ceftriaxone 250 mg once IM are recommended for chemoprophylaxis.

Meningococcal Vaccine

Routine immunisation with meningococcal conjugate vaccine continues to be recommended, despite ongoing concern about a possible association between vaccination and Guillain-Barré syndrome. Vaccination is recommended to provide pre-exposure immunity to persons who are at high risk for meningococcal disease.

Two types of vaccines are licensed. Meningococcal polysaccharide vaccine [bivalent (for serogroup A and C) and quadrivalent (for serogroup A, C, Y, and W-135)] and meningococcal conjugated polysaccharide vaccine. Both vaccines elicit protective antibodies in more than 97% of recipients (as measured at 28 days).

Both vaccines can be given with other vaccines, but at a different anatomical site. Mild-to-moderate local reactions and minor systemic symptoms may occur with either vaccine. A major limitation of these two vaccines is that neither provides immunity against serogroup B, which is responsible for approximately one-third of meningococcal disease worldwide. The meningococcal conjugate polysaccharide vaccine induces a T-cell dependent response, resulting in an improved immune response in infants, priming immunological memory and leading to a booster response to subsequent doses. Nasopharyngeal carrier rates also decreases by use of conjugate vaccine, thereby interrupting the transmission of *N. meningitidis* and establishing herd immunity. The recommendations for the use of meningococcal vaccines in previously unvaccinated persons are summarised in **Table 3**.

Table 3: Recommendations for the Use of Meningococcal Vaccines in Previously Unvaccinated Persons*

General Population	Persons at Increased Risk
A single dose of conjugate vaccine for persons 11 to 12 years of age or on entry into high school (~ 15 years of age)	A single dose of conjugate vaccine in persons 11 to 55 years of age A single dose of polysaccharide vaccine for persons 2 to 10 years of age or ≥ 55 years and is an acceptable alternative to the conjugate vaccine in 11 to 55 years age group. Vaccination of persons younger than 2 years is not recommended**

Dato from Centres for Diseose Control and Prevention, Atlonto, USA

***Meningococcol polysoccharide voccine may be used to elicit short-term protection agoinst serogroup A in trovellers to endemic areos. For children 3 to 18 months of oge, the voccine is given in two doses 3 months aport, ond in o single dose in children 19 to 23 months of oge.*

Newer approach to meningococcal vaccine

The development of quadrivalent glycoconjugate meningococcal ACWY vaccine has broadened protection against meningococcal disease. A novel meningococcal MenACWY-CRM (Menveo) glycocongugate vaccine, formulated by selective conjugation chemistry of intermediate-chain-length meningococcal saccharides was found to be immunogenic in individuals aged 2 months to 65 years of age, a need that remains unmet.

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17.13 Gonococcal Infections

Chander Grover

INTRODUCTION

Gonococcal infections are a spectrum of clinical disorders which are an important public health problem. The causative organism is *Neisseria gonorrhoeae*, a Gram-negative, non-spore forming diplococcus, closely related to *N. meningitidis*, *N. lactamica* and *N. catarrhalis*.

The infection is transmitted almost exclusively through sexual contact or perinatally with occasional reports of fomite borne transmission. The organism is an obligate human parasite. It causes gonorrhoea (also known as strangury or clap) apart from causing rectal, pharyngeal, conjunctival or disseminated infections.

EPIDEMIOLOGY

Worldwide, gonorrhoea is an important bacterial sexually transmitted infection (STI). It is the second most commonly reported notifiable disease in USA with 600,000 new infections occurring annually. No such comprehensive data are available from India. However, the prevalence is reported to be 9.7% in females attending STI clinics and could be as high as 16.9% in female sex workers. Along with other bacterial STIs, the incidence of gonorrhoea has reduced over the years but has remained static for the past decade. The risk factors include unprotected sexual contact, multiple sex partners, use of intra-uterine devices, and child abuse or child birth in an infected mother.

AETIOPATHOGENESIS

N. gonorrhoeae is capable of infecting columnar epithelia where it attaches with its long pili. From here, it penetrates the epithelial cells, multiplies within them, releasing lipo-oligosaccharides and peptidoglycans and causing release of tumour necrosis factor-alpha (TNF-α). Resulting neutrophilic infiltration leads to tissue damage and purulent discharge. The organism is exocytosed from the basal side, may invade the blood stream and disseminate. Bactericidal humoral immunity is also activated. However, cell mediated immune response is generally poor. Haematogenous dissemination is produced by strains resistant to antibody and complement-mediated damage.

CLINICAL FEATURES

The manifestations of gonococcal infections are summarised in **Table 1**. *N. gonorrhoeae* infects the non-cornified epithelium of the urogenital tract, rectum, pharynx or conjunctiva. The incubation period is 1 to 14 days. However, symptoms appear earlier in males (2 to 5 days) and later in females (10 days). The risk of transmission through a single vaginal penetrative contact is 20% for males and 50% to 90% for females. The clinical features vary according to the site and severity of the infection.

1. Males

Onset is with a mild discharge which rapidly becomes profuse, purulent, associated with marked discomfort, pain, burning sensation, frequency and urgency (**Figure 1**). In 15% cases the infection may be mild or asymptomatic.



Figure 1: Thick pus extruding from the urethral meatus in a male with gonorrhoea.

2. Females

Only 50% of those infected are symptomatic and may present with increased vaginal discharge or mild urethral discharge. On examination, the cervix is inflamed, with mucopurulent or purulent discharge (**Figure 2**). Intermittent bleeding or menorrhagia may occur.



Figure 2: Inflamed cervix with purulent discharge extruding from the cervical os. The discharge is less profuse than a male urethral discharge.

3. Ano-Rectal Infection

This is seen more commonly in females and homosexuals. It may present with minimal anal pruritus and discharge to frank proctitis.

4. Pharyngeal Infection

More than 90% of these infections remain asymptomatic. Fellatio transmits the infection more efficiently than cunnilingus.

5. Conjunctivitis

This is encountered in a neonate born to an infected mother or rarely through accidental inoculation.

DIAGNOSIS

The diagnostic tests for gonococcal infections include the following:

1. Microscopy

A highly sensitive (>95%) and specific (>99%) test for symptomatic males where demonstration of more than 5 neutrophils per oil immersion field with Gram-negative, intra-cellular *Diplococci* is diagnostic (**Figure 3**). The test is not very sensitive for females, asymptomatic males or for sites other than urethra.

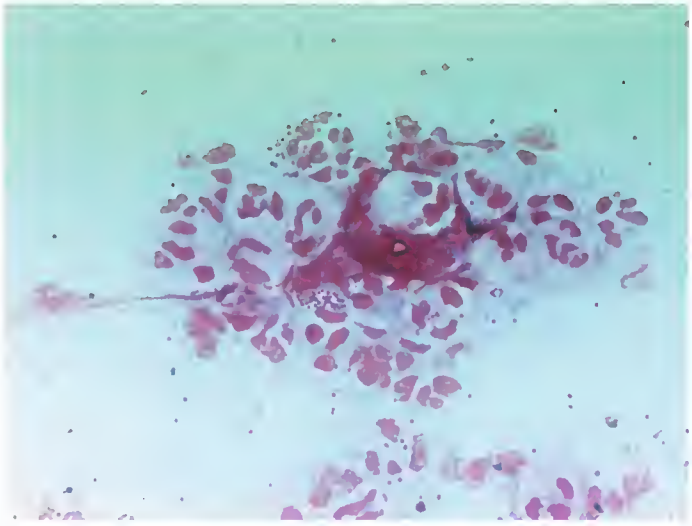


Figure 3: Multiple neutrophils in a Gram-stained smear of urethral discharge. Multiple Gram-negative intracellular *Diplococci* can be visualised.

2. Culture

This is the gold standard for diagnosis and is carried out on selective media, like modified Thayer-Martin, New York City medium. The plate is incubated under 5% carbondioxide at 37°C. This can be used to diagnose the infection from sites like endocervix, pharynx and rectum. Culture also provides the opportunity for antibiotic susceptibility testing.

3. Serology

Various tests available to detect serum antibodies against *N. gonorrhoeae* include complement fixation, latex agglutination, immunoflorescence or radio-immunoassay.

4. Nucleic Acid Amplification Tests

These are highly sensitive tests, currently approved by the FDA for the diagnosis of gonorrhoea. Widest range of specimens can be conveniently tested. However, some tests may cross-react with other *Neisseria* species.

COMPLICATIONS

These have been summarised in **Table 1**. Many complications of gonorrhoea cause long-term morbidity and are of profound public health importance. Apart from reflecting the load of reproductive tract infections (RTIs) in the society, gonococcal infections indicate high-risk behaviour and also facilitate the transmission of HIV. Hence, National STI/RTI control programmes place substantial emphasis on them.

Table 1: Clinical Manifestations of Gonococcal Infections

Primary Gonococcal Infections
Anterior urethritis
Endocervicitis
Proctitis
Pharyngitis
Conjunctivitis
Complicated Gonococcal Infection
Males
Posterior urethritis, periurethral abscess
Infection of Cowper's/Tyson's glands
Urethral stricture
Prostatitis, epididymo-orchitis
Females
Bartholin's gland abscess
Pelvic inflammatory disease (PID)
Tubo-ovarian abscess
Infertility
Spontaneous abortion, premature delivery, chorio-amnionitis
Both
Corneal perforation, blindness
DGI (arthritis-dermatitis syndrome)
Medical emergencies
Scrotal swelling, epididymo-orchitis
Severe PID
DGI

The risk factors for developing disseminated gonococcal infection (DGI) include pregnancy, pharyngeal carriage, female sex, complement deficiency and specific gonococcal serotypes. After an incubation period of 7 to 30 days, the patient develops arthralgias and synovitis of wrist, ankle and metacarpo-phalangeal joints. By this time, the primary genital infection may have regressed. Subsequently, tender, necrotic pustules on an erythematous base develop on acral areas. Few patients may develop meningitis or endocarditis. If blood, joint fluid or pustules grow the organism, the patient is said to have *proven* DGI. If cultures are positive from the primary mucosal site or from sexual partner, then the diagnosis is *probable* DGI. In the absence of any culture positivity but response to therapy, the patient is said to have *possible* DGI.

TREATMENT

The treatment of gonorrhoea is challenging because of the rapidity with which antibiotic resistance develops. From time to time, guidelines for its treatment are issued by national and international authorities. Indian National Guidelines for Syndromic Management of STIs recommend the use of Cefixime (400 mg) + Azithromycin (1 gm) orally as single dose treatment for urethral or cervical discharge. Treatment for scrotal swelling or PID (both may be medical emergencies) involves 7 days administration of Cefixime and Doxycycline tablets. High levels of quinolone resistance preclude their use as of now. *Chlamydial* co-infection needs to be treated simultaneously. Abstinence, partner notification and

treatment also need to be ensured. The WHO/IUSTI guidelines 2009 for the treatment of gonorrhoea are detailed in **Table 2**.

Table 2: WHO/IUSTI Guidelines for the Treatment of Gonorrhoea (2009)

Uncomplicated Infection – all single dose treatments
- Ceftriaxone 250 mg intramuscularly (preferred for pharyngeal infections)
- Cefixime 400 mg orally
- Spectinomycin 2 g intramuscularly (preferred for beta-lactam allergy
- Azithromycin 2 g orally

Complicated/Disseminated Infection
- Initial therapy
  - Ceftriaxone 1 g intramuscularly or intravenously 24 hourly
  - Cefotaxime 1 g intravenously 8 hourly
  - Spectinomycin 2 g intramuscularly 12 hourly.
- Continue for 7 days, may switch 24 to 48 hours after symptoms improve to
  - Cefixime 400 mg twice daily

Ophthalmia neonatorum
- Ceftriaxone 25-50 mg/kg intravenously or intramuscularly as a single dose
- Cefotaxime 100 mg/kg intramuscularly as a single dose
- Frequent conjunctival irrigation with saline

PREVENTION

Partner management and abstinence during the course of treatment are important measures which help bring down the incidence of gonococcal infections. Proper use of barrier contraception in the form of condoms, diaphragms or cervical caps reduces the risk of transmission of gonococcus. Similar effect is seen with spermicidal and bactericidal agents. Oral contraceptives increase the risk of infection. Prophylactic administration soon after exposure is likely to decrease the risk of developing gonorrhoea.

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17.14 Typhoid Fever (Enteric Fever)

Swapan Kumar Niyogi

INTRODUCTION

Typhoid fever is a systemic infection caused by the bacterium *Salmonella enterica* serotype typhi (*S. typhi*). *Salmonella enterica* serotype paratyphi (*S. paratyphi*) A, B and C cause the clinically similar condition, paratyphoid fever. Typhoid and paratyphoid fever are collectively referred to as enteric fever.

In 1873, William Budd described the contagious nature of the disease and incriminated faecally contaminated water sources in transmission. The causative organism was visualised in tissue sections from Peyer's patches and spleen of infected patients by Eberth in 1880 and was grown in pure culture by Gaffky in 1884. In 1911, Elie Metchnikoff fulfilled one of Koch's postulates reproducing disease in chimpanzees after throat inoculation with *S. typhi*.

EPIDEMIOLOGY

Typhoid fever was a major cause of morbidity and mortality in the US and Europe in the 19th century. However, with the provision of clean water and good sewage systems, there has been a marked decline in the incidence of typhoid in developed countries, but the disease still remains a major public health problem in developing countries, the true burden of typhoid fever in developing countries is difficult to estimate.

Age Group

Typhoid fever is considered to be a disease mainly of children and young adults. In endemic areas, the highest attack rate occurs in children aged 5-13 years. Paratyphoid fever has the highest incidence in teenagers and young adults.

Gender

Typhoid fever is more commonly seen in males. Female have a special predilection to become chronic carriers.

Socioeconomic Factors

It is a disease of poverty and associated with inadequate sanitation facilities and unsafe water supplies.

Incubation Period

Usually 10 to 14 days but it may be as short as 3 days or as long as 21 days depending on the size of the initial inoculum. For paratyphoid fever the range is 1 to 10 days.

MODE OF TRANSMISSION

The disease is transmitted by the faecal-oral route, via contaminated food and water. Usually, water-borne transmission involves the ingestion of fewer organisms and as a result, has a longer incubation period and lower attack rate than food-borne transmission. Occasionally, health care workers can acquire the disease from infected patients, while laboratory workers can acquire the disease after accidents. *S. paratyphi* is mainly transmitted by contaminated food from street vendors.

Environmental Factors

Typhoid fever is usually observed throughout the year.

Reservoir of Infection

Humans are the natural host and reservoir for both typhoid and paratyphoid fevers.

AETIOPATHOGENESIS

The *Salmonella* are a heterogenous group of bacteria in the genus *Salmonella* of the family enterobacteriaceae. The *Salmonella* genus contains two species, which are divided into seven subspecies: *S. enterica* (six subspecies, i.e. *enterica, salamae, arizonae, diarizonae, houtenae* and *indica*) and *S. bongori* (one subspecies). The subspecies are divided into over 50 serogroups based on somatic (O) antigens present. The serogroups are further divided into over 2300 serotypes based on flagellar (H) antigens in one or both of two phases. Some have capsular (K) antigens, referred to as Vi, which may interfere with agglutination by O antisera and are associated with invasiveness. Agglutination tests with absorbed antisera form the basis for serologic classification.

The agents that cause enteric fever are, therefore, *Salmonella enterica* subspecies *enterica* serovar typhi (commonly referred to as *S. enterica* serovar typhi) and serovars paratyphi A, B and C. From a clinical perspective, the serogroups of *Salmonella* are usually considered as two broad groups. Firstly, those which are human-host restricted and responsible for the systemic invasive disease known as enteric fever, which include *S. typhi and S. paratyphi* A, B and C. The remaining serotypes (non-typhoidal *Salmonella*) often cause gastroenteritis and can be associated with localised infections and/or bacteraemia.

S. typhi is ingested with food and water. It passes through the stomach and invades the gut epithelium (distal ileum). In the small intestine, the bacteria adhere to mucosal cells and then invade, translocate to the intestinal lymphoid follicles and the draining mesenteric lymph nodes and some pass on to reticulo-endothelial cells of the liver and spleen. Salmonella are able to survive and multiply within the mononuclear phagocytic cells of the lymphoid follicles, liver and spleen. After a 7 to 14 day incubation period, the onset of a sustained secondary bacteraemia results in clinical disease.

The bacteraemia of typhoid fever persists for several weeks if antibiotic therapy is not given. In this phase the organism disseminates widely to the liver, spleen, bone marrow, gall-bladder and the Peyer's patches of terminal ileum. The symptoms and signs of typhoid fever are not thought to be entirely due to circulating endotoxin. Increased levels of circulating pro- and anti-inflammatory cytokines have been demonstrated in typhoid fever as well as a reduced capacity of whole blood to produce pro-inflammatory cytokines in severe

diseases. Ulceration of Peyer's patches is seen where the inflammatory process has resulted in ischaemia and necrosis. These ulcers are ovoid in shape with irregular undermined edges; they lie along the long axis of the gut and if extensive may lead to erosion of blood vessels or perforation of gut wall. Relapse probably occurs because of persisting organisms within the reticulo-endothelial system. Gall bladder infection may become chronic in individuals with gall bladder pathology. Typhoid fever induces systemic and local humoral and cellular immune responses but these confer incomplete protection against relapse and re-infection.

CLINICAL FEATURES

The most important symptom is prolonged fever, initially low-grade, rises progressively, and by the second week is often high and sustained (38.8 to 40.50°C or 101.8 to 104.9°F). Characteristically, continuous fever rising in a step-ladder fashion is observed. A prodorme of non-specific symptoms often precedes fever and includes chills, headache, anorexia, cough, weakness, sore throat, dizziness and muscle pain. In general, the symptoms associated with *S. typhi* are more severe than those associated with *S. paratyphi.*

Physical signs are few, but a coated tongue, tender abdomen, hepatomegaly and/or splenomegaly may be found. Relative bradycardia and dicrotic pulse may develop. Approximately, in 30% of patients, at the end of the first week, small maculo-papular, blanching and erythematous rash ('rose spot') typically on the trunk and chest may be seen particularly in fair-skinned patients. The rash resolves after 2 to 5 days without leaving a trace. Constipation is generally more common in adults, but in young children and adults with HIV infection, diarrhoea predominates.

A rapid drop in temperature, rising pulse, falling blood pressure and worsening of abdominal pain during the later period of the illness suggests intestinal bleeding or perforation. This drop is usually followed by a rise in temperature after a few hours as peritonitis develops. These complications result from necrosis at the initial site of *Salmonella* infiltration at the Peyer's patches. Both these life-threatening complications require immediate medical and surgical interventions. In typhoid state of 'coma vigil' patients become profoundly toxic, lie prostrated, semiconscious and tremulous, muttering continuously, picking at bed clothes or imaginary objects (carphology). Typhoid encephalopathy, often accompanied by shock is associated with a high mortality.

In the past, paratyphoid fever was believed to cause a milder disease than typhoid fever, but recent reports showed indistinguishable clinical features in both. *S. paratyphi* A or S. *paratyphi* B can manifest with jaundice, thrombosis, and systemic infections. *S. paratyphi* B might occasionally have an onset similar to non-specific *Salmonella* gastroenteritis. Relapse has been reported with *S. paratyphi* A. *S. paratyphi* C has a limited distribution (common in Guyana and Eastern Europe). It causes mainly bacteraemia and occasionally abscesses, arthritis, and cholecystitis.

DIAGNOSIS

Typhoid should be considered in any patient with prolonged unexplained fever (sustained or remittent temperature) around 39.5°C (103°F) and appearance of rose spot in such a case would be diagnostic.

Definitive diagnosis of typhoid fever depends on isolation of *S. typhi* or *S. paratyphi* from blood, bone marrow, stool, urine or other body fluids. Blood culture followed by microbiological identification is the mainstay diagnosis of typhoid fever. The yield of blood culture is quite variable; it can be as high as 90% during the first week of infection and decrease to 50% by the third week. A low yield is related to low numbers of *Salmonella* in infected patients and/or to recent antibiotic treatment. Bone marrow culture is more sensitive and gives positive results in up to 80% to 95% of patients even after antibiotics have already been given. Blood culture facilities are often not available in many regions, and *the method is laborious and long.* However, in the absence of a culturable organism, patient's antibodies may provide evidence of infection with the serovars of *Salmonella.* The Widal test has long been used as a serological aid in diagnosis of typhoid fever. The high number of false-positive and false-negative test result limit its clinical usefulness. To make a diagnosis, results from a single acute sample should be interpreted against the appropriate local cut-off value or there should be a four-fold rise in the antibody titres between convalescent and acute sera.

Other new-generation, rapid, serological diagnostic tools have limitation because of their low sensitivity and/or specificity. The most promising recently published results are from PCR-based amplification of DNA from the blood of enteric fever patients but again this technique is not available in resource poor countries.

Haematological investigations are non-specific, leucopaenia and neutropaenia are common. However, leucocytosis can develop (especially, in children) during the first 10 days of the illness, or later if the disease course is complicated by intestinal perforation or secondary infection.

A chronic carrier state can be distinguished by the serological response to the Vi polysaccharide, since carriers often have very high antibody titres to this antigen.

TREATMENT

General Management

Supportive measures such as adequate rest, tepid bath and sponging, appropriate nutrition and diet, all are important in the management of typhoid fever. Anti-pyretics (such as paracetamol 250-750 mg orally every 4 to 6 hours) may be given to control fever.

Anti-Microbial Therapy

In the pre-antibiotic era, the mortality rate of typhoid fever was as high as up to 15%. The introduction of treatment with chloramphenicol in 1948 greatly altered the disease course, decreasing mortality to less than 1% and duration of fever from 14 to 28 days to 3 to 5 days. Chloramphenicol (2 to 4 gm/day for adults or 50 mg/kg for children, in divided doses) remained the standard treatment for enteric fever until the emergence of plasmid-mediated resistance to this drug in 1970s. Due to global spread of chloramphenicol resistant *S. typhi* by the 1980s, ampicillin (1gm orally every 6 hour) and trimethoprim-sulphamethoxazole (TMP-SMX; one double strength tablet

twice daily) became the mainstay of the treatment. Multi-drug resistance *S. typhi*, defined as resistance to all first-line anti-microbials (ampicillin, co-trimoxazole, and chloramphenicol), were first described in India in 1990. With the emergence of multi-drug resistance, either quinolones or third-generation cephalosporins are currently recommended for empirical antibiotic treatment of typhoid fever. The greatest experience has been gained for ciprofloxacin (500mg orally twice a day for 10 days). Ciprofloxacin is also the drug of choice for patients with *S. paratyphi* infection. Ofloxacin (10 to 15 mg/kg in two divided doses) has also been successful. More recently, the emergence of high-level ciprofloxacin resistance in *S. typhi* and *S. paratyphi* A, third-generation cephalosporins, i.e. ceftriaxone (1 to 2 gm intravenous or intramuscular for 10 to 14 days) and azithromycin (1 gm orally once a day for 5 days or 1 gm orally on day 1 followed by 500 mg orally for 6 days) are the drugs of choice.

Treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hours for 48 hours) has been recommended among severely ill patients with shock, obtundation, stupor or coma.

Patients who develop chronic carriage of *Salmonella* can be treated with oral amoxicillin, TMP-SMX, ciprofloxacin, or norfloxacin for 6 weeks.

COMPLICATIONS

The commonest complications, occurring in the 3rd and 4th weeks of infection, include intestinal perforation and/or gastrointestinal haemorrhage and typhoid encephalopathy. Gastrointestinal bleeding occurs in 10% to 20 % of cases due to erosion of a necrotic Peyer's patch into an intestinal vessel and is usually restricted to either occult blood in stool or melaena. In 1% to 2% of cases, bleeding is significant, and can be rapidly fatal if a large vessel is involved. Intestinal (usually ileal) perforation is the most serious complication occurring in 1% to 3% of cases. Some patients manifest neuropsychiatric symptoms. Severe complications, such as disseminated intravascular coagulation and haemorrhages can lead to rapid death. Rare complications whose incidences are reduced by prompt antibiotic treatment include pancreatitis, hepatic and splenic abscesses, endocarditis, pericarditis, orchitis, hepatitis, meningitis, nephritis, myocarditis, pneumonia, arthritis, osteomyelitis and parotitis. There is no difference between complication rates between *S. paratyphi* and *S. typhi*.

Approximately 1% to 5% of patients with enteric fever become asymptomatic carriers. Carriers of *S. typhi* are either convalescent carriers who excrete the organism for a limited period of time after apparent clinical cure, or chronic carriers in whom persistent excretion of *S. typhi* in stool or urine can be detected a year after clinical illness. The incidence of chronic carriage is higher among persons with biliary abnormalities and gastrointestinal malignancies. Asymptomatic intestinal carriers are common in endemic areas and are important sources of infection.

PROGNOSIS

Despite prompt antibiotic treatment, relapse occurs in 5% to 10% of patients, usually 2 to 3 weeks after defervescence. When untreated, the fever persists for 2 weeks or more and defervescence occurs slowly over the following 2 to 3 weeks. Convalescence may last for 3 to 4 months. Death occurs in between 10% and 30% of untreated patients following complications.

If an appropriate antibiotic is given the fever gradually falls over 3 to 4 days. Morbidity and mortality are increased in those individuals infected with multi-drug resistance isolates of *S. typhi*.

PREVENTION

At present enteric fever prevention focuses on improving sanitation, ensuring the safety of food and water supplies, identification and treatment of chronic carriers of *S. typhi*, and use of typhoid vaccines to reduce the susceptibility of hosts to infection. Vaccination is recommended for use in travellers to endemic areas, for household contacts of typhoid carriers, and laboratory workers likely to handle *S. typhi* in preventing and controlling epidemics, as well as for children in endemic settings aged 2 to 20 years.

The old parenteral killed whole-cell typhoid-paratyphoid A and B vaccine has been largely discontinued because of its high reactogenecity. Two safe and efficacious vaccines, the injectable Vi polysaccharide and the oral Ty21a, have been licensed.

The parenteral Vi polysaccharide vaccine is composed of purified Vi polysaccharide from *S. typhi*. It is suitable for adults and children over the age of 2 years and is without serious side effects. A single subcutaneous or intra-muscular dose of 0.5 ml (25 µg) confers protection within 7 to 10 days of inoculation and requires a booster every 2 years.

The *S. typhi* strain Ty21a is a live attenuated oral vaccine. Enteric coated capsules are given on alternate days for four doses. It is safe for adult and children over 6 years of age. The vaccine confers protection within 10 to 14 days after the last dose and a booster dose is recommended every 5 years. The vaccine is well tolerated but as it is a live attenuated vaccine should not be given to immunocompromised patients or patients taking anti-microbials.

A new *S. typhi* Vi conjugate vaccine has been developed, conjugating Vi to a carrier protein to enhance immunogenecity, and is highly effective in children younger than 5 years but it has not been tested in infants.

Since there is no licensed vaccine for paratyphoid fever, it is important that travellers are additionally encouraged to exercise basic food and water hygiene measures while visiting endemic areas.

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17.15 Bacillary Dysentery

Pankaj Tyagi, Jyotsana

Dysentery is an acute inflammatory condition of the large intestine characterised by diarrhoea with blood and mucous in the stool. Bacillary dysentery is an acute bacterial disease involving the large and small intestine manifested by the presence of loose stool mixed with blood and mucous, accompanied by fever, abdominal cramps and tenesmus (a symptom characterised by incomplete sense of evacuation with rectal pain). It is caused by bacteria of the genus *Shigella*, of which *S. dysenteriae* type 1 causes the most severe disease and the largest outbreaks (other species include *S. flexneri, S. sonnei* and *S. boydii)*. It is the most important cause of acute bloody diarrhoea.

EPIDEMIOLOGY

Shigellosis occurs worldwide, and it tends to occur whenever war, natural calamities (e.g. earthquakes, floods), or unhygienic living conditions result in overcrowding (refugees in camp, soldiers in campaigning armies and groups in pilgrims) and poor sanitation. *S. boydii* and *S. dysenteriae* are more common internationally. Disease from *Shigella* species cause an estimated 1 million deaths and 165 million cases of diarrhoea annually worldwide. In India, infectious diseases kill about 11 million children each year while acute diarrhoeal diseases account for 3.1 million deaths in children under 5 years of age, of which 6,00,000 deaths annually are contributed by shigellosis alone. In India, epidemics were mainly encountered in Southern India (Vellore—1972-73, 1997-2001), Eastern India (1984) and Andaman and Nicobar Islands (1986). Recent outbreaks (2002-03) of multi-drugresistant *S. dysenteriae* type 1 have been reported from Siliguri, Diamond Harbour, Kolkata, and Aizwal and Bangladesh. *S. flexneri* is the most common serogroup isolated in India.

Shigellosis is a highly contagious disease. Humans are the principal reservoir of infection. The organism is acid resistant and can easily pass the gastric acid barrier. The infective dose is as low as 10 to 100 organisms. The disease is transmitted faeco-orally, the commonest modes being person-to-person contact and contaminated food and water. Infected food handlers can spread the disease. Sometimes consumption of raw vegetables harvested in fields where sewage is used as fertiliser can cause contamination. Flies can breed in infected faeces and contaminated food, which further spread the infection. **Table 1** enlists the groups which are particularly at high-risk of dysentery.

Table 1: High-risk Groups for Developing Bacillary Dysentery

1. Children under 5 years of age, infants, severely malnourished and history of measles in past 6 weeks
2. Older children and adults who are obviously malnourished
3. Patients who are severely dehydrated, have had a convulsion, or are seriously ill when first seen
4. Adults 50 years of age or older
5. International travellers
6. Homosexual men
7. People with human immunodeficiency virus (HIV) infection

CLINICAL FEATURES

After an incubation period of 1 to 7 days (average 3 days), *Shigella* organisms invade the intestinal mucosa and cause inflammation. The hallmark of clinical shigellosis is an acute rectocolitis manifesting as fever and bloody diarrhoea, with tenesmus. Initially patient presents with history of sudden onset severe abdominal cramping, high-grade fever, emesis, anorexia, and large-volume watery diarrhoea and this is followed by abdominal pain, tenesmus, urgency, faecal incontinence, and small-volume mucoid diarrhoea with frank blood. As such shigellosis is often self-limiting and mild but occasionally it can be serious.

Complications of shigellosis, such as electrolyte imbalance (especially, hypokalaemia), metabolic acidosis and shock, are not common but may be fatal in children and patients who are debilitated. Seizures, the most common neurologic complication, are always associated with fever and are generalised. They are typically non-recurring and uncomplicated. Seizures are least common with *S. dysenteriae*. The prevalence of seizures is approximately 10% across all ages. Encephalopathy with lethargy, confusion, and headache has been noted in up to 40% of children hospitalised with *Shigella* infections.

Less common complications include conjunctivitis, iritis, arthritis, rectal prolapse, secondary bacterial infection, acute blood loss from mucosal ulcers, and toxic neuritis.

DIAGNOSIS

1. Acute diarrhoea often with blood and mucous.
2. Crampy abdominal pain and systemic toxicity.
3. White blood cells in stool; organism isolated on stool culture.

The diagnosis of acute bacillary dysentery should be suspected by the acute onset of the triad of lower abdominal pain, rectal burning and diarrhoea. Stool examination plays a very important role in diagnosis and differentiating it from other aetiologies. Faecal specimens are the best source of a positive culture; blood and urine are only rarely positive in acute cases. Collection and transport of faecal sample should be handled carefully as *Shigella* spp. may not survive the pH changes that occur in faeces specimens which are not properly delivered to the laboratory even if refrigerated. Cary and Blair transport medium which is available at most of the intermediate laboratories, is a satisfactory transport medium.

Blood tests are indicated for severely dehydrated patients and/or those who will undergo intravenous rehydration. These should include a complete blood count, acid-base status, glucose, electrolytes, creatinine and blood urea nitrogen. The urine output should be monitored in all patients with severe dehydration and impaired renal function.

Most of the PCR methods established for the identification of *Shigella* in stool and blood are targeted towards either invasive-

associated locus (*ial*) gene or invasive plasmid antigen (*ipa*) H locus. In most of these studies, PCR was found to be more sensitive and specific technique than the conventional culture methods and has the potential to be employed in routine diagnosis.

DIFFERENTIAL DIAGNOSIS

Various infectious and non-infectious conditions come in the differential diagnosis of dysentery and are enumerated in **Table 2**.

Table 2: Differential Diagnosis of Dysentery

Infectious	Non-infectious
Shigella	Diverticular disease
Campylobacter	Rectal or colonic malignancy
Non-typhoidal *Salmonella*	Inflammatory bowel disease
Entero-invasive *E. coli*	Anal fissure
Enterohaemorrhagic *E. coli*	Ischaemic colitis
Clostridium difficile	Intussusception
Vibrio parahaemolyticus	Haemorrhoids
Entamoeba histolytica	

Among infectious causes, clinically, it is very important to differentiate between bacillary and amoebic dysentery as management differs in both the cases. Bacillary dysentery usually occurs in the form of outbreaks while amoebic dysentery presents as sporadic cases. The diagnosis is based upon microscopic examination and isolation of the organism in stool in most cases, but blood culture positivity is less than 5% in bacillary dysentery. **Table 3** outlined the microscopically differentiating features for bacillary and amoebic dysentery.

Table 3: Differentiating Features between Bacillary and Amoebic Dysentery

Microscopic Features	Bacillary Dysentery	Amoebic Dysentery
Pus cells	Numerous	Scanty
Red blood cells (RBCs)	Discrete	In clumps
Macrophages	Present and show ingested RBC	Absent
Eosinophils	Absent or rare	Present
Charcot Leyden crystals	Absent	Present
E. histolytica	Absent	Trophozoites present
Growth on MacConkey agar	Positive for *Shigella*	Negative

Another clinical condition to be differentiated from dysentery is acute episode of ulcerative colitis. Differentiating features between the two are: self-limiting episode without relapse and positive culture of pathogen in case of bacillary dysentery, sigmoidoscopy reveals an inflamed, engorged mucosa with punctuate and sometime large area of ulceration.

TREATMENT

General principles of treatment include:

1. Fluid therapy
2. Correction of electrolyte imbalance
3. Supportive treatment for fever
4. Antibiotic therapy

Shigella infection generally is a self-limited diarrhoeal illness that lasts 5 to 7 days and may not require antibiotics in individuals who are otherwise healthy. Antibiotic treatment is recommended for infants or older patients, malnourished children, patients infected with HIV, food handlers, health care workers and children in day care centres.

Ampicillin was previously the preferred antibiotic with trimethoprim-sulphamethoxazole (TMP-SMX) as an alternative choice. With development of resistance against these drugs, quinolones, such as ciprofloxacin, ofloxacin, and norfloxacin, are the drugs of choice. Single-dose therapy with 1 g of ciprofloxacin is as effective as two doses or a 5-day standard regimen in patients with *Shigella* infection; however, single-dose therapy proved less effective than multiple-dose regimens for patients with *S. dysenteriae* 1.

Broad spectrum third-generation cephalosporins with Gram-negative activity have higher efficacy against resistant organisms. Even azithromycin can also be used to treat mild-to-moderate infection. Drug dosages are mentioned in **Table 4**.

Table 4: Drug Dosages for Dysentery

Drug	Adult Dose
TMP-SMX	SMX 800 mg/160 mg TMP PO bid for 5 d
Ciprofloxacin	500 mg PO bid for 5 d
Ceftriaxone	Uncomplicated infections 250 mg IM once; not to exceed 4 g Severe infections 1-2 g IV qd, or divided bid; not to exceed 4 g/d
Azithromycin	Day 1: 500 mg PO Days 2-5: 250 mg PO qd

Anti-diarrhoeals that slow the intestinal motility are contraindicated in shigellosis because they delay faecal excretion of *Shigella* and prolong fever and diarrhoea. Vaccination offers the greatest hope as an effective and sustainable strategy against enteric illness. The greatest barrier to the use of vaccine against shigellosis in developing areas is the poor immune responses to oral vaccines in children, who have minimal maternal antibodies, and are therefore, susceptible to infection. An investigational vaccine containing attenuated strains of *Shigella* appears promising in preventing the shigellosis.

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17.16 Cholera

SK Bhattacharya, Dipika Sur

HISTORICAL PERSPECTIVE

Cholera is prevalent since ancient times and is of immense public health importance. Severe cholera is characterised by passage of profuse watery diarrhoea; vomiting and life-threatening dehydration. Occasionally, the disease is mild or asymptomatic.

Pacini, an Italian scholar was the first scientist to find *Vibrio cholerae* in the intestinal contents of patients who had died from cholera in 1854. Robert Koch a German bacteriologist first isolated and cultured *Vibrio cholerae* in Kolkata Medical College in 1884. In 1959, Dr SN De, pathologist in Kolkata, first discovered the enterotoxin of *V. cholerae* in animal experiments.

EPIDEMIOLOGY

Cholera is caused by toxigenic *Vibrio cholerae*. There are two serogroups of *Vibrio cholerae* namely O1 and O139. *Vibrio cholerae* O1 is divided into two biotypes: Eltor and Classical. Each of them can further be classified into serotypes: Ogawa and Inaba. Cholera can occur as sporadic cases, as epidemics and even pandemics. In 1992, a new strain of *Vibrio cholerae* non-O1 designated as Cholera O139 Bengal, originated in South India and spread through the Gangetic delta of India and Bangladesh and to neighbouring countries. Clinically the disease is indistinguishable from cholera O1 and WHO has recommended it as a notifiable disease.

Cholera is reported every year from one or the other part of India. Of India's 35 states and union territories, 21 reported cholera cases during at least one year between 1997 and 2006. The state of West Bengal reported cases during all 10 years, while the state of Maharashtra and the union territory of Delhi reported cases during nine, and Orissa during seven. There were 68 outbreaks in 18 states, and 222,038 cases were detected overall. This figure is about six times higher than the number reported to WHO (37,783) over the same period. The states of Odisha, West Bengal, Andaman and Nicobar Islands, Assam and Chhattisgarh accounted for 91% of all outbreak-related cases.

Cholera is spread by oro-faecal route, and rarely, from person to person contact. The incubation period is 2 to 5 days. For each symptomatic case, there are about five asymptomatic cases of classical cholera and 25 of El Tor cholera. It has a seasonal predilection occurring during summer and monsoon months. A person who has recovered from cholera may have long lasting immunity and is protected from subsequent infection for at least three years. Immunity is correlated with vibriocidal antibody titre in blood. Persons with blood Group O are more susceptible to cholera.

PATHOGENESIS

After ingestion of water or food contaminated with *Vibrio cholerae* O1 or O139 (at least 10^9 live organisms), the organisms pass the acid barrier of the stomach (achlorhydria facilitates the passage of the bacteria from the stomach to small intestine) and settle down in the small intestine. The bacteria then colonise the small intestine with the help of toxin-coregulated pillus (Tcp) and produces cholera toxin (CT). The CT has two subunits—A (active) and B (binding). The B subunit attaches to the GM1 ganglioside present in the gut mucosal surface. Subunit A consists of A1 and A2. The A1 subunit enters the mucosal cell and A2 helps to stabilise the toxin. The A1 subunit stimulates the adenylate cyclase and cyclic AMP and produces loss of fluid and electrolytes from the cell to the gut lumen. This occurs in the small intestine. The colon is also in a secretory phase. When the intestinal secretion exceeds the capacity of colonic absorption, it results in watery diarrhoea with flecks of mucous suspended in it (known as 'rice-watery stools'). However, there is no evidence of structural change in the gut mucosa in cholera.

In the inter-epidemic period, *V. cholerae* has been shown to reside in riverine, estuarine, and coastal waters along with its host, the copepod, a significant member of the zooplankton community. They remain in a viable but non-culturable form. With change of temperature, salinity, rainfall and bloom of the planktons, the organisms multiply which is an important factor in the ecology of *V. cholerae*, influencing the transmission of the disease in those regions of the world where the human population relies on untreated water as a source of drinking water.

CLINICAL FEATURES

In cholera, there is loss of large amount of fluid rich in electrolytes in the stool and this loss results in 'dehydration'. It can be classified into mild, moderate and severe. WHO manual on treatment of acute diarrhoea, however, classifies dehydration as 'diarrhoea with no dehydration' and 'diarrhoea with dehydration' (sub-classified as 'some' and 'severe'). In mild dehydration, the patient is thirsty and may not have other signs of dehydration. In moderate to severe dehydration, the patient has reduced skin turgor, sunken eyes, dry mouth with loss of tear, tachycardia, hypotension and may even become comatose. Hypotension can result in acute tubular necrosis and acute renal failure.

Cholera can affect all ages including children below two years. Pregnant women are believed to be more susceptible and the disease commonly results in abortion. Cholera occurring in the third trimester of pregnancy is associated with 50% risk of foetal mortality, even when the mother receives prompt and adequate therapy. Such women also suffer a great degree of fluid deficit than do non-pregnant women.

Haemoconcentration, neutrophilic leucocytosis, pre-renal azotaemia, acidosis and elevated anion gap are discernible on investigations in severe cases.

DIAGNOSIS

The diagnosis of cholera in endemic countries and in a field/emergency situation is on the basis of a hanging drop preparation wherein the characteristic darting motility can be identified. Serotype identification is by immobilisation using specific sera. For laboratory isolation, selective media need to be employed (TCBS- thiosulphate-citrate-bile salt-sucrose agar). PCR and monoclonal-antibody-based kits are also available for identification of *V. cholerae*.

TREATMENT

Treatment of cholera is essentially prevention and correction of dehydration. Prevention of dehydration in cholera can be done by giving extra fluid [like oral rehydration salt solution (ORS) or home-available fluid like salt-sugar solution, weak tea, coconut water, etc.], extra food to prevent undernutrition and watching for symptoms of severe dehydration like passage of many watery stools, fever, sleepiness, sunken eyes, not recovering in three days and for blood in stool (shigellosis). Mild-to-moderate (some) dehydration is treated with ORS (sodium chloride 3.5 g, potassium chloride 1.5 g, sodium bicarbonate 2.5 g or tri-sodium citrate dehydrate 2.9 g and glucose 20 g dissolved in 1 litre of clean water, osmolarity 311). It should be given as 75 ml/kg body weight within 4 hours. Cholera with 'severe' dehydration must be treated with intravenous Ringer's Lactate (30 ml/kg in 30 minutes and then 70 ml/kg in 2-1/2 hours to correct initial fluid deficit and then maintenance can be done with ORS. Sometimes during the maintenance phase, severe dehydration may recur which may again require IV fluid. With the low osmolarity ORS recommended by WHO, unscheduled IV requirement is cut down by 33%. The composition of hypo-osmolar ORS is sodium chloride 2.6 g, potassium chloride 1.5 g, trisodium citrate dehydrate 2.4 g, and glucose 16.2 g in 1 litre of water, osmolarity 224.

Antibiotic should be given orally in case of severe cholera as an adjunct to rehydration therapy. The antibiotic of choice is oral tetracycline 500 mg 4 times daily for 3 days or doxicycline 300 mg single dose. Such use of antibiotic helps in reduction of stool volume, minimize IV fluid requirement and shortens the duration of hospitalisation and excretion of vibrios in stool. Quinolones in standard doses can also be used. Anti-secretory and anti-motility drugs are not recommended.

Zinc supplementation during an episode of diarrhoea, reduces duration and severity of the episode. Additionally, supplements given daily for 10 to 14 days following the episode, reduces the occurrence of diarrhoea for the next 3 to 4 months. Recommended daily dose is 10mg zinc for infants under 6 months of age and 20 mg for older children for 10 to 14 days.

Probiotics may have a beneficial effect on the health and well being of the host and can offer a safe intervention in acute diarrhoea. However, role in cholera treatment has not been established.

PREVENTION AND CONTROL

While cholera no longer poses a threat to countries with minimum standards of hygiene, it remains a challenge to countries where access to safe water and proper sanitation are not guaranteed and especially in areas where overcrowding and poor sanitation are common, such as slums and refugee camps. Health education and social mobilisation for behaviour change with regard to personal hygienic measures are helpful for control of not only cholera but all water borne diseases. Hand washing with soap especially before eating, after defaecation and before cooking reduces the incidence of diarrhoeal cases in the community by interruption of transmission of the pathogens.

CHOLERA VACCINES

Vaccination against cholera can be used for prevention. Oral cholera vaccine (Shanchol®), which is effective (68% protection at the end of 2 years), cheap and safe, is now available in India. Heat or formalin killed whole-cell *V.cholerae* O1 vaccine with a recombinant B subunit of cholera toxin, (Dukoral®) is licensed in several industrialised countries and used mostly for travellers' diarrhoea but is prohibitively expensive. A live attenuated (CVD 103-HgR) oral cholera vaccine (Orochol®, Mutacol®) was licensed internationally but presently manufacture has been withdrawn.

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17.17 Diseases Caused by Gram-Negative Enteric Bacilli

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Gram-negative bacilli (GNB) are responsible for numerous diseases. Some are commensal organisms present among normal intestinal flora. These commensal organisms plus others from animal or environmental reservoirs may cause disease. Every year an estimated 21.25 lakh deaths are reported worldwide and around 60 million DALYs are lost. GNB are responsible for around 20% to 30% episodes of intestinal infections. Besides, various extra-intestinal infections like urinary tract infections (UTIs), peritonitis, and bloodstream infections are commonly caused by GNB. Gram-negative enteric bacilli include *Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia, Citrobacter, Morganella, Providencia, Edwardsiella, and Acinetobacter* spp.

ESCHERICHIA COLI INFECTIONS

Gram-negative enteric bacilli are associated with intestinal and various extra-intestinal diseases. Depending on both the host and the pathogen, nearly every organ or body cavity can be infected with GNB.

Extra-Intestinal *E. Coli* Infections

E. coli is responsible for several extra-intestinal syndromes which include: (a) UTIs, (b) septicaemia, (c) neonatal meningitis, and (d) other infections.

Urinary tract infections

E. coli is the most common bacterium responsible for causing more than 80% community-acquired UTI. *E. coli* can cause wide range of manifestations including uncomplicated urethritis or cystitis, symptomatic cystitis, pyelonephritis, acute prostatitis, prostatic abscess, or urosepsis. Uncomplicated cystitis occurs primarily in sexually active females due to faecal contamination of the periurethral region by uropathogenic strains of *E. coli*. The bacteria reach the urinary bladder during sexual intercourse. Most of the strains of *E. coli* are capable of causing UTI, but the disease is more common with certain specific *E. coli* serogroups. These serogroups are known as nephritogenic strains which include *E. coli* serotypes O1, O2, O4, O6, O7, O18, etc.

The most frequent symptom of UTI is dysuria, often associated with urgency and increased frequency of micturition. Associated symptoms are fever, chills, backache, suprapubic pain, and nausea and vomiting. The incidence of UTI is much higher in females during adolescence and child-bearing years. After 60 years of age incidence is similar in men and women.

Septicaemia

E. coli causes septicaemia which is usually associated with UTI, especially in cases of urinary obstruction. The endotoxin or lactamase producing strains (LPSs) of the bacteria cause a systemic reaction which can lead to disseminated intravascular coagulation and even death. The mortality and morbidity associated with *E. coli* septicaemia is similar to other aerobic Gram-negative bacilli.

Neonatal meningitis

E. coli are an important cause of meningitis in neonates. In adults, it occurs following neurosurgical procedures, central nervous system (CNS) trauma, or complicating *Strongyloides stercoralis* hyper-infection involving the CNS. Neonatal meningitis has a mortality rate of 8%.

Other infections

These include intra-abdominal infections due to *E. coli*, often resulting from a perforated appendix, diverticulum, or due to intra-abdominal abscess, cholecystitis, and ascending cholangitis. Septic arthritis, endophthalmitis, sinusitis, osteomyelitis, endocarditis, or skin and soft tissue infections are the other pyogenic infections caused by *E. coli*.

Diagnosis

The strains grow both aerobically and anaerobically within 24 hours on standard diagnostic media. Most strains ferment lactose rapidly and are indole positive.

Treatment

Currently isolated strains are resistant to quinolones, cephalosporins, monobactams, and aminoglycosides except amikacin. Till recently, carbapenems and amikacin were considered the most predictable active agents. But with the evolution of superbugs carrying New Delhi beta-metallo lactamase (NDML) gene for beta-metallo lactamase, no available broad-spectrum antibiotic can be relied upon. In practice the sensitivity results should guide the choice of anti-microbial therapy.

Antibiotic Resistance

Antibiotic sensitivities of different strains of *E. coli* vary widely. Antibiotics which may be used to treat *E. coli* infection include amoxicillin as well as other semi-synthetic penicillins, cephalosporins, carbapenems, aztreonam, trimethoprim-sulphamethoxazole, ciprofloxacin, nitrofurantoin and the aminoglycosides.

Antibiotic resistance is a growing problem. This is attributed to overuse of antibiotics in humans, and as growth promoters in food of animals. Once acquired, the antibiotic-resistant *E. coli* pass on the genes responsible for antibiotic resistance to other species of bacteria, such as *Staphylococcus aureus*. *E. coli* carry multidrug resistant plasmids and under stress readily transfer these plasmids to other species. *E. coli* is frequently present over biofilms with many other species of bacteria. This mixing of species allows *E. coli* strains to accept and transfer plasmids to other bacteria. Thus, *E. coli* and the other enterobacteria are important reservoirs of transferable antibiotic resistance. The most important mechanism of drug resistance is by enzymatic destruction of drugs with the aid of beta-lactamase enzymes. These beta-lactamase enzymes make many penicillins and cephalosporins ineffective. Extended-spectrum

beta-lactamase-producing *E. coli* are highly resistant to an array of antibiotics and infections by these strains are difficult to treat. Recently concern has been raised about the prevalence of a form of 'superbug' in the United Kingdom. This name is given due to presence of carbapenemases, which destroy most of the broad-spectrum antibiotics including carbapenems. Gene encoding these enzymes has been termed as New Delhi beta-metallo lactamase, because it was first identified in patient treated in New Delhi. Preliminary reports of *in vitro* sensitivity to only 2 available antibiotics (colistin and tigecycline) are available.

Gastroenteritis

Gastroenteritis is caused by exogenous infections acquired from water, food, or vegetables contaminated with faecal *E. coli*. The strains of *E. coli* that cause gastroenteritis are classified into the following six groups: (1) enteropathogenic (EPEC), (2) enterotoxigenic (ETEC), (3) enteroinvasive (EIEC), (4) enterohaemorrhagic (EHEC), (5) enteroaggregative (EAEC), (6) diffusely adherent *E. coli* (DAEC) (**Table 1**).

EPEC, EAEC, and DAEC cause watery diarrhoea and dysentery. EPEC primarily affects infants and children in developing countries. It can lead to dehydration, if acute and failure to thrive when chronic. Specific serogroups commonly associated with outbreaks of EPEC include O26, O55, O86, O111, O114, O119, O125, O126, O128, and O142.

ETEC is distributed widely in areas with poor sanitation with contaminated food and water. Person-to-person transmission does not occur. ETEC is the primary cause of traveller's diarrhoea in the developed countries. In developing countries, ETEC causes diarrhoea among all ages but infants and children suffer more severe disease because of lack of immunity to ETEC surface antigens. Incubation period is short, varies from 1 to 3 days. The condition manifests by the sudden onset of watery diarrhoea without blood, mucous, or faecal leucocytes. Vomiting may be present. Fever is typically absent. This is a self-limiting condition and persists for less than 5 days.

EIEC produce diarrhoea and dysentery, similar to that caused by *Shigella* species. These strains cause watery diarrhoea, dysentery, fever, vomiting, painful abdominal cramps, and tenesmus. Stools often contain blood and leucocytes.

EHEC is an important cause of food-borne illness, particularly in developed countries. EHEC is a common microbiological flora of the intestine of cattle. Thus, cattle are the primary reservoir of EHEC. The infection is acquired by ingestion of beef products or foods contaminated with cattle faeces containing EHEC strains. EHEC is responsible for causing two distinct syndromes: haemorrhagic colitis and haemolytic uraemic syndrome (HUS) by producing two shiga toxins (Stx). The Stx is responsible for the systemic complication and manifestations of the infection.

Haemorrhagic Colitis

Incubation period varies from 1 to 5 days. The condition manifests as watery diarrhoea to severe haemorrhagic colitis. Watery diarrhoea is often accompanied by abdominal cramping and vomiting. In most patients, diarrhoea becomes bloody in 1 to 2 days, but usually is not associated with faecal leucocytes. Fever is present in about a third of cases. The infection typically lasts for 10 days. *E. coli* O157:H7, the most common strain causing EHEC diarrhoea has a small infective dose (around 100 bacilli) and spreads easily from child-to-child by the faecal-oral route.

Haemolytic Uraemic Syndrome (HUS)

It is a serious life-threatening complication seen in around 10% to 20% of children suffering from EHEC diarrhoea. The three important manifestations of HUS include: microangiopathic haemolytic anaemia, thrombocytopaenia, and renal insufficiency. This condition usually develops in the second week of illness, after the child has recovered from diarrhoea. The condition presents with anaemia, weakness, irritability, and oliguria or anuria. Chronic renal failure may develop in 10% of patients with HUS. Nearly 3% to 5% of patients with HUS die of the disease. Stool culture for EHEC is always negative in patients with HUS.

Epidemiology

Geographical distribution: E. coli diarrhoea primarily affects population in the developing countries. There is a worldwide variation in the prevalence of the strains.

Table 1: Diarrhoeal Illness Caused by *Escherichia Coli*

Pathogroup	Subgroup	Toxin/Phenotype	Epidemiology	Clinical Syndrome	Virulence Gene
Enterotoxigenic *E. coli* (ETEC)		Heat-labile toxin (LT) and/or heat-stable toxin (ST)	Food, water; young children and in travellers from developed countries	Traveller's diarrhoea	*elt/est* or both
Enteropathogenic *E. coli* (EPEC)	Typical EPEC Atypical EPEC	Actin accumulation Actin accumulation	Person-to-person; young children and neonates in developing countries	Watery diarrhoea	*eae, bfpAeae*
Shiga toxin-producing *E. coli* (STEC)	Typical STEC Atypical STEC	Verocytotoxin and enterohaemolysin Verocytotoxin	Food, water, person-to-person; all ages, industrialised countries	Haemorrhagic colitis, haemolytic-uraemic syndrome	*eae, stx* and *ehxAstx* with or without *eae*
Enteroaggregative *E. coli* (EAEC)	Typical EAEC Atypical EAEC	Aggregative adherence Aggregative adherence	Food, water; children and travellers from developed countries; all ages, industrialised countries	Traveller's diarrhoea, acute diarrhoea, persistent diarrhoea	*aggR* regulon *(aai)* *(aat)*
Enteroinvasive *E. coli* (EIEC)		Invasion	Food, water; children and travellers from developed countries	Dysentery	Multiple genes

ETEC is the primary cause of traveller's diarrhoea and is the major cause of infantile diarrhoea in poor and developing countries. ETEC cause nearly more than 600 million cases of diarrhoea every year and 700,000 deaths in children below 5 years of age. EHEC are an emerging cause of food-borne disease, particularly in developed countries. EPEC, EAEC, and DAEC have been reported to occur in the developing countries.

Habitat: Most strains of *E. coli* causing diseases in humans are present in intestine. Few strains such as EHEC also inhabit the cattle intestine.

Reservoir, source and transmission of infection: Most extra-intestinal infections are caused by endogenous *E.coli* as a result of direct faecal contamination of the urinary tract. Diarrhoea caused by *E. coli* is exogenous via intake of food and water contaminated with human or cattle faeces. Beef, apple juice, and alfalfa sprouts contaminated with cattle faeces are important source of infection caused by EHEC (O157:H7).

Diagnosis

The diagnosis requires specialised assays, that are not routinely available. Definite diagnosis is generally not necessary. *E. coli* diarrhoea is generally self-limited. The evaluation for STEC/EHEC infection, particularly when associated with bloody diarrhoea is appropriate if resources are available. For screening, serotyping of non-sorbitol fermenting *E.coli* is done for O157. Testing for shiga toxins or shiga genes is more sensitive, specific and rapid.

Treatment

Rehydration and replacement of salt is the mainstay of treatment for all diarrhoeal diseases. Treatment with quinolones shortens duration of illness and hastens recovery. Antibiotic therapy for STEC/EHEC (suggested by the presence of bloody diarrhoea in the absence of fever) should be avoided, because antibiotics may increase the incidence of HUS possibly via increased production and/or release of Stx toxin. For prophylaxis, rifaximin is indicated in patients, who are susceptible to serious infections or cannot afford even minor illness.

KLEBSIELLA

Klebsiella organisms cause a variety of clinical syndromes in humans. These are: (a) community-acquired pneumonia, (b) UTI, (c) nosocomial infection, and (d) bacteraemia and sepsis.

Community-acquired pneumonia is most frequently caused by *Klebsiella pneumoniae* serotypes 1, 2 and 3. It has a rapid onset and often fatal outcome if not diagnosed early. Lobar pneumonia is associated with massive mucoid inflammatory exudates, involving one or more lobes of the lung. Necrosis and abscess formation is more common than pneumococcal pneumonia.

Patients present with an acute onset of high fever with chills, flu-like symptoms, and productive cough with an abundant, thick, tenacious, and blood tinged sputum. Blood culture is positive in about 25% of the cases.

UTI caused by *K. pneumoniae* is a common problem in patients with indwelling catheters. It cannot be distinguished clinically from UTI due to *E. coli* and other common bacteria.

K. pneumoniae are emerging as important agents of nosocomial infections in hospitals. The presence of invasive devices, contamination of respiratory support equipments, use of urinary catheters, and use of antibiotics greatly increases the likelihood of nosocomial infections. In addition, poor health status and treatment in an intensive care unit (ICU) or nursing home are other factors. UTI, pneumonia, bacteraemia, wound infection, cholecystitis, and catheter-associated bacteriuria are the common nosocomial infections associated with *K. pneumoniae.* Other rare nosocomial infections include cholangitis, meningitis, endocarditis, and bacterial endophthalmitis.

Klebsiella bacteraemia and sepsis produce clinical manifestations similar to those caused by *E. coli* and other gram-negative enteric organisms. In neonatal units, outbreaks of infection caused by extended-spectrum beta-lactamase (ESBL) producing *Klebsiella* strains present a more serious problem and may be associated with high mortality. *Klebsiella* has been isolated from hepatic abscesses in diabetic patients. Associated bacteraemia with metastatic complications are common.

Members of *Klebsiella* are found as normal flora in many parts of gastrointestinal tract and biliary tract in humans. They may also colonise the skin and pharynx. Oropharyngeal carriage is usually associated with endotracheal intubation, impaired host immunity and anti-microbial use. The gut of the patient and the hands of hospital personnel are the principal reservoirs of *K. pneumoniae.* Bacteria usually spread rapidly, often leading to nosocomial outbreaks in hospitals.

K. pneumonia typically affects middle-aged and older persons with chronic debilitating diseases such as alcoholism, diabetes, or chronic bronchopulmonary disease. Extensive use of broad-spectrum antibiotics in hospitals has contributed to an increase carriage of *Klebsiella* and, subsequently, the development of multi-drug resistant strains.

K. rhinoscleromatis and K. ozaenae

Rhinoscleroma caused by *K. rhinoscleromatis* is a chronic granulomatous inflammatory disease involving the naso-pharynx. Patients present with a purulent nasal discharge with formation of crusts and nodules that may lead to respiratory obstruction. Ozena is a chronic atrophic rhinitis occurring mostly in elderly persons.

Klebsiella oxytoca

K. oxytoca is responsible for sepsis in neonates admitted in ICU, especially in premature infants.

Diagnosis

Klebsiellae are readily isolated and identified in laboratory. They are usually lactose fermenters except for rhinoscleromatis and ozaenae.

Treatment

Due to the resistance to aminoglycosides, quinolones, cephalosporins, penicillins, empirical treatment of serious *Klebsiellae* infection should include amikacin, carbapenems or tigecycline. Polymyxin B is the agent of last resort because of potential toxicity.

PROTEUS

The genus *Proteus* comprises of four species: *Proteus mirabilis*, *Proteus vulgaris*, *Proteus penneri* and *Proteus myxofaciens*. *P. mirabilis* is the most important species responsible for 90% *Proteus* infections and is associated with community-acquired UTI, bacteraemia, intra-abdominal abscesses, surgical wound infection and the infection of decubitus ulcers. Presence of urease is responsible for the generation of ammonium ions in urine which imparts alkaline pH to the urine. *P. vulgaris* and *P. penneri* are usually associated with hospital-acquired infections.

Diagnosis

Most strains are lactose negative, produce hydrogen sulphide, and demonstrate swarming motility on agar plates.

Treatment

P. mirabilis is usually susceptible to most antibiotics except tetracycline, polymyxin B, and tigecycline. 90% to 100% isolates demonstrate excellent susceptibility to imipenem, cefepime, amikacin and cotrimoxazole.

MORGANELLA, PROVIDENCIA AND ERWINIA

Morganella is an opportunistic pathogen in hospitalised patients. It causes UTI, sepsis, pneumonia, wound infection, pericarditis and spontaneous bacterial peritonitis. *Providencia* is associated with catheter-related UTI and septicaemia in the elderly patients. Some species can also lead to invasive and traveller's diarrhoea. *Erwinia* has occasionally been isolated from respiratory and urinary infections in chronic debilitated and hospitalised patients.

Treatment

These are extensively resistant to antibiotics. Imipenem, amikacin and cefepime are the most active agents.

ACINETOBACTER INFECTIONS

Acinetobacter is being isolated from immunocompromised patients in ICUs. The respiratory tract and intravascular devices are the favoured sites.

Diagnosis

These are GNB or coccobacilli seen on Gram's stain. They are strictly aerobic, non-fermenting, and oxidase negative.

Treatment

These are extensively drug resistant. Empirical therapy using ampicillin/sulbactam, rifampin, tetracyclines, imipenem/cilastatin, tigecycline, and amikacin are often effective though resistance has been reported to all of them.

CAMPYLOBACTER

Campylobacter organisms are microaerophilic, motile Gram-negative rods. Two species infect humans: *Campylobacter jejuni*, causing diarrhoea and *C. fetus*, associated with systemic infection. Dairy cattle and poultry are principal reservoir. Outbreak of enteritis is associated with consumption of raw milk. *Campylobacter enteritis* presents with fever, abdominal pain, and loose, watery, or bloody stools. The disease is self limited.

C. fetus causes fatal systemic infections including primary bacteraemia, endocarditis, meningitis and focal abscesses. Patients are usually old, debilitated or immunocompromised. Closely related species collectively termed 'campylobacter-like organisms' cause bacteraemia in HIV patients. Reactive arthritis and other rheumatological complaints may develop after weeks of primary infection mostly in HLA-B27 phenotype. *C. jejuni* particularly O19 serotype can also trigger Guillain-Barre syndrome or its Miller Fisher or cranial polyneuropathy variant.

Treatment

Fluid and electrolyte replacement is central to the treatment of diarrhoeal illnesses. Antibiotics are indicated for patients with high fever, bloody diarrhoea, severe diarrhoea or persistence for more thant 1 week. Erythromycin in a dosage of 250 mg four times a day for 5 to 7 days is the treatment of choice. Alternatively clarithromycin, azithromycin, ciprofloxacin can be given. For systemic infections, parenteral gentamycin, imipenem, or chloramphenicol can be used for 2 to 4 weeks.

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17.18 *Haemophilus Influenzae* Infections

M Sabir, Mansoor Ahmed

INTRODUCTION

The name *Haemophilus* is derived from the Greek nouns 'haima' and 'philos' meaning 'blood lover'. *Haemophilus* species primarily infect human respiratory tract, skin, or mucous membranes. From these sites, organisms can invade and cause bacteraemia, meningitis, epiglottitis, endocarditis, septic arthritis, or cellulitis.

PATHOGEN

It is the first free living organism to have its entire genome sequenced. A member of the *Pasteurellaceae* family, discovered in 1892 by Richard Pfeifer, formerly called Pfeifer's bacillus or Bacillus influenzae, was mistakenly considered to be the cause of influenza (until 1933).

It is a small, pleomorphic, non-motile, non-spore-forming, fastidious, aerobic but a facultative anaerobe, Gram-negative coccobacillus. Two major categories of *H. influenzae* have been defined: encapsulated strains possessing a polysaccharide capsule, are serotyped into 6 different types (a-f) based on their biochemically different capsules, and others having no capsule are termed non-encapsulated *H. influenzae* or non-typeable *H. influenzae* (NTHi).

The most virulent strain is *H. influenzae* type b (Hib), accounts for more than 95% of *H. influenzae* invasive diseases in children and half of invasive diseases in adults.

H. influenzae type a (Hia) has been known to cause invasive disease (e.g. meningitis) clinically indistinguishable from that caused by Hib. The non-encapsulated, or NTHi, strains usually cause mucosal infections. Less commonly, these strains cause invasive disease in children but account for half of the invasive infections in adults.

EPIDEMIOLOGY

The precise prevalence and incidence of *H. influenzae* infections are unknown. This organism can be detected in the nasopharynx of both children and adults. Non-typeable *H. influenzae* can be detected in nasopharyngeal cultures of more than 70% of young children, but infection occurs in only a small proportion of colonised patients. The frequency of Hib infections is more amongst immunocompromised individuals (e.g. asplenia, splenectomy, sickle cell disease, malignancies, and congenital or acquired immune deficiencies) and unvaccinated infants.

Currently, the incidence of Hib invasive diseases has greatly decreased in developed countries because of the widespread use of the Hib conjugate vaccine (while NTHi strains have become the most common cause of invasive disease in all age groups).

However, in many developing countries, invasive Hib disease is still a significant cause of morbidity and mortality. Overall mortality from Hib meningitis is approximately 5% but morbidity rates are high. In one of the Indian study case—fatality rate was 11% overall and 20% in infants with Hib meningitis.

PATHOGENESIS AND IMMUNE RESPONSE

Humans are the only natural hosts. Transmission is by direct contact or by inhalation of respiratory tract droplets. The incubation period is not known. A larger bacterial load or the presence of a concomitant viral infection (especially in immunodeficient individuals, alcoholics and smokers) and winter season can potentiate the infection.

The colonising bacteria invade the mucosa and enter the bloodstream. The presence of antibodies, complements, and phagocytes determines the clearance of the bacteraemia. The anti-phagocytic nature of the Hib capsule and the absence of the anticapsular antibody, lead to increasing bacterial proliferation. When the bacterial concentration exceeds a critical level, it can disseminate to various sites, including meninges, subcutaneous tissue, joints, pleura, pericardia, and lungs.

Host defenses include the activation of the alternative and classical complement pathways and antibodies to the PRP capsule. The antibody to the Hib capsule plays the primary role in conferring immunity. Newborns have a low risk of infection, likely because of acquired maternal antibodies. By the age of 5 years, most children have naturally acquired antibodies. The NTHi strains colonise in the nasopharynx. The spread of bacteria by direct extension to the eustachian tubes causes otitis media, sinusitis, bronchitis and pneumonia.

CLINICAL FEATURES

Clinical manifestations of *H. influenzae* infections range from varying grades of fever, malaise and other constitutional symptoms to life-threatening disease, mostly depending on tissue or organ affected, host defenses, age of the patient, affecting strain of *H. influenzae* and bacterial load.

Meningitis

H. influenzae meningitis commonly occurs in children younger than 5 years. Adults with history of skull trauma or cerebrospinal fluid (CSF) leaks are particularly prone to it. Meningitis is the most serious manifestation of Hib infection.

Clinical manifestations are indistinguishable from other causes of bacterial meningitis. The usual presentation consists of a few days of mild illness, usually antecedent URTI, followed by ominous deterioration. Altered mental status and fever are the most common findings with headache and photophobia (common in older children) followed by seizures and coma as the disease advances. Neck rigidity is often absent in children younger than 18 months. In infants, the disease course may be fulminant, with death occurring within a few hours.

Most patients have CSF white blood cell counts greater than 1000/mm^3 and hypoglycorrhachia (low levels of glucose in CSF

with high levels of protein). CSF Gram stain shows pleomorphic gram-negative bacilli which can sometimes be mistaken for pneumococcal meningitis.

Cellulitis

Fever and a raised, indurated, tender area with indistinct margins mostly on the head and neck, particularly the buccal and preseptal areas are common. Orbital cellulitis is uncommon, and is distinguished from preorbital cellulitis based on the presence of proptosis, chemosis, impaired vision, limitation of extraocular movements, and pain with eye movement.

Epiglottitis

Hib is the commonest cause of acute epiglottitis in both children and adults. In children younger than 5 years, it is a life-threatening infection that usually presents with fever, drooling, dysphasia, and respiratory distress or stridor, which appear over the course of hours.

In adults, fever, sore throat, dysphagia and odynophagia occur. Cervical tenderness and lymphadenopathy can be found at all ages. Laryngoscopy demonstrates a swollen, cherry-red epiglottis, but should be avoided as it may precipitate acute airway obstruction.

Pneumonia

Hib pneumonia is clinically indistinguishable from other bacterial pneumonias except for its insidious onset.

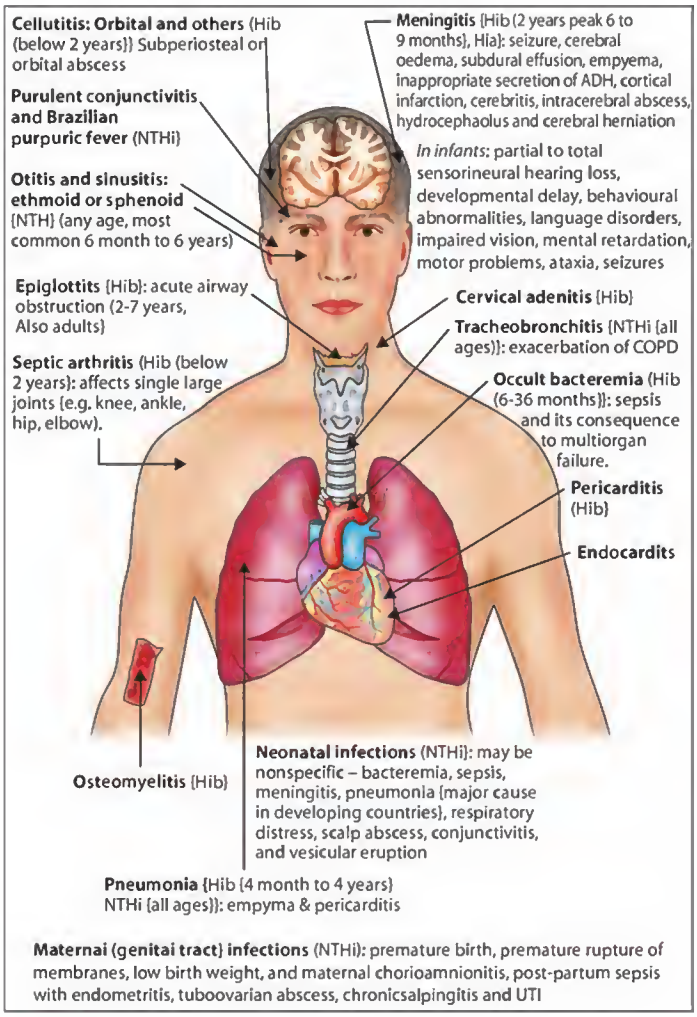


Figure 1: *H. Influenzae* infections: common age of occurrence and complications.

Infection in different organs may lead to local complications and systemic manifestations in the form of sepsis and multiorgan failure as shown in **Figure 1**.

LABORATORY STUDIES

1. Gram-negative, pleomorphic coccobacilli with polymorphonuclear cells are strong evidence of infection.
2. Bacterial culture of blood, CSF and other body fluids is the most reliable method for the diagnosis of Hib infection. It is performed on chocolate agar plate with added X (hemin) and V (nicotinamide-adenine-dinucleotide) factor at 37°C in an enriched CO_2 incubator.
3. The different strains can be identified with slide agglutination for serotyping or polymerase chain reaction for capsular typing.
4. Detection of the PRP polysaccharide capsule via countercurrent immunoelectrophoresis, latex particle agglutination, co-agglutination, and enzyme-linked immunosorbent assay is an important adjunct to culturing in establishing a rapid diagnosis.
5. Chest radiography: Patients with Hib pneumonias tend to have more pleural and pericardial involvement (50% of patients) than those with other bacterial pneumonias. Community-acquired pneumonias due to NTHi show alveolar infiltrates in patchy or lobar distributions.
6. Lateral neck radiography in epiglottitis shows dilatation of the hypopharynx and a swollen epiglottis (the thumbprint sign).
7. Head computed tomography helps identify subdural effusion and other neurological sequelae of meningitis and extent of orbital or other cellulitis.
8. ECG and echocardiography.
9. *Procedures* are performed to obtain appropriate fluid to establish an aetiologic diagnosis: lumbar puncture, bronchoscopy, aspiration (joint, lung, sinus, and soft-tissue), transtracheal aspiration, tympanocentesis, pericardiocentesis, laparoscopy and culdocentesis in women.

TREATMENT

Antibiotics and supportive care in the form of maintenance of airways, nutrition, fluids and electrolyte balance; and treatment and prevention of shock is the main stay of the treatment of *H. influenzae* infections.

Third-generation cephalosporins are highly effective in *H. influenzae* infections. Meropenem or ampicillin and chloramphenicol are alternative regimens. In an Indian study up to 60% of all isolates were resistant to chloramphenicol, ampicillin, trimethoprim-sulphamethoxazole, or erythromycin; 32% were resistant to ≥3 anti-microbial drugs, but none were resistant to third-generation cephalosporins.

Initially, patients with invasive and serious *H. influenzae* infections are best treated with an intravenous ceftriaxone (adult dose: 1 to 2 g intravenously every 12 hours) or cefotaxime (adult dose: 2 g intravenously every 6 hours).

Penicillins are useful in the management of mucosal infections caused by NTHi, but production of beta-lactamase restrict their use.

Table 1: Treatment of *H. influenzae* Infections

Diagnosis	Antibiotics		Other Measures
	Name and Route (P-parenteral, O-oral)	Duration	
Meningitis	Ceft., Cefo., Cftz., Amp., Salb., Fluq., Aztm. (P)	7-14 days	Treatment/prevention of seizures. Patency of airway and *dexamethasone* to prevent neurological complications
Cellulitis Orbital cellulitis	Same (P) till symptoms disappears than (O) Same (O)	7-10 days 14 days	
Epiglottitis	Same (P) till airway is secured, than (O)	7-10 days	Patency of airway, surgical drainage, if needed
Arthritis	Same (P) than (O) until ESR and C-reactive begins to normalise	7 days, 2-3 weeks	
Bacteremia	Same (P) for 2 to 5 days than (O)	Min.10 days*	Same
Non-encapsulated	Amox., Clavn., In penicillin-allergy Erym.,	10 days	
H. influenzae Otitis media	Sulph., Cefc., Trim., Sulx., Cefu. axetil.,Cefm., Clat., Aztm., Fluq. (mostly O)		
Sinusitis	Same (O)		
Conjunctivitis	Topical Sulm. and Erym.	15 days	
Invasive NTHi infection	Same as invasive Hib (P)	14 days	

Note: Generol Meosures – fluid ond electrolyte bolonce, treatment of shock ond other complicotions.

Ceft. *= ceftrioxone;* ***Cefo.*** *= cefotoxime;* ***Cftz.*** *= ceftozidime;* ***Amp.*** *= ompicillin;* ***Salb.*** *= sulboctom;* ***Fluq.*** *= fluoroquinolones;* ***Aztm.*** *= ozithromycin;* ***Amox.*** *= omoxicillin;* ***Clavn.*** *= clovulonote;* ***Erym.*** *= erythromycin;* ***Sulph.*** *= sulphisoxazole;* ***Cefc.*** *= cefoclor;* ***Trim.*** *= trimethoprim;* ***Sulx.*** *= sulphomethoxozole;* ***Cefu.*** *= cefuroxime oxetil;* ***Cefm.*** *= cefixime;* ***Clat.*** *= clorithromycin;* ***Sulm.*** *= sulphocetomide.*

**Potients with pericorditis, empyema, endocorditis, endophtholmitis, or osteomyelitis require ontibiotic for 3 to 6 weeks.*

The site of infection and the clinical response determine the length of antibiotic treatment (**Table 1**).

PREVENTION

Vaccination

The Hib conjugate vaccine induces protection by inducing antibodies against the PRP capsule; it does not provide protection against NTHi strains. It is used for routine immunisation of children but is not indicated in adults.

CHEMOPROPHYLAXIS

The risk of secondary disease is greater among household contacts of patients with Hib disease. Therefore, all members (except children less than 4 years who are completely immunised) should receive oral rifampicin in the doses of 600 mg/day for adults and 20 mg/kg/day for children (<12 years) for 4 days.

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17.19 Legionnaires' Disease

PS Shankar

Legionnaires' disease (legionellosis) is a multi-system disorder affecting the lungs, heart, kidney, alimentary tract and central nervous system, and it is due to the infection caused by the bacteria of genus *Legionella*. Legionnaires' disease refers to the pneumonia caused by *Legionella* species. An acute and mild form of the disease, referred as Pontiac fever, is also recognised and it presents as a febrile, self-limited, flu-like illness. There are more than 49 species with more than 64 sero-groups in the family of *Legionellaceae*.

AETIOLOGY

Legionnaires' disease is caused by a Gram-negative, fastidious aerobic, coccobacillus—*Legionella pneumophila*. The serogroups 1, 4, and 6 of *Legionella pneumophila* are the most commonly involved. The *L. micdadei, L. bozemanii, L. dumoffii* and *L. longbeachae* may sometime, cause pneumonia in immunocompromised patients. These organisms are present in soil excavation, construction sites, lakes, ponds, streams, and in air-conditioning cooling towers, refrigerated water, and evaporative condensers. The organism has an affinity for water, particularly if blue-green algae are present. The source of Legionnaires' disease is water. The incidence depends on the degree of contamination of the water reservoir. Often potable water distribution system in hospitals, hotels and large buildings spread the organism. The immune status of the person exposed and the intensity of exposure play important role in the development of infection. The organism does not grow on routine microbiologic media, and can only be grown on a specialised medium of buffered-charcoal yeast extract (BCYE) agar. It needs L-cysteine for its growth.

EPIDEMIOLOGY

The bacterium was first isolated in 1943. Legionnaires' disease was first recognised in 1976 in Philadelphia, USA, when it caused an outbreak of pneumonia amongst the members attending the American Legion (small army) convention in a hotel.

The condition occurs in middle-aged or elderly persons, frequently among males. It spreads by airborne route through inhalation of aerosols, aspiration and direct instillation into the lungs. Aspiration appears to be the predominant mode of transmission. Person-to-person transmission does not take place. Though majority of the cases are sporadic, epidemics have been noted to occur frequently in hotels, and hospital surroundings, building sites and factories, which are exposed to contaminated water reservoirs. The most common risk factors for the development of Legionnaires' disease are presented in the **Table 1**.

Table 1: Risk Factors for Legionnaires' Disease

Cigarette smoking
Alcoholic liver disease
Chronic lung disease
Advanced age
Recent hospitalisation
Recent foreign travel
Immunocompromised patients
Recent surgery under general anaesthesia
Exposure to unhygienic hot-tub spa
Local epidemics around point source or potable water supply
Hairy cell leukaemia

PATHOGENESIS

It has an incubation period of 2 to 10 days. After gaining entry to the lungs, the bacterium gets attached to the host cells. It undergoes phagocytosis by pulmonary alveolar macrophages, where some organisms are killed and some proliferate within the cells till the cell ruptures. The emerging organisms are phagocytosed by newly recruited macrophages and cycle begins afresh. Bacterial uptake and multiplication are halted by cytokines produced by macrophages and lymphocytes. The natural killer (NK) cells lyse the infected macrophages. Thus, cell-mediated immunity by T-lymphocytes plays a dominant role in the immune process as compared to humoral immunity through formation of type-specific IgM and IgG antibodies.

The pathologic changes are essentially confined to the lungs where it produces an acute fibrinopurulent bronchopneumonia and the alveoli are filled with polymorphs admixed with macrophages and a large amount of fibrin. Toxins released by the bacteria may cause an acute necrosis and encephalopathy.

CLINICAL FEATURES

The condition has an acute onset with prodromal features consisting of malaise, fatigue, slight headache and anorexia. Occurrence of myalgia or arthralgia is uncommon. It is followed by high-grade fever, recurrent shaking chills, non-productive cough, dyspnoea, chest pain, breathlessness, and prostration. Later there may be mucopurulent or bloody sputum. Upper respiratory symptoms are uncommon. There can be vomiting, abdominal pain and watery diarrhoea. There may be headache, lethargy, and mental confusion. Patients are occasionally obtunded during the acute phase of illness. Many a times the non-respiratory manifestations may mask the features of pneumonia. There is relative bradycardia especially in elderly patients. Chest examination shows the presence of crackles early in the course of the disease, and later signs of consolidation. Abdominal examination may show localised or generalised tenderness.

INVESTIGATIONS

There is moderate polymorphonuclear leucocytosis. It is associated with thrombocytopaenia. The urine examination may demonstrate presence of proteinuria, microscopic

haematuria or pyuria. Chest radiograph may show patchy infiltrates, which later progress to lobar shadows either unilaterally or bilaterally. The lower lobes are more commonly involved. Pleural effusions are common. Immunosuppressed patients especially those receiving glucocorticoids may show rounded nodular opacity. Computed tomography of the chest demonstrates sharply demarcated peri-bronchial foci of consolidation. These may be unilateral or bilateral, single or multifocal ground-glass opacities. There is marked hypoxaemia, and mild-to-moderate increase in liver enzymes. Often there is hyponatraemia, hypoalbuminaemia, and hypophosphataemia. There is elevation of alkaline phosphatase, creatine phosphokinase and serum creatinine.

The Gram's staining of the sputum reveals numerous leucocytes but no organisms. The organisms may appear as small, pleomorphic, and faintly gram-negative. The *L. micdadei* organisms may be weakly or partially acid-fast. Causative agent may be demonstrated by direct immunofluorescence of the transtracheal or percutaneous lung aspirate, sputum, bronchoalveolar lavage fluid and pleural fluid by using appropriate antibody test. Recognition of the organism in histopathologic sections is easy. The fresh lung tissue imprints can be stained with Gimenez stain whereas the paraffin-embedded sections with buffered Dieterle's silver impregnation stain. The organism can be cultured on the buffered charcoal yeast extract agar (cysteine-supplemented with alpha-ketogluconate). The colonies grow slowly in 3 to 5 days. *Legionella* soluble antigen is detectable in urine in 3 days after onset of clinical manifestations and it remains positive for nearly 2 months. A four-fold rise in indirect fluorescent antibody of more than 1:128 against *L. pneumophila* develops after three weeks of infection.

PROGNOSIS

The severity of the illness ranges from a trivial cough to a rapidly progressive and lethal pneumonia. The disease is considered severe when there is confusion, urea >7 mmol/L, respiratory rate >30/min, hypotension: systolic <90 mm Hg or diastolic <60 mm Hg, and age above 65 years. There is worsening of radiologic shadows. Death occurs from respiratory failure, shock, hypotension and acute renal failure. The mortality varies with patient's underlying disease, severity of the disease, immune status, severity of pneumonia and the time of initiation of therapy. Haematogenous dissemination of organisms may affect heart, lymph nodes, liver and spleen.

TREATMENT

Legionnaires' disease is treated with macrolides and flouro-quinolones. The organisms fail to show a response to beta-lactam antibiotics (penicillin or cephalosporins) and aminoglycoside antibiotics. *Legionella* being an intracellular pathogen, antibiotics that can reach intracellular concentration greater than that of minimal inhibitory concentration are only effective. Newer macrolides, such as azithromycin or clarithromycin compared with erythromycin exhibit superior *in vitro* activity and exhibit greater intracellular activity. They reach higher concentrations in respiratory secretions and in lung tissues. Azithromycin or clarithromycin may be given in a dose of 500 mg intravenously or orally for a period of 5 to 10 days.

Fluoroquinolones (levofloxacin) are advocated for transplant patients. Doxycycline is advocated in patients intolerant of erythromycin or azithromycin. It is to be given 100 to 200 mg orally or intravenously every 12 hours. Levofloxacin 500 mg or ciprofloxacin 750 mg or ofloxacin 400 mg may be administered orally twice a day. *Legionella* is also sensitive to tetracycline and trimethoprim-sulphamethoxazole (Septran). Rifampicin in a dose of 600 mg twice a day may be used in combination with a macrolide or a fluoroquinolone, in those who are severely ill or with extensive cavitatory disease. The condition needs supportive therapy with oxygen, mechanical ventilators, volume replacement, vaso-active agents and dialysis.

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17.20 Plague and Other Yersinia Infections

Veena Mittal

PLAGUE

Definition

Plague is an acute specific communicable disease caused by *Yersinia pestis*. It is primarily a zoonosis, being a disease of rodents, and man is affected incidentally. Infection is transmitted to humans typically by flea bite, less commonly by contact with infected animal tissues or airborne droplets. Three major clinical forms of disease are: bubonic, septicaemic and pneumonic plague. *Y. pestis* is considered as a potential biological warfare agent because of its transmissibility and virulence.

Plague is endemic in many countries in Africa, former Soviet Union, the Americas and Asia. From 2004 to 2009, a total of 12,503 cases of human plague, including 843 deaths, were reported by 16 countries in Africa, Asia and the Americas. In India, plague re-emerged in 1994 when outbreak of bubonic plague in Beed and pneumonic plague in Surat led to 876 cases with 54 deaths. Again in 2002, outbreak of pneumonic plague in Himachal Pradesh was reported with 16 cases and 4 deaths and in 2004 a localised outbreak of bubonic plague in Uttarkashi, Uttaranchal with 8 cases and three deaths.

Epidemiology

The epidemiology of plague is extremely complex.

Vector

Fleas are the natural vectors of plague in the world. Nearly 31 species of fleas all over the world have been incriminated as vectors of plague. In India, the fleas considered important for plague transmission are *Xenopsylla cheopis, X. astia and X. brasiliensis*. Out of these *X. cheopis* is the principal vector.

Reservoirs

A large number of mammals may be infected with *Y. pestis*. Rodents are the true natural hosts of *Y. pestis*. At least 220 species of rodents are known to be infected with plague bacillus. *Tatera indica* among the wild rodents and *R. norvegicus* and *R. rattus* among the commensal rodents are found to play an important role as reservoir of *Y. pestis*.

Modes of Transmission

The starting point is always the plague focus. Man can get the infection by bite of infected rat flea, by handling infected animals or material or by droplet infection (primary pneumonic plague).

Aetiological Agent

Y. pestis is a short, thick coccobacillus measuring 1.5-2 x 0.5-0.7 microns in size. It has rounded ends, which with polychromatic stains, i.e. Wayson, Giemsa stain gives a characteristic bipolar appearance to the organism. It is Gram-negative, nonmotile and non-sporing, oxidase and urease negative biochemically non-reactive. True capsules are seen in living tissues but are less readily seen in culture. The organism grows well on blood agar, brain heart infusion agar, Macconkey agar. The optimum temperature for growth is 28°C but for capsular material (envelope substance), organism should be grown at 37°C.

Pathogenesis

Y. pestis is highly invasive and pathogenic. The mechanism by which the organism causes disease are incompletely understood. Three plasmids encode for a variety of virulence factors and a chromosomally encoded lipopolysacchride endotoxin is important in sepsis, triggering the systemic inflammatory response syndrome and its complications.

After *Y. pestis* is inoculated into the skin by flea bite, bacteria migrate to local lymph nodes, where they are taken up but not killed by mononuclear cells. Intracellular multiplication results in development of capsular envelopes containing capsular antigen (fraction 1 antigen) and toxins are liberated. An acute inflammatory response is provoked in the lymph nodes in the ensuing 2 to 6 days (incubation period) resulting into a bubo. Haemorrhagic necrosis of lymph nodes with lysis of macrophages next occurs, from which large number of bacteria gain access to blood stream and other organs.

Primary septicaemic plague consists of sepsis in the absence of a bubo. Secondary septicaemic plague is a complication of bubonic or pneumonic plague that occurs when local host defenses are breached.

Primary plague pneumonia generally begins as a lobular process and then extends by confluence, becoming lobar and then multilobar. In advanced cases of both primary and secondary plague pneumonia, affected lung tissue is characterised by oedema, haemorrhagic necrosis with infiltration by neutrophilic leucocytes.

Clinical Features

Y. pestis infection in humans occurs in one of the three main clinical forms—bubonic, septicaemic and pneumonic.

Bubonic plague

After an incubation period of 2 to 6 days, patients typically experience a sudden onset of illness characterised by malaise, headache, shaking chills, fever and pain in the affected regional lymph nodes which get swollen (buboes) (**Figure 1**). Buboes may occur in any regional lymph node sites such as inguinal, axillary, supraclavicular, cervical, post-auricular, epitrochlear, popliteal or pharyngeal. The bubo may remain enlarged and tender for weeks following an otherwise satisfactory clinical recovery. The surrounding tissue often becomes oedematous and overlying skin may be erythematous, warm and tense. Buboes may also get suppurative. Necrotic material from such buboes may contain viable *Y. pestis*. Lymphadenitis conditions that can be confused with plague include *Staphylococcus aureus*, and Group A β-haemolytic streptococcal infection, cat-scratch disease, tularemia.



Figure 1: Patient with bubonic plague.

Septicaemic plague

This is usually secondary to bubonic plague. Primary septicaemic plague is a progressive, overwhelming infection with *Y. pestis* in the apparent absence of a primary lymphadenopathy. Plague septicaemia, whether primary or secondary to bubonic plague, may lead to metastatic infection of other organ systems. Blood stream infection may result in a wide spectrum of pathological events including disseminated intravascular coagulopathy (DIC), multiple organ failure, and acute respiratory distress syndrome (ARDS). Complications include plague pneumonia, plague meningitis, plague endophthalmitis, hepatic or splenic abscesses, or generalised lymphadenopathy. The differential diagnosis of septicaemic plague includes sepsis of other Gram-negative bacterial aetiology, meningococcaemia, and acute severe viral infections, such as hantavirus illness.

Pneumonic plague

Pneumonic plague occurs in two distinct and epidemiologically significant forms. Secondary plague pneumonia results from haematogenous spread of *Y. pestis* to the lungs. This invasive infection provokes an inflammatory response and results in bacterial multiplication in pulmonary tissue. This process then spills over into the alveolar spaces and provides a mechanism for *Y. pestis* to be expelled during coughing episodes (patient's sputum may be bloody). Spread of *Y. pestis* to contacts by the respiratory droplet route can initiate an epidemic of primary pneumonic plague.

Primary pneumonic plague is the most fulminating and fatal form of plague. The incubation period is usually 1 to 3 days. The onset of the disease is typically manifested by the sudden onset of chills, fever, headache, body pains, weakness and chest discomfort. Cough, sputum production, increasing chest pain, difficulty in breathing, hypoxia and haemoptysis become prominent as the disease rapidly progresses. Death usually ensues if specific antibiotic therapy is not begun within the first 18 to 24 hours of disease onset. Uncommon manifestations of plague include meningeal, pharyngeal, cutaneous and intestinal clinical features.

Diagnosis

A high index of clinical suspicion as well as elicitation of a thorough clinical and epidemiologic history and a careful physical examination are required for timely diagnosis and prompt institution of specific therapy.

When plague is suspected, specimens should be collected promptly for laboratory studies, chest roentgenograms should be obtained and specific anti-microbial therapy should be initiated pending confirmation. Appropriate specimen for smear and culture include whole blood, lymph node aspirate from those with suspected buboes, sputum samples, tracheal or pulmonary alveolar aspirates from those with pneumonic plague and cerebrospinal fluid (CSF) from those with suspected plague meningitis. For *Y. pestis* demonstration/isolation from the specimen smear examination (Wayson, Gram stain), Direct fluorescent antibody testing (DFA), PCR analysis and culture should be carried out. For detection of antibodies against *Y. pestis*, an acute sample and if possible a convalescent sample should be tested. In case of death, autopsy specimens from liver, spleen, lungs, buboes, bone marrow may be collected.

Laboratory confirmation of plague can be done by isolation and *Y. pestis* specific bacteriophage lysis of the isolate or demonstration of fourfold difference in antibody titres in paired sera samples.

In patients with plague, white blood cell counts range between 10,000 to 25,000/µl, with a predominance of polymorphonuclears (PMNs). In patients with plague meningitis, PMN pleocytosis and the bacilli are usually visible in stained CSF smears.

Treatment

If untreated, plague is fatal in more than 50% of cases of bubonic disease and nearly all cases of septicaemic and pneumonic plague. Streptomycin is the drug of choice for the treatment of plague, but patients with simple, uncomplicated plague diagnosed early respond well to treatment with tetracycline. Treatment with tetracycline should be started with loading oral dose of 4-6 grams followed by 500 mg 6 hourly. Doxycycline should be given 200 mg/day. Chloramphenicol should be given in dose of 50 mg/kg/day 6 hourly orally or IV. For treatment of patients with advanced bubonic plague or those with pneumonia or specticaemia, streptomycin is recommended in dose of 2 gm/dL intramuscularly in adults and 30 mg/kg/day in children. Gentamycin has been found to be effective and has special value in treatment of plague in pregnancy. For those patients with complications such as meningitis or endophthalmitis chloramphenicol should be used, it is used in combination with streptomycin or another first line agent. Standard patient-care precautions should be applied to management of all suspected plague patients and standard

droplet precautions for those with suspect or presumptive or confirmed pneumonic plague. Delay in the treatment of plague lead to complications which include DIC, ARDS, multiple organ failure and other complications of Gram-negative sepsis. The patients with these disorders require intensive monitoring and close physiologic support.

Antimicrobial therapy should be continued for 7 to 10 days or for at least 3 days after patient has become afebrile and has made clinical recovery.

Prevention and Control

Long-term prevention and control measures for plague consist of surveillance, education and environmental management. Personal protective measures include the use of repellents, insecticides and protective clothing when at risk of exposure to rodent fleas; and the wearing of gloves when handling animal carcasses. Short-term antibiotic prophylaxis is recommended for persons known to have had close contact with a patient with suspected or confirmed pneumonic plague and persons visiting areas where a plague outbreak is in progress or who may be caring patients with plague.

The preferred antibiotics are the tetracycline, doxycycline, chloramphenicol. Chemoprophylaxis is given until one week after the exposure ceases. Patients in whom pneumonic plague is suspected should be managed under respiratory droplet precautions until it is ruled out or up to 48 hours of effective anti-microbial therapy has been administered, after which standard infection-control precautions should be undertaken.

Rodent food and habitats should be eliminated in domestic, periodomestic and working environments. The control of fleas with insecticides is a key public health measure in situations where epizootic plague activity places humans at high risk.

A formalin killed plague vaccine is produced in limited quantity by Haffkine Institute, Mumbai. Vaccination is recommended only for high risk group of individuals, e.g. laboratory workers or medical or public health workers dealing with patients of plague. Vaccination is of little use during human plague outbreaks, since a month or more is required to develop protective immune response. All persons exposed to patients with suspected pneumonic plague should receive antibiotics regardless of their immunisation status as the vaccine is unlikely to provide complete protection.

OTHER YERSINIA INFECTIONS

Yersiniosis is an uncommon bacterial zoonosis caused primarily by infection with either *Y. enterocolitica* or *Y. pseudotuberculosis*. Reservoir hosts of these bacteria include swine and other wild and domestic animals and transmission to human is predominantly by oral route. Both sporadic and common source outbreaks occur. The most frequent clinical manifestations are: enteritis or enterocolitis with self limited, diarrhoea (especially with *Y. enterocolitica*) and mesenteric adenitis and terminal ileitis (especially with *Y. pseudo tuberculosis*) which can be confused with acute appendictis. Yersiniosis can be complicated by nonsuppurative, extraintestinal, inflammatory sequelae, e.g. reactive arthritis, and erythema nodosum. The diseases by these *Yersinia* are usually self limited and the treatment is symptom-based and supportive. For prevention and control, safe food handling and food preparation practices should be observed.

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17.21 Clostridial Infections

MK Daga, Rakshit Kumar

The genus *Clostridia* comprises of obligate anaerobic rods that usually stain Gram-positive. Clostridial species are widespread in the environment, partly due to their ability to form resistant spores. They are commonly found in soil, faeces, sewage, marine sediments and also in large numbers as indigenous microbiota of the intestinal tract of humans and animals.

Although exogenous infections, such as tetanus, food-borne botulism and hospital acquired *C. difficile* are serious, endogenous infection by commensal clostridia can complicate head and neck infections, respiratory tract infections, gynaecological and, bone and soft tissue infections. Intravenous drug users are increasingly found to be at risk of wound botulism, soft tissue infection and toxic shock.

TETANUS

Tetanus is life threatening infection, but is non-contagious. The word 'tetanus' is derived from the Greek *tetanos* meaning 'taut', and *teinein* to 'stretch'.

Aetiopathogenesis

Once the spores of *C. tetani* gain entry into damaged tissue, they transform into rod-shaped bacteria and produce the neurotoxin tetanospasmin, which when released and activated by proteases, is carried by retrograde axonal transport to the spinal cord and brain stem where it binds irreversibly to receptors at these sites. It cleaves membrane proteins involved in neuroexocytosis, which in turn blocks neurotransmission, producing the symptoms of the disease. Damaged upper motor neurons can no longer inhibit lower motor neurons, also they cannot control reflex responses to afferent sensory stimuli. Both mechanisms produce the hallmark muscle rigidity and spasms. Similarly, a lack of neural control of the adrenal glands results in release of catecholamines, thus producing a hypersympathetic state and widespread autonomic instability.

C. tetani also produces tetanolysin, another toxin whose role in tetanus is unknown.

Clinical Features

Tetanus affects only skeletal muscle; other types of striated muscle, cardiac muscle, cannot be tetanised because of their intrinsic electrical properties. Mortality rates reported vary from 40% to 78%. The highest mortality rates are among the unvaccinated and people over 60 years of age.

The incubation period of tetanus may be up to several months but is usually about eight days. In general, the further the injury site is from the central nervous system (CNS), the longer is the incubation period. The shorter the incubation period, the more severe the symptoms and more worse the prognosis. Clinically, four different forms of tetanus have been described.



Figure 1: Risus sardonicus: contraction of facial muscles during a tetanic spasm. Retraction of the upper lip and angles of mouth, narrowing of the palpebral fissures and overactivity of the frontalis muscles with wrinkling of the forehead gives rise to the typical sneering appearance.

Generalised tetanus (80% of cases)

The first sign is trismus or lockjaw, and the facial spasms contributing to the typical facies 'risus sardonicus' (**Figure 1**), followed by stiffness of the neck, difficulty in swallowing, and rigidity of pectoral and calf muscles. Fever, sweating, elevated blood pressure, and episodic rapid heart rate are accompaniments. Spasms may occur frequently and last for several minutes with the body shaped into a characteristic bow-shaped form called opisthotonus (**Figure 2**). Spasms can continue for up to four weeks, and complete recovery may take months.



Figure 2: Opisthotonus: Note arched back.



Figure 3: Neonatal tetanus with opisthotonus: Note clenched hands and flexed limbs.

Neonatal tetanus

It is a form of generalised tetanus (**Figure 3**) that occurs in newborns. Infants born to unvaccinated mothers do not acquire passive immunity and tend to be at risk. It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with a non-sterile instrument.

Local tetanus

It is an uncommon and milder form of the disease, in which patients have persistent contraction of muscles in the same anatomic area as the injury. The contractions may persist for many weeks before gradually subsiding or may proceed to generalised form.

Cephalic tetanus

It is a rare form of the disease, occasionally occurring with otitis media or following injuries to the head. There is involvement of the cranial nerves, especially in the facial area.

Diagnosis

The diagnosis is on purely clinical grounds and does not depend upon isolation of the bacteria, which are recoverable from the wound in only 30% of cases and can also be isolated from patients who do not have tetanus. Laboratory identification of *C. tetani* can only be demonstrated by production of tetanospasmin in mice.

The *'spatula test'* is a clinical test for tetanus that involves touching the posterior pharyngeal wall with a sterile, soft-tipped instrument, and observing the effect. A positive test is the involuntary contraction of the jaw (biting down on the 'spatula'), and a negative test would normally be a gag reflex attempting to expel the foreign object. The spatula test has a high specificity (100%) and sensitivity (94%).

Differential Diagnosis

Tetanus must be differentiated from various acute CNS infections, such as meningitis. Cerebrospinal fluid (CSF) analysis is helpful. Trismus can occasionally develop with phenothiazine use. Strychnine poisoning is another differential diagnosis.

Prevention

General preventive measures

- Universal active immunisation with adsorbed tetanus toxoid, gives durable protection (antitoxin titre >0.01 IU/mL) for at least 10 years; after the initial basic series has been completed, single booster doses elicit high levels of immunity.
- For adolescents 11 to 12 years of age, a single dose of Tdap is recommended for routine booster, and for adolescents and adults 13 to 64 years of age, a single dose of Tdap is recommended to replace the next decennial Td booster or when indicated as part of wound prophylaxis.
- In countries with incomplete immunisation programme for children, all pregnant women should receive two doses of tetanus toxoid in the first pregnancy, with an interval of at least one month, and with the second dose at least 2 weeks prior to childbirth. Active protection should be maintained by administering booster doses of Td every 10 years, preferably before or between pregnancies.
- For immunocompromised people or those infected with HIV, tetanus toxoid is indicated in the same schedule and dose as for immunocompetent persons.

Prophylaxis in wound management

Passive immunisation with at least 250 IU of tetanus immunoglobulin IM (or 1,500 to 5,000 IU of antitoxin of animal origin, if globulin is not available), regardless of the patient's age, is indicated for patients with other than clean, minor wounds and a history of no, unknown, or fewer than three previous tetanus toxoid doses.

Treatment

General principles

The patient should be kept in a quiet room. Three principles should guide all therapeutic interventions: prevent further toxin release by debriding the wound and giving an antibiotic; neutralize toxin outside the CNS with human tetanus immune globulin and tetanus toxoid, taking care to inject into different body sites and thus avoid neutralising the antitoxin; and minimise the effect of toxin already in the CNS.

Antitoxin

The human-derived antitoxin neutralises only free toxin. For adults, human tetanus immune globulin 3000 units IM is given once; this large volume may be split and given at separate sites. Dose can range from 1,500 to 10,000 units, depending on wound severity, although some authorities feel that 500 units is also adequate. Antitoxin of animal origin is far less preferable because it does not maintain the patient's serum antitoxin level well and the risk of serum sickness is considerable. If horse serum must be used, the usual dose is 50,000 units IM or IV. General wound care is more important, rather than direct injection of immunoglobulin or anti-toxin in the wound.

Benzodiazepines

Benzodiazepines are the standard to control seizures, counter muscle rigidity, and induce sedation. Dosage varies and requires meticulous titration and close observation. The most severe cases may require 10 to 20 mg IV q3 h (not exceeding 5 mg/kg). Less severe cases can be controlled with 5 to 10 mg PO q2 to 4h. Although diazepam has been used most extensively, midazolam (adults, 0.1 to 0.3 mg/kg/h IV infusion; children, 0.06 to 0.15 mg/kg/h IV infusion) is water-soluble and preferred for prolonged therapy. Midazolam reduces the risk of lactic acidosis due to the absence of propylene glycol solvent, which is required for diazepam and lorazepam, and reduces the risk of long-acting metabolites accumulating and causing coma.

Benzodiazepines may not prevent reflex spasms, and effective respiration may require neuromuscular blockade with Vecuronium 0.1 mg/kg IV or other paralytic drugs and mechanical ventilation. Pancuronium has been used but may worsen autonomic instability.

Management of Autonomic Dysfunction

Morphine may be given q 4 to 6 h to control autonomic dysfunction, especially cardiovascular; total daily dose is 20 to 180 mg. Sudden cardiac death is a feature of tetanus, and β-blockade can increase the risk; however, esmolol, a short-acting β-blocker, has been used successfully. Atropine at high doses has also been used; blockade of the parasympathetic nervous system markedly reduces excessive sweating and secretions.

Intravenous magnesium sulphate at doses that maintain serum magnesium levels between 4 and 8 mEq/L (e.g. 4 g bolus followed by 2 to 3 g/h), has a stabilising effect, eliminating catecholamine stimulation. The patellar tendon reflex is used to assess overdosage. Tidal volume may be impaired, so ventilatory support must be available.

Pyridoxine (100 mg once/day) lowers mortality in neonates. Other drugs that may prove useful include sodium valproate, angiotensin-converting enzyme (ACE) inhibitors (which inhibit angiotensin II and reduce norepinephrine release from nerve endings), and adenosine (which reduces presynaptic norepinephrine release and antagonizes the inotropic effect of catecholamines). Corticosteroids are of unproven benefit; their use is not recommended.

Antibiotics

The role of antibiotic therapy is minor compared with wound debridement and general support. Typical antibiotics include penicillin G 6 million units IV q 6 h, doxycycline 100 mg PO bid, and metronidazole 500 mg PO q 6 to 8 h. Administration of metronidazole decreases the number of bacteria but has no effect on the bacterial toxin. Penicillin was once used to treat tetanus, but is no longer the treatment of choice, owing to a theoretical risk of increased spasms. However, its use is recommended if metronidazole is not available.

Supportive care

In moderate or severe cases, patients should be intubated. Mechanical ventilation is essential when neuromuscular blockade is required to control muscle spasms that impair respiration.

In order to survive a tetanus infection, the maintenance of an airway and proper nutrition are required. An intake of 3500 to 4000 Calories, and at least 150 g of protein per day, is given to compensate for the increased metabolic rate due to increased muscle activity. Because constipation is usual, stools should be kept soft. A rectal tube may control distention. Bladder catheterisation is required if urinary retention occurs. Full recovery takes 4 to 6 weeks because the body must regenerate destroyed nerve axon terminals.

Chest physiotherapy, frequent turning and forced coughing are essential to prevent pneumonia. Analgesia with opioids is often needed.

Prognosis

Tetanus has a worldwide mortality rate of 50% and 80% to 90% in neonates, even if treated. Mortality is highest at the extremes of age and in drug abusers. The prognosis is poorer if the incubation period is short and symptoms progress rapidly or if treatment is delayed. The course tends to be milder when there is no demonstrable focus of infection. Contaminated lesions about the head and face are more dangerous than wounds on other parts of the body. Tetanus infection does not confer immunity due to the extreme potency of tetanospasmin; patients who have recovered from clinical tetanus should be fully vaccinated.

BOTULISM

Botulism is a paralytic disease caused by the botulinum toxin, produced by *C. botulinum*. Four toxin types A, B, E, and F cause human disease. Botulinum toxin is a zinc metalloprotease that cleaves a specific component of the synaptic vesicle membrane docking and fusion complex at the neuromuscular junction blocking release of the neurotransmitter acetylcholine. Naturally occurring botulism occurs in one of three forms: food-borne botulism, infant botulism, or wound botulism. Food-borne botulism is caused by ingestion of preformed toxin present in canned, smoked, or vacuum-packed foods, such as home-canned vegetables, smoked meats and vacuum-packed fish. Infant botulism (associated with ingestion of honey) and wound botulism (which typically occurs in association with injection drug use) result from organisms present in the gut or a wound that elaborate toxin *in vivo*.

Botulism and Bioterrorism

- Botulism toxin is the most toxic substance known to man; lethal dose is less than 1 mcg. A deliberate release may involve airborne dissemination of toxin, or contamination of food or water supplies with toxin or bacteria.
- Water treatment inactivates the toxin, the toxin cannot penetrate intact skin and it loses activity within a few days.
- The most likely scenarios would therefore be:
  - A deliberate contamination of foodstuffs; large doses may lead directly to neurological symptoms without the gastrointestinal symptoms of nausea, vomiting, and diarrhoea followed by constipation.
  - Aerosol release; most effective in an enclosed environment. After inhalation, the onset of symptoms may be as rapid as within 1 hour. However, in cases of accidental inhalation, symptom onset can be after 3 to 4 days.

Clinical Findings

Twelve to thirty six hours after ingestion of the toxin, visual disturbances appear, particularly diplopia and loss of accommodation. Ptosis, cranial nerve palsies with impairment of extra-ocular muscles, and fixed dilated pupils are characteristic signs. The sensory examination is normal. Other symptoms are dry mouth, dysphagia and dysphonia. Nausea and vomiting may be present, particularly with type E toxin. The sensorium remains clear and the temperature normal. Paralysis progressing to respiratory failure and death may occur unless mechanical assistance is provided.

Laboratory Findings

Toxin in patients' serum and in suspected foods can be demonstrated by mouse inoculation and identified with specific antiserum.

Differential Diagnosis

Differential diagnosis is limited because of the typical presentation. Cranial nerve involvement may be seen with vertebrobasilar insufficiency, the Miller-Fisher variant of Guillain-Barré syndrome, myasthenia gravis, or any basilar meningitis (infectious or carcinomatous). Intestinal obstruction or other types of food poisoning are considered when nausea and vomiting are present.

Treatment

Trivalent antitoxin should be administered in a dose of 50.000 units IV stat and may be repeated after two hours. Skin testing is recommended to exclude hypersensitivity to the antitoxin preparation. Antitoxin should be administered as early as possible, ideally within 24 hours of the onset of symptoms or signs, to arrest progression of disease; its administration should not be delayed for laboratory confirmation of the diagnosis. Guanidine hydrochloride, orally, in doses of 15-20 mg/kg may help reverse neuromuscular blockade. Respiratory failure is managed with intubation and mechanical ventilation. Parenteral fluids or alimentation should be given while swallowing difficulty persists. Nasogastric suction and urinary catheterisation are indicated for paralytic ileus and atonic bladder, respectively. The removal of unabsorbed toxin from the gut may be attempted by using laxatives if paralytic ileus is absent. Any remnants of suspected foods should be assayed for toxin.

CLOSTRIDIUM DIFFICILE INFECTION

C. difficile is a Gram-positive, anaerobic, spore-forming bacillus that is responsible for the development of antibiotic-associated diarrhoea and colitis. The disturbance of the normal bacterial flora of the colon, colonisation with *C. difficile*, and release of toxins A and B cause mucosal inflammation and damage. The chief risk factor is exposure to antibiotics, commonest being cephalosporins, ampicillin/amoxicillin, and clindamycin. Prolonged and multiple antibiotic courses (even antibiotics traditionally used to treat *C. difficile* colitis) have been shown to cause disease. Other risk factors include – advanced age (more than 60 years) prolonged hospitalisation, antineoplastic agents principally methotrexate, immunocompromised state and enteral feeding.

C. difficile infection commonly manifests as fever, mild-to-moderate diarrhoea, occasionally with abdominal cramping, and rarely as acute abdomen and fulminant life-threatening colitis. Approximately 20% of hospitalised individuals acquire *C. difficile* during hospitalisation, but symptomatic illness is relatively rare in India due to widespread use of metronidazole.

The diagnosis should be suspected in any patient with diarrhoea who has received antibiotics within the previous two months and/or when diarrhoea occurs 72 hours or more after hospitalisation. Differentials include inflammatory bowel disease, irritable bowel syndrome, malabsorption and bacterial gastroenteritis.

Laboratory Studies

- Complete blood counts: Leucocytosis may be present.
- Stool examination: Faecal leucocytosis is present in 50% patients and occult blood may be positive in severe colitis.
- Stool assays: Stool culture is the most sensitive (sensitivity 90% to 100% and specificity 84% to 100%) but results are slow and may lead to delay in diagnosis if used alone. Glutamate dehydrogenase enzyme immunoassay (EIA) is very sensitive (sensitivity 85% to 100% and specificity 87% to 98%). This test detects the presence of glutamate dehydrogenase produced by *C. difficile*. The stool cytotoxin test (demonstration of a cytopathic effect) is expensive, and it requires an overnight incubation and a tissue culture facility. Enzyme immunoassay for detecting toxins A and B is used in most laboratories. The sensitivity is moderate (79% to 80%) and specificity is excellent (98%).

Endoscopy may demonstrate the presence of raised, yellowish-white, 2 to 10-mm plaques overlying an erythematous and oedematous mucosa. These plaques are termed pseudomembranes. Typical pseudomembranes are beyond the limit of flexible sigmoidoscopy in 10% of patients. Therefore, colonoscopy is required.

Biopsy of pseudomembranous plaques reveals an inflammatory exudate composed of mucinous fibrinous material containing polymorphonuclear cells.

Treatment

Initial therapy: In mild cases (i.e. patients without fever, abdominal pain, or leucocytosis), cessation of causative antibiotics may be the only treatment necessary. Specific therapy aimed at eradicating *C. difficile* is indicated if symptoms are persistent or if antibiotics cannot be discontinued safely.

- Oral metronidazole and vancomycin have similar efficacy for mild to moderate disease. Metronidazole 200 mg PO QID for 10 days is the drug of first choice because of its lower cost.
- For severe cases, vancomycin 125 mg PO QID for 10 days is considered first line and higher dosing 250 mg PO QID may be used if poor absorption is a concern due to situations such as ileus. For patients who are unable to tolerate oral medication, IV metronidazole is effective. IV vancomycin is ineffective. Fidaxomicin, a newer antibiotic (not yet approved) has shown better efficacy than vancomycin in phase 3 trials.

In relapsed and resistant cases, prolonged therapy and agents like probiotics, intravenous immunoglobulin (IVIG) and cholestyramine are used. Anti-diarrhoeal agents (e.g. diphenoxylate with atropine) have been reported to increase the duration and severity of symptoms. Fulminant colitis and toxic megacolon may require operative intervention.

GAS GANGRENE (CLOSTRIDIAL MYONECROSIS)

Gas gangrene or clostridial myonecrosis is produced by any one of several clostridia (*C. perfringens, C. ramosum, C. bifermentans, C. histolyticum, C. novyi*, etc). Trauma and injection drug use are common predisposing conditions. Toxins produced in devitalised tissues under anaerobic conditions result in shock, hemolysis, and myonecrosis.

Clinical Findings

The onset is usually sudden, with rapidly increasing pain in the affected area, hypotension and tachycardia. Fever is present but

is not proportionate to the severity of the infection. In the last stages of the disease, severe prostration, stupor, delirium and coma occur.

The wound becomes swollen, deeply discoloured, with coalescent, red, fluid-filled vesicles and serosanguinous foul smelling discharge. Gas may be palpable in the tissues. Intravascular haemolysis by aflatoxin may lead to jaundice, haemoglobinuria and acute renal failure.

Laboratory Findings

Gas gangrene is a clinical diagnosis, and empiric therapy is initiated in suspected cases. Radiography may demonstrate gas within the soft tissues, but this finding is not specific. Smear from wounds shows absence of neutrophils and the presence of Gram-positive rods. Anaerobic culture confirms the diagnosis. Other bacteria can produce gas in infected tissue, e.g. enteric Gram-negative organisms or anaerobes.

Treatment

Penicillin, 2 MU IV q 3h is effective. Tetracycline, clindamycin, metronidazole, chloramphenicol, or cefoxitin can also be used. Antitoxin is of doubtful value but may be administered as 10,000 units of polyvalent serum, followed by 50,000 units six hourly. Adequate surgical debridement and exposure of infected areas are essential, with radical surgical excision often necessary. Hyperbaric oxygen at three atmospheres for 1-2 hr, three times in a day dramatically relieves constitutional symptoms.

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17.22 Diphtheria

Sandeep B Bavdekar

Diphtheria is an acute infectious disease caused by *Corynebacterium diphtheriae*. The incidence of the disease has decreased dramatically due to the implementation of vigorous public health control measures. However, some countries have witnessed re-emergence of diphtheria due to waning immunity amongst adults, decreasing immunisation coverage amongst infants and children, movement of large groups of people and irregular vaccine supply.

AETIOLOGY AND PATHOGENESIS

Corynebacterium diphtheriae is not an invasive organism. A lysogenic bacteriophage confers toxin-producing potential to it. The toxin inhibits protein synthesis and mediates DNA fragmentation and cytolysis.

Patients with diphtheria and asymptomatic carriers are the sources of infection. Infection spreads through airborne respiratory droplets or direct contact with respiratory secretions or exudate from infected skin lesions. The toxin induced local necrosis and inflammatory reaction results in the formation of a pearly-grey membrane. As the toxin production increases, the area of necrosis and inflammation increase leading to extension of the membrane. On entry into the systemic circulation, the toxin can damage various organs and systems, predominantly the heart and the nervous system.

CLINICAL MANIFESTATIONS

Clinical manifestations appear after an incubation period of 1 to 6 days and depends upon site of infection, host immunity and if toxin has entered the systemic circulation.

Nasal Diphtheria

It begins with mild rhinorrhoea without much of systemic symptoms; gradually progressing to a serosanguinous and mucopurulent discharge with foul odour. It causes excoriation and shallow ulceration of the external nares and upper lip. A white membrane is noticed on the nasal septum. Differential diagnosis include common cold, sinusitis, adenoiditis and nasal foreign body.

Tonsillar and Pharyngeal Diphtheria

It begins as an insidious but more severe form of the disease. Sore throat is universal and anorexia, malaise, low-grade fever and headache are noted in some patients. Within 1 to 2 days a white or grey membrane appears (may not develop in partially immune individuals). The adherent membrane may cover the tonsils and pharyngeal walls and even extend on to the uvula, soft palate, larynx and trachea. Attempts to remove the membrane lead to bleeding. Associated lymphadenitis and soft tissue oedema in the neck is referred to as 'bull neck'.

Differential diagnosis include streptococcal pharyngitis (usually characterised by severe dysphagia, high fever, non-adherent membrane limited to the tonsils), infectious mononucleosis (associated with membrane limited to tonsils whose removal does not lead to bleeding, presence of lymphadenopathy and splenomegaly), primary herpetic tonsillitis (usually characterised by the presence of gingivitis, stomatitis, and discrete lesions of the tongue and palate), agranulocytosis, thrush, Vincent angina (associated with the involvement of the gums and presence of necrotic and ulcerative lesions on the pharynx).

Laryngeal Diphtheria

It is a downward extension of pharyngeal membrane and presents with noisy-breathing, dry cough, hoarseness and progressive stridor. Supra-sternal and supra-clavicular retractions reflect severe laryngeal obstruction, which may be fatal unless alleviated.

Infection at Other Sites

Cutaneous diphtheria presents as a superficial, non-healing ulcer with a sharp border and grey-brown membranous base. Purulent and ulcerative conjunctivitis, aural diphtheria (otitis externa with a purulent and foul-smelling discharge) and purulent and ulcerative vulvovaginitis are manifestations of infection at other sites.

DIAGNOSIS

A presumptive diagnosis of diphtheria is made on purely clinical grounds. Confirmation is by culturing *C. diphtheriae* from the infection site. However, therapy should be initiated on the basis of clinical diagnosis as any delay in starting therapy has grave consequences.

COMPLICATIONS

Complications, especially those related to elaboration of toxin or respiratory obstruction are responsible for the morbidity and mortality associated with diphtheria. Toxic myocarditis commonly occurs in the second (range: 1 to 6) week of the illness. Its manifestations include tachycardia, muffled heart sounds, murmurs, arrhythmias (varying degree heart blocks, atrioventricular dissociation and ventricular tachycardia) and congestive heart failure. A prolonged PR interval and changes in ST-T wave on an electrocardiographic tracing are relatively frequent findings.

Neurological complications appear after a variable latent period (2 to 12 weeks). Paralysis of the soft palate is most common and generally appears in the third week. It presents with nasal twang or regurgitation and difficulty in swallowing. Cranial neuropathies usually occur in the 5th week. They lead to oculomotor and ciliary paralysis and manifest with strabismus, blurred vision and difficulty with accommodation. Paralysis of the diaphragm and peripheral neuropathy involving the limbs occur from 10 days to 3 months after oropharyngeal infection. When these manifestations occur with elevated cerebrospinal fluid protein content, the manifestations mimic those of

Guillain-Barre syndrome. Rarely, affliction of vasomotor centres 2 to 3 weeks after the onset of illness manifests with tachycardia, hypotension and cardiac failure.

Secondary bacterial infection may occur. Extension of membrane into the larynx or its detachment and tissue oedema can lead to life-threatening airway obstruction. Gastritis, hepatitis, nephritis and haemolytic-uraemic syndrome are known to occur following diphtheria.

PREVENTION

Diphtheria-pertusis-tetanus (DPT) vaccine containing diphtheria toxoid is administered at the age of 6, 10 and 14 weeks and a booster is provided at 18 months. The second booster consisting of diphtheria and tetanus toxoids (DT) is administered at the age of 5 to 6 years. Although immunisation does not totally prevent subsequent infection with *C. diphtheriae*, it decreases the severity of local manifestations, diminishes the frequency and severity of toxic complications, reduces the probability of transmission of infection and provides herd immunity when at least 70% of the population is immunised.

TREATMENT

Specific therapy includes administration of anti-toxin (anti-diphtheritic serum) of equine origin, which neutralises the free circulating toxin. Subjects sensitive to antitoxin should undergo desensitisation before receiving the full dose. The dose of anti-toxin to be administered is empirically based on the site of infection, duration of illness and severity of manifestations as follows: mild nasal or pharyngeal diphtheria: 20,000 to 40,000 units, nasopharyngeal lesions: 40,000 to 60,000 units, moderately severe pharyngeal diphtheria: 80,000 to 100,000 units and severe pharyngeal or laryngeal diphtheria, symptoms involving multiple sites, presence of brawny oedema or illness over 48 hours: 120,000 units. The antitoxin should be administered as an intravenous infusion over 60 minutes to ensure rapid inactivation. Intravenous immunoglobulin (IVIG) preparations are not recommended for the treatment of diphtheria, as they contain only low-titres of anti-diphtheria antibodies.

Antibiotics, such as penicillin and erythromycin, help in halting toxin production, treating localised infection and preventing transmission of organisms to contacts. Appropriate therapy consists of using aqueous crystalline penicillin G (100,000-150,000 U/kg/day divided q 4 hr IV or IM), procaine penicillin G (25,000-50,000 U/kg/day divided q 12 hr IM) or erythromycin 40-50 mg/kg/day divided in 6 hourly doses; maximum 2 gm/day, orally). Amoxicillin, rifampin and clindamycin may also be effective. Therapy should be continued for 14 days, elimination of organism should be documented by obtaining two negative cultures taken at least 4 hours apart.

PROGNOSIS

Infancy, inadequate immunity, high virulence of organisms, extensive pharyngeal infection and delay in administration of toxin are associated with poor prognosis. Recovery, when it occurs, is usually complete.

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17.23 Pertusis—Whooping Cough

YK Amdekar

INTRODUCTION

Whooping cough (pertusis) is a highly contagious disease caused by *Bordetella pertusis*. It is a respiratory tract infection characterised by paroxysmal cough. Bordet first identified this organism as a cause of whooping cough in the year 1906, and hence, the organism came to be known as *Bordetella pertusis*. *Bordetella parapertusis* is also known to cause whooping cough in humans. Prior to the advent of vaccination against whooping cough, the disease had high morbidity and mortality especially in infants and young children. Vaccine against whooping cough was introduced in the year 1940 along with diphtheria and tetanus. Disease prevalence did go down significantly thereafter. In spite of advances in the field of control of infectious diseases, whooping cough still continues to be a major public health concern. In fact, wider coverage of vaccination in children has resulted in epidemiological shift to adolescent and adult age groups. However, there have been outbreaks reported in adults from different parts of the world. This has necessitated change in policies to control this disease.

PATHOPHYSIOLOGY

Humans are the sole reservoirs of *Bordetella pertusis* and *parapertusis*. It is a gram-negative pleomorphic bacillus that spreads through aerosolised droplets from coughing of infected individuals. Organism attaches itself to the ciliated respiratory epithelium and damages it. Typically incubation period varies from 3 to 12 days.

CLINICAL FEATURES

Disease runs about 6 weeks of course and its pattern of presentation is broadly divided into three stages: catarrhal, paroxysmal and convalescent stages. Each stage lasts for about 2 weeks.

In stage 1, catarrhal stage, symptoms are indistinguishable from common respiratory infection as it presents with rhinorrhoea, congested eyes and often low-grade fever. It is in this stage that the patient is most infectious and infectivity diminishes over next few weeks and becomes non-infectious at the end of 4 weeks.

In stage 2, paroxysmal stage, is characterised by bouts of severe cough that is often followed by a whoop, a loud noise as a result of air rushing through narrow airway during inspiration, and hence, the name, whooping cough. However, whoop is not seen in adults, and therefore, diagnosis is easily overlooked. In young infants less than 6 months of age, severe bout of cough is followed by apnoeic spell that may even endanger life due to hypoxia. Post-tussive vomiting and redness of face are common after bout of cough.

In stage 3, convalescent stage, chronic cough gradually diminishes in severity till patient recovers completely.

PHYSICAL EXAMINATION

It is almost not contributory as there are no positive findings on physical examination. Periorbital oedema, congestion of face and sub-conjunctival haemorrhage are some of the findings suggestive of severe cough but not specific to whooping cough. Umbilical or inguinal hernia and rectal prolapse may develop during the course of the disease as a result of straining at the time of severe bouts of cough. Infants and young children may show considerable loss of weight.

DIFFERENTIAL DIAGNOSIS

Adenoviral infection mimics whooping cough to an extent that it is not possible to differentiate one from the other. However, course of progression in classical whooping cough may help to define correct diagnosis.

Respiratory syncitial virus infection also presents with severe cough but has signs of lower respiratory tract involvement, such as crepitations and wheeze.

Mycoplasma or *Chlamydia pneumoniae* may mimic whooping cough but systemic symptoms are more prominent, such as high fever and also have lower respiratory tract involvement.

In older infants and toddlers, inhaled foreign body may be mistaken for whooping cough. Abrupt onset of severe cough in inhaled foreign body and absence of progression of cough as in whooping cough helps to differentiate it from pertusis.

Cough variant asthma presents with severe cough without any other systemic symptoms and may be devoid of physical signs at the time of physical examination. Past history of similar illness and atopic diathesis or family history of atopy would help to make correct diagnosis.

LABORATORY DIAGNOSIS

Diagnosis of whooping cough is largely clinical. It is not easy to confirm diagnosis of whooping cough through laboratory tests. Lymphocytic leucocytosis is non-specific as it is seen in many other diseases as well; though severe neutrophilic leucocytosis is considered as a marker of severe infection. Classically low ESR may at times be seen.

Bacteriological diagnosis is the 'gold standard' and may be attempted by deep posterior nasopharyngeal swab or direct cough plate culture. Special culture media need to be used, such as Regan-Lowe, Bordet-Gengoi agar or Strain and Scholt culture medium. Positive yield on culture is most likely in early stages of the disease but not later than 4 weeks of the onset of symptomatology.

Serology is non-specific and not useful. Direct fluorescent assay is unreliable. Polymerase chain reaction is highly sensitive but not widely available and costly for routine application.

IMAGING STUDIES

They are of little use in the diagnosis of whooping cough. In an uncomplicated whooping cough, there is no need for imaging study. However, in case of doubtful diagnosis or in case of complications, such as pneumonia, chest radiograph may be useful. Subtle findings such as small segmental emphysema may help in diagnosing inhaled foreign body. Fluoroscopy may demonstrate mediastinal flutter in case of inhaled foreign body and it can also be picked-up by chest radiograph done in both phases of respiration that demonstrates retained air in a segment during the phase of expiration. Reactivation of tuberculosis (TB) may be diagnosed by imaging. Computed tomography of chest is of no help in the diagnosis.

COMPLICATIONS

Most of the patients recover without complications. However, infants and young children are prone to complications, such as pneumonia or encephalopathy and convulsions. Young infants less than 6 months age are at a risk of death due to severe apnoeic spell that may result in asphyxia. Umbilical or inguinal hernia and rectal prolapse may develop as a result of straining during severe bouts of cough, especially in malnourished children.

Reactivation of TB is known to occur after recovery from whooping cough in children harbouring silent dormant TB. Malnutrition may result after long illness that disturbs feeding especially in infants and toddlers.

MANAGEMENT

Mainstay of the management in acute illness is mostly supportive. Goal of therapy is to minimise severity of paroxysms of cough, providing assistance during severe bout of cough especially in infants and maximising nutrition.

Hospitalisation is indicated in infants less than 6 months of age and also in children suffering from co-morbid conditions, such as congenital heart defects or chronic respiratory disease and severe malnutrition. It is important to ensure adequate oxygenation during apnoeic spells.

During early stages of the disease, child may have to be isolated to prevent spread of infection, until 4-5 days after antibiotic therapy is started. It is not easy to suppress severe bouts of cough once disease has gone past catarrhal stage. Cough suppressants, such as dextromethorphan, pholcodine or codeine, may be tried. Steroids are generally of no great benefit.

Macrolides are the antibiotics of choice against whooping cough. They may abort the attack and further progression of the disease if administered early in the course of illness. As diagnosis is usually delayed beyond catarrhal stage, antibiotic may not be useful in a given patient but is necessary to ensure prevention of spread of infection to other contacts. Antibiotic is continued for 7-10 days irrespective of clinical progress.

PREVENTION

Immunisation is the best way of prevention of whooping cough. Expanded immunisation programme in India recommends three primary doses at the interval of 4 to 8 weeks starting early in infancy at 6 to 8 weeks of age followed by booster doses at 18 months and 4 to 5 years of age. Immunisation against whooping cough has not been recommended beyond 5 years of age due to consideration of disease not being common beyond that age and also fearing high reactogenicity of the whole cell pertusis component of the vaccine. However, increasing prevalence of whooping cough beyond early childhood into adolescents and adults has made it necessary to revise vaccination schedules recently. With the availability of acellular component of pertusis in DTaP vaccine, there is no fear of severe reactions at any age.

Evidence is overwhelming that parents and older siblings constitute the major source of infection to infants and young children, and therefore, adolescents and adults need protection to control infection in children. With the availability of small dose of diphtheria toxoid and acellular component of pertusis along with tetanus toxoid in usual dose in a combined vaccine (TdaP), American Academy of Paediatrics has approved use of TdaP for adolescents since December 2005.

FUTURE CONSIDERATIONS

As vaccination coverage in children increases in population, there is always a possibility of epidemiological shift in the disease prevalence into adolescents and adults. Coming decade may witness adult vaccination programmes in India as most of the infectious diseases are acquired by children from infected adults and it is not possible to control such diseases in children without adequate control in adult population.

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17.24 Syphilis

Debabrata Bandyopadhyay

Syphilis is a chronic infective disease caused by the pathogenic spirochaete *Treponema pallidum* subspecies *pallidum*. Syphilis is mainly transmitted through the sexual route, but transplacental transmission can also occur, causing congenital disease. The protean manifestations of syphilis have been described for centuries and the disease is aptly designated as the 'great imitator'. The clinical course of untreated disease, which may last for decades, is characterised by periods of activity with intervening asymptomatic periods of clinical latency.

EPIDEMIOLOGY

Syphilis occurs throughout the world, the prevalence varying significantly with geographic location. According to the World Health Organisation (WHO) estimates, the annual global incidence of syphilis is approximately 12.2 million cases, mostly occurring in the developing countries of Asia and Africa. The prevalence of pregnant seropositive cases may exceed 10% in many developing countries and congenital syphilis remains a significant global problem. Small high-risk groups of core transmitters such as female sex workers, men who have sex with men, and injecting drug users serve as the main source of transmission to the general population.

AETIOLOGY

The causative spirochaete of syphilis, *Treponema pallidum* sub species *pallidum*, was discovered by Schaudinn and Hoffmann in 1905. It is pathogenic only to humans. It cannot be cultured in artificial media, but can be grown in rabbits as a source of *T. pallidum* for use in diagnostic tests. The generation time is 30 to 33 hours and the bacteria is susceptible to heat, drying, freezing, soaps, and mild disinfectants. It is a slender cork-screw shaped organism with a length of 6 to 20 µm and a diameter of 0.10 to 0.18 µm making it invisible by light microscopy. The organism is actively motile and the movements demonstrated by dark-field microscopy are pathognomonic. Sequencing of the genome of *T. pallidum* has showed that it lacks many vital biosynthetic and metabolic pathways explaining the organism's extreme host-dependence for survival.

TRANSMISSION

The disease is almost exclusively transmitted during sexual intercourse. Although it can penetrate intact mucosa, it more readily enters the body through breaks in the skin caused by microtraumas induced by sex. Congenital syphilis is caused by mother-to-child transmission through transplacental route. The likelihood of transmission is inversely proportional to the duration of the disease in the mother. Syphilis can very rarely be transmitted by blood transfusion or accidental puncture.

PATHOGENESIS AND NATURAL COURSE

The natural course of untreated syphilis (**Figure 1**) had been documented by large-scale long-term studies (some are ill-famous for being highly unethical). After inoculation, *T. pallidum* readily penetrates intact mucosa or microabrasions in the skin to reach the systemic circulation via the lymphatics and disseminate widely before the appearance of the chancre. The length of the primary incubation period (9 to 90 days) is inversely proportional to the size of the inoculum. The primary lesion develops as a local disease at the site of inoculation and heals spontaneously within weeks with development of immune response. After about 6 to 12 weeks, there occurs widespread proliferation of the bacteria leading to the secondary stage of the systemic disease. Antigenic variation of the bacteria is believed to be responsible for its escape from immune response and proliferation. The secondary stage may last for weeks to months and heals spontaneously. The disease then enters a period of latency in which there are no clinical manifestations but the serology is positive. Although

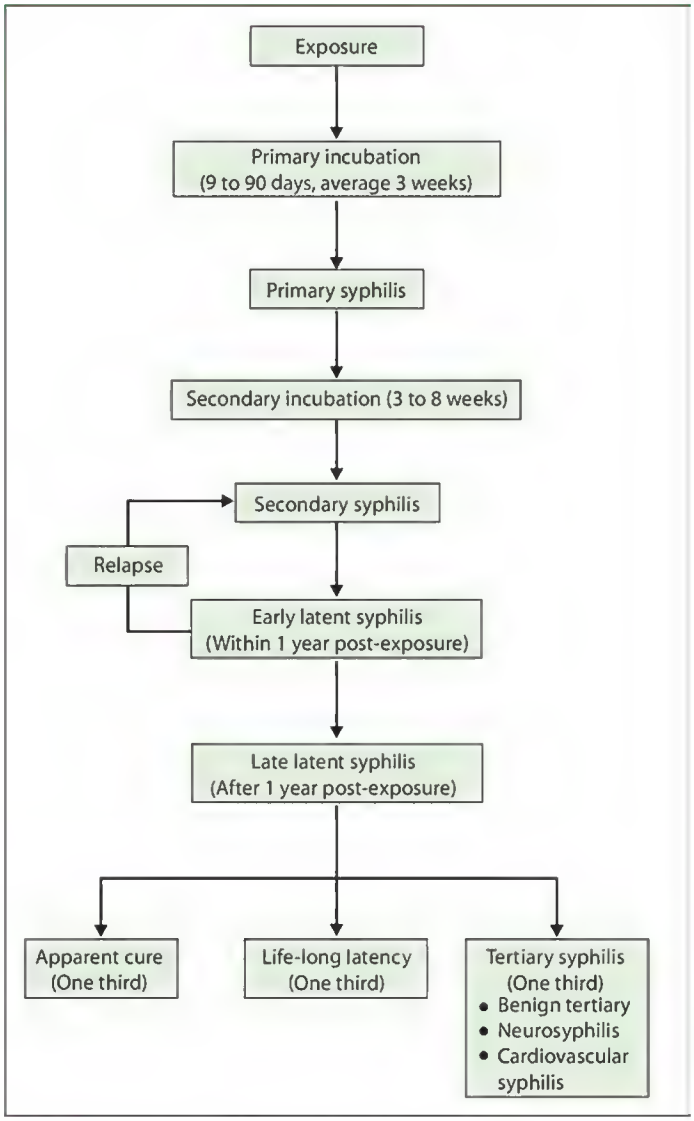


Figure 1: Natural course of untreated syphilis.

transplacental transmission can still occur, sexual transmission does not occur during late syphilis.

CLINICAL FEATURES

Primary Syphilis

Although *T. pallidum* disseminate systemically soon after the infection, the first clinical manifestation of the disease occurs locally, at the site of inoculation. The most common site of the lesion is the genitalia. The coronal sulcus, prepuce, glans, and shaft of penis are the usual sites in males and the vulva, fourchette, cervix, and vagina in the females. Anal and rectal ulcers may occur following anal sex. Extragenital inoculation may lead to lesions on the lips, breast, fingers, and tongue.

The classical ulcer of primary syphilis (the 'Hunterian chancre') is a solitary, painless and non-tender, circular or oval ulcer with a raised well-defined margin and a rubbery, firm base. Classical lesions, however, are less commonly found and multiple ulcers and mixed ulcers (with chancroid or herpes genitalis) are not infrequent. Regional lymphadenopathy develops within a week; it is generally bilateral with genital ulcers, and unilateral with extragenital lesions. The nodes are painless and non-tender, discrete, mobile, and have a rubbery consistency. Untreated, the lesions of primary syphilis heal spontaneously in 3 to 8 weeks.

Secondary Syphilis

Three to ten weeks after the ulcer appears, features of secondary syphilis set in. At this stage, the systemic nature of the illness becomes clinically apparent. The chancre may still be present in a minority. Constitutional features such as fever, malaise, headache, weight loss, arthralgia, and sore throat may be present.

The characteristic syphilitic rash develops in most of the patients. The rash is generalised, symmetrical, and usually asymptomatic. Starting as faint macules of rose-pink colour, these roundish lesions gradually evolve into dull red scaly papules characteristically involving the palms and soles in addition to other areas of the body. The lesions, however, may be polymorphic and follicular, annular and pustular lesions may also occur. Skin lesions at warm, moist sites may become broad, flat, and moist (condyloma lata). These lesions are commonly seen around the anus, on the scrotum, vulva, axilla, or under the breast. Mucosal ulcers ('mucous patches') may occur on any mucosal surface including oral cavity, pharynx, larynx, or the genitalia. Exudative secondary syphilitic lesions are highly infective.

Generalised lymphadenopathy is a common finding. Neurological involvement occurs in a minority but cerebrospinal fluid abnormality may be found in about a third of the patients. A variety of other manifestations may also occur in the secondary stage. These include diffuse or localised ('moth-eaten') alopaecia, hepatosplenomegaly, hepatitis, conjunctivitis, iridocyclitis, and nephrotic syndrome.

Latent Syphilis

With or without treatment, the manifestations of secondary syphilis resolve after 4 to 12 weeks, the patient becomes asymptomatic, and a period of latency begins. Latent syphilis is diagnosed on the basis of positive serology in the setting of no clinical evidence of disease. Latent syphilis is divided into the *early latent stage* (within one year of infection) and *late latent stage* (beyond one year post-infection). Lesions of secondary syphilis may relapse in a portion of patients during the early latent period and the patient may be infectious. If the period of infection cannot be reliably ascertained from history, the patients are regarded as having late latent disease.

Tertiary Syphilis

In the pre-antibiotic era the manifestations of tertiary syphilis used to occur in one third of untreated patients. These are now very rarely seen with the exception of neurosyphilis in the setting of HIV infection. The various manisfestations of tertiary syphilis have been briefly described in **Table 1**.

Table 1: Manifestations of Tertiary Syphilis

Late benign (gummatous) syphilis
Cutaneous nodules and noduloulcerative lesions
Gummatous lesions of bone, liver, tongue, myocardium, or GI tract
Cardiovascular syphilis
Uncomplicated aortitis
Aortic incompetence
Aortic aneurysm
Coronary artery stenosis
Neurosyphilis
Asymptomatic neurosyphilis
Early
Late
Acute syphilitic meningitis
Meningovascular syphilis
Cerebral form
Spinal form
Parenchymatous neurosyphilis
Cerebral form (General paresis)
Spinal form (Tabes dorsalis)
Optic atrophy
Gummatous neurosyphilis
Cerebral form
Spinal form

Late benign syphilis (gummatous syphilis)

Granulomatous, chronic inflammatory, proliferative and destructive lesions of syphilis (gummas) most commonly occur in the skin in the form of nodular or noduloulcerative lesions that heal with scars.

Cardiovascular syphilis

Cardiovascular syphilis may develop after a latency period of 15 to 30 years. Obliterative endarteritis of the vasa vasorum of proximal aorta may lead various complications.

Neurosyphilis

Neurosyphilis may be asymptomatic, while cerebrovascular disease in syphilis results from infarctions resulting from syphilitic endarteritis, parenchymatous neurosyphilis (general paresis and tabes dorsalis) is caused by direct treponemal invasion of the brain. Gummas may also involve the CNS.

Congenital Syphilis

Transplacental transfer of *T. pallidum* can occur throughout pregnancy, but foetal damage usually occurs after the fourth month of gestation, after the foetus becomes immunocompetent. Untreated maternal infection may lead to foetal loss, prematurity, neonatal death, or congenital syphilis. Congenital syphilis is divided into three stages: early congenital syphilis (<first 2 years' of life), late congenital syphilis (after >2 years), and the residual stigmata.

Early congenital syphilis

Symptoms generally appear within the first three months of life. Rhinitis or 'snuffles' is generally the first sign of the disease; this is followed by features which include a generalised rash with blisters and later papulosquamous lesions, mucous patches, and condylomata lata. Skeletal changes including osteochondritis, osteitis, and periostitis; generalised lymphadenopathy; hepatosplenomegaly; jaundice; anaemia, and thrombocytopaenia occur commonly. Pneumonitis, nephrotic syndrome, and congenital neurosyphilis may also occur.

Late congenital syphilis

Late congenital syphilis corresponds to the tertiary stage of acquired syphilis but cardiovascular disease develops rarely. Interstitial keratitis is the commonest lesion. Other manifestations include eighth-nerve deafness and recurrent arthritis. Neurosyphilis and gummatous syphilis may occur. Gummas may involve the skin, viscera and bones and may lead to perforated nasal septum and palate.

Stigmata

The stigmata are the residual consequences of the inflammatory lesions of early congenital syphilis. These include perioral radial scars (rhagades), frontal bossing, saddle-nose, saber tibias and Clutton's joints. Hutchinson's teeth (incisors shaped like tip of a screwdriver, often notched), together with interstitial keratitis and eighth nerve deafness forms the Hutchinson's triad.

DIAGNOSIS

Syphilis is diagnosed on the basis of history, physical examination, examination of lesional material for treponemes, and serological tests.

Demonstration of Treponemes

Dark-field microscopy is the main diagnostic method for primary syphilis. Moist lesions of secondary syphilis, such as condyloma lata can also be similarly tested. Direct fluorescent-antibody testing for *T. pallidum* (DFA-TP) can also be done. None of these, however, can distinguish *T. pallidum* from the other pathogenic treponemes.

Serologic Tests for Syphilis (STS)

These remain the mainstay of laboratory diagnosis for secondary, latent, and tertiary syphilis.

Nontreponemal tests

Nontreponemal tests include the venereal disease research laboratory (VDRL) and the rapid plasma reagin (RPR) card tests. Nontreponemal tests detect an antibody against cardiolipin (generated from damaged mammalian cell membranes) that is present in the syphilitic sera. Limitations on these tests are their lack of sensitivity in early primary syphilis and false-positive reactions. False-positive reactions may result from advanced age, pregnancy, and autoimmune diseases, and some viral, protozoal, or mycoplasma infection. Quantitative nontreponemal tests are useful for evaluating disease activity and response to treatment.

Treponemal tests

These tests use treponema-specific antigens and include the serum fluorescent treponemal antibody absorption test (FTA-ABS), *Treponema pallidum* haemagglutination assay (TPHA) and the microhaemagglutination test for *T. pallidum* (MHA-TP). These tests have high sensitivity and specificity and are used to confirm the results of positive VDRL tests. These tests, however, remain positive for years after successful treatment of syphilis and cannot be used as indicators of disease activity.

Other Tests

Tissue biopsy using special stains such as silver stain may be used to visualise treponemes. Nucleic acid amplifications tests (polymerase chain reactions) may be valuable in detecting small numbers of treponemes in tissues, but these tests are not routinely available.

SYPHILIS AND HIV INFECTION

Syphilis may cause several-fold increase in the risk of transmission of HIV. The course of syphilis in HIV-coinfected patients is generally similar to that in patients without HIV infection. In advanced immunosuppression, however, clinical features could be severe, serological test results may be unpredictable, and response to treatment may be impaired. There may be early and more frequent incidence of neurosyphilis in presence of HIV infections.

TREATMENT

Parenteral penicillin is the recommended first-line treatment for all stages of syphilis. Although alternative regimens are available, for syphilis in pregnancy and neurosyphilis, penicillin is the only drug with proven efficacy and even in penicillin-allergic patients it is preferable to administer penicillin after desensitisation (see **Table 2** for different regimens for treatment of syphilis).

PREVENTION AND CONTROL

Primary prevention of syphilis consists of modification of risk behaviours, such as avoiding multiple sexual partners and correct and consistent use of condoms. Targeted intervention for high-risk groups such as female sex workers should include regular health check-ups including syphilis serology, education and condom promotion. Modes of secondary prevention include early diagnosis and treatment, partner management, and education and counselling regarding risk reduction. Every patient with sexually transmitted infections should be screened for syphilis serology. An antisyphilitic drug is incorporated in the regimens for the syndromic case management of genital ulcer disease. Routine antenatal maternal screening and treatment of pregnant women is a time-tested strategy for prevention of congenital syphilis.

Table 2: Treatment of Syphilis

Early syphilis (primary, secondary, and early latent syphilis)		
Recommended	:	Benzathine penicillin 2.4 million units IM single dose or procaine penicillin 1.2 million units IM OD for 10 days
Alternative regimen for penicillin allergic patients	:	Doxycycline 100 mg orally BID for 14 days or tetracycline 500 mg orally QID for 14 days or ceftriaxone 1 g IM or IV OD for 8-10 days or azithromycin 2 g orally OD single dose
Late latent (more than 1 year post-infection or unknown duration), cardiovascular, or gummatous syphilis		
Recommended	:	Benzathine penicillin 2.4 million units IM weekly for 3 doses or procaine penicillin 1.2 million units IM OD for 20 days
Alternative regimen for penicillin allergic patients	:	Doxycycline 100 mg orally BID for 28 days, or tetracycline 500 mg orally QID for 28 days
Neurosyphilis		
Recommended	:	Aqueous penicillin G 3-4 million unit IV 4 hourly for 10-14 days or procaine penicillin 2.4 million units IM OD plus probenecid 500 mg QID both for 10-14 days
For penicillin allergic patients	:	Desensitise and administer penicillin or ceftriaxone 1 g IM or IV OD for 10-14 days
Pregnancy		
Recommended	:	Benzathine penicillin 2.4 million units IM weekly for 2 (early syphilis) or 3 (late syphilis) doses or procaine penicillin appropriate for stage
For penicillin allergic patients	:	Desensitise to penicillin or azithromycin 500 mg OD for 10 days or ceftriaxone 1 g IM/IV OD for 10-14 days
HIV infection		
Benzathine penicillin 2.4 million units IM weekly for 3 doses or aqueous penicillin G 3-4 million unit IV 4 hourly for 10-14 days		
Congenital syphilis		
Neonates with proven or highly probable disease or born to mother with untreated early syphilis: Aqueous penicillin G, 50000 U/kg IV 12 hourly for first 7 days then 8 hourly for 3 days or, procaine penicillin 50000 U/kg IM once daily for 10 days		
Neonates with no sign of disease born to mother with adequately treated syphilis		
Benzathine penicillin G 50000 U/kg IM single dose		

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17.25 Non-Syphilitic Treponematoses

Taru Garg

Infections caused by treponemes include venereal syphilis and non-venereal (endemic) treponematoses. Non-venereal treponematoses include distinctive spirochaetal infections, such as Yaws, Pinta, and endemic syphilis. Endemic treponematoses are restricted to certain remote areas of few developing countries. The causative organisms cannot be distinguished morphologically or serologically from *Treponema pallidum*. Diagnosis relies mainly on clinical features and epidemiology. However, occasionally clinical resemblance is striking.

YAWS

The term yaws is thought to be of Caribbean origin. Locally used synonyms in some of the endemic areas are: *Pian* (French), *framboesia* (Dutch), *buba* (Spanish), *parangi* (Sri Lanka). Considered as one of the neglected tropical diseases by World Health Organisation (WHO), yaws is a chronic infectious disease, characterised clinically by early, late and latent stages. Clinically, it causes skin lesions and bone pains, and has the potential to cause significant deformity and disability.

Epidemiology

The disease mainly affects children less than 15 years of age. It occurs in South-East Asia, Western Pacific and Africa. After significant steps taken by the WHO to control the disease, it is now endemic to few countries like Indonesia, Timor Leste, etc. Approximately 7000 new cases of yaws are estimated to occur annually in South-East Asia. In India, it was first observed in 1887 in tea plantation workers in Cachar district of Assam. It was endemic in several states including Andhra Pradesh, Assam, Chattisgarh, Gujarat, Jharkhand, Madhya Pradesh, Maharashtra, Tamil Nadu and Uttar Pradesh (**Figure 1**). In India, the disease is mostly known by the name of the tribe affected most in that area: Maharashtra (*Madia rogam*), Andhra Pradesh (*Koya rogam*), Uttar Pradesh (*Vyadhi, Dakhinia*). The disease is transmitted by close contact with an infected person with infectivity being greatest in the early stages. The organism gains entry through an abrasion or a scratch. Conditions that favour the disease transmission are low socioeconomic status, poor hygiene, overcrowding and sparse clothing. Hot and humid climate also promotes the disease transmission. Indirect transmission of disease by insects and fomites probably occurs. Vertical transmission is not known.

Aetiopathogenesis

The disease is caused by *Treponema pallidum* subspecies *pertenue (T. pertenue)*, which was discovered by Castellani in 1905. The organism cannot be cultured in artificial media. The initial lesion develops at the site of entry of organism after an incubation period of 9 to 90 days. Generalised dissemination of treponemes occurs during the incubation period. After a gap of 3 to 6 weeks, multiple scattered skin lesions appear. This stage is called early yaws. Environment may influence the early skin lesions. In dry season few macular lesions occur, while humidity favours papillomas, especially involving body folds, such as axillae and anal cleft. For the first few years there can be multiple spells of cutaneous and/or bone lesions with intervening periods of latency, following which the condition either remains latent or evolves into late yaws.

Clinical Features

The skin lesions of early yaws are highly infectious, exuding serum rich in treponemes. Skin and bone involvement occur both in early and late yaws. However, the process is more destructive in late yaws.

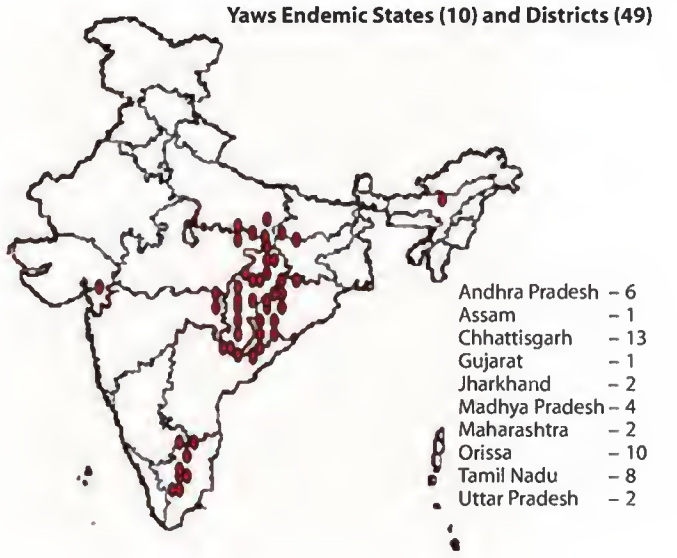


Figure 1: Sketch map of India showing yaws endemic districts (one dot represents one district).

Early yaws

It comprises of primary and secondary stages. In the primary stage, an erythematous papule (mother yaws) forms at the site of contact. It may gradually enlarge in size, or become ulcerated. It persists for a few months, and then heals spontaneously leaving behind an atrophic scar. During the secondary stage, a crop of skin lesions appear (daughter yaws). The skin lesions can be of varying morphologies, such as erythematous macules (resembling roseolar syphilis) with or without scaling, papules, plaques, nodules or papillomas. Papillomas are the characteristic lesions of early yaws. In the moist areas of the body these can mimic condyloma lata of secondary syphilis. Mucous membranes are also involved with similar lesions. Palms and soles have erythematous scaly macules, papillomas or hyperkeratotic lesions. Papillomas may lead to painful walking (crab yaws). Osteoperiostitis especially affects the long bones. Hypertrophic osteoperiostitis of nasal process of maxilla is known as goundou. Polydactylitis involving the phalanges is common.

Late yaws

Late yaws develops in about 10% of cases after 5 to 10 years. It is characterised by cutaneous lesions (plaques, nodules, noduloulcerative), juxta-articular nodes, osteitis and periostitis. The ulcers are either superficial with coarse granular floor, or deep resembling gummas of venereal syphilis. Ulcers heal with significant scarring, contractures, and depigmentation. Juxta-articular nodes are fibrosed areas overlying sacrum, greater trochanter, elbows, etc. Bone lesions are very destructive, as opposed to early yaws. It causes destruction of palate and nasal bones called, rhinopharyngitis mutilans (gangosa). Neuro-ophthalmological findings have been reported with yaws. However, generally yaws does not involve eyes, nervous system, or cardiovascular system.

Attenuated yaws

In areas with low endemicity of yaws, only few clinical cases are identified for many sub-clinical cases and that too in mild form. This may cause difficulty in diagnosis.

Diagnosis

Diagnosis can be made on clinico-epidemiological grounds. Clinically, it should be differentiated from impetigo, echthyma, scabies, leprosy, lupus vulgaris, chromomycosis, tropical ulcers, warts, callosities, etc. Treponemes can be demonstrated from the infectious lesions on dark ground microscopy. Histopathology shows acanthosis, papillomatosis and neutrophilic micro-abscesses, and dermal infiltrate comprised mainly of plasma cells. Treponemes can be demonstrated in epidermis by silver impregnation stains, or by immuno-fluorescence. Treponemal and non-treponemal serological tests are important aids for diagnosis. Periostitis may be evident on bone radiographs.

Treatment

Patients and their contacts should be treated with benzathine penicillin 1.2 MU in patients above 10 years of age and half the dose for younger patients. Tetracycline, doxycycline or erythromycin can be used in penicillin-sensitive patients.

Course and Prognosis

Early treatment causes regression of early yaws and prevents development of destructive lesions in late yaws. Sero-reversion does not occur with the treatment. Untreated disease causes significant destruction of skin, bones and cartilage culminating into gross deformity.

Prevention and Control

Between 1952 to 1964, WHO and United Nations International Children Educational Fund (UNICEF) had taken measures to control the disease in a few countries. Recurrence of yaws was observed in many countries in 1970. Government of India approved yaws eradication programme in Koratpur district of Orissa in 1996-1997. In 1999, it was extended to cover 49 districts in 10 states. The number of cases declined from 3571 in 1996 to nil in 2004. Following successful implementation of the programme, the disease has been eliminated from India in 2006. South-East Asia region of WHO has set a goal of regional eradication of yaws by 2012. Factors favourable for the eradication of disease are:

1. Man is the principal reservoir.
2. Patients with early lesions are the main source of infection.
3. Effective treatment for cure available.
4. Disease restricted to a few backward tribal communities.
5. Mass campaigns aimed at total population examination to detect cases and treat them along with contacts have greatly reduced the prevalence and transmission.

PINTA

Pinta is a Spanish word to describe mottled appearance. It is most benign of the endemic treponematoses where only skin is involved. The disease is characterised clinically by papules and plaques in the early stage and pigmentary changes at the late stage.

Epidemiology and Aetiology

Pinta is caused by *Treponema carateum*. The organism is morphologically indistinguishable from other treponemes. Mode of transmission is same as for yaws. It mainly affects children. The disease is mainly restricted to isolated areas of Central and South America.

Clinical Features

Primary lesion develops on exposed site after an incubation period of 7 to 21 days. It is an erythematous papule or plaque associated with regional lymphadenopathy, which heals spontaneously. After several months or years, multiple widely disseminated similar lesions appear (pintids). Pintids may persist as such for years, or may become depigmented. Late stage develops after 2 to 5 years, with conspicuous pigmentary changes and atrophy. At first there is hyperpigmentation of varying shades, followed by achromia and atrophy. Different stages may present simultaneously.

Diagnosis

Clinically dyschromic lesions should be differentiated from, erythema dyschromicum perstans, Riehl's melanosis, pityriasis alba, pityriasis versicolor, vitiligo and leprosy. Investigations and treatment are the same as for yaws.

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17.26 Leptospirosis

AP Sugunan

Leptospirosis is a zoonosis caused by spirochaetes of the genus *Leptospira*. Manifestations range from mild febrile illness to severe disease with multiple organ dysfunctions. Haemorrhages and renal failure are common causes of death. Weil's disease is a severe form characterised by renal failure, jaundice and haemorrhages.

BACTERIOLOGY

Leptospires are motile helical bacteria measuring 0.1 μ by 6 to 20 μ in size. Motility is characterised by flexion, extension and rotation about the longitudinal axis. The genus *Leptospira* is classified into several genospecies. Pathogenic species include *L. interrogans*, *L. kirschneri*, *L. borgpetersenii*, *L. santarosai*, *L. weilii*, *L. noguchii*, *L. alexandrei* and *L. alstoni*. Based on antigenic similarities pathogenic leptospira are further classified into more than 230 serovars arranged in 24 serogroups. Some genospecies and serovars of leptospira cause more severe disease than others, e.g. *L. interrogans* serovar icterohaemorrhagiae is highly pathogenic, though such an association cannot always be demonstrated. Species and serovar specific host preference is also documented.

Leptospires are aerobes utilising long chain fatty acids as source of carbon and energy. In culture media, fatty acids should be detoxified with albumin. Commonly used culture media include Ellinghausen McCullough Johnson Harris (EMJH) medium containing bovine serum albumin and Fletcher's and Stuart's media containing rabbit serum as fatty acid detoxifiers. Pathogenic leptospira produce cytochromes c, c1, oxidase and catalase and some strains of lipases. Several genes coding for predicted haemolysins were identified in the genome of *L. interrogans* including a pore-forming protein and a sphingomyelinase. These haemolysins may play a fundamental role in the toxic process leading to the pathogenesis of leptospirosis.

EPIDEMIOLOGY

Any mammalian species can be a potential carrier of leptospira but rodents are the most important reservoirs. Infection in rodents is usually asymptomatic and results in lifelong carrier state. Infected domestic animals may become temporary carriers. In warm and wet environments the organisms can survive for long period and probably also multiply. Acidity, salinity, desiccation and disinfectants are detrimental to their survival. Infection may occur directly from carrier animals or indirectly through environmental vehicles of transmission. Leptospira enter human body through abraded skin, mucous membrane or possibly through intact skin when the skin is sodden by prolonged contact with water. People exposed to potential carrier animals or contaminated environment, such as farmers, sewage workers, abattoir workers, veterinarians and participants of water sporting events are at risk of infection. Floods or flash-floods expose large numbers of people to wet environment and trigger epidemics.

Leptospirosis is endemic in South Asia (including India) and Southeast Asia, the Amazon delta regions of South America and many island nations of Indian and Pacific Oceans. Sporadic cases and small clusters of cases do occur in developed countries also. Many states on the west and east coasts of India, such as Gujarat, Maharashtra, Kerala, Tamilnadu and Andaman and Nicobar Islands are endemic to leptospirosis. The peak incidence coincides with southwest monsoon on west coast and northeast monsoon in Tamilnadu. Large outbreaks occurred in Orissa in 1999 after a cyclone and in Mumbai following flash floods in 2005.

PATHOGENESIS

The usual incubation period is one to two weeks, but could be in the range of 2 to 30 days. Rotational motion of the bacteria, chemotaxis and degradation of extracellular matrix proteins by collagenase and metalloprotease facilitate invasion of host tissues. Once the tissue barriers are crossed, leptospires spread by haematogenous dissemination and establish systemic infection. Leptospiral lipopolysaccharide has low endotoxic potency and therefore, fulminating disease does not occur during the leptospiraemic phase. Vascular endothelial damage is the primary lesion and this leads to capillary leakage, haemorrhage, vasculitis and localised ischaemia in organs. In severe disease coagulation cascade is activated leading to disseminated intravascular coagulation (DIC). Pro-inflammatory cytokines released as a result of immune-killing of leptospires mediate tissue inflammation and damage. TNF-α is also believed to play a key role in disease progression.

Renal involvement is characterised by tubulo-interstitial nephritis induced by outer membrane components and mediated by inflammatory cytokines. In liver, phagocytosis of leptospirae by Kupffer cells induces production of oxygen radicals and release of inflammatory cytokines that initiate hepatocyte damage and elevation of hepatic enzymes. Myocarditis with myocyte necrosis and intra-myocardial and pericardial haemorrhages are observed in the heart.

The pathogenesis of leptospirosis-associated pulmonary haemorrhage syndrome (LPHS) presenting with acute lung injury and massive pulmonary bleeding appears to be different from that of Weil's disease. Lung tissues have high amounts of leptospiral DNA, but few intact organisms. Immunoglobulin and complement are deposited along alveolar basement membrane and in intra-alveolar spaces suggesting an underlying autoimmune mechanism. The main lesion in the lung is vascular endothelial damage.

CLINICAL FEATURES

About 70% to 80% of persons with serologically confirmed leptospiral infection remain asymptomatic. Majority of

symptomatic infections result in mild febrile illness. A small proportion progress to severe disease with multiple organ dysfunctions. Severe disease may have two distinct phases, a leptospiraemic phase and an immune phase. The leptospiraemic phase begins with remittent fever (38°C to 40°C), chills, rigors, headache, myalgias, nausea and vomiting. Conjunctival suffusion without purulent discharge and muscle tenderness most notable in calf and lumbar areas are characteristic findings. Diarrhoea, macular or maculopapular rash, sub conjunctival haemorrhage, lymphadenopathy, hepatomegaly and splenomegaly are seen less frequently. Symptoms subside within a week and, in a subset of patients, the disease progress to immune phase after a remission lasting for 1 to 3 days.

The immune phase, which coincides with the appearance of antibodies and disappearance of the organisms from blood, is characterised by manifestations of organ dysfunctions. Renal pathology is a combination of interstitial nephritis and acute tubular damage, which may be due to direct toxic effect or due to the indirect effect of hypovolaemia and ischaemia. Oliguria and hyperkalaemia have been identified as predictors of foetal outcome. Non-oliguric forms have better prognosis. Acute renal failure may also present as a non-oliguric hypokalaemic state. Although the pathological changes in the liver may be non-specific and mild, functional disturbances could be disproportionately high. Death due to liver failure virtually never happens in leptospirosis. Aseptic meningitis presents with frontal and bitemporal headache and occasionally delirium. Severe neurologic complications are rare. Cardiac arrhythmias occur in about two-thirds of the patients and include atrial fibrillation, AV blocks, bundle-branch blocks, alterations in ventricular repolarisation, supraventricular and ventricular extrasystole. Myocarditis, pericarditis, congestive cardiac failure, cardiogenic shock, adult respiratory distress syndrome and necrotising pancreatitis have been occasionally reported. LPHS is the most common cause of fatality in several case series. It can also occur in the absence of hepatic and renal dysfunctions and sometimes even in the leptosiraemic phase. Uveitis is a recognised delayed complication of leptospirosis.

DIAGNOSIS

Anaemia and leucocytosis are usually present. ESR is elevated. Thrombocytopaenia may be present in patients with renal failure. Urine analysis shows erythrocytes, leucocytes, granular or hyaline casts and proteinuria. Bilirubin levels may rise markedly accompanied by rise in alkaline phosphatase and modest rise in aminotransferases, which are usually below 200 U/L. Blood urea nitrogen and serum creatinine levels are elevated. CPK level may be elevated and this helps to distinguish leptospiral hepatitis from viral hepatitis. CSF shows elevated protein and normal glucose concentrations and predominance of polymorphs and at later stages mononuclear cells. Radiographic abnormalities of the lungs are more often seen in lower lobes and include nodular opacities to patchy alveolar infiltrates and occasionally confluent consolidation. Darkground microscopic examination of clinical specimens to visualise leptospira is unreliable. The most reliable serological test is microscopic agglutination test (MAT) using live pathogenic leptospira as antigen. A four-fold rise in titre on two samples obtained 5 to 7 days apart confirms the diagnosis. When a single sample is used, the optimum cut-off titre is 1 in 100 in non-endemic areas and 1 in 200 in endemic areas. MAT using killed leptospira or live saprophytic strains is used by some laboratories, but are of doubtful accuracy. IgM ELISA and several rapid test kits for detection of antibodies are available and can be used for a presumptive diagnosis. Isolation of leptospires from blood, urine or CSF is a definite proof of infection. Blood and CSF samples for culture should be obtained during the first week and urine samples after first week. PCR assays using primers G1/G2, B64-I/B64-II and A/B are sensitive, but do not detect all cases.

DIFFERENTIAL DIAGNOSIS

It is difficult to differentiate between mild anicteric leptospirosis and other febrile illnesses such as malaria, dengue and enteric fever. Icteric leptospirosis may mimic viral hepatitis and haemorrhagic form can mimic other haemorrhagic fevers, such as Hantavirus infection, rickettsial diseases and dengue haemorrhagic fever. Epidemiological information may aid in differentiating leptospirosis from other diseases and positive serological test or PCR confirms the diagnosis.

TREATMENT

Pathogenic strains of leptospira are susceptible to a range of anti-microbial drugs including penicillins, cephalosporins, carbapenems, tetracyclines, macrolides and fluoroquinolones. Recommended anti-microbial drugs for the treatment and prophylaxis of leptospirosis are summarised in **Table 1**. A recent cost-benefit analysis has concluded that empirical treatment of suspected cases with oral anti-microbial drugs is the most beneficial strategy unless reduction in antibiotic use is a health policy priority. Although there are conflicting reports about the role of anti-microbial drugs in severe leptospirosis, anti-microbial therapy is recommended and will shorten morbidity and dysfunction. Early initiation of therapy improves prognosis, but even if the patient reports late, anti-microbial therapy still has a role. Jarisch-Herxheimer reaction may rarely occur as a complication of anti-microbial therapy.

Table 1: Recommended Anti-Microbial Drugs for the Treatment and Prophylaxis of Leptospirosis

Indication	Anti-Microbial Drug	Dose
Chemoprophylaxis	Doxycycline	200 mg PO per week
Treatment of mild leptospirosis	Doxycycline	100 mg PO bid
	Ampicillin	500-750 mg PO qid
	Amoxycillin	500 mg PO qid
Treatment of moderate/severe leptospirosis	Penicillin G	1.5-2 MU IV qid
	Ampicillin	1 g IV qid
	Ceftriaxone	1 g IV OD

Patients with renal failure may require dialysis. Peritoneal dialysis is used as a supportive care, but some studies indicate that blood exchange therapies (haemodialysis, haemofiltration) may reduce mortality and shorten recovery time. Assisted ventilation, glucocorticoid pulse therapy, cyclophosphamide and plasma exchange are reported to improve the survival of patients with pulmonary haemorrhage. However, this is not based on controlled clinical trials and requires confirmation.

PREVENTION AND CONTROL

Measures for prevention and control may target rodent reservoirs, domestic animal carriers, environment or the population at risk. Rodent control, vaccinating, testing and treating domestic animals, decontamination of environmental sources and use of personal protective devices at workplace are all effective risk reduction methods. When there is a short-term high risk of infection in a defined population group as in the case of travellers from non-endemic to endemic areas, participation in water sporting events or natural disasters chemoprophylaxis with doxycycline can be used. In spite of decades of research, human vaccine development is still unsuccessful.

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17.27 Lyme Disease, Rat Bite Fever and Other Spirochaetal Infections

Kamlesh Tewary

LYME DISEASE

Lyme disease is a systemic infection caused by the spirochaete *Borrelia burgdorferi*. The bacterium is inoculated into the skin by a tick bite. The tick is almost always of the genus *Ixodes*. Lyme disease was recognised in 1975 in Lyme county of Connecticut, in children suffering from arthritis.

Pathophysiology

While active infection by the spirochaete causes many manifestations, others may be caused by immunopathogenic mechanisms. The bacterium is introduced into the skin with a bite from an infected *Ixodes* tick (**Figure 1**). Once in the skin, the spirochaete can:

1. Be overwhelmed and eliminated by host defense mechanisms.
2. Remain viable and localised in the skin where it produces the pathognomonic skin lesion, or erythema migrans (EM) (**Figure 2**).
3. Disseminate through the lymphatics or blood. Haematogenous dissemination can occur within days to weeks of initial infection; the organism can travel to the skin, heart, joints, central nervous system (CNS), and other parts of the body.

Clinical Features

The disease is classically divided into stages:

I. *Early localised disease* refers to isolated EM and patients with an undifferentiated febrile illness.

II. *Early disseminated disease* refers to the extra-cutaneous manifestations and secondary skin lesions that occur during the first weeks to months after infection.

III. *Late disease* refers to manifestations (usually in the nervous system and joints) that occur months to years later.

Systemic manifestations

1. Fever
2. Fatigue
3. Myalgias and arthralgias
4. Flu like illness
5. Nausea and vomiting



Figure 1: Ixodes tick.



Figure 2: Erythema migrans.

Cutaneous symptoms

1. EM is present in about 75% of patients.
2. Borrelial lymphocytoma, a nodule usually found on the ear lobe or areola of the nipple, develops in some patients early in the course of disease.
3. Acrodermatitis chronica atrophicans is a rash that patients describe as inflammation or thinning of the skin, usually on the distal legs and hands.

Neurologic symptoms

1. Headache can herald CNS penetration and lymphocytic meningitis.
2. Facial weakness is similar to a typical Bell's palsy and bilateral in 25% of cases.
3. Late Lyme disease can cause paraesthesias or pain due to peripheral neuropathy and personality, cognitive and sleep disturbances from chronic encephalopathy.

Cardiovascular involvement

Palpitations, light-headedness and syncope may be a manifestation of varying degrees of heart block, including complete heart block. Chest pain and dyspnoea can occur in the setting of Lyme pericarditis and myocarditis.

Musculoskeletal involvement

Migratory pains in and around the joints and muscles; may occur from myositis, tendonitis, and bursitis.

Ocular

Red, itchy eyes from conjunctivitis.

Diagnosis

A clinical history of tick bite and characteristic rash are diagnostic of the condition. The CDC recommends a 2-step procedure consisting of a screening ELISA or immunofluorescent assay and a confirmatory Western blot for specimens that have positive or equivocal results with ELISA. A negative Lyme test result does not indicate the absence of disease, nor does a positive result indicate the presence of disease.

Treatment

Solitary EM

Oral antibiotics (e.g. amoxicillin, doxycycline, cefuroxime, erythromycin, azithromycin, amoxicillin-clavulanate) should be administered for 10 to 30 days.

Early disseminated disease findings, such as isolated facial palsy or secondary skin lesions (not meningitis) or disease with first-degree heart block (not a high-degree heart block) is treated with oral antibiotics for 21 to 30 days.

Early disseminated disease with meningitis or a high-degree heart block is treated with intravenous ceftriaxone for 2 to 4 weeks.

RAT BITE FEVER

Rat bite fever includes: Streptobacillary fever; Streptobacillosis; Haverhill fever; Epidemic arthritic erythema; Spirillary fever; and Sodoku.

Rat bite fever is an infectious disease transmitted by the secretions of the mouth or nose or the urine of an infected rodent. Rat-bite fever can be caused by two different organisms, *Streptobacillus moniliformis* and *Spirillum minus*. Most people acquire rat-bite fever through contact with urine or oral (mouth) or conjunctival (eye or nose) secretions from an infected animal. This most commonly occurs via a bite, yet some cases may occur simply through contact with these secretions. Apart from rats, squirrels, weasels and gerbils can also be the source.

In rat bite fever due to *Streptobacillus moniliformis*, fever, chills, headache, and muscle pain usually occur within 10 days of exposure (incubation period 1 to 22 days). This is followed within 3 days by a diffuse rash, primarily in the extremities. One or several large joints may become swollen, red, and painful. If untreated, severe complications including infection of the heart valves may occur.

The illness caused by *Spirillum minus* is common in Asia, particularly Japan, where it is called sodoku. In this form of rat bite fever, a particular skin rash characterised by red or purple plaques is frequently seen, and the previously healed wound at the site of the bite may re-activate and open. Joint involvement is rare.

Diagnosis is made by the detection of the organism in skin, blood, joint fluid or lymph nodes. Blood antibody tests may also be used.

Rat bite fever is usually treated with penicillin or tetracyclines for 7 to 10 days. The prognosis is excellent with early treatment.

Complications include pericarditis, endocarditis, parotitis, tenosynovitis and abscesses of the brain or soft tissue.

COMMON SPIROCHAETAL INFECTIONS

The common spirochaetal infections are listed in the **Table 1** below.

Table 1: Common Spirochaetal Infections

Organism	Condition
Borrelia recurrentis	Relapsing fever
Borrelia vincentii	Vincent's angina
Borrelia burgdorferi	Lyme disease
Leptospira icterohaemorrhagiae	Weil's disease
Leptospira andamana	Weil's disease of Andamans
Leptospira canicola	Canicola fever
Treponema pallidum	Venereal syphilis
Treponema pertenue	Yaws
Treponema carateum	Pinta

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17.28 Anaerobic Infections

R Sajithkumar

INTRODUCTION

Anaerobic infections are caused by bacteria which require reduced oxygen tension for growth (oxygen concentration below 18%). Most of these organisms occur as commensals in mouth, gastrointestinal tract, skin and female genital tract and become pathogenic in presence of tissue injury, ischaemia or necrosis, along with breakdown of anatomic barriers. Their growth is usually inhibited by oxygen. These infections are usually caused by mixed organisms. Anaerobic infections must be kept in mind in patients presenting with low grade fever, abscesses, with foul smelling and brownish/blackish discharges or gas production, especially following a rupture of the viscous or procedures therein. They are associated with late diagnosis and high mortality in many settings. Special culture media, techniques and difficulty in growing these organisms hinder timely diagnosis and correct data. Many commensal organisms also grow in healthy adults. They produce a spectrum of illnesses ranging from localised abscesses to multi system involvement. The response to therapy is good with surgical management (if needed), combined with antibiotics *(Tetanus, botulism and food poisoning are covered in other chapters).*

The organisms are classified for practical purposes as shown in **Table 1**.

Table 1: General Classification of Anaerobic Organisms

Gram-positive bacilli
Clostridium (tetani, botulinum, perfringens, histolyticum, septicum), Spore forming
Actinomyces (israelii, odontolyticus)
Propionibacterium acnes
Gram-negative bacilli
Bacteroides (fragilis, ovatus, vulgatus, uniformis, melaninogenicus)
(renamed as *Porphyromonas gingivalis*, asaccharolytica, *Prevotella oralis*)
Fusobacterium (nucleatum, necrophorum, varium)
Gram-positive cocci
Peptostreptococcus (micros, magnus, asaccharolyticus, anaerobius)
Gram-negative cocci
Veillonella parvula, montpellierensis

The virulence of the organism is related to the production of exoproteins, endotoxins, cytokines and chemokines like interleukins 8, 17, tumour necrosis factor, etc., which facilitate chemotaxis of polymorphonuclears, adhesion to host tissues and abscess formation. These are also important in creating a disseminated intravascular coagulation (DIC) like state.

CLINICAL MANIFESTATIONS

Infections of the mouth and gums can lead to necrotising ulcerative gingivostomatitis (Vincent's stomatitis) characterised by sudden onset swelling, bleeding gums and foul smell. It can spread to teeth, mandible or maxilla. Acute necrotising tonsillitis/pharyngitis with lymphadenopathy and leukocytosis are common. Peritonsillar, perimandibular abcesses and infections of paranasal sinuses, middle ear or meninges may occur by contiguous spread (*Fusobacterium*, *Peptostreptococcus* and *Bacteroides* are the common organisms in this group). Ocular infections (corneal ulcer, endophthalmitis and panophthalmitis) occur following trauma.

Pleuropulmonary infections occur following aspiration of oropharyngeal contents. Low grade fever, malaise and sputum production bring the patient to the hospital. These are also seen in patients with a defective gag reflex. Necrotising pneumonia, anaerobic lung abscesses, empyema, etc. can occur (*Peptostreptococcus* and *Bacteroides* are the common organisms).

Intra-abdominal infections are manifested as enterocolitis, peritonitis, appendicitis, hepatic and splenic abscess and diarrhoea. Patients with necrotising enterocolitis present with fever, abdominal pain, tenderness and distension (*Bacteroides*, *Actinomycetes* and *Clostridium* species are involved). Antibiotic associated *C. difficile* pseudomembranous colitis presents with diarrhoea.

Skin and soft tissue infections are usually triggered by an injury, trauma, ischaemia or surgery. These usually occur in areas closer to respiratory or faecal contamination. There may be crepitant cellulitis, oedema, fasciitis and gangrene. Localised pain and foul smelling pus are usual (*Bacteroides*, *Peptostreptococcus*, clostridia are the usual organisms).

Osteomyelitis due to *Actinomycetes*, *Clostridium* and *Fusobacterium* are described following trauma. Peptostreptococcal infection can occur following implants.

Bacteremia due to *B. fragilis* following dental procedures, gastrointestinal procedures, etc., are associated with high mortality. Endocarditis due to *B. fragilis* and peptostreptococci may be associated with pericarditis as well.

Genitourinary system is a favoured site for anaerobes. The organisms are found in the vagina of healthy women. *B. fragilis*, peptostreptococci and clostridia can produce purulent vaginitis, endometritis, tubo-ovarian, pelvic abscesses. Septic abortions and pelvic inflammatory diseases can occur. *Actinomycetes* infection can occur following intrauterine device (IUD) insertions. Neonatal sepsis with anaerobic organisms are also reported following vaginal infection.

DIAGNOSIS

The diagnosis of anaerobic infections is difficult and requires a high index of suspicion. Sites where multiple pathogens are suspected along with presence of necrotic tissue or gas in tissues and no growth on routine culture techniques suggests the possibility of anaerobic infections. Culture of the aetiological

agent is paramount for the diagnosis and proper treatment. Proper specimen collection, rapid transport to the laboratory in specialised anaerobic transport media and proper handling of specimens in the laboratory are all critical steps to isolate the pathogen. Infections at sites of poor vascularity or in close proximity with urine/faeculent material, necrotic tissue or debris at the site of infection and a foul smelling discharge from the site along with numerous pleomorphic bacilli and cocci on Gram's stain of the pus, are highly suggestive of anaerobic infections.

TREATMENT

The treatment of anaerobic infections should include measures to: (i) reduce the microbial growth; (ii) remove the precipitating environment; and (iii) supportive care. Surgical resection, debridement and drainage are done on emergency basis. The areas of necrosis, ischaemia and trauma must be explored. Exposure of the tissues to air/oxygen will itself inhibit the organisms significantly.

Supportive care includes correction of shock, bleeding tendencies, immobilisation of affected extremity, adequate nutrition, maintenance of fluid and electrolyte balance, etc. Hyperbaric oxygen and antitoxins have only doubtful value.

The possibility of mixed infections (including aerobic) must be kept in mind. Isolation of the organism and antibiotic susceptibility testing is difficult and controversial. Most pathogenic strains (including *B. fragilis*) are developing resistance to penicillin G which was extensively recommended earlier. Combination of beta-lactamase inhibitors (clavulanic acid, sulbactam, tazobactam) with a beta lactam antibiotic (ampicillin, amoxicillin, ticarcillin, piperacillin) can overcome this. Newer anti-microbials (cefoxitin, meropenem, imipenem, etc.) are reported to have less resistance. Metronidazole is very effective against many organisms and good concentrations are achieved even in abscesses, but inactive against aerobes. High dose parenteral therapy instituted as quickly as possible is effective in many clinical settings. Quinolones like trovafloxacin and moxifloxacin are useful in soft tissue infections.

Specific Recommendations

An anti-Gram-negative enteric agent is generally added to treat *Enterobacteriaceae* when treating intra-abdominal infections. Penicillin is added to metronidazole to cover microaerophilic *Streptococci, Peptostreptococci,* and *Actinomycetes* species in intracranial and dental infections. Beta lactam resistance must be expected in all head and neck infections. Oral infections can be treated with metronidazole or clindamycin. Lung abcesses caused by *B. fragilis* or *Fusobacterium* respond more easily to clindamycin than penicillin G. Chloramphenicol, Metronidazole and Penicillin cross blood-brain barrier and are advocated for intracranial infections. Intra-abdominal infections require one of the carbapenem antibiotics with metronidazole. In case of septic thrombophlebitis, anticoagulation may be needed. Doxycycline effective against chlamydial and mycoplasmal infections, is added to most regimens when treating pelvic infections.

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17.29 Atypical Mycobacteria

PD Khandelwal

INTRODUCTION AND CLASSIFICATION

Atypical mycobacteria are also called non-tuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT). They are ubiquitous in environment. Therefore their diagnosis is not confirmed if they are isolated from sites which remain unsterile, normally like urine, sputum, skin or faeces. Runyon classified these mycobacteria on the basis of colony, rate of growth, pigment formation and simple biochemical reaction into four types (**Table 1**). In India, *Mycobacterium tuberculosis* infection has always overshadowed true prevalence of NTM. Though the exact magnitude of NTM is difficult to predict as culture is not a routine part of diagnosing tuberculosis in India, it varies from 1 to 28 per cent. NTM cause pulmonary and generalised infections in immunocompromised individuals and cervical lymphadenitis in children. The important NTM are *M. kansasii*, *M. xenopi*, *M. fortuitum-chelonei* complex and *Mycobacterium avium-intracellular* complex group (MAIC). MAIC infections were commonly seen in pre-acquired immunodeficiency syndrome (AIDS) era in patients with chronic obstructive pulmonary disease (COPD), bronchiectasis and occupational lung diseases like silicosis, etc. However, MAIC infections are common with AIDS when CD4 count falls below 50/mm^3. *M. genavense* is a new atypical mycobacterium seen in AIDS patients.

Table 1: Classification of Non-tuberculous Mycobacteria

A.	Photochromogens	*M. kansasii* *M. marinum* *M. simiae*
B.	Scotochromogens	*M. scrofulaceum* *M. gordonae* *M. avium*
C.	Non-chromogens	*M. tuberculosis* *M. avium intracellulare* *M. xenopi* *M. ulcerans* *M. terrae*
D.	Rapid growers	*M. fortuitum* *M. chelonae* *M. smegmatis* *M. phlei*

*Non-culturable Mycobacterium is *M. leprae*. ** *A, B and C are together classified as slow-growers.*

DIAGNOSIS

The clinical features overlap with *M. tuberculosis*. Chest radiograph may show suggestive features like thin walled cavities with less parenchymal infiltrates in upper lobe. In high-resolution computed tomography (HRCT) scan, clusters of small nodules associated with areas of bronchiectasis in lower and middle-zone are common. When patient has not showed response on adequate regimen of standard anti-tuberculous drugs, diagnosis of NTM must be kept in mind. Clinical presentation and treatment are listed in **Table 2**.

Table 2: Summary of Recommended Treatment of Non-tuberculous Mycobacterial Infections

Mycobacterial species	Commonest clinical features	Recommended treatment
Kansasii	Pulmonary disease	Streptomycin [first three months], rifampicin, isoniazid and etham butol for at least two years. Consider resection surgery
Marinum	Swimming pool and fish tank granuloma	Usually heal spontaneously. Trimethoprim and sulpha-methoxazole, minocycline
Avium	Lymph nodes Pulmonary disease	At least four drugs rifabutin, streptomycin, clarithromycin, ethambutol for two years Consider resection surgery
Scrofulaceum	Cervical lymph node in children	Rifampin/rifabutin, clarithromycin, ethambutol as for avium
Xenopi	Pulmonary disease in hot water supply of hospital	As for avium but may be possible to modify as some strains are sensitive to a number of drugs, quinolones, ethionamide
Ulcerans	Skin ulcers (Buruli ulcers)	Surgical excision and skin graft; rifampicin, clofazimine in addition to other 2-3 drugs
Fortuitum	Injection abscess Pulmonary disease Post cardiac surgery	Resistant to primary ATT. Clarithromycin, amikacin, doxycycline, imipenem, cefoxitin, quinolones
Chelonae	Injection abscess, Post cardiac surgery, Rarely mycobacterial septicaemia, dissemination after renal homografts	Four drugs from gentamicin, amikacin, streptomycin, erythromycin and ethionamide according to sensitivity test

Other methods are culture on Lowenstein-Jensen medium or radiometric system (BACTEC), identification of isolates by biochemical tests, molecular methods by gene probes, polymerase chain reactions using gene amplification methods and determining the sensitivity profile of NTM.

TREATMENT

The treatment of NTM is usually with a combination of 4-5 drugs for 2 years or 12 months after the culture is negative. Dosages are as per standard chemotherapy for *M. tuberculosis* and drugs are given depending on sensitivity pattern, if available. Surgical options may need to be explored in individual cases.

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17.30 Brucellosis

BG Mantur

A specific-pathogen now called *Brucella melitensis* causing brucellosis was recognised in 1887 by David Bruce and clinical features were comprehensively described in 1897 by Hughes. Brucellosis is also known as Malta fever and undulant fever.

EPIDEMIOLOGY

Brucellosis—a leading zoonosis has been recognised for more than 100 years and continues to be an important public health problem worldwide, particularly in Latin America, Southern Europe, Africa and Asia. Brucellosis has been endemic in India for many years. Animals are almost exclusively the source of infection for people. The major reservoirs include goats and sheep (*B. melitensis*), cattle (*B. abortus*), swine (*B. suis*), and dogs (*B. canis*). Infection occurs through consumption of infected raw milk and their products, or raw meat. It is also transmitted by direct contact with infected animals or abortive material. Inhalation of infected aerosols is also an important route of transmission. In adults, brucellosis is an occupational hazard for veterinarians, abattoir workers, farmers, shepherds, butchers, dairy workers, hunters and laboratory workers. It is estimated that there are 50-100 million nomads and seminomads in the developing world. Living in close contact with sheep, goats, and cattle exposes nomads to a great risk of brucellosis. Person to person transmission is a rare occurrence. However, it is a common imported disease in developed world, being in the list of travel-related infections.

AETIOPATHOGENESIS

Brucella spp. are Gram-negative, facultative intracellular cocco-bacilli. *B.melitensis, abortus, suis, canis, pinnipediae, cetaceae* are reported to infect humans; *B. melitensis* being the most important zoonotic agent.

Brucella organisms are virulent due to their ability to survive, adapt to acidic environment and even multiply within cells of the mononuclear-phagocytic system. Humoral as well as cell mediated immune responses do develop after the infection; antibodies are not protective but are useful in serodiagnosis, while cellular immunity provides protection against re-infection.

CLINICAL FEATURES

Brucellosis is a re-emerging infection that affects both farm and wild animals as well as humans. Brucellosis can affect people of any age. Males are affected more often than females. The incubation period ranges from 7 to 90 days. The disease presents as an acute (<2 months), subacute (2 to 12 months) or chronic infection (>12 months). The clinical presentation is non-specific and heterogeneous in its course and severity and it presents as a multi-system disease invading many organs and tissues. The main clinical symptoms are fever, night sweats, arthralgia, and weight loss. Hepatomegaly and or splenomegaly and arthritis are presenting signs. However, the most common presenting symptom is fever. Most frequently reported complications include arthritis, epididymo-orchitis, meningitis, brain abscess, endocarditis and hepatitis. Mortality rate is less than 2%; 80% of deaths being attributed to endocarditis. Brucellosis during pregnancy results in spontaneous abortion or intrauterine transmission of infection to the infant.

DIAGNOSIS

Human brucellosis is a protean disease. The wide spectrum of clinical features and general inexperience with the disease contribute vastly to its underdiagnosis. It is often misdiagnosed as typhoid, malaria, tuberculosis, rheumatoid arthritis. Brucellosis, therefore, could be missed if it is not considered seriously in making a differential diagnosis and diagnosis should always be supported by laboratory tests. The diagnosis is generally made when a standard tube agglutination test shows antibody titre of 1:160 or more in the presence of compatible clinical manifestations. In endemic areas, a titre of 1:320 as cutoff makes the test more specific. However, a firm diagnosis should be based on either a positive blood culture or a rise in antibody titre between acute and convalescent phase serum specimens obtained 2 weeks apart and performed in the same laboratory.

TREATMENT

The treatment in adults is the combination of oral rifampicin 600 to 900 mg and doxycycline100 mg twice daily for 6 weeks, and in place of rifampicin, injectable streptomycin (1 gm/d) for two to three weeks is also endorsed. Patients require three to seven days to become afebrile. Average relapse rates are ~10% especially in patients on short courses and significantly higher with monotherapy. The use of antituberculosis drugs especially rifampicin should be reduced to a minimum especially in endemic areas for both brucellosis and tuberculosis to prevent the development of community resistance to rifampicin. Fluoroquinolones have been suggested to be a useful option. The search for alternatives becomes a necessity in the view of today's treatment regimens incorporating antituberculosis drugs. **Table 1** lists the treatment in special situation.

Table 1: Therapy for Special Situations

Complications and relapsed patients	
	Standard regimen extending treatment to 12 weeks.
Brucellosis during pregnancy	
	Oral rifampicin for 8 weeks together with intramuscular streptomycin for initial 2 weeks.
	or
	Oral rifampicin and cotrimoxazole 960 mg twice daily for 8-12 weeks.
Indications for steroids	
	Severe toxaemia
	Thrombocytopaenia
Indications for surgery	
	Thrombocytopaenia leading to gastrointestinal bleeding and anaemia (splenectomy)
	Endocarditis in presence of congestive heart failure, abscess formation and involvement of prosthetic valves (valve replacement)

PREVENTION AND CONTROL

Vaccines have varying degrees of success in controlling brucellosis in animals. There are still no approved human vaccines available, and the animal vaccines currently in use are pathogenic to humans. Because brucellosis is preventable, an organized effort must be done in order to eradicate *Brucellae* from animals. Increasing public awareness, and educating the public regarding the health hazards of ingesting raw milk and its products is important for prevention of the disease.

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17.31 Donovanosis

Dwijendra Nath Gangopadhyay

DEFINITION

Donovanosis is an uncommon chronic granulomatous ulcerative disease of the genitalia caused by *Klebsiella granulomatis* being transmitted sexually. It is also known by various names like granuloma inguinale, granuloma venereum or sclerosing granuloma.

EPIDEMIOLOGY

It is endemic in the tropical and subtropical countries among the backward classes with poor hygienic habits, being more common in the male than in female.

AETIOLOGY

It is caused by a Gram-negative intracellular bacillus *Klebsiella granulomatis* formerly known as *Calymmatobacterium granulomatis*. The infectivity of the bacillus is low so that repeated exposure is needed before occurrence of the disease.

Incubation Period

It is difficult to assess the true incubation period of the disease because of its low infectivity and the asymptomatic nature of the disease in its initial phase. It may vary between 1 week and 3 months, usually 1 to 4 weeks.

CLINICAL FEATURES

The lesions are mostly found on the genitalia (90%), sometimes in the surrounding area. The disease begins as small subcutaneous nodules that soon rupture producing beefy-red, velvety (**Figure 1**), relatively painless ulcer that bleeds easily on touch. The disease progresses slowly and relentlessly through surface continuity without any tendency to spontaneous healing. There is no involvement of local lymph nodes. Subcutaneous nodules in the inguinal region may mimic inguinal lymphadenopathy (pseudobubo) which eventually rupture to form ulcer. The ulcer is commonly seen in males over the prepuce, coronal sulcus, frenum, and in females over the labia minora, fourchette. In addition, the lesions may spread to thighs and lower abdomen and scrotum in male and cervix in female.



Figure 1: Donovanosis: Beefy-red velvety ulcerogranulomatous masses.

Four clinical types are recognised:

(a) Ulcerogranulomatous type—the most common type; as described above.

(b) Hypertrophic type—the ulcer presents with a raised cauliflower-like margin.

(c) Necrotic type—a deep ulcer is seen.

(d) Sclerotic type—when there is excessive scar formation.

DIAGNOSIS

It is difficult to culture the organism. The most effective method is direct visualisation of the organism within the macrophages as bipolar staining, safety pin-shaped intracytoplasmic inclusions known as Donovan bodies in tissue crush smear stained by Wright or Giemsa stain. Histopathological examination of biopsy material from the edge of an ulcer is the 'gold standard' in the diagnosis of Donovanosis. Recently a diagnostic PCR has been developed to detect the organism.

TREATMENT

The ulcer responds to common broad-spectrum antibiotics early after initiation of therapy. However, it needs prolonged therapy for complete healing of the ulcer and prevention of recurrence. Recommended regimen includes doxycycline 100 mg twice daily for at least 3 weeks or until the ulcers heal completely. Other antibiotics that may be used are:

- Azithromycin 1 g once weekly on empty stomach
- Ciprofloxacin 750 mg twice daily
- Erythromycin base 500 mg four times daily
- Sulphamethoxazole-trimethoprim combination double strength one tablet twice daily.

The antibiotic irrespective of choice should be continued for at least three weeks for complete healing and prevention of recurrence. Injection streptomycin or gentamicin may be added if the lesions fail to respond to above medication within few days.

Since it is a sexually transmitted disease (STD), patient's sex partners should be traced and managed as necessary. If there

is no sign of active disease in the sex partner, prophylactic therapy is not recommended because of low infectivity of the bacteria.

FOLLOW-UP

Even after total clearance of the ulcers the patient should be followed-up for prolonged period as recurrence has been reported even one year after successful treatment.

COMPLICATION

The disease tends to continue without any tendency of self-healing. It leads to extensive scarring that may cause much mutilation of the genitalia. Dissemination of the infection to distant parts of the body may be seen, particularly to bones. The tibia is involved in 50% of the cases of dissemination. Systemic spread is accompanied by general symptoms like fever, malaise, etc. Dissemination is more common among females. Elephantiasis of the genitalia secondary to scarring may be seen more frequently among females. Malignant changes have been reported occasionally over the scar.

PREVENTION

Since presence of any genital ulcerative disease is an increased risk for transmission of HIV, an attempt to prevent the occurrence of the disease should be undertaken. However, usual promotion of condom may not be able to prevent this disease. Sex contacts of a patient should be kept under surveillance and early treatment of the condition is the only preventive measure.

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17.32 Actinomycosis and Nocardiosis

A Muruganathan

INTRODUCTION

Actinomycosis is a chronic disease characterised by abscess formation, draining sinus tracts, fistulae and tissue fibrosis. It can mimic a number of other conditions, particularly malignancy and granulomatous disease. *Actinomycetes* are a group of aerobic and anaerobic bacteria in the order *Actinomycetales*.

AETIOPATHOGENESIS

Actinomycosis is a subacute-to-chronic bacterial infection caused by filamentous, Gram-positive, non acid-fast, anaerobic-to-microaerophilic bacteria.

Actinomycetes are prominent among the normal flora of the oral cavity. They require a break in the integrity of the mucous membranes and the presence of devitalised tissue to invade deeper body structures and to cause human illness. Furthermore, actinomycosis is generally a polymicrobial infection, with isolates numbering as many as 5 to 10 bacterial species. Haematogenous dissemination to distant organs may occur in any stage of actinomycosis, whereas lymphatic dissemination is unusual. Moisture helps their survival and ability to produce infection.

EPIDEMIOLOGY

Actinomyces are not found in the environment and humans are the only natural reservoir. Predisposing factors include the following:

1. Dental caries and extractions
2. Gingivitis and gingival trauma
3. Infection in erupting secondary teeth, poor oral hygiene
4. Diabetes mellitus
5. Immunosuppression
6. Malnutrition
7. Local tissue damage caused by neoplastic disease or irradiation

CLINICAL FEATURES

Cope, in 1938, classified actinomycosis infection into 3 distinct forms: (1) cervicofacial (50%); (2) pulmonothoracic (30%); and (3) the abdomino-pelvic (20%).

Patients with cervicofacial actinomycosis present with nodular lesion(s), usually located at the angle of the jaw. These gradually increase in size and number (i.e. multiple abscesses) and ultimately form sinuses that open onto the cheek or submandibular area. Sulphur granules may be seen in the exudate. Nodules may be tender in the initial stages but are typically non-tender and woody hard in the later stages. Lymphadenopathy is typically absent. Trismus is present if the mastication muscles are involved. Fever is variably present.

Thoracic actinomycosis has the following features:

Aspiration of oropharyngeal secretions containing actinomycetes is the usual route of infection. Fever, cachexia, abnormal breath sounds, cough, haemoptysis are the presenting symptoms. Sinus tracts with drainage from the chest wall (i.e. pleurocutaneous fistula).

Abdominal actinomycosis is characterised by:

It presents as scar(s) from antecedent abdominal surgery. Low-grade fever and cachexia are variably present. Mass is most often located in the right lower quadrant, less frequently in the left lower quadrant, typically firm-to-hard in consistency, non-tender, often fixed to underlying tissue. Haematogenous spread occurs to liver, kidney and presents as liver abscess and perinephric abscess. Sinus tracts with drainage from either the abdominal wall (i.e. peritoneocutaneous fistula) or the perianal region.

Pelvic actinomycosis usually presents as pelvic mass and menometrorrhagia.

MYCETOMA

Mycetomas are chronic, slowly progressive infections of the subcutaneous tissue, usually of the foot and rarely of other parts of the body. The disease was originally reported by Gill (1842) from Madurai. It is commonly known as Madura mycosis or Madura Foot. It is seen mainly in the tropics. Bacterial mycetomas are usually caused by—*Actinomycetes (A. israelii, A. bovis), Nocardia (N. asteroides, N. brasiliensis. N. caviae), Actinomadura (A. madurae, A. pelletieri), Streptomyces (S. somaliensis).*

Diagnosis

A Gram-stained smear of the specimen may demonstrate the presence of beaded, branched, Gram-positive filamentous rods, suggesting the diagnosis of actinomycosis.

Nocardia can be differentiated from *Actinomycetes* by its acid fastness due to the mycolic acid content of the cell wall. *Nocardia* grow under aerobic conditions while *Actinomycetes* grow under anaerobic conditions.

Cultures should be placed immediately under anaerobic conditions in a suitable media and incubated for 48 hours or longer; the isolation and definitive identification of actinomycetes may require 2 to 3 weeks.

Actinomycosis needs to be differentiated from tuberculosis, mycosis, granulomatous diseases or malignancy. Demonstration of sulphur granules in discharge and histopathology are diagnostic. Sun Ray appearance is typically seen. A culture of tissue or fluid shows *Actinomycetes* species.

Prognosis

When actinomycosis is diagnosed early and treated with appropriate antibiotic therapy, the prognosis is excellent.

Treatment

The current recommended therapy includes 4 weeks of high dose intravenous penicillin followed by a 3 to 6 month course of oral penicillin, continuing treatment even after total resolution of symptoms. Other anti-microbials that have been found to be effective include tetracycline, erythromycin,

clindamycin, ceftriaxone and imipenem. These can be used in penicillin-allergic patients with good success rates. Amoxicillin/clavulanic acid can be used in mild to moderately severe cases of actinomycosis; covers both pathogenic *Actinomycetes* and companion bacteria, which frequently are resistant to penicillin. Ciprofloxacin has been used for treatment of recalcitrant cases.

Surgery

For more complicated cases, surgery for excision of recalcitrant fibrotic lesions or necrotic tissue or for drainage can be done.

Prevention

Maintenance of good oral hygiene and adequate regular dental care are important. Patients and physicians alike should be aware of the increased risk of infection associated with insertion of IUCD.

NOCARDIOSIS

Introduction

Nocardiosis is an acute, subacute or chronic suppurative infection. Two characteristics of nocardiosis are its ability to disseminate to virtually any organ, particularly the central nervous system and its tendency to relapse or progress despite appropriate therapy.

Aetiopathogenesis

Nocardiosis is an uncommon Gram-positive bacterial infection caused by aerobic *Actinomycetes* in the genus *Nocardia*. *Nocardia* species are found worldwide in soil, decaying vegetable matter and aquatic environments and can become airborne, particularly on dust particles. Inhalation of free-living organism is the likely route of infection of the pulmonary system. Haematogenous spread can occur to all organs of the body. Ingestion of contaminated food may produce disease via gastrointestinal tract. Localised cutaneous or lymphocutaneous infections occur after contamination of an abrasion and may result in abscess.

Classic histologic lesion of nocardiosis is an abscess with predominant neutrophils and prominent necrosis. T-cell population capable of direct lymphocyte-mediated cytotoxicity is necessary to kill the *Nocardia*.

Risk Factors

The risk of nocardial infection is increased in immunocompromised patients particularly those with defects in cell-mediated immunity, glucocorticoid therapy, human immunodeficiency virus (HIV) infection, malignancy and diabetes mellitus. Chronic lung disease and alcoholism are additional risk factors for pulmonary nocardiosis.

Clinical Features

The clinical features and differential diagnosis of nocardiosis is given in **Table 1**.

Table 1: Clinical Features, Differential Diagnosis and Treatment of Cutaneous, Pulmonary and Disseminated Nocardiosis

Clinical Presentation	Cutaneous Nocardiosis	Pulmonary Nocardiosis	Disseminated Nocardiosis
Susceptible patients	Agricultural workers, traumatic exposure	Chronic pulmonary disease, deficient cell-mediated immunity	Deficient cell-mediated immunity
Main clinical features	Dermo-hypodermitis, lymphangitis, or mycetoma	Onset of pulmonary nocardiosis may be acute, subacute, or chronic and is not distinguished by any specific signs or symptoms. Fever, night sweats, fatigue, anorexia, weight loss, dyspnoea, cough, haemoptysis and pleuritic chest pain have all been described	The hallmark of CNS nocardiosis is formation of a parenchymal abscess that can occur in any region of the brain. Brain abscesses may have no signs or symptoms or may present with headache, seizures and coma and CSF usually does not show nocardia
Main clinical differential diagnosis	Sporotrichosis and other subcutaneous mycoses, fungal mycetomas	Complications, such as empyema, mediastinitis, pericarditis and superior vena cava syndrome Bacterial lung abscesses, tuberculosis, aspergillosis and other opportunistic fungal infections.	Pyuria is seen in kidney involvement; other sites of involvement have been reported include sinuses, eyes, spleen, liver, adrenal glands, pancreas, thyroid gland, prostate, and testicles Bacterial brain abscesses, abscesses in other organs, aspergillosis and other opportunistic fungal infections
Suggested initial treatment	TMP-SMX TMP/SMX + fluoroquinolone minocycline is alternative oral drug in a dose of 100-200 mg twice daily	TMP-SMX TMP-SMX + ceftriaxone TMP-SMX + moxifloxacin Imipenem + amikacin	Imipenem + amikacin TMP-SMX + imipenem + amikacin TMP-SMX + ceftriaxone + amikacin
Comments	Fluoroquinolone must be considered for deep infections, especially mycetoma	TMP/SMX monotherapy only in immunocompetent patients with mild disease Combination therapy is preferred in the immunocompromised patients	Linezolid could replace any of the proposed drugs At least 2 weeks of initial intravenous treatment is recommended Surgical treatment must be considered for deep abscesses

Anti-microbiol susceptibilities should be performed on oll Nocordio isolotes os o guide to theropy. Potients on immunosuppressive theropy or underlying diseose theropy should be continued. In immunocompromised patients whose immunosuppression connot be reversed, indefinite mointenonce suppressive theropy with TMP-SMX (Doxycycline is a reosonoble olternotive); the dose is 10-20 mg/kg in two divided dosoges.

TMP-SMX: Trimethoprim-sulphomethoxozole.

Diagnosis

A definitive diagnosis of nocardiosis requires the isolation and identification of the organism from a clinical specimen.

Staining with modified acid-fast stain and especially Gram stain is particularly important to provide a rapid presumptive diagnosis while awaiting the results of the culture which may take from 48 hours to 3 weeks. The typical colonies are usually seen after 3 to 5 days. In general, the colonies have a chalky white or cotton-ball appearance because of the presence of abundant aerial filaments.

Imaging Studies

Plain radiography and computed tomography (CT) of chest are useful in the evaluation of pulmonary nocardiosis. The common radiographic findings are parenchymal nodules, infiltrates, lung abcesses and rarely pleural effusion.

All patients with nocardiosis, except of mycetoma, should be subjected to brain imaging in the form of CT or MRI head as asymptomatic brain abscess are a common finding and can help in making a diagnosis if the abscess is spreading to the contiguous structures.

Treatment

The treatment of nocardiosis can be divided into medical care and surgical care. The medical treatment of nocardiosis is outlined in **Table 1**. Localised abscesses generally require prompt surgical therapy. Prognosis depends upon the severity and site of infection.

Patients with nocardiosis must be educated about the need for protracted anti-microbial therapy with periodic follow-up by the treating physician.

CONCLUSION

The diagnosis actinomycosis and nocardiosis can be challenging, as signs and symptoms are not specific and a high index of clinical suspicion is necessary. Each case needs a careful multi-disciplinary evaluation.

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17.33 Bartonella Infections

Pallavi Bhargava

The *Bartonella* species are small Gram-negative bacilli that adhere to mammalian erythrocytes and endothelial cells. The genus *Bartonella* was first described by Dr AL Barton in 1909. The three most common species responsible for human infections are: *B. bacilliformis, B. henselae* and *B. quintana.* Depending on the species and host immunity, these agents cause a wide variety of clinical illnesses, viz. cat-scratch disease (CSD), bacillary angiomatosis (BA), peliosis hepatis, oroya fever, Verruga peruana, trench fever and endocarditis. BA is the only *Bartonella* infection reported in the literature from India.

The clinical syndromes, modes of transmission, risk factors and treatment are described in **Table 1**.

BACILLARY ANGIOMATOSIS

BA was first described as a vascular skin lesion occurring in acquired immunodeficiency syndrome patients. But now it is well-known that BA caused by *B. henselae* and *B. quintana* in immunocompromised patients can disseminate to involve many organ systems particularly liver (peliosis hepatis). The skin legions of BA are red or purple vascular papules or nodules (**Figure 1**).

BA is characterised by angiogenesis and a neutrophilic inflammatory response to the organisms. The diagnosis of BA is confirmed on histopathological examination. Differential diagnosis is from Kaposi's sarcoma and pyogenic granuloma. Cutaneous lesions respond well to a 3-week course of either macrolides or tetracycline.



Figure 1: Cutaneous bacillary angiomatosis in an AIDS patient from India.

CAT-SCRATCH DISEASE

Cat-scratch disease is usually a self-limited disease characterised by regional lymphadenopathy presenting 1 to 2 weeks after scratch by a cat and lasting for several weeks to months. A papule or pustule can sometimes be seen preceding the lymphadenopathy. Systemic symptoms, like malaise, anorexia or weight loss may be present. Rarely encephalitis, meningitis, transverse myelitis, seizures, liver, spleen involvement and osteomyelitis have been reported. Acute neuroretinitis and

Table 1: Clinical Syndrome, Mode of Transmission and Treatment (for Bartonella Infections)

	Disease	Transmission/Risk factor	Treatment
Bartonella henselae	Cat-scratch disease	Cat-scratch or cat bite	Azithromycin, ciprofloxacin Doxycycline (5 days)
	Bacillary angiomatosis	Cat-scratch or cat bite Immunocompromised state, especially HIV infection	Erythromycin, rifampicin Doxycycline, ciprofloxacin (3 to 6 weeks)
	Peliosis hepatis endocarditis	Exposed to cats and cat flea	Azithromycin, doxycycline (4 to 6 months)
Bartonella quintana	Bacillary angiomatosis	HIV infection Infestation by body louse	Erythromycin, doxycycline Azithromycin, doxycycline
	Trench fever	Homelessness Body louse homelessness	(4 to 6 weeks)
	Endocarditis	As above	Ceftrioxone, doxycycline Gentamicin Valve replacement
Bartonella bacilliformis	Oroya fever	Sandfly (*Lutzomyia)* bite	Chloramphenicol, ciprofloxacin (3 weeks)
	Verruga peruana	Convalescent phase of Oroya fever or chronic infection	Rifampicin, ciprofloxacin Chloramphenicol (1 to 2 weeks)

HIV = Human immunodeficiency virus.

Perinaud's oculoglandular syndrome can occur with conjunctival inoculation by *B. henselae*. Suspect Cat-Scratch disease if skin lesions and lymphadenopathy are seen in a patient with exposure to cats. Diagnosis is confirmed by histopathologic examination of lymph nodes. The bacterial clumps can also be seen if tissue is stained with Warthin-Starry stain. Oral azithromycin for 5 days is reserved for patients with severe manifestations. Erythromycin, rifampicin, doxycycline and ciprofloxacin are other active drugs.

TRENCH FEVER

Trench fever was first described as a relapsing and debilitating febrile illness in soldiers fighting during World War I. It is caused by *B. quintana* transmitted from person to person by body lice. Lately Trench fever has re-emerged in France and United States in urban homeless people with history of alcohol abuse. Clinical features are high grade fever, headache, malaise, aseptic meningitis and severe musculo-skeletal pain. Diagnosis is established by growing *B. quintana* in blood culture. A 4 to 6 week course of doxycycline (100 mg BD) or erythromycin (2 gm/day) or azithromycin (500 mg/day) is effective.

OROYA FEVER AND VERRUGA PERUANA

B. bacilliformis causes both these infections. Oroya fever presents with fever, severe anaemia and high mortality without treatment. Sandfly found in Andes mountains transmits the illness to non-immune individuals. *Verruga peruana* presents as skin lesions in patients recovering from Oroya fever or patients with chronic infection with *B. bacilliformis*. Diagnosis of Oroya fever is confirmed by culturing bacteria from blood while *Verruga peruana* is diagnosed on histopathological examination. Oroya fever in South America is treated with intravenous chloramphenicol while rifampicin is the drug of choice for *Verruga peruana*.

ENDOCARDITIS

Some of the culture-negative endocarditis is caused by *Bartonella* species. Once diagnosis is confirmed by blood culture or serology, treatment is modified to include drugs that are active against *Bartonella* (azithromycin or doxycyline). Duration of treatment is 4 to 6 months.

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17.34 Melioidosis

Kavitha Saravu

The name melioidosis is derived from the Greek word 'melis' referring to distemper of asses. Melioidosis, caused by *Burkholderia pseudomallei*, has a wide spectrum of presentations with acute and chronic form, localised form to systemic disease and asymptomatic to septicaemic illness.

EPIDEMIOLOGY AND AETIOLOGY

Melioidosis is endemic in Northern Australia, Thailand, Singapore, Malaysia, Myanmar and Vietnam. In India, it is sporadic with increasing trend in Southern states. *B. pseudomallei* is a Gram-negative, motile bacillus isolated from soil and surface water. The disease is acquired by inoculation through abraded skin, inhalation or ingestion. Its incubation period ranges from 24 hours to many years. It produces necrotising inflammation, abscess or granuloma with multinucleated giant cells.

CLINICAL FEATURES

Melioidosis is more common in males aged 40 to 60 years. Other risk factors are diabetes, alcoholism, malignancy, chronic kidney and lung diseases. It occurs in farmers exposed to soil and surface water and the incidence is highest during monsoon. Depending upon the innoculum size, route, virulence factors and host responses, the *B. pseudomallei* infection can have several disease outcomes—asymptomatic seroconversion, acute or chronic disease or latent infection. Severe disease or septicaemia occurs in patients with risk factors.

Clinical disease may present acutely or chronically with more than 2 months of fever. Localised disease presents as skin ulcers, and subcutaneous abscesses or pneumonia. Disseminated disease can present with pneumonia, abscesses in liver, spleen, kidney, prostate, skin and subcutaneous tissue, septic arthritis and osteomyelitis with or without septicaemia. Meningo-encephalitis or subdural empyema are rare presentations. Lymph nodal swelling with necrosis can occur as part of disseminated melioidosis or local forms. Relapse may occur after many years.

DIAGNOSIS

In systemic disease, laboratory tests indicate anaemia, neutrophilic leucocytosis, elevated ESR, CRP and plasma sugar. Liver enzymes may be elevated with alkaline phosphatase more than transaminases. Renal failure may be present in septicaemia. Forty to sixty percent of patients are bacteremic.

On Gram-staining *B. pseudomallei* has a characteristic bipolar staining with 'safety pin' appearance. It can be cultured easily from blood, pus, sputum and urine, but may be mis-identified as *B. cepacia*, *Pseudomonas stutzeri*, or other Pseudomonas species. *B. pseudomallei* is identified by the characteristic colony morphology and biochemical reactions.

TREATMENT

Anti-Microbial Therapy

Initially intensive parenteral therapy is with ceftazidime 50 mg/kg (up to 2 g) q6h or meropenem 25 mg/kg (up to 1 g) q8h, or imepenem 25 mg/kg (up to 1 g) q6h with or without sulphamethoxazole/trimethoprim 40/8 mg/kg (up to 1600/320 mg) q12h for 10 to 14 days. Deep seated collections, extensive pulmonary disease, osteomyelitis, septic arthritis and neurological melioidosis require 4 to 8 weeks of intensive phase.

Subsequent oral eradication therapy is required to prevent recrudescence or relapse. Sulphamethoxazole/trimethoprim with doxycycline 2 mg/kg, (up to100 mg) q12h is recommended for 12 to 20 weeks. Amoxicillin-clavulanate 20/5 mg/kg q8h is recommended in pregnancy.

Adjunctive Therapy

Abscesses need surgical drainage. Septicaemic melioidosis patients require aggressive therapy with management of septic shock, renal failure, respiratory failure and hyperglycaemia.

PROGNOSIS AND PREVENTION

Overall mortality ranges from 19% to 44% with relapse rate of 9.7%. Prevention is by avoidance of contact with *B. pseudomallei* in the environment and adequate chlorination of water supplies.

RECOMMENDED READINGS

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17.35 Rickettsial Infections

Raminder Singh

INTRODUCTION

Rickettsial infections are re-emerging and are prevalent throughout the world. In India, they are reported from Maharashtra, Tamilnadu, Karnataka, Kerala, Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Rajasthan, Assam and West Bengal. In view of low index of suspicion, non-specific signs and symptoms and absence of widely available sensitive and specific diagnostic test, these infections are notoriously difficult to diagnose. Failure of timely diagnosis leads to significant morbidity and mortality. With timely diagnosis, treatment is easy, affordable and successful. The pattern of rickettsial infections is given in **Table 1**.

Table 1: Classification of Rickettsial Agent

Disease	Rickettsial Agent	Geographical Area	Insect Vector	Mammalian Reservoir
Spotted fever group				
Rocky mountain spotted fever	*R. rickettsii*	United States	Tick	Rodent, dogs
Mediterranean spotted fever, Boutonneuse fever, Kenya tick typhus, South African tick fever, Indian tick typhus	*R. conorii*	Africa, India, Mediterranean regions	Tick	Rodent, dogs
Queensland tick typhus	*R. australis*	Eastern Australia	Tick	Rodents
Siberian Asian tick typhus	*R. sibirica*	Siberia, Mongolia	Tick	Rodents
African tick bite fever	*R. africae*	Rural sub-Saharan Africa, Eastern Caribbean	Tick	Cattle
Rickettsial pox	*R. akari*	United States, Korea	Mite	Mice
Typhus group				
Epidemic (louse-borne) typhus	*R. prowazekii*	South America, Central Africa	Louse	Human, flying squirrels
Endemic (murine) typhus	*R. typhi*	Worldwide	Flea	Rodents
Scrub typhus group				
Scrub typhus	*Orientia tsutsugamushi*	Southeast Asia, Japan, Australia, Western Siberia	Mite	Rodents
Other				
Q-fever	*Coxiella burnetii*	Worldwide	None	Cattle, sheep, goat
Ehrlichiosis and anaplasmosis				
Human monocytic	*Ehrlichia chaffeensis, Anaplasma equi, Ehrlichia canis*	Southeastern United States	Tick	Dogs
Human granulocytic	*Anaplasma phagocytophilum, Ehrlichia ewingii*	Northeastern United States	Tick	Rodent, deer, sheep

PATHOLOGY

The *Rickettsia* species are small, pleomorphic coccobacilli and obligate intracellular pathogens that depend on the host as a source of energy. Humans are accidental host for these organisms and are usually infected by means of an arthropod vector like tick, mite, louse and flea. *Rickettsia* multiplies at the bite site, invade the bloodstream and establish an infection by infecting endothelial cells throughout the microvasculature. Subsequent vascular lesions caused by damage to endothelial cells account for the pathological changes that occur throughout the body. The damage is most marked in Rocky Mountain Spotted Fever. *Rickettsia* are diverse collections of organisms categorised by antigenic similarities, they cause illness from mild to life threatening or recrudescent.

DIAGNOSIS

Haematology

Leucocytosis and low platelet counts may be present with high ESR.

Biochemistry

Hyponatraemia, hypoalbuminaemia, elevated hepatic transaminases and blood urea are frequently present.

Serology

Serology is used for detection of convalescent antibodies by various tests like microimmunoflorescence, immunoperoxidase

assay, latex agglutination, indirect haemagglutination, enzyme-linked immunosorbent assay, dot blot immunoassay (including dipstick test) and Weil-Felix test.

- *Weil-Felix Test* is positive 7 days after infection, uses agglutinins from OX-2, OX-19 and OX K strains of Proteus bacteria and causes them to clump; a four fold rise in titre is seen.
- *Indirect fluorescent antibody:* This test is considered as 'gold standard'.
- *Polymerase chain reaction assay:* It can be used to detect rickettsial DNA in whole blood, buffy coat fraction or tissue specimen. It is most rapid assay for the diagnosis.
- *Immunohistological detection* of microorganisms in skin biopsy.
- *Isolation of rickettsial agents*

TICK AND MITE BORNE-SPOTTED FEVERS

Rocky Mountain Spotted Fever (RMSF)

The causative agent *R. rickettsii* is transmitted to humans by the bite of Rocky Mountain wood tick, *Dermacentor andersoni* in Western United States and by the bite of American dog tick *Dermacentor variabilis* in Eastern United States. The symptoms begin with fever, chills, headache, nausea, myalgia, restlessness and irritability, pneumonitis may develop. Delirium, lethargy, seizure and coma may appear. The face is flushed and conjunctiva injected. The rash (faint macules that progress to maculopapules and petechiae) appear on palms and soles and spread to whole body. In some cases there is hepato-splenomegaly, jaundice, myocarditis, uraemia or ARDS. The mortality rate for RMSF is 70% in untreated elderly due to cardiac or respiratory failure.

The drug of choice is doxycycline (200 mg/dL) orally or chloramphenicol (50 mg/kg/day). Patient usually responds within 48 hours.

Rickettsial Pox

The causative agent is *R. akari* and is maintained by mice and their mites, is recognised principally in New York City and others states of USA. A papule appears at the site of mite bite and develops a central vesicle that becomes painless black crusted eschar surrounded by erythematous halo. Lymph nodes draining the area of eschar appear. After 10 to 14 days, fever, headache, chills, myalgia occur along with a macular rash which turns into papules, vesicles and crusts that heal without scarring. Disease resolves within 6 to 10 days and is non-fatal.

Treatment options are doxycycline (100 mg bid for 1 to 5 days), ciprofloxacin (750 mg bid for 1 to 5 days), and chloramphenicol (500 mg qid for 7 to 10 days).

Other Tick Borne Spotted Fevers

Other tickborne spotted-fever-group rickettsial infections include Mediterranean spotted fever, African tick-bite fever, Queensland tick typhus, Siberian tick typhus, Japanese spotted fever, Flinders Island spotted fever, tick-borne lymphadenopathy (TIBOLA), and *R. parkeri* infection.

TIBOLA is not usually associated with a generalised rash; rather, this unusual rickettsiosis is characterised by a localised area of scalp alopaecia. The alopaecia typically follows the development of a crusted lesion at the site of a resolving tick bite. Localised hair loss may be prolonged. Cervical or regional lymphadenopathy is common in TIBOLA. Only a minority of TIBOLA patients have fever, and rash occurs in fewer than 10% of patients.

Infection with a newly recognised rickettsial agent, *R. mongolotimonae*, has been seen in southern France. In the few cases reported to date, clinical manifestations have typically been similar to those of Mediterranean spotted fever.

All of these illnesses respond to treatment with tetracyclines or chloramphenicol. Most are milder in course and severity than RMSF, although Mediterranean spotted fever may, in rare cases, be fatal.

FLEA AND LOUSE-BORNE TYPHUS GROUP RICKETTSIOSES

Endemic Murine Typhus (Flea-Borne)

It has worldwide distribution and caused by *R. typhi* and transmitted by rat flea (Xenopsylla cheopis). Humans become infected when *Rickettsia* laden flea faeces are scratched into pruritic bite lesions. Initial symptoms include headache, malaise, fever, chills. The pink rash appears on 5th day and spreads to whole body but do not involve palms and soles. Pulmonary disease is common and chest radiograph shows interstitial pneumonia, pulmonary oedema and pleural effusions. Abdominal pain, confusion, stupor, coma and jaundice occur less commonly. Treatment with doxycycline (100 mg bid for 7 to 15 days) or chloramphenicol (500 mg qid for 7 to 15 days) is effective.

Epidemic Louse-Borne Typhus

R. prowazeki is carried by body louse (Pediculus humanus corpori) was responsible for deaths of millions of people during World War I and II. It is now most commonly reported from Northeastern, Central Africa, Himalayan regions of India, Pakistan and Afghanistan. After incubation period of one week, there is abrupt onset of high fever, headache, cough and myalgia. Rash appears on trunk on fifth day and spreads to involve all body surface except face, palms and soles. Confusion, coma, skin necrosis and gangrene of digits are noted. Untreated disease is fatal because of multiorgan involvement. Treatment is with doxycycline (200 mg daily till patient becomes afebrile).

Brill-Zinsser Disease

It is a recrudescent and mild form of disease that occurred years ago, treatment is same as above.

Scrub Typhus

Disease is prevalent in rural Asia. *Orientia tsutsugamushi*, agent of scrub typhus is transmitted by infected larva of trombiculid mite or chiggers in areas of heavy scrub vegetation during wet season. It causes mild to fatal disease; there is eschar at the site of chigger feeding, lymphadenopathy and maculopapular rash. Severe cases include encephalitis and interstitial pneumonia. A 7 to 15 days course of doxycycline (100 mg bid) or chloramphenicol (500 mg qid) is effective.

Q-FEVER (QUERY FEVER)

Coxiella burnetti a small Gram-negative organism causes Q-fever. This disease name originated in 1935 with an outbreak of febrile

illness of unknown aetiology in nine abattoir workers in Brisbane, Australia. The organisms exist in highly infectious or phase I form within humans and animals or as an avirulent phase II form.

Q-fever is a zoonosis that occurs worldwide. The primary sources of human infection are sheep, cattle and goat. At parturition the organism is dispersed as an aerosol, and infection usually follows inhalation.

Acute Q fever: Presents as flu like syndrome, fever, pneumonia, hepatitis, myocarditis meningoencephalitis. CXR shows multiple rounded opacities highly suggestive of Q fever pneumonia. Treatment is with doxycycline (100 mg bid for 14 days).

Chronic Q fever: Q fever valvular endocarditis presents exclusively in patients with previous valvular heart disease, in transplant recipients. Aortic and prosthetic valves are commonly involved. Hepatosplenomegaly, purpuric rash, renal insufficiency and embolism may be seen. Treatment is with at least two drugs. The combination of rifampicin (300 mg daily) plus doxycycline (100 mg bid) or ciprofloxacin (750 mg bid) is given for 18 months to 3 years.

EHRLICHIOSIS AND ANAPLASMOSIS

Human Ehrlichiosis was first recognised in the United States in 1986 as a life-threatening tick-borne illness similar to Rocky Mountain spotted fever, but with a much lower incidence of rash. *Ehrlichia* are small Gram-negative intracellular bacteria that grow in cytoplasmic vacuoles to form clusters called morulae.

Human Monocytotropic Ehrlichiosis (HME)

This is caused by *E. chaffeensis* and tick vector is *Amblyomma americanum*. Patient develops fever, headache, myalgia, nausea, vomiting, diarrhoea. Complications include toxic shock syndrome, respiratory distress, meningoencephalitis and haemorrhage. Bone marrow shows non-caseating granulomas. Morulae are rarely seen in peripheral smear. Treatment is doxycycline (100 mg bid) or tetracycline (500 mg qid) is effective and should be continued for 3 to 5 days until defervescence.

Ehrlichiosis ewingii

It is caused by *E. ewingii* and tick vector is *Amblyomma americanum*. It resembles HME but is less severe, seen in immunocompromised patients. Treatment is same as for HME.

Human anaplasmosis

It is caused by *A. phagocytophilum* and tick vector is *Ixodes scapularis*. It presents as influenza-like illness. Respiratory insufficiency, toxic shock syndrome and opportunistic infections are troubling complications. It should be considered as severe presentation of Lyme disease as they share the *Ixodes scapularis* vector. Treatment with doxycycline is effective. Pregnant woman may be treated with rifampicin.

PREVENTION

These diseases are prevented by debugging, use of protective clothing, removal of ticks, tick repellents along with good personal hygiene. Flea control can be achieved with the use of BHC, 10% DDT or 1% malathion.

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1. Parola P, Raoal D. Rickettsial diseases. In: *Oxford Textbook of Medicine;* 5th Ed; 2010: pp 903-19.

17.36 Chlamydial Infections

TK Suma

Chlamydia are small, Gram-negative, obligate intracellular organisms. Three of them are pathogenic to humans: *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*, *Chlamydophila* (formerly *Chlamydia*) *psittaci*, and *Chlamydia trachomatis*. Infection occurs in humans either through aerosol inhalation, when the upper and lower respiratory tracts are affected or via the sexual route involving the genitourinary system or through direct contact as in trachoma. All three species can cause pneumonia in humans.

EPIDEMIOLOGY

C.pneumoniae is estimated to cause 10% to 20% of community-acquired pneumonia cases among adults. Approximately 50% of young adults and 75% of elderly persons have shown serological evidence of previous infection. Approximately 5% to 22% of pregnant women are thought to have *C. trachomatis* infection of the cervix, and 30% to 50% of neonates born to infected mothers show culture evidence of infection. Among these neonates 15% to 25% present with clinical conjunctivitis and/or nasopharyngitis that in some cases develop into neonatal pneumonitis. Studies including those from India have suggested an association between *C. trachomatis* and HIV infections and re-inforced the need for routine screening for *C. trachomatis*. Cases of ornithosis caused by *C. psittaci* have declined after the introduction of antibiotic-laced bird feed. The mortality from pneumonias caused by Chlamydiae is estimated to be 5.4% to 9.8%.

CHLAMYDIA BIOLOGY

Chlamydiae possess both DNA and RNA, and have a cell wall and ribosomes. The unique feature of chlamydiae is the reproductive cycle with two morphological forms: the extracellular, elementary body (EB) which is the infectious form and the intra-cellular, reticulate body (RB) which is non-infectious. The EBs (0.3-0.4 μ) bind to receptors on epithelial, respiratory or genital cells of host and initiate infection. They are internalised by endocytosis and/or by phagocytosis. Within the host cell endosome, the EBs reorganise and become RBs. The entire intra-cellular life cycle of the chlamydia occurs within the endosome. The RBs replicate by binary fission and reorganise into EBs within 36 hours prior to exocytosis (cell lysis). The resulting inclusions may contain 100 to 500 progeny. Eventually the cells and inclusions lyse in case of *C. psittaci* or extruded by reverse endocytosis in *C. trachomatis* and *C. pneumoniae*. The released EBs then infect the adjacent cell or transmit infection from one person to another.

PNEUMONIA

Chlamydia pneumoniae is the causative agent of an atypical pneumonia similar to those caused by *Mycoplasma pneumoniae* and *Legionella pneumophila*. Humans are the only known reservoir and mode of transmission is via infected respiratory secretions. Immunity is short-lived and re-infection can occur. *C. pneumoniae* can be isolated from the nasopharynx of about 2% to 5% of healthy asymptomatic adults and children. Over half the adult population has serologic evidence that suggests previous or persistent infection. It can precipitate onset of asthma in adults.

Clinical Features

The incubation period is approximately 3 to 4 weeks. The onset is usually gradual or may be biphasic. Symptoms of bronchitis or pneumonia follow upper respiratory tract symptoms, like rhinitis, laryngitis, pharyngitis and/or sinusitis after 1 to 4 weeks. Horder's spots (pink maculopapular eruption), erythema marginatum and urticaria may be present on the skin. Hoarseness of voice is more common in *C.pneumoniae* infection than in mycoplasmal or other pneumonias. Fever is more often present in the first few days and could be absent by the time of examination. Cough could be predominant with scanty sputum. In patients with a pre-existing obstructive lung disease, it may be responsible for exacerbation. Rhonchi and crackles are present even in mild disease. Complete resolution could take about 5 to 6 months.

Complications include otitis, erythema nodosum, endocarditis, Guillain-Barré syndrome and encephalitis. New onset asthma has been observed after *C. pneumoniae* infection.

The first suggestion of an association between *C. pneumonia* and atherosclerosis came from sero-epidemiological studies from Finland. Evidence of presence of the organism in the atherosclerotic tissue in coronary and other arteries has been presented by various techniques including PCR, immunohistology and micro-immunofluorescene (MIF). The presence of *C. pneumoniae* in atherosclerotic lesions raised the possibility that antibiotic treatment might have a favourable effect on the course of coronary artery disease (CAD). But large randomised antibiotic trials did not show any beneficial effect of long-term antibiotic therapy in patients with established acute or chronic CAD and concluded that, there is no role for long-term antibiotic treatment in secondary prevention of CAD. Studies from the West and also from India could not establish definite pathogenic mechanisms for initiation or progression of atherosclerotic plaques by *C. pneumoniae*. In conclusion, though there is a strong association of *C. pneumoniae* with atherosclerotic CAD, there is lack of sufficient data to establish an aetiologic relationship between the two.

Laboratory Diagnosis

The commonly used serologic criteria are an IgM titre exceeding 1:16 or a 4-fold increase in the IgG titre by specific MIF. The absence of detectable antibodies several weeks after the onset of infection does not exclude a diagnosis of acute *C. pneumoniae* pneumonia because the IgM antibody response may take as long as 6 weeks and the IgG antibody response may take as

long as 8 weeks to appear in primary infections. It is of little use in determining treatment. *C. pneumoniae*-specific DNA can be demonstrated in pharyngeal swab, bronchoalveolar lavage, sputum, or tissue by PCR and is the most promising rapid test. Cell culture with oropharyngeal swabs is probably the best test, but it requires specialised culture techniques, which are expensive and difficult to perform.

Treatment

Doxycycline (100 mg PO bid) is the treatment of choice except in children and in pregnant women. Treatment should be continued for at least 10 to 14 days after defervescence. If symptoms persist, a second course with a different class of antibiotics is usually effective. Alternatives include erythromycin (500 mg qid), clarithromycin (1 g qid) for 7 to 10 days or azithromycin (total dose of 1500 mg in five days). Telithromycin is the first antibiotic in a new class called ketolides and is approved for *C. pneumoniae* pneumonia by the US FDA but has many drug interactions and adverse drug reactions. It is contraindicated in patients with *Myasthenia gravis*. Fluoroquinolones, including levofloxacin (500 mg PO/IV qid) and moxifloxacin (400 mg PO/IV qid) for 10 to 14 days also have some activity, although less than that of tetracyclines or macrolides.

PSITTACOSIS

C. psittaci infection (psittacosis or ornithosis) occurs among pet bird's (pigeon and parrot) owners and poultry (chicken and duck) farmers. The respiratory tract is the main portal of entry. Infection is by inhalation of organisms from infected birds or their droppings. Person-to-person transmission is rare. From the lungs the organisms enter the blood stream and are transported to the liver and spleen. The bacteria replicate at these sites where they produce focal areas of necrosis. Haematogenous spread to the lungs and other organs also occurs. A lymphocytic inflammatory response in the alveoli and interstitial spaces leads to oedema, infiltration of macrophages, necrosis and sometimes haemorrhage. Mucous plugs may develop in the alveoli causing cyanosis and anoxia.

The illness develops after an incubation time of 7 to 15 days. Symptoms include fever, chills, headache and a mild pneumonitis. The pneumonic form is the most common and is characterised by a non-productive cough with very few signs on examination of the chest. Chest radiograph, however, reveals extensive multilobar patchy consolidation out of proportion to the clinical findings. In uncomplicated cases, the disease subsides by 5 to 6 weeks after infection. Asymptomatic infections are common. In complicated cases, convulsions, coma and death (5% mortality rate) can occur. Other complications include endocarditis, hepatosplenomegaly, glomerulonephritis, meningitis. Treatment is with oral doxycycline 100 mg twice daily for 21 days.

TRACHOMA

C. trachomatis species is divided into three biovars (biological variants): trachoma, lymphogranuloma venereum (LGV) and mouse pneumonitis. The human biovars have been further subdivided into several serovars (serological variants) that differ in their major outer membrane proteins and are associated with different diseases. The organisms stimulate infiltration of polymorphonuclear cells and lymphocytes which leads to lymphoid follicle formation and fibrotic changes. Infection does not stimulate long lasting immunity and re-infection results in an inflammatory response and subsequent tissue damage.

Chronic infection or repeated re-infection with *C. trachomatis* (biovar: trachoma A, B and C) results in trachoma, which is a common cause of blindness in endemic countries. Infection spreads from person to person, especially where there is shortage of water, numerous flies and crowded living conditions. The infection begins in the conjunctiva, causing follicles in the lower lid and tenderness of the regional preauricular nodes. Repeated episodes of re-infection cause chronic follicular or intense conjunctival inflammation (active trachoma), which leads to tarsal conjunctival scarring. The scarring distorts the upper tarsal plate, and in some individuals, leads to entropion and trichiasis (cicatricial trachoma). The end result includes corneal abrasions, corneal vascularisation, corneal scarring, opacification and ultimately blindness.

Inclusion conjunctivitis is also caused by the same biovar, associated with genital infections (serovars: D to K). In neonates infection results from passage through an infected birth canal and becomes apparent after 5 to 12 days. Ear infection and rhinitis can accompany the ocular disease. Infants can develop pneumonia at birth preceded by neonatal conjunctivitis. Recurrence occurs in 35% of the cases.

Trachoma is treated with single dose oral azithromycin 1 g and tetracycline ointment applied locally to the conjunctiva twice or thrice daily for 2 to 3 months. After control of active infection, surgical reconstruction of the eyelids and keratoplasty for removal of corneal opacities may be required. WHO guidelines for the community-based management of trachoma include integrated SAFE strategy—surgery for trichiasis, community wide antibiotic treatment, facial cleanliness, education and environmental improvements.

GENITOURINARY INFECTIONS

C. trachomatis immunotypes D to K cause non-gonococcal urethritis, epididymitis, and prostatitis in males and cervicitis, salpingitis, and endometritis and perihepatitis (Fitz-Hugh-Curtis syndrome) in females. It is responsible for tubal infertility, ectopic pregnancy and pelvic inflammatory disease.

Reiter's syndrome, a triad of conjunctivitis, polyarthritis and urethritis is also associated with *C. trachomatis*. Approximately 50% to 65% of patients have an acute *C. trachomatis* infection at the onset of arthritis and greater than 80% have serological evidence for *C. trachomatis* infection. The pathogenesis remains obscure.

Treatment for urethritis and cervicitis is with a single oral dose of 1 g azithromycin. For more severe illness, alternative regimens are oral doxycycline 100 mg twice daily or oral erythromycin 500 mg given four times daily for two weeks.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is caused by LGV serovars. The primary lesion of LGV is a small painless and inconspicuous vesicular lesion that appears at the site of infection, often in the penis or vagina. The patient may also experience fever, headache and myalgia. The second stage of the disease presents as a marked inflammation of the draining lymph nodes 1 to 3 weeks later. The enlarged nodes become painful 'bubo' that can

eventually rupture and drain to form multiple discharging sinuses. The important differential diagnosis at this stage are tuberculosis, pyogenic abscesses, tularaemic plague or neoplasms. The healing that follows results in extensive tissue scarring.

Proctitis is common in females as the genital lymph drains into peri-rectal glands. The healing that follows this results in rectal strictures. Therefore, in females, this condition needs to be clinically differentiated from ulcerative colitis and rectal neoplasm.

Laboratory diagnosis is confirmed by the isolation of the LGV strains of *C. trachomatis;* immunofluorescence and use of monoclonal antibodies to identify organism in pus obtained from a bubo; and rising titres in serum when complement fixation tests are done. The intradermal Frei's test is non-specific and unreliable.

The LGV is treated with oral doxycycline 100 mg administered twice daily for 2 to 3 weeks. *As C. trachomatis* is susceptible to sulphonamides, trimethoprim/sulphamethoxazole 160/800 mg thrice daily for 21 days can also be used. Surgical drainage may be required when bubo is present.

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17.37 *Mycoplasma* Infections

Dilip Mathai

MYCOPLASMA

Mycoplasma, previously called L-forms (Lister), Eaton agent, and pleuro-pneumonia-like organisms (PPLO), is the smallest free-living bacterium (0.1 to 0.3 µm) and the most common bacterial agent to cause 'atypical pneumonia'.

Aetiopathogenesis

Human infections are caused by two main genera: *Mycoplasma* and *Ureaplasma*. As a group, they lack a cell wall and the cytoplasmic contents are limited by a cell membrane containing sterols. They are distributed worldwide and colonise human oropharyngeal, respiratory and genitourinary mucosa. Their tissue pathogenicity is difficult to establish.

About 11 species of *Mycoplasma* colonise the body, four of them causing human infections. *M. pneumoniae* causing atypical pneumonia is the only confirmed pathogen; *M. hominis* is believed to cause cervicitis, vaginitis, pelvic inflammatory disease, post partum fever and pyelonephritis in women, conjunctivitis in men and sepsis in neonates. *M. orale* and *M. salivarum* colonising oropharynx are suspected to cause periodontal disease.

Non-gonococcal urethritis (NGU) may be due to *Mycoplasma;* a few of the genital *Mycoplasma* can cause non-genital disease.

Clinical Features

Atypical pneumonia

Mycoplasma pneumoniae is one of the leading aetiological agents causing community acquired atypical pneumonia. Other agents are influenza virus, adenovirus, respiratory syncitial virus (RSV), cytomegalovirus (CMV), *Legionella*, *Pneumocystis jirovecii*, and numerous other viral agents. One sixth of the adult pneumonias seen in the community could be attributed to *Mycoplasma*. The illness occurs during the winter months, with a long incubation period of 2 to 3 weeks. Outbreaks are seen to occur within families and among residents in institutions, as spread occurs via the inhalation of aerosolised droplets. Epidemics occur with four to seven year periodicity and may be non-seasonal. *Mycoplasma* is an extra-cellular organism that binds itself to the surfaces of both ciliated and non-ciliated respiratory epithelial cells. Intra-cellularly, it inhibits the catalase enzyme in the host-cell resulting in the accumulation of hydrogen peroxide that is toxic to the cell. Smoking and low pre-existing IgG levels are strongly associated with *M. pneumoniae* respiratory infection. These findings emphasise the importance of immunity and cessation of smoking for the prevention of disease.

The onset of illness is typically insidious with moderate fever, ranging between 101 and 102°F, malaise, headache with the characteristic gradually worsening cough resembling tracheo-bronchitis. The characteristic non-productive, severe and incessant cough (a hallmark of the atypical pneumonia it causes) is due to ciliostasis and the destruction of the superficial epithelial cell layer. It is called a 'walking pneumonia' as patient remains ambulant without manifesting chills, rigors or toxicity that commonly occur in pneumonias caused by bacteria, such as pneumococcus or *Klebsiella* species. The chest pain is pleuritic, and must be distinguished from the non-descript myalgia that occurs with a viral infection. Bullous myringitis is rare in active illness. Most patients recover in two weeks with normalisation of the chest radiography in 6 weeks. The disease can be protracted, with cough and X-ray appearances lasting for 3 to 4 weeks. Bronchiolitis obliterans is seen in some patients and is characterised by respiratory insufficiency.

Extra-pulmonary complications though rare, can occur at any time during the illness and may occasionally dominate the clinical picture. They include myocarditis and pericarditis. Cardiac conduction defects, or congestive cardiac failure, rashes and erythema multiforme (Stevens-Johnson syndrome); coagulopathies, haemolytic anaemia (sickle-cell disease is associated with more severe illness), thrombocytopaenia, Raynaud's phenomena, monoarticular arthritis, meningo-encephalitis and transverse myelitis.

Diagnosis

The diagnosis of *M. pneumoniae* causing respiratory illness is infrequent, primarily because of the lack of standardised, rapid and specific diagnostic tests. Light microscopy is not useful as these lack a cell wall and are too small to be seen. They are fastidious to cultivate and cultures take 4 to 6 weeks. Rapid bedside test demonstrating a raised erythrocyte mean corpuscular volume (MCV) is a useful clue. Cold agglutinins (IgM antibodies) that bind to the antigen on the surface of the RBCs occur in over half of the cases but are not specific for *Mycoplasma*. Early in the course of the infection low titres (less than the significant value 1:64) may be seen. The diagnosis is confirmed by a rising antibody titre (four-fold increase) or a diagnostic titre more than 1:128. Detection of IgM antibodies during the second week by direct immunofluorescent antibody test (IFAT) or other more specific serological testing methodology such as ELISA. Complement fixation (CF) or immunofluorescence (IF) are useful. Commercial kits with PCR probes directly applied on to clinical materials (sputum, nasopharyngeal swab or bronchoalveolar lavage) to detect antigen have been used with a high-degree of specificity and sensitivity. However, laboratory performance of such tests cannot be assessed.

Treatment

Erythromycin 500 mg qid or doxycycline 100 mg administered twice daily for 2 to 3 weeks are the most effective. Penicillin is ineffective as *Mycoplasma* lack a cell wall. Alternate choices are the newer azalides, (azithromycin and clarithromycin) or the fluoroquinolone (sparfloxacin), all of which achieve adequate *in situ* levels. Due to lack of tests that reliably support the diagnosis of *Mycoplasma*, treatment is usually empirical.

UREAPLASMA

Ureaplasma urealyticum (previously called T-strain) as it is extremely tiny, causes urethritis (non-gonococcal) and upper genitourinary infections in the female. The prevalence of genital infection caused by such organisms depends on several factors like age, sex (more common in women), socioeconomic status and number of sex partners. *Ureaplasma* may also play a role in male infertility as a result of the production of antisperm antibodies. Genital infections can be prevented by using barrier precautions during sexual intercourse. Infants can get colonised during passage through the birth canal of the infected mother. Colonisation in pregnant women is associated with a decrease in birth weight and gestational length of infants.

Erythromycin 500 mg qid for 2 to 3 weeks is the drug of choice.

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17.38 Basic Considerations of Viral Diseases

Usha K Baveja

INTRODUCTION

The word '*virus*' is Latin in origin and literally means 'toxin or poison'. Viruses are ultra small, metabolically inert particles which can cause endemic, epidemic and pandemic outbreaks of sometimes life-threatening infections in man, animals, plants and bacteria. Viruses can't exist outside the living cells, as viruses use the living cell machinery to replicate, establish and may or may not cause harm to the system. Viruses have emerged and are emerging as serious pathogens. Since the initial discovery of tobacco mosaic virus by Martinus Beijerinck in 1898, about 5,000 viruses have been described in detail, although there are millions of different types. Viruses are found in almost every ecosystem on earth. The origins of viruses in the evolutionary history of life are unclear: some may have evolved from plasmids —pieces of DNA that can move between cells, while others may have evolved from bacteria.

STRUCTURE

Each virus is made of three components. These are DNA (single stranded or double stranded) or RNA (double stranded or single stranded) in the centre surrounded by protein coat formed from identical protein subunits called capsomeres which may be organised to form a helical or icosahedral or more complex symmetry and a lipid envelope derived from host cell membrane, which carries the specific receptors for attachment to host cells. A virus has either DNA or RNA genes and is called a DNA virus or a RNA virus, respectively. Proteins associated with nucleic acid are known as nucleoproteins, and the association of viral capsid proteins with viral nucleic acid is called a nucleocapsid. The nucleic acid of the virus carries all the genes and information required to replicate. In general, there are four main morphological virus types: helical, icosahedral, enveloped and complex.

There are 'prions' and 'viroids' that were earlier considered as viruses. Prions do not have nucleic acid and viroids do not have the protein coat, just are naked nucleic acid. Prions are infectious proteins that cause an infection in sheep called scrapie and cattle bovine spongiform encephalopathy ('mad cow' disease). In humans they cause Kuru and Creutzfeldt-Jakob disease. They are able to replicate because some proteins can exist in two different shapes and the prion changes the normal shape of a host protein into the prion shape. This starts a chain reaction where each prion protein converts many host proteins into more prions, and these new prions then go on to convert even more protein into prions which cause the diseases.

GENOMIC DIVERSITY AMONG VIRUSES

Genetic diversity is very common in viruses. Viruses undergo genetic change by a process called genetic drift where individual bases in the DNA or RNA mutate to other bases. Most of these point mutations are 'silent'—they do not change the protein that the gene encodes—but others can confer evolutionary advantages, such as resistance to anti-viral drugs. Antigenic shift occurs when there is a major change in the genome of the virus. This can be a result of recombination or reassortment (the DNA breaks into pieces and different pieces join together to form a changed DNA, **Figure 1**). When this happens with influenza viruses, pandemics might result. RNA viruses often exist as quasi-species or swarms of viruses of the same species but with slightly different genome nucleoside sequences (as seen in HIV). Such quasi-species are a prime target for natural selection.

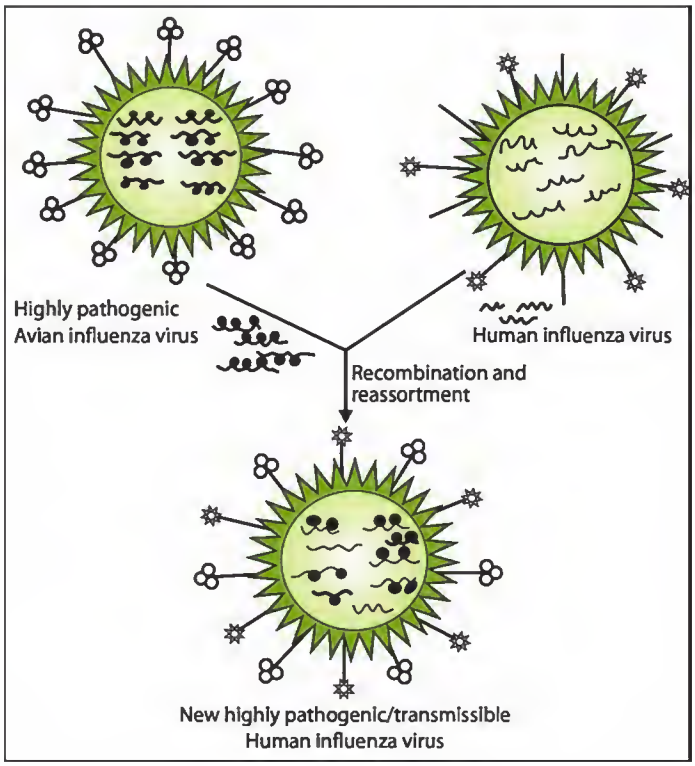


Figure 1: Recombination and reassortment resulting in a new strain (human avian influenza virus).

VIRAL REPLICATION

Viruses are acellular and they use the host cell machinery and metabolism to produce multiple copies of themselves, *assemble* in the cell and get out either by budding or after lysis of the host cell. The life cycle of different viruses varies to some extent. The basic stages in replication are the same for all viruses as shown in **Figures 2 and 3**.

- *Attachment/adsorption* is a specific binding between viral capsid proteins and specific receptors on the host cellular surface. For example, HIV infects only human T cells, because its surface protein, gp120, can interact with CD4, and receptors on the T cell's surface. Attachment to the receptor can induce the viral-envelope protein to undergo conformational changes that results in the fusion of viral and cellular membranes.

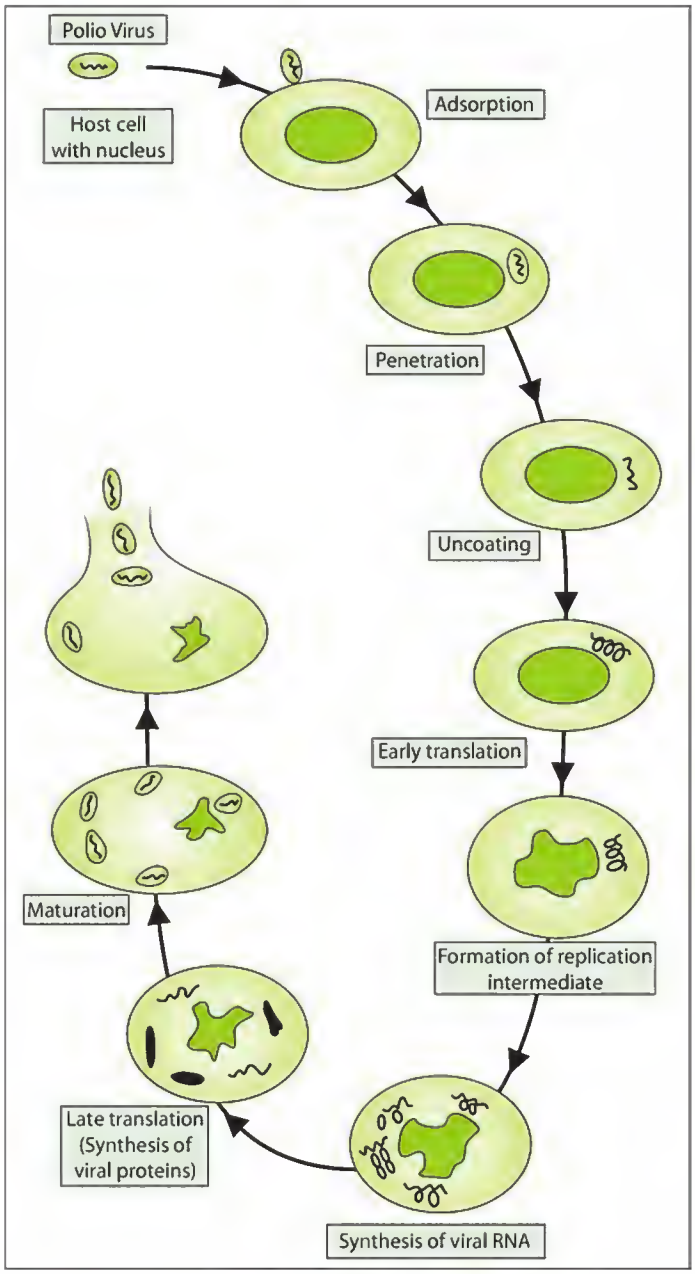


Figure 2: Virus replication cycle-RNA virus (Polio-virus) diagrammatic representation.

- *Fusion and entry into the host cell* follows attachment: viruses enter the host cell through receptor mediated endocytosis or membrane fusion. Some viruses have evolved mechanisms that inject their genome into the bacterial cell while the viral capsid remains outside (as in bacteriophages).
- *Uncoating* is a process in which the viral capsid is degraded by viral enzymes or host enzymes, thus, releasing the viral genomic nucleic acid.
- *Replication* involves synthesis of viral messenger RNA (mRNA) for viruses except positive sense RNA viruses, viral protein synthesis and assembly of viral proteins and viral genome replication.
- *Assembly* of the virus particles: post-translational modification of the viral proteins often occurs. In viruses such as HIV, this modification (sometimes called maturation) occurs *after* the virus has been released from the host cell.
- *Release* from the host cell by lysis: A process that kills the cell by bursting its membrane. Enveloped viruses (e.g. HIV) typically are released from the host cell by budding. During this process the virus acquires its envelope, which is a modified piece of the host's plasma membrane.

Most DNA viruses replicate in the cell's nucleus after entry and are entirely dependent on the host cell's DNA and RNA synthesising machinery, and RNA processing machinery.

RNA viruses carry their genetic information encoded in RNA. Replication usually takes place in the cytoplasm. RNA viruses use their own RNA replicase enzymes to create copies of their genomes.

Reverse transcribing viruses replicate using reverse transcription, which is the formation of DNA from an RNA template. Reverse transcribing viruses containing RNA genomes use a DNA intermediate to replicate (HIV), whereas those containing DNA genomes use an RNA intermediate during genome replication. Retroviruses often integrate the DNA produced by reverse transcription into the host genome. They are susceptible to antiviral drugs that inhibit the reverse transcriptase enzyme, e.g. zidovudine and lamivudine.

CLASSIFICATION

Viruses are classified on the basis of the type of nucleic acid, presence or absence of the envelope, type of structure (as described above), site of replication, etc.

On the basis of nucleic acid viruses are classified into DNA viruses and RNA viruses. DNA viruses further can be those which are ssDNA viruses and dsDNA viruses. RNA viruses are +ssRNA viruses and – ssRNA viruses. On the basis of presence or absence of envelope, viruses can be enveloped or naked (non-enveloped), respectively. On the basis of structure viruses can be icosahedral (cubical), helical or complex. Viruses can replicate in host cell nucleus or cytoplasm and some can replicate in both.

PATHOGENESIS OF VIRAL DISEASES

Viruses produce disease by different mechanisms in the host. The degree of virulence, that is the ability to cause disease and severity of diseases, produced largely depends on the viral species. Mechanisms at the cellular level primarily include cell lysis caused by replication of virus either in the cytoplasm or the nucleus. The virus release subsequent to replication is either by breaking open of cell wall or punching holes in cell wall due to budding and release of virus and subsequent death of the cell. When there is viraemia and large number of cells in different organs are involved, the disease symptoms manifest. Although viruses cause disruption of healthy homeostasis, resulting in disease, sometimes they may exist relatively harmlessly within a host. An example, would include the ability of the herpes simplex virus, which causes cold sores, to remain in a dormant state within the human body. This is called latency and is a characteristic of all herpes viruses including the Epstein-Barr virus, which causes glandular fever, and the Varicella zoster virus, which causes chickenpox. Some viruses like HIV, HBV and HCV cause chronic, lifelong infections.

HOST DEFENCE MECHANISMS

The first line of defense against viruses is the innate immune system. It comprises cells and other mechanisms that defend

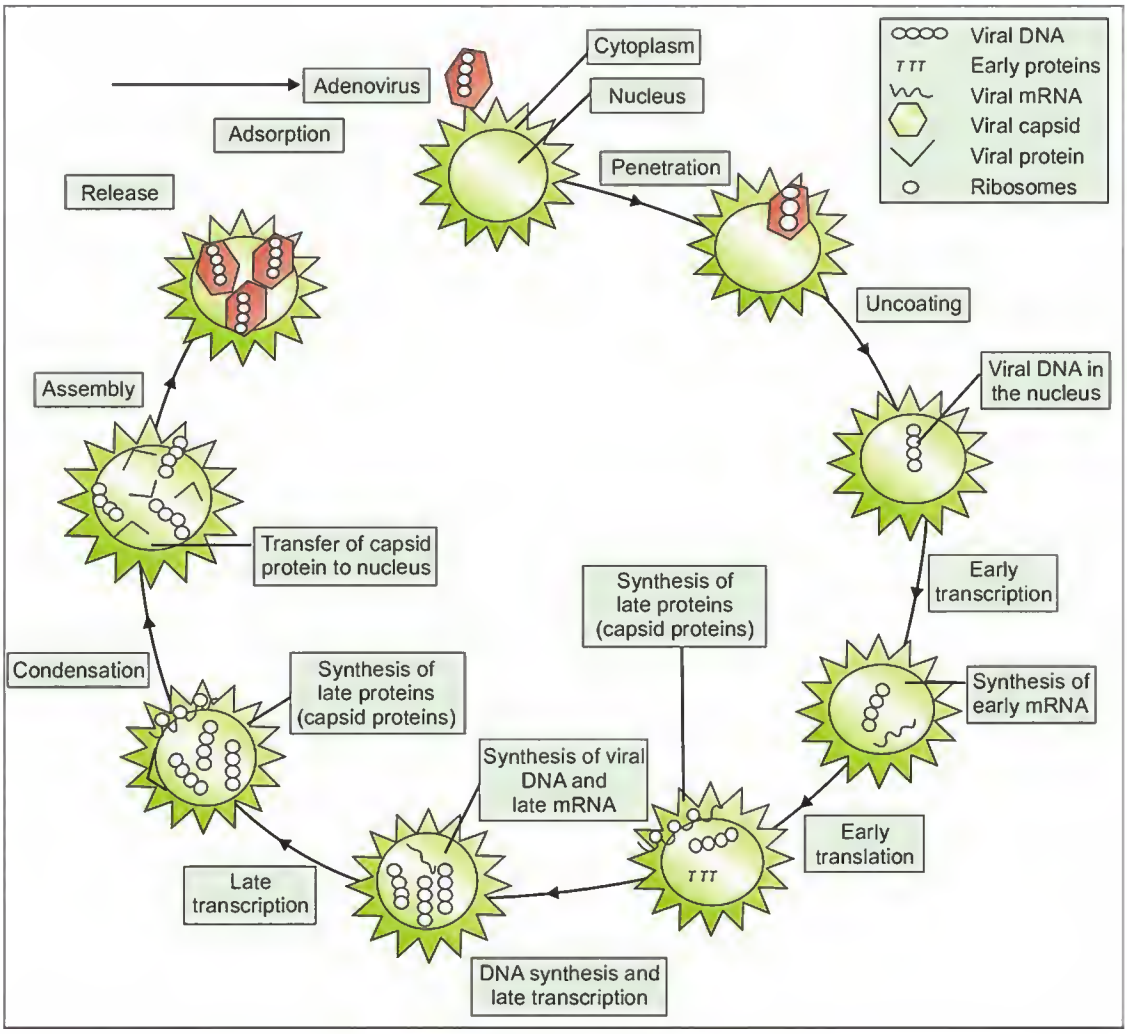


Figure 3: Virus replication cycle-DNA virus.

the host from infection in a non-specific manner. However, it does not confer long-lasting or protective immunity to the host.

RNA interference is an important innate defense against viruses. Many viruses have a replication strategy that involves double-stranded RNA (dsRNA). When such a virus infects a cell, it releases its RNA molecule or molecules, which immediately bind to a protein complex called dicer that cuts the RNA into smaller pieces. A biochemical pathway called the RNA-induced silencing complex (RISC) complex is activated, which degrades the viral mRNA and the cell survives the infection.

When the adaptive immune system encounters a virus, it produces specific antibodies that bind to the virus and render it non-infectious. This is called humoral immunity. Two types of antibodies are important. The first called IgM is highly effective at neutralising viruses but is only produced by the cells of the immune system for a few weeks. The second, called IgG, is produced indefinitely. The presence of IgM in the blood of the host is used to test for acute infection, whereas IgG indicates an infection sometime in the past. IgG antibody is measured when tests for immunity are carried out.

A second defense against viruses is called cell-mediated immunity and involves immune cells known as T cells. The body's cells constantly display short fragments of their proteins on the cell's surface, and if a T cell recognises a suspicious viral fragment there, the host cell is destroyed by killer T cells and the virus-specific T-cells proliferate. Cells such as the macrophage are specialists at this antigen presentation. The production of interferon is an important host defense mechanism. This is a hormone produced by the body when viruses are present. Its role in immunity is complex, but it eventually stops the viruses from reproducing by killing the infected cell and its close neighbours.

The immune response is not always protective. HIV evades the immune system by constantly changing the amino acid sequence of the proteins on the surface of the virion. These persistent viruses evade immune control by sequestration, blockade of antigen presentation, cytokine resistance, evasion of natural killer cell activities, escape from apoptosis, and antigenic shift. Neurotropic viruses are disseminated by neural spread where the immune system may be unable to reach them.

COMMON DISEASES PRODUCED BY VIRUSES IN HUMANS

Viruses produce a wide spectrum of diseases in humans ranging from mild infections like common colds, influenza, chickenpox and cold sores to many serious diseases, such as Ebola virus fever, Lhasa fever, AIDS, Avian influenza (H5N1), Swine influenza (H1N1) hepatits and severe acute respiratory syndrome (SARS) to malignancies like cervical cancers (human Papilloma virus) and leukaemias (HTLV I and HTLV II), etc.

Some viruses can cause life-long or chronic infections, where the viruses continue to replicate in the body despite the host's defense mechanisms. This is common in HIV, hepatitis B virus and hepatitis C virus infections. People chronically infected are known as carriers, as they serve as reservoirs of infectious virus. In contrast to acute lytic viral infections this persistence implies compatible interactions with the human host. Some viruses produce acute infection followed by long latency and recurrences time and again (HSV 1 and HSV 2). Viruses that infect the humans are listed in the **Table 1**.

SYMPTOMS OF VIRAL DISEASES

Symptoms of viral infection vary depending on the type of viral infection, the area of the body that is infected, the age and health history of the patient and other factors. The symptoms of viral infection can also resemble symptoms of other diseases, such as bacterial infections.

Symptoms may affect almost any area of the body or body system and include fever, chills, headache, stiff neck, irritability, enlarged glands, diarrhoea, nausea, vomiting, rash, abdominal pain, sore throat, ear pain, cough, weight loss, fatigue, body aches, and other flu-like symptoms.

In infants, signs of viral infection can include excessive crying, excessive sleepiness, difficulty with feeding, and a bulging of the soft spot on the top of the head.

Many viral infections, such as upper respiratory infection and seasonal influenza, are self limiting. People who are generally healthy are often able to survive these infections without developing serious complications. However, even young and healthy people may develop serious complications to some viral infections. For example, women infected with certain strains of human papillomavirus (HPV) are at risk for developing cervical cancer.

Certain risk factors make it more likely that a person will develop serious, even lethal, complications from a viral infection. People who are generally at risk for developing complications include those who have a compromised immune system due to such diseases as HIV/AIDS or combined immunodeficiencies. People who take certain medications, such as corticosteroids, which suppress the body's natural immune response, are also at risk. Other risk factors include malnutrition, high stress levels and being very young or very old.

Complications of a viral infection can include a secondary bacterial infection, pneumonia, dehydration, shock, the development of some forms of cancer and coma.

The viral infection HIV leads to the critical and eventually fatal complication of AIDS in all people who contract the infection in absence of anti-retroviral treatment (ART).

TREATMENT

Viruses are obligate intra-cellular parasites, so the anti-viral drugs which are going to kill the virus will also damage the host cell, thus limiting the benefits of treatment. The development of new, effective anti-viral drugs is limited due to the requirement that the agent should selectively stop viral replication and not affect the host cell functions. This is not possible to achieve all the time. So, the repertoire of anti-viral agents, available currently is limited. Anti-viral drugs are not available for all the human viral infections. Another problem is that by the time the viral infection is diagnosed the virus has already seeded most organs, caused the damage so drug treatment is not effective. Due to rapid replication of viruses and genetic diversity the viruses become resistant to available agents as seen in cases of anti-retroviral treatment of HIV/AIDS cases.

However, antiviral drugs that selectively interfere with viral replication have been and are used for treatment of cases and are used as chemoprophylaxis during outbreaks of viral diseases.

Treatment of viral illnesses varies greatly depending upon the infecting virus and the underlying health status of the patient.

Treatment

- Symptomatic management—many viral infections require only treatment of their symptoms and will self-resolve.
- Supportive care—some patients may require hospitalisation and care such as IV fluids and oxygen, especially the very young and the elderly.
- Anti-viral therapy—indicated in some viral illness, such as herpes zoster, H1N1 influenza and HIV.

Most children with viral infections get better without treatment but some of the measures taken include:

- Anti-viral drugs
- Palliative treatment

PREVENTION (VIRAL VACCINES)

Prevention of viral infections is the most effective medical approach to control viral diseases. Vaccinations provide immunity to infection, and are used under the universal immunisation programme of the country. Vaccines are administered by different routes—oral, subcutaneous or scarification and/or intra-muscular.

VIRAL VACCINES

There are three basic types of viral vaccines.

Inactivated/Killed Viral Vaccines

The virus is grown in appropriate tissue/culture cell lines and inactivated/killed by various methods (exposure to denaturing agents-heat, formaldehyde, beta-propiolactone) which results in loss of infectivity of virus without loss of antigenicity. Killed vaccines are not available for all the viruses, do not induce mucosal immunity and immunity induced may be for limited period. However, these vaccines are stable and there is no danger of reversion to the virulent form.

Live Viral Vaccines

These vaccines are prepared from live attenuated viruses which have reduced pathogenicity, have retained antigenicity and so provide immune response without causing disease. Such attenuated viruses may be naturally occurring (e.g. Jenner, cowpox, 1776 (variolation) or artificially attenuated (oral poliovirus vaccine). These vaccines are good immunogens and induce long-lived, appropriate immunity. Disadvantage is that these vaccines are unstable: biochemically (live virus) and genetically (reversion to virulence); contamination with other viruses from cell culture can happen and these vaccines have limited use in immunocompromised hosts, and rubella if administered to a pregnant woman may lead to disease in foetus. The yellow fever virus vaccine, a live-attenuated strain called 17D, is probably the safest and most effective vaccine ever generated.

Table 1: Viruses that Infect Humans

Nucleic acid	Capsid symmetry	Enveloped or naked	Physical type-nucleic acid	Virus family
DNA	Icosahedral	Naked	ss	Parvoviridae
			ds circular	Polyomaviridae
			ds circular	Papillomaviridae
			ds	Adenoviridae
		Enveloped	ds circular	Herpesviridae
			ds	Hepadnaviridae
Complex	Complex coats	ds	Poxviridae	
RNA	Icosahedral	Naked	ss	Picornaviridae
			ss	Astroviridae
			ss	Caliciviridae
			ds segmented	Reoviridae
		Enveloped	ss	Togaviridae
	Unknown or complex	Enveloped	ss	Flaviviridae
			ss segmented	Arenaviridae
			ss	Coronaviridae
			ss diploid	Retroviridae
	Helical	Enveloped	ss segmented	Orthomyxoviridae
			ss segmented	Bunyaviridae
			ss	Bornaviridae
			ss	Rhabdoviridae
			ss	Paramyxoviridae
			ss	Filoviridae

Live vaccines can be dangerous when given to people with a weak immunity, (immunocompromised), because in these people, the weakened virus can cause the original disease.

Sub Unit Vaccines

These are newer vaccines; are completely safe, except for rare adverse reactions. Problem is the relatively poor antigenicity (especially short peptides). Biotechnology and genetic engineering techniques are used to produce subunit vaccines. These vaccines use only the capsid proteins of the virus. Hepatitis B vaccine is an example of this type of vaccine. Subunit vaccines are safe for immunocompromised patients because they cannot cause the disease. These can be *synthetic vaccines, recombinant vaccines* (HBV produced in yeast), *Virus Vectors* which carry genes coding for the viral antigens which induce immune response (vaccinia virus-HIV genes).

Use of viral vaccines has resulted in a dramatic decline in morbidity (illness) and mortality (death) associated with viral infections, such as polio, measles, mumps, rubella, HBV, influenza. Smallpox infections have been eradicated through successful immunisation.

Human anti-viral vaccines currently in use include Hepatitis A, Hepatitis B, influenza, Japanese B encephalitis, measles, mumps, rubella (MMR), poliovirus, rabies, smallpox, varicella-zoster, yellow fever, HPV and tick-borne encephalitis.

Problems Faced with Viral Vaccines

- Complications after immunisation can occur in rare cases. These include sensitisation to proteins present in the vaccine, reversion back to virulent form and disease (e.g. polio).
- Attenuated vaccines preferably should not be given to pregnant or immunocompromised.
- Developing effective vaccines to some viruses is proving very difficult, e.g. influenza, common cold viruses, HIV-1, herpes, papilloma and more. Common problems include the existence of many serotypes, antigenic drift and shift.

Success Stories

Smallpox

WHO declared smallpox *'Eradicated'* from the world in 1980. Next targets for eradication are polio and measles through immunisation.

Polio: can it be eliminated by vaccination?

Intensified *Pulse Polio* Programme started in India in 1994 officially, but it was spread throughout the country in 1995 with the main aim of eradicating polio by 2000 AD by vaccinating annually all children under age five against poliovirus. According to it there is no need of giving oral polio vaccine to the children after 2000 AD. The campaign had limited success and the incidence of poliomyelitis in India has decreased dramatically: India recorded 4,791 cases of polio in 1994; 2,489 in 1997; 1,600 in 2002; 225 in 2003; and 135 in 2004. But this was not completely successful and so the programme was extended up to 2005 with a vision of declaring India a polio free state by 2005. But this also failed. According to National Plan of Action 2005 developed by Department of Women and Child Development 2007 the objective under child survival was to certify by 2007 the eradication of polio, which is not possible under present conditions with almost 1000 cases of polio being reported from different states of India. Now it is 2011, the Pulse Polio programme is still on and maybe this will be another success story in a couple of years.

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17.39 Herpes Virus Infections

Aditya Prakash Misra

INTRODUCTION

Herpes has been known for at least 2000 years. Emperor Tiberius banned kissing in Rome for a time due to so many people having cold sores. In 16th century Romeo and Juliet, it is mentioned that there are blisters over ladies lips.

Exact data from the Indian population are not known, but its incidence is rapidly increasing over last four decades. In the United States 16.2% of people, aged 14 to 49 years have genital herpes simplex virus-2 (HSV-2) infection. Many people infected with HSV-2 display no physical symptoms and are described as asymptomatic or having sub-clinical herpes.

Herpes virus infections primarily include infections caused by HSV-1 and HSV-2, these viruses are also known as human herpes virus 1 and 2 (HHV-1 and HHV-2). These viruses belong to the family of *herpesviridae*. Both HSV-1 and HSV-2 are ubiquitous and contagious. They can spread when an infected person is producing and shedding the virus by inoculation, kissing and sexual intercourse.

VIRUS AND TRANSMISSION

Virus consists of a large double stranded, linear deoxyribonucleic acid (DNA) genome, encased within an icosahedral protein cage called capsid, which is wrapped in a lipid bilayer called the envelope. This complete particle is known as the virion. Both HSV-1 and HSV-2 contain at least 74 genes or open reading frames (ORF). These viruses contain two unique regions called the long unique region (UL) and the short unique region (US).

Entry of HSV into the host cell involves interaction of several glycoproteins on the surface of the enveloped virus, with receptors on the surface of the host cell. After binding the virus fuses with the host cell membrane and creates an opening or pore through which the virus enters the host cell. From the cellular cytoplasm, viral capsid enters the cell nucleus by creating a nuclear entry pore. HSV evades the immune system through interference with MHC class I presentation of antigen on the cell surface.

HSV-1 and HSV-2 are transmitted both horizontally and vertically. Horizontal transmission occurs during close contact with an infected person who is shedding virus from the skin, often in saliva or in secretion from the genitals. Transmission is most likely when sores are present, through viral shedding and transmission can occur in the absence of visible sores and most HSV-2 infection results from asymptomatic shedding. HSV-2 is primarily a sexually transmitted disease whereas HSV-1 is usually acquired orally during childhood. Both viruses may be transmitted from mother-to-child before or during child birth. The risk of the infection is highest if the mother becomes infected at around the time of delivery (transmission risk 30% to 60%); the risk fall to 3% if it is a recurrent infection and is less than 1% if there are no visible lesions.

As with most sexually transmitted disease (STD), women are more susceptible to acquiring genital HSV-2 than man. Risk of transmission of infection without the use of anti-virals or condoms from infected male to female is approximately 8% to 10%. Risk of transmission of infection from infected female to male is approximately 4% to 5% annually.

Following a primary infection, the virus enters the nerve at the site of primary infection, migrates to the cell body of the neuron and becomes latent in ganglion. As a result of primary infection, body produces antibodies to the particular type of HSV involved, preventing a subsequent infection of that type at a different site, for example, if a patient gets HSV-1 oral infection, then after recovery, he would not get additional HSV-1 infections, e.g. whitlow, genital herpes and keratitis. Prior HSV-1 seroconversion seems to reduce the symptoms of a later HSV-2 infection although HSV-2 can still be contracted. There are some indications that a prior HSV-2 infection confers partial immunity against subsequent HSV-1 infection.

CLINICAL FEATURES

HSV infections cause several distinct medical disorders. Most common is muco-cutaneous infection which may affect the face and mouth (orofacial herpes, **Figure 1**), genitalia (genital herpes, **Figure 2**) or hands (herpes whitlow). More serious disorders occur when the virus infect and damages the eye (herpes keratitis), on invades the central nervous system (CNS), damaging the brain (herpes encephalitis). It may also affect the newborn (neonatal herpes) which is a life-threatening condition.



Figure 1: Herpes labialis—vesicular eruption at angles of mouth.

After initial or primary infection some infected people experience sporadic episodes of viral reactivation or outbreaks. In an outbreak, the virus in a nerve cell becomes active and is transported via the nerve's axon to the skin, where virus replication and shedding occurs and causes new sores.



Figure 2: Herpes genitalis (on penis).

Mucocutaneous Infections

Lesions may appear anywhere on the skin or mucosa, but are most frequent around or in the mouth or on the lips, conjunctiva, cornea, and genitalia. After a prodromal period of tangling discomfort or itching, the clusters of small, tense vesicles appear on an erythematous base. Clusters vary in size from 0.5 to1.5 cm but may coalesce. Lesions on nose, ears, eyes, fingers or genitalia may be particularly painful. Vesicles typically persist for a few days, then rupture and dry forming a thin yellowish crust. Healing generally occur 8 to 12 days after the onset. Lesions usually heel completely but recurrent lesions at the same site may cause atrophy and scarring. Skin lesions can develop secondary bacterial infection. Localised infections can disseminate in immunocompromised patients.

Herpes Labialis

It usually occurs as a secondary outbreak of HSV. It develops as ulcers (cold sores) on the vermilion border of the lip.

Acute Herpetic Gingivostomatitis

This usually results from primary infection with HSV-1, typically in children. Occasionally through oral-genital contact, the HSV-2 can also lead to gingivostomatitis. Intra-oral and gingival vesicles rupture, usually within several hours to 1 or 2 days. Fever and pain are often present, at times there may be difficultly in eating and drinking.

Herpetic Whitlow

It is a painful swollen lesion of the distal phalanx of finger or thumb. It results from inoculation of HSV through the skin and is most common among health care workers. Occasionally infection occurs on the toes or on the nail cuticle.

Herpes Gladiatorum

Individuals that participate in contact sports, such as wrestling, rugby, or soccer, sometimes acquire this condition caused by HSV-1. It presents as skin ulceration on face, ears and neck, accompanied by fever, headache, sore throat and swollen glands. It occasionally affects the eyes or eyelids.

Herpetic Keratoconjunctivitis

Primary infection typically presents as swelling of the conjunctiva and eyelids (blepharoconjunctivitis). Infection of the corneal epithelium causes pain, tears, photophobia and corneal ulcers, that often have a branching pattern.

Genital Herpes

Genital herpes is the most common ulcerative STD in the developed countries. It is usually caused by HSV-2 although 10% to 30% of cases involve HSV-1. Genital HSV-2 is more common in women. In US approximately 1 of 5 women aged 14 to 49 years and about 1 of 9 men to 14 to 49 years suffer from genital herpes. Primary lesions develop within 4 to 7 days after contact. The vesicles usually erode to form ulcer that may coalesce. Lesions may occur on prepuce, glans penis and penile shafts in men and on the labia, clitoris, vagina, perineum and cervix in women. These may occur around the anus and in the rectum in men or women who engage in receptive anal intercourse. Genital HSV infection may cause urinary hesitancy, dysuria, urinary infection in counterparts. In some cases severe sacral neuralgia may occur. Scarring may follow healing and re-currences occur in 80% with HSV-2 and in 50% with HSV-1 cases. Primary genital lesions are usually more painful, prolonged and widespread and are more likely to be bilateral and involve regional lymphadenopathy and constitutional symptoms than recurrent genital lesions. Recurrent lesions may have severe prodromal symptoms and may involve the buttocks, groin or thigh. Some individuals with HSV-2 infection never have sores, or they may have very mild sign that they do not even notice. People diagnosed with a first episode of genital herpes can expect to have several (typically four or five) symptomatic recurrences within a year. Over the time these recurrences usually decrease in frequency. It is possible that a person becomes aware of the first episode years after the infection is acquired.

HSV Encephalitis

It is the commonest form of sporadic viral encephalitis. Cases are seen throughout the year and the age distribution is biphasic with peaks at 5 to 30 years and above 50 years of age. HSV-1 causes more than 95% of cases of HSV encephalitis. The pathogenesis of HSV encephalitis varies. In children and young adults, the primary HSV infection may result in encephalitis, presumably exogenously. Acquired virus enters the CNS by neurotropic spread from the periphery via olfactory bulb. However, most adults with HSV encephalitis have clinical or serological evidence of HSV-1 infection prior to the onset of CNS symptoms. Reactivation of the latent HSV-1 infection may be another mechanism for the development of HSV encephalitis.

Patient may present with headache, seizures, confusion, stupor or coma. In some patients these manifestations are preceded by symptoms and finding that betray the propensity of this disease to involve inferomedial portion of the frontal and temporal lobes. Late manifestations include olfactory or gustatory hallucinations, anosmia, temporal lobe seizures, aphasia, hemiparesis and abnormalities in behaviour. Rarely an affliction of memory may be present, but this becomes evident only later in the convalescent states of illness, as the patient awakens from stupor or coma. Swelling and herniation of one or both temporal lobes through tentorium may occur, leading to deep coma and respiratory arrest during the first three days. Early diagnosis and treatment can limit the sequlae. Even on the slightest suspicion one should start anti-HSV therapy, since this is the only encephalitis which is treatable.

Herpes Viral Meningitis

HSV-2 is the most common cause of Mollaret's meningitis, a type of recurrent viral meningitis.

Besides the above-mentioned disorders, HSV has been associated with various neuronal disorders, like Bell's palsy and Alzheimer's disease. The presence of HSV-1/DNA in saliva at a higher frequency in patients with Bell's palsy relative to those without the condition, has supported that reactivation of latent HSV-1 inside the geniculate ganglia may cause it. In the presence of certain gene variation (APOE-epsilon 4 carriers), HSV-1 increases one's risk of developing Alzheimer's disease.

DIAGNOSIS

Diagnosis is clinical, based on the characteristic lesions. Laboratory confirmation can be helpful, especially if infection is severe, the patient is immunocompromised, pregnant or if the lesions are atypical. It is important to determine whether the genital herpes infection is caused by HSV-1 or HSV-2 as the prognosis and treatment may differ. Virologic and serologic tests can be used to confirm herpes infection.

Virologic Tests

Viral culture tests are made by taking a fluid sample or culture from the lesions as early as possible, ideally within three days. Usually it takes 1 to 10 days, but in severe infection it may yield result in 24 hours. Viral culture is very accurate if the lesions are in early stage but not for older ulcerated sores, recurrent lesions or latency. Polymerase chain reaction (PCR) tests are much more accurate than viral culture but more expensive. Center for Disease Control and Prevention of United States (CDC) recommends PCR for detecting herpes in cerebrospinal fluids for diagnosing HSV encephalitis. An older test, Tzanck smear test using scrapping from the lesion is quick but accurate only in 50% to 70% of the cases. It cannot distinguish between virus types or between herpes simplex and herpes zoster and is not recommended.

Serologic Tests

Serologic tests can identify antibodies that are specific to the virus and its type. These tests are most accurate when done 12 to 16 weeks after exposure. Newer 'type-specific' arrays test for antibodies to two different proteins, associated with herpes virus. Glycoproteins gG-1 is associated with HSV-1, and glycoprotein gG-2 is associated with HSV-2. Various recommended tests include:

1. Herpe-Select: Includes enzyme-linked immunosorbent assay on immunoblot, results take larger time.
2. Biokit HSV-2: Detects only HSV-2, less expensive, results are provided in less than 10 minutes.
3. Western-Blot: This is gold standard, expensive and not widely available.

Serologic tests are recommended for patients with recurrent genital symptoms but negative viral cultures, confirming infection in genital herpes, to determine whether partner of someone diagnosed with genital herpes has acquired infection and people who have multiple sex partners. Serologic tests are not recommended for screening of HSV-1 or HSV-2 in general population.

Electroencephalography (EEG), computed tomography and magnetic resonance imaging may be useful in diagnosing.

TREATMENT

There is no medical cure that can eradicate HSV from body, but antiviral medication can reduce the frequency, duration and severity of the outbreaks. Antiviral drugs work by interfering with viral replication. They effectively slow the replication rate of virus and provide a greater opportunity for immune system to intervene. Various antivirals for controlling HSV are: acyclovir, valacyclovir, famciclovir and penciclovir (**Table 1**).

Acyclovir is the only approved drug for use during last trimester of pregnancy. Some reports suggest that famciclovir, when used during first herpes episode, reduces further outbreak by 5-fold as compared to acyclovir.

Topical treatment using docosanol has not shown any proven benefits, though it is sold as over the counter product in USA and Canada.

The virulite (1072 nm wavelength light) has proven to be effective against the cold sores and also reduces the outbreaks.

PREVENTION

Condoms offer moderate protection against HSV-2 in both man and women. Condom does not prevent skin or bodily fluid contact with scrotum, anus, buttocks, upper thighs or area immediately surrounding the penis, all of which are susceptible for transmission of virus. Wearing undergarments such as boxer shorts along with condoms should offer added protection. Long-term mutually monogamous relationship with a partner who has been tested and found to be uninfected can prevent genital HSV-2 to a greater extent. Persons with herpes should abstain from sexual activity with uninfected partners.

National Institutes of Health (NIH) in United States are conducting phase 3 trials of Herpevac, a vaccine against HSV-2.

Table 1: Treatment Strategies for HSV Presentations

Clinical Presentation	Drug Therapy
Keratitis	Topical idoxuridine or trifluridine Antibiotics if superinfection
Gingivostomatitis	Topical anaesthetics – 0.5% Benzocaine* – 5% Lidocaine as mouth rinse in large areas Severe cases oral: acyclovir valacyclovir, famciclovir
Herpes labialis	Topical acyclovir 1% q 2 hourly for 4 days Oral acyclovir 200 mg 5 times a day Famciclovir 1500 mg single dose Valacyclovir 2 g q 12 hourly for 1 day
Genital herpes	Acyclovir** 200 mg 5 times a day for 10 days Valacyclovir 1g q12 hourly for 10 days Famciclovir 250 mg q 8 hourly for 7 to 10 days
Recurrence	Acyclovir 200 mg q 4 hourly for 5 days Valacyclovir 500 mg q 12 hourly for 3 days Famciclovir 1 g q 12 hourly for 1 day
Herpes encephalitis/ meningitis	Acyclovir 10 mg/Kg IV q 8 hourly for 21 days
Neonatal herpes simplex	Acyclovir 20 mg/Kg IV q 8 hourly for 14 to 21 days

**Must not be swallowed as anaesthetises oropharynx, hypopharynx, etc. especially in children.*

***Doses should be adjusted in renal insufficiency.*

RECOMMENDED READING

1. US Centre for Disease Control official website www.CDC.gov.HSV

17.40 Human Papilloma Virus and Parvovirus Infections

Neerja Bhatla, Biswa B Dash

HUMAN PAPILLOMA VIRUS INFECTION

Introduction

Human papillomavirus (HPV) is a double stranded DNA virus that belongs to the family *Papovaviridae* and causes asymptomatic slow growing epithelial proliferation of skin and mucosa. Clinically three types of HPV are described based on the similarities of the genomic sequences: anogenital and/or mucosal, nongenital cutaneous and epidermodysplasia verruciformis (EV).

Epidemiology of HPV Disease

Warts occur at any age and in both sexes. An incidence of 10% has been estimated for children and young adults. It is low in early childhood, peaks between 12 and 16 years of age, then declines sharply by the age of 20. Warts are contagious. Impairment of cell mediated immunity increases the susceptibility to HPV infection. Anogenital warts have shown increased incidence in recent years and are regarded as a sexually transmitted condition. They are uncommon in children and when seen may be sexually transmitted as a consequence of sexual abuse.

Cervical cancer is the most important public health problem caused by HPV with a huge disease burden. It is the second most common cancer among women worldwide and the commonest cancer among women in India. Factors that increase the risk of progression include early age at sexual debut, multiple partners of self or partner, multiparity, smoking, prolonged oral contraceptive use, infection with other sexually transmitted diseases (STDs) such as herpes simplex, *Chlamydia* or gonorrhoea, poor nutrition and hygiene.

Aetiological Agent

The papillomavirus is a small 52 to 55 nm diameter DNA virus. Papillomaviruses are highly host and species-specific; thus HPV only infects humans. The virus lacks an envelope and its replication depends on differentiation of the epidermis. It is resistant to inactivation, freezing or desiccation. Till date more than 100 types of HPV have been detected and the genomes of more than 80 types have been completely sequenced.

Mode of Transmission

Transmission of HPV to uninfected persons occurs by close contact with infected individuals. Desquamated keratinocytes may also transmit the virus. In fully keratinised skin, a breach in the epithelial barrier function by trauma, maceration or both increase the predisposition to inoculation of virus. When these basal cells divide the viral genome is also replicated and transported within the daughter cells as they migrate upwards to form the differentiating epithelium. The greatest concentration of the virus is found in the granular layer. Warts are often distributed on hands, feet and knees. Plantar warts are acquired from swimming pool and hand warts spread widely around and beneath the nail in those who bite the nails. Autoinoculation results in local spread of warts.

Genital warts have high infectivity. The thinner mucosal surface is more susceptible to inoculation of virus than is thicker keratinised skin. Anogenital HPV infection is an STD. Females with multiple sexual partners or a single male partner who in turn has multiple female partners are more prone to genital HPV infection and genital cancers (cervical, vaginal and vulvar).

Pathology

The cytological changes of HPV were first recognised by Koss and Durfee in 1956 and given the term 'koilocytosis'. The characteristic histologic feature of viral warts is vacuolisation in cells, in and below the granular layer with basophilic inclusion bodies, composed of viral particles and eosinophilic inclusions representing abnormal keratohyaline granules, with hyperplasia of all layers of epidermis. Koilocytes are more often seen in benign than in malignant infection. Benign giant condylomas may be difficult to differentiate from malignant condylomas and repeated biopsies may be required to reveal malignant transformation. The final diagnosis in the case of cervical lesions rests on histopathology. Cervical intra-epithelial neoplasia (CIN) is divided into three grades. Based on the presence of abnormal cells up to the lower, middle or upper one-third of the epithelium, CIN is graded as CIN 1, 2 or 3. Full thickness abnormality is carcinoma *in situ* and disruption of the basement membrane is invasive cancer.

Clinical Manifestations of HPV Infections

The commonest presentation is benign proliferative lesions of the cutaneous epithelium, referred to as warts, and that of non-keratinising squamous epithelium of the mucosae known as condylomas or papillomas. HPVs have tropism for stratified squamous epithelial cells but vary in their specificity for different anatomical sites. For example HPV-1 replicates heavily in palms and soles, whereas HPV-11 replicates in genital and laryngeal epithelium. **Table 1** outlines characteristics of different types of warts.

The incubation period varies from a few weeks to more than a year in the case of common and plantar warts and from 3 weeks to 8 months in the case of genital warts.

Benign HPV infection can manifest as two types of clinical lesions—cutaneous and extra-cutaneous.

Table 1: Types of Warts, Location and Characteristics

Cutaneous Warts	HPV Types	Characteristics
Common warts (verruca vulgaris)	2, 57, 1 and 4	Can occur anywhere on skin, common on dorsal aspects of hands and fingers and on knees in children. Rough, keratotic firm papules, single/ multiple, discrete/ confluent, 1 mm to 1 cm size (**Figure 1**)
Plantar warts (myrmecia and mosaic)	1, 2, 4 and 57	Sharply defined, rounded lesions with a rough keratotic surface surrounded by smooth collar of thickened horn
Flat warts (verruca plana)	3 and 10	Smooth, flat, slightly elevated, skin colour to greyish brown; round or polygonal; 1 mm to 5 mm in diameter. Face, back of the hands and shins are common sites (**Figure 2**)
Anogenital warts	6 and 11	Classical protuberant type, commonly termed '*Condylomata acuminata*' (**Figures 3 and 4**) and may be confused with '*Condylomata lata*' of syphilis
Butcher's warts	2 and 7	Seen on skin of occupational handlers of meat, poultry or fish following prolonged contact with animal flesh, usually on hands. Lesions are papillomatous and/ or dome-shaped
Extracutaneous (along orificial mucous membranes)	6 and 11	Oral common warts, Oral *Condyloma acuminata*, Nasal and conjunctival papillomas, Laryngeal papillomatosis



Figure 1: Common warts.

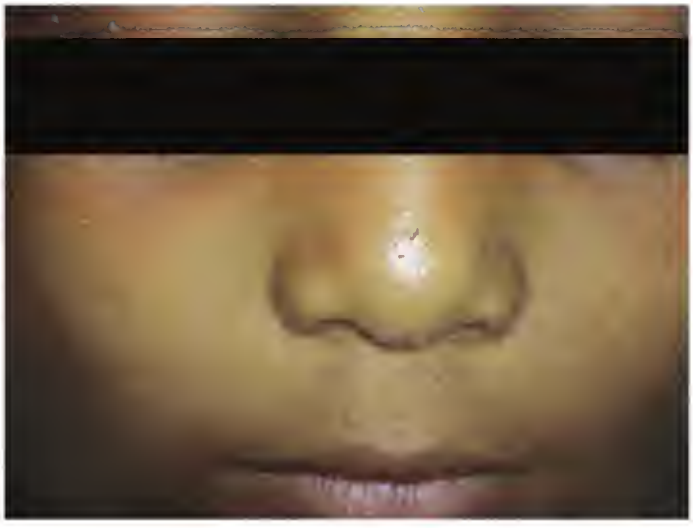


Figure 2: Verruca plana with Koebner's phenomenon.

Cervical Intraepithelial Neoplasia and Cervical Cancer (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58)

Many studies have revealed that 70% of genital HPV infection may be subclinical or latent and, therefore, asymptomatic. The infection goes unnoticed as there are no morphological changes but it can be detected by full clinical examination, cytology and histology. Usually the infection does not persist and clears in 9 to 15 months.

CIN lesions are acetowhite, iodine negative lesions. Benign lesions are usually located away from the squamocolumnar junction, while premalignant and malignant lesions are found abutting the squamocolumnar junction.

Patients with high grade CIN or invasive cancer may complain of vaginal bleeding between periods or after sexual intercourse, postmenopausal bleeding, persistent foul smelling vaginal discharge, dyspareunia and fullness in the pelvis. Speculum examination may reveal a frank cauliflower or ulcerative growth that is necrotic and bleeds on touch, easily detectable with the naked eye.

HPV Infection in Immunocompromised Patients

The lesions are refractory to treatment, persist and may undergo malignant transformation with development of squamous cell



Figure 3: Condyloma acuminata on penis.



Figure 4: Condyloma acuminata on labia.

carcinoma. The transition time to invasive cancer is typically shorter in these cases.

Diagnosis

Clinical diagnosis of warts is often sufficient; but atypical subclinical dysplastic lesions may need laboratory confirmation of HPV infection. Various diagnostic methods include histology, detection of viral particles by electron microscopy, immunohistochemistry, DNA hybridisation on tissue extracts and polymerase chain reaction (PCR). For routine clinical use, the vinegar test, application of 5% acetic acid may suffice to identify genital lesions.

Cervical and vaginal infections are detected on *Papanicolaou* smear and are broadly speaking reported as either normal, inflammatory smear, low-grade squamous intra-epithelial lesion or high-grade squamous intra-epithelial lesion according to the Bethesda classification. Pap smear has an overall sensitivity of only about 50% but has the advantage of high specificity of about 95%. Further examination after application of 3% to 5% acetic acid and colposcopy show characteristic acetowhite changes and abnormal blood vessel patterns indicative of HPV-triggered dysplasia. However, final diagnosis is based on histopathology. Obvious lesions can be biopsied with a punch biopsy forceps. Otherwise a colposcope is used to visualise the cervix under magnification and take a directed biopsy.

HPV DNA testing is a more sensitive method of cervical cancer screening than cytology. It is postulated that a negative HPV test can offer protection against CIN2+ for 5 to 8 years. The newer liquid based cytology has the same accuracy in detecting cervical cytology abnormality as the conventional Pap but has the additional advantage that HPV testing and typing can be done from the same sample. HPV DNA detection from the sample is possible by various methods such as hybrid capture method, PCR, etc. In the future, affordable HPV tests like *care*HPV™ may change the paradigm of cervical cancer screening.

Treatment

Warts can be expected to resolve spontaneously. Treatment failures and recurrences are common. Choice of treatment depends on the location, size, number and type of warts. The most commonly used treatments involve destruction of the infected area of the epidermis using topical preparations or surgical modalities. Other therapies are aimed at modifying the growth of the epidermis or stimulating an immune response.

Topical agents

Strong (40%) salicylic acid plaster or salicylic and lactic acid in a flexible collodion base is very effective in common warts on the hand and plantar warts. 5-Fluorouracil (5-FU) and topical podophyllin resin are common and effective treatments for anogenital warts. Podophyllin is contraindicated in pregnancy. Canthardin is a vesiccant which can be used for periungual warts. Trichloroacetic acid (50%), silver nitrate, formalin (37%) and glutaraldehyde (2%) also can be used.

Imidazoquinoline (5%) cream is especially useful for genital and perianal warts, especially in HIV positive patients. It stimulates peripheral monocytes and macrophages to release interferons and interleukins in HPV-infected cells when applied topically. Cidifovir, an antiviral purine nucleotide, applied topically is extremely effective in plantar, anogenital and laryngeal warts.

Systemic agents

Oral retinoids: Etretinate (1 mg/kg/dL) and acitretin are useful in common warts, epidermodysplasia verruciformis and laryngeal papillomatosis. Systemic interferons (IFN-α) can be tried in genital warts. Bleomycin is a cytostatic drug used intralesionally in plantar verrucae and recalcitrant periungual warts.

Surgical and physical methods

Liquid nitrogen and carbon dioxide ice is effective in various types of warts. Curettage and cautery/electrodessication/electrocoagulation usually in combination may be used for painful, persistent or resistant warts. Use of carbon dioxide laser assures high cure rates in periungual and plantar verrucae. Cryotherapy is a useful method for treatment of low grade CIN also. High grade CIN lesions may require excision with a loop electrosurgical excision procedure. These methods are effective in treating more than 95% of precancerous lesions of the cervix by simple outpatient procedures.

Immunotherapy

Immunotherapy in the form of introduction of allergic contact dermatitis with dinitrochlorobenzene (DNCB) allows localisation of inflammation to warts on which allergen is painted and stimulates local immunity.

Prevention

Secondary prevention has already been discussed.

Primary prevention—vaccination

The prophylactic HPV vaccine could lead to potential reduction in the incidence of HPV related diseases. It contains virus like particles that give immunity against infection with the specific vaccine type, with some degree of cross-protection against related types.

The bivalent vaccine (Cervarix™, GlaxoSmithKline) contains HPV types 16 and 18. It has been shown to have an efficacy of 98% for cervical intra-epithelial neoplasia caused by the vaccine types. There is also evidence of cross-protection against some related types including HPV 31, 33 and 45. The quadrivalent vaccine (Gardasil®, Merck and Co.) contains HPV 6 and 11 in addition to HPV 16 and 18. It gives protection against 99% of cervical intra-epithelial neoplasia and 100% against benign genital warts caused by the vaccine types. Screening for cervical cancer is to be recommended even after vaccination to detect cases caused by other types.

PARVOVIRUS INFECTION

Aetiological Agent

Parvovirus is a linear, non-segmented single-stranded DNA virus, with an average genome size of 5000 nucleotides. Parvoviruses are some of the smallest viruses found in nature. The B19 virus, generally referred to as parvovirus B19 or sometimes erythrovirus B19 was the first known human virus in the family of parvoviruses, genus erythrovirus. Parvovirus infection is a common and highly contagious childhood ailment, sometimes called slapped-cheek disease because of the distinctive face rash that develops. Parvovirus infection also has been known

as fifth disease because, historically, it was one of five common childhood illnesses characterised by a rash.

Epidemiology

A significant increase in the number of cases is seen every 3 to 4 years; the last epidemic year was 1998. Outbreaks can arise especially in nurseries and schools. One infection gives life-long immunity. Parvovirus B19 causes an infection in humans only. Cat and dog parvoviruses do not infect humans. There is no vaccine available for human parvovirus B19. However, there is a vaccine available for parvovirus that infects small mammals.

Transmission

The virus is primarily spread by infected respiratory droplets; blood-borne transmission, however, has been reported. The secondary attack risk for exposed household persons is about 50%, and about half of that for classroom contacts.

Infectivity

Symptoms begin some 6 days after exposure and last about a week. Infected patients with normal immune systems are contagious before becoming symptomatic, but probably not after then. Individuals with B19 IgG antibodies are generally considered immune to recurrent infection, but reinfection is possible in a minority of cases. About half of adults are B19-immune due to a past infection.

Manifestation of the Infection

Fifth disease

Fifth disease or erythema infectiosum is only one of several expressions of parvovirus B19. Any age may be affected, although common in children aged 6 to 10 years.

Patients usually develop the illness after an incubation period of 4 to 14 days. The disease commences with fever and malaise while the virus is most abundant in the bloodstream, and patients are usually no longer infectious once the characteristic rash of this disease has appeared.

Teenagers or young adults tend to develop the so called 'Papular Purpuric Gloves and Socks Syndrome'. Unlike young children, these patients may be infectious with this rash. The 'slapped cheek' appearance typical of fifth disease is erythema across the cheeks and sparing the nasolabial folds, forehead, and mouth. These rashes can last for up to 5 weeks and are worse after sun exposure, exercise, or hot baths.

Arthritis

In adults (and perhaps some children), parvovirus B19 can lead to a sero-negative arthritis which is usually easily controlled with analgesics. Women are approximately twice as likely as men to experience arthritis after parvovirus infection. Possibly up to 15% of all new cases of arthritis are due to parvovirus, and a history of recent contact with a patient and positive serology generally confirms the diagnosis. This arthritis does not progress to other forms of arthritis. Typically joint symptoms last 1 to 3 weeks, but in 10% to 20% of those affected, it may last weeks to months.

Aplastic crisis

Although most patients have an arrest of erythropoiesis [production of red blood cells (RBCs)] during parvovirus infection, it is most dangerous in patients who have sickle cell anaemia or hereditary spherocytosis, and are therefore heavily dependent on erythropoeisis due to the reduced lifespan of the red cells. This is termed 'aplastic crisis' (also called reticulocytopaenia). It is treated with blood transfusion.

Hydrops foetalis

Parvovirus infection in pregnant women is associated with miscarriage and hydrops foetalis sometimes leading to stillbirth. The virus has an affinity for the RBCs precursors in the bone marrow and causes destruction of these cells leading to anaemia. Adult RBCs are not usually affected for which the bilirubin level in the amniotic fluid remains unaffected. Foetal blood sampling (by cordocentesis) is an effective method to evaluate foetal anaemia. Foetal middle cerebral artery peak systolic velocity (MCA-PSV) on ultrasonographic colour Doppler is an indirect method of evaluation of foetal anaemia. The MCA-PSV is usually high (>1.5 MOM) in anaemic foetuses.

The risk of foetal loss is about 10% if infection occurs before pregnancy week 20 (especially between weeks 14-20), but minimal after then. The risk to the foetus will be reduced with correct diagnosis of the anaemia (by ultrasound scans) and treatment (by blood transfusions). There is some evidence that intrauterine parvovirus B19 infection leads to developmental abnormalities in childhood.

AIDS Patients

Parvovirus B19 is a cause of chronic anaemia in individuals who have acquired immunodeficiency syndrome (AIDS). It is frequently overlooked. Treatment with erythropoietin or intravenous immunoglobulin has been helpful in some patients. The parvovirus infection may trigger an inflammatory reaction in AIDS patients who have just begun anti-retroviral therapy.

Diagnosis

In acute phase, the virus can be detected in the serum by electron microscopy or DNA hybridisation and after rash appears specific IgM antibodies to human parvovirus. Foetal infection may be recognised by hydrops foetalis and presence of B19 DNA in amniotic fluid or foetal blood in association with maternal IgM antibodies to B19.

Treatment

Acute parvovirus infection requires no treatment and same is true for arthropathy. Transient aplastic crisis is usually treated with erythrocyte transfusion. Immunodeficient anaemic patients are treated by intravenous immunoglobulin.

RECOMMENDED READINGS

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17.41 Bird Flu and Swine Flu

Sandhya Kamath

Three influenza pandemics have occurred in recent years, each of these being caused by the appearance of a new strain of the influenza virus in human beings. An avian strain named H5N1 caused the 'Bird Flu'. In April 2009, a novel flu strain evolved that combined genes from human, pig, and bird flu, initially dubbed 'swine flu' and also known as 'Influenza A/H1N1' or '2009 H1N1 flu'. WHO officially declared the outbreak to be a pandemic on June 11, 2009. WHO's declaration of a pandemic level 6 was an indication of spread, not severity. The strain actually has a lower mortality rate than common flu outbreaks. On August 10, 2010, WHO declared the H1N1 influenza pandemic to be over, saying worldwide flu activity had returned to typical seasonal pattern.

BIRD FLU

Bird flu is an infection caused by avian influenza viruses. These flu viruses occur naturally among birds. Wild birds worldwide carry the viruses in their intestines, but usually do not get sick from them. However, bird flu is very contagious among birds and serious, fatal infection may occur in domesticated birds, including chickens, ducks, and turkeys.

Bird flu viruses do not usually infect humans, but more than 100 confirmed cases of human infection with bird flu viruses have occurred since 1997.

Epidemics of 'Bird Flu' in India

The first reports of bird flu in India came from the village of Nawapur in the Nandurbar district of Maharashtra on 19 February 2006. Villagers reported a large number of bird deaths in the village. Laboratory analysis proved that the poultry was affected with the H5N1 virus. Avian flu also occurred in July 2007 in Manipur, in the North Eastern part.

On January 11, 2008, unusual mortality of birds was reported from state poultry farm in Dakshin Dinajpur district and in some areas of Birbhum district in West Bengal. In January 2010, once again India reported the return of 'bird flu'. West Bengal's Murshidabad district tested positive for H5N1 infection.

Avian influenza infection (H5N1) in humans was noted in south-east Asia in 2003-2004 in Vietnam, Cambodia, Thailand, Indonesia. The expanding geographic distribution of this infection, with recent outbreaks in Kazakhstan, Mongolia, and Russia, indicates that more human populations are at risk. However, H5N1 case in humans has not been reported from India.

Bird Flu Virus

There are many different subtypes of type A influenza viruses. They do not usually infect humans, even though it now has been seen that they can. There are only three known influenza A virus subtypes of human flu viruses (H1N1, H1N2, and H3N2). Influenza A viruses are constantly mutating, and they might adapt over time to infect and spread among humans.

Influenza A (H5N1) virus—also called H5N1 virus—is influenza A virus subtype that occurs mainly in birds. Like all bird flu viruses, H5N1 virus circulates among birds worldwide, is very contagious among birds, and can be deadly. A variant of the H5N1 virus has been implicated as the causative agent of bird flu in humans. Infected birds shed flu virus in their saliva, nasal secretions, and faeces. Susceptible birds become infected when they have contact with contaminated excretions or surfaces that are contaminated with excretions. It is believed that most cases of bird flu infection in humans have resulted from contact with infected poultry or contaminated surfaces. The spread of avian influenza viruses from one ill person to another has been reported very rarely, and transmission has not been observed to continue beyond one person.

Transmission

The risk from bird flu is generally low to most people because the viruses occur mainly among birds and do not usually infect humans. However, during an outbreak of bird flu among poultry (domesticated chicken, ducks, turkeys), there is a possible risk to people who have contact with infected birds or surfaces that have been contaminated with excretions from infected birds. The recent outbreak of avian influenza A (H5N1) among poultry in Asia and Europe is an example of a bird flu outbreak that has caused human infections and deaths. In such situations, people should avoid contact with infected birds or contaminated surfaces, and should be careful when handling and cooking poultry. In rare instances, limited human-to-human spread of H5N1 virus has occurred, and transmission has not been observed to continue beyond one person.

Because all influenza viruses have the ability to change, scientists are concerned that the H5N1 virus one day could be able to infect humans and spread easily from one person to another. Since these viruses do not commonly infect humans, there is little or no immune protection against them in the human population. If the H5N1 virus were able to infect humans and spread easily from person-to-person, an influenza pandemic (worldwide outbreak of disease) could begin.

Clinical Features of Bird Flu

Symptoms of bird flu in humans range from typical flu-like symptoms (fever, cough, sore throat and muscle aches) to eye infections, pneumonia, severe respiratory diseases (such as acute respiratory distress), and other severe and life-threatening complications. The symptoms of bird flu may depend on which virus caused the infection.

Fever may be high, cough and shortness may develop early in the course of illness. X-ray chest may be non-specific and include diffuse multifocal and patchy infiltrates and segmental or lobular consolidation with air bronchogram. The illness can rapidly progress to ARDS and subsequently respiratory failure within 1 week of onset of symptoms. Mortality is high in such cases.

Laboratory Findings

Laboratory diagnosis depends upon demonstration of the virus and/or rising antibody titre. Available tests include virus culture, RT-PCR, immunofluorescence using monoclonal antibody to H5N1 and ELISA for detection of antibodies.

Treatment

The H5N1 virus currently infecting birds in Asia that has caused human illness and death is resistant to amantadine and rimantadine, two antiviral medications commonly used for influenza. Two other anti-viral medications, oseltamivir and zanamivir, would probably work to treat flu caused by the H5N1 virus. These have fewer side-effects and resistance to these is not common.

SWINE FLU

Influenza A H1N1 virus is a subtype of influenza A virus and was the most common cause of human influenza (flu) in 2009. Some strains of H1N1 are endemic in humans and cause a small fraction of all influenza-like illness and a small fraction of all seasonal influenza. Other strains of H1N1 are endemic in pigs (swine influenza) and in birds (avian influenza).

Transmission

Flu viruses are spread mainly from person to person through coughing or sneezing by people with influenza. Sometimes people may become infected by touching something—such as a surface or object—with flu viruses on it and then touching their face.

Epidemic of 'Swine Flu' in India

The 2009 flu pandemic in India was the outbreak of swine flu. This was the first epidemic attributed to this infection in India. Soon after the outbreak of H1N1 virus in the United States and Mexico in March 2009, the Government of India started screening people coming from the affected countries for swine flu symptoms at airports. The first case of the swine flu in India was found at Hyderabad airport on 13 May 2009, when a man travelling from US to India was found H1N1 positive. Subsequently, more confirmed cases were reported and the rate of transmission of the flu increased in the beginning of August 2009 till November 2009, after which there was a reduction in the number of cases. The 2009 swine flu outbreak in India had affected mostly its main cities.

Symptoms and Signs

The symptoms of H1N1 flu are similar to other influenzas, and include fever, dry cough, running nose, sore throat, headache, muscle pain, joint pain, chills, and fatigue. Diarrhoea, vomiting, and neurological problems have also been reported in some cases.

People at higher risk of serious complications include elderly age group, children less than 5 years of age, children with neurodevelopmental anomalies, pregnant women (especially during the third trimester), and those of any age with underlying medical conditions, such as asthma, diabetes, obesity, heart disease, or those who are immunosuppressed.

Symptoms in Severe Cases

WHO reported that the clinical picture in severe cases is strikingly different from the disease pattern seen during epidemics of seasonal influenza. While people with certain underlying medical conditions are known to be at increased risk, many severe cases occur in previously healthy people. In these patients, predisposing factors that increase the risk of severe illness are not presently understood, though research is under way. In severe cases, patients generally begin to deteriorate around three to five days after the onset of symptoms. Deterioration is rapid, with many patients progressing to respiratory failure within 24 hours. Most patients need immediate ICU admission and respiratory support with mechanical ventilation.

CDC recommends immediate medical attention should be sought if a person experiences any one of the following 'emergency warning signs':

- In adults they include difficulty in breathing or shortness of breath, pain or pressure in the chest or abdomen, sudden dizziness, confusion, severe or persistent vomiting and low temperature.
- In children they include fast breathing or working hard to breathe, bluish skin colour, not drinking enough fluids, not waking up or not interacting, being so irritable that the child does not want to be held, flu-like symptoms that improve but then return with fever and worse cough, fever with a rash, not eating, having no tears when crying.

Complications

Most complications have occurred among previously healthy individuals, with obesity and prior respiratory disease as the strongest risk factors. Pulmonary complications are common. Primary influenza pneumonia occurs most commonly in adults and may progress rapidly to acute lung injury requiring mechanical ventilation. Secondary bacterial infection is more common in children. Staphylococcus aureus, including MRSA, is an important cause of secondary bacterial pneumonia with a high mortality rate. Neuromuscular and cardiac complications are unusual but may occur. Fulminant myocarditis and pulmonary emboli were other complications detected.

Diagnosis

To confirm the diagnosis, testing of a nasopharyngeal, nasal, or oropharyngeal tissue swab from the patient is required. Real-time (RT) PCR is the recommended test as others are unable to differentiate between pandemic H1N1 and regular seasonal flu. However, most people with flu symptoms do not need a test for pandemic H1N1 flu specifically, because the test results usually do not affect the course of treatment. CDC recommends testing only for people who are hospitalised with suspected flu, pregnant women, and people with weakened immune systems. For the mere diagnosis of influenza and not pandemic H1N1 flu specifically, more widely available tests include rapid influenza diagnostic tests (RIDT), which yield results in about 30 minutes, and direct and indirect immunofluorescence assays (DFA and IFA), which take 2 to 4 hours. Due to the high rate of RIDT false negatives, CDC advises that patients with illnesses compatible with novel influenza A (H1N1) virus infection but with negative RIDT results should be treated empirically based on the level of clinical suspicion, underlying medical conditions, severity of illness, and risk for complications, and if a more definitive determination of infection with influenza virus is required, testing with RT-PCR or virus isolation should be performed.

A new test called the 'CDC Influenza 2009 A (H1N1) pdm Real-Time RT-PCR Panel (IVD)' has been launched. It uses a molecular biology technique to detect influenza A viruses and specifically the 2009 H1N1 virus. The new test will replace the previous RT-PCR diagnostic test used during the 2009 H1N1 pandemic, which received an emergency use authorisation by the FDA in April 2009. Test results are available in four hours and are 96% accurate.

Treatment

Adequate fluid intake and rest have been recommended to help ease symptoms. Pain medications, such as acetaminophen and ibuprofen are useful to reduce symptoms. Aspirin and other salicylate products should not be used by people under 19 years with any flu-type symptoms because of the risk of developing Reye's syndrome.

If the fever is mild and there are no other complications, fever medication is not recommended. Most people recover without medical attention, although those with pre-existing or underlying medical conditions are more prone to complications and may benefit from further treatments.

People in at-risk groups should be treated with antivirals (oseltamivir or zanamivir) as soon as possible when they first experience flu symptoms. The dose of oseltamivir is 75 mg twice a day for 5 days. The at-risk group includes pregnant and post partum women, children under two years old, and people with underlying conditions, such as respiratory problems. People who are not from the at-risk group who have persistent or rapidly worsening symptoms should also be treated with antivirals. These symptoms include difficulty in breathing and a high fever that lasts beyond three days. People who have developed pneumonia should be given both anti-virals and antibiotics, as in many severe cases of H1N1-caused illness, bacterial infection develops. Antivirals are most useful if given within 48 hours of the start of symptoms and may improve outcomes in hospitalised patients. In those beyond 48 hours who are moderately or severely ill, antivirals may still be beneficial. If oseltamivir is unavailable or cannot be used, zanamivir is recommended as a substitute. Peramivir is an experimental anti-viral drug approved for hospitalised patients in cases where the other available methods of treatment are ineffective or unavailable. Both medications have known side effects, including lightheadedness, chills, nausea, vomiting, loss of appetite, and troubled breathing. Children were reported to be at increased risk of self-injury and confusion after taking oseltamivir.

Infection Control

Reasonably effective ways to reduce the transmission of influenza include good personal health and hygiene habits such as: not touching your eyes, nose or mouth; frequent hand washing (with soap and water, or with alcohol-based hand rubs); covering coughs and sneezes; avoiding close contact with sick people; and staying home yourself if you are sick. Avoiding spitting is also recommended. Although face masks might help prevent transmission when caring for the sick, there is mixed evidence on beneficial effects in the community. Prophylaxis with anti-viral drug is recommended for high risk population in contact with confirmed cases. Oseltamivir is given in the dose of 75 mg once daily for 10 days.

Vaccines

Vaccines that have been developed to protect against the pandemic H1N1/09 virus either contain inactivated (killed) influenza virus, or live attenuated virus. The killed vaccine is injected, while the live vaccine is given as a nasal spray. In studies, the vaccine appears both effective and safe, providing a strong protective immune response and having similar safety profile to the normal seasonal influenza vaccine. Killed vaccine is used in pregnant women and immunocompromised persons.

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17.42 Dengue

ME Yeolekar

DEFINITION AND EPIDEMIOLOGY

Dengue, the most common arboviral disease worldwide is usually endemic but several epidemics have been recorded. The causative agent, dengue virus belongs to genus Flavivirus. It has a single-stranded ribonucleic acid genome surrounded by an icosahedra nucleocapsid covered by lipid envelope. Dengue fever (DF) and dengue haemorrhagic fever (DHF) are caused by four antigenically related dengue viruses 1, 2, 3 and 4. Infection with one serotype provides life-long immunity to that virus but not to the others. Dengue viruses are maintained in an urban transmission cycle in tropical and sub-tropical areas by the mosquito vector closely associated with human habitation, *Aedes aegypti*.

In Southeast Asia, epidemic DHF first appeared in the 1950s. By 1975 it had become a leading cause of hospitalisation and death among children in many countries. In the 1980s, DHF began a second expansion into Asia. Different serotypes have been observed in 1996 (DEN-2) and 2003 (DEN-2 and 3) outbreaks in north India. Rapid urbanisation, inadequate supply of piped water, increased movement of human population within and between countries, and further development and spread of insecticide-resistance in the mosquito vector population, are some of the reasons for the increase of dengue transmission in recent years (**Table 1**).

Table 1: Criteria for Diagnosis of DHF and DSS

Criteria for dengue haemorrhgic fever (all 4 criteria required)

- Fever or history of fever lasting 2 to 7 days.
- Haemorrhagic tendencies indicated by at least one of the following:
  - A positive tourniquet test
  - Petechiae, ecchymoses, purpura
  - Bleeding per mucosa, GIT, other
  - Haematemesis, melaena.
- Thrombocytopenia <100,000/mm³
- Plasma leakage evidenced by at least one of the following:
  - Rise in haematocrit >20%
  - Fall in haematocrit >20% after intravenous fluids
  - Pleural effusion, ascites, hypoalbuminaemia.
- Tourniquet test is performed by inflating the sphygmomanometer cuff on the upper arm to midway between systolic and diastolic pressure for 5 minutes. A positive test is identified by appearance of more than 20 petechiae per 2.5 cm.

Criteria for DSS

- DSS require all DHF criteria and in addition a circulating failure manifested by:
  - Rapid and weak pulse
  - Narrow pulse pressure (<20 mm Hg)
  - Hypotension for age ≤5 yr <80 mm Hg and for age ≥5 year ≤90 mm Hg
  - Cold dry skin, restlessness.

AETIOPATHOGENESIS

Macrophage/monocyte infection is central to the pathogenesis of DF and to the origin of DHF/dengue shock syndrome (DSS). Previous infection with a heterologous dengue-virus serotype may result in the production of non-protective anti-viral antibodies. Subneutralising levels of dengue antibodies enhance the infectivity of the virus. The major pathophysiological change that determines the severity of disease in DHF and differentiates it from DF is the leakage of plasma. Extravasations occur through endothelial gaps, without necrosis or inflammation of the capillary endothelium. Complement activation and release of cytokines and other mediators cause capillary leakage and coagulopathy, so characteristic of DHF. Vascular instability, decreased vascular integrity, increased permeability, decreased platelet function individually and in sequential combination can cause abnormalities in control of local circulation manifested clinically by cutaneous flushing, conjunctival suffusion, and with widespread vascular damage the clinical haemorrhagic manifestations/bleeding and/or loss of blood volume leading to shock. In severely ill patients even disseminated intravascular coagulation may occur.

CLINICAL FEATURES

Classic Dengue ('Break-Bone Fever') (Table 1)

The incubation period is usually 4 to 6 days (range 3 to 14 days) followed by abrupt onset of fever, chills, headache, retro-orbital pain, conjunctival suffusion and backache that is quite often severe. The fever is typically of 39 to 40°C and is occasionally followed by remission lasting few hours to 2 days followed by a second febrile phase for 1 to 2 days (biphasic curve or saddleback pattern). Fever lasts for 5 to 7 days. A transient generalised erythematous rash may be present during the first 24 to 48 hours. The typical morbiliform rash appears on the trunk and spreads centripetally to face, trunk and limbs and spares palms and soles, lasts for 1 to 5 days, and sometimes resolves with desquamation. Generalised myalgia, arthralgia and constitutional symptoms like anorexia, nausea, vomiting, and dysgeusia can also be present. The physical examination may reveal relative bradycardia and lymphadenopathy. Marked leucopaenia and neutropaenia are typical, and thrombocytopaenia may occur between 3rd to 8th day. Thrombocytopaenia results from impaired megakaryocytic production and increased platelet destruction. Platelet function abnormalities also contribute to bleeding. In some epidemics DF has been associated with haemorrhagic phenomena, particularly petechial haemorrhages and epistaxis, gastrointestinal bleed, haematuria, menorrhagia, but in the absence of signs of plasma leakage, a diagnosis of DHF is unwarranted. South-east Asian serotype 2 strains have more potential to cause DHF/DSS than others.

Dengue Haemorrhagic Fever

DHF is primarily a disease of older children and young adults. DHF is defined as an acute febrile illness with minor or major bleeding, thrombocytopaenia (platelet count $<10^5/mm^3$) and evidence of plasma leakage documented by haemoconcentration (haematocrit increased by at least one-fifth) and pleural and other effusions (serositis). Susceptibility to DHF/DSS drops considerably after 12 years of age. Type 2 is more dangerous than other serotypes. DHF commonly begins with a sudden rise in temperature and other symptoms resembling DF. The temperature is typically high (38-40°C) and continues for 2 to 7 days. DHF and dengue shock usually develop around the 3rd to 7th day of illness. The most common haemorrhagic feature is a positive tourniquet test. Petechiae, easily bruised skin and subcutaneous bleeding at venepuncture sites are present in most cases. Transudate due to excessive capillary permeability collects at the pleural and abdominal cavities. The development of DHF provides warning of an increased probability of shock. A progressively decreasing platelet count and a rising haematocrit (signalling abnormal capillary permeability) indicates increased probability of impending shock.

Dengue Shock Syndrome

DSS is defined as DHF (Grade III/IV) with signs of circulatory failure, including narrow pulse pressure (30 mm Hg), hypotension or frank shock. The four warning signs for impending shock are intense, sustained abdominal pain, persistent vomiting, restlessness or lethargy and a sudden change from fever to hypothermia with sweating and prostration. Blotchy skin, cyanosis, tachypnoea, hepatomegaly, pleural effusion, oedema and oliguria are other physical findings. The patient may recover rapidly after volume replacement but shock may recur during the period of excessive capillary permeability. The prognosis in DHF/DSS depends on prevention or early recognition and treatment of shock.

DIAGNOSIS

Microbiology

The virus should be sought from serum obtained during febrile phase of illness. Serum is the specimen of choice for both virological and serological studies. Circulating virus remains detectable in the blood during the febrile period (for an average of 5 days after onset of symptoms), and is then rapidly cleared with the appearance of specific antibody. Serologic diagnosis is achieved by demonstrating a rise in haemagglutination inhibition, complement fixation, or neutralising antibody titres in appropriately timed paired sera drawn 7 to 14 days apart. The IgM antibody capture ELISA is especially useful in the diagnosis of recent infection. IgM antibodies are relatively specific for dengue, but do not distinguish between various serotypes. Rising titre of IgM antibodies is much more specific. Newer diagnostic techniques like reverse-transcriptase polymerase chain reaction (RT-PCR) are very sensitive and specific for detection of viral RNA. Hybridisation probe identify viral nucleic acids. Modified RT-PCR using fluorescent labeled oligonucleotide probe and nucleic acid sequence based amplification are recent research developments.

Blood Chemistry

Thrombocytopaenia and haemoconcentration are constant findings in DHF. A drop in platelet count below $100,000/mm^3$ is usually found between 3rd and 8th day of illness. Haemoconcentration with an increase in the haematocrit of 20% or more is considered to be definitive evidence of increased vascular permeability and plasma leakage. However, it should be noted that the haematocrit level may be affected by volume replacement or bleeding. A drop in total white blood cell count with reduction in number of neutrophils is observed near the end of febrile phase of illness. A relative lymphocytosis with more than 15% atypical lymphocytes is also common at early shock stage. Deranged hepatic and renal function tests and prolonged prothrombin time are observed in severe cases of DHF. The above haematological parameters have to be performed on a repetitive basis during the early stages as well as for monitoring/prognostic purpose, more often when patient is in intensive care unit (ICU) set-up.

Differential Diagnosis

Dengue should be differentiated from malaria, leptospirosis, infectious hepatitis, chikungunya, sepsis, meningococcaemia, rubella, influenza and other haemorrhagic fevers. Presence of haemoconcentration along with thrombocytopaenia differentiates DHF from other diseases. Normal erythrocyte sedimentation rate differentiates DHF from septic shock and bacterial infection. Case definitions of dengue are summarised in **Table 2**.

Table 2: WHO Case Definitions of Dengue Fever

Probable Case

An acute febrile illness with two or more of following:
- Headache
- Retro-orbital pain
- Myalgia and arthralgia
- Nausea and vomiting
- Skin rash
- Haemorrhagic manifestations

AND

Supportive serology

OR

Occurrence at the same location and time as other confirmed cases of dengue fever

Confirmed Case

Confirmation of dengue fever is based on laboratory criteria:

Virus isolation from serum or tissue samples

OR

Demonstration of four-fold or more rise in IgG and IgM antibody titres to dengue antigens in paired serum samples

OR

Demonstration of dengue antigen in tissue CSF by immunocytochemistry or detection of genomic sequence by PCR

WHO = Warld Health Organisatian; Ig = Immunaglabulin; CSF = Cerebrospinal fluid; PCR = Palymerase chain reactian.

TREATMENT

Treatment of DF is symptomatic with paracetamol (aspirin and NSAIDs are avoided due to risk of bleeding), rest, and oral rehydration therapy. Patient can be managed at home in absence of signs of dehydration or bleeding. Patient should be alerted for danger signs, like abdominal pain, melena, bleeding and cold skin. In DHF, careful and repeated estimation of volume status and fluid replacement are the cornerstones of management. This should include measuring vital signs,

urine output, haematocrit, and serum protein concentration. Insufficient volume replacement will allow worsening of shock, acidosis, and disseminated intravascular coagulation, while fluid overload will produce massive effusions, respiratory compromise, and congestive heart failure. Because patients have loss of plasma (through increased vascular permeability into serous spaces) they must be given isotonic solution or plasma expanders. Initial fluid challenge is given with 6 mL/kg/hour and up to 10 to 20 mL/kg/hour, if no improvement occurs. Drop in haematocrit to approximately 40% and improvement of urine output indicates adequate hydration.

DSS requires close monitoring, oxygen administration, much more aggressive fluid replacement therapy, sometimes colloid infusion, ionotropic support and ICU care. Platelets are replaced in case of profound thrombocytopaenia (platelet count <10,000/mm^3) or clinical bleeding. Patients with DF should preferably receive single donor aphaeresis platelets as compared to random donor platelets to lower the risk of alloimmunisation. There is no role of steroids in the management of DHF. Correction of metabolic acidosis, electrolyte imbalance and hypoglycaemia are essential.

Complications

Overt bleeding (haematemesis, melena and severe ecchymoses) is the main complication. Other complications include acute respiratory distress syndrome, renal failure, hepatic failure and encephalopathy. DSS in association with haemorrhagic signs is a serious complication.

PROGNOSIS AND PREVENTION

Classic DF is rarely fatal. However, general weakness and depression may persist for several weeks following the acute illness in adults. Although DF is a self-limiting disease, timely intervention is required to prevent complications and fatal outcome in patients with DHF/DSS. At its worse, the case fatality rate in patients with DSS can be up to 44% where patient is hospitalised late and developed multiple complications.

The key to control of DF/DHF/DSS is the control of mosquitoes that live and breed in stagnant water in and around the house. Vector control includes simple measures, like eliminating larva habitats, using repellents/indoor space-spray insecticides and mosquito-nets while sleeping. Control efforts have been handicapped by the presence of non-degradable tyres and long-lasting plastic containers in trash repositories, insecticide resistance, urban dwelling and poverty. As there is no cross protection between the 4 dengue serotypes and because of fear of immune enhancement by heterotypic antibodies, only a tetravalent vaccine will be acceptable. Tetravalent live attenuated vaccine is presently going through Phase II trials. In view of emerging outbreaks of DF in various states of India, it becomes imperative for primary care physicians to be aware of the management guidelines.

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17.43 Ebola and Marburg Infections

Partha Pratim Chakraborty

A haemorrhagic fever is an acute febrile illness clinically manifested at times by severe muco-cutaneous bleeding. The term originates from the Greek '*Haima*' meaning blood and '*rhegnynai*' meaning to burst forth. Viral haemorrhagic fevers (VHFs) are caused by viruses from four distinct families (Arenaviridae, Bunyaviridae, Filoviridae, Flaviviridae) and vary in severity from relatively mild to life-threatening complications. Filoviruses ('thread' viruses) are causative agents of such a haemorrhagic fever in man. They are enveloped, non-segmented negative-stranded RNA viruses and are separated into 2 types, Marburg and Ebola, which can be serologically, biochemically and genetically distinguished. Both of them share the same morphology, characterised by a filamentous structure. They can appear like a 'U', a '6', or spiralled like a snail; and can sometimes be branched. Filoviruses are prime examples for emerging pathogens.

EPIDEMIOLOGY

Ebola virus infection was first recognised in 1976 with almost simultaneous outbreaks in Sudan and Zaire (now the Democratic Republic of Congo). It was named after a river in the Democratic Republic of Congo. The Ebola virus has four subtypes: Zaire, Sudan, Reston, and Ivory Coast.

Marburg is named after the German town where some of the first identified cases were described. Endemic areas appear to be Central and East Africa. Another fertile area is the Mt. Elgon region on the border of Kenya and Uganda. It also has a natural reservoir in Zimbabwe.

Although the natural host and the route of transmission are uncertain, bats may be the possible candidates for spread of Marburg disease (MD). The viruses appear to be spread mainly by close and prolonged contact with infected persons or by inoculation from syringes and needles contaminated with blood or body fluids.

Factors involved in the emergence of these viruses are international commerce and travel, limited experience in diagnosis and therapy, import of non-human primates, and their potential for rapid evolution.

AETIOPATHOGENESIS

Development of new technologies and extensive studies on animal models has substantially expanded the knowledge on the pathogenic mechanisms of these diseases. Two major factors postulated in pathogenesis of Ebola disease (ED) are immune dysregulation and vascular endothelial dysfunction.

As with Ebola, the exact mechanism of MD is also unknown. It is presumed that virion surface spikes made of large glycoprotein bind to receptors on the host cell and mediate entry into susceptible cells. Viral replication takes place in the cytoplasm and then it involves the liver, lymphoid organs, and kidneys.

CLINICAL FEATURES

Incubation period of ED is 4 to 16 days and that of MD is 3 to 10 days. Clinical pictures are indistinguishable.

Although all begin with constitutional symptoms, some may develop more serious manifestations, including severe internal and external bleeding with widespread tissue necrosis and shock. Early signs and symptoms mimic any of the viral illnesses and include: fever, severe headache, joint and muscle aches, chills, sore throat and prostration. Over time, symptoms become increasingly severe and may include: nausea and vomiting, diarrhoea (may be bloody), red eyes, maculopapular rash, chest pain and cough, epigastric pain, confusion, irritability or aggression and massive haemorrhage from many sites, including nose, mouth, rectum, eyes, ears and solid organs.

The fever typically lasts for around 7 days. On the 5th day of fever, a maculopapular petechial rash appears, and bleeding begins. In survivors, the skin will eventually begin to shed or peel.

Renal, cardiac and adrenal failures are common. Some patients may become jaundiced. Unusual symptoms may include inflammation of the eyelid, polyserositis and pulmonary interstitial oedema. Patients finally experience coma and convulsions, followed by death. Death from shock usually occurs 6 to 9 days after clinical onset of symptoms.

Within 7 to 10 days, patients who will survive begin to recover. Recrudescence occurs by 12th day and can be complicated with secondary bacterial infections. Recovery can take 5 weeks or more, and is marked by prostration, weight loss, and amnesia for the period of acute illness. Complications during convalescence can include recurrent hepatitis, as well as inflammation of the spinal cord, bone marrow, eyes, testes, and parotid gland.

For patients presenting with filovirus symptoms, initial possible diagnoses can include malaria, dengue, chikungunya, leptospirosis and typhoid fever. Other differentials are rickettsial diseases and different VHFs.

DIAGNOSIS

Laboratory findings are non-specific and include lymphopaenia, neutrophilia and thrombocytopaenia. Transaminase levels are elevated (AST>ALT). Alkaline phosphatase and bilirubin levels are usually normal or only mildly elevated.

Diagnosis is confirmed by IgG ELISA (high or rising titres), although IgM ELISA can be used to distinguish acute infections from old infections. IFA results can be misleading. Electron microscopy is useful, but does not distinguish MD from ED. Other modalities are immunohistochemistry of skin biopsies, virus isolation, or PCR of blood or tissue specimens.

TREATMENT

There are no drugs that work against these diseases. Supportive therapy and control of complications is the rule. Therapy involving blood plasma from convalescent patients, anticoagulants and interferon has been used with limited success. Another emerging option is recombinant nematode anticoagulant protein with therapeutic antibodies. However, the effectiveness of these still remains controversial.

PROGNOSIS AND PREVENTION

ED can have up to 90% mortality. It has been placed in the category A list of potential biothreat agents by World Health Organisation.

The case fatality rate in MD is approximately 25%. The virus is classified as a biosafety level 4 agent because of its extreme pathogenicity and the lack of a vaccine or anti-viral drug.

Till date no effective vaccines are available and exposure to filoviruses does not confer subsequent immunity. The antibody response in convalescent patients does not neutralise or protect against subsequent infection by the same virus. Until additional vaccines are developed, the best approach is prevention.

The most effective way to reduce or prevent transmission in an outbreak is through the proper use of barrier protection for doctors and nurses. This includes the use of gloves and masks, with gloves being changed after every patient. Another important aspect is proper sterilisation of equipments. The virus is sensitive to lipid solvents, detergents, commercial hypochlorite disinfectants, and phenolic disinfectants. The virus can also be destroyed by ultraviolet and gamma radiation.

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17.44 Japanese Encephalitis

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INTRODUCTION

Japanese encephalitis (JE) is the commonest human endemic encephalitis in the world and is prevalent throughout the Eastern and Southern Asia. JE was recognised in horses and humans as early as 1871. The term Japanese B encephalitis was used to distinguish it from summer epidemics of von Economo's lethargica known as type A encephalitis. Later the term type B was dropped and it is known as Japanese encephalitis instead.

EPIDEMIOLOGY

Japanese encephalitis virus (JEV) is a single stranded RNA virus which belongs to the family Flaviviridae. Most members of the Flavivirus genus are arthropod borne (arbo) viruses, a term that emphasises the need of a blood sucking arthropod to complete the life cycle. JE virus is transmitted through zoonotic cycle between mosquitoes, pigs and water birds. Humans are accidentally infected when bitten by an infected mosquito (**Figure 1**).

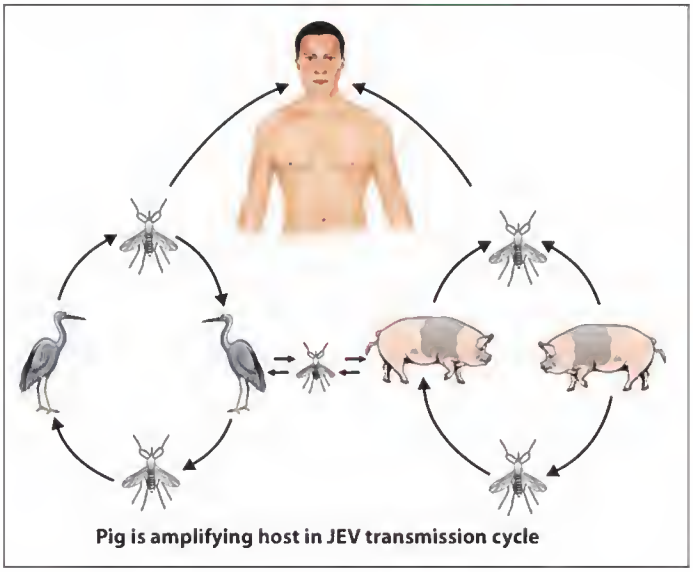


Figure 1: Life cycle of Japanese encephalitis virus. Humans are the accidental dead-end host.

Vector

Culex tritaeniorhynchus is the most important vector for JEV transmission which is present in stagnant water in large numbers shortly after the rainy season and prefer pigs and birds over humans for blood meal but bite humans with high enough frequency to transmit JEV.

Host

Pigs and ardeid birds are the most important host for maintenance, amplification and spread of JEV. Pigs are the most important natural host for transmission of JEV to humans because they are often kept close to human habitat, have prolonged and high viraemia and produce many offspring, resulting in a continuous supply of new hosts. JEV infected animals generally remain asymptomatic, however, fatal encephalitis occurs in horses and foetal wastage occurs in cows.

Human Infection

Humans develop JEV infection coincidentally when living or travelling in close proximity to the enzootic cycle to JEV (**Figure 1**). JE is a rural disease but is also found in the suburban areas due to pigs and mosquito breeding. Most human infections, however, are asymptomatic or result in a nonspecific flu like illness. The ratio of symptomatic to asymptomatic infection varies from 1 in 25 to 1 in 1000. In the endemic areas, JE affects mainly the children whereas in non-endemic or newly affected areas both adults and children are affected. The highest age specific attack rates of JE are between 3-6 years of age which is due to high outside exposure especially playing in the evening with high risk of mosquito bites to poorly clothed village children. Age specific attack rates decline after 14 years of age and are attributed to high levels of antibodies due to natural exposure to JEV (subclinical infection).

Environment

JEV transmission occurs throughout the year in the tropics, but seasonal epidemics occur during the rainy season when the mosquito density is maximum. Two epidemiological patterns of JE are recognised: in the northern region, the epidemics of JE occur during the summer months whereas in the southern region JE tends to be endemic and the cases occur throughout the year with the peak incidence during the rainy season. This difference has been attributed to temperature rather than rainfall.

PATHOGENESIS

The incubation period of JE is 6-16 days. Local replication of virus occurs at the site of mosquito bite followed by lymphatic or haematogenous spread. Replication of JEV beyond the primary site results in secondary viraemia which can result in central nervous system (CNS) involvement. In most patients, primary viraemia is terminated by a macrophage response and subsequently by the development of antibodies. JEV infects the endothelial cells of the capillaries of the brain and crosses the blood brain barrier. JEV spreads to both extracellular and intracellular spaces and results in inflammatory response leading to formation of characteristic glial nodules (foci of degenerating neurons surrounded by inflammatory cells). Both humoral and cellular immune responses occur following JEV infection. A rapid and potent IgM response occurs in the serum and CSF following primary JEV infection. By day 7, most patients have raised IgM titres. Antibodies to JEV prevent viral replication and also limit damage by neutralising extracellular virus and facilitating lysis of infected cells by antibody dependent cytotoxicity.

On autopsy, leptomeninges are normal or hazy and the brain parenchyma is congested with petechiae or focal haemorrhages.

Thalamus, basal ganglia, midbrain, cerebral cortex, cerebellum and anterior horn cells are commonly affected. In some patients, the grey matter of the spinal cord is confluently discoloured as in poliomyelitis.

CLINICAL FEATURES

Following 2 to 4 days of nonspecific illness, the patients develop headache, fever, rigours, flu-like symptoms or gastrointestinal symptoms which improve in a few days. The encephalitis syndrome is characterised by behavioural abnormality; altered sensorium, seizures and focal neurological deficits in the form of hemiplegia, quadriplegia or cerebellar signs. Neck stiffness and Kernig's sign may also be present. Severely affected patients may have decerebrate or decorticate posturing. Cranial nerve palsy is rare although visual blurring, diplopia and blindness have been reported. Tremulous eye movements subside as fever abates. In some patients, particularly older children and adults, abnormal behaviour may be the only presentation, which may be confused with a psychiatric illness.

Seizure

During the acute stage of JE, seizures have been reported in 6.7% to 67.2% patients. The seizures may be focal or generalised and rarely may progress to status epilepticus. The seizures are commoner in children compared to adults. In children, subtle seizures manifest with twitching of digits and facial muscles, nystagmus, ocular deviation, irregular respiration or excessive salivation. Occurrence of seizures in JE may also be contributed by co-infection with cysticercosis which may either suggest the role of neurocysticercosis in the predisposition of JE or co-existence of both the diseases because of common pig reservoir.

Acute Flaccid Paralysis

Japanese encephalitis is actually an encephalomyelitis. Patients with encephalitis may manifest with variable focal lower motor neuron signs, which may be as subtle as focal reflex loss or as severe as flaccid quadriparesis followed by wasting and muscle atrophy (**Figure 2**). Acute flaccid paralysis in JE has been reported in 5% to 20% patients. Majority of these patients have features of encephalitis.

Movement Disorders

The movement disorders in JE have been reported in 20-80% patients as the patient recovers from deep coma. Three major groups of movement disorders in JE are:

1. *Parkinsonian features*: Parkinsonian features in JE are characterised by mask facies, paucity of blinking, abulia, akinesia and rigidity with or without tremor.
2. *Dystonia*: In JE, wide varieties of dystonia, such as orofacial, limb and axial are described (**Figure 3**). These are fixed dystonia with varying severity and are usually superimposed on parkinsonian features.
3. *Miscellaneous movement disorders:* Other movement disorders, such as chorea, athetosis and myoclonus are also rarely observed in JE. Sometimes dystonia in JE patients may be very severe, simulating status dystonicus which is difficult to treat and refractory to various drugs, such as anticholinergic, tetrabenazine, haloperidol, diazepam, clonazepam and baclofen in various combinations. Most of the patients, however, improve to variable extent over months to years.



Figure 2: Photograph of a Japanese encephalitis patient shows severe wasting of both the legs.

DIAGNOSIS

Currently IgM capture ELISA is the most reliable method. Presence of IgM antibodies in the CSF has a reported sensitivity and specificity of 90% for the diagnosis of JE. Rapid IgM capture ELISA (JEV Chex) has been reported as robust and user friendly, with similar sensitivity as conventional ELISA. On CT scan or MRI, involvement of thalamus, basal ganglia and brainstem is highly suggestive of JE (**Figure 4**) especially in post monsoon period in the endemic area.

MANAGEMENT

There is no specific antivira l therapy against JE, therefore, the treatment is symptomatic and supportive. Fever and convulsions are managed symptomatically. Seriously ill patients may require artificial ventilation. Dexamethasone and IFNα have not been found to be beneficial in JE. Management of nutrition and electrolytes and prevention of aspiration pneumonia, bed sores and urinary tract infection are important.

PREVENTION

The application of larvicide to the rice field and insecticide spray in the community have been tried to combat JEV infection. Inactivated and live attenuated JEV vaccines have been used



Figure 3: Photograph shows marked axial and limb dystonia.

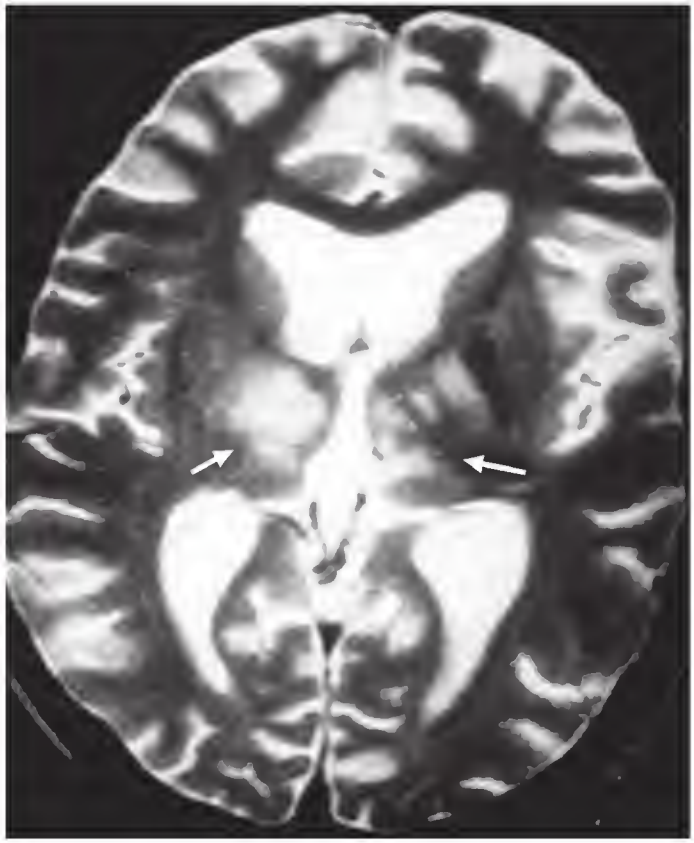


Figure 4: Characteristic cranial MRI changes on T2 sequence in Japanese encephalitis. Bilateral thalamic lesions are demonstrated (white arrows).

to protect the swine against JEV infection but is not feasible in developing countries. The residents and travellers to JE endemic areas should take personal precaution to avoid mosquito bite by minimising outdoor exposure at dusk and dawn, wearing clothing that leaves a minimum of exposed skin, using insect repellents and sleeping under bed-nets. The above mentioned measures though are possible for short term travellers but are not practical for permanent residents.

Immunisation

Immunisation is the only effective measure for long term protection against JEV infection. There are two types of JEV vaccines—formalin inactivated vaccine and live attenuated vaccine.

Purified formalin inactivated JEV vaccine: Formalin inactivated Nakayama BIKEN vaccine is produced by Osaka University and is available under the BIKEN label from 1968. Similar vaccines are prepared by various Asian countries, such as Thailand, India, Korea, China and Vietnam. Two doses may be sufficient (0.5-1 ml subcutaneously 1 to 4 weeks apart) and booster dose is recommended after 1 to 3 years. In travellers from Western countries, vaccine is recommended at 0, 7 and 30 days and a booster dose at 1 year. The protective antibodies after 3 doses are reported in 80% to 100% of recipients. Formalin inactivated JE vaccine is associated with moderate frequency of local and systemic side effects. Local tenderness, redness and swelling occur in about 20% and fever, malaise and dull headache in 10% of recipients. The neurological complications implicated due to mouse myelin basic protein in the vaccine have not been universally seen; however, encephalitis, encephalopathy, seizures and peripheral neuropathy have been reported in 1 to 2.3/million recipients.

PROGNOSIS

Approximately 20% to 40% patients with JE die during acute stage. About 50% of survivors have severe neurological sequelae. Seizures may persist in 20% and focal weakness in 30% patients. The poor prognostic predictors include extremes of age, high fever, CSF pleocytosis, deep coma, hypotonia, features of raised intracranial pressure and low level of IgG and IgM antibodies against JEV.

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17.45 Rabies

Tarun Kumar Dutta, Ashish Kumar Panigrahi

INTRODUCTION

Rabies is a fatal disease of nearly worldwide distribution caused by a filterable neurotropic virus, which is present in the saliva of infected animals and transmitted to man through their infected saliva.

Urban rabies is propagated chiefly by unimmunised domestic or street dogs and cats. Street virus is the natural virus present in rabid animals. Wild-life or sylvatic type rabies is propagated by wolves, foxes, raccoons, skunks, jackals and other wild-life carriers, which are the main reservoir and transmitters of rabies. These animals maintain a cycle amongst themselves and transmit the disease to dogs and domestic animals. Man may contract rabies by intrusion into the wild-life cycle of rabies. Bat rabies occurs in certain Latin American countries where the vampire bat serves as an important host and vector for rabies. In USA, at present, insectivorous bats and wild animals are the most important vectors.

The source of infection in man is the saliva of rabid animals. Domestic dog is the cause of more than 90% of human rabies in India. Dogs also infect cats and other domestic species.

Rabies-free countries are Australia, New Zealand, Japan, Taiwan, Hong Kong, Singapore, Fiji, UK, Ireland, Norway, Sweden, Jamaica and Barbados. In India, the islands of Andaman and Lakshadweep are rabies-free.

EPIDEMIOLOGY

The true incidence is unknown due to lack of published figures. In India, the estimated mortality is 25,000 to 50,000 deaths per year. Recent figures in China showed less than 1000 cases per year. In Bangladesh, about 2000 deaths and in Nepal, about 200 deaths occur per year. Only 0.01% cases of human rabies occur in the temperate zones. On an average, two persons die of rabies, every year in USA.

AETIOPATHOGENESIS

Rabies virus is the prototype of the genus *Lyssavirus* of the large family of Rhabdoviridae. It is a bullet-shaped virus containing a single-strand of ribonucleic acid (RNA) combined with nucleoprotein, that forms a helical coil. The virus is rapidly inactivated by heat. At 56°C, half-life is less than one minute. The lipid coat is disrupted by 1% soap solution.

Humans are infected by inoculation of virus-laden saliva by the bite of a rabid dog or animal. Licking on abraded skin or mucous membrane may also result in infection. Scratching by claws can also cause infection. The virus cannot enter through intact skin. However, there are other modes of transmission also.

The rabies virus travels in the nerves and is carried centripetally by the flow of axoplasm to the dorsal root ganglion. It multiplies further in the dorsal root ganglion and causes characteristic prodromal symptoms and paraesthesiae at the site of inoculation. From there it travels to the brain, where massive viral replication occurs. Then the virus migrates along the efferent nerves to almost every organ such as adrenal medulla, cornea, pancreas, nerve twiglet of the hair follicle and salivary gland, and this leads to virus shedding in the saliva. Virus may also be shed in milk and urine.

At autopsy, widespread infection is usually found in the brain particularly in the brainstem, hippocampus and basal ganglia. Congestion of blood vessels of central nervous system (CNS) and petechial haemorrhages of the pia-arachnoid are found. Histological examination shows perivascular cellular infiltration of lymph spaces. Negri bodies can be detected within the cytoplasm of nerve cells as round or oval eosinophilic inclusion bodies, particularly in the hippocampus and Purkinje cells of the cerebellum. Negri bodies in the brain are also found in more than 95% of rabid animals.

CLINICAL FEATURES

Incubation period is usually 4 to 8 weeks but may vary from 5 days to 7 years. Face, neck and head bites which are close to the CNS have a shorter incubation period.

It may be of two types:

- Encephalitic type (Furious rabies)—observed in the majority of cases
- Paralytic type (Dumb rabies)—observed in about 20% of cases

Encephalitic Type (Furious Rabies)

The onset is usually sudden. But prodromal symptoms are noted for 2 to 3 days before the hydrophobic syndrome appears. Only a proportion of people bitten by a rabid animal develop the disease, but once manifest, the disease is almost invariably fatal. Specific prodromal features include pain, paraesthesiae and itching over the healed bite wound scar. Other features are fever, headache, tachycardia, anxiety, insomnia, restlessness and myalgias. After 2 to 3 days, the stage of excitement supervenes. There is mental excitement, restlessness, hyperaesthesia and hydrophobia. Hyodrophobia consists of sudden spasm of muscles of the mouth, pharynx, larynx and whole of the respiratory musculature, particularly the diaphragm and muscles of inspiration. The attack can be induced by offering water to patients. As the glass of water approaches the mouth, typical spasmodic jerks with violent contraction of diaphragm and other inspiratory muscles occurs and water is ejected from the mouth. Afterwards the sight and even the sound of water may provoke the distressing spasm. In the later stage a wide number of stimuli like sudden sound, strong lights and even the suggestion of water may induce the attack. Cold air or blowing of air due to fan may also induce an attack (aerophobia). The mind remains clear during the intervals. Hallucinations, delusions accompanied by biting, mania and spitting may develop later. There is malfunction of brain stem, limbic system and higher centres.

Death occurs within a week after the onset of symptoms.

Paralytic Type (Dumb Rabies)

It is characteristic of bat-transmitted rabies. It also occurs in partially vaccinated persons. Patient presents with flaccid paralysis. It resembles Guillain-Barre syndrome. The stage of excitement is absent. In a few days, paralysis may ascend to involve the respiratory muscles. There is fever and profuse sweating.

The patient has a comparatively longer survival.

Rabies in Dogs

There is no hydrophobic syndrome like man. There is change of temperament and the animal runs amok, biting wildly anything and everything in its way. There is profuse frothing and its bark is altered. The jaw drops, and general paralysis ensues.

Death occurs within five days.

DIAGNOSIS

Diagnosis is confirmed by virus isolation, identification of antigen and detection of antibodies. Virus culture is positive in the first week from saliva, throat swab, eye swab and cerebrospinal fluid (CSF).

Antigen Detection

Direct fluorescent antibody test is used to identify antigen in skin biopsies taken from the nape of the neck, where hair follicles are highly innervated. It is a sensitive test and positive results are found in 60% to 100% cases. The corneal smear test is not so sensitive and false-positive results occur.

Antibody Detection

Seroconversion occurs during the second week of illness in unvaccinated patients. Antirabies antibody detection in serum and CSF confirms the diagnosis.

Negri Body Detection

The offending animal is captured (if possible) and humanely killed for demonstration of Negri bodies in the brain. Fluorescent antigen can also be detected in the animal's brain, and confirms the diagnosis of rabies.

DIFFERENTIAL DIAGNOSIS

This includes other causes of encephalitis or bulbar paralysis (including post-vaccinial encephalomyelitis or ADEM—acute disseminated encephalomyelitis), Guillain-Barre syndrome and hysterical pseudorabies.

TREATMENT

Once symptoms develop, only palliative treatment is possible. Seizures should be controlled by heavy sedation. Diazepam 10 mg, six hourly supplemented by chlorpromazine 50 mg, if necessary can be used to control seizures. Fluid balance and nutrition must be maintained by IV route. Airway and oxygenation should be maintained. On rare occasions, partially immunised patients survive due to extensive intensive care. To date, there are six survivors of rabies including one six year old girl from India, the majority with some neurological sequelae.

PROPHYLAXIS

Rabies vaccine can be used for pre-exposure, as well as post-exposure prophylaxis. The commonly used regimen of intramuscular administration (1 mL) of vaccine is being superseded by intradermal vaccination, which requires lesser quantity of vaccine (0.1mL) and is equally effective.

Post-Exposure Prophylaxis

Post-exposure prophylaxis (PEP) is indicated for persons possibly exposed to a rabid animal. Possible exposure include animal bites or mucous membrane contamination with an infectious secretion, such as saliva. PEP should begin immediately after an exposure. Before initiating anti-rabies treatment one should establish the category of the animal bite (**Table 1**). This categorisation helps in deciding the future course of action. **Figure 1** gives an algorithmic guide for the management of rabies exposure. In addition, tetanus toxoid and proper antibiotics should be used.

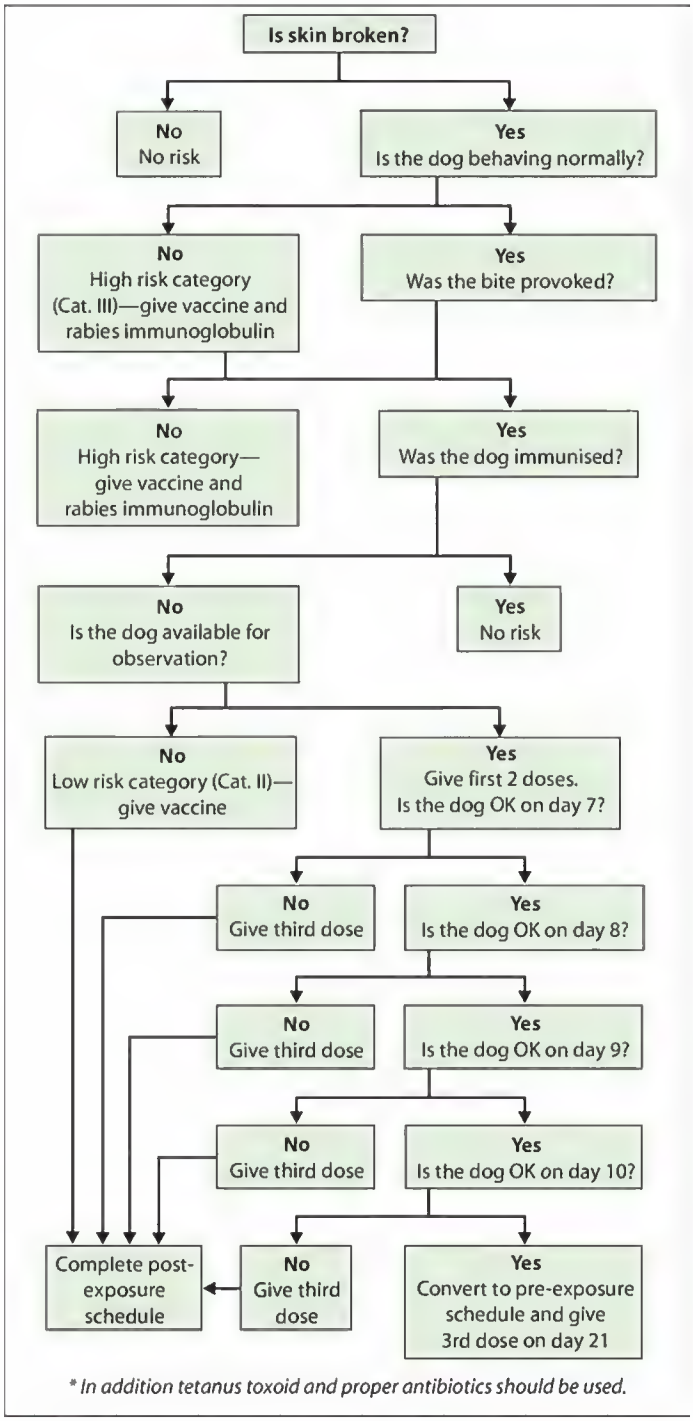


Figure 1: Management of rabies exposure.

Table 1: WHO Classification of Wound

Recommended post-exposure prophylaxis category	Type of contact with a suspect or confirmed rabid domestic or wild[a] animal, or animal unavailable for testing	Type of exposure	Recommended post-exposure prophylaxis
I	Touching or feeding of animals Licks on intact skin	None	None, if reliable case history is available
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding	Minor	Administer vaccine immediately[b] Stop treatment if animal remains healthy throughout an observation period of 10 days[c] or if animal is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques
III	Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva (i.e. licks), exposures to bats[d]	Severe	Administer rabies immunoglobulin and vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is found to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques

[a] Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies post-exposure prophylaxis.

[b] If on apparently healthy dog or cat in or from a low-risk area is placed under observation, the situation may warrant delaying initiation of treatment.

[c] This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be humanely killed and their tissues examined for the presence of rabies antigen using appropriate laboratory techniques.

[d] Post-exposure prophylaxis should be considered when contact between a human and a bat has occurred unless the exposed person can rule out a bite or scratch, or exposure to a mucous membrane.

PEP consists of a regimen of one dose of immunoglobulin (passive immunisation) and five doses of rabies vaccine over a period of 28 days. Vaccines should be given intramuscularly. Alternatively, vaccine can be given intradermally also. Human rabies immunoglobulin 20 IU/kg should be infiltrated around the wound and any remaining volume should be administered intramuscularly at an anatomical site distant from the site of vaccine administration, preferably in the gluteal region. Rabies immunoglobulin (RIG) should not be administered in the same syringe as that of the vaccine. Alternatively, equine immunoglobulin 40 IU/kg may be administered. Equine immunoglobulin is cheaper, but the incidence of serum reactions is more.

Intramuscular (IM) Regimen

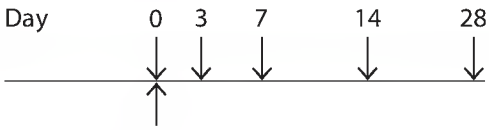
There are currently four types of vaccines available, and the regimen most commonly used in India for IM administration is described below:

Vaccines:

1. Tissue Culture Vaccines
   i. Human diploid cell vaccine (HDCV): One dose—1 mL (IM)
   ii. Purified chick embryo cell vaccine (PCEC): One dose—1 mL (IM)
   iii. Purified vero cell rabies vaccine (PVRV): One dose—0.5 mL (IM)
2. Purified duck embryo vaccine (Vaxirab): One dose—1 mL (IM)

Regimen: Essen schedule (Standard WHO five dose intramuscular regimen)—the course for post-exposure prophylaxis should consist of intramuscular administration of five injections on days 0, 3, 7, 14 and 28.

Dose: one IM dose into deltoid



The sixth injection (D90) should be considered as optional and should be given to those individuals who are immunologically deficient, are at the extremes of age or on steroid therapy. Day 0 indicates date of first injection.

Site of inoculation: The deltoid region is ideal for the inoculation of these vaccines. Gluteal region is not recommended because the fat present in this region retards the absorption of antigen and hence impairs the generation of optimal immune response. In case of infants and young children, the antero-lateral part of the thigh is the preferred site.

Vaccination in special situations

Any of the cell culture vaccines is safe in pregnancy. Same dose of the vaccine, as mentioned above, is used in pregnancy, neonates and old age.

In case of re-exposure, only two doses of vaccine are required to be given, i.e. on days 0 and 3.

Previously used nerve tissue vaccine has been abandoned totally due to its serious neuro-paralytic side-effects. Its manufacture in India has been stopped since 2004.

Intradermal (ID) Regimen

Intradermal recommendation by WHO is a newer attempt to have effective antibody titres against rabies with a lower total

requirement of vaccine. The principle that allows intra-dermal vaccination to be effective at lower dose is the better response to an equal volume of antigen when placed in contact with Langerhans cells of the epidermis and use of multiple sites of vaccination at a time to obtain maximum drainage of antigen-presenting cells to lymph nodes. The intradermal regimens have had remarkable success in Thailand. However, some expertise is necessary for correct intradermal administration.

Regimen: Considering the recommendations on intra-dermal administration of rabies vaccine by WHO and reports of safety, efficacy and feasibility trials conducted in India, the Drug Controller General of India (DCGI) approved the use of reduced dose, economical intra-dermal vaccination regimen in 2006 for post-exposure prophylaxis of rabies.

The following vaccines are currently approved by DCGI for use by intradermal route:

Vaccines:

PVRV – Verorab, Aventis Pasteur (Sanofi Pasteur) India Pvt. Ltd.

PCECV – Rabipur, Chiron Behring Vaccines Pvt. Ltd.

PVRV – Pasteur Institute of India, Coonoor

PVRV – Abhayrab, Human Biologicals Institute.

DCGI has recommended the updated Thai Red Cross 2-2-2-0-2 schedule of ID vaccination, which is as follows:

Dose: one ID dose 0.1 mL

Day	0	3	7		28
ID Sites	X2	X2	X2		X2

Rabies Immunoglobulin

This involves injection of only 0.1ml of reconstituted vaccine per ID site and the vaccination has to be given at two different sites on a single visit (one on each deltoid area, an inch above the insertion of deltoid muscle) on days 0, 3, 7 and 28, using 1 ml insulin syringe. A bleb formed after injection is a sign of successful ID administration (**Figure 2**). It is best used in anti-rabies clinics for group vaccinations (minimum 10 persons at a time), because contents of a broken ampoule of 1 ml have to be used within eight hours and single person requirement on a single visit will be just 0.2 ml and rest will thus go waste.

Intra-dermal vaccination is contra-indicated in patients with immuno-compromised states or those on immunosuppressants like chloroquine or prednisolone. They should take full dose of IM injections.

Wound Treatment

Wound treatment is the most important part of treatment and should begin immediately. It minimises viral load. Thorough cleaning of all wounds with soap and water should be done immediately. A viricidal agent, such as povidone iodine 1% solution or 70% alcohol should be used to irrigate the wound. Suturing of the wound is to be avoided. Bites of rats, mice, rabbits, guinea pigs do not require anti-rabies PEP.



Figure 2: Bleb raised after intradermal inoculation.

Pre-Exposure Prophylaxis

Pre-exposure prophylaxis is recommended for persons in high risk groups, such as veterinarians, animal handlers and certain laboratory workers. Other persons whose activities bring them into frequent contact with the rabies virus or potentially rabid bats, dogs, cats, skunks and raccoons should also be considered for pre-exposure prophylaxis. Pre-exposure prophylaxis consists of three doses of rabies vaccine either intramuscularly (1 mL or 0.5 mL according to vaccine used) or intra-dermally on day 0, 7 and 21.

PROGNOSIS

The prognosis of rabies encephalomyelitis is grave. At the time of the bite, before the virus has invaded the nervous system, correct and prompt cleansing of the wound and use of proper post-exposure immunisation reduces the risk of development of rabies from 30% to 50% in untreated cases to less than 5%. The risk varies with the biting species and the site and severity of the bite. It is highest following head bites by rabid wolves. Interposition of clothing, extent of tissue laceration and immediate local treatment modify the prognosis.

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17.46 Viral Gastroenteritis

Prabhash Chandra Bhattacharyya, Rupjyoti Talukdar

DEFINITION AND EPIDEMIOLOGY

Viral gastroenteritis (VGE) constitutes up to 40% of all cases of infectious diarrhoea worldwide. It is the most common disease associated with diarrhoea and vomiting in children. Four major groups of viruses are associated with VGE: rotavirus, enteric adenovirus, calcivirus (including genus norovirus and sapovirus) and astrovirus. Except for adenovirus, which contains double stranded DNA, all others are RNA viruses. Rotavirus is an enveloped virus, while the other three groups are non-enveloped. Other viruses that are infrequently associated with VGE include parvovirus B19, torovirus, coronavirus, enterovirus and picornavirus.

Rotavirus is the leading cause of VGE worldwide, particularly in children occurring in the first 2 years of life and contributes to 40% of severe gastroenteritis in children in India. Norovirus, rotavirus, astrovirus, enteric adenovirus and sapovirus infections are all endemic, although norovirus can also cause epidemics. VGE does not have a clear-cut geographic distribution, but does have a seasonal distribution. In North India, rotavirus associated diarrhoea occurs predominantly in winter while in South India it occurs all the year round. Astrovirus associated VGE is more prevalent during winters in Western India.

PATHOGENESIS

Rotavirus, norovirus, astroviruses and possibly adenovirus are transmitted by close contact via faeco-oral route. However, norovirus can also spread through contaminated food and water.

After oral inoculation, viruses infect cells of the small intestinal villi. Infection of the mature villous enterocytes of the small intestine, which have digestive and absorptive functions, lead to cell death and sloughing of the villous cells leading to villous blunting. Diarrhoea due to rotavirus infection is both osmotic and secretory due to loss of absorptive surface and opening up of calcium channels, respectively. Following infection, viruses are shed in the stool in large quantity during acute illness. Rotavirus, norovirus and astrovirus can be shed for 1 or 2 days prior to the illness and for several days after resolution. Asymptomatic infection is also common and may be the source of infection. Partial immunity due to infection in childhood is possible.

CLINICAL MANIFESTATIONS

Severity of the disease ranges from subclinical infection to mild, moderate or severe illness. The incubation period is short and the disease begins with vomiting followed by frequent watery diarrhoea without blood or mucous. Fever is seen in 50% of patients, which along with vomiting cease within 1 to 2 days; while diarrhoea often persists. Additional symptoms include malaise and abdominal cramps. The clinical profile of various types of viral gastroenteritis causing viruses and fever are presented in **Table 1**.

DIAGNOSIS

There are no diagnostic clinical features for VGE. For rotavirus, stool for enzyme immunoassay (EIA) or latex particle agglutination (LPA) are available. For adenovirus, only EIA is available and for norovirus and sapovirus, RT-PCR can be employed.

COMPLICATIONS

Dehydration, electrolyte disturbance and malabsorption can occur as complications. Rare complications, like encephalitis, myositis, polio like paralysis and sudden infant death syndrome have been reported with rotavirus infection.

TREATMENT AND PREVENTION

No definite treatment is available for VGE. After rapid assessment, fluid and electrolyte disturbance should be corrected and nutrition should be maintained. Oral rehydration with glucose and electrolyte containing solutions is usually sufficient. However, in severe cases with vomiting, dehydration and shock, intravenous rehydration may be required. Both infants and older children should be given their usual diet, including breastfeeds. Breastfeeding confers some protection against rotavirus infection. Two live attenuated oral vaccines against rotavirus have been licensed globally so far.

Table 1: Summary of Viral Gastroenteritis Caused by the Common Organisms

Feature	Rotavirus	Astrovirus	Adenovirus	Norovirus	Sapovirus
Age of illness	<5 years	<2 years	<2 years	All ages	<5 years
Incubation period	1-3 days	1-4 days	1-4 days	12-48 hours	12-48 hours
Duration of illness	2-8 days	1-5 days	3-10 days	1-5 days	1-4 days
Mode of transmission	Faeco-oral	Faeco-oral	Faeco-oral; food	Faeco-oral	Faeco-oral
Diarrhoea	Up to 10 episodes per day	Mild	Mild, prolonged	Mild	Mild
Vomiting	~ 90%	Mild	Mild	>50%	Mild
Fever	Common	Mild	Mild	Mild	Mild

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17.47 Mumps

Falguni S Parikh

DEFINITION

Mumps is an acute generalised viral infection caused by mumps virus which is a paramyxovirus. The virus has a strong predilection for glandular and nervous tissue. It is characterised by non-suppurative swelling and tenderness of one or both parotid glands. The infection is readily transmissible.

EPIDEMIOLOGY

With introduction of mumps vaccine since 1967, the incidence is on the decline. Most cases occur in young adults. The infection is common in late winter and early spring. Males are more affected as compared to females. Infection in pregnancy especially in the first trimester is associated with adverse foetal outcome.

AETIOPATHOGENESIS

Mumps virus spreads from infected persons via direct contact, droplet nuclei, fomites or secretions. The transmission is greatest from before 48 hours up to 9 days of parotid swelling. Incubation period is 14 to 18 days. Virus replicates in the upper respiratory tract epithelium leading to viraemia which is followed by infection of glandular tissues and/or central nervous system.

Approximately 20% to 40% of mumps infection goes unrecognised due to subclinical infection which does not produce parotitis.

Single attack confers life-long immunity. Antibodies to mumps virus are transferred across the placenta and persist during first 2 to 3 months of life.

CLINICAL FEATURES

Although parotid involvement has been emphasised, mumps can occur without parotid swelling.

Prodromal period is characterised by low grade fever, malaise, headache and anorexia. After 1 to 2 days, parotid swelling and tenderness is often the first sign to appear. The swelling is unilateral or bilateral and persists for 4 to 5 days before decreasing. Slight redness of the orifice of Stenson's and Wharton's duct may be diagnostic.

Pre-sternal oedema may be present due to pressure on the lymphatics. Patient may experience pain whilst chewing. Sub-maxillary and sublingual glands are involved less often.

Central nervous system involvement is not uncommon and may occur 1 week before or 2 weeks after the onset of parotitis. Meningitis, encephalitis, transverse myelitis, cerebellar ataxia, Guillian-Barre syndrome (GBS) and cranial nerve involvement have been described.

Epididymo-orchitis is the most common extra-salivary gland complication of mumps. It occurs in 38% of post-pubertal men with mumps. It may be the only manifestation of mumps. Two thirds of cases develop it during first week of parotitis. Presentation is in the form of severe pain, swelling and tenderness of testes and scrotal erythema. Sterility is rare.

Pancreatitis, oophoritis, arthritis, myocarditis, hepatitis, thyroiditis and dacryocystitis are some of the rare complications of mumps.

DIAGNOSIS

History of exposure, constitutional symptoms, and parotid tenderness in presence of serologic confirmation or isolation of mumps virus is diagnostic of mumps.

Influenza, parainfluenza, coxsackie, HIV and cytomegalovirus infections can cause parotid enlargement. Tumours, sarcoidosis, Mikulicz syndrome and stone in the Stenson's duct are some of the non-infectious causes of parotid enlargement. Mumps virus can be isolated from throat swabs and cerebrospinal fluid. Infection can be confirmed by rising antibody titres in paired sera by complement fixation, haemagglutination inhibition or ELISA test. Serum amylase levels are elevated in mumps parotitis and pancreatitis.

TREATMENT AND PROGNOSIS

Supportive treatment in the form of adequate hydration, nutrition, analgesics and anti-pyretics is advocated. Bitter and acidic foods are best avoided. Most patients recover completely. Deafness and sterility are rare complications.

PREVENTION

Attenuated live mumps vaccine is given in combination with Measles and Rubella as MMR Vaccine at 12 to 15 months and 4 to 6 years of age. Seroconversion rate is 98% to 100%.

It is contraindicated in pregnant women and immuno-suppressed individuals. Patients with asymptomatic HIV infection without immunosuppresion can receive MMR vaccine.

The second dose of MMR vaccine is to protect children failing to seroconvert against primarily mumps and less commonly against rubella.

Vaccination with two doses of the vaccine should be given to all those not previously immunised (with no upward age limit) and especially to health care workers, adolescent girls and students travelling for studies overseas.

The burden of mumps has been reduced in developed countries following the use of MMR vaccine. Outbreaks have been noted in previously vaccinated populations and hence two doses are needed for durable protection. There is no causal relationship between MMR vaccine and autism, inflammatory bowel disease and Guillain-Barre syndrome.

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17.48 Measles (Rubeola)

RK Goyal, Prashant Mathur

DEFINITION

Measles (Rubeola) is a highly contagious, acute respiratory viral disease with a characteristic clinical picture, rash and a pathognomonic enanthem Koplik's spot.

Measles is uncommon in most developed countries where measles vaccine is used, but contributes to significant childhood morbidity and mortality in developing countries.

EPIDEMIOLOGY

Measles has a worldwide distribution. Human beings are the only natural hosts. Before availability of live attenuated measles vaccine, the epidemics were common. It is transmitted by direct contact with respiratory secretions, mainly through exposure to aerosols and infectious droplets. Patients are contagious from 1 or 2 days before onset of symptoms (3 to 5 days before onset of rash) and up to 4 days after the rash appears. The infectivity is maximum during the prodromal phase. The mean intervals from infection to onset of symptoms and appearance of rash are about 10 and 14 days respectively.

The mortality rates are highest among children below 2 years of age. Approximately 3,50,000 childhood death occur due to measles; out of these 80,000 are accounted by India. In adults with impaired cell mediated immunity (immunocompromised patients), mortality is high.

AETIOPATHOGENESIS

Measles virus is a RNA virus which belongs to the genus *Morbillivirus* of *Paramyxoviridae* family. The viruses are pleomorphic spheres with a diameter of 100 to 250 nm having inner capsid and outer envelope.

Measles virus invades the respiratory epithelium and spreads via the blood stream (viraemia) to the reticuloendothelial system and white blood cells, especially monocytes.

The respiratory and lymphoid tissues have pathognomonic multinucleated giant cells with inclusion bodies in the nucleus and cytoplasm (Warthin-Finkeldey cells). There is transient depression of cellular immunity with direct invasion of T lymphocytes and increased levels of suppressive cytokines (e.g. interleukin-4) which accounts for high-risk for severe measles in some patients. Infection of the entire respiratory tract produces generalised damage with loss of cilia and predisposition to secondary bacterial infection with characteristic cough, coryza, bronchiolitis and pneumonia.

The immune reaction of measles virus in the endothelial cells of cutaneous capillaries accounts for pathognomonic Koplik's spots and cutaneous rash. Pathologic changes in measles encephalitis include focal haemorrhage, congestion and perivascular demyelination.

CLINICAL FEATURES

The prodromal phase (2 to 4 days) is most infectious. The catarrhal stage with upper respiratory symptoms like cough, coryza, conjunctivitis with lacrimation, nasal discharge, increasing high grade fever is present before appearance of rash.

The pathognomonic enanthem Koplik's spots appear as 1-2 mm blue-white spots on a bright red background, typically located on the internal buccal mucosa alongside second molar. Koplik's spots may spread to involve lips, hard palate and gingiva. They may also occur in conjunctival folds and in the vaginal mucosa. The spots usually disappear after onset of rash.

The characteristic maculopapular, erythematous rash begins at the hairline on forehead and behind the ears, spreading down to trunk and limbs including soles and palms. By the fourth day, fever and rash begin to fade with desquamation and brownish discolouration of skin. The other features include diarrhoea, vomiting, splenomegaly and generalised lymphadenopathy due to involvement of reticuloendothelial cells. The entire illness usually lasts for about 10 days.

Milder forms of the illness with less intense symptoms and milder rash termed as modified measles may occur in individuals with pre-existing partial immunity induced by active or passive vaccination or in infants less than one year of age having passively acquired maternal antibodies.

Children who had received the original formalin inactivated measles vaccine at times develop a more severe form of disease called atypical measles with high fever and headache followed by appearance of a maculopapular rash on the extremities that become petechial and purpuric and progress in a centripetal direction. The illness is frequently complicated by pneumonia and pleural effusion. The cause of atypical measles may be formation of immune complexes due to an abnormal immune response to vaccine.

COMPLICATIONS

Respiratory

The manifestations are due to generalised involvement of respiratory tract and include laryngitis, croup, otitis media, bronchitis, bronchiolitis, bronchopneumonia (giant cell pneumonia) and secondary bacterial infections.

Central Nervous System

Acute measles encephalitis-mild to severe/fatal may present with fever, headache, drowsiness, coma and/or seizures resulting from an immune mediated response to myelin proteins (post-infectious encephalomyelitis). Rarely transverse myelitis follows measles. Subacute sclerosing panencephalitis (SSPE) results from a persistent infection with an altered measles virus that is

harboured intra-cellularly in the central nervous system for several years. It begins insidiously 7 to 13 years after primary measles infection with permanent sequelae (mental retardation, progressive dementia and seizures). Prognosis is usually fatal.

Gastrointestinal System

Gastroenteritis, hepatitis, appendicitis, ileocolitis and mesenteric adenitis.

Rare Complications

Myocarditis, glomerulonephritis, post-infectious thrombocytopenic purpura and exacerbation of pre-existing tuberculosis. In immunocompromised patients with decreased cell mediated immunity, e.g. patients with congenital cellular immune defects, recipients of immunosuppressive therapy, malignancy, infection with HIV, may have severe protracted and fatal measles.

Measles in Adults

Measles is a disease of childhood and like many other viral infections, it is more severe in adults than children. Primary viral pneumonia with severe bronchospasm, confluent rashes, hepatitis with bacterial superinfection are the predominant features of measles in adults.

LABORATORY FINDINGS

Lymphopaenia and neutropaenia are common which may be due to invasion of leucocytes by the virus with subsequent cell death. Presence of leucocytosis heralds bacterial superinfection.

DIAGNOSIS

It is primarily clinical. A specific diagnosis can be made by staining a smear of respiratory secretions. Measles virus can be demonstrated by culture or detected by polymerase chain reaction (PCR). Specific IgM antibodies are detectable within 1 to 2 days after onset of rash and the titre of IgG antibodies rises significantly after 10 days.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of measles includes other exanthematous fevers, scarlet fever, infectious mononucleosis, drug eruption, pneumonias and Kawasaki syndrome.

MANAGEMENT

It is largely supportive and symptomatic, like tepid sponging and antipyretics. Antibiotic therapy should be given only for complications like pneumonia, otitis media, etc. No specific antiviral treatment is available. WHO recommends high dose of vitamin A to all children with measles in developing countries, especially with malnutrition. The doses are 50,000 IU for infants 1 to 6 months, 100,000 IU for infants 7 to 12 months and 200,000 IU for children over one year.

PREVENTION

Measles is rapidly transmitted in large families, crowded and urban slums. Proper hygiene of mouth, eyes and skin prevents infection. Without immunisation, every child is prone to get measles. Two types of vaccines are available: (a) measles vaccine, (b) MMR vaccine.

Measles Vaccine

It is a live attenuated vaccine. Indian vaccines are usually formulated from the Edmonston-Zagreb strain grown on human diploid cells or purified chick embryo cells. The dose is 0.5 mL sub cutaneously or intra-muscularly preferably over upper arm or anterolateral aspect of thigh. Appropriate age for vaccination is completed nine months of age. Administration of vaccine within two days of exposure protects or modifies the severity of clinical illness. The vaccine may be given along with all vaccines except BCG vaccine.

The adverse effects reported are local pain and tenderness, mild measles like illness (7 to 12 days after vaccination), thrombocytopaenic purpura, etc.

Measles vaccine is contraindicated in severely immunocompromised, in those with history of severe allergic reactions and in pregnancy. It may be safely given to those with history of egg allergy.

MMR (Measles, Mumps, Rubella) Vaccine

Two doses are recommended: one at the age of 12 to 15 months and second at school entry (4 to 6 years) or at any time 4 to 8 weeks after the first dose.

Post-Exposure Prophylaxis

Susceptible children and adults who are exposed to the disease should receive post-exposure prophylaxis with immune globulin (0.25 mL/kg for healthy persons and 0.5 mL/kg for immunocompromised patients) given intra-muscularly.

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17.49 Smallpox

Ramesh Balwant Pandit

HISTORY

In 1796, Edward Jenner developed smallpox vaccine from material of cowpox lesion (same family as Variola). Current formulation of smallpox vaccine is a live virus preparation of infectious vaccinia virus. Routine childhood vaccination was discontinued in USA in 1972 and in most European countries in 1970. Vaccination is now primarily recommended for laboratory workers and for army personnel. In December 1979, WHO certified that smallpox is eradicated globally. Smallpox is the only human infectious disease eradicated and certified so by WHO.

AETIOPATHOGENESIS

Smallpox is caused by variola virus (Genus: *Orthopox virus*). Two types, variola major and variola minor are responsible. Infection is man to man, through droplet. Virus enters respiratory tract causing viraemia in 10 to 12 days, lesions localise in small blood vessels of skin, mouth, throat, etc. Incubation period is around 12 days. There are 4 types of variola major infection based on Rao's classification. Infections with variola minor are milder in nature.

CLINICAL FEATURES

Prodromal phase is with fever and malaise like in any other viral fever lasting 4 to 5 days. By 12 to 15 days rash develops on the skin and mucous membrane (macules on skin). Rashes are mainly on face, trunk and proximal portions of extremities and lastly on distal portion of extremities including palms. Rash develops within 24 to 36 hours. Ordinary type of infection is the most common seen in unvaccinated persons. The skin rash becomes papules and later on by 3rd or 4th day it becomes umbilicated postules filled with tissue debris. By 2nd week pustules deflate and scabbing occurs causing scars. Other types of smallpox are modified, haemorrhagic and malignant variety.

DIAGNOSIS

Light microscopy and electron microscopy demonstrate viral particles in vesicular fluid. Cytoplasmic inclusions known as Guarnieri bodies are identified in skin lesions.

DIFFERENTIAL DIAGNOSIS

The typical centrifugal distribution of umbilicated eruptions at one time with severe toxic illness helps to distinguish smallpox from chickenpox. Palms are spared from rash in chickenpox (**Figure 1**).

COMPLICATIONS

Commonly seen complications are secondary infections, toxaemia, eye complications due to corneal ulceration, bronchopneumonia, post-infective encephalitis and osteomyelitis.

PREVENTION

Primary vaccination confers full immunity to smallpox. If vaccinated within 4 days of exposure, smallpox can be prevented, or its severity reduced. Recently, syndrome of myopericarditis has been described in vaccinated persons. Post-vaccination encephalitis is rarely seen.

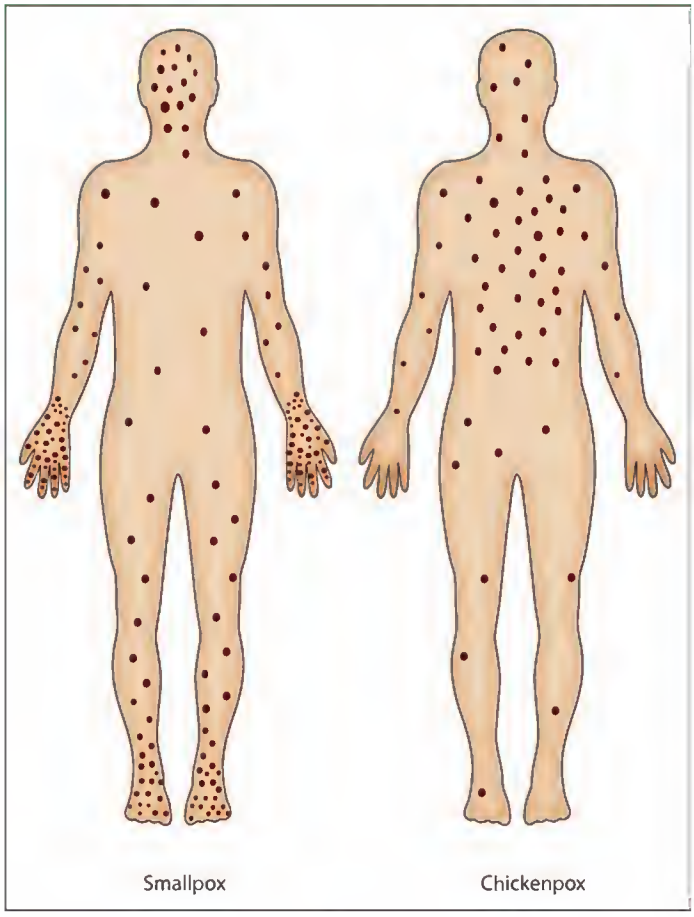


Figure 1: Distribution of skin rash in smallpox and chickenpox.

PROGNOSIS

The overall case fatality rate for ordinary type smallpox is about 30% but varies by pock distribution. Malignant and haemorrhagic types of smallpox are highly fatal.

TREATMENT

There is no specific treatment for smallpox. Suspected cases should be handled with strict isolation procedure. Treatment is mainly supportive (e.g. IV fluids, acetaminophen for fever and pain). Several anti-viral agents, including cidofovir, used in other viral fevers have *in vitro* activity against variola major. Vaccinia immune globulin has no benefit in patients with clinical smallpox cases.

RECOMMENDED READINGS

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17.50 Lymphocytic Choriomeningitis and Other Arena Virus Infections

Deepti Vibha, Garima Shukla

INTRODUCTION

Lymphocytic choriomeningitis (LCM) is a rodent borne viral infectious disease that presents as aseptic meningitis, encephalitis or meningoencephalitis in Europe, the Americas, Australia and Japan. The causative agent is lymphocytic choriomeningitis virus (LCMV), which was the first of the arenavirus family isolated in 1933 during an epidemic of St Louis encephalitis. Other viruses of this family are Lassa virus (causing Lassa fever in Africa), Junin, Machupo, Guanirato and Sabia virus (all causing haemorrhagic fever in parts of South America). No case reports exist from India.

AETIOPATHOGENESIS

LCMV is transmitted from the common house mouse (*Mus musculus*) to humans by aerosols of excreta and secretions. It is maintained in the mouse mainly by vertical transmission from infected female mouse. The vertically infected mouse remains viremic for life, with high concentrations of virus in all tissues. Infected colonies of pet hamsters have also served as a link to humans. Individuals become infected with LCMV after exposure to fresh urine, droppings, saliva, or nesting materials. Transmission can also occur when these materials are directly introduced into broken skin, the nose, the eyes or the mouth or presumably, via the bite of an infected rodent. Person-to-person transmission has not been reported, with the exception of vertical transmission from infected mother to foetus. Recent investigations indicate that organ transplantation may also be a means of transmission. Patients with LCM may have a history of residence in rodent-infested housing or other exposure to rodents. An antibody prevalence of approximately 5-10% has been reported among adults from the United States, Argentina and endemic areas of Germany.

CLINICAL MANIFESTATIONS

LCM presents with gradual fever and myalgia. Other symptoms are orchitis, transient alopaecia, arthritis, pharyngitis, cough and maculopapular rash. Less than 25% patients experience a febrile phase of 3 to 6 days with transient remission followed by recurrence of fever with severe headache, nausea and vomiting, and meningeal signs lasting for approximately 1 week. These patients virtually always recover fully, as do the uncommon patients with clear-cut signs of encephalitis. Recovery may be delayed by transient hydrocephalus.

In pregnant women, LCM virus infection may lead to foetal invasion with consequent congenital hydrocephalus and chorioretinitis. Since the maternal infection may be mild, consisting of only a short febrile illness, antibodies to the virus should be sought in both the mother and the fetus in suspicious circumstances, particularly TORCH-negative neonatal hydrocephalus.

DIAGNOSIS

During the initial febrile phase, leucopaenia and thrombocytopaenia are common and virus can usually be isolated from blood. In cases of aseptic meningitis, any of the following should suggest a suspicion of LCM: well-marked febrile prodrome, adult age, autumn seasonality, low cerebrospinal fluid (CSF) glucose levels, or CSF mononuclear cell counts of >1000/L.

The IgM-capture ELISA of serum and CSF is usually positive; RT-PCR assays have been developed for application to CSF. Recent infections transmitted by organ transplantation did not include evidence of an immune response, followed a fulminant course, and required immunohistochemistry or RT-PCR for diagnosis.

COMPLICATIONS AND MORTALITY

No chronic infection has been described in humans. Nerve deafness and arthritis have been reported. Infection of the human foetus during the early stages of pregnancy may lead to developmental deficits that are permanent. Mortality is less than 1% except in transplant recipients where high mortality has been reported.

TREATMENT

The patients require hospitalisation and supportive care, based on the severity of symptoms. Although studies have shown that ribavirin, a drug used to treat several other viral diseases, is effective against LCMV *in vitro*, there is no established evidence to support its routine use for treatment of LCM in humans.

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17.51 Prion Diseases

PK Maheshwari, A Pandey

DEFINITION

Prion diseases are a group of relentlessly progressive and fatal human and animal neuro-degenerative conditions associated with the deposition of abnormal prion protein (PrP) in the brain. The most common human form is Creutzfeldt-Jakob disease (CJD), a syndrome that can be manifested as a genetic, infectious (including 'variant'), or sporadic disorder.

EPIDEMIOLOGY

CJD is found throughout the world. The annual incidence of CJD is approximately one per million.

CLASSIFICATION

Human Prion Diseases

- Creutzfeldt-Jakob disease (CJD)
- Variant Creutzfeldt-Jakob disease (vCJD)
- Gerstmann-Straussler-Scheinker syndrome
- Fatal familial insomnia
- Kuru

PATHOGENESIS

The term 'prion' derives from proteinaceous infectious particle. Moreover, the hallmark of all prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of PrP. In humans, the PrP gene is designated PRNP and is located on the short arm of chromosome 20.

CLINICAL MANIFESTATIONS

Subacute Spongiform Encephalopathy (Creutzfeldt-Jakob Disease) (See Also Neuropathy)

The classic diagnostic triad of sporadic CJD is rapidly progressive multi-domain dementia, myoclonus, and a characteristic periodic electroencephalogram (EEG). Diffuse myoclonic jerks are seen in 80% of cases. It is asymmetrical, arrhythmic, asynchronous, and sensitive to stimuli; and most frequently found in the limbs. Additional features include cerebellar ataxia, extra-pyramidal signs, pyramidal involvement, and cortical blindness.

DIAGNOSIS

Routine blood test results are usually normal. Cerebrospinal fluid (CSF) characteristically lacks a pleocytosis or fall in glucose, but an elevated protein level (only very rarely greater than 100 mg/dL) occurs in about 40% of cases.

The only specific diagnostic tests are measurement of PrPSc by conformation-dependent immunoassay (CDI). The CDI is extremely sensitive and quantitative and can be applied in both the post- and ante-mortem detection of prions.

EEG shows typical pattern of repetitive, high-voltage, triphasic, and polyphasic sharp discharges of less than 200 ms duration, occurring every 1 to 2 seconds, seen in 60% of cases.

CT head may be normal or show cortical atrophy. MRI is valuable. On FLAIR sequences and diffusion-weighted imaging, ~90% of patients show increased intensity in the basal ganglia and cortical ribboning.

Brain, tonsillar, and olfactory mucosal biopsy can demonstrate spongiform changes.

DIFFERENTIAL DIAGNOSIS

Many conditions may mimic CJD superficially.

1. Dementia with Lewy bodies: Absence of abnormalities on diffusion-weighted and FLAIR MRI distinguishes from CJD.
2. Hashimoto's encephalopathy is diagnosed by the finding of high titers of anti-thyroglobulin or anti-thyroid peroxidase antibodies in the blood and improves with glucocorticoid therapy.
3. Intracranial vasculitides: Prominent headache, absence of myoclonus, and focal white matter changes on MRI or angiographic abnormalities favour vasculitis.
4. Paraneoplastic conditions: Detection of the paraneoplastic antibodies is the only way to distinguish these from CJD.
5. Other conditions include neurosyphilis, AIDS dementia complex, progressive multifocal leucoencephalopathy, subacute sclerosing panencephalitis, progressive rubella panencephalitis, herpes simplex encephalitis, diffuse intracranial tumour, anoxic encephalopathy, dialysis dementia, uraemia, hepatic encephalopathy, and lithium or bismuth intoxication can simulate CJD.

TREATMENT

Currently there is no available treatment. All forms of prion diseases are ultimately fatal. Treatment approaches, directed to arrest or reverse the detrimentatal secondary structures of protein are under investigation. Another approach is immunological. The ultimate goal of these studies is to produce a vaccine or compound using peptidomimetic technology that would interact with the PrP^{sc} molecule to prevent its multiplication.

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17.52 Malaria

AK Agarwal, Sarit Chatterjee

Malaria is the most important parasitic disease of humans and is caused by protozoa of the genus *Plasmodium*. The malarial parasite is transmitted by the mosquito vector of the *Anopheles* family. Although primarily a disease of the tropics, it is transmitted in 107 countries (eliminated from the United States, Canada, Europe, and Russia) causing 1 to 3 million deaths each year.

AETIOLOGY

More than 200 species of the genus *Plasmodium* are known. Only ten cause human infection. Five species cause nearly all malarial infections in humans. These are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Human infection begins when a female anopheline mosquito inoculates plasmodial sporozoites from its salivary gland during a blood meal. Rarely, malaria may be transmitted by a blood transfusion, needle sharing, organ transplant or vertically from mother to foetus.

EPIDEMIOLOGY

Malaria occurs mostly in the tropics. India harbours both *P. vivax* (50% to 55%) and *P. falciparum* (45% to 50%) and contributes 70% of malarial cases in the South East Asian region. *P. falciparum* predominates in Africa, New Guineas, and Haiti; *P. vivax* is more common in Central America. The prevalence of these two species is approximately equal in South America, the Indian subcontinent, Eastern Asia, and Oceania. *P. malariae* and *P. ovale* are unusual outside Africa. The true burden of malaria in India is difficult to ascertain. There are an estimated 70 to 100 million cases each year, but only 1.6 to 1.8 million cases are reported by the National Vector Borne Disease Control Programme (NVBDCP). The state-wise distribution of malaria in India is shown in **Figure 1**.

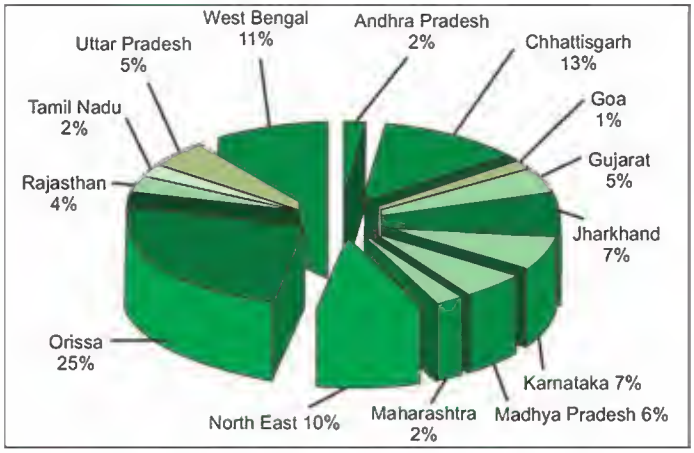


Figure 1: State-wise distribution of malaria cases in India.

Endemicity (parasitaemia rates or palpable-spleen rates in children 2 to 9 years of age) has been defined as hypoendemic (<10%), mesoendemic (11% to 50%), hyperendemic (51% to 75%), and holoendemic (>75%). With constant, frequent, year-round infection (stable transmission) adults develop immunity to severe disease. In hypoendemic areas, where transmission is low, full protective immunity is not acquired and symptomatic disease may occur at all ages (unstable transmission). In areas with unstable transmission, such as northern India, malaria behaves like an epidemic disease. To transmit malaria, the mosquito must survive for more than 7 days. In general, at altitudes above 1,000 meters and at temperatures below 16°-18°C transmission does not occur. A comparison between malaria endemicity in India in 1948 and 2004 is shown graphically in **Figure 2**.

PATHOGENESIS

The sporozoites, upon reaching the liver, begin asexual reproduction (pre-erythrocytic schizogony or merogony) and a single sporozoite produces 10,000 to >30,000 daughter merozoites. The swollen liver cell bursts and discharges merozoites into the bloodstream. These invade the red blood cells (RBCs) and multiply six- to twenty fold every 48 to 72 hour. The RBC then ruptures to release 6 to 30 daughter merozoites, each potentially capable of invading a new RBC and repeating the cycle. After a series of asexual cycles, some of the parasites develop into sexual forms (gametocytes) that can transmit malaria.

In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic sporozoites may remain dormant as hypnozoites for three weeks to a year and cause relapses.

Erythrocyte Changes in Malaria

Within the erythrocyte, haem is detoxified to haemozoin (malaria pigment). The RBC becomes more irregular in shape and less deformable.

Cytoadherence, rosetting, and agglutination leading to sequestration of RBCs are central to the pathogenesis of falciparum malaria. Membrane protuberances (knobs) appear which extrude an adhesive protein PfEMP1 (*P. falciparum*–specific, erythrocyte membrane protein 1) promoting cytoadherence. Moreover, these infected RBCs also adhere to uninfected RBCs (to form rosettes) and to other parasitised erythrocytes (agglutination). This results in the sequestration of RBCs containing mature forms of the parasite in vital organs (especially the brain), where they interfere with microcirculatory flow and metabolism. Therefore, only the younger ring forms are seen in the peripheral blood leading to under estimation of the true level of parasitaemia.

In other forms of malaria, sequestration does not occur and all stages are seen on peripheral smears. *P. vivax* and *P. ovale* show a marked predilection for young RBCs, while *P. malariae* prefer old cells. They produce a level of parasitaemia that is seldom more than 2%. *P. falciparum* invades erythrocytes of all ages and may be associated with very high levels of parasitaemia.

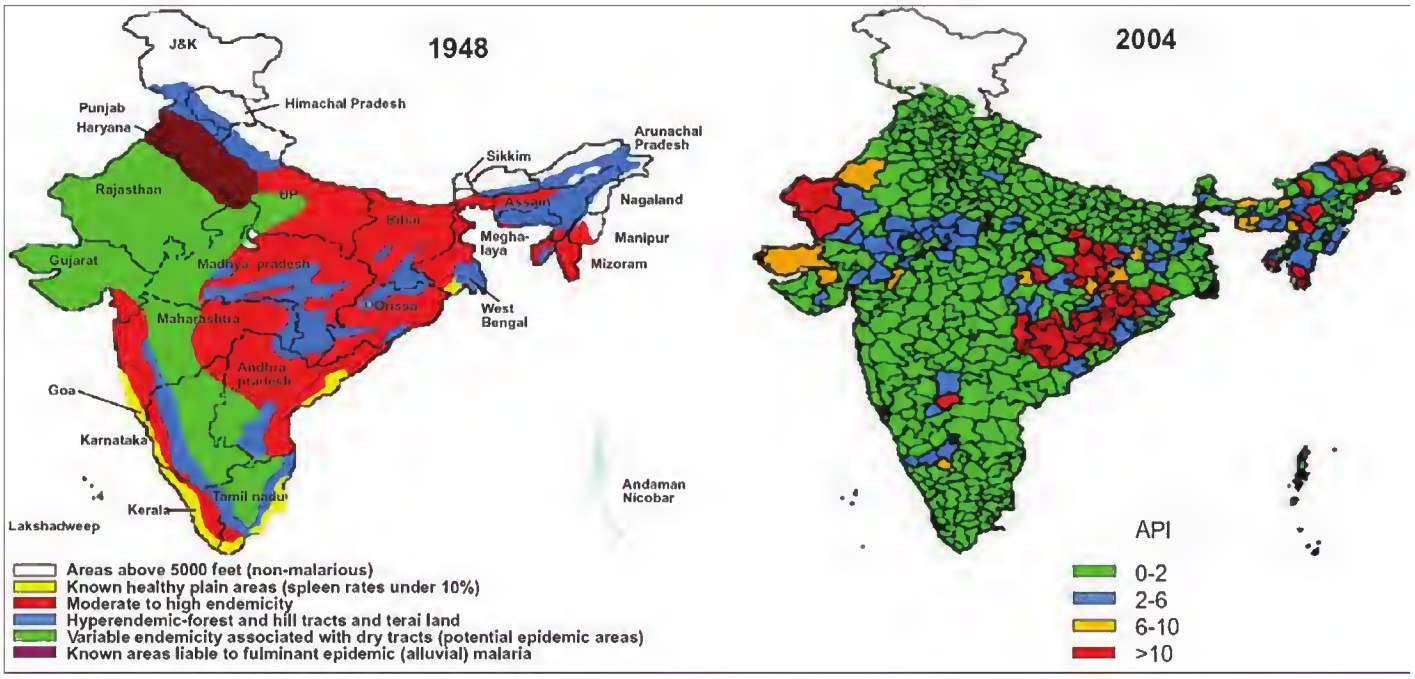


Figure 2: Malaria endemicity in India.

Source: World Health Organisation Regional Office for South-East Asia. Malaria situation in SEAR countries, India. Available at the URL: http://www.searo.who.int/Linkfiles/Malaria_in_the_SEAR_MalEndemicity_india.pdf.

API = Annual parasite incidence (a malariometric index to express malaria cases per thousand population).

Host Response

Splenic removal of both parasitised and uninfected erythrocytes is accelerated. The ruptured schizont releases cytokines causing fever. Synchronisation of the parasitic cycle eventually produces the regular fever spikes and rigors. These regular fever patterns (tertian, every two days; quartan, every three days) are seldom seen today in patients who receive prompt and effective antimalarial treatment.

Sickle cell disease, ovalocytosis, thalassaemia, haemoglobin C and glucose-6-phosphate dehydrogenase (G6PD) deficiency confer protection against death from falciparum malaria. West Africans lacking RBC Duffy antigen and individuals with haemoglobin E are refractory to infection by *P. vivax*.

Repeated exposure confers protection from disease, but not from infection. Immunity is both species and strain specific. Both humoral immunity and cellular immunity are necessary for protection.

CLINICAL FEATURES

Uncomplicated Malaria

Malaria begins with nonspecific symptoms like headache, fatigue, abdominal discomfort, and muscle aches followed by fever; but there is no neck stiffness or photophobia. Nausea, vomiting and orthostatic hypotension are common. The classic malarial paroxysms (fever spikes, chills, and rigors at regular intervals), are common in infection with *P. vivax* or *P. ovale*. The fever often rises above 40°C with tachycardia and delirium. Generalised seizures are specifically associated with falciparum malaria and may herald the onset of cerebral disease. Slight enlargement of the liver and a palpable spleen are common. Mild jaundice is common in patients with otherwise uncomplicated falciparum malaria and usually resolves over one to three weeks.

Severe Malaria

Severe malaria is a medical emergency. Unlike *P. falciparum*, *P. vivax* rarely causes severe disease in healthy travellers or in temperate endemic regions and has been regarded as readily treatable with chloroquine. However, in tropics recent reports have highlighted severe and fatal disease associated with *P. vivax* infection. Studies from Indonesia, Papua New Guinea, Thailand and India have shown that 21% to 27% of patients with severe malaria have *P. vivax* monoinfection. The clinical spectrum of these cases is broad with an overall mortality of 0.8% to 1.6%. Major manifestations include severe anaemia and respiratory distress with infants being particularly vulnerable. Other features observed were hepatic dysfunction and jaundice, renal failure, shock, cerebral malaria, thrombocytopaenia and hypoglycaemia. However, it has been observed that in the majority of cases where *P. vivax* was initially attributed as the cause of severe disease, concurrent mixed infection with *P. falciparum* was identified. A laborious search for *P. falciparum* even after an initial *P. vivax* positive report is of great value. A nested PCR when available can be very useful in detection of the causal species.

Clinical features of severe malaria are presented in **Table 1**. Poor prognostic features in severe falciparum malaria are shown in **Table 2**.

Cerebral Malaria

Cerebral malaria is characterised by a deep unarousable coma with a Glasgow coma scale (GCS) less than 7/15 with an onset which may be gradual or sudden following a convulsion. The eyes may remain open (coma vigil) (**Figure 3A**). It carries a mortality of >20%.

Table 1: Manifestations of Severe Falciparum Malaria

Signs	Manifestations
Cerebral malaria	Unarousable coma, coma persisting for >30 min after generalised convulsions
Jaundice	Serum bilirubin level of ≥3.0 mg/dL
Renal failure	Urine output <400 mL/24 hrs; serum creatinine >3.0 mg/dL
Acidosis	Arterial pH <7.25 or plasma bicarbonate level of <15 mmol/L
Severe anaemia	Haematocrit of <15% or haemoglobin level of <5 g/dL
Pulmonary oedema/ adult respiratory distress syndrome	Non-cardiogenic pulmonary oedema, often aggravated by overhydration
Hypoglycaemia	Plasma glucose level of <40 mg/dL
Hypotension/shock	Systolic blood pressure of <80 mm Hg in adults; core/skin temperature difference of >10°C; capillary refill >2 s
Bleeding/ disseminated intravascular coagulation	Significant bleeding and haemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation
Convulsions	More than two generalised seizures in 24 hours
Haemoglobinuria	Macroscopic black, brown, or red urine (*should not be associated with G6PD deficiency*)
Hyperparasitaemia	Parasitaemia level of >5%

Table 2: Features Indicating a Poor Prognosis in Severe Falciparum Malaria

Clinical	Marked agitation, deep coma, absent corneal reflexes, decerebrate/decorticate rigidity, opisthotonus, papilloedema, respiratory distress (acidosis), hypothermia (<36.5°C), bleeding, repeated convulsions, anuria, shock.
Biochemistry	Hypoglycaemia (<40 mg/dL), acidosis (arterial pH <7.3, serum HCO_3 <15 mmol/L), serum creatinine (>3 mg/dL), total bilirubin (>3 mg/dL), elevated liver enzymes (AST/ALT>3 times the upper limit of normal), elevated muscle enzymes (CPK, myoglobin), high CSF lactate >6 mmol/L, low CSF glucose, venous lactate >5 mmol/L, elevated plasma 5'nucleotidase, low antithrombin III levels, very high plasma tumour necrosis factor (TNF).
Haematology	Leucocytosis (>12,000/µL), severe anaemia (PCV <15%, haemoglobin <5 g/dl), coagulopathy, decreased platelet count (<50,000/µL), prolonged prothrombin time (>3 s), prolonged partial thromboplastin time, decreased fibrinogen (<200 mg/dL).
Parasitology	Increased mortality at >100,000/µL, high mortality at >500,000/µL, >20% mature pigmented parasites, >5% of neutrophils with visible pigment.

It clinically manifests as a diffuse symmetric encephalopathy without focal neurological or meningeal signs. Retinal haemorrhages, papilloedema and cotton wool spots may be evident on ophthalmoscopy. Convulsions (usually generalised and multiple) are common. Patients surviving cerebral malaria (especially children) may have neurologic sequelae.



Figure 3A: Clinical photograph of a patient lying in coma due to severe complicated malaria. The eyes are open even though the patient is in unarousable coma suggestive of a vigil-like state. When a patient is in coma-vigil, assessment of the eye signs in the Glasgow coma scale becomes difficult.

Hypoglycaemia

Hypoglycaemia results from failure of hepatic gluconeogenesis and increased consumption of glucose by both the host and the malarial parasites. Moreover, quinine and quinidine are powerful insulin secretagogues and compound the problem. Hypoglycaemia can be a significant problem in children and pregnant women.

Acidosis

Lactic acidosis results from anaerobic glycolysis in tissues, hypovolaemia, lactate production by the parasites and a failure of hepatic and renal lactate clearance. In children, ketoacidosis may also be present. The prognosis of severe acidosis is poor.

Non-cardiogenic pulmonary oedema

The pathogenesis of non-cardiogenic pulmonary oedema is unclear. The mortality rate is more than 80%. This condition can be aggravated by over-vigorous administration of IV fluids.

Renal impairment

Renal impairment manifests as acute tubular necrosis and is the result of erythrocyte sequestration interfering with renal microcirculatory flow and metabolism. Early dialysis enhances the likelihood of a patient's survival.

Haematologic abnormalities

Anaemia results from accelerated RBC removal by the spleen, obligatory RBC destruction during parasite schizogony and ineffective erythropoiesis. Mild coagulation abnormalities and mild thrombocytopaenia are usual in falciparum malaria. Significant bleeding due to disseminated intravascular coagulation is uncommon.

Liver dysfunction

Mild haemolytic jaundice is common in malaria. Severe jaundice in severe falciparum malaria results from haemolysis, hepatocyte injury, and cholestasis and is usually associated with manifestations of acute renal failure (ARF). This association is a common clinical presentation of severe and complicated falciparum malaria.

Other complications

Sepsis, especially due to *Salmonella* bacteraemia has been specifically associated with *P. falciparum* infections. Aspiration pneumonia and catheter-induced urinary tract infections are not uncommon. Haemoglobinuria may occasionally be a manifestation of severe malaria in patients with massive intravascular haemolysis (**Figure 3B**).



Figure 3B: Cola coloured urine in a patient with severe malaria with haemoglobinuria.

Sequelae: Post-Malaria Neurological Syndrome (PMNS)

Rarely, adults (<3%) and children (>10%) suffer from a syndrome of neurological and psychiatric symptoms within two months after treatment of malaria (PMNS). Psychosis (paranoia, mania, hallucinations, and delusions) are the commonest sequelae. Hemiplegia, cerebral palsy, cortical blindness/deafness, impaired cognition and learning have been reported. Rare cases of Guillain-Barré syndrome (GBS) and cerebellar ataxia have also been observed.

Malaria in Pregnancy

Falciparum malaria is associated with low birth weight, foetal distress, premature labour, stillbirth and increased infant and childhood mortality. *P. vivax* malaria in pregnancy is also associated with a reduction in birth weight.

Malaria in Children

Convulsions, coma, hypoglycaemia, metabolic acidosis, and severe anaemia are relatively common among children with severe malaria. Deep jaundice, acute renal failure, and acute pulmonary oedema are unusual. Anti-malarial drugs are well tolerated.

Transfusion Malaria

Malaria can be transmitted by blood transfusion, needle-stick injury, sharing of needles and organ transplantation. The incubation period is short as there is no pre-erythrocytic stage. Radical chemotherapy with primaquine is not necessary for *P. vivax* infections.

Malaria and HIV

HIV infection increases the frequency of clinical malaria and parasite density. There is greater parasitaemia with advancing immunosuppression. Morbidity is more and chemoprophylaxis is less effective. Maternal HIV infection predisposes pregnant women to malaria.

CHRONIC COMPLICATIONS OF MALARIA

Tropical Splenomegaly (Hyperreactive Malarial Splenomegaly)

Chronic or repeated malarial infections stimulate reticulo-endothelial hyperplasia and clearance activity and eventually produce splenomegaly. Hyperreactive malarial splenomegaly (HMS) is characterised by massive splenomegaly, hepatomegaly, marked elevations in serum titres of IgM malarial antibody. Peripheral smears usually do not reveal malarial parasites. The patient usually presents with an abdominal mass or a dragging sensation in the abdomen and occasional sharp abdominal pains suggesting perisplenitis. Anaemia and some degree of pancytopaenia are usually evident. There is hepatic sinusoidal lymphocytosis. PCR can detect low levels of parasitaemia, but the cost and complexity preclude widespread use. Long-term antimalarial prophylaxis is required in endemic areas. Chloroquine, proguanil and pyrimethamine are the agents of choice.

In some cases of HMS, a malignant lymphoproliferative disorder may develop.

Quartan Malarial Nephropathy

Chronic or repeated infections, especially with *P. malariae,* cause immune-complex injury to the renal glomeruli, resulting in nephrotic syndrome. Some cases respond to cytotoxics, but antimalarials and corticosteroids do not prevent progression.

Burkitt's Lymphoma

There is a strong association between Burkitt's lymphoma and malaria. Progression of Epstein-Barr virus (EBV) infection in B lymphocytes is controlled by cytotoxic T cells. This response is decreased in malaria which may predispose to malignant transformation.

DIAGNOSIS

Demonstration of the Parasite

The diagnosis of malaria requires demonstration of asexual forms of the parasite. Both thin and thick blood smears should be examined. Giemsa at pH 7.2 is the preferred stain. While the thick film has the advantage of concentrating the parasites, the thin smear helps in identifying the species. Sequential blood smears should be obtained particularly for detection of *P. falciparum*, sexual as well as asexual forms. The appearance of malarial parasites on

peripheral blood smears are shown in **Figures 4A to D**. Antibody-based diagnostic stick or card tests that detect *P. falciparum*–specific, histidine-rich protein 2 (PfHRP2) or lactate dehydrogenase antigens are rapid, simple, sensitive and specific (**Figure 5**). Some of these tests allow falciparum malaria to be distinguished from the other forms of malaria. Microtube concentration methods with acridine orange staining are ideal for processing large numbers of samples rapidly and have sensitivity similar to or superior to that of thick films (**Figure 6**). PCR can detect as few as 5 parasites/μL and is the most sensitive and specific test. Availability of equipment and trained personnel and cost are the limiting factors.



Figure 4A: Photomicrograph showing ring form (circle) and gametocytes (arrows) in erythrocytes (Giemsa x 400).
Kind courtesy: Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati.

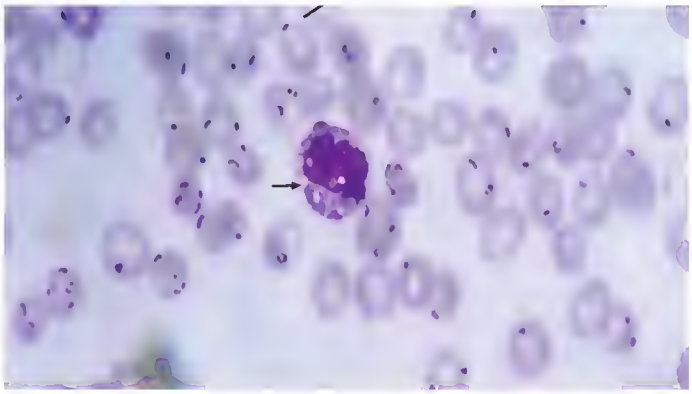


Figure 4B: Photomicrograph showing multiple ring forms in erythrocytes. A monocyte is also seen in the centre (arrow) (Giemsa x 1000).
Kind courtesy: Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati.

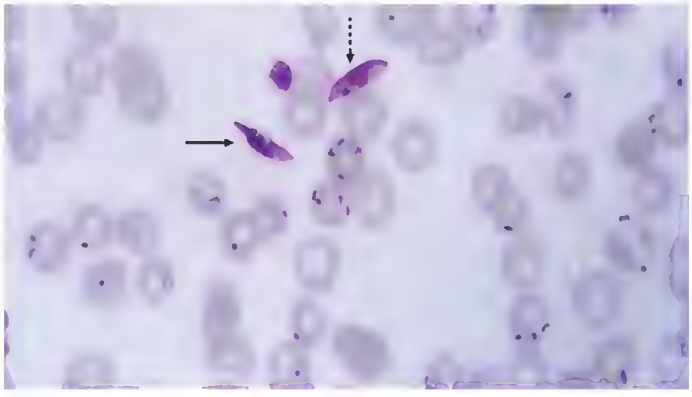


Figure 4C: Photomicrograph showing multiple ring forms in erythrocytes, male (solid arrow) and female (interrupted arrow) gametocytes (Giemsa x 1000).
Kind courtesy: Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati.

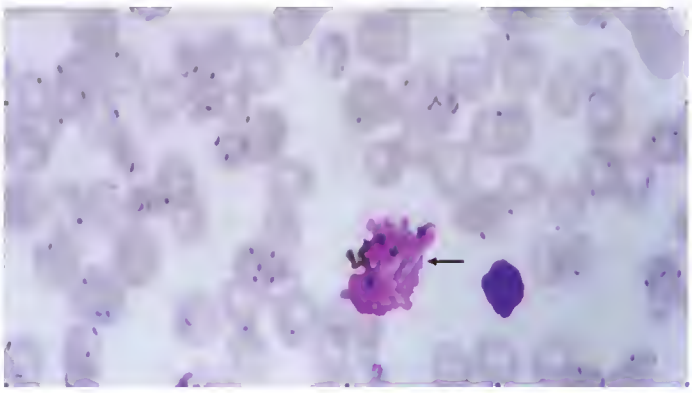


Figure 4D: Photomicrograph showing multiple ring forms in erythrocytes with high parasitaemia. Monocyte [arrow] showing engulfed haemozoin pigment can also be seen (Giemsa x 1000).
Kind courtesy: Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati.

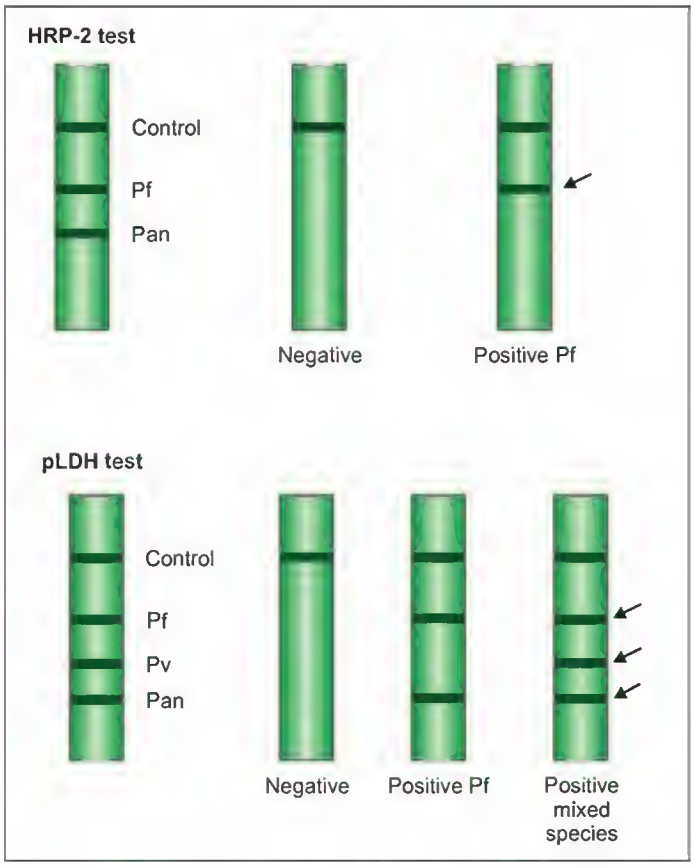


Figure 5: Antibody-based diagnostic stick / card tests that detect *P. falciparum*–specific, histidine-rich protein 2 (PfHRP2) or lactate dehydrogenase antigens.

Laboratory Findings

In uncomplicated malaria, normochromic, normocytic anaemia and a normal leucocyte count are usual. The erythrocyte sedimentation rate, plasma viscosity and levels of C-reactive protein are high. The platelet counts is usually reduced to <100,000/μL. At times, severe thrombocytopaenia may be associated with vivax malaria. Urinalysis generally gives normal results. Usually the CSF is normal.

Laboratory findings of severe malaria have been discussed earlier.

TREATMENT

Malaria cannot be diagnosed clinically. However, presumptive treatment may occasionally be given by experienced clinicians,

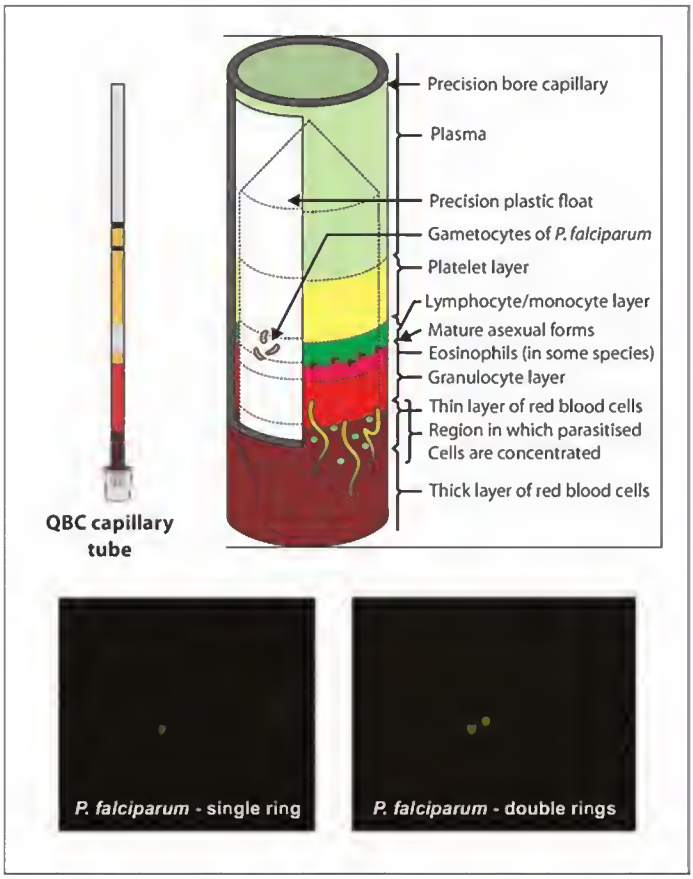


Figure 6: Quantitative buffy coat technique for identification of malarial parasites.

if the situation warrants such an approach. The treating physician should know the seasonal distribution and resistance pattern of malaria in his area. *P. vivax* cases tend to occur more during the monsoon season and *P. falciparum* cases in the post-monsoon season. When a patient presents with fever, thick and thin blood smears should be prepared and examined immediately. Alternatively, a rapid antigen detection card or stick test should be performed. Patients with severe malaria or those unable to take oral drugs should receive parenteral anti-malarial therapy. If in doubt, the parasitic agent should be considered resistant. The treatment of uncomplicated malaria is summarised in **Table 3**.

Chloroquine remains the drug of choice for uncomplicated vivax malaria. Artemisinin-based combination therapy (ACT) regimens now constitute first-line recommended treatment for falciparum malaria. In 117 districts in India, ACT (artesunate + sulphadoxine-pyrimethamine) has been used. In areas with multidrug-resistant falciparum malaria, either artemether-lumefantrine or artesunate-mefloquine should be used. Artesunate plus sulphadoxine-pyrimethamine combination may not be preferred due to emerging resistance to sulphadoxine-pyrimethamine. Furthermore, this combination is not recommended for *P. vivax* infection. These 3-day regimens are well tolerated, although mefloquine is associated with increased rates of vomiting and dizziness. Gametocidal therapy with primaquine is not required when ACT regimens have been used. ACT use is associated with minimal incidence of recrudescence and is designed to prevent or delay the emergence of resistance to artemisinins. The treatment of severe malaria is shown in **Table 4**.

Table 3: Treatment of Uncomplicated Malaria

Known chloroquine-sensitive strains:

1. Chloroquine (10 mg of base/kg body wt stat followed by 5 mg/kg body wt at 12, 24, and 36 hours or 10 mg of base/kg body wt stat followed by 10 mg/kg body wt at 24 hours and 5 mg/kg body wt at 48 hours)
2. Amodiaquine (10-12 mg of base/kg body wt OD for 3 days)

Nowadays, chloroquine-sensitive falciparum malaria occurs in only limited regions of India.

Radical treatment for P. vivax or P. ovale infection:

In addition to chloroquine or amodiaquine as detailed above, primaquine (0.25 mg of base/kg body wt OD) should be given for 14 days. Primaquine should not be given to patients with severe G6PD deficiency.

Uncomplicated P. falciparum malaria:

1. Artemether-lumefantrine (1.5/9 mg/kg body wt at hours 0 and 8 on day 1 and bid on day 2 and 3)
2. Artesunate (4 mg/kg body wt OD for 3 days) plus Mefloquine (25 mg of base/kg body wt – either 8 mg/kg body wt OD for 3 days or 15 mg/kg body wt on day 2 and then 10 mg/kg body wt on day 3)
3. Artesunate (4 mg/kg body wt od for 3 days) plus sulphadoxine (25 mg/kg body wt)/pyrimethamine (1.25 mg/kg body wt) as a single dose
4. Artesunate (4 mg/kg body wt od for 3 days) plus amodiaquine (10 mg of base/kg body wt OD for 3 days)

Note: All drugs are administered orally.

Table 4: Treatment of Severe Malaria

Chloroquine resistant:

1. Artesunate (2.4 mg/kg bw stat IV followed by 2.4 mg/kg body wt at 12 and 24 h and then daily)*

OR

2. Artemether (3.2 mg/kg body wt stat IM followed by 1.6 mg/kg body wt qd)*

OR

3. Quinine dihydrochloride (20 mg of salt/kg body wt infused over 4 hours, followed by 10 mg of salt/kg body wt infused over 2-8 hours q8h)#

OR

4. Quinidine (10 mg of base/kg body wt infused over 1-2 hours, followed by 1.2 mg of base/kg body wt per hour with electrocardiographic monitoring). (Not easily available in India)#

Chloroquine sensitive:

1. Chloroquine dihydrochloride 10 mg base /kg body wt in isotonic fluid IV over 8 hours followed by 15 mg/kg body wt over next 24 hours.

OR

2. Chloroquine dihydrochloride 5 mg base /kg body wt in isotonic fluid IV over 6 hours followed by 5 mg/kg body wt every 6 hours over next 30 hours.

OR

3. If IV infusion is not possible chloroquine dihydrochloride 3.5 mg base/kg body wt every 6 hours by intramuscular or subcutaneous route (contraindicated in children less than 7 years of age).

** Complete course of artemisinin-based combination therapy (ACT) should be administered to all cases following parenteral treatment as soon as oral treatment is feasible (Pregnancy being an exception).*

As soon as possible oral therapy (same drug) may be administered and a 7-10 day course completed. It is preferable to add doxycycline (3 mg/kg body wt qd for 3-7 days) or clindamycin (10 mg/kg body wt bid for 3-7 days).

GUIDELINES FOR PARENTERAL ADMINISTRATION OF ANTI-MALARIAL DRUGS IN SEVERE MALARIA

Treatment of severe and complicated malaria should be initiated without any delay, preferably with intravenous antimalarials. Artesunate is the drug of choice for severe and complicated falciparum malaria; intravenous quinine by infusion is an alternative.The data from large studies in Southeast Asia showed a 35% reduction in mortality rate compared to quinine. Artesunate is preferably given by the IV route, but can also be given by IM injection. Artemether and arteether (oil-based formulations given by IM injection) do not confer the same survival benefit as artesunate. The administration of quinidine must be closely monitored for dysrhythmias and hypotension. Total plasma levels >8 microg/ml, a QTc interval >0.6 sec or saline-unresponsive hypotension warrant treatment stoppage. Quinine is safer than quinidine; cardiovascular monitoring is not required except when the recipient has cardiac disease. All patients treated with IV quinine or quinidine should receive a continuous infusion of 5% or 10% dextrose. A loading dose of quinine should not be used if the patient has received quinine, quinidine or mefloquine in the preceding 12 to 24 hours. If the patient remains seriously ill or in acute renal failure after 48 hours of IV quinine therapy, the maintenance dose should be reduced by one-third to half. The initial dose of antimalarials should never be reduced in the presence of renal or hepatic dysfunction. In areas where IV artemisinins are unavailable, rectal preparations have been used. The possibility of developing resistance with artemisinin monotherapy is real and it should be avoided. All patients should receive the preferred form of ACT (for three days) as soon as they can take fluids. In case parenteral treatment needs to be continued, artemisinins and quinine are to be continued for five days and seven days respectively.

Ancillary drugs, such as high-dose glucocorticoids, urea, heparin, dextran, desferrioxamine, antibody to tumour necrosis factor, and high-dose phenobarbital (20 mg/kg) have proven to be either ineffective or harmful and should not be used. Recombinant human erythropoietin has shown promise in the management of cerebral malaria. In ARF or severe metabolic acidosis, haemofiltration or haemodialysis should be started as early as possible. Exchange blood transfusions can be lifesaving in severely ill patients with very high levels of parasitaemia, but conclusive evidence regarding their efficacy is yet to be established.

Whole blood (preferably fresh) or packed cells should be transfused if the hematocrit falls to <20%. Renal function should be checked daily. Central venous pressure should be measured and maintained in the low-normal range.

Malaria in Pregnancy

The expert group on chemotherapy of malaria, NVBDCP has recommended a combination of quinine plus clindamycin for the treatment of falciparum malaria in all trimesters of pregnancy. Use of ACT, though safe in 2nd and 3rd trimesters, is under evaluation in an ongoing trial by National Institute of Malaria Research (NIMR). Anti-malarial activity and toxicity of drugs are listed in **Table 5**.

Table 5: Characteristics of Anti-Malarial Drugs

Drug(s)	Anti-malarial Activity	Toxicity
Quinine, quinidine	Trophozoites, gametocytes of *P. vivax*, *P. ovale*, and *P. malariae*	Hypoglycaemia, hypotension, blindness, deafness, cardiac arrhythmias, thrombocytopaenia, haemolysis, haemolytic-uraemic syndrome, vasculitis, cholestatic hepatitis, neuromuscular paralysis, 'Cinchonism'; postural hypotension; QTc interval prolongation, diarrhoea, visual disturbance, rashes, very bitter taste
Chloroquine	As for quinine	Bitter taste, hypotensive shock (parenteral), cardiac arrhythmias, neuropsychiatric reactions, retinopathy, myopathy, nausea, dysphoria, pruritus, postural hypotension
Amodiaquine	As for quinine	Nausea, agranulocytosis; hepatitis (mainly with prophylactic use)
Mefloquine	As for quinine	Neuropsychiatric reactions, convulsions, encephalopathy, nausea, dysphoria, sleeplessness, nightmares
Halofantrine	As for quinine	Atrioventricular block; QTc interval prolongation, ventricular tachyarrhythmias, diarrhoea, abdominal pain, cough, rash
Artemisinin derivatives (artemether, artesunate)	Kills all but fully mature gametocytes of *P. falciparum*, no action on liver stages	Anaphylaxis, urticaria, fever, reduction in reticulocyte count (but not anaemia)
Pyrimethamine	For blood stages	Megaloblastic anaemia, pancytopaenia, pulmonary infiltration, methaemoglobinaemia
Proguanil (chloroguanide)	Primary tissue stages; not used alone for treatment	Megaloblastic anaemia, renal failure, mouth ulcers, alopaecia
Primaquine	Radical cure; eradicates hepatic forms of *P. vivax* and *P. ovale*; kills all stages of gametocyte development of *P. falciparum*	Massive haemolysis in subjects with severe G6PD deficiency, nausea, vomiting, diarrhoea, abdominal pain, haemolysis, methaemoglobinaemia
Atovaquone	Acts mainly on trophozoite blood stage	Needs to be taken with food, contraindicated in renal compromise, pregnancy, lactating mothers and children <5 years
Lumefantrine	As for quinine	None identified

Table 6: Chemoprophylaxis in Malaria

Drug	Usage	Dose	Comments
Atovaquone/ proguanil	Prophylaxis only in areas with chloroquine or mefloquine-resistant *P. falciparum*	250 mg of atovaquone and 100 mg of proguanil hydrochloride OD	Begin 1-2 days before and for 7 days after leaving such areas
Chloroquine phosphate	Prophylaxis only in areas with chloroquine-sensitive *P. falciparum*	300 mg of base (500 mg of salt) PO once weekly	Begin 1-2 weeks before and for 4 weeks after leaving such areas
Doxycycline	Prophylaxis in areas with chloroquine or mefloquine-resistant *P. falciparum*	100 mg PO OD	Begin 1-2 days before travel and for 4 weeks after leaving such areas
Mefloquine	Prophylaxis in areas with chloroquine-resistant *P. falciparum*	228 mg of base (250 mg of salt) PO once weekly	Begin 1-2 weeks before travel and for 4 weeks after leaving such areas

PREVENTION

Vector Control

Vector control measures include spraying of insecticides and biological methods. These have not been very successful due to resistance and changing breeding habits of vectors.

Personal Protection

These measures include the avoidance of exposure to mosquitoes at their peak feeding times, the use of insect repellants, suitable clothing, and insecticide-impregnated bed nets.

Containment

Malaria may be contained by judicious use of insecticides to kill the mosquito vector, rapid diagnosis, appropriate patient management, and chemoprophylaxis.

Malaria Vaccine

Currently, several antigen and adjuvant combination vaccines are in clinical trials.

Chemoprophylaxis

Recommendations for prophylaxis (**Table 6**) depend on knowledge of local patterns of plasmodial drug sensitivity and the likelihood of acquiring malarial infection. When there is uncertainty, drugs effective against resistant *P. falciparum* should be used.

Atovaquone/proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate <30 ml/min). Atovaquone/proguanil is not recommended for children weighing <5 kg, pregnant women, or women breastfeeding infants weighing <5 kg. It should be taken with food or a milky drink.

Mefloquine is the only prophylactic drug advised for pregnant women. This drug is generally considered safe in the second and third trimesters of pregnancy. For pregnant women residing in endemic regions (Pf% >30) IPTp (Intermittent Preventive Therapy in pregnant women) with sulphadoxine-pyrimethamine is recommended.

Children born to nonimmune mothers in endemic areas should receive prophylaxis from birth.

RECOMMENDED READINGS

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17.53 Amoebiasis and Giardiasis

MP Sharma, Vaibhav Gupta

GIARDIASIS

Giardiasis (beaver fever) is a parasitic infection caused by a single celled organism called *Giardia lamblia*. Leeuwenhoek is credited with discovering it; however, its current name was given by an American parasitologist, Charles Wardell Stiles, to commemorate the work done on *Giardia* by Dr Giard and Dr Lambl.

Epidemiology

There are six species of Giardia, namely *G. lamblia* (mammals), *G. agilis* (amphibians), *G. muris* (rodents), *G. ardeae* and *G. psittaci* (Birds) and *G. microti* (Muskrats). Only *G. lamblia* is responsible for clinical disease in humans.

G. lamblia is seen throughout the world with a prevalence ranging between 20% and 30% in the developing world and 2% to 5% in the developed world. It commonly infects individuals who drink unclean/unfiltered water directly from taps, ponds, rivers, etc., campers, swimmers, hikers, international travelers and child care workers.

Life Cycle

Giardia has no vector. Humans, aquatic and semi-aquatic mammals, rodents, etc., serve as important reservoirs.

Giardiasis is caused by ingestion of infective cysts (10 to 25 cysts) which are transmitted through water-borne, person-to-person and venereal routes. Cysts are non-motile, egg shaped, measure 8 to 14 µm by 7 to 10 µm and encased by a smooth colourless, thick refractile wall. Upon ingestion, they survive the acidic environment of the stomach, reach the small intestine and upon excystation give rise to two binuclear trophozoites which are actively motile owing to the presence of four pairs of flagellae. They attach themselves to the intestinal mucosa and divide by binary fission. They do not cause invasive disease. As trophozoites migrate towards the lower intestine, they retreat into the cyst form which are excreted in the faeces, and are responsible for spread of infection. Cysts are resistant to routine chlorination but not to heating and drying.

Clinical Features

Majority of patients remain asymptomatic. Acute symptoms include crampy abdominal pain, watery diarrhoea, vomiting and fever which may last for few days. In the chronic stage, patients will have bloating, nausea, abdominal fullness, epigastric or substernal burning, malaise, fatigue, etc. A few patients may also develop malabsorption syndrome.

Diagnosis

Diagnosis can be made by stool examination and looking for cysts and trophozoites. Trophozoites are visible only in fresh watery stools. Usually three stool samples are taken and the trichrome stain is used.

Trophozoites can also be seen in a duodenal aspirate, which is more specific and sensitive than stool examination, but is more cumbersome and technically demanding.

Immunofluorescent antibody (IFA) assay or a capture enzyme linked immunosorbent assay (ELISA) against cyst or trophozoite antigens are available commercially. They have a sensitivity of 85% to 98% and specificity of 90% to 100%. Stool antibody tests are not readily available.

Differential Diagnosis

Other causes of acute diarrhoea should be considered like amoebiasis, viral infection, helminths, salmonellosis, etc., while making a diagnosis of giardiasis.

Treatment and Prevention

Treatment includes antibiotics like metronidazole (400 mg PO tid x 5d), albendazole (400 mg PO od x 3d), tinidazole (2 gm PO once), furazolidone and nitazoxanide.

Cyst excretion stops after 2 to 3 days of initiation of antibiotics. Paromomycin is the drug of choice for pregnant woman, as it is poorly absorbed and excreted almost 100% in faeces.

Prevention is of utmost importance and includes maintenance of personal hygiene like washing hands properly with soap, drinking clean boiled water, avoiding eating from unhygienic open places where food is washed in contaminated water.

An important step in prevention of infection is an effective and good excreta disposal system and regular cleaning of swimming pools, wells and other water sources.

AMOEBIASIS

Entamoeba histolytica is one of the most prevalent intestinal protozoa in developing countries.

E. histolytica exists in either trophozoite or cyst form. Trophozoite is the motile form of *Entamoeba*. Actively motile amoebae are elongated whereas resting trophozoites tend to be spherical. The cysts are round or oval hyaline bodies, surrounded by a refractile wall composed of fibrillar material. There are two separate species—*E. histolytica* and *E. dispar*, morphologically indistinguishable from one another.

E. dispar also colonises the human gut but has no pathogenic potential.

Life Cycle of *E. histolytica* (Figure 1)

A human acquires infection by ingestion of the cyst form which is resistant to the acidic pH of the stomach. Excystation occurs in the small bowel, with division of the mature quadrinucleated cyst into four, and then eight trophozoites by nuclear and cytoplasmic division. The trophozoites move to, and colonise in, the large bowel, where they feed on bacteria and cellular

debris. If luminal conditions are unfavourable, the trophozoites may encyst. The cysts are excreted and remain viable for weeks or months. Trophozoites excreted during episodes of acute colitis rapidly degenerate and do not transmit infection. Infection results from ingestion of cysts in contaminated food or water.

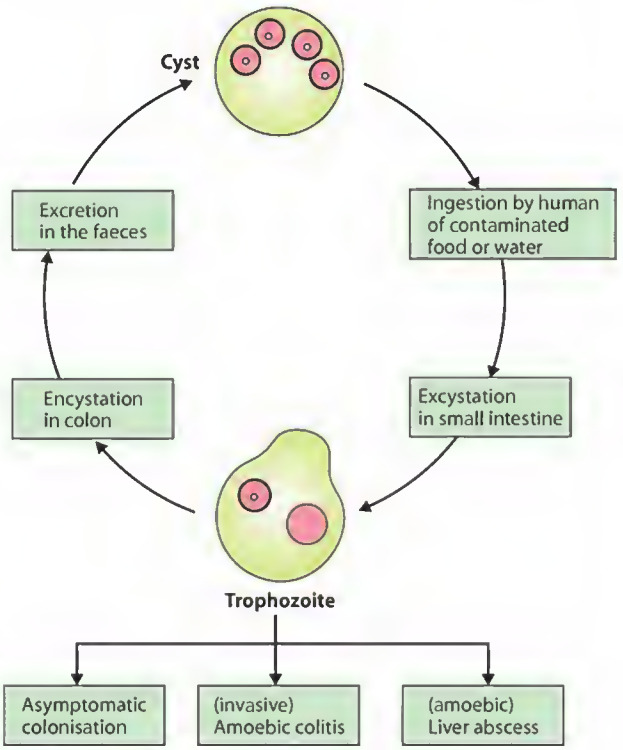


Figure 1: Life-cycle of *Entamoeba histolytica* and the clinical manifestations of infection in humans.

Epidemiology

The main reservoirs of *E. histolytica* are humans. It is estimated that 10% of the world's population is infected by *E. dispar* or *E. histolytica*. *E. dispar* infection is approximately 10-fold more common than *E. histolytica* infection. Symptomatic invasive amoebiasis develops in 10% of individuals with *E. histolytica* infection.

High rates of amoebic infection are seen in the Indian subcontinent, in Southern and Western Africa, in the Far East and in areas of South and Central America.

Patients with a high mortality from invasive amoebiasis, though not necessarily at increased risk of infection, include malnourished individuals, children younger than one year, pregnant women, and individuals receiving steroid therapy.

INTESTINAL AMOEBIASIS

Pathogenesis

Intestinal invasive amoebiasis is associated with a myriad of clinical presentations and surgical complications (**Tables 1 and 2**).

The typical amoebic intestinal ulcers are found in the caecum, sigmoid colon, and rectum. These ulcers are characteristically shallow with broad elevated margins.

Post intestinal infection with *E. histolytica*, the antibodies (IgA and IgE) response develops after an unknown period. The protective role of secretory (IgA and IgE) in amoebiasis has not been established. They can be detected for more than three years after an invasive amoebic episode, in the absence of any recurrent infection.

Table 1: Clinical Syndromes Associated with *E. histolytica* Infection

Intestinal amoebiasis
Asymptomatic cyst passers
Acute amoebic colitis
Mucosal disease
Transmural disease
Ulcerative postdysenteric colitis
Appendicitis
Amoeboma
Amoebic stricture
Extraintestinal amoebiasis
Amoebic liver abscess
Perforation and peritonitis
Pleuropulmonary amoebiasis
Amoebic pericarditis
Cutaneous amoebiasis

Table 2: Surgical Complications of Intestinal Amoebiasis

Fulminant colitis
Toxic dilatation
Necrosis
Perforation
Bleeding
Stricture

Clinical Features

Patients with acute amoebic dysentery present with a 1 to 2 week history of abdominal pain, tenesmus, and frequent loose, watery stools containing blood and mucous. Despite the presence of mucosal ulcerations and occult blood in stools, leucocytes may not be found in faeces because of the lytic activities of the parasites. Colonoscopy may show the characteristic appearance of the punctate, haemorrhagic ulcers dispersed throughout a normal appearing mucosa.

Diagnosis

A definitive diagnosis of invasive intestinal amoebiasis is made by demonstration of *E. histolytica* cysts/trophozoites in the stool. These amoebae may have ingested red blood cells (haematophagus trophozoites). The cysts may remain viable for some time in unpreserved stools while trophozoites are labile and remain in stool for about 30 minutes. The diagnostic yield is better if the specimen is collected over a period of 3 days or longer.

Serum antibodies in amoebiasis develop only during *E. histolytica* infection and not during *E. dispar* infection. The absence of serum antibodies to *E. histolytica* after 1 week of symptoms is strong evidence against the diagnosis of invasive amoebiasis of the colon or liver. Serum antibodies to amoebae are detected in 85% to 95% of all patients who present with invasive amoebiasis or liver abscess. However, as antibodies persist for many years, ELISA or an indirect haemagglutination (IHA) cannot differentiate acute from remote infection in areas of high endemicity.

Treatment

The drug treatment of uncomplicated amoebiasis is given in **Table 3**.

Table 3: Pharmacotherapy for *E. histolytica* Infection in Adults

Intraluminal infection	Diloxanide furoate 500 mg PO tid × 20 days
	Paromomycin 30 mg/kg/day PO × 10 days (3 divided doses)
	Iodoquinol 650 mg PO tid × 20 days
Invasive colitis	Metronidazole 800 mg PO tid × 5 days
	Tinidazole 1 g PO bd × 3 days
Amoebic liver abscess	Metronidazole 800 mg PO tid × 14 days (500 mg qid IV)

EXTRAINTESTINAL AMOEBIASIS

Syndromes of extraintestinal amoebiasis include amoebic liver abscess, and abscess involving the pleura, lung, pericardium or peritoneum, brain, skin, and, rarely, genitourinary disease. Lesions in the lung and brain are complications of amoebic liver abscess. Genital amoebiasis is rare and is probably sexually transmitted.

Amoebic liver abscess (ALA) is the most common form of extraintestinal amoebiasis. It is an inflammatory space occupying lesion of the liver caused by *E. histolytica*.

Epidemiology

The incidence of ALA varies between 3% and 9% of all cases of amoebiasis. A liver abscess accounts for about 0.2% of hospital admissions and for about 75% of all liver abscesses.

Clinical Features

Amoebic liver abscess occurs most commonly in the age group of 20 to 45 years and has been noted infrequently at the extremes of age. It is seven to nine times more common in males.

It is classified by the duration of illness and severity into:

Acute	Acute benign
	Acute aggressive
Chronic	Chronic benign
	Chronic accelerated

Most patients present with acute symptoms of less than two weeks. The main presenting symptoms are abdominal pain, fever and anorexia. Abdominal pain is usually moderate and localised to the right upper quadrant or epigastrium.

Epigastric pain is commonly seen in left lobe abscesses. Fever is of moderate degree in most instances, while high fever with chills is suggestive of secondary bacterial infection. Cough, with or without expectoration and pleuritic chest pain, is also seen in ALA.

During the course of illness one-third of the patients may develop clinical jaundice. Diarrhoea and weight loss are not uncommonly seen.

Tender hepatomegaly is detected in up to 80% of patients. The liver surface is generally smooth. Ascites developing in patients with ALA suggest the development or presence of inferior vena caval obstruction; and cough with copious expectoration suggests rupture and communication with the right lower lobe bronchus.

ALA usually occurs in the right lobe of the liver and is solitary (30% to 70%). Unusual presentations include multiple lobe abscesses, left lobe abscesses, abscesses presenting as compressive lesion and abscesses rupturing into viscera.

Diagnosis

Ultrasound is very useful for the diagnosis of amoebic liver abscesses. Classically, the abscess appears as a non-homogeneous hypoechoic round or oval mass with well defined borders. Complete sonologic resolution of an amoebic liver abscess may take up to two years. The CT scan shows the liver abscess well, but is infrequently required.

Treatment

Drug therapy with nitroimidazole is highly effective and the requirement of invasive aspiration or surgical procedure is required rarely and especially in late cases (**Tables 4 and 5**).

Table 4: Indications of Aspiration in Liver Abscess

Lack of clinical improvement in 2-3 days
Left lobe abscess
Thin rim of liver tissue around the abscess (<10 mm)
Seronegative abscess

Table 5: Poor Prognostic Markers in Amoebic Liver Abscess

Bilirubin >3.5 mg/dL
Encephalopathy
High volume
Hypoalbuminaemia (<2g/dL)

Medical therapy

Nitroimidazoles including metronidazole are effective in over 90% of cases. Therapy should continue for at least 14 days. The dose of metronidazole is 40 mg/kg/dL in divided dosages. Chloroquine, emetine and dehydrometine have also been used.

Surgical therapy

Open surgical drainage is infrequently required. Relative indications include a large abscess with a poor yield on needle aspiration, clinical deterioration despite aspiration, and repeated symptomatic recurrences after aspiration. Rupture into the peritoneal cavity is an absolute indication.

Long-term follow-up

The mean time for disappearance of the sonographic abnormality is 6-9 months. Relapses are very uncommon and the sonographic abnormality does not warrant continued therapy. Clinical resolution does not correlate with ultrasonographic resolution, and clinical criteria rather than ultrasonography should monitor the result of therapy.

Vaccine

Recombinant peptides of three *E. histolytica* antigens show promise for prevention of experimental amoebic liver abscess: the serine-rich *E. histolytica* protein (SREHP), the 170 kDa subunit of the N-acetyl D-galactosamine inhibitable lectin, and the 29 kDa cysteine-rich antigen.

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17.54 Leishmaniasis

Shyam Sundar

Leishmaniasis occurs in 102 countries, majority of them developing or least developed, and 350 million people are at risk. Annual incidence is 2 million with a prevalence of 12 million. It is caused by unicellular flagellate intracellular protozoa belonging to the genus *Leishmania* (Order Kinetoplastida) comprising of 21 species. Leishmaniasis presents as several diverse clinical syndromes consisting of three broad groups: i) visceral leishmaniasis (VL, kala-azar), ii) cutaneous leishmaniasis (CL), and iii) mucosal leishmaniasis (ML). Clinical syndromes are caused either by zoonotic transmission of parasites from animal reservoirs (chiefly canine and rodents in Old World and big mammals in New World) to humans through phlebotomine sandfly vectors, humans are the only known reservoir (anthroponotic) in major VL foci in India and Sudan.

VECTOR

Different species of sandfly vectors (*Phlebotomus* in Old World, *Lutzomyia* in New World) are responsible for transmission of leishmaniasis. Female sandflies bite during the night and preferentially feed on animals; humans are incidental hosts.

LIFE CYCLE

The parasite occurs in two forms, flagellar promastigotes (10 to 20 μm), found in vectors, and aflagellar amastigotes (2 to 4 μm) in vertebrate hosts including humans. Promastigotes are introduced through the proboscis of the female sandfly into vertebrate hosts. Neutrophils take up the promastigotes where they transform into amastigotes and undergo apoptosis, and released parasites are taken up by macrophages. Once inside the macrophages, they multiply, ultimately causing rupture and invasion of another cell. While feeding on infected hosts, sandflies pick up amastigotes, which transforms into the flagellar form. It multiplies by binary fission in the gut of the vector and infects a new host by migrating to the proboscis.

VISCERAL LEISHMANIASIS (KALA-AZAR)

Visceral leishmaniasis also known as kala-azar (Hindi word for black fever) is caused by the protozoon *Leishmania donovani* complex. An annual incidence of 500,000 is estimated, and 90% of it occurs in India, Sudan, Bangladesh and Brazil. Other regions with low incidence of VL include the Mediterranean, Eastern Africa, China, Arabia, Israel, Brazil and other South American countries.

Immunology and Pathogenesis

A great majority of infected persons mount a successful immune response, and remain asymptomatic. In some individuals, leishmania is able to evade immunity in which significantly elevated levels of immunosuppressive cytokine IL-10 plays an important role. Progressive systemic disease develops with involvement of spleen, liver, bone-marrow and lymph nodes primarily, though lymphadenopathy is rare in India. Other unusual modes of transmissions are *in utero*, through blood transfusion, through needle sharing in drug addicts. Immunosuppression due to HIV infection or immunosuppressive medications makes these patients vulnerable to development of VL.

Clinical Features

Except in Indian subcontinent where all age groups are affected, it is a disease of infants and small children, however, HIV infection predisposes adults to VL. Poor housing conditions (mud or straw houses), high level of humidity, sleeping on the floor, living in close proximity of animals leads to increased vector density and exposure. The incubation period ranges from weeks to months. Clinical illness is heralded by high grade fever with rigour and chills. Spleen soon becomes palpable, and becomes remarkably enlarged. Fever decreases over time and patient may become afebrile for short periods, however, fever relapses. Mild hepatomegaly might occur at a later stage. Pancytopaenia is an important feature, and occurs early in the course of illness. Anaemia may become severe enough leading to cardiac failure and other related manifestations. Thrombocytopaenia might result in epistaxis, retinal haemorrhages and gastrointestinal bleed. Hypoalbuminaemia, leading to anasarca suggests advanced illness and indicates poor prognosis. Though initially there is leishmania specific immunosuppression, in later stages profound immunosuppression occurs leading to secondary infections like tuberculosis, pneumonia, herpes zoster, chicken pox, recurrent gastrointestinal infection. Skin infections like boils, cellulitis and scabies are common. Without adequate treatment, VL is fatal.

Laboratory Features

Granulocytopaenia occurs very early accompanied by anaemia and thrombocytopaenia soon thereafter. Polyclonal hypergammaglobulinaemia is a feature of advanced disease. Patients are anergic to leishmanin antigen skin test (LST), which recovers after successful chemotherapy. Immunological parameters measuring T-helper lymphocyte activity suggest absence of a polarised response as increased levels of the pro-inflammatory Th1 cytokine, γ-interferon as well as that of the anti-inflammatory Th2 cytokine, interleukin-10 are detected in lesions.

Diagnosis

Parasites (amastigotes) can be demonstrated in tissue smears from spleen (**Figure 1**), bone-marrow or lymph nodes. Splenic smear is highly sensitive, but carries the risk of serious haemorrhage; sensitivity with other tissues is unsatisfactory. In HIV co-infected, buffy coat smears may demonstrate parasites. Culture, though efficient, is seldom used in diagnosis as it is expensive and extensive facilities are needed. Detection of nucleic acids through polymerase chain reaction (PCR) from peripheral blood is an efficient non-invasive way, but yet to be used routinely. Serodiagnosis, by ELISA, or

immunofluorescence antibody test, is used in the developed world. In endemic regions, however, rapid immunochromatographic k39 strip test have become increasingly popular being simple and it does not require any expertise or equipment and can be performed anywhere. Up to 30% of healthy people in endemic region test positive, and these tests remain reactive for years after cure; thus, results must be interpreted in light of strong clinical suspicion. Tests relying on the raised globulin levels (e.g. Aldehyde test) have no value in the diagnosis of VL.

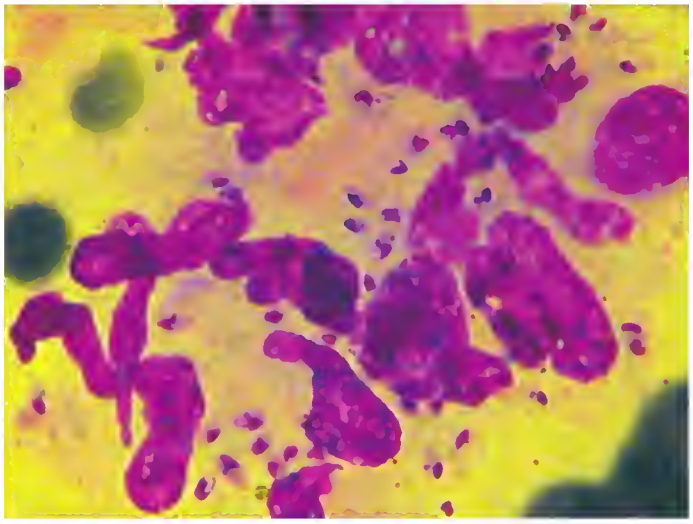


Figure 1: Splenic aspirate smear showing multiple amastigotes (LD bodies).

Differential Diagnosis

Malaria is the commonest illness which may be mistaken for VL. Other common illnesses which might mimic VL include enteric fever, tuberculosis, chronic myeloid leukaemia, portal hypertension and other infectious diseases with splenomegaly with/without lymphadenopathy.

Treatment

For more than eight decades, pentavalent antimonials have been used for the treatment of all forms of leishmaniasis. It is available as sodium stibogluconate (100 mg/ml) in India. Its daily dose is 20 mg/kg body weight intravenous (IV) or intramuscular (IM) for 28 to 30 days. Adverse events are common and include arthralgias, myalgias and raised hepatic transaminases. Chemical pancreatitis is common in HIV co-infected patients, cardiotoxicity-manifested by concave ST segment elevation and prolongation of QTc >0.5 sec are ominous features. Unfortunately, in Northern Bihar in India, more than 50% patients are refractory to antimonials.

Amphotericin B deoxycholate has powerful antileishmanial activity, and is now used as 15 intravenous infusions (dose 0.75 to 1 mg/kg body weight), daily or on alternate days as first line drug in the antimony refractory regions. Though its cure rate is approximately 100%, infusion related adverse events like high grade fever with chills, thrombophlebitis are almost universal, gastrointestinal symptoms like vomiting or diarrhoea, renal insufficiency occur occasionally. Life-threatening toxicity like myocarditis, refractory hypokalaemia are rarely seen. Several lipid formulations of amphotericin B have been developed to alleviate the organ toxicity, however, liposomal amphotericin B (AmBisome, Gilead Sciences, USA) has the best safety profile, and is approved by US Food and Drug Administration (FDA) of USA for VL. For immunocompetent patients, recommended total doses are – in the Indian subcontinent 10-15 mg/kg, in Africa ~18 mg/kg and 21-24 mg/kg for South America and Europe. Orally administrable alkyl phospholipid, miltefosine is approved in India for treating VL. The doses are 50 mg twice daily for adults weighing ≥ 25 kg, and once daily for those <25 kg, after meals for 28 days. For children between 2 and 11 years, the dose is 2.5 mg/kg for 28 days. Mild gastrointestinal adverse events like vomiting and diarrhoea are common. Nephro- and hepatotoxicity can occur rarely. Being teratogenic, miltefosine cannot be used in pregnancy and contraception up to three months after the end of treatment is advised for women with pregnancy potentials. Paromomycin, an aminoglycoside, is highly effective if given intramuscularly at 15 mg/kg body weight daily for three weeks. It was approved in 2006 in India for treatment of VL, no significant auditory or renal toxicity is seen.

Due to limited number of antileishmanial drugs, their inherent weaknesses like long half life of miltefosine, long regimens of 3-4 weeks, and frequent non-compliance makes these drugs vulnerable to development of drug resistance and these could become rapidly ineffective if not used judiciously. Multi-drug regimens are being tested to shorten the duration of therapy, and perhaps prolong the effective life of these drugs.

Successful treatment results in prompt resolution of fever, weight gain, regression of spleen and blood counts recover toward normalcy. Patients must be followed adequately to detect relapse of the disease. Increase in the spleen size, fever, and drop in blood counts indicate relapse, and it should be treated with amphotericin B.

POST KALA-AZAR DERMAL LEISHMANIASIS (PKDL)

After complete recovery from VL, some patients (~1%) develop hypopigmented areas (macules) or nodules (occasionally may appear as papule or plaque) on skin six months to several years later in the Indian subcontinent. The lesions occur predominantly over face in the area around chin (**Figure 2**). In Sudan, PKDL occurs in 50% of patients, and may occur concomitantly with VL or shortly after recovery. Sudanese PKDL occurs like a generalised rash, a papular or nodular form is most frequent; ulceration might occur. In contrast to Sudanese PKDL where spontaneous recovery is the rule, it is not so in India. Diagnosis is clinched by typical clinical features in a background of VL, and positive serology, however, demonstration of parasites in slit skin smears or culture of aspirate material can only be done from nodules, but recovery of parasites from macules is uncommon. PKDL is treated with sodium stibogluconate in the usual daily doses for 120 days or up to 60 amphotericin B infusions. In Sudanese PKDL, treatment with Sb^{v} for up to 2 months is required only in exceptional patients with persistent skin lesions. Since there are no systemic symptoms, non-compliance is the rule.

HIV-VISCERAL LEISHMANIASIS CO-INFECTION

Immunosuppression due to HIV infection increases the vulnerability of VL co-infection several hundred fold. Though initially majority of HIV-VL co-infected cases were from Southern Europe (Spain, South France, Italy, Greece and Portugal), after the introduction of antiretroviral therapy (ART), the incidence has reduced significantly. However, there has been an increase



Figure 2: Post kala-azar dermal leishmaniasis – extensive nodules over face along with facial erythema.

in the co-infected cases from Ethiopia in Africa, Brazil and India. Classical presentation of fever, pancytopaenia, and hepatosplenomegaly/lymphadenopathy is found only in 75%. Atypical presentations, common in those with low CD4+ counts, comprise of dysphagia or odynophagia and diarrhoea or rectal discomfort. Other manifestations include ascites, pleural or pericardial effusion, and involvement of tonsil, oral mucosa, or skin. Parasitic diagnosis is easy as amastigotes can be demonstrated in the buffy coat or recovered from mucosa (gastrointestinal biopsies, bronchoalveolar lavage). PCR detection of nucleic acid from peripheral blood is highly sensitive, and is used in tracking parasites for relapses and re-infections. Sensitivity of serological tests is lower in HIV co-infected patients.

Treatment of HIV co-infected patients is similar with a different outcome. In Europe, the drug of choice is AmBisome (4 mg/kg on day 1-5, 10, 17, 24, 31, 38), though this regimen induces high cure rate, relapse rate is high. Sodium stibogluconate (20 mg/kg for 28 to 30 days) is effective in Africa, amphotericin B deoxycholate (regimen similar to immunocompetent patients) is used in Bihar, India. Miltefosine was less effective than sodium stibogluconate in a large study from Ethiopia. Though every locally effective regimen is expected to induce high initial cure rate, most patients experience relapse within one year. It is important to initiate ART regimen, which is likely to increase the duration of symptom free periods.

CUTANEOUS LEISHMANIASIS

In Old World, anthroponotic CL (oriental sore; caused by *L. tropica*) occurs mostly in urban and suburban areas, and Afghanistan is currently the biggest focus, though western deserts of India, Pakistan, Iran, Iraq, Syria and other areas of Middle East are highly endemic, and in sub-saharan West Africa and Sudan, around the Mediterranean basin, the disease is also endemic. There has been an increase in the incidence of Zoonotic CL (ZCL) in both Old and New World, largely due to man-made ecological changes, transmission cycle, and increase in the animal reservoir population (small rodents in Old and big mammals in New World). Old World ZCL is caused by *L. major, L. aethiopica* and dermotropic *L. infantum*. New World CL is caused by *L. mexicana* complex comprising of *L. mexicana, L. amazonensis*, and *L. venezuelensis*; and Viannia subgenus *L. (V) braziliensis* complex constituted by *L. (V) guyanensis, L. (V) panamensis, L. (V) braziliensis*, and *L. (V) peruviana*. Species causing CL is important, as the clinical presentation, treatment and outcome vary.

Clinical Features

After inoculation, parasites are taken by the dermal macrophages and multiply. After an incubation period of 2-3 months, a papule develops followed by skin ulceration with raised margins (**Figure 3**). Satellite lesions might develop especially in *L. major* and, occasionally, in *L. tropica* infections. Secondary bacterial infection, pain and regional lymphadenopathy are common. *L. mexicana* and *L. peruviana* produce lesions similar to those seen in the Old World, but chronic and destructive lesions on the pinna of the ear are common. Self healing is common in presence of good immunity in *L. tropica, L. major* and *L. mexicana* lesions. However, in patients with anergy to leishmania, the ulcerative skin lesions of *L. aethiopica, L. mexicana*, and *L. amazonensis* infections develop into diffuse cutaneous leishmaniasis characterised by non-ulcerative nodules involving the whole body including face. Persistent relapse of *L. tropica* infections, after apparent healing is called as recidivans (lupoid) leishmaniasis.



Figure 3: Ulcers due to cutaneous leishmaniasis with secondary infection.

MUCOSAL LEISHMANIASIS

Prevalence of the *Vianna* subgenus is extensive in the New World from the Amazon basin as far as Paraguay and Costa Rica and is responsible for deep sores and mucosal leishmaniasis. In *L. (V) braziliensis* complex infections, initial cutaneous ulcers may culminate into mucosal spread of the disease concurrently or in later years. Mucosal lesions begin

as a perivascular infiltration; later endarteritis may cause destruction of the surrounding tissues, up to 40% of patients develop metastatic lesions in the mucosa of the nose or mouth (espundia), with erythema and thickening of the nasal mucosa typically starting at the junction of the nose and upper lip. At a later stage it ulcerates, and involves lips, soft palate, fauces and larynx, ultimately destruction and deformity occur (**Figure 4**). Massive destruction of the pharynx causes severe respiratory tract infections, and death may occur. There is no self healing of ML.



Figure 4: Mucosal leishmaniasis leading to extensive destruction of nasopharynx.

Laboratory Diagnosis of CL and ML

Diagnosis: Slit-skin smears from the nodular edge of lesion or scrapping from within the ulcer may demonstrate parasites. Impression smears or culture of aspiration material yield parasites. PCR is now increasingly employed both for diagnosis and speciation. Demonstration of parasites is usually difficult in mucosal leishmaniasis. Leishmanin skin test is usually positive except in diffuse cutaneous leishmaniasis.

Management

Small lesions may self-heal. Treatment is individualised on the basis of severity of lesions, local resistance pattern, and leishmania species responsible for the illness. Fewer and small lesions at obscure sites can be treated with local therapy with intralesional antimony (0.2-0.8 ml/lesion) every other day for 30 days up to a total of 2 gm. Topical application of Paromomycin 15% plus methylbenzethonium chloride 12% is beneficial in both Old and New World CL. Local cryotherapy with liquid nitrogen or heat therapy through a FDA approved radiofrequency generator (ThermoMed) have also been used. Multiple lesions and those at disfiguring sites are best treated with parenteral Sb^v (20 mg/kg) for 20 days. Pentamidine is the drug of choice in French Guyana in lesions caused by *L. guyanensis* (2 injections in doses of 4 mg/kg 48 hours apart). Fluconazole 200 mg daily for six weeks was effective in *L. major* CL in Saudi Arabia. In India, itraconazole 200 mg daily for 6 weeks was effective in *L. tropica* CL. Drug resistant CL or ML should be treated with amphotericin B.

PREVENTION AND CONTROL OF LEISHMANIASIS

In the absence of prophylactic vaccine against any form of leishmaniasis, vector control remains the key public health measure. Sandflies are extremely sensitive to insecticides, residual insecticide spray is extremely effective. Insecticide impregnated mosquito nets or curtains treated with insecticides will keep out the tiny sandflies. Other measures include active and early detection and treatment of human infections, which will reduce the reservoir and control the epidemic.

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17.55 Toxoplasmosis

Madhukar Rai

Toxoplasmosis is caused by an obligate intracellular coccidian parasite *Toxoplasma gondii*. It is among the most prevalent of human infections with an estimated one third of the world's population infected by *T. gondii*. However, in immunocompetent host the infection is mostly asymptomatic and when it causes clinical disease, manifestions are usually mild in form of chorioretinitis, lymphadenitis and rarely myocarditis or myositis. In majority of those symptomatically or asymptomatically infected individuals the infection becomes latent and chronic, which can get activated on encountering immune-compromised state in the host.

T. gondii cause severe and life-threatening illness when it infects or gets reactivated in immune-suppressed host, especially with impaired T cell function (patient of haematological malignancies, bone marrow or solid organ transplant recipients and HIV infection). It also causes significant disease in foetus and newborn of mother infected with toxoplasmosis during pregnancy.

AETIOLOGY

T. gondii has sexual cycle which is completed only in the gastrointestinal tract of the definitive host; the cat family and asexual cycle in the secondary hosts, which are warm blooded animals like birds, rodents and mammals including humans. It exists in three forms; in definitive host, oocyst containing sporozoite, excreted in cat faeces; while in secondary host it exists as tachyzoites (disease producing stage) and tissue cyst containing bradyzoites (dormant form).

EPIDEMIOLOGY AND TRANSMISSION

Prevalence of *T. gondii*-specific antibodies increases with advancing age, proximity to cat, undercooked non-vegetarian diet, and warm moist climate. In developed countries, incidence of IgG positivity is around 10% to 80%. Few data are available from India. Seroprevalence of *T. gondii* in India on 23,094 serum samples tested for *T. gondii* IgG and IgM antibodies and use of a solid-phase immunocapture ELISA revealed antibodies (IgG) in 24.3%; IgM antibodies in 2% of the samples. The lowest seroprevalences were in the northern parts of India, with the highest in the south. These data probably reflect the effects of significantly drier conditions and, therefore, a negative impact on the survivability of *T. gondii* oocysts.

TRANSMISSION

All the three stages of parasite are infectious. Oral transmission occurs through ingestion of sporulated oocyst through contamination of food, unwashed vegetable, unfiltered contaminated water, or through undercooked meat containing bradyzoites. Transplacental transmission occurs due to acute infection during pregnancy. Direct transmission occurs due to administration of infected blood or transplantation of toxoplasma-positive organ in negative recipient.

PATHOGENESIS AND IMMUNITY

Sporozoites or bradyzoite infects intestinal epithelial cells and tachyzoites are formed. They multiply and disseminate particularly to lymphatic tissue, skeletal muscle, myocardium, retina, placenta and CNS. Cell death and focal necrosis with surrounding inflammatory reaction develops. In immunocompetent individual, immune mechanisms like macrophage, CD8+ cells, natural killer cell with help of interferon gamma, IL-12, IL-2 tries to kill or inhibit replication of this organism. Humoral antibodies like IgA, IgM, and IgG develop. Tissue cysts are formed in as early as 7 days and remain dormant for the life span of host. Tissue cyst is around 60 µm in diameter and contain up to 60,000 organisms. They are responsible for reactivation of disease and chorio-retinitis in children. In patients with AIDS, bradyzoites reactivation in 12 months correlates with CD4 count, i.e. 48% in < 50 cells/mm^3 to 20% in 150-100 cells/mm^3. HLA-DQ3 is associated with high susceptibility.

PATHOLOGY

Changes depend upon dissemination of parasite, cytolytic action of it and immune response of host. Tissue necrosis and intense mononuclear inflammatory response containing monocyte, lymphocyte and plasma cells is seen. Lymph node biopsy reveals follicular hyperplasia and macrophages with eosinophilic cytoplasm. Granulomatous lesions are present in retina and choroid. CNS shows necrosis and microglial nodules in focal or diffuse form. Interstitial pneumonia with mononuclear cells and plasma cell infiltration is observed in lungs. Focal necrosis with inflammation and muscle cysts is seen in heart. Disseminated infection will lead to necrosis and destructive changes in variety of organs leading to myositis, pancreatitis, glomerulonephritis and others.

CLINICAL MANIFESTATIONS

Immunocompetent Patient

Acute stage toxoplasma infections can be asymptomatic in 80% to 90% patients, but often give flu-like symptoms in the early acute stages. The acute stage fades in a few days to months, leading to the latent stage. In symptomatic patient headache, malaise, fever, cervical lymphadenopathy will occur. Myositis, chorioretinitis and other complications are rare. Lymphadenopathy needs differentiation from infectious mononucleosis, lymphoma, CMV, cat-scratch disease and tuberculosis. Latent infection is normally asymptomatic.

Immunocompromised Patient

In the case of immunocompromised patients severe toxoplasmosis can develop. Acute infection or reactivation of bradyzoites occurs in them. The most notable manifestation of toxoplasmosis in immunocompromised patients is toxoplasmic encephalitis, which can be deadly. Toxoplasma encephalitis (TE)

will have either focal dysfunction to non-focal meningo-encephalitis due to vasculitis, oedema and haemorrhage. Patient has altered mentation (75%), seizures (30%), focal neurological signs (60%), headache (56%) and fever (50%). Motor or sensory deficit, brainstem basal ganglia or cerebellar dysfunction, movement disorder and many other manifestations can be seen. Meningeal signs, spinal cord involvement, hydrocephalus, pituitary involvement are uncommon. CSF is usually normal or shows rise in protein and cell count. Differential diagnosis includes cryptococcal meningitis, herpes simplex encephalitis, tuberculoma and tuberculous meningitis and primary CNS lymphoma. Lung involvement shows ARDS, haemoptysis, DIC and needs differentiation from *Pneumocystis carinii* infection. Multiple other organ involvement in these patients is documented on post-mortem.

Ocular Toxoplasmosis

Retinal lesion can be detected at birth or in second/third decade. Fundoscopy reveals yellow-white elevated cotton-wool patches during active stage and punched out and pigmented (black) lesions during quiescent stage. Severe congenital disease has cataract, micro-ophthalmia, strabismus and nystagmus.

Congenital Toxoplasmosis

It occurs when toxoplasma infection occurs during first time in pregnancy. Transmission rate to the foetus is 10% to 25% in first, 30% to 54% in second and 60% to 65% in third trimester. However, the severity of congenital disease decreases with increasing gestational age. Clinical manifestations vary a lot, like chorioretinitis, strabismus, blindness, epilepsy, psychomotor or mental retardation, anaemia, jaundice, rash, microcephaly, intracranial calcification, hydrocephalus, and pneumonitis. The symptoms may be present at birth or develop later in life, leading to blindness, psychomotor retardation, and hearing difficulties. Infants with HIV infection and toxoplasmosis run rapid course. Congenital toxoplasmosis needs to be differentiated from CMV, ruboella, herpes simplex, syphilis, listeriosis and other infections.

DIAGNOSIS

Strong suspicion is required for proper diagnosis. Isolation of *T. gondii* by tissue culture and mouse inoculation can be done from body fluids. Isolation of *T. gondii* from amniotic fluid is diagnostic of congenital toxoplasmosis. Detection of its antigen in blood or body fluid by ELISA indicates acute infection. Histological diagnosis is made by fluorescent antibody and immunoperoxide staining. Polymerase chain reaction (PCR) is useful.

Lymphocytic transformation to *T. gondii* antigen is an indicator of previous toxoplasma infection in adults. IgG antibodies could be detected by specific neutralisation test for toxoplasma (Sabin Feldman dye test) or by immuno-fluorescent antibody test which denote prior infection. Parallel testing of IgG showing four-fold rise in paired sera of 3 weeks apart indicates acute infection. IgG has low avidity in acute infection and high avidity in chronic infection. IgM, IgE and IgA antibodies denote new infection. Double sandwich IgM ELISA is most specific and sensitive to detect acute infection.

CT brain in AIDS patient with TE classically shows multiple bilateral hypodense lesions, ring enhancing lesions with asymmetric target sign in basal ganglia region. However, solitary lesion may also be seen. MRI with gadolinium contrast is superior to CT and may detect lesions not seen on CT. Decreased Thallium^{201} uptake on SPECT scan and decrease activity on PET scan is suggestive of infection (to differentiate from CNS lymphoma). Response to empiric therapy is also used for diagnostic purpose.

MANAGEMENT

Treatment is directed against tachyzoites. Combination therapy is preferred. Pyrimethamine in combination with sulphdiazine is most effective. Folinic acid is used to avoid megaloblastic anaemia. Treatment schedule is shown in **Table 1**.

Table 1: Treatment Schedule

Group	Treatment	Duration
AIDS and immuno-compromised patients	Pyrimethamine: 200 mg loading + 75 mg/dL + Sulphadiazine 1 gm qid *or* clindamycin 600 mg-1200 mg qid *or* TMP + SMX: 20 mg/kg/dL of trimethoprim in four divided doses (without pyrimethamine in resource poor setting) + *Folinic acid: 5-10 mg/dL*	To continue in full dose till cessation of disease activity followed by maintenance till CD4 $\geq$ 200 for 3 months
Immunocompetent	—	—
Acute chorioretinitis	Pyrimethamine:100 mg loading + 25-50 mg/day + sulphadiazine 1 gm qid + folinic acid	Usually for 6 weeks but as per clinical response
Acute lymphadenitis	No treatment	
Pregnancy	Spiramycin 1 gm tid (if no evidence of foetal infection)	Till term
Other drugs which can be used		
TMP-SMX	20 mg/kg/dL of trimethoprim	
Atovaquone	1500 mg 12 hourly	
Clarithromycin	500 mg 12 hourly	
Azithromycin	900-1200 mg/dL	
Dapsone	100 mg once a day	

In immunocompetent patient disease is self-limited. Treatment for 2 to 4 weeks is indicated, if severe persistent symptoms occur.

In immunocompromised patients, treatment is recommended for 4 to 6 weeks or till there is no evidence of disease activity. Response is seen in 68% to 95% patients with TE. Measures to control increased intracranial tension and seizures should also be included in treatment. Maintenance therapy of pyrimethamine 25 mg with sulphadiazine 500 mg four times a day is required. Maintenance therapy is withdrawn, if CD4 cells >200/mm^3 on HAART for a period of more than 6 months. For primary prophylaxis, all AIDS patients with CD4 <100 cells/mm^3 should receive TMP-SMX one double strength tablet per day. Primary prophylaxis is discontinued, if on HAART, CD4 cells > 200/mm^3 for 3 months.

For congenital infection, oral pyrimethamine 0.5-1 mg/kg and sulphadiazine 100 mg/kg for one year is given. In addition spiramycin 100 mg/kg with prednisolone 1 mg/kg/dL has shown improvement.

In pregnancy to prevent transmission to foetus, spiramycin 3 gm/dL is continued throughout pregnancy. Since, spiramycin does not cross placental barrier, if foetus is suspected to have infection then usual treatment should be used. However, pyrimethamine is contraindicated in first 12 to 14 weeks of gestation.

PREVENTION

To reduce primary infection in AIDS patients, avoid undercooked meat, oocyst contaminated material and feed domestic cat on canned or dried commercial food. Serological screening and prophylaxis should be used for organ transplant recipient and to prevent congenital toxoplasmosis.

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17.56 Trypanosomiasis

Prashant P Joshi

Protozoan parasites of the genus *Trypanosoma* cause trypanosomiasis. Human trypanosomiasis, a vector borne disease, is endemic in sub-Saharan Africa and South America. In Africa it is known as Human African Trypanosomiasis (HAT), or 'sleeping sickness', whereas in South America it is known as Chagas disease. Trypanosomiasis is common in cattle in India and is called 'Surra'.

HUMAN AFRICAN TRYPANOSOMIASIS (SLEEPING SICKNESS)

Sleeping sickness is caused by human strain of *Trypanosoma brucei* (**Figure 1**) and it is found in two forms, depending on the two protozoan parasite species of *Trypanosoma brucei*, that are morphologically similar but cause different diseases: (a) chronic sleeping sickness or West African Trypanosomiasis, caused by *Trypanosoma brucei gambiense*, occurs in Central and West Africa. Symptoms may be virtually absent for several years, and when they do appear, the disease is already in advanced stage. Its reservoir is mainly human, (b) acute sleeping sickness or East African Trypanosomiasis, caused by *Trypanosoma brucei rhodesiense* occurs in East Africa. It has an acute, virulent and faster course causing death in a matter of weeks or months. It has a large animal reservoir. It is transmitted by infected saliva of blood sucking tsetse flies (**Figure 2**) of the genus *Glossinia* species during its blood meal.

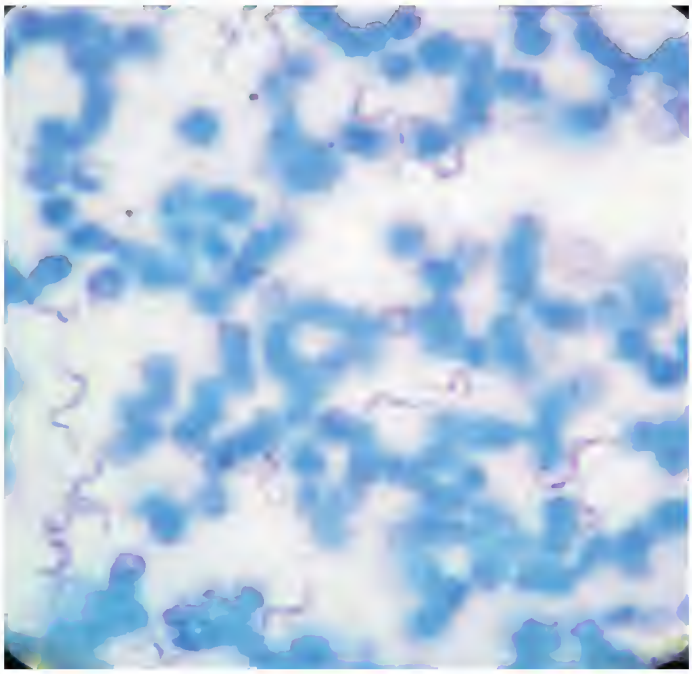


Figure 1: Plenty of long, slender, flagellated, dividing forms of trypanosomes.

Clinical Course

At the site of inoculation, a painful trypanosomal chancre accompanied by regional lymphadenopathy develops after five days in many cases. Symptoms begin with fever, headaches, and joint pains with haematogenous spread. *Stage 1 or Haemolymphatic stage* is characterised by fever, cervical lymphadenopathy, especially in the posterior triangle (Winterbottom's sign), splenomegaly, rash, pruritus, muscular pain, anaemia, thrombocytopaenia, and carditis, which can sometimes be fatal. This is followed by *Stage 2, the neurological phase or the meningoencephalitic stage* with central nervous system (CNS) invasion, in which there is marked sleep disturbance characterised by day-time somnolence and night-time insomnia. Behaviour changes, lack of concentration, mood changes, headache, personality changes, incoordination, ataxia, chorea and cachexia develop with bouts of lethargy alternating with manic and aggressive periods progressing to confusion, delirium, convulsions and coma. 'Sleeping sickness' gets its name from symptoms of second stage. Damage caused in the neurological phase can be irreversible.



Figure 2: Glossinia (Tsetse Fly).

Diagnosis

A definitive diagnosis is made by demonstration of the parasite in blood, bone marrow, lymph node aspirate or chancre aspirate, which is fixed and stained with Giemsa. The mini-anion exchange centrifugation technique (mAECT), a chromatographic-based system concentrates and purifies trypanosomes in the blood. CSF involvement indicates Stage 2. Serological tests, like card agglutination test for trypanosomes (CATT), have varying sensitivity and specificity and are particularly useful in epidemiological surveys. Molecular studies [polymerase chain reaction (PCR)] help in species identification.

Management Issues

Drugs (suramin, malarsoprol and eflornithine) used to treat sleeping sickness are toxic and expensive. The treatment is not standardised due to lack of evidence from good randomised clinical trials. Although not available in India; drugs can be

obtained on request from WHO free of cost. Concomitant parasitic, bacterial, viral infections, nutritional deficiencies, and severe anaemia should be treated prior to administration of anti-trypanosomal drugs so as to improve the patient's general condition.

Choice of drug therapy depends on: (a) stage of disease, (b) species of the parasite involved, (c) adverse reactions and (d) Drug resistance. Treatment began in the 1920s with suramin while eflornithine (difluoromethylornithine or DFMO), is the most modern treatment. Trials of combination therapy are ongoing in cases of drug resistance.

Prognosis

The disease is fatal if left untreated. If treatment is initiated in early *Stage 1* cure rates are high, but initiation of treatment in late *Stage 2* cannot prevent irreversible neurological damage.

Prevention

Vector control using screens and traps, surveillance of the population at risk and treatment of infected individuals are the main focus of control programmes. Risk of trypanosomiasis can be reduced by wearing protective clothes, use of insect repellants, avoiding tsetse infested areas. No chemoprophylaxis is recommended nor is any vaccine available.

HUMAN TRYPANOSOMIASIS IN INDIA

Recently, a new form of human trypanosomiasis, has been described with the report from India of the first formally identified human case of trypanosomiasis, caused by cattle species *Trypanosoma evansi*, which was probably transmitted from infected cattle blood. *T. evansi* was not known previously to cause infection in humans and tsetse fly is not found in India; however, this patient had significant fluctuating trypanosome parasitaemia due to *T. evansi*, associated with febrile episodes for five months, without CNS involvement. He was successfully treated and completely cured with suramin, a drug used exclusively in early stage HAT with no CNS invasion. The disease is linked to the absence of the trypanolytic factor apolipoprotein L-I in the patient. In contrast to human trypanosomiasis, which is endemic in Africa and South America, animal trypanosomiasis is distributed worldwide. Trypanosomiasis due to *T. evansi* is common in Indian livestock and causes a disease called 'Surra' (derived from Hindi word meaning rotten) in cattle. High seropositivity prevalence for *T. evansi* among other villagers of the area indicates frequent exposure to *T. evansi* in the villagers. Subsequently, one infant from Mumbai and another adult from Pune have been diagnosed with trypanosomiasis. There are also reports of a few scientifically unconfirmed cases of human carriers of animal trypanosomes during the last century in India, Malaysia and in Sri Lanka, and these cases always had transient infections (suggesting infection with *T. lewisi*, a common rat parasite). The disease is unlikely to be a major threat to human health, if the human infective strains of *T. evansi* do not infect the central nervous system and remain sensitive to suramin or cause only transient self limiting infection.

AMERICAN TRYPANOSOMIASIS OR CHAGAS DISEASE

Chagas disease is caused by flagellate protozoan, *Trypanosoma cruzi* and is transmitted to man by infected faeces of haematophagous triatomine insects, often called reduviid (kissing) bugs. Contamination of bite wound with infected faeces passed by reduviid bugs result in human infection. Chagas disease can also be transmitted through blood transfusions, organ transplantation, transplacentally, breast milk, consumption of uncooked contaminated food and by accidental laboratory exposure. The disease is characterised by an asymptomatic latent period followed by chronic cardiac and gastrointestinal symptoms.

Clinical Features

There are three stages:

1. *Acute stage* occurs shortly after infection. A local skin nodule accompanied by erythema and induration called a *chagoma* can appear at the site of inoculation with regional lymphadenopathy. *Romana's sign* (unilateral painless periorbital oedema, conjunctivitis and periauricular lymphadenitis) occurs when inoculation site is conjunctiva. Fever, malaise, tiredness, lymphadenopathy, hepatosplenomegaly, rash, myocarditis and meningoencephalitis can be present. The acute phase resolves in 8 to 10 weeks and is followed by
2. *Asymptomatic or indeterminate stage,* in which the infected persons have no symptoms.
3. The *symptomatic chronic stage* develops after 10 to 20 years of infection and some people develop serious irreversible damage to the heart and gastroinstestinal tract. The myocardial damage results in cardiomyopathy, right bundle branch block, atrioventricular block, premature beats, arrhythmias, heart failure, and thromboembolism. Gastrointestinal system involvement causes dilatation of oesophagus (megaoesophagus) and colon (megacolon), with symptoms of dysphagia and constipation. Dementia can also occur in some patients. Most patients die due to cardiomyopathy, if left untreated.

Laboratory Diagnosis

T. cruzi can be demonstrated by microscopic examination of fresh anticoagulated blood or buffy coat and thick and thin blood smears stained with Geimsa. The agent can be isolated by mouse inoculation, culture of blood in specialised media (e.g. NNN, LIT), or xenodiagnosis (where uninfected reduviid bugs are fed on the patient's blood, and their gut contents examined for parasites 4 weeks later). Serologic tests to detect antibodies to *T. cruzi* can be used like complement-fixation or immunofluorescence tests and ELISA. Diagnosis based on molecular techniques like PCR are promising, but not available for routine use.

Treatment

The treatment is unsatisfactorys and effective only when initiated in the acute stage. **Tables 1 and 2** tabulate the drugs, dosage and side effects. Nifurtimox or benznidazole are both toxic and resistance is reported. Amphotericin is used as second line drug, but is also toxic. Allopurinol, fluconazole, itraconazole and recombinant interferon γ are under evaluation. Cardiac and gastrointestinal complications are treated symptomatically.

Prevention

Prevention is important since drug therapy is unsatisfactory and no vaccine is available for commercial use. Preventive measures focus on vector control by use of insecticide sprays and paints,

Table 1: Anti-trypanosomal Drugs

Drug	Indication	Dose	Adverse Effects
Suramin	Stage 1 of *T b. rhodesiense*	20 mg/kg (maximum dose 1 gm per injection), at weekly intervals x 5 doses, as slow IV infusion of freshly prepared 10% aqueous solution, preceded by a test dose of 0.2 ml IV	Common: anaphylactic reactions, renal complications, fever, photophobia, pruritus, arthralgias, exfoliative dermatitis, nausea, vomiting
Pentamidine	Stage 1 *T b. gambiense*	4 mg/kg/day by IM injection for seven consecutive days	Rare and reversible: Hypotension, pancreatitis, hypoglycaemia, arrhythmias, reversible renal failure
Melarsoprol	Stage 2 of *T b. rhodesiense* or *T b. gambiense*	3.6 mg/kg/day slow IV injections for 3 consecutive days. Three such courses repeated at intervals of 8 to 10 days	Severe, sometimes fatal: Reactive encephalopathy (coma, convulsions), in 5 to 10% of treated cases, (fatal in 10 to 70% of afflicted patients), thrombophlebitis, necrosis if drug extravasates, significant drug resistance, exfoliative dermatitis
Elornithine	*T. b gambiense*	400 mg/kg/day administered in four doses daily slow IV infusions diluted in 250 cc isotonic saline solution over 2 hours, (in children 150 mg/kg per infusion) for 7 days where melarsoprol has failed and for 14 days when used as first-line treatment	Common: Anaemia, thrombocytopaenia, diarrhoea, convulsions, hearing loss, vomiting
Nifurtimox	*T. Cruzi*	8 to 10 mg/kg for adults, 12.5 to 15 mg/kg for adolescents, 15 to 20 mg/kg for children 1 to 10 years of age, given orally in four divided doses each day for 90 to 120 days	Abdominal pain, anorexia, nausea, vomiting, and weight loss. Neurological reactions to the drug may include restlessness, disorientation, insomnia, twitching, paraesthesia, polyneuritis and seizures

Table 2: Choice of Anti-trypanosomal Drugs

	Stage 1	Stage 2
West African Trypanosomiasis *(T b. gambiense)*	First line: Pentamidine Second line: Eflornithine or Melarsoprol	Eflornithine or Melarsoprol
East African Trypanosomiasis *(T b. rhodesiense)*	First line: Suramin Second line: Melarsoprol	First line: Melarsoprol Second line: Nifurtimox combined with Melarsoprol

improvement of housing and screening the parasite before blood transfusion in endemic areas.

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17.57 Cryptosporidiosis, Trichomoniasis, Balantidiasis and Isosporiasis

Atul Bhasin

CRYPTOSPORIDIOSIS

Introduction

Cryptosporidiosis is caused by *Cryptosporidium*, a protozoan that was identified in 1976, and is one of the most common water-borne diseases found worldwide. Though initially thought to be caused by single species, but recent molecular studies have revealed that several species cause human cryptosporidiosis and there are different hosts for various species—*Cryptosporidium hominis* (human host) and *Cryptosporidium parvum* (bovine and human host). Parasite typically causes acute short-term infection via faeco-oral route through contaminated water. It is an intracellular but extra-cytoplasmic parasite, which contributes to marked resistance to treatment. Contact with fresh water bodies, including recreational (swimming pool), insufficiently treated water supplies, contaminated food, or exposure to faeces makes more susceptible to infection. Single host life cycle results in microbial oocyst stage, which are highly infectious. 10^1 to 10^3 oocysts are required to cause human disease (50% infectious dose, 10^2). These when excreted in faeces are fully capable of transmission to a new host. When ingested, they excyst in the small intestine resulting in an infection of intestinal epithelium. Though it usually presents as self-limiting diarrhoea in immunocompetent host, but it can be fatal in immunocompromised individuals. *Cryptosporidium* is most commonly isolated in HIV positive patients presenting with diarrhoea. Increased risk of transmission is seen in those who swim in pools with insufficient sanitation (chlorine resistant strains of *Cryptosporidium*), child care workers, parents and health care associated workers taking care of people with cryptosporidiosis. Drinking unfiltered, untreated water and people exposed to human faeces through rectal sexual contact are also at risk.

Clinical Features

Presentation is asymptomatic, acute or persistent chronic diarrhoea. Diarrhoea with mucous, abdominal cramps, low-grade fever, nausea, vomiting and dehydration is seen in acute cases, while chronic infection presents with persistent loose stools, malabsorption and weight loss. The parasite can infect the biliary tract, causing biliary cryptosporidiosis, resulting in cholecystitis, cholangitis and pancreatitis. Immunocompromised people and those at extremes of age have very severe disease. Water loss exceeding up to 2 litres per day, severe malabsorption with weight loss are seen in severest forms. In AIDS, extra-intestinal involvement is seen involving lungs, middle ear, pancreas, biliary tract.

Diagnosis

It is diagnosed by stool microscopy—staining and detection of antibodies. Microscopic identification of oocysts in faeces by using concentrating methods like modified formalin-ethyl acetate (FEA), modified zinc sulphate centrifugal floatation technique and Sheather's sugar floatation procedure are utilised. Inspection of at least 3 stool samples increase sensitivity. Fluorescent microscopy is done by staining with auramine. Detection by modified acid-fast or direct fluorescent antibody (DFA), indirect immunofluorescence assay and ELISA are helpful. Polymerase chain reaction (PCR) can identify the species specifically.

Treatment

Immunocompetent host usually has self-limiting disease, thus requiring only supportive rehydration till spontaneous recovery is achieved. Nitazoxanide 500 mg twice daily for 3 days can be used to combat diarrhoea, while spiramycin can help shorten the amount of time oocytes are passed as well as duration of diarrhoea in children. In immunocompromised individuals, Cryptosporidiosis resolves slowly or never at all. Patients with CD4+ counts greater than 180 cells/mm^3 recover well with medication and supportive care, but in counts below 50 cells/mm^3 it is fatal within 3 to 6 months. Nitazoxanide, paromomycin, and azithromycin in combination with anti-retroviral therapy that includes an HIV protease inhibitor is associated with marked improvement. Nucleoside reverse transcriptase inhibitors are malabsorbed in chronic cryptosporidiosis, thus active anti-parasitic drugs should be administered prior to anti-retroviral therapy.

Prevention

Enhancing the immune status with probiotic, *Saccharomyces boulardii*, and somatostatin analogues (octreotide acetate) are partially beneficial in reducing resistant secretory diarrhoea. Handwashing after contacting stool and sanitation system prevents its spread. Patients should avoid anal sexual activity and swimming in communal bathing areas for at least 2 weeks after diarrhoea stops, as *Cryptosporidium* resides in the ano-genital region. Boiling water and filtering with conventional filtration technologies, slow sand filters diatomaceous earth filter and membranes can remove 99% of *Cryptosporidium*.

TRICHOMONIASIS

Introduction

Trichomoniasis is a sexually transmitted disease caused by protozoan *Trichomonas vaginalis* and is a common cause of vaginitis. It is primarily an infection of the urogenital tract.

Clinical Features

It usually presents as intense itching and burning sensation with frothy and foul-smelling discharge. Incubation period is 5 to 28 days, though dormant infection can last for years. Women are more symptomatic then men. Men usually present with irritation inside the penis, discharge, or burning after urination/ejaculation.

Diagnosis

It can be done microscopically by PAP test or smear demonstrating trichomonas (pear-shaped multi-flagellar parasites with whip like tails at one end). Chronic infection causes increased risk of premature births, cervical cancers, transmission of HIV in women and prostatic cancers in males.

Treatment

In both pregnant and non-pregnant women, metronidazole or tinidazole 2 g by mouth as single dose can be given except in the first trimester of pregnancy, where clotrimazole is used topically. Single high dose of metronidazole could cause nausea and vomiting and, therefore, alternatively metronidazole 500 mg twice a day for 7 days can be administered. In pregnant women clotrimazole vaginal tablets are administered at night for 14 days. It decreases symptoms, but the cure rate is only 20%. Asymptomatic sexual partners need concurrent treatment as re-infection often causes treatment failure. Use of male condoms may help in preventing its spread.

BALANTIDIASIS

Introduction

Balantidiasis also known as balantidiosis, is a large-intestinal infection (from caecum to rectum) with a protozoan called *Balantidium coli*. It is the largest ciliated protozoan, infecting humans handling pigs or water and fertiliser contaminated with pig excrement. Protozoa dwell in the intestinal lumen, but can cause penetrating mucosal ulcers.

Clinical Features

Immunocompetent individuals are asymptomatic. Usual symptoms are diarrhoea (watery, bloody and mucoid), nausea, vomiting, abdominal pain, anorexia, weight loss, fever and marked fluid loss.

Diagnosis

Microscopic examination of stool or tissue obtained via colonoscopy, demonstrate trophozoites. Repeated stool collection and immediate examination enhances its detection.

Treatment

Drug of choice is tetracycline. Metronidazole and iodoquinol are alternatives. Tetracycline is contraindicated in pregnancy and in children less than 8 years of age.

Prevention

Effective personal and community hygiene, purification of drinking water, proper handling of food, careful disposal of human faeces and monitoring the contacts of balantidiasis patients contains its spread.

ISOSPORIASIS

Introduction

Isosporiasis is an intestinal disease caused by the protozoan *Isospora belli* seen commonly in tropical and sub-tropical areas in immunocompromised individuals. Humanbeings are the only known hosts for *Isospora belli*, with no known animal reservoir. Commonly seen in persons with AIDS, but is being increasingly reported in patients with lymphoma, leukaemia, renal and liver transplant recipients. Increased prevalence is being seen due to widespread use of *Pneumocystis jiroveci* pneumonia prophylaxis with trimethoprim-sulphamethoxazole in HIV-infection.

Clinical Features and Diagnosis

It is an initial AIDS-defining illness in approximately 0.2% of patients. This infection is transmitted from person to person by faeco-oral route and usually has a mild and protracted course, unless host is immunocompromised. Profuse, watery, non-bloody, offensive-smelling diarrhoea, with mucous, cramping pain, vomiting, anorexia, weight loss, low-grade fever and steatorrhoea are usual presentations. Peripheral eosinophilia is an important clue. Multiple stool specimens showing large oocysts on modified acid-fast stains along with Charcot-Leyden crystals clinch the diagnosis. There are no serologic tests for isosporiasis. Auramine-rhodamine fluorescent, modified Kinyoun acid-fast stain, ultraviolet autofluorescence microscopy, zinc sulphate or sugar floatation-stool concentration technique and a recent promising real-time polymerase chain reaction (PCR) are helpful in diagnosing the parasitic infestation. Examination of duodenal aspirate or string test may aid in the diagnosis.

Treatment

Treatment of choice is with trimethoprim-sulphamethoxazole 160/800 mg 4 times per day for 10 days. For HIV-infected individuals, extended treatment, 3 times daily for 3 more weeks is required. In patients intolerant to TMP-SMX combination, pyrimethamine 50 to 75 mg daily can be given for 2 to 4 weeks.

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17.58 Ankylostomiasis, Ascariasis and Other Nematodal Infestations

Narender Pal Jain

Diseases caused by Helminths are referred to as Helminthiasis. It is estimated that more than 3 billion people live with helminths across the world. Helminths are intestinal parasitic worms, nematodes (roundworms) and two groups of the trematodes (flukes) and cestodes (tapeworm). They have large variation in size, complex life cycle and migratory habits within their host. Helminths do not multiply in humans (*Strongyloides stercoralis* being an exception), so repeated or prolonged exposure may be needed for acquisition of sufficiently high worm burdens for symptomatic infections to develop. Stool examination helps in the diagnosis (**Figure 1**).

NEMATODES

Nematodes belong to the phylum nematoda (Ancient Greek words- nema and ode means thread and like, respectively). Nematodes commonly parasitic on humans include ascarids (*Ascaris*), filarids, hookworms, pinworms (*Enterobius*), and whipworms (*Trichuris trichiura*). They are non-segmented, fusiform, cylindrical shape with a complete digestive system with oral and anal openings; and have a tough outer coating (cuticle) that may be smooth or textured, generally cream-white in colour. They are divided into intestinal, tissue-dwelling roundworms and those which are parasitic to humans only or zoonotic infections (**Table 1**).

Table 1: Nematodes or Round Worms

Intestinal human nematodes: *Enterobius vermicularis, Ascaris lumbricoides, Trichuris trichiura. Necator americanus, Ankylostoma duodenale, Strongyloides stercoralis, Capillaria philippinensis*

Tissue-dwelling human nematodes: *Wuchereria bancrofti, Brugia malayi, Loa loa, Onchocerca volvulus* (all filarial worms), *Dracunculus medinensis* (Guinea worm)

Zoonotic nematodes: *Toxocara canis, Ankylostoma braziliense, Oesophagostenum* species, *Angiostrongylys cantonensis, Trichinella spiralis, Gnathostoma spinigerum*

INTESTINAL HUMAN NEMATODES

Ankylostomiasis (Hookworm Infestation)

Aetiopathogenesis and epidemiology

Common hookworms are *Ankylostoma duodenale* and *Necator americanus*. Both species may infect the same person. The highest incidence of infection is in men in their second and third decades of life.

The two principal species vary slightly in size and structure, with the adult female *Ankylostoma duodenale* measuring 10 to 13 mm in length and 0.6 mm in diameter, whereas the male is 8 to 11 mm long and 0.45 mm wide. *Necator americanus* is a shorter and more slender worm, with the female measuring 9 to 11 mm in length by 0.35 mm in width and the male being 5 to 9 mm long by 0.3 mm wide. Adult hookworms are creamy white in colour when alive but grey when dead. When engorged with blood, they are reddish-brown.

The adult hookworm may remain alive in the intestine for as long as 6 years. The female *Ankylostoma* produces 25,000 to 35,000 eggs per day or up to 50 million in her life-time; the female *Necator* is less productive, producing a mere 6,000 to 20,000 eggs per day. Within 48 hours, eggs double in size, molts, and become a second-stage rhabditiform larva. Within a week after first hatching, it will again molt to become a third-stage or infective filariform larva while feeding upon the faeces in moist earth or water.

Humans are infected when larvae penetrate the skin of the foot and then they enter venules or lymphatics. By either route they reach the pulmonary capillaries and break into alveoli, from where they migrate up the bronchioles and trachea and pass over the epiglottis and down the oesophagus to mature in the small intestine, usually the jejunum. Here they molt again to become fourth-stage larvae possessing a buccal capsule by which they attach themselves to the intestinal mucosa. Within a week, a fourth and final molt results in development of the adult parasite. Female begins laying eggs within 2 months after the larvae penetrate the skin (**Figure 2**).

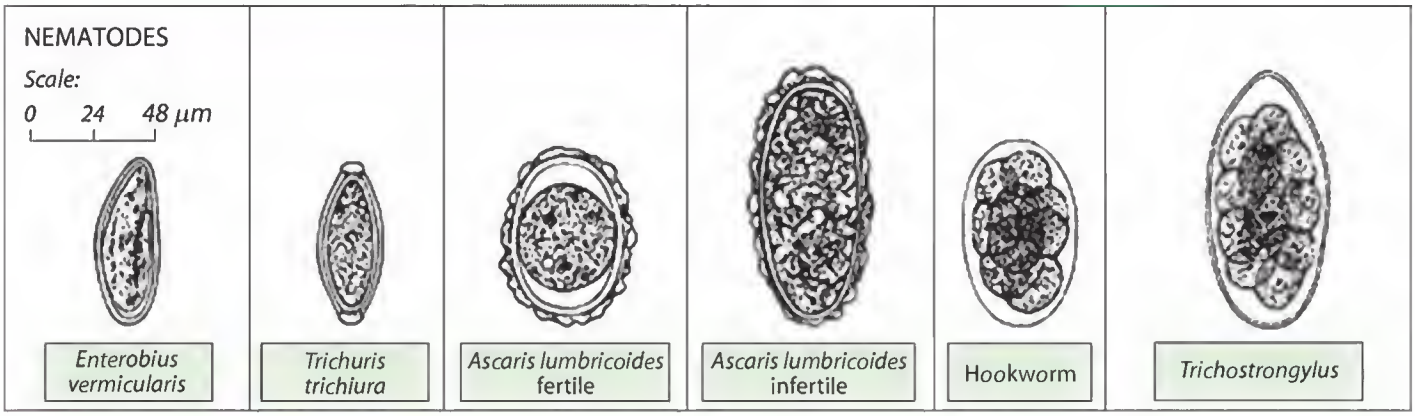


Figure 1: Ova and cysts of helminths found in the stool.

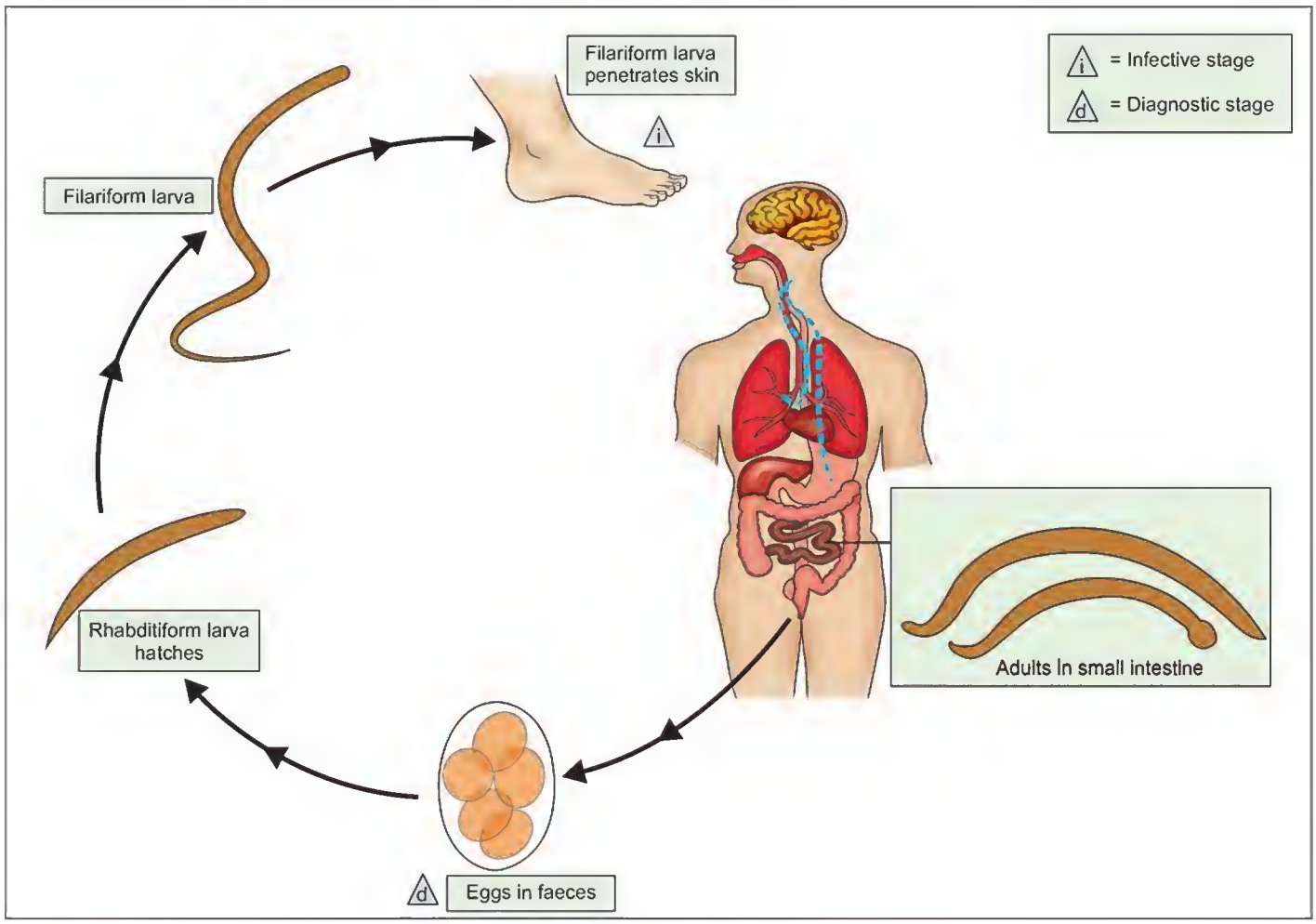


Figure 2: Life-cycle of *Ankylostoma duodenale*.

Clinical features

The disease caused by worms is classified into two phases clinically; namely, the phase of migration and development, and the symptomatic phase. In the migratory phase, pruritus, erythema and vesiculation will occur once the filariform larvae have penetrated the skin of the feet or hands. This is known as 'ground or dew itch' in people who go barefoot. Within 1 to 2 weeks, pulmonary symptoms may develop. The pulmonary symptoms are more common with *A. duodenale* and enteritis with *N. americanus* infection.

Diagnosis

The diagnosis of clinical Ankylostomiasis is usually made by counting the number of eggs in direct saline smear of a fresh sample of faeces or by a stool concentration method. Sputum examination may reveal occult blood, eosinophils and rarely migrating larvae. A skin test antigen derived from *N. americanus* has been used for screening populations.

Treatment

Mebendazole 100 mg twice a day for three days or single dose of albendazole 400 mg. Alternative drugs are pyrantel pamoate 10 mg/kg dL for 3 or 4 doses and a single dose of ivermectin 200 µg/kg.

Ascariasis

Ascaris lumbricoides is the largest of the intestinal nematodes affecting humans, measuring 15 to 35 cm in length in adulthood. The gravid female produces 2, 50,000 eggs daily. These take 3 or 4 weeks to develop into infective stage. Once ingested, eggs hatch, usually in the small intestine, releasing small larvae that penetrate the intestinal wall. Larvae migrate to the pulmonary vascular beds and then to the alveoli via the portal veins usually 1 to 2 weeks after infection. After migrating up the respiratory tract and being swallowed, they mature, copulate and lay eggs in the intestines. Adult worms may live in the gut for 6 to 24 months, where they can cause partial or complete bowel obstruction in large numbers, or they can migrate into the appendix, hepatobiliary system, pancreatic ducts, kidneys or brain (**Figure 3**).

Clinical features

Most patients are asymptomatic. When symptoms occur, they are divided into 2 categories: early (larval migration) and late (mechanical effects).

- In the early phase (4 to 16 days after egg ingestion), respiratory symptoms result from the migration of larvae through the lungs with symptoms of eosinophilic pneumonia (Löffler syndrome). Patient may present with fever, non-productive cough, dyspnoea, wheezing.
- In the late phase (6 to 8 weeks after egg ingestion), gastrointestinal symptoms may occur. Patient may present with passage of worms (from mouth, nose and anus) diffuse abdominal pain, nausea, vomiting, biliary and intestinal obstruction, appendicitis and pancreatitis.

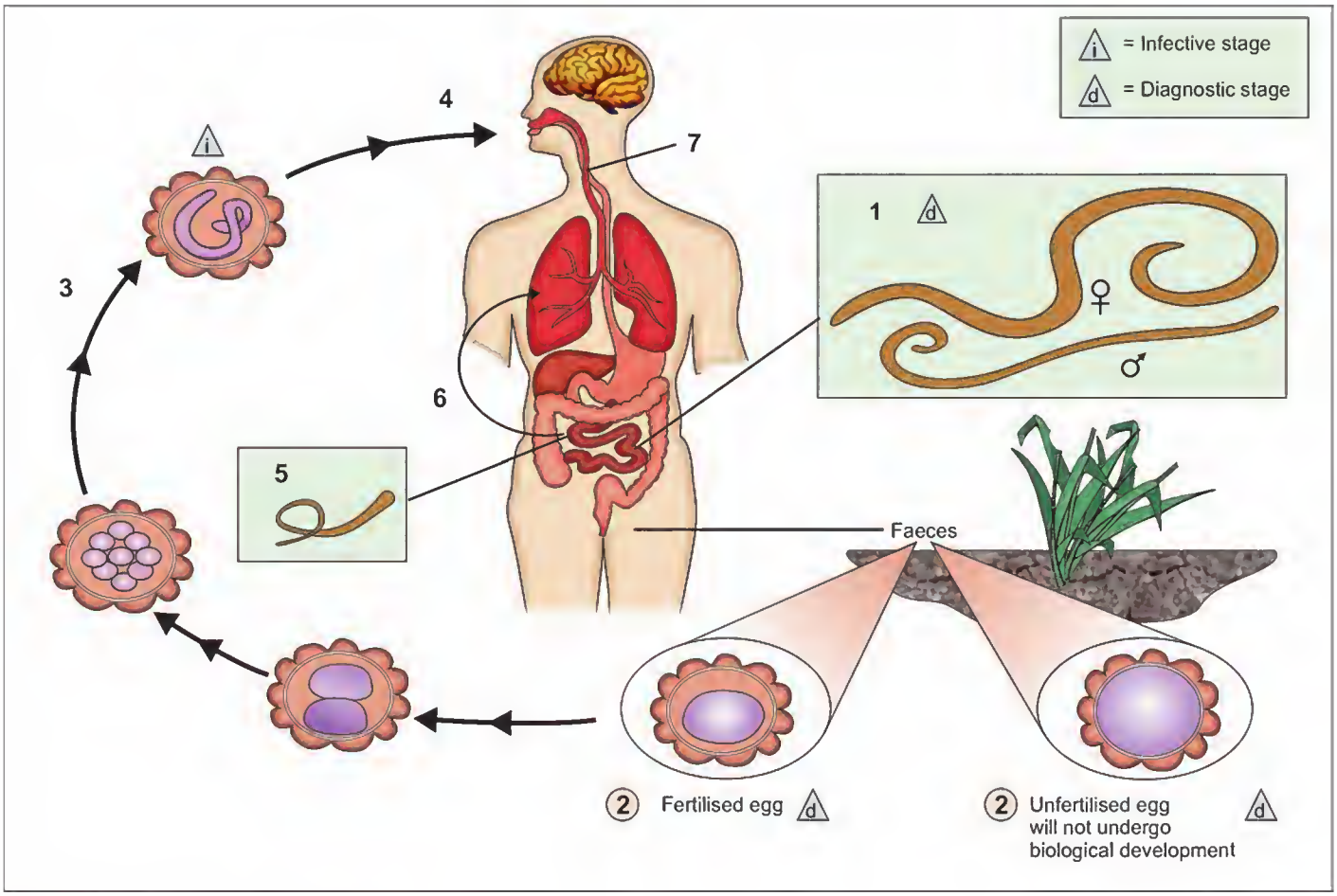


Figure 3: Life-cycle of *Ascaris lumbricoides*.

Diagnosis

1. In early infection (larval migration) complete blood count (CBC) may show peripheral eosinophilia. Sputum analysis may reveal larvae or Charcot-Leyden crystals. Chest radiograph may reveal patchy infiltrates of eosinophilic pneumonia.
2. In late infection (adult phase): Microscopic examination findings of stool show characteristic eggs. Abdominal radiographs or contrast computed tomography scans may reveal adult worms or cylindrical filling defects, respectively. Magnetic resonance cholangiopancreatography (MRCP) may detect adult worms in bile or pancreatic ducts.

Treatment

Albendazole 400 mg one dose orally is the drug of choice. Alternative therapy is mebendazole 100 mg bid for three days, pyrantel pamoate 10 mg/kg, and nitazoxanide 500 mg bid for three days.

Mebendazole is not recommended during pregnancy. Paralysing vermifuges (e.g. pyrantel pamoate, piperazine, ivermectin) should be avoided in patients with complete or partial intestinal obstruction since the paralysed worms may necessitate or further complicate surgery.

Surgical therapy

Conservative management of partial intestinal obstruction and biliary ascariasis is usually effective.

- Recommended criteria for surgical exploration include the following:
  - Passage of blood per rectum
  - Multiple air fluid levels on abdominal radiographs
  - An ill child with abdominal distension and rebound tenderness
  - Unsatisfactory response to conservative therapy
  - Appendicitis and primary peritonitis
  - Hepatobiliary disease
  - Pancreatic pseudocyst

Enterobiasis

Pinworm (*Enterobius vermicularis*), is prevalent throughout the temperate regions of the world.

Aetiopathogenesis

E. vermicularis is a white slender nematode with a pointed tail. In humans, they reside in the caecum, appendix and ascending colon. Female pinworms (8 to 13 mm long) are larger than their male counterparts (2 to 5 mm long). Pinworm infection is primarily a paediatric condition. Transmission can occur via direct contact with contaminated furniture, bed clothes, toilets and sexual contact. A gravid female pinworm migrates to the anal area and inserts her tail pin into the mucosa for ova deposition (**Figure 4**).

Clinical features

Pinworm infection is generally asymptomatic. The primary symptoms of pinworm infection usually occur at night which include pruritus or a prickling sensation in the perianal area.

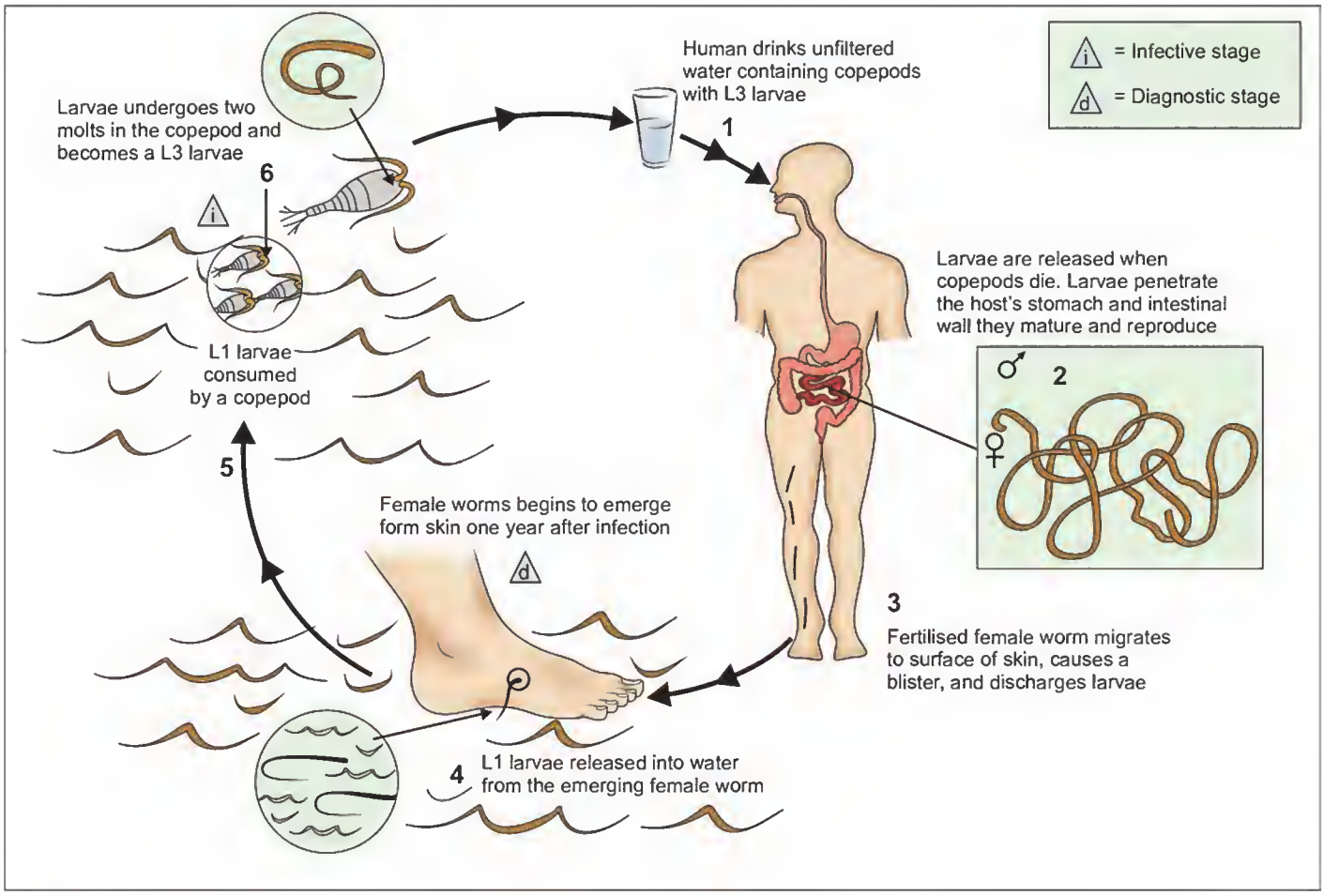


Figure 4: Life-cycle of *Entrobius vermicularis*.

Diagnosis

Use a perianal cellophane swab or cellophane tape to detect eggs.

Treatment

A single dose of mebendazole 100 mg or pyrantel pamoate 10 mg/kg or piperazine 4 gm is given and may be repeated after 2 weeks to control auto-reinfection. Treat all family members. Prescribe drugs at least 3 times at 3-week intervals.

Trichuriasis

Trichuris trichiura (whipworm) infects about one quarter of the world's population.

Aetiopathogenesis and epidemiology

The infection is common in India and South-East Asia. Poor hygiene and poor sanitary conditions are associated with trichuriasis transmission, and children are especially more vulnerable to the disease.

The whipworm derives its name from its characteristic whiplike shape; the adult male is 30 to 45 mm in length and adult female is 35 to 50 mm in length. It buries its thin, thread-like anterior half into the intestinal mucosa and feeds on tissue secretions, not on blood. The caecum, descending colon and rectum are the most commonly infected sites (**Figure 5**).

Clinical features

Most patients are asymptomatic. Patients may present with nocturnal loose stools, failure to thrive, vague abdominal discomfort, stunted growth. *Trichuris* spreads via faecal-oral transmission. Worms may live from one to five years. Adult female poduces up to 20,000 eggs per day.

Diagnosis

Complete blood count shows eosinophilia and anaemia. Stool examination reveals oval eggs with transparent bipolar plugs. Sigmoidoscopy shows adult worms attached to the bowel mucosa.

Treatment

Mebendazole 100 mg 12 hourly for 3 to 5 days or a single dose of pyrantel palmoate 10 mg/kg is effective.

Strongyloidiasis

The most common and clinically important pathogenic species in humans is *Strongyloides stercoralis*. The parasitic female worm is a very small nematode (2 mm × 0.4 mm).

Aetiopathogenesis

The life-cycle of *S. stercoralis* is complex and has two types of life-cycles – a free living life cycle and a parasitic life-cycle.

Human infection is acquired via penetration of intact skin by filariform larvae during contact with contaminated soil. The larvae then enter the circulation and are carried haematogenously to the lungs, where they enter the alveolar space. They then ascend the tracheobronchial tree and are swallowed. When they reach the small bowel, they molt twice and mature into adult females (2 mm × 0.05 mm in diameter).

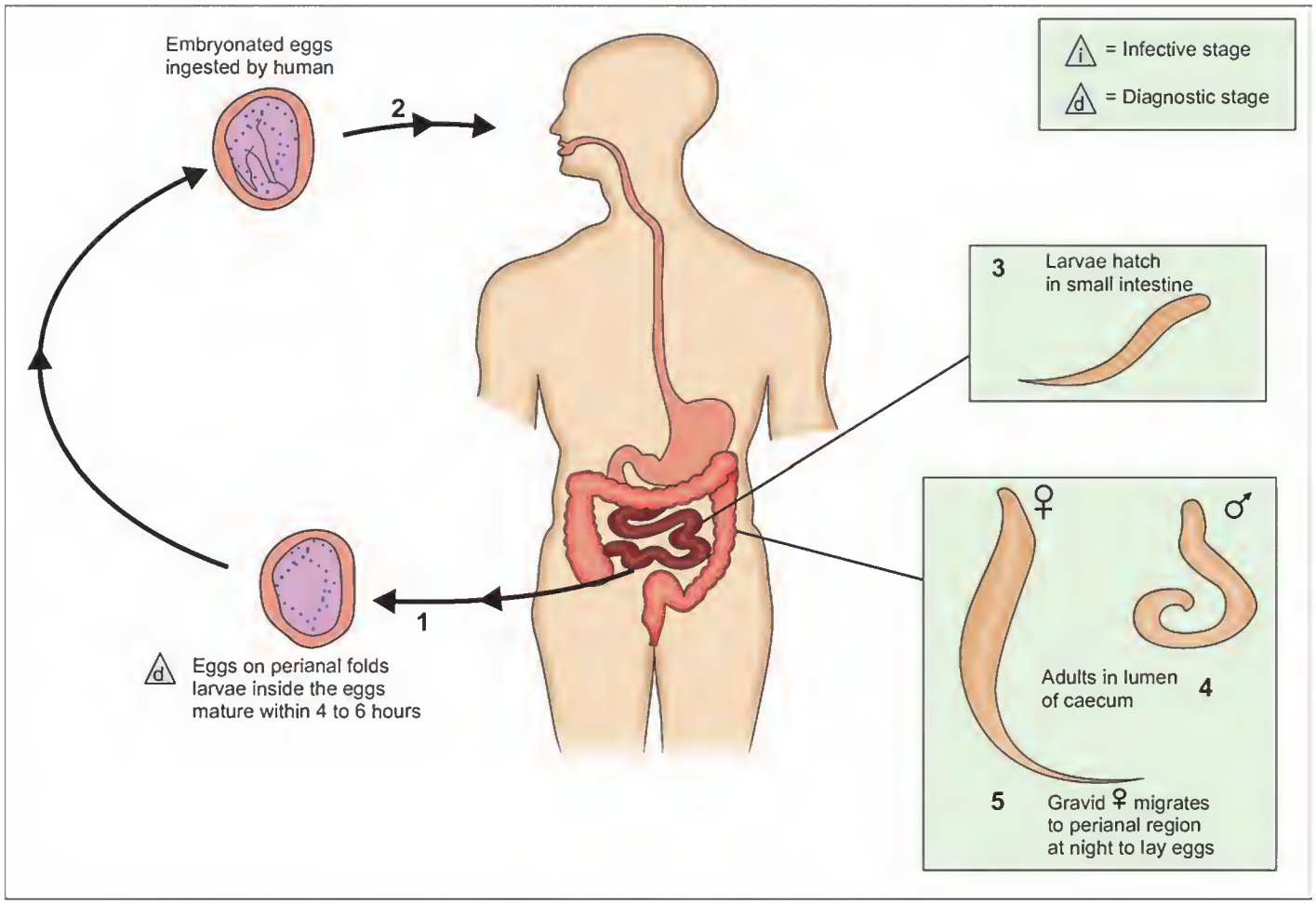


Figure 5: Life-cycle of *Trichuris trichiura*.

All parasitic adult worms are females. The parasitic females produce eggs via parthenogenesis. These eggs hatch into non-infective rhabditiform larvae, which may then be passed through the stool into the environment, where they mature into adult males and females. Alternatively, they may cause autoinfection (**Figure 6**).

Clinical features

- Acute strongyloidiasis presents with pruritic erythematous maculopapules at the site of larval skin penetration, usually on the feet, wheezing, low grade fever.
- Chronic strongyloidiasis presents with epigastric tenderness, urticaria. Larva currens ('racing larva') – Rapidly progressive serpiginous wheels beginning perianally and extending to the buttocks, upper thighs and abdomen at a rate of 5 to 10 cm/hr.
- Severe strongyloidiasis presents with diffuse abdominal tenderness, abdominal distension, absent bowel sounds, vomiting, haematemesis and haematochezia; altered mental status, rash over the trunk and proximal extremities, cough, wheezing, haemoptysis and fever.

Investigations

Complete blood count with eosinophillia (600/mm^3) is common in acute infection.

Diagnosis is established by motile larvae seen on microscopic examination of the faeces, by using special methods, such as the Baermann funnel method, the Harada-Mori filter paper method and the agar plate method. Serology (e.g. enzyme immunoassay, indirect fluorescent antibody) is helpful.

Treatment

Ivermectin 200 µg/kg as a single dose or 2 doses. Albendazole can be given in dose of 15 mg/kg twice daily for 3 days. For systemic strongyloidosis, ivermectin is given at 200 µg/kg on day 1, 2, 15 and 16.

Dracunculiasis

Dracunculiasis is an infection caused by the nematode *Dracunculus medinesis*, also known as the guinea fire worm. It was eradicated from India about a decade before.

ZOONOTIC NEMATODES

Toxocariasis

Visceral larva migrans is caused by the migration of larvae through the internal organs of humans and the resulting inflammatory reaction. It is mainly caused by migrating larvae in the dog (*Toxocara canis*) and cat (*T. oxocara catis*).

Epidemiology and aetiopathogenesis

Adult worms of the *Toxocara* species live in the small intestine of dogs and puppies. During the summer and in wet conditions, Toxocara eggs are embryonated in 2 to 5 weeks and become infective. They survive for years in the environment, and humans typically ingest the eggs via oral contact with contaminated

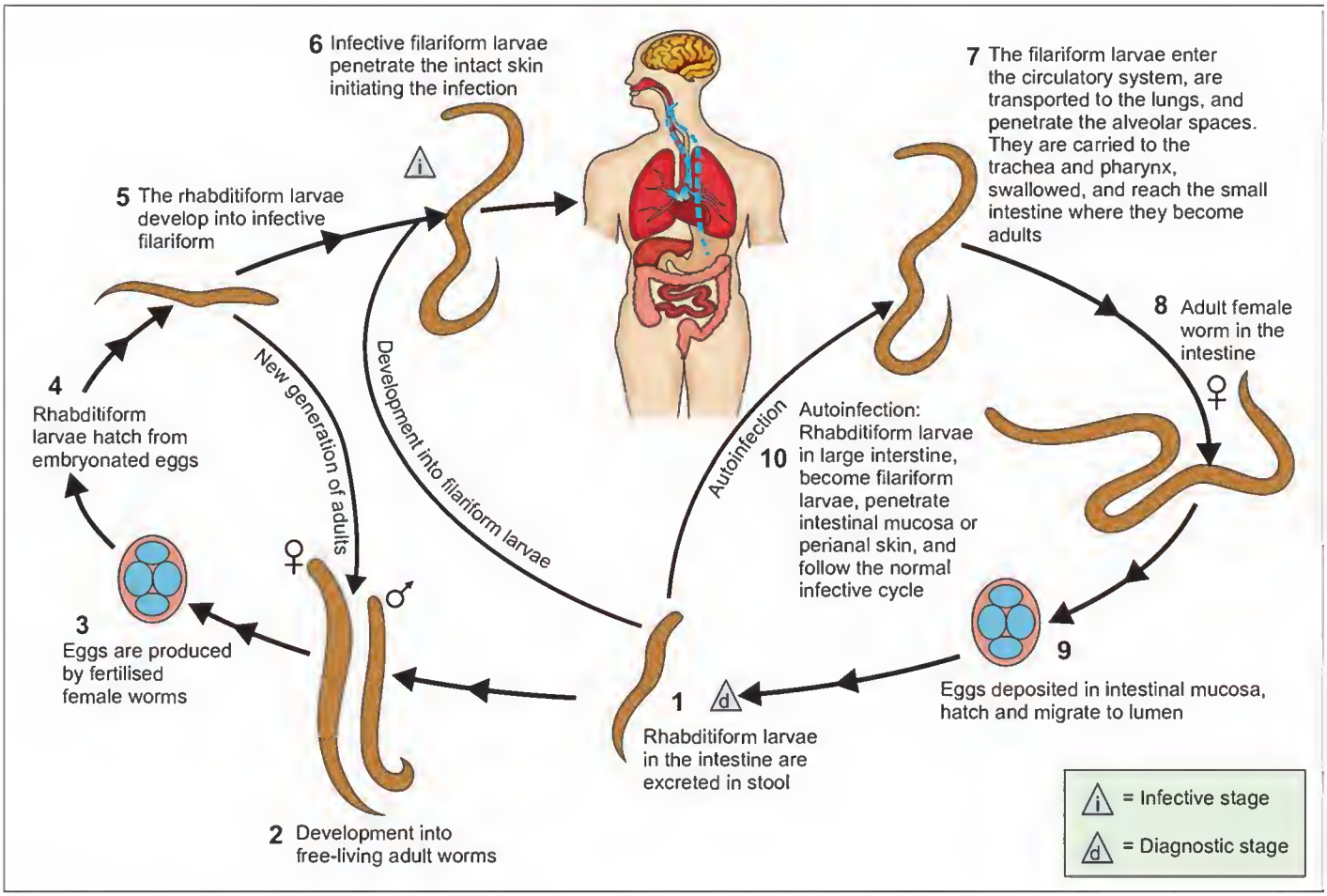


Figure 6: Life-cycle of *Strongyloides stercoralis*.

hands. Once introduced into the human intestine, the eggs decorticate, releasing the larvae. The larval form is visible only under a microscope because it is less than 0.5 mm in length and 0.02 mm wide. The larvae penetrate the bowel wall and migrate through vessels to the muscles, liver, lungs and sometimes to the eye and brain.

Clinical features

Toxocariasis cause two different clinical pictures, subclinical toxocariasis or the classical visceral larva migrans syndrome and the ocular toxocariasis.

Classical visceral larva migrans: Patients in the acute phase may have abdominal pain, decreased appetite, fever, wheezing, history of seizures, ocular involvement- decreased visual acuity, seeing floaters or bubble like images.

Ocular larva migrans: Patients with ocular involvement may present with retinal detachment due to traction caused by retinal fibrosis, pre-papillary inflammation and peripheral retinal exudates. Fundoscopic examination reveals rounded swelling near the optic disc.

Diagnosis

Leucocytosis with peripheral blood eosinophilia is the most important finding. When ocular toxocariasis is suspected ELISA of aqueous fluid for toxicariasis is useful. Chest radiography may show multiple pulmonary nodules or pleural effusion. Ultrasonography reveals multiple hypoechoic areas in the liver. CT scan may reveal hepatic lesions, multiple pulmonary nodules and surrounding ground-glass opacities or, pleural effusion or CNS granulomas.

Treatment

Mebendazole 1 gm 3 times a day for 21 days or Thiabendazole 25 mg/kg twice daily for 5 days is effective.

In ocular larva migrans, ocular involvement with retinal detachment, photocoagulation by laser treatment may be considered. Vitrectomy and use of steroids (local and intraocular) have shown good results.

Trichinosis

Trichinosis is the result of infection by the nematode *Trichinella spiralis*. Humans are infected incidentally when they eat inadequately cooked meat that contains larvae of *Trichinella* species.

Epidemiology and aetiopathogenesis

Trichinella species require 2 hosts to maintain their life-cycle. The free larvae migrate into the small intestine. After 4 molts and over a period of 30 to 36 hours, they develop into adult worms. The adult male measures 1.5 × 0.05 mm, and the adult female measures 3.5 × 0.06 mm. Approximately 5 days after infection, the female begins shedding live newborn larvae (L1 stage). The female remains in the intestine for 4 weeks, releasing up to 1500 larvae. After an adequate inflammatory response develops in the intestine, the female is eventually expelled in the faeces.

The newborn larvae enter the lymphatics and blood circulatory system and migrate to well-vascularised striated skeletal muscle. The larvae continue to grow over the next 2 to 3 weeks until they reach the fully developed L1 infective stage, when they increase in size up to 10-fold. The complete cycle takes 17 to 21 days. Life-cycle is complete when a compatible host ingests the infected muscle.

Clinical features

The degree of infection is categorised as light (0 to 10 larvae ingested), moderate (50 to 500 larvae ingested), or severe (>1000 larvae ingested).

Trichinellosis may manifest as an enteric (i.e. intestinal) phase, parenteral (i.e. invasive) phase, convalescence phase.

The enteric phase (intestinal) causes symptoms in the first week of illness. The patients may have diarrhoea, constipation, anorexia, and diffuse weakness may occur.

The parenteral (invasive) phase corresponds to the migration of the larvae from the intestine to the circulatory system and eventually to the striated muscles. This phase is associated with severe myalgia, headache, deafness, ocular disturbances, monoparesis, dyspnoea, cough and hoarseness.

The convalescent phase, which corresponds to encystment and repair, may be present for months to years after infection. The encystment of larvae can lead to cachexia, oedema and extreme dehydration.

Diagnosis

It is based on clinical, laboratory and epidemiological criteria:

- Clinical criteria: At least 3 of the following: (1) fever, (2) muscle soreness and pain, (3) gastrointestinal symptoms, (4) facial oedema, (5) eosinophilia (> 1000 eosinophils/mm^3) or (6) subconjunctival, subungual, and retinal haemorrhages.
- Laboratory criteria: At least 1 of the following: (1) demonstration of *Trichinella* larvae in tissue obtained by muscle biopsy, or (2) demonstration of *Trichinella*-specific antibody response by indirect immunofluorescence, ELISA, or Western blot.
- Epidemiological criteria: At least one of the following:
  1. Consumption of laboratory-confirmed parasitised meat
  2. Consumption of potentially parasitised products from a laboratory-confirmed infected animal
  3. Epidemiological link to a laboratory-confirmed human case by exposure to the same common source.

Treatment

If tissue invasion occurs, the most effective treatment modalities include bed rest, analgesics and antipyretics. Within one week of ingestion of contaminated meat, administer albendazole (5 mg/kg/dL for 1 week), mebendazole (5 mg/kg/dL for 8 to 14 days), or thiabendazole (25 mg/kg/dL for 8 to 14 days). Prednisone at 50 mg/dL can be used in involvement of the central nervous system, cardiac or pulmonary system.

Angiostrongyliasis

Cerebrospinal angiostrongyliasis (eosinophilic meningitis)

Angiostrongyliasis is caused by *Angiostrongylus cantonensis*, a nematode parasite that is considered the most common infectious cause of eosinophilic meningitis. Most of the described cases have occurred in Asia and the Pacific Basin.

Pathogenesis: Various species of rats are the definitive hosts of the parasite, also known as the rat lungworm. Infected rats shed first-stage larvae in their faeces, which are infective for snails and slugs but not for humans or for transport hosts.

Snails and slugs serve as intermediate hosts. Snails, fresh water shrimps, prawns, crabs, frogs and slugs become infected by ingesting first-stage larvae in rat faeces. These immature larvae mature to third-stage larvae, which are infective for rats (in which they develop to adult worms), humans, and various other animals.

Clinical features: Ingested larvae can migrate to the central nervous system and cause eosinophilic meningitis. Typically, the incubation period is 1 to 3 weeks. Common manifestations include fever, headache, photophobia, stiff neck, nausea, vomiting, fatigue and body aches. Abnormal skin sensations (e.g. tingling or painful feelings) are more common. Severe cases can be associated with sequelae (e.g. paralysis, blindness) or death.

Diagnosis: Cerebrospinal fluid examination in bright light with hand lens may show tiny moving larva. The opening pressure of CSF is usually high, over 500 mm of water. RBCs may be seen occasionally and eosinophils form 10% to 90% of cells in the CSF. Confirmation of the diagnosis is by detecting *Angiostrongyliasis cantonensis* larvae in the CSF.

Treatment and clinical course: The larvae die spontaneously, and supportive care usually suffices (e.g. analgesics and sedatives). Antihelminthics should not be given because the reaction to the dead worms in the brain can be disastrous.

The use of corticosteroids like prednisolone 0.5 to 1.0 mg/kg/dL is advocated in critical cases with cerebral involvement and in those with cranial nerve involvement.

Abdominal angiostrongyliasis (eosinophilic enteritis)

Abdominal angiostrongyliasis (eosinophilic enteritis) is caused by *Angiostrongylus costaricensis*. Cases have been reported from Central and South America and occur most commonly in young children.

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17.59 Tapeworm and Hydatid Diseases

Anurag Saxena

Parasitic helminthic infestations are an important cause of morbidity and mortality in the humans, worldwide, but the low-income countries are the worst affected. The helminths that commonly infest humans include soil-transmitted intestinal nematodes (roundworms), trematodes (flukes) and cestodes (tapeworms).

INTRODUCTION

The adult tapeworm consists of a head (scolex); a neck; and a segmented body, which contains multiple segments, called proglottids (**Figure 1**). Once anchored to the host's intestinal wall with its scolex, the tapeworm absorbs nutrients through its integument as the food being digested by the host flows past it and it begins to grow a long tail, with each proglottid containing an independent digestive system and reproductive tract. True tapeworms are exclusively hermaphrodites having both male and female reproductive systems in each of their proglottids. Older proglottids are pushed toward the tip of the tail as new ones are produced by the neckpiece. These mature and gravid proglottids leave the host in its faeces. Adult tapeworms, especially. *Taenia* species, can measure up to 50 feet long and can survive as long as 20 years in a host.

CLASSIFICATION OF TAPEWORMS

There are three tapeworm species that are commonly found in the Indian subcontinent – *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm) and *Echinococcus granulosus* (hydatid tapeworm).

TAENIA SOLIUM AND TAENIA SAGINATA

Out of about nine Taenia species causing infection in humans (*T. solium, T. saginata, T. asiatica, T. taeniformis, T. bremneri, T. africanus, T. multiceps, T. serialis and T. glomerulatus*), *Taenia solium* (pork tapeworm) and *Taenia saginata* (beef tapeworm) are the commonest tapeworm infections that are prevalent in India. *Taenia solium* is Latin for 'Ribbon Throne'. Ribbon is a reference to the flattened appearance of the tapeworms in the genus *Taenia*, while 'throne' is a reference to the ring of hooks present on its scolex.

Pathogenesis

Taeniasis (taenia infection) spreads by ingestion of raw or undercooked beef (*T. saginata*) or pork (*T. solium*) infected with cysticerci or by ingestion of tapeworm eggs through contaminated water and food. Humans are the primary host harbouring the adult tapeworm. The life-cycle of both *T. solium* and *T. saginata* are similar, with the exception of having a different intermediate host-pig for *T. solium* and cattle for *T. saginata* (**Figure 2**).

T. solium (pork tapeworm) larvae—cysticerci, can invade the human tissue and inhabit various organs of the human body, e.g. skeletal-muscles, brain, spinal cord or eyes. The most common of these sites being the brain tissue and this infection is known as neurocysticercosis (NCC). In humans, adult *T. solium* worm infestation also carries a risk of autoinfection (in approximately 25% of cases) due to reverse peristalsis of gravid

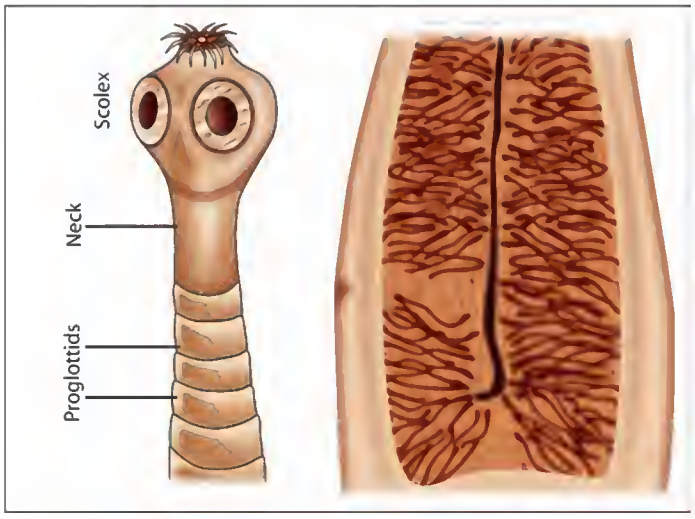


Figure 1: Tapeworm showing scolex, neck and gravid proglottid.

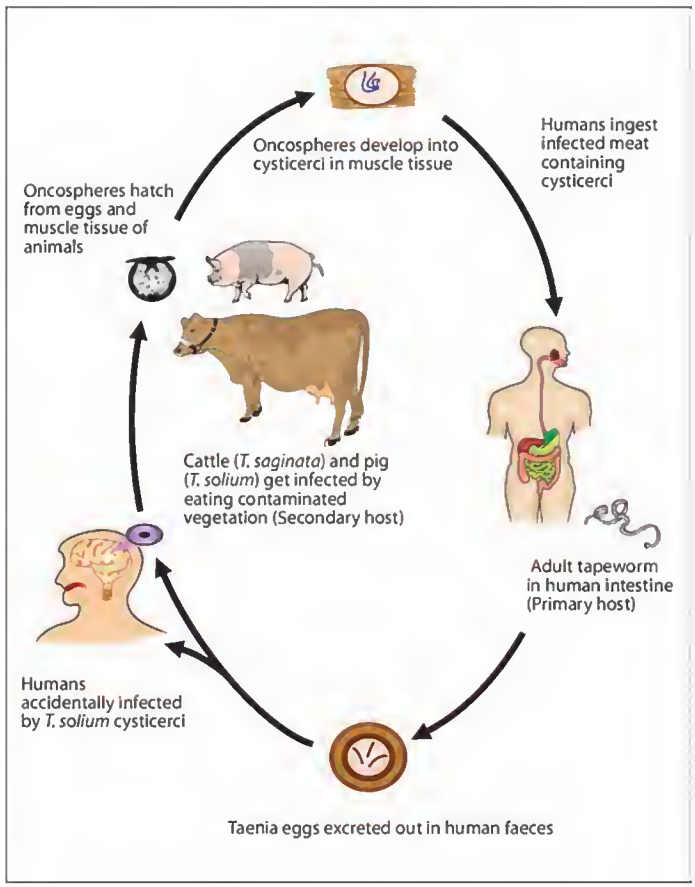


Figure 2: Life-cycle of *Taenia solium* and *Taenia saginata*.

proglottids resulting in cysticercosis. Unlike *T. solium*, *T. saginata* (beef tapeworm) does not utilise man as an intermediate host, and therefore, pathology due to its larval form (cysticercosis) is not a feature in *T. saginata* infection.

Clinical Presentation

Intestinal T. solium and T. saginata infestations are usually asymptomatic; however, patients may have generalised complaints including epigastric or periumbilical discomfort; nausea; weight loss with anorexia or increased appetite.

Neurocysticercosis (NCC) has seizures as its most common form of presentation, occurring in up to 80% of patients with parenchymal brain cysts or calcifications. Most patients have normal neurologic examinations. However, few may present with focal neurologic deficits along with possible hydrocephalus, meningitis, and dementia.

There are certain unique features of NCC in India. The solitary form of the disease (solitary cysticercus granuloma, SCG) is the most common presentation and is seen in nearly two-third of all patients with NCC. Anywhere between 26% to 50% of all Indian patients presenting with partial seizures are diagnosed with a SCG on the CT scan. More than 95% of Indian patients with NCC are vegetarians or who do not consume pork. The cause of infection in such patients is probably autoinfection or from food contaminated with *T. solium* ova.

Spinal, ventricular or menigeal neurocysticercosis manifestations are non-specific and dependent on the size and the location of the cysts.

Ocular cysticercosis presents with decreased vision, pain and recurrent redness of the affected eye and it can affect almost all parts of eye, including the anterior and posterior chambers and the retina.

Cholangitis or biliary obstruction can be seen due to reverse peristaltic movement of proglottids in some *T. saginata* infestations.

Diagnosis

Laboratory studies

Stool test and perianal swab: Diagnosis of intestinal taeniasis can be made by recovery of the characteristic ova or proglottids in the stool. The ova of *T. solium* and *T. saginata* are identical and diagnosis is made by the recovery of the proglottids or scolex. Collecting 2 to 3 stools samples is necessary for detection of the parasite because eggs and proglottids are released irregularly into the stool, thus rendering stool microscopy relatively insensitive. In *T. saginata* infections, eggs may be observed in the perianal area and can be detected by using a cellophane tape swab. This method detects eggs in 85% to 90% of patients.

Eosinophil count and serum IgE levels: Eosinophilia and raised serum IgE levels are sporadically present in taeniasis, but it does not correlate with the severity of the infection, thus rendering them diagnostically unreliable.

Imaging studies

In NCC, neuro-imaging studies like CT or MRI are not only useful in differential diagnosis and evaluation, but are also important in identifying the number, location, and the stage of the infestation e.g. vesicular stage (viable parasite) or calcified stage (dead parasite) of the lesion (**Figures 3A and B**).

Generally, MRI is better than CT for the diagnosis of NCC, detecting up to 60% of cases missed on a CT scan. However, MRI is less sensitive than CT in identifying small calcifications, as many patients have parenchymal calcifications as the sole evidence of the disease (up to 40% of symptomatic patients).

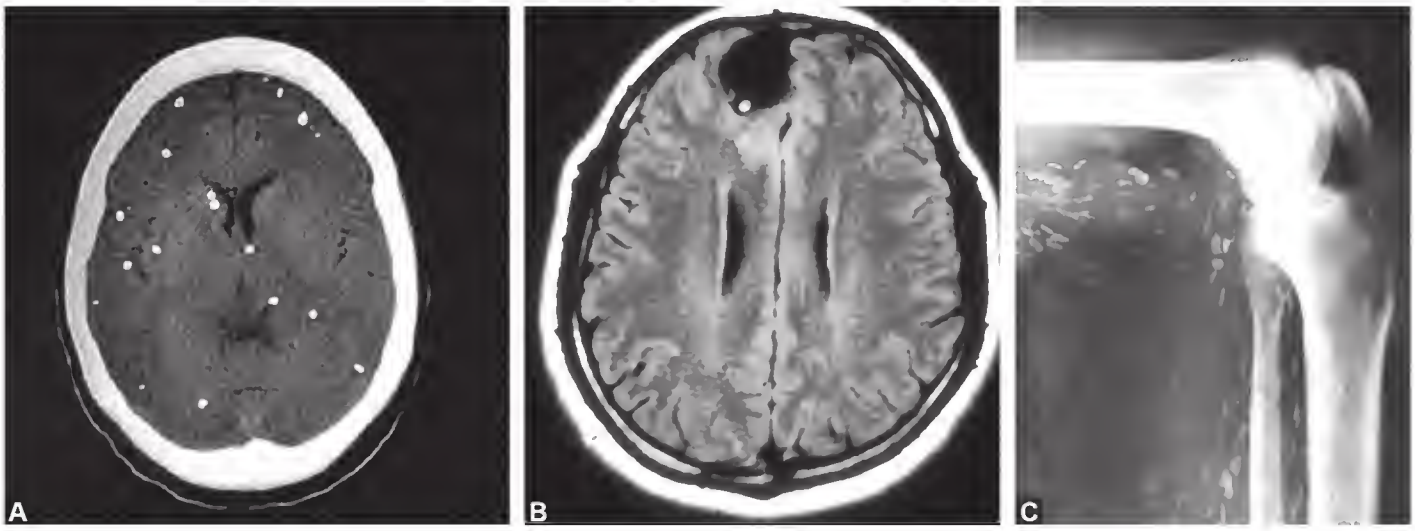
Ocular cysticercosis, can be seen on ophthalmologic examination of the eye. Ultrasonography may be useful in evaluation of patients with orbital cysticercosis.

Cysticercosis of the muscle and subcutaneous tissues can be palpated or seen on a plain radiograph and is most typically seen as spindle-shaped calcifications, most numerous in the thighs (**Figure 3C**).

Serology

(a) Stool antigen testing detects at least 2 to 3 times more cases of *Taenia* infection than stool microscopy.

(b) Various serological tests like complement fixation, haemagglutination, radioimmunoassay, ELISA, and immunoblot can be used for the detection of anticysticercal



Figures 3A to C: CT scan showing multiple calcified neurocysticercosis (A), MRI scan showing solitary cyst in frontal lobe with a scolex (B), and X-Ray of leg showing calcified cysticerci in muscle and subcutaneous tissue (C).

antibodies in serum, cerebrospinal fluid (CSF), and saliva. Imaging studies only reveal the presence of lesions in cysticercosis. However, the confirmation of its aetiology can only be done by serological testing.

The immunoblot (QualiCodeTM Cysticercosis Kit) is the most effective, with sensitivity and specificity as high as 100% and 98%, respectively; however, the sensitivity decreases to about 70% in patients with a single cyst or in those with only calcified lesions. In NCC, ELISA is more reliable when performed in CSF than in serum, but the accuracy depends on the viability and location of the cysticerci.

Treatment

Anthelmintics

Treatment of intestinal taeniasis: Most anthelmintic drugs have broad spectrum of activity and are well tolerated. They are used as single dose for several helmintic infections. The most recommended drugs for tapeworm infestations are Albendazole or Praziquantel. In intestinal taeniasis, albendazole 400 mg daily for 3 days is prescribed and may be repeated after 3 weeks. Praziquantel dose for intestinal taeniasis is 10 to 20 mg/kg PO once. Mebendazole, 100 mg PO bid for 3 days or Niclosamide, 2 g PO once can also be used. It has a cure rate of about 90% for *Taenia* species. Ivermectin, a broad-spectrum anti-parasitic drug, is not effective against tapeworms. In *T. solium* infection, a purgative following the anthelmintic medication is recommended to flush out the ova released after the death of adult worm.

Treatment of neurocysticercosis: Albendazole 15 mg/kg/dL PO in two divided doses to a maximum of 800 mg/d for 8 to 30 days. Even a 7 day course has been reported to have similar efficacy. Praziquantel is now less preferred as the duration of therapy is longer (50 mg/kg/dL PO divided tid for 14 days).

In neurocysticercosis, inflammatory response to dead and dying parasites may lead to fever, cerebral oedema, raised intracranial pressure and convulsions. Thus, if either drug is used, the patient must be started on dexamethasone. Patients with cysticercotic encephalitis develop intracranial hypertension with anthelmintic use and thus, may require a ventricular shunt prior to drug therapy. Antiepileptic drugs are needed in patients with seizures.

Surgery

In neurocysticercosis, some patients require surgery in addition to anthelmintic treatment. For example, subarachnoid neurocysticercosis with hydrocephalus and cysticercotic encephalitis requires shunting surgery and intraventricular cysts require neuroendoscopic removal. Surgery is the treatment of choice for intraocular cysts. However, in extra-ocular muscles these cysts can be treated with anthelmintic drugs or surgery. In either case, it must be administered with steroids.

In skeletal muscle and subcutaneous tissues the problem is mainly aesthetic, not medical, as these cysts cause no further problems. They are usually left untreated, unless they are painful, in which case, surgical removal is the most common course of action.

HYDATID DISEASE

Hydatid disease is a parasitic infestation caused by the larvae of the tapeworm *Echinococcus*. Among all the echinococcal species found to infect humans (*E. granulosus*, *E. multilocularis*, *E. vogeli*, *E. canadensis* and *E. borealis*), *E. granulosus* is most commonly found in India.

Pathogenesis

The adult worm of *E. granulosus* lives in the intestine of carnivores, and the larval stages parasitise in various mammalian intermediate hosts. The larval or metacestode forms are referred to as hydatid cysts and the diseases caused by them as hydatidosis or hydatid disease. Dogs and other canines are the primary hosts and the intermediate hosts include sheep, cattle, and humans. The sheep is the optimum intermediate host, and man is an accidental host (**Figure 4**).

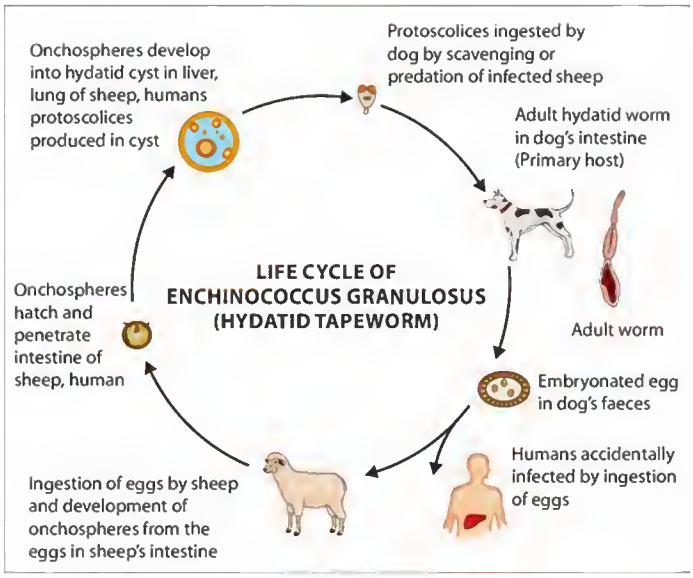


Figure 4: Life-cycle of hydatid tapeworm.

In humans, liver is the most common site (60% to 70%) of hydatid cyst development, followed by the lungs (10% to 30%), peritoneal cavity (8%), kidneys (3%) and brain (1%). Cardiac involvement is rare, with a reported occurrence between 0.5% and 2.0% of all hydatid disease. Hydatid cysts in the liver may be approximately 20 cm in diameter, but those found in the peritoneal cavity may sometimes be larger, containing several litres of fluid.

Clinical Presentation

Echinococcus infestations are potentially dangerous because they typically remain asymptomatic until the cysts cause a mass effect on an organ, which can occur 5 to 20 years after the initial infestation. Hepatic hydatid cysts can cause epigastric pain and dyspepsia (up to 35%) and can mimic cholelithiasis or jaundice (up to 45%) from compression in the bile duct. In one third of the cases, the disease is found incidentally during the check-up for non-specific symptoms (fatigue, weight loss, hepatomegaly). Hydatid cysts do not metastasise. Hydatid cyst may disseminate by accidental spillage. Rupture or leakage of the hydatid cyst due to blows to the body, muscular strain, or during operations causes contents of the hydatid to be released into the body's

circulatory system, and the liberated protoscolices may give rise to numerous secondary cysts throughout the body. The hydatid cyst fluid is highly allergenic and accidental cyst rupture may result in anaphylactic shock and rapid death.

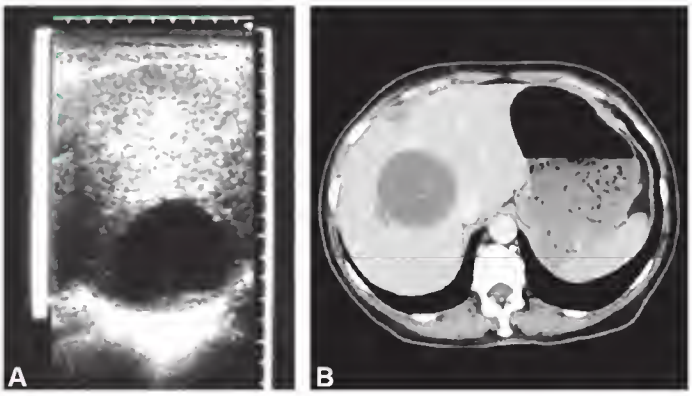
Alveolar hydatid disease presents as a lesion that does not appear as a cyst but is a firm solid mass primarily in the liver. Approximately 60% to 80% of the cysts are located in the right lobe of the liver. Single or multiple foci may be present.

Pulmonary cystic rupture may result in clinically impressive and misleading symptoms of cough, chest pain, and haemoptysis.

Diagnosis

Imaging studies

Ultrasonography, CT and MRI are the modalities used to diagnose hydatid cysts. CT is better in detecting calcified lesions, and MRI visualises necrotic or fibrotic non-calcified lesions and extrahepatic lesions of alveolar echinococcosis more clearly (**Figures 5A and B**).



Figures 5A and B: Ultrasonographic and MRI appearance of hydatid cysts .

Serological tests

In echinococcosis, ELISA is positive in more than 90% of patients with hepatic cysts, however, only 50% of patients with pulmonary hydatid cysts have the same.

One serological test which has proved to be of value to diagnosing hydatid disease is the Western Blot (Qualicode TM Hydatid Disease Kit). The test presents a definitive means for detection of human antibodies to *E. granulosus*. Diagnosis can be achieved using the Western Blot assay for the detection of IgG antibodies in serum reactive with *E. granulosus* antigens present on a membrane. Field studies support a sensitivity of 80% and specificity of 100% in patients with hepatic cysts.

Treatment

The treatment of echinococcosis requires drug therapy (albendazole) along with surgical drainage or excision of the cyst.

Drug therapy

Albendazole reduces the viability of protoscolices and cysts. It is active against the larval cestodes. Drug therapy is also indicated in inoperable cases (where long-term therapy is used), spontaneous or operative rupture of the cyst, or before and after aspiration and surgery. The recommended dose of albendazole is 400 mg twice daily (or 10 to 15 mg/kg/day) for 3 to 6 months started 1 to 3 months before surgical intervention.

Surgery

Surgical resection of the hydatid cysts is the definitive treatment. Surgical resections performed along with medical treatment; has significantly dropped the operative mortality rate from about 7% to 23% before 1980 to 0% to 5% in more recent years.

A newer modality called PAIR (puncture, aspiration, injection and re-aspiration) has also been described as an alternative treatment for hepatic cysts. Here the cysts are punctured percutaneously and fluid is aspirated out. Following this, a protoscolicidal agent (e.g. cetrimide) is injected in the cyst and then cyst is re-aspirated. Currently, the efficacy and safety of the PAIR method has not been confirmed, therefore, this method cannot be regarded as an established alternative to surgery.

PREVENTION OF TAPEWORM DISEASES

Despite the high cure rates re-infection is very high in cestode infections. Improving basic sanitation, proper hygiene education, wearing shoes, anti-worm treatment of all household members, periodic mass treatment of targeted population groups and de-worming of livestock and domestic animals is required to prevent re-infection.

Treating *Taenia solium* infected livestock with oxfendazole (OFZ) is another way of reducing the incidence. Treatment of porcine cysticercosis with OFZ should, in combination with other intervention measures be considered as an important, cost-effective measure in the control of taeniasis and cysticercosis. OFZ is equally effective in treating infected sheep and goats having echinococcosis and thus, helps in the eradication of hydatid disease.

IMMUNISATION

Immunisation against experimental infection with cestode parasites has been highly successful, in marked contrast with the relative in effectiveness of vaccines against infection with most non-cestode parasitic organisms. A recombinant antigen vaccine against infection in sheep with the parasite *Taenia ovis*, the first highly effective, non-living vaccine against a parasitic infection in animals or humans, has been developed recently. The cestode vaccines are now being developed towards practical and commercial application. The high level of efficacy of the vaccines against *T. saginata*, *T. solium*, cysticercosis and *E. granulosus* in animals brings hope for the development of an effective vaccine for human use in near future.

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17.60 Filariasis and Other Related Infestations

Sanjay Zachariah

DEFINITION

Lymphatic filariasis is a mosquito borne parasitic disease caused by the three lymphatic dwelling nematode parasites: *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. It is characterised by progressive lymphoedema leading to disfiguring elephantiasis. It is the second leading cause of permanent disability in South East Asia leading onto social stigmatisation and poverty.

EPIDEMIOLOGY

According to WHO estimates approximately 120 million people in tropical and subtropical countries are infected with filariasis of whom 25 million men have genital disease and 15 million persons developed lymphoedema. In India a total of 553 million people are at risk, 21 million have symptomatic filariasis and 27 million are microfilaria carriers. Endemic areas in India are illustrated in **Figure 1**. India contributes to 40% of the global burden of filariasis and accounts for 50% of the people at risk of infection. *Wuchereria bancrofti* is the main causative organism accounting for 98% of infection in India (90% worldwide). *Brugia malayi* accounts for 2% of lymphatic filariasis in India and shows a decreasing trend. *Brugia timori* has been found only in Indonesia.

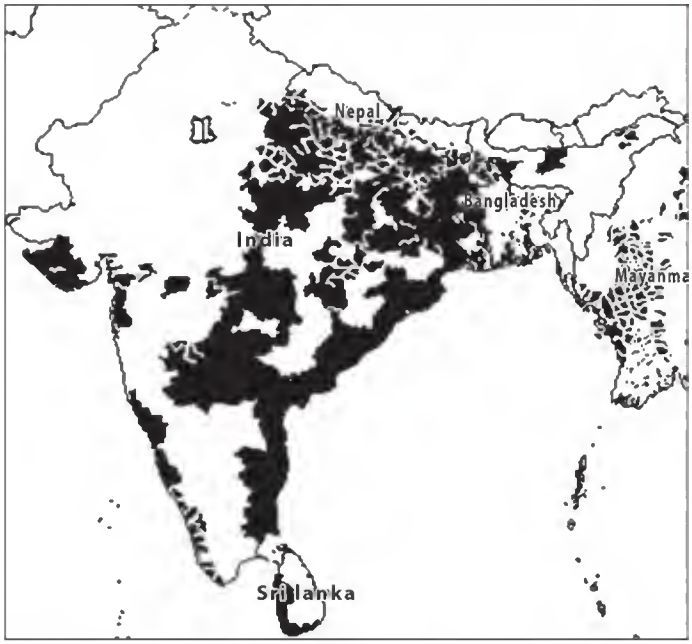


Figure 1: Distribution of filariasis in India.

AETIOLOGY

Wuchereria bancrofti is transmitted in the endemic regions by the ubiquitous day biting mosquito *Culex quinquefasciatus* (by *Aedes* in Nicobar Islands only) and *Brugia malayi* by *Mansonia* spp. Life cycle of both the filarial worms are similar and described in **Figure 2**. The period from the entry of the infective stage 3 larva into the human host till the first appearance of microfilariae in circulation is called the biological incubation period which varies from 8 to 12 months. A gravid female worm can release as many as 50,000 microfilariae per day, which enter the circulation through the thoracic duct. The clinical incubation period which varies from 8 to 16 months denotes the period from the entry of the infective stage three larva to the development of the earliest clinical manifestation.

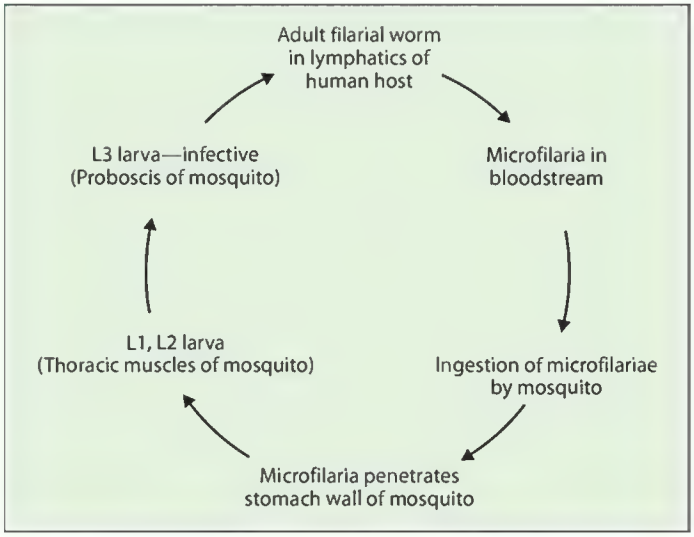


Figure 2: Life cycle of *Wuchereria bancrofti*.

PATHOGENESIS

Once the adult filarial worms take up residence in the lymphatics of the human host, further pathogenesis depends on various host factors like immune response, superadded bacterial infections and agent factors like the *Wolbachia* endosymbionts.

The initial event is lymph vessel dilatation when the adult worms are still alive though at that stage there is little reaction histologically. When they die, either naturally at the end of their life span or with drugs, an inflammatory reaction including granulomas, macrophages and eosinophils develops. At this time the release of *Wolbachia*, which are rickettsial endosymbionts found in the hypodermis of the adult worms, also add to the inflammatory response. The release of *Wolbachia* at worm death and the filarial degeneration products results in an increase in Th1, Th2 and Th17 numbers leading to the release of inflammatory cytokines TNF, IL-1β and IL-6. These contribute to lymphangiectasia and lymphangiogenesis through vascular endothelial growth factors (VEGF-A, VEGF-C, VEGFR-3). Enlarged lymph vessels are less efficient at transporting lymph from the periphery especially in the legs where the movement of lymph is against gravity. This lymph stasis in the legs further predisposes the patient to infections with exogenous microorganisms especially *Streptococci* causing bacterial acute dermatolymphangioadenitis (ADLA). Repeated episodes of

ADLA in legs with previously damaged lymph vessels cause progressively increasing secondary lymphoedema resulting in the irretrievable skin and dermal changes of elephantiasis. The pathophysiology of hydrocoele development does not necessarily involve exogenous bacterial infections. *Wuchereria bancrofti* shows a predilection for localisation in the scrotal lymphatics. Its presence there stimulates the proliferation of lymphatic endothelium and transudation of hydrocoele fluid which is similar to serum chemically. The lymphatic drainage of the penis is separate and more superficial than that of the tunica vaginalis. Therefore, a patient can develop a massive hydrocoele without any elephantiasis of the penis or scrotum. Occasionally there is a vigorous immune reaction against microfilariae reflected by hypereosinophilia and elevated IgE levels leading to tropical pulmonary eosinophilia (TPE).

All infected patients do not develop hydrocoele or elephantiasis. The development of immune tolerance in endemic regions to filarial antigens is mediated through IL-10 promoted IgG4 responses. This leads to a clinical subset of microfilaraemic patients with high parasite numbers and absence of pathological manifestations. Patients who develop lymphoedema typically have few or no parasites.

CLINICAL FEATURES

The clinical manifestations of lymphatic filariasis can vary from asymptomatic to disfiguring and disabling elephantiasis. The common manifestations are listed in **Table 1**.

Table 1: Clinical Manifestations of Lymphatic Filariasis

Acute	Chronic
Tropical Pulmonary Eosinophilia	Hydrocoele
Acute Filarial Lymphangitis	Lymphoedema (Elephantiasis)
Acute Dermatolymphangioadenitis	Chyluria
'Expatriate fever'	

Asymptomatic Carriers

Infected patients who have a downregulated immune system towards filarial antigens demonstrate high levels of microfilariae in their blood with no clinical manifestations. The microfilariae in peripheral blood show nocturnal periodicity with maximum density between 10 pm and 4 am. Even these asymptomatic patients have hidden damage to their lymphatics on lymphoscintigraphy though progression to chronic complications is rare. Patients continue to be infective till 5 years in *Wuchereria* and 3 years in *Brugia* infection.

Acute Manifestations

Tropical pulmonary eosinophilia (TPE)

At the other end of the clinical spectrum, some patients develop an exaggerated immune response to microfilariae. They present with cough, dyspnoea, nocturnal wheezing, and occasionally fever, anorexia and weight loss. Chest radiographs reveal diffuse reticulo-nodular infiltrates and pulmonary function tests show primarily restrictive defects with mild obstruction. Blood tests are characterised by marked peripheral blood eosinophilia (>3000 cells/mm^3) and high serum concentrations of IgE and filarial-specific IgG and IgE antibodies. Patients get rapid relief with diethylcarbamazine (DEC) and might progress to chronic interstitial lung disease if left untreated. Diagnostic criteria for TPE are listed in **Table 2**.

Table 2: Diagnostic Criteria of Tropical Pulmonary Eosinophilia

1. Living in or visited an endemic area
2. Paroxysmal nocturnal cough and breathlessness
3. Pulmonary infiltrations on chest radiograph
4. Absolute eosinophil count > 3000/mm^3
5. Elevated serum IgE levels
6. Elevated serum antifilarial antibodies (IgE or IgG)
7. Clinical improvement with diethylcarbamazine

Acute filarial lymphangitis

Acute filarial lympangitis is uncommon (10% to 20% as compared to ADLA) and is caused by the spontaneous or drug induced destruction of adult worms. Small tender nodules develop at the site of worm death either in the scrotum or along the lymphatics. The inflammation is retrograde progressing from the lymph node to the periphery with the lymphatics standing out as inflamed tender cords. A transient oedema (cold oedema) might occur which resolves along with the other manifestations without treatment. There is no fever, toxaemia or evidence of secondary bacterial infection.

Acute dermatolymphangioadenitis (ADLA)

ADLA is far more common and is important in the progression of lymphoedema. It is caused by secondary bacterial (usually *Streptococci*) infections. It is clinically characterised by fever, toxaemia and a swollen, red, tender extremity. The draining lymph nodes are also enlarged and tender. Minor injuries, insect bites, eczema and fungal infection of toe webs all predispose to episodes of ADLA. Notably, fungal infections of the skin act only as entry points for the bacteria but fungi themselves do not cause ADLA.

Expatriate fever

People from a nonendemic area exposed to the filarial larva for the first time in an endemic area develop a vigorous immune reaction to the same causing an 'expatriate fever'. Acute lymphangitis develops around the larva or the immature adult worm with a primarily eosinophilic infiltrate. Lymphadenitis, genital pain, hepatomegaly, splenomegaly and allergic manifestations like rashes, hives, might all develop.

Chronic Manifestations

Hydrocoele

Hydrocoele is the most common manifestation of lymphatic filariasis. In endemic areas, the prevalence of filarial hydrocoele exceeds 50% in males aged 45 years or more. It is caused only by *W. bancrofti* and not by *Brugia*. A thickened spermatic cord might be found on clinical examination due to the presence of adult filarial worms in its lymphatics.

Lymphoedema

Lymphatic filariasis is the commonest cause of secondary lymphoedema worldwide. Filarial lymphoedema commonly involves the lower limbs (**Figure 3**) and genitalia, but can also affect the upper limbs and breasts. In the initial stages, the lymphoedema is due to lymph stasis and is reversible with postural drainage. The oedema gradually becomes brawny and

non-pitting with hardening of the skin. The swollen limb develops deep skin folds along with hyperkeratosis and hyperpigmentation. The skin folds harbour bacteria and fungi which perpetuate episodes of ADLA. Gradually warty protuberances develop which are nothing but nodular tissue with dilated lymphatics inside. These nodules might breakdown leading to direct leakage of lymph (lymphorrhoea). WHO describes three grades of lymphoedema progressing from: (1) reversible pitting oedema to; (2) irreversible non-pitting oedema; and finally (3) severe swelling with sclerosis and skin changes. A more comprehensive and clinically appropriate staging is described in **Table 3**.



Figure 3: Stage 3 filarial lymphoedema.

Table 3: Dreyer Staging of Filarial Lymphoedema

Stage	Characteristic clinical feature
1	Swelling is reversible overnight
2	Swelling is not reversible overnight
3	Presence of shallow skin folds (base of fold can be seen with movement of leg)
4	Presence of skin knobs
5	Presence of deep skin folds (base of fold can only be seen if opened up)
6	Presence of 'mossy lesions'. Warty looking epidermal skin lesions
7	Unable to care for self or perform daily activities

Chyluria

The rupture of swollen lymphatics into the renal pelvis results in the passage of white milky urine called chyluria. This loss of intestinal lymph (chyle) which is rich in lipids and proteins leads to severe malnutrition, hypoalbuminaemia and weight loss. Occasionally rupture of small vessels at the fistulous site leads to haematochyluria wherein the urine is milk-like with a pale pink colour.

Other Manifestations

Chylous ascites, chylocoele and chylothorax can result from the rupture of swollen lymphatics into the peritoneum, tunica vaginalis and thoracic cavity respectively. Acute glomerulonephritis of a diffuse mesangial proliferative pathology responsive to diethylcarbamazine has been described in filariasis. Rare instances of endomyocardial fibrosis have also been reported. Filarial arthritis of two clinical types have been identified. Oligoarticular filarial arthritis affects a single large joint, commonly the knee and is due to a tissue reaction to filarial worms in the vicinity. Microfilariae are not found in the synovial fluid. The second type, filarial pseudorheumatism is thought to be due to intra-articular deposition of immune complexes. In endemic areas of India and Sri Lanka, filarial granulomas can present as hard nodular masses in the breast fixed to overlying skin mimicking a malignant lesion. Histopathology reveals a eosinophilic granulomatous reaction around degenerating adult filarial worms or microfilariae. Filarial antibodies are usually positive and patients respond very well to diethylcarbamazine.

Filariasis in Children

In endemic areas, filariasis is mostly acquired in childhood as evidenced by widespread presence of filarial antigenaemia, microfilaraemia and demonstration of adult worms on doppler ultrasonography. Children under 10 have prevalence rates averaging 30% and 10 to 19 year olds about 69% of the adult rate. Subclinical damage to the lymphatic system in the form of dilatation is visible on lymphoscintigraphy but children usually develop only lymphadenopathy overtly. Hydrocoele and lymphoedema are seen only after puberty.

DIAGNOSIS

Microfilarial Detection

Microfilariae can be detected in blood, urine or hydrocoele fluid through direct microscopy. A thick and thin blood smear, with the thick part dehaemoglobinised with distilled water, is prepared and stained with Giemsa or Leishman stains. The thick film is used for detection of microfilariae and the thin film for microfilarial morphology. In view of the nocturnal periodicity, blood sample should be collected between 10 pm to 4 am. To increase the sensitivity of the test, blood or other fluid could be passed through a millipore (5 micron pore size) membrane filter which will retain most of the microfilariae. The filter is then washed (to lyse RBC), stained and examined for microfilariae. DEC provocation test is used to facilitate daytime detection of microfilariae. A single dose of DEC (2 mg/kg body weight) is given and blood collected after 30 minutes for microscopy.

Antigen Detection

Detection of specific circulating filarial antigens (CFA) is regarded by WHO as the 'gold standard' for diagnosis of lymphatic filariasis. In comparison with microfilarial detection in blood, testing for CFA has been found to be 94% to 100% sensitive and 90% to 100% specific. An ELISA test which gives semi-quantitative results and an Immuno-chromatographic test (ICT, available as a card test) can be used. The ICT card test is especially useful in the field in view of its simplicity; portability and needing only fingerpick sampling.

DNA Based Diagnosis

Though not as sensitive as antigen detection, DNA based techniques like polymerase chain reaction (PCR) are more specific. PCR amplification of the glutathione peroxidase gene helps in the diagnosis of lymphatic filariasis and restriction fragment length polymorphism (RFLP) enables differentiation of species. These tests have a greater role as epidemiological tools as they detect parasite DNA in both humans and vectors.

Antibody Detection

Elevated levels of anti-filarial IgG4 antibody levels are associated with active lymphatic filarial infections; however cross-reactivity with other filarial parasites (*Onchocerca, Loa loa, Mansonella*) is common. Extremely raised levels of serum IgE might be seen in TPE.

Chest Radiography

Chest radiographs may demonstrate diffuse reticulonodular infiltrates in TPE.

Ultrasonography

In asymptomatic microfilaraemic patients, ultrasonography can visualise adult filarial worms in scrotal lymphatics in males and retroperitoneal and breast lymphatics in females. Spontaneous movement of the worms inside the lymphatics is described as filarial dance sign.

Lymphoscintigraphy

Lymphoscintigraphy though not helpful in diagnosis, has been useful in understanding pathogenesis of lymphoedema in filariasis. A gamma camera is used to visualise the movement of radiolabelled albumin through the lower limb after being injected into the web space of the toes. Lymphatic dilatation is visible even in the early asymptomatic phase, dermal back flow and obstruction becoming evident later.

MANAGEMENT

The management of lymphatic filariasis involves not only antifilarial drug therapy, it also encompasses the management and prevention of ADLA, management of lymphoedema/elephantiasis and patient counselling/education.

Antifilarial Drugs

Diethylcarbamazine (DEC)

DEC has direct cidal effect on both adult worms and microfilariae. It markedly lowers microfilariae levels even in single annual doses of 6 mg/kg body weight which makes it perfect weapon in the campaign to eliminate filarial transmission through mass drug administration. It is effective against the adult worms in only 50% of patients with the effectivity not improving with repeated dosing. Direct adverse effects of DEC are rare; most of the side effects like rash, fever, myalgia and cough are attributed to the rapid destruction of microfilariae and the subsequent immune reaction to the degenerating parasites. These adverse effects last from 24 to 48 hours and require only symptomatic therapy. It is the drug of choice for TPE in which the duration of therapy is 4 weeks.

Albendazole

This commonly used anthelmintic is effective against adult filarial worms destroying them at a dose of 400 mg twice a day for two weeks. It has no direct effect on microfilariae. A single dose of albendazole 400 mg greatly accelerates the microfilaricidal action of DEC. Therefore, the strategy of combining a single annual dose of DEC 6 mg/kg body weight with albendazole 400 mg is appropriate for eliminating filarial transmission in India. This has the added benefit of clearing intestinal helminths thereby improving the nutritional status of the community. Severe scrotal reactions might be induced by the death of the adult worms inside the scrotal lymphatics.

Ivermectin

In single annual doses of 200-400 µg/kg body weight, ivermectin markedly reduces the blood microfilariae count. The adverse effects are similar to DEC but milder due to the slower clearance of parasitaemia. Its principal use is in countries co-endemic for onchocerciasis and loasis where DEC cannot be used due to possible severe immune reaction. It has no proven action against the adult worms. Ivermectin is effective in louse infestations, scabies and against many intestinal helminths.

Doxycycline

Doxycycline is effective in clearing *Wolbachia* endosymbionts from the adult filarial worms apparently leading to long-term adult female worm sterility and subsequent reduction in microfilaraemia. It has to be given in a dose of 200 mg/dL for 8 weeks resulting in a sustained decrease in blood microfilariae levels at 1 year. It is most effective when combined with DEC-albendazole or ivermectin with the added advantage of doxycycline pre-treatment markedly reducing the adverse events following DEC-albendazole administration.

Lymphatic filariasis has a wide variety of clinical presentations and its management could be subdivided into the individual treatment of the three main clinical subgroups, i.e. asymptomatic carriers, ADLA and patients with lymphoedema/elephantiasis.

Asymptomatic Carriers

DEC is the drug of choice for treatment of asymptomatic microfilaraemia at a dosage of 6mg/kg bw/day divided into 3 doses for 12 days, preferably combined with single dose of albendazole or ivermectin. Pre-treatment with doxycycline 200 mg/day for 6 weeks before DEC-albendazole administration gives superior results with less adverse events.

Acute Dermatolymphangioadenitis (ADLA)

Aggressive management and prevention of episodes of ADLA is the key to halting the progression towards elephantiasis. During an acute episode, patients should be treated with crystalline penicillin as the commonest causative organism is *Streptococcus*. Pain could be reduced with cold compresses or soaking the limb in cold water. The patient should take rest, be hydrated well and elevate the limb for as long as possible. Prevention of ADLA is detailed in **Table 4**. Washing and drying of skin should be done in a gentle manner to avoid abrasions or injury. Exercise involves flexion-extension at the ankle and rotatory movement at the ankle joint. In selected cases with repeated episodes of ADLA despite above measures, benzathine penicillin 1.2 MU, deep IM every 3 weeks may be used as a preventive measure.

Table 4: Prevention of Acute Dermatolymphangioadenitis

1. Twice daily gentle washing of limb with soap and water
2. Thorough gentle drying after washing
3. Massage with simple emollients like coconut oil
4. Applying antiseptics to any wounds/abrasion
5. Treatment of any fungal infections with systemic and local therapy
6. Elevate affected limb day and night
7. Constant gentle exercise of affected limb
8. Wearing comfortable shoes preferably with adjustable straps
9. Nails to be kept clean and trimmed.

Lymphoedema/Elephantiasis

All the measures mentioned in **Table 4** for preventing ADLA are just as important in decreasing lymphoedema progression, in some cases even reversing it. Following options can additionally be offered to patients with lymphoedema/elephantiasis:

Manual massage

Massage with an emollient with a gentle upward milking pattern has shown to be effective in reducing lymphoedema. It can be administered by a physiotherapist or by relative/ patient who has received training.

Compression bandage

An ideal compression bandage would apply uniform pressure all around and would adjust to the smaller diameter of the limb as the day proceeds. Crepe bandage is commonly used with the normal activity during the day, increasing lymph flow by muscle pump action. Tailor made elastocrepe stockings are also used. Compression bandaging immediately after a manual massage session helps in maintaining the reduction in limb diameter.

Intermittent pneumatic compression

The limb is encased in a plastic inflatable connected to an electric pump. Pressure is gradually increased to 80-100 mm Hg over 120 seconds and then rested for 30 to 45 seconds. Therapy is usually continued for 2 to 3 hours in a day followed immediately by compression bandaging to maintain volume reduction.

Heat treatment

Application of heat externally in a heated oven (which leads to greater heating of epidermis than dermis) or uniformly with a microwave oven has been tried but is less effective in filariasis though results in lymphoedema of other causes has been better.

Interferential therapy

Interferential therapy is a form of physical therapy in which medium frequency currents are crossed inside the limb tissue to create a low frequency current, mainly used in relieving painful muscle spasms. In filarial lymphoedema a faradic current of 15 to 30 millivolts is passed in 5 second pulses for 30 min through selected portions of the limb. It is less effective than massage or bandaging.

Surgical therapy

Surgery is the last resort in elephantiasis. Drainage procedures like lympho-nodo-venous anastomosis, lymphatico-venous anastomosis and omentoplasty, attempt to enhance lymphatic drainage in the limb. Excisional surgery of the affected skin and subcutaneous tissue, closed by skin flap or graft is usually complicated by lymphorrhoea, haemorrhage and lymphangitis. Hydrocoele would require surgical management when response to medical therapy is incomplete.

Counselling and education

It is very important to educate the patient regarding the nature of the disease, its cause and its progression. Such education will help in enlisting the patient's and relative's assistance for lymphoedema amelioration measures. Lymphatic filariasis leads to physical disfigurement leading to social stigmatisation. Patients suffer from chronic pain, physical disability and sexual dysfunction for which psychological support and counselling is essential.

PREVENTION

The WHO announced the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 1998 with target for elimination being the year 2020. India is a signatory to the GPELF and through its National Filaria Control Programme (NFCP) has started a campaign of Mass Drug Administration (MDA) of single annual dose of DEC or DEC-Albendazole to interrupt transmission of the disease. DEC medicated salt has been successfully used in Tamil Nadu but has operational problems related to distribution and community acceptance. Vector control is through anti-larval spray at weekly intervals with appropriate larvicides, biological control through larvivorous fishes and environmental engineering through source reduction and water management to eliminate mosquito breeding sites.

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17.61 Schistosomiasis/Bilharziasis

Kirti C Patel

HISTORY

Theodor Bilharz in 1851 described this disease. Around 200 to 300 million people are affected in 74 countries of the world. Schistosomiasis is caused by several species of *Schistosoma*, each giving rise to a characteristic form of the disease.

Schistosomiasis is endemic in Egypt, exacerbated by the country's dam and irrigation project along the Nile. Focus of schistosomiasis in Ratnagiri district of Maharashtra, India was described by Gadgil and Shah in 1952. The twentieth century was marked by the development of control measures including effective drugs, particularly praziquantel, for schistosomiasis.

STATUS IN ANIMAL KINGDOM

Phylum *Platyhelminthes* and genus *Schistosoma*. Among these, *S. haematobium*, *S. mansoni* and *S. japonicum* can cause important human diseases (**Table 1**).

Table 1: Common Schistosomiasis

Differentiating Features	*S. haematobium*	*S. mansoni*	*S. japonicum*
Synonym	Vesical blood fluke	Manson's blood fluke	Oriental blood fluke
Location	Tanzania, Middle East, Egypt, Ratanagiri in Maharashtra (India)	Cairo, Egypt, Sudan, USA, East African Coast	China, Japan, Philippines, Taiwan, Sulawesi

LIFE CYCLE

Metacercariae or schistosomules gain entry into the venous system and finally lodge into the portal circulation via the mesenteric artery having gone through the pulmonary circuit. Metacercariae of *S. haematobium* pass into the vesical venous plexus and develop into sexually matured worms. Females lay lateral spined eggs in vesical venules which are passed into the urine. Metacercariae of *S. mansoni* and *S. japonicum* ultimately enter the rectal venous plexuses and mature into adult worms. Females lay eggs in rectal venules with terminal spine or small knob, which enter the rectum and are ultimately expelled into stool. The eggs of all species develop into miracidia and enter the snail. In snails they develop into sporocysts and then fork-tailed cercariae which are released into the surrounding water and are ready to enter human skin.

PATHOLOGICAL FINDINGS

S. haematobium worms may lead to formation of granulomata, ulceration, fibrosis and finally calcification in the bladder. The *S. mansoni* and *S. japonicum* worms are found in the tributaries of inferior mesenteric veins, and consequently, lesions are found in the large intestines. *S. japonicum* have detrimental effect on the portal system. These lesions are located in the upper part of the colon, small intestines and liver.

CLINICAL FEATURES

In the early stages of infection there may be itching lasting 1 to 2 days at the site of penetration. After a symptom-free period of 3 to 5 weeks, acute schistosomiasis (Katayama syndrome) may present with allergic manifestations, such as urticaria, fever, muscle aches, abdominal pain, headache, cough and sweating. Examination reveals hepatomegaly, splenomegaly, lymphadenopathy. Patients with *S. haematobium* infection commonly present with painless haematuria, bladder calculi and malignancy. Manifestations of *S. mansoni* and *S. japonicum* include intestinal colic and bloody diarrhoea. Long standing infection is known to cause cirrhosis of the liver, portal hypertension, haemolysis and progressive anaemia. Increased incidence of urinary bladder stone and malignancy is noticed with *S. haematobium*.

DIAGNOSIS

During acute stage, anaemia, leucocytosis and marked eosinophilia are common. Other causes of haematuria, dysentery and hepatosplenomegaly require to be excluded. Definite diagnosis is established by the demonstration of terminally spined eggs in the centrifuged deposits of urine or in compressed bladder tissue between two slides in case of *S. haematobium*. The rapid simple and inexpensive kato-katz thick smear stool examination is widely used in field studies. Stool examination, proctoscopic aspiration of material and rectal biopsy would be useful to demonstrate species of *S. mansoni* and *S. japonicum*.

Imaging Studies

Lower abdominal plain radiograph may show calcification of bladder wall or ureters. Ultrasonography may show periportal fibrosis and obviates the need for biopsy. However, it might fail to show calcification of bladder or ureter. Computed tomography of abdomen may demonstrate pathognomonic turtle-back calcification. Cystoscopy in advanced cases show sandy patches, ulcers and areas of squamous metaplasia.

TREATMENT

The management is outlined in **Table 2**.

Table 2: Management of Schistosomiasis

Name of Drug	Dose
Praziquantel (effective against all species)	40 mg/kg single oral dose for *S. haematobium*, *S. mansoni* and *S. intercalatum* after meals. 20 mg/kg three oral doses or 30 mg/kg two oral doses for *S. japonicum* and *S. mekongi*.
Metrifonate	10 mg/kg given in three oral doses at an interval of 14 days.
Surgery	Removal of polyps/splenectomy

PREVENTION AND CONTROL

Improved sanitary facilities can prevent eggs excreted by infected persons from reaching water that harbours the intermediate host, the snail. Avoiding swimming or wading through contaminated water is important in the endemic areas. Molluscicidal compounds, like sodium pentochlorphenate can reduce the snail population. Large-scale community-based chemotherapy in the endemic areas may also interrupt the eggs-miracidium-snail cycle, thereby diminishing the risk of severely-damaged organs even though re-infection may occur. Introduction or augmentation of existing crey fish population can control the snail population.

Devastating effect of the disease stems from the immune response initiated by entrapped eggs in tissues. Recombinant derived *Schistosoma mansoni* antigen vaccines have encouraging results.

PROGNOSIS

Co-infection with either hepatitis-B virus (HBV) or hepatitis-C virus may lead to hepatocellular carcinoma than that attributable to HBV alone. Chronic disease has a bad prognosis. In children, schistosomiasis may perpetuate malnutrition and may result in growth retardation.

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17.62 Systemic Fungal Infections

Shruti Prem, Rajat Kumar

INTRODUCTION

Systemic or invasive fungal infections refer to bloodstream infection by fungi or involvement of deep seated organs like the lung or the brain. The term differentiates it from the more common superficial fungal infections which have a better prognosis. Invasive fungal infections (IFI) have become more common with the increase in immunocompromised patients. This chapter deals with, systemic fungal disease in immunosuppressed patients but endemic fungal infections (histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and sporotrichosis) have been mentioned in passing only.

Changing Epidemiology of Invasive Fungal Infection in Immunocompromised Patients

Candida species are the most common cause of invasive fungal infections in humans, producing infections that range from non life-threatening mucocutaneous disorders to invasive disease that can involve any organ. The most common risk factors from Indian studies are shown in **Table 1**. *Candidemia* is the fourth most common cause of nosocomial bloodstream infections in the United States and in much of the developed world. The attributable mortality of invasive candidiasis is as high as 47%.

In the epidemiology of fungal infections there has been a decrease in *C. albicans*, *C. tropicalis* and *C. parapsilosis* infections with an emergence of occasional infections by azole-resistant species, such as *C. glabrata*, and *C. krusei*. An increase in the incidence of mould infections, particularly aspergillosis, has been observed together with an emergence of infections by other moulds (*Fusarium* spp. *Zygomycetes* and others). *Aspergillus fumigatus* is the most common species recovered from cases of invasive aspergillosis followed by *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus*.

FUNGAL INFECTIONS IN INDIA

Most systemic fungal infections remain undiagnosed in the country. The limited literature, mainly derived from a few tertiary centers, confirms a rising trend of invasive candidiasis, aspergillosis and zygomycosis in India.

Invasive Candidiasis

The most common IFI in India is candidiasis, where the organism enters the blood stream from the gastrointestinal tract or from the skin through indwelling intravenous catheters. The incidence varies from 1 to 12 per thousand admissions in different hospitals across the country. *Candidemia* was associated with a mortality of 55%. *C. tropicalis* is the most common among the non-*C. albicans* candidiasis. The brain, heart, kidneys, liver, spleen and any other organ may be involved. Disseminated macronodular lesions may be present in the skin and fundoscopy may reveal chorioretinitis. Skin and eye involvement suggest a high probability of disseminated deep organ abscesses.

Invasive Aspergillosis

Invasive pulmonary, paranasal and cerebral aspergillosis are common presentations in India, but the infection may be disseminated. The most common isolate is *A. flavus*, rather than *A. fumigatus* which is the most common isolate in temperate countries.

Zygomycosis

Despite the lack of diagnostic mycology facilities, India contributes about 40% of the global burden of the disease. More than 300 cases of zygomycosis have been reported from a single tertiary centre in India. Diagnosis has been made mainly on autopsy, as ante-mortem diagnosis is difficult without high clinical suspicion. Zygomycosis/Mucormycosis refers to several different diseases caused by infection with fungi in the order of *Mucorales*. These

Table 1: Prominent Risk Factors of Mycosis in Indian Studies

Risk Factors	Candidiasis	Aspergillosis	Zygomycosis	Cryptococcosis
Hospitalisation > 30 days	++	++	–	–
Broad spectrum antibiotics	++	++	–	–
Immuno-suppression	++	++	++	+
Intensive care unit stay	++	++	–	–
Central venous access	++	–	–	–
Total parenteral nutrition	++	–	–	–
Mechanical ventilation	++	++	++	–
Major abdominal surgery	++	–	–	–
Renal transplantation	–	++	–	++
Haematological malignancy	++	++	++	++
Diabetes mellitus-uncontrolled	–	–	+++	+
Human immunodeficiency virus (HIV)	++	++	++	+++

have little intrinsic pathogenicity in normal hosts, but are important causes of fungal disease among immunocompromised individuals. *Rhizopus* species are the most common causative organisms. Others being *Rhizomucor, Cunninghamella, Absidia and Mucor.* The commonest presentation is sino-nasal infection which may extend into the brain. Pulmonary, cutaneous, and gastro-intestinal infections are also recognised. Successful treatment requires correction of the underlying risk factors. Surgical debridement of necrotic tissue in combination with medical therapy is mandatory for survival. The mortality rate associated with rhinocerebral disease is 50% to 70%. Disseminated disease carries a mortality rate that approaches 100%.

Cryptococcosis

Cryptococcus neoformans is a yeast fungus and has been isolated from the droppings of pigeons, munia birds and canaries. *Cryptococcus grubii* (serotype A) is the most prevalent (>90%) of *Cryptococci* isolated in India. Its main clinical manifestation is a meningoencephalitis with markedly raised intracranial pressure. The route of infection is via inhalation. It occasionally causes pneumonia, skin lesions that resemble molluscum contagiosum or a frankly disseminated illness. It is common in individuals with advanced AIDS. Controlling cerebrospinal fluid (CSF) pressure with repeated lumbar punctures or other manoeuvres is important in management. Long-term anti-fungal suppressive therapy till the immunosuppressed state improves is necessary to prevent relapse.

Diagnosis

The diagnosis of invasive fungal infections is generally based on the following three steps:

(a) High index of suspicionbased on risk factors and clinical situation.
(b) Recognising clinical syndromes associated with invasive fungal infections, such as persistent fever, pneumonia, paranasal sinusitis.
(c) Specific investigations: microbiology, histopathology, detection of fungal antigens in body fluids and radiology.

Microscopy

The diagnostic yield for microscopy is more than that of culture alone in fungal infections. Another advantage is the rapidity of microscopy, with results being available in 2 to 4 hours of a sample being received. Microscopy can also differentiate between septate *(aspergillus)* or non-septate *(mucor)* mould.

Culture

All fungi (yeasts and moulds) obtained from sterile sites including blood, intravenous line-tips, urine should be identified up to species level by referral to a specialist laboratory. Bronchoscopy fluid is deemed sterile in this context for all fungi except for *Candida* species. Blood cultures in aspergillosis are of limited utility, because the results are often not positive even in disseminated infection. Bronchoalveolar lavage, transthoracic percutaneous needle aspiration, or video assisted thoracoscopic biopsy are standard procedures for establishing a diagnosis of invasive pulmonary aspergillosis. For serious candidal infections, blood cultures remain the standard for diagnosis although serial mucosal cultures have an excellent negative predictive value (NPV) and an acceptable positive predictive value (PPV). Growth of *Candida* from respiratory secretions rarely indicates invasive candidiasis.

Histopathology

All tissues from immunocompromised patients with suspected infection should be stained with fungal stains, such as periodic acid-schiff, silver or fluorescent stains, in parallel with regular stains. Identification of a fungus invading tissue accompanied by evidence of an inflammatory response is required for confirmation of diagnosis. This is especially true for *Aspergillus* infection, as *Aspergillus* is ubiquitous and can float from the air onto biopsy material. When positive, an India ink preparation of cerebrospinal fluid is diagnostic for cryptococcosis.

Radiology

Imaging plays an important role in diagnosis and management of pulmonary mould infection, fungal sinusitis, meningitis, endocarditis and disseminated candidiasis. Chest radiographs are often falsely negative in invasive pulmonary aspergillosis whereas high-resolution CT scans of the chest give the best results. The lung findings in invasive aspergillosis include nodules with 'halo sign' (due to haemorrhage secondary to angio-invasion by fungus) during early phase of severe neutropaenia, this may be followed by 'air-crescent sign' (due to cavitation in an area of consolidation) on recovery from myelosuppression. Of note, an increase in size of pulmonary lesions does not necessarily mean progression of infection as it could be related to the immune recovery. Immunocompromised patients with new neurological features (seizure, stroke, persistent headache, or possible meningitis) should have a CT or MRI of the brain. If a lesion is identified, a biopsy or aspirate should be done, if feasible. Characteristic signs are shown in **Figures 1 to 5**.

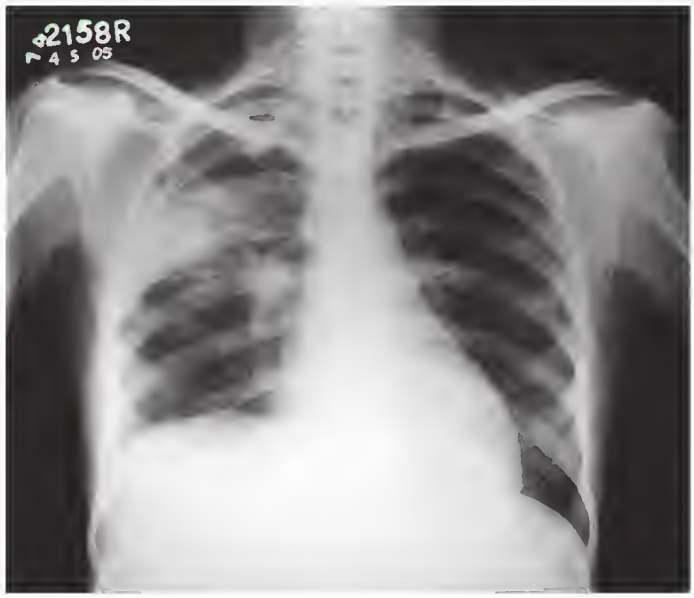


Figure 1: Chest radiograph showing consolidation and air-crescent sign in a patient of *Aspergillus* pneumonia.

Serology

The availability of enzyme linked immunosorbent assay (ELISA) for detection of circulating serum galactomannan (an *Aspergillus* cell wall antigen) has contributed toward a non-culture-based diagnosis of invasive aspergillosis. Galactomannan antigen has also been detected in CSF samples from patients with central nervous system (CNS) aspergillosis and in bronchoalveolar lavage fluid specimens

from patients with invasive pulmonary aspergillosis. The galactomannan antigen test has several advantages: it is non-invasive, easy to use, semi-quantitative and specific for *Aspergillus* species. False positive results may be observed in patients receiving piperacillin/tazobactam or amoxicillin/clavulanate. Another promising test is the 3-beta-D-glucan antigen test that appears to be useful in detecting all fungal infections (yeasts and moulds) in the bloodstream and is currently undergoing evaluation. Polymerase chain reaction (PCR) is a very sensitive test for detecting *Aspergillus* nucleic acids in various tissues.

Consensus Definitions

The European Organisation for Research in Treatment of Cancer-Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC-MSG study group) formed a Consensus Committee to develop a standard definitions for invasive fungal infections for clinical research. These definitions are principally applicable to immunocompromised patients with cancer and haematopoietic stem cell transplantation (HSCT) recipients. Although the definitions are intended for use in the context of clinical and/or epidemiological research, they provide a standard set of criteria. Three levels of certainty of invasive aspergillosis were defined: proven, probable and possible (**Tables 2 and 3**).

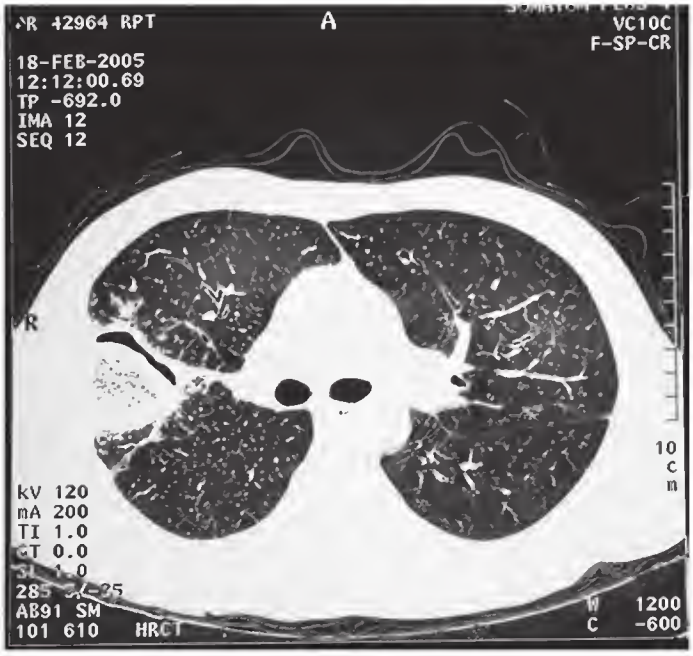


Figure 2: CT chest showing consolidation and air-crescent sign in a patient of *Aspergillus* pneumonia.

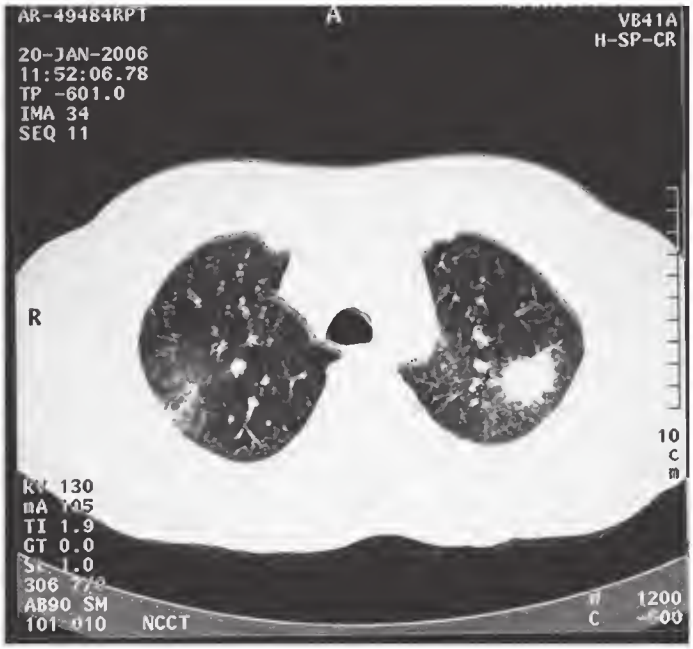


Figure 3: CECT chest showing consolidation/nodule with surrounding 'halo sign'.

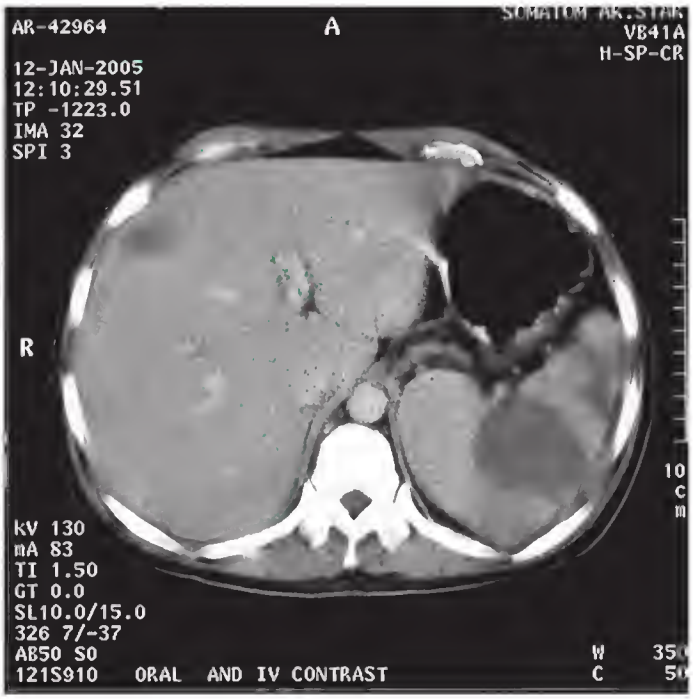


Figure 4: CECT abdomen showing hypoechoic lesions in liver and spleen in a case of disseminated aspergillosis.



Figure 5: CECT paranasal sinuses showing opacification of all the sinuses and bony destruction of the orbital floor in a patient of fungal sinusitis.

Table 2: Criteria for Proven Invasive Fungal Disease (Except for Endemic Mycosis)

Analysis and Specimen	Moulds	Yeasts
Microscopic analysis: sterile material	Histolopathologic, cytopathologic or direct microscopic examination of specimen obtained by needle aspiration or biopsy in which hyphae or melanised yeast-like forms are seen accompanied by associated tissue damage	Findings as in mould infection: from normally sterile site (other than mucus membrane) showing yeast cells
Culture: sterile material	Recovery of mould or 'black yeast' by culture of specimen from normally sterile and clinically/radiologically abnormal site* (excluding bronchoalveolar lavage, cranial sinus cavity and urine)	Recovery of yeast by culture of sample obtained by sterile procedure and from normally sterile site showing clinical or radiological abnormality*
Culture: Blood	Yields a mould (e.g. *Fusarium species*)*	Yields yeast or yeast like fungi
Serological analysis: CSF	Not applicable	Cryptococcal antigen in CSF indicates disseminated cryptococcosis

**Consistent with infectious process.*

Table 3: Outline of Criteria for Probable and Possible Invasive Fungal Disease (Except Endemic Mycosis)*

Host factors	Severe neutropaenia (<500 neutrophils/µl) for >10 days, temporally related to onset of fungal disease
	Recipient of allogeneic stem cell transplant
	Prolonged use of corticosteroids (mean minimum dose 0.3 mg/kg/dL of prednisolone equivalent for >3 weeks)
	Treatment with T-cell immunosuppressants during past 90 days
	Inherited severe immunodeficiency
Clinical criteria	Lower respiratory tract fungal disease
	Presence of one of the following three signs on CT scan chest: (a) Dense, well-circumscribed lesion(s) +/- halo sign, (b) Air-crescent sign, (c) Cavity
	Tracheobronchitis: Ulceration, nodule, pseudomembrane, plaque or eschar on bronchoscopy
	Sinonasal: Imaging showing sinusitis plus at least one of the following three signs: (a) acute localised pain, (b) nasal ulcer with black eschar, (c) extension from paranasal sinus across bony barrier, including into orbit.
	CNS infection: one of the following two signs: (a) focal lesions on imaging, (b) meningeal enhancement on MRI or CT
	Disseminated candidiasis: At least one of the following two entities after an episode of candidemia within the previous 2 weeks (a) small, target-like abscesses in liver or spleen, (b) progressive retinal exudates
Mycological criteria	Direct test (cytology, microscopy, culture)
	Mould in sputum, bronchoalveolar lavage, bronchial brush, or sinus aspirate, indicated by one of the following: (a) presence of fungal element indicating a mould, or (b) recovery by culture of a mould (*Aspergillus*, *Fusarium*, *Zygomycetes* or *Scedosporium*)
	Indirect tests (detection of antigen or cell-wall constituent): (a) Aspergillosis: Galactomannan antigen in plasma, serum, bronchoalveolar lavage, or CSF, (b) invasive fungal disease other than cryptococcosis or zygomycosis: beta-D-glucan detected in serum

**Probable IFD: Requires presence of o host foctor, o clinicol criterion ond o mycologicol criterion; Possible IFD: Requires criterion for o host ond clinicol feotures, but for which mycologicol criterion ore missing.*

One of the Indian Experience

In a study conducted in All India Institute of Medical Sciences (AIIMS), New Delhi, patients with persistent febrile neutropaenia unresponsive to broad spectrum antibiotics were screened for invasive pulmonary aspergillosis (IPA) using high resolution CT scan of the chest, fungal cultures and serology for galactomannan over one year. According to EORTC defining criteria there were 32 cases of suspected IPA based on clinical and microbiological criteria (including galactomannan serology) and the overall sensitivity and specificity of radiology for diagnosing IPA was 96% and 65.4% respectively.The sensitivity and specificity of the halo sign was 39.3% and 81.1% and that of the air crescent sign was 28.6% and 94.3% in diagnosing IPA. Some of the larger nodules and consolidations in patients with suspected IPA showed a central hypodensity on non-contrast CT ('hypodense sign'). These radiological findings were useful in the early institution of anti-fungal therapy in these patients. The overall mortality in patients of IPA was 43.75%.

Treatment

Anti-fungal therapy can be classified into four groups:

1. *Prophylactic therapy:* It targets a population of patients at risk for IFI over a defined period of risk, but who do not yet have evidence of either infection or clinical disease.
2. *Pre-emptive or presumptive therapy:* It targets a population of patients with evidence of IFI based upon a surrogate marker such as an antigen or genomic detection test, but without evidence of clinical disease.
3. *Empirical anti-fungal therapy:* It may be regarded as a variant of pre-emptive therapy where persistent neutropaenic fever despite broad-spectrum anti-bacterial therapy is considered the surrogate marker of IFI.
4. *Directed or targeted therapy:* It applies to patients with evidence of infection and clinical disease.

Anti-fungal agents

The three major groups of anti-fungal agents are: polyenes, azoles, echinocandins (**Table 4**). The first effective antifungal agent against systemic fungal infections was conventional Amphotericin B deoxycholate preparation (AmB). A comparison of the available agents is given in **Table 5**. In most of the affluent countries, the liposomal preparations are used in preference to the deoxycholate preparation. In India, where cost is a major limiting factor, AmB is still used in most patients as first line therapy. The major advantage of AmB is that it has the most broad spectrum anti-fungal spectrum activity even against zygomycosis and low rates of resistance. The azoles are available in oral and intravenous form (**Table 6**). The echinocandins have three preparations licensed for use: caspofungin, micafungin and anidulafungin. These have no renal toxicity and are among the safest anti-fungals but are expensive.

Table 4: Comparison of Major Systemic Antifungal Drugs

Features	Polyenes	Azoles	Echinocandins
Examples of class agent	Amphotericin	Voriconazole	Caspofungin
Mechanism of action	Binds to cell membrane ergosterol, altering membrane permeabilty	Inhibits synthesis of cell membrane ergosterol	Inhibits cell wall formation by inhibiting glucan synthase
Activity	Fungicidal	Fungistatic	Fungicidal for *Candida*, fungistatic for *Aspergillus*
Preparation	Parenteral	Oral and parentral	Parenteral
Class side-effect	Infusional toxicity, nephrotoxic, electrolyte disturbances	Hepatotoxic	Safe, dose reduction in patients with moderate hepatic impairment
Efficacy	Broadest spectrum, also active against zygomycosis, resistance rare	(a) Against *Candida* (b) New agents against aspergillosis (c) *C. glabrata* resistant to voriconazole and posaconazole	Against *Candida*, and Aspergillosis *C. parapsilosis* less susceptible

Table 5: Comparison of Amphotericin B and its Lipid Preparations

	Amphotericin B (AmB)	Liposomal AmB	AmB lipid complex (ABLC)	AmB colloidal dispersion (ABCD)
Therapeutic dose	0.6-1.5 mg/kg/day	3-5 mg/kg/day	5 mg/kg/day (low doses 1mg/kg/d also effective)	2-6 mg/kg/dL
Infusional toxicity	+++	+	+	++
Nephrotoxicity	++++	+	++	++
Cost	Low	+++	++	++
Efficacy	Same	Same	Same	Same

Table 6: Comparison of Different Azole Preparations

	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Preparation	Oral/IV	Oral (capsule and suspension)/IV	Oral/IV	Oral
Therapeutic dose	400 to 800 mg	200 mg bd	IV: Loading 6 mg/kg q12h, maintenance: 4 mg/kg q 12h Oral: Loading 400 mg q 12 h, maintenance: 200 mgq12h	400 mg bd
Limitation		Oral absorption erratic		
Toxicity	Hepatotoxic	Hepatotoxic, gastrointestinal toxicity, Oral suspension and IV preparation contain cyclodextrin (nephrotoxic)	Hepatotoxic with increased liver enzymes in 12%, Visual disturbances (transient) in 30%, skin rashes, Drug interactions frequent. Avoid IV preparation in renal failure as it contains cyclodextrin	Hepatotoxicity, Cardiac arrythmias in patients with QT prolongation or hypokalaemia, drug interactions
Efficacy	*Candida*, *Cryptococcus*	*Candida*, *Aspergillus* (less effective)	*Candida*, *Aspergillus*, *Scedosporium*, *Fusarium*	*Candida*, *Aspergillus*, *Zygomycetes* (mucormycosis)
Ineffective against	*Aspergillus*, mucormycosis, *Scedosporium* , Less effective against *C. glabrata*, *C. krusei*	Zygomycosis	Zygomycosis	

Recommendations for anti-fungal therapy

For IFI caused by common organisms, the anti-fungal agents recommended for use are summarised in **Table 7**. For severe infections, parenteral preparations are preferred. Immunosuppression should be reversed, as far as possible. For neutropaenic patients, recovery from neutropaenia is crucial.

CONCLUSION

It is not easy to make a definitive or even a probable diagnosis of fungal disease in many hospitals with limited facilities. The clinical presentation, radiological features and an active attempt to reach a mycological diagnosis will help in detecting fungal disease. Many of the recently available anti-fungal agents are very effective and devoid of serious toxicity, but the cost is a limiting factor. Amphotericin B is the most affordable anti-fungal agent available in public sector hospitals.

Table 7: Summary of Recommendations for Anti-Fungal Agents

Indication	First line	Second line	Comments
Disseminated candidiasis	Caspofungin, Anidulafungin, Micafungin	Fluconazole Voriconazole Amphotericin or its lipid preparations	The choice of 1st line or 2nd line depends on the microbiological epidemiology in an institution and immune status of the patient
Invasive aspergillosis	Voriconazole	Amphotericin B, Caspofungin, Posaconazole, Micafungin, Itraconazole	Surgical debridement if indicated
Zygomycosis (Mucormycosis)	Amphotericin or its lipid preparations	Posaconazole (limited literature)	Aggressive surgical debridement. No role for azoles (other than posaconazole) or echinocandins
Empirical therapy for persistent neutropaenic fever (not responding to antibiotics)	Amphotericin B or lipid preparations, Caspofungin	Voriconazole	
CNS *Aspergillus* infection	Voriconazole	Amphotericin B	No role for Caspofungin
Cryptococcal meningitis	Amphotericin B or lipid preparation plus Flucytosine		

OTHER FUNGAL INFECTIONS

Histoplasmosis

Histoplasma capsulatum infection is endemic in certain areas of North, Central, and South America, Africa and Asia. Clinical manifestations include acute and chronic pulmonary infection, mediastinal lymphadenitis, mediastinal granuloma, ocular and CNS involvement.

Treatment

(a) Moderately severe to severe pulmonary histoplasmosis: Lipid formulation of amphotericin B for 1 to 2 weeks followed by itraconazole for a total of 12 weeks.

(b) Mild to moderate pulmonary histoplasmosis and mediastinal lymphadenitis/granuloma: Treatment is usually unnecessary. Itraconazole for 6 to 12 weeks is recommended for patients symptomatic for more than a month.

(c) Progressive disseminated histoplasmosis and CNS histoplasmosis: Liposomal amphotericin B is recommended for 1 to 2 weeks, followed by oral itraconazole for a total of at least 12 months.

Pneumocystis Infection

See chapter 63 of section 17.

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17.63 *Pneumocystis Jirovecii* Infections

Prasanta Raghab Mohapatra

INTRODUCTION

Pneumocystis carinii was renamed as *Pneumocystis jirovecii* infections. *Pneumocystis carinii* was considered a protozoal disease but now it is considered to be a fungal infection and hence the change in nomenclature. Pneumocystis has gained significant importance since last decade due to changes in the spectrum of HIV related pulmonary infection and increasing use of immunosuppressive drugs. Pneumocystis pneumonia is a severe opportunistic infection, associated with a high mortality rate.

HISTORICAL BACKGROUND

Pneumocystis was first identified as a protozoan by Chagas (1909) and Antonio Carini (1910) in the lung of guinea pigs and rats respectively and was named *Pneumocystis carinii*, in the honour of the latter. In 1952, Czech pathologists Vanek and Jirovec reported the organism from humans. It was reclassified as a fungus in 1988. In 2001, it was renamed as *Pneumocystis jirovecii* that infects humans. The acronym 'PCP' was retained and stands for pneumocystis pneumonia (earlier *Pneumocystis carinii* pneumonia).

EPIDEMIOLOGY

The route of transmission of human pneumocystis infection is still not understood. The existence of pneumocystis in environment is uncertain. Pneumocystis is fairly common in humans who have depressed immune function. Pneumocystis colonisation is more prevalent in the HIV-infected population (CD4 counts <200/mm^3) and the colonisation has been demonstrated in patients with diabetes mellitus, multiple myeloma, chronic lymphoid leukaemia, sarcoidosis, corticosteroid treatment, pregnancy, chronic obstructive pulmonary disease, children below 2 years with bronchiolitis or acute respiratory infection, infants dying of sudden infant death syndrome and aborted foetuses from immunocompetent women. Person-to-person transmission has been suggested during hospital outbreaks of pneumocystis pneumonia. The PCP is reported in immunocomprised patients who are HIV negative.

BIOLOGY, IMMUNOPATHOGENESIS AND PATHOLOGY

There are two life-cycle forms, the trophic form and the cyst form. In an infected host, pneumocystis exists almost exclusively within the alveoli of the lung. The trophic forms are tightly attached to one another and to the alveolar epithelium, through interdigitation of their cell membranes with those of the host cells. Pneumocystis maintains an extracellular existence within alveoli, and probably obtains essential nutrients from the alveolar fluid or living cells. Alveolar macrophages are the primary resident phagocytes that mediate uptake, degradation and clearance of the organisms from the lung and mount an inflammatory response by releasing mediators viz. macrophage-derived tumour necrosis factor α (TNF-α) and interleukin-1 involving T cells. This response may be subdued in HIV-infection and may contribute to colonisation. The alveoli are filled with a typical foamy, vacuolated exudate. Severe disease may include interstitial oedema, fibrosis, and hyaline membrane formation.

CLINICAL FEATURES

Pneumocystis pneumonia classically presents with insidious onset progressive dyspnoea, non-productive cough, and low-grade fever developing over 1 to 3 weeks. Physical examination is dominated by tachypnoea and tachycardia. The breath sounds on auscultation may be normal. Severe hypoxaemia may compel hospitalisation. Acute dyspnoea with pleuritic chest pain may be a sign of the development of a pneumothorax. HIV-infected persons may present with a subacute course and longer symptom duration than other immunocompromised persons. Respiratory involvement is usually less severe in HIV-infected persons, with a high arterial oxygen tension and a lower respiratory rate.

RADIOLOGICAL FEATURES

On chest radiograph, PCP usually presents with bilateral, diffuse, reticular, or granular opacities. The chest radiograph may be normal at diagnosis but typically displays bilateral interstitial infiltrates (**Figure 1**). High-resolution computed tomography (HRCT) scanning is more useful when chest radiograph is non-contributory. A CT scan typically shows ground-glass opacities with patchy distribution, predominating in perihilar regions of lungs. These interstitial infiltrates become increasingly homogeneous and diffuse as the disease progresses (**Figure 2**). Thickened septal lines and areas of consolidation may be present. Less commonly, multiple bilateral cysts are observed. Cyst formation increases the risk of pneumothorax. Other atypical manifestations include multiple thick-walled cavitatory nodules and non-cavitatory nodules. Lymphadenopathy and effusions are infrequent.



Figure 1: Chest radiograph (PA view) showing bilateral reticulo-nodular shadows with dense consolidation predominantly in lower and mid zones.

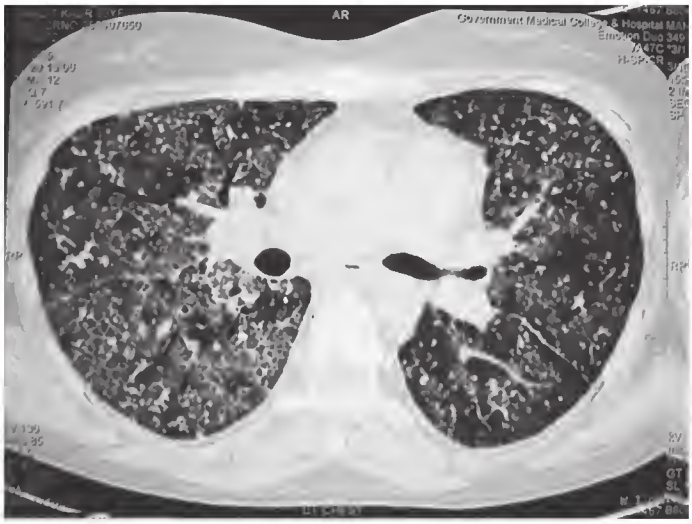


Figure 2: HRCT scan of the thorax at the level of carina showing bilateral patchy ground glass opacity with reticulations and septal thickening.

DIAGNOSIS

Pneumocystis pneumonia is not easy to diagnose because of multiple co-infections like cytomegalovirus and moreover, it cannot be cultured in the laboratory. The diagnosis is made by microscopic demonstration of the characteristic organisms in respiratory specimens such as BAL fluid or induced sputum. Trophic forms can be detected with the use of certain stains, such as modified Papanicolaou, Giemsa, or Gram-Weigert. Cysts can be stained with Gomori-methenamine silver (**Figure 3**) cresyl violet, and toluidine blue O or Calcofluor white. Fluorescein-labeled monoclonal anti-pneumocystis antibodies have the ability to stain both trophic forms and cysts, which is important because the trophic forms are generally more abundant during PCP. Monoclonal antibodies are more sensitive than the general stains and represent the 'gold standard' technique for the diagnosis of PCP.

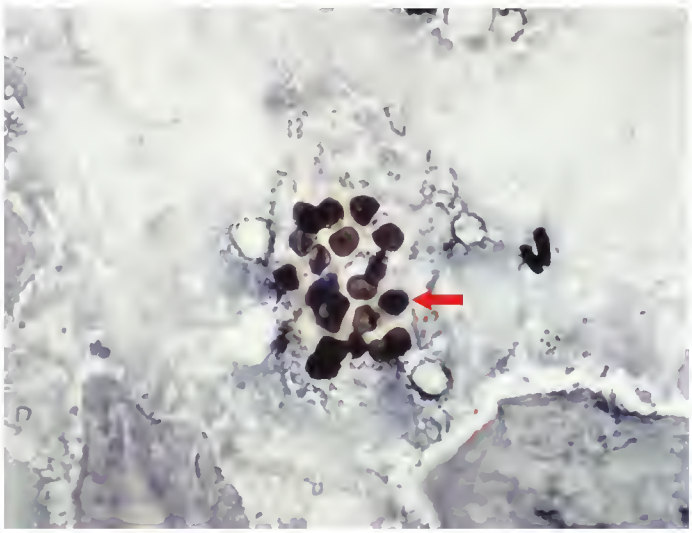


Figure 3: Photomicrograph showing cysts of *Pneumocystis jirovecii* (arrow) in bronchoalveolar lavage fluid specimen stained with Gomoris methenamine silver (GMS) stain.

When sputum induction is negative, bronchoscopy with BAL is the preferred diagnostic procedure, with reported sensitivity from 89% to 98% using immunofluorescent monoclonal antibody staining. PCR can be useful for the diagnosis of PCP when BAL microscopy is not diagnostic. But PCR testing of serum samples is not helpful.

Anaemia and lymphocytopaenia may be observed with PCP. Serum lactate dehydrogenase level may be increased. It is possibly reflection of the underlying lung inflammation and injury rather than a specific marker for the disease. Lower levels of plasma S-adenosylmethionine may be observed in some patients with confirmed pneumocystis pneumonia.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of pneumocystis pneumonia (diffuse reticulo-nodular infiltrates of lung) are miliary tuberculosis, lymphocytic interstitial pneumonia, Kaposi's sarcoma, sarcoidosis, cytomegalovirus, severe influenza, mycoplasma and acute respiratory distress syndrome.

TREATMENT

Mild cases can be treated as outpatient with close follow-up. Hypoxaemic patients with abnormal chest radiograph need hospitalisation. First-line and alternative therapies, adverse reactions are summarised in **Table 1**.

Parenteral pentamidine is nearly as effective as TMP-SMX. Adverse drug reactions occur in 71% of patients, leading to drug withdrawal in 18% patients. Clindamycin-primaquine and dapsone-TMP exhibit comparable efficacy and toxicity to TMP-SMX. A recent systematic review showed that clindamycin-primaquine was associated with a better outcome of second-line treatment compared with pentamidine. Recommended duration of treatment is 3 weeks in HIV-infected patients and two weeks in non-HIV immunocompromised hosts. Treatment should be extended in non-HIV infected patients when a higher organism burden and clinical improvement is prolonged. Caspofungin, a new drug which targets pneumocystis glucans synthetase may be a promising drug as alternate therapy.

Corticosteroids in HIV-Infected Patients

Benefit of survival on corticosteroid administration begins during the first 72 hours of treatment, and is most useful whose arterial oxygen pressure is equal or less than 70 mm Hg or whose alveolar-arterial oxygen gradient is 35 mm Hg or more. The recommended regimen is 40 mg prednisone twice daily for 5 days, then 40 mg once daily for 5 days, followed by 20 mg once daily for 11 days.

Corticosteroids in Non-HIV Infected Patients

Non-HIV immunocompromised hosts constitute a non-homogeneous group of patients and most of them have been on corticosteroids at the time they developed PCP. Tapering of corticosteroid should be avoided and increasing the dose must be individualised.

PROGNOSIS

The mortality with PCP is high. Recent studies demonstrate a better survival (86-92%) in AIDS patients compared to non-AIDS patients (survival 51-80%).

PREVENTION

As PCP is associated with high mortality, prevention is essential for the groups at risk. Respiratory isolation is not currently recommended since person-to-person transmission has not been clearly demonstrated.

CHEMOPROPHYLAXIS

HIV-infected adults and adolescents, including pregnant women and those on antiretroviral therapy, may require

Table 1: Treatment of Pneumocystis Pneumonia

Drug	Dose (daily)	Route	Comments	Adverse reactions
Trimethoprim-sulphamethoxazole (TMP-SMX)	15-20 mg/kg TMP 75-100 mg/kg SMX in divided doses	Oral or intravenous	First choice	Pancytopaenia, skin rash, hepatitis, pancreatitis, renal insufficiency, hyperkalaemia
Pentamidine	4 mg/kg/dL 600 mg/dL	Intravenous Aerosol	Alternate choice	Nephrotoxicity, arrhythmia, dysglycaemia, pancreatitis, hyperkalaemia
Primaquine plus Clindamycin	30 mg/dL 600 mg thrice daily	Oral	Alternate choice	Fever, anaemia, neutropaenia, abdominal pain, methemoglobinaemia

Table 2: Prophylaxis for Pneumocystis Pneumonia

Type of patients	Duration of PCP prophylaxis
HIV-infected (CD4+ count < 200/ml) or oropharyngeal candidiasis CD4+ T-cell percentage of less than 14%	Primary and secondary prophylaxis till CD4+ count > 200/ml for at least 3 months
Non-HIV Hosts	
Acute lymphoblastic leukaemia or haematologic malignancies on T-cell depleting agents Allogenic haematopoietic stem cells transplantation	From engraftment until 6 months and till receiving immunosuppressive therapy
Lung, heart, and heart-lung transplant recipients	Life-long
Liver transplant recipients	One year
In renal transplant recipients	4 months after transplantation or 4 months after a rejection episode
Wegener granulomatosis	While on corticosteroids

Table 3: Drugs for Prophylaxis against Pneumocystis Pneumonia

Drug	Dose	Route	Comments
Trimethoprim-sulphamethoxazole	80-160 mg TMP + 400-800 mg SMX daily	Oral or intravenous	First choice
Dapsone	50 mg twice daily or 100 mg daily	Oral	Contraindication in G6PD deficiency, cross-reaction with sulfa allergy
Dapsone plus pyrimethamine plus leucovorin	50 mg daily 50 mg weekly 25 mg weekly	Oral	—
Dapsone plus pyrimethamine plus leucovorin	200 mg weekly 75 mg weekly 25 mg weekly	Oral	—
Pentamidine	300 mg monthly	Aerosol	Administration in decubitus position to optimise lung distribution

chemoprophylaxis. Indications and duration of prophylaxis in various risk groups are mentioned in **Table 2**.

Generally the protection rates are excellent, reaching 89-100% with TMP-SMX prophylaxis. The drugs and dosages of prophylaxis are mentioned in **Table 3**.

Resistance and Prophylaxis Failure

Mutations of the gene encoding dihydropteroate synthase in pneumocystis have aroused concern about the potential for the emergence of resistance to TMP-SMX and dapsone, which have been the mainstay of prophylaxis and treatment of pneumocystis pneumonia.

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Section 18

Disorders of Metabolism

Section Editor: B.K. Sahay

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18.1 Basic Considerations of Metabolism

BK Sahay

The varied and complex process involved in utilisation and storage of macros and micro-nutrients either assimilated from diet or metabolites, generated *de novo* as well as elimination of undesirable by-products by the organism is called as metabolism. The intricate process involves not only the major organs like the liver but also each and every cell in the body. Metabolic events have a special predilection for particular cell types, e.g. adipocytes in lipid metabolism. Therefore, metabolic abnormality involving one element can manifest with symptoms and signs referable to many systems and organs in the body.

Most of the metabolic disorders are consequent to defects at enzymatic levels, either intracellular or at plasma tissue interface. The current understanding has also revealed that the defect can be involving various substrates, protein or nuclear receptors inside the cell that modulate gene expression and subsequent protein synthesis. From the cellular molecular point of view it appears that metabolic diseases could be secondary to congenital or genetic defects in the metabolic process but in practice the acquired causes are encountered more often.

In inborn errors of metabolism, mutation affects a protein with metabolic activity in such a way that a characteristic clinical and metabolic lesion, which is a defective enzyme or enzyme activator, can be identified. Although the symptoms of metabolic diseases may appear vague and protean, many diseases can be strongly suspected from clinical manifestations (**Table 1**). An inherited disease cannot be diagnosed in the absence of appropriate family history. In the family history specific enquiries should be made about affected siblings, possible parental consanguinity, paternity, miscarriage, perinatal deaths, sex of likely affected relatives and the geographic and ethnic origin of parents.

Metabolic disorders can be classified by mode of inheritance or by abnormal metabolites produced or deficiency on any specific protein or metabolite necessary for that particular metabolic event. The specific enzyme deficiency, gene coding for expression of the specific protein in question can be labeled. This section deals with disorders related to lipids, amino acids, purine, carbohydrates (other than diabetes mellitus), iron, melanin, copper metabolism along with amyloidosis.

Table 1: Clinical Features of Common Inborn Errors of Metabolism

Unexplained acute neonatal illness and/or failure to thrive in infancy
Slowing of development and arrest followed by retrogression
Slowing of development and arrest leading to unexplained mental handicap
Unusual physiognomy, multiple skeletal deformities with developmental delay and retrogression
Multiple skeletal deformities
Gross visceromegaly
Specific dietary intolerance
Haemolytic anaemia
Unusual body odour
Urolithiasis
Cataracts in early life and dislocation of optic lenses
Persistent jaundice in infancy
Abnormal cutaneous photosensitivity, hypopigmentation
History of recurrent perinatal deaths or still-births

Advances in molecular biology, genetics and imaging techniques have improved outlook for early diagnosis, possible gene therapy in treating and preventing some of these disorders. Advances in stem-cell therapy may also offer an effective treatment in some of these diseases.

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18.2 Inborn Errors of Carbohydrate Metabolism

Siddharth N Shah

Inborn errors of carbohydrate metabolism include a wide variety of genetic defects relating to storage of carbohydrate in the form of glycogen, gluconeogenesis from its usual precursors, and breakdown of glycogen into glucose during the state of demand and energy requirement. Many types of glycogen storage disorders (GSDs) have been described in literature but 9 types which have been well characterised are discussed.

GLYCOGEN STORAGE DISORDERS

Glycogen is a polymer of glucose where the residues are mostly in 1,4 linkage and may constitute up to 6000 glucose molecules. Decreased or increased branching of residues can lead to abnormalities of glycogen structure and storage (**Table 1**). The rate of glycogen synthesis and degradation to liberate free glucose along with the site of action of the key enzymes is depicted in **Figure 1**.

Free glucose gets converted to glucose-6-phosphate (Glu-6-P) through phosphorylation in the presence of the enzyme glucokinase in the liver and different hexokinases at other tissues. Glu-6-P is then converted to glucose-1-phosphate (Glu-1-P) by phosphoglucomutase and this process is reversible. Uridine diphosphate glucose (UDP Glu) is generated from UDP and Glu-1-P with the help of the enzyme pyrophosphorylase. UDP Glu is the key substrate for glycogen synthesis. Glucose residues from UDP Glu get linked to form glycogen in the presence of glycogen synthase. This linear linkage gets converted to form the highly branched structure of glycogen, under the influence of the branching enzyme system which transfers the linked glucose residues to appropriate 1,6 positions. These processes are stimulated by insulin but inhibited by glucagon and catecholamines.

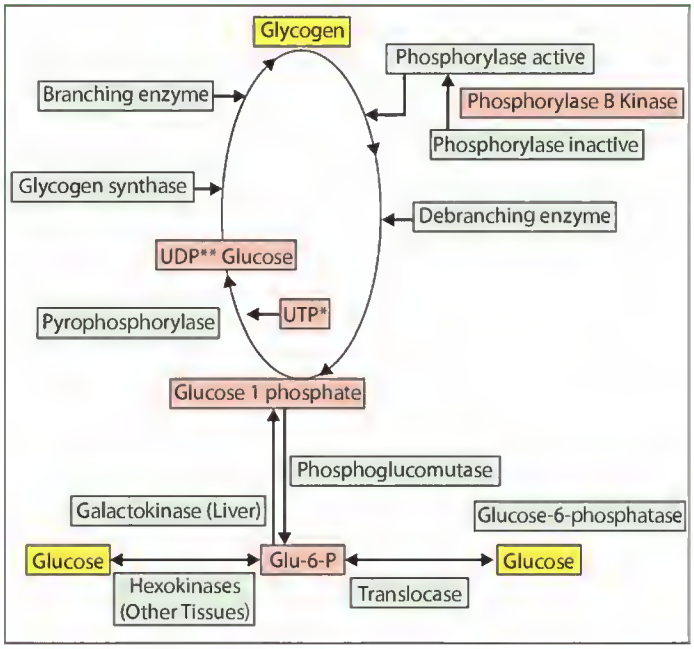


Figure 1: Glycogen metabolism.

**UTP = Uridine 5'-triphosphate; **UDP = Uridine diphosphate.*

Glycogenolysis is an equally complex process where the enzyme phosphorylase acts directly on glycogen and removes individual glucose residues to generate Glu-1-P. This enzyme phosphorylase exists in an inactive form and gets converted to its active form through a series of stimulatory reactions mediated by phosphorylase kinase, which converts inactive phosphorylase to active phosphorylase or re-enters the process of glycogen synthesis depending on the metabolic

Table 1: Glycogen Storage Disorders

Nomenclature	Enzyme Defect	Age at Onset	Mode of Inheritance	Salient Clinical Features
Hepatic hypoglycaemic disorders				
Ia (Von Gierke)	Glu-6-phosphatase	Early infancy	Autosomal recessive	Hypoglycaemia, hepatomegaly, growth retardation, hyperuricaemia, hyperlipidaemia
Ib	Glu-6-P microsomal translocase	Early infancy	Autosomal recessive	Same as Ia and neutropaenia with recurrent infections
III (Cori)	Debrancher enzyme	Post-infancy	Autosomal recessive	Hypoglycaemia, splenomegaly, growth retardation, myopathy
VI (Hers)	Hepatic phosphorylase	Childhood	Autosomal recessive	Hepatomegaly with inconsistent hypoglycaemia
VIb, VIII, IX	Hepatic phosphorylase b kinase	Adult	X-linked in most, autosomal recessive in some	Undiagnosed or hepatomegaly with mild hypoglycaemia
Muscle hypoglycaemic disorders				
V (McArdle)	Muscle phosphorylase	Adult	Heterogenous	Myoglobinuria, muscle pains and cramps
VII (Tauri)	Muscle phosphofructokinase	Adult	Heterogenous	Same as V and haemolytic anaemia
Unclassified disorders with individual pathophysiology				
II (Pompe)	Lysosomal alpha glucosidase	Three forms: infantile, juvenile, adult	?	Hypotonia, congestive heart failure, enlarged tongue
IV (Anderson)	Brancher enzyme	Early infancy	?	Failure to thrive, cirrhosis of liver

demand (**Figure 1**). Besides, the glucose residues can be removed by the debranching enzyme system from glycogen. These glucose residues are in the form of Glu-1-P and get converted to Glu-6-P as discussed above. Glu-6-P then enters the endoplasmic reticulum by the action of the enzyme translocase. There dephosphorylation occurs in the presence of glucose-6-phosphatase and free glucose is liberated. Where glycogen is utilised as source of direct energy, viz. in the muscles, the entire process of glycolysis has to take place along with the activation of glycolytic pathways and the tricarboxylic acid cycle.

Deficiency of required enzymes at any of these steps can lead to abnormalities of glycogen metabolism. Therefore, it is necessary to enumerate GSDs as per the enzyme involved, though the conventional classification is as I to IX. Further, the defect can be in the liver or muscles, producing specific disorders, i.e. hepatic hypoglycaemic or muscle hypoglycaemic pathophysiology-related GSDs. Besides these, there are a few unclassified varieties with individual pathophysiology.

HEPATIC HYPOGLYCAEMIC DISORDERS

Type Ia, Glucose-6-Phosphatase Deficiency (Von Gierke)

This was first described by Von Gierke in 1929 and accounts for nearly one-third of the cases with GSDs. It usually manifests in the first year of life and has an autosomal recessive mode of transmission. Repeated attacks of hypoglycaemia are the presenting symptom and the blood glucose level may be as low as 15 mg/dL. Hepatosplenomegaly is the most marked sign. Round face, protuberant abdomen due to hepatomegaly, thin limbs with presence of xanthoma, or lipaemia retinalis may herald the diagnosis of type Ia GSD. Hypoglycaemia in infancy often produces convulsions but mental development is usually normal. Initial somatic growth may be normal but retardation with delayed adolescence is usual. Lactic acidosis occurs frequently and may be life-threatening while hyperuricaemia can lead to gouty arthropathy and nephropathy. Deficiency of glucose occurs in the cytosol and nuclei of hepatocytes as well as there is renal tubular dysfunction. Hyperlipidaemia makes the patients susceptible to accelerated atherosclerosis. Haematological abnormalities like platelet dysfunction cause epistaxis and bleeding.

Diagnosis is made by liver biopsy. Assay of glucose-6-phosphatase enzyme level reveals very low values in hepatocytes. Microscopy shows deposition of glycogen within hepatocytes with presence of lipid vacuoles but absence of fibrosis. Plasma levels of lipids and uric acid are often high.

Frequent feeds with diet containing about 60% carbohydrates are the treatment of choice. Foods rich in galactose or fructose should be avoided as they cannot be metabolised to maintain glucose homoeostasis. Patients with elevated serum uric acid levels have to be treated with allopurinol. Management requires a team effort by all family members.

Type Ib, Glucose-6-Phosphate Microsomal Translocase Deficiency (Pseudo Von Gierke's Disease)

This was often referred to as pseudo von Gierke's disease. The defect is at the level of the endoplasmic reticulum and so formation of Glu-6-P is normal while liberation of free glucose is deficient (**Figure 1**). The patients have a more severe course than those with Type Ia as there is marked neutropaenia and recurrent infections.

Type III, Debrancher Deficiency (Cori Disease)

This is the next common type of GSDs and is usually known as Cori disease. It is an autosomal recessive disorder seen more frequently in Jews originating from North Africa. Cleavage of glycogen stops short at the branching points in the absence of the enzyme. Partially degraded glycogen accumulates in the liver, heart and muscles. Symptoms appear after the first year of life. Hepatomegaly and hypoglycaemia are less severe than in Type I and tend to ameliorate with adolescence. Ketosis is common but not lactic acidosis. Splenomegaly is more marked. Some patients have deficiency of this enzyme only in the muscles. There is growth retardation and abdominal protuberance due to hepatosplenomegaly. Some cases may present with myopathy at a later age.

Glucagon and epinephrine are effective in raising blood glucose only if injected closely after meals. Excess of glycogen can be demonstrated in liver tissue and erythrocytes in all patients but in the muscles of a few. Management consists of frequent feeds with diet containing more protein and unrestricted milk, cane sugar, fruits or sorbitol.

Type VI, Hepatic Phosphorylase Deficiency (Hers' Disease)

This is an autosomal recessive disorder also called Hers' disease where the primary defect is deficiency of hepatic phosphorylase. The disease is suspected in a child with hepatomegaly and frequent attacks of hypoglycaemia. This is a milder form of GSD and the management is similar to that of Type III.

Type VIII/Type IX/Type VIb, Phosphorylase B Kinase Deficiency

This constitutes a heterogenous group of disorders as the enzyme phosphorylase kinase is made of various subunits and a defect in any of the subunits can lead to the disorder. Although X-linked in most cases, it could be autosomal recessive in some. Therefore different nomenclatures, i.e. Type VII, Type IX and Type VIb, have been assigned to this group of disorders. Depending on the severity of the condition it may remain undiagnosed or may present with hepatomegaly, hypoglycaemia and growth retardation in a child. The management is similar to that in Type III.

MUSCLE ENERGY HYPOGLYCAEMIC DISORDERS

See chapter 32 Section 20.

INBORN ERRORS OF GALACTOSE METABOLISM (GALACTOSAEMIA)

Lactose, the principal sugar of milk, is a disaccharide containing glucose and galactose. Galactose is metabolically available only on conversion to glucose, which occurs in the liver through the following steps:

$$\text{Galactose} + \text{ATP} \xrightarrow{\text{Galactokinase}} \text{Galactose-1-phosphate} + \text{ADP}$$

$$\text{Galactose -1 - phosphate} + \text{UDP Glucose} \xrightarrow{\text{Transferase}} \text{UDP - Galactose} + \text{Glucose-1-phosphate}$$

$$\text{UDP - Galactose} \xrightarrow{\text{Epimerase}} \text{UDP - Glucose}$$

The first reaction is mediated by the enzyme galactokinase, the gene for which is located on chromosome 17; the next step is catalysed by galactotransferase, an enzyme encoded in a gene on chromosome 9.

Galactosaemia develops when conversion of galactose to glucose fails to occur due to deficiency of one of the key enzymes. The disorders are inherited as autosomal recessive.

CLASSICAL GALACTOSAEMIA

Galactose-1-Phosphate Uridyl Transferase Deficiency

The disease is rare, with an incidence around 1:60,000 live-births. Damage to liver and nerve tissue occurs possibly due to accumulation of Glu-1-P and galactitol. In the more severe forms, symptoms start with feeding of breast milk. Vomiting, diarrhoea, hepatomegaly, jaundice, and ascites may appear within one week. Acidosis, hypoglycaemia, dehydration or Gram-negative septicaemia (*E. coli* infection) results in death within days or weeks. In others, manifestations appear gradually during the first three to six months. Failure to thrive and irreversible mental retardation occur in the absence of treatment. Cataract, detectable by slit lamp, may be obvious during the first week of life. Galactosuria can be detected in the urine. Proteinuria, aminoaciduria and phosphaturia due to proximal tubular damage can present as Fanconi's syndrome. The diagnosis may be suspected from the presence of sugar in urine, hypoglycaemia, and raised blood levels of galactose vis-à-vis deficiency of enzyme in red blood cells. Cultured amniotic fluid cells or red blood cells from cord blood may be tested to determine the enzyme content when family history is positive.

Treatment consists of omission of galactose-containing food. Even soyabean preparation contains galactose and should be avoided. All defects regress with institution of appropriate diet. Mothers of babies with galactosaemia should have restricted milk intake in subsequent pregnancies for complete prevention of mental defects.

Galactose Kinase Deficiency

The incidence of this rare disorder is around 1 in 100,000 births. Cataracts are the only clinical manifestation and occur in early childhood. Investigations reveal the presence of a non-glucose reducing substance in urine, high level of galactose in blood and absence or reduced galactokinase in red blood cells. Early introduction of galactose-free diet prevents formation of cataract.

Uridine Diphosphate Glucose Epimerase Deficiency

This asymptomatic disorder can only be recognised by assay of the enzyme in erythrocytes.

INBORN ERRORS OF FRUCTOSE METABOLISM

Fructose is present principally in fruits and honey and as a component of sucrose. After absorption it is metabolised in the following manner-

$$\text{Fructose} + \text{ATP} \xrightarrow{\text{Fructokinase}} \text{Fructose-1-phosphate} + \text{ADP}$$

$$\text{Fructose-1-phosphate} \xrightarrow{\text{Aldolase}} \text{Dihydroxyacetone phosphate} + \text{Glyceraldehyde}$$

Both the above trioses are further metabolised through the glycolytic pathway. The latter may be utilised as a substrate for gluconeogenesis. Deficiency of the above enzymes leads to fructosuria or fructose intolerance.

Essential Fructosuria

This rare form of non-glucose mellituria occurs due to relative or absolute deficiency of hepatic fructokinase. Inherited as autosomal recessive, its incidence is around 1 in 130,000. Renal excretion varies depending on the amount of intake; part of the ingested fructose is utilised by adipose and muscle tissue.

18.3 Lipids and Lipoprotein Metabolism

Soneil Guptha

INTRODUCTION

Cholesterol in our body is generally obtained from dietary (animal) sources or synthesised in the liver. All cells rely on cholesterol as building blocks to create the multiple membranes. Besides helping in regulating membrane fluidity, lipids (cholesterol being one of the lipids) are utilised by living organisms as:

1. Precursor to steroid hormones and bile acids;
2. Major source of energy in the post-absorptive state;
3. Absorption, synthesis and transport of fat soluble vitamins;
4. Maintenance of the cell membrane; and
5. Other biological activities such as production of prostaglandins, leukotrienes, lipoxins, prostanoids, prostacyclines, thromboxanes and gangliosides.

However, in the past 30 years, role of cholesterol as a causal factor for atherosclerotic vascular disease also had a transforming influence in understanding of cardiovascular illness and its treatment strategies.

LIPIDS AND LIPOPROTEINS

Lipids

Fat (Lipid) is insoluble in plasma, and hence, cannot be transported directly through the blood. It is now recognised that lipids (fat/cholesterol) in their various forms are transported by lipoproteins (**Figure 1**).

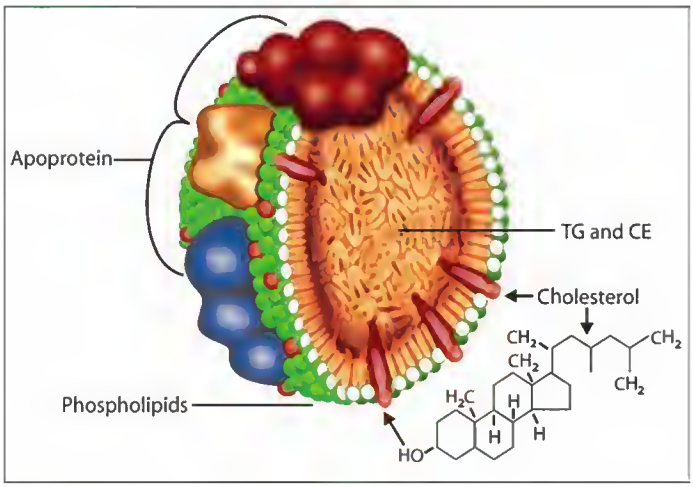


Figure 1: Diagrammatic representation of lipoprotein and cholesterol molecule. *Source: http://www.peprotech.com.*

Lipoproteins

Lipoproteins are a group of heterogenous substances, metabolically active, constantly circulating through the vasculature and existing in a state of dynamic equilibrium between tissues and liver. Triglyceride-fats and cholesterol esters are carried internally in a lipoprotein and shielded from water by the phospholipids monolayer and the apoproteins. Such characteristics make them soluble in the salt water-based blood pool. These lipoprotein particles have hydrophilic groups of phospholipids (PL), cholesterol and apoproteins directed outward. Constitution of the four major classes of lipoproteins is shown in **Table 1**.

Table 1: Compositions of Major Lipoproteins

Class	Protein (%)	Cholesterol (%)	Phospholipid (%)	Triacylglycerol (%)
High density lipoprotein	33	30	29	8
Low density lipoprotein	25	50	21	4
Intermediate density lipoprotein	18	29	22	31
Very low density lipoprotein	10	22	18	50
Chylomicrons	<2	8	7	84

Source: www.lipid-diagnostic.com/toosogie.

The functions of lipoprotein particles includes absorption of dietary fat and transportation of lipids (triglyceride and cholesterol), absorption of and transportation of fat-soluble vitamins; and transportation of cholesterol from peripheral tissues back to the liver.

Chylomicrons

Chylomicrons are produced in the intestinal lumen following the absorption of digested fat. These are the largest lipoproteins and are rich in triglyceride (TG). Because of their particle size, chylomicrons scatter more light and may cause the serum to take on a cloudy appearance after meals or in patients with dyslipidaemia characterised by the inability to catabolise chylomicrons and TG rich lipoproteins. Chylomicrons are transported in the blood to tissues, such as skeletal muscle, fat, and the liver.

Very low density lipoprotein and intermediate density lipoprotein cholesterol

Very low density lipoprotein (VLDL) is a lipoprotein particle similar to chylomicrons, which contains a high concentration of TG. VLDL is synthesised from free-fatty acids formed in the catabolism of chylomicrons in the liver, or from endogenous production of TG. The TG component of VLDL also undergoes hydrolysis by capillary lipoprotein lipase (LPL) to provide fatty acids to adipose and muscle tissue. The remaining lipid portion is called intermediate density lipoprotein (IDL). IDL is then converted to low density lipoprotein (LDL) by enzymatic action of hepatic lipase or is taken up by the liver via the LDL receptor.

Low density lipoprotein cholesterol

In human body, LDL, the products of VLDL and IDL metabolism, are the most cholesterol-rich of all lipoproteins. LDL particles have a plasma life of 3 to 4 days. Each LDL particle contains one molecule of apoprotein B, which is the major protein constituent of LDL. There are two forms of LDL: large buoyant and small, dense LDL. Small, dense LDL is especially rich in cholesterol esters, associated with metabolic disturbances such as hypertriglyceridaemia and insulin resistance; and especially atherogenic. The main role of LDL is to transport cholesterol from the liver to the peripheral tissues, including adrenocortical cells, lymphocytes, muscle cells, and renal cells. About two-thirds to three-fourths of the cholesterol in normal human plasma is contained in LDL particles. LDL is mostly taken up by the liver and other cells via LDL receptors (**Figure 2**) and to a much lesser degree by the LDL-receptor-independent pathway, or scavenger pathway. This scavenger pathway contributes to the deposition of cholesterol in arterial walls and in macrophages of tendons and skin (xanthomas).

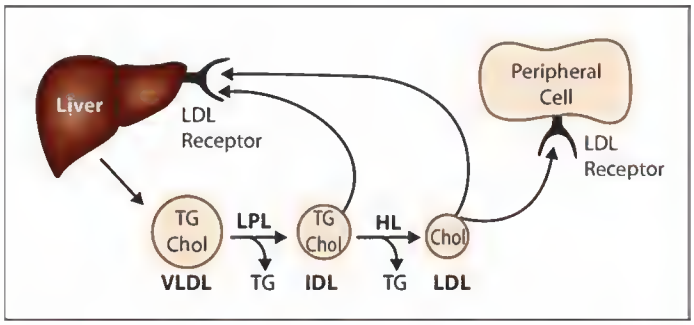


Figure 2: Schematic representation of low density lipoprotein metabolism. *Source: http://ethesis.helsinki.fi.*

LDL= Low density lipoprotein; TG= Triglyceride; Chol= Cholesterol; VLDL= Very low density lipoprotein; LPL= Lipoprotein lipase; IDL= Intermediate density lipoprotein; HL= Hepotic lipose.

High density lipoprotein cholesterol

High density lipoproteins (HDLs) are the smallest and densest of the plasma lipoproteins. These are a heterogenous class of lipoproteins with relatively high protein content (40% to 55%), which is the reason for their high density. HDL-C accounts for approximately 25% of blood cholesterol and is a source of cholesterol for endocrine tissues such as the adrenal glands, ovaries, and testes. HDL-C is an important contributor to reverse cholesterol transport, the process whereby cholesterol from peripheral tissues is transported to the liver, where it can be disposed of in bile. HDL is also reported to have anti-oxidant and anti-inflammatory properties that prevent development of atherosclerotic plaques or atheromas. These effects include the inhibition of apoptosis, the inhibition of thrombosis and the restoration of endothelial function.

Lp(a)

The mechanism and sites of Lp(a) production and catabolism are debated. Kidney has been identified as playing a role in Lp(a). Vegetarians have higher levels of Lp(a) than fish eaters. Lp(a) because of LDL cholesterol content, contributes to atherosclerosis and also has been demonstrated to cross-bind with receptors for LDL. Lp(a) physiological structure is similar to plasminogen and tissue plasminogen activator (t-PA). Thus, it competes with plasminogen for its binding site, leading to reduced fibrinolysis. Also because Lp(a) stimulates secretion of plasminogen activator inhibitor 1 (PAI-1) it leads to thrombogenesis. These unique features of Lp(a) suggest that it causes generation of clots and atherosclerosis.

Apolipoproteins

Apo is a protein moiety associated with lipoprotein. It is responsible for the structural integrity of lipoprotein molecules. Apo activates enzymes that are responsible for lipoprotein production. It also helps in binding of the lipoproteins to the cell surface receptors. The classification of Apo along with its primary source and its association with various lipoproteins is presented in **Table 2**.

Table 2: Different Apoproteins (Apo) and Their Activities

Type	Primary Source	Constituent of Lipoprotein	Role in Lipid Metabolism
Apoprotein AI	Intestine, liver	HDL, CM	Structural protein of HDL, LCAT activator
Apoprotein B48	Intestine	CM	Structural apoprotein of CM
Apoprotein B100	Liver	VLDL, IDL and LDL	Structural apoprotein of these LPs and ligand for binding to LDL receptor
Apoprotein C	Liver	CM, VLDL and remnants	Inhibit binding of LDL receptor related protein
Apoprotein D	Spleen, brain, testes, adrenals	HDL	Unknown
Apoprotein E	Liver	CM, VLDL, IDL and HDL	Structural apoprotein and ligand for binding of these lipoproteins to LDL receptor/ remnant receptor (?)

Source: http://www.peprotech.com/lipoprotein & apoproteins.

LIPID HOMEOSTASIS/TRANSPORT (Cholesterol Balance)

Cholesterol balance is maintained through hepatic and extra-hepatic activity. Depending on the diets, typical daily consumption varies from 300 to 700 mg and three times (approximately 1000 to 2000 mg) of that is secreted in the bile and subsequently into the intestines. Three major lipid transport pathways in the body are described below.

Exogenous Cholesterol Transport

The exogenous pathway of lipoprotein metabolism is responsible for the transport of lipids from the intestine (**Figure 3**). Dietary fats are digested in the stomach and duodenum and converted into monoglycerides (MGs) and free fatty acids (FFAs) by gastric lipase. Dietary cholesterol esters are de-esterified into free cholesterol (FC) by these same mechanisms. MGs, FFAs, and FC are then hydrolysed by the pancreatic cholestryl ester hydrolase, emulsified/solubilised by bile acid into micelles in the intestinal lumen and shuttled to intestinal villi for absorption. After absorption, the FC along with fat soluble

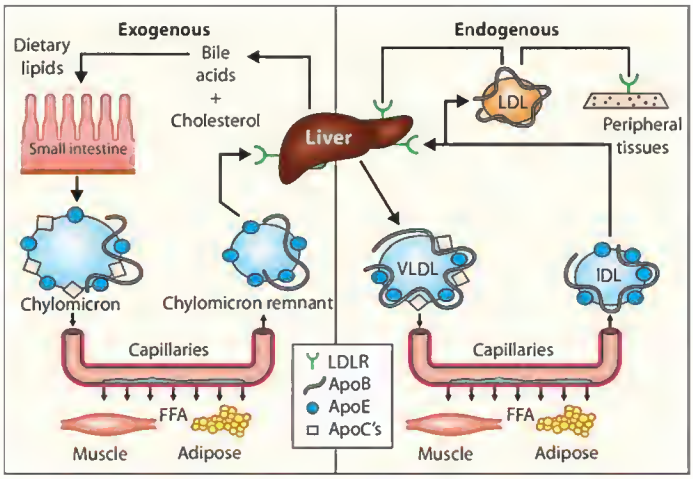


Figure 3: Schematic representation of lipid transport pathways.
Source: Harrisons's Online chapter 350, Transport of Dietary Lipids.

vitamins and retinol combine (re-esterified) with FFAs by acylCoA:cholesterol acyltransferase (ACAT) to form cholesteryl and retinyl esters, respectively. Following this process these esters are packaged with Apo-B48 to form chylomicrons. The chylomicrons are then transported across the enterocytes and released into the lymphatics and through the cisterna – chyle thoracic duct system enter the blood circulation. Unlike other digested nutrients, chylomicrons do not enter the portal blood. While in circulation, chylomicron acquires ApoA and ApoC and binds to endothelial cells of capillaries supplying the skeletal muscles and adipose tissue. At the capillary endothelium tissue interface, the enzyme LPL hydrolyses the chylomicron to release FFAs and MGs and the chylomicrons are reduced to chylomicrons remnants. The FFAs are utilised either for energy purposes or for resynthesis of triglycerides (TGs) in the adipose tissue or in liver combined with glycerol for endogenous TGs synthesis. The chylomicrons remnants which are less and less laden with TGs but are relatively richer in their cholesterol content, can be removed rapidly by the liver with the assistance of hepatic lipase (HL) or if they are small enough may be able to penetrate the endothelial surface of the arterial wall where they may contribute to plaque formation. In the hepatic bed and the chylomicrons, remnants bind to hepatocytes through ApoE receptors. By this exogenous pathway, on an average, 100 g of TGs and 1000 mg of cholesterol are transported every day. The process is brisk with a short half-life of few minutes, and therefore, no chylomicron and chylomicron-remnant is found in the circulation after 10 hours of fasting in a healthy individual.

Endogenous Cholesterol Transport

The circulation and metabolism of VLDL molecules constitute the endogenous lipid transport (**Figure 3**). The liver is a cross road of cholesterol metabolism, regulating and maintaining cholesterol balance by responding to variations in cholesterol uptake and export. Synthesis of cholesterol in liver involves generation of TG and cholesterol ester and packaging into VLDL particles which are released into the circulation. Besides triglycerides and cholesterol derived from liver (endogenous), VLDL contains a very specific apoprotein synthesised by hepatocytes called ApoB100. Over and above ApoB100, the VLDL molecules acquire ApoE and ApoC in circulation. The VLDL is then processed (similar to the chylomicrons from the exogenous pathway, though at a slower rate) by LPL in tissues to release FFAs and MGs. The fatty acids are taken up by muscle cells for energy or by the adipose cells for storage. Once processed by LPL, the VLDL becomes a VLDL remnant or intermediate density lipoproteins (IDL), a smaller, denser lipoprotein than VLDL. These molecules further go on liberating FFAs from their residual TGs content to the peripheral tissues, for the purpose of fuel and ultimately converted to LDL. Thus, LDL is the end-product of VLDL metabolism. The LDL molecules are relatively homogenous having no TGs, rich in cholesterol and contain only ApoB100. The LDL molecule binds to a variety of peripheral tissues like endothelial cells, kidney, adrenal, lymphocyte etc, through ApoB100 – receptors. By the process of receptor mediated endocytosis, the LDL is then taken inside the lysosomes of these cells. Cholesterol liberated from LDL is utilised for cell membrane synthesis of every cell, steroid hormone synthesis by appropriate cells and inhibition of ApoB100 receptors synthesis so as to prevent excess deposition of cholesterol in the peripheral cells. Over and above this, some quantity of LDL and IDL are taken up by liver through the ApoB100 receptors present on hepatocytes or are hydrolysed in the liver by hepatic-triglyceride lipase to form LDL, a smaller, denser particle than IDL. As LDL is taken up by receptors, free cholesterol is released and accumulates within the cells. LDL receptor activity and uptake of LDL regulate plasma LDL concentration by several mechanisms, including decreasing the synthesis of hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase that controls the rate of cholesterol synthesis, suppressing the synthesis of new LDL receptors in the cells, and activating the enzyme, acyl-coenzyme A cholesterol acyltransferase, which esterifies free cholesterol into cholesterol ester, storing cholesterol in the cell. Scavenger cells also engulf excess of LDL in circulation so as to maintain homeostasis in health. Approximately 70% of the cholesterol in the body remains in the form of LDL. Liver is responsible for clearing 70% of the LDL circulating in the body.

Reverse Cholesterol Transport

The cholesterol produced by the peripheral cells is transported back to the liver through HDL-mediated pathway called the reverse cholesterol transport (**Figure 4**). Liver and the intestine synthesise nascent HDL particles that contain ApoA-I and phospholipids (mainly lecithin). These molecules contain ApoA, -C and -E but give off ApoC during the course of metabolism ApoA interacts with a molecular complex known as the ATP-

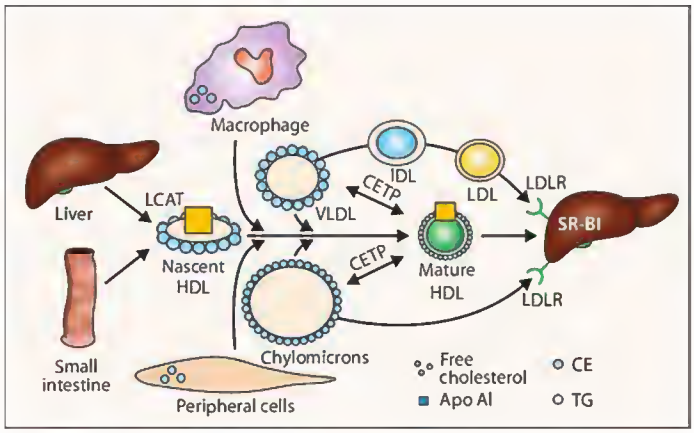


Figure 4: Schematic representation of reverse cholesterol transportation pathways.
Source: http://www.fracp.bigpondhosting.com/images/hdlmetabolism.jpg.

binding cassette transporter 1 (ABCA1) in the hepatocyte, and is then secreted into the plasma as a lipid-poor particle. Through further interactions with ABCA1 expressed on the surfaces of macrophages in the arterial wall, the circulating lipid-poor apoA removes excess cholesterol from these macrophages, forming what is known as nascent pre-beta HDL particles. The enzyme lecithin-cholesterol acyltransferase (LCAT) converts free cholesterol to cholesteryl ester, thereby moving the esterified cholesterol inside the HDL particles, causing the nascent HDL to swell up into a round, "mature" HDL particle. Both the pre-beta HDL molecules and alpha-HDL are then returned to the liver for excretion in the bile through 1 of 2 pathways. This process of mobilising cholesterol from peripheral tissue to liver, which is reverse to both endogenous and exogenous lipid transport and is called, 'reverse cholesterol transport'.

DYSLIPIDAEMIA: CLASSIFICATION OF LIPID DISORDERS

Definition

Dyslipidaemia is a disorder of lipoprotein metabolism, which can include overproduction or deficiency of lipoproteins or both. The disorder can manifest as an elevation of plasma cholesterol, TGs, or both, or a low high density lipoprotein level or all three together that contributes to the development of atherosclerosis.

Classification of Dyslipidaemia

Conventionally, dyslipidaemia is classified based on patterns of elevation in lipids and lipoproteins (Fredrickson phenotype classification) (**Table 3**).

Table 3: Fredrickson Classification (Phenotypic) of Hyperlipidaemias

Phenotype	Lipoprotein Elevated	Lipid Elevated	Atherogenecity
I	CM	TG ↑↑↑ Chol N to ↑	Not known
II-a	LDL	TG N Chol ↑↑	Very high
II-b	VLDL and LDL	TG ↑↑ Chol ↑↑	Very high
III	IDL(Remnants)	TG ↑↑↑ Chol ↑↑	Very high
IV	VLDL	TG ↑↑ Chol N to ↑	High
V	VLDL and CM	TG ↑↑↑↑ Chol ↑ / ↑↑	Higher

CM = Chylomicrons; LDL = Low density lipoprotein; VLDL = Very low density lipoprotein; IDL = Intermediote density lipoprotein; TG = Triglyceride; N = Normol level; ↑ Mildly roised; ↑↑ = Moderotely roised; ↑↑↑ = Severely roised; ↑↑↑↑ = Very severely roised; Chol = Cholesterol.

Source: Fredrickson DS et ol. Circulotion 1965:35:321-327.

This classification does not consider specific dyslipidaemia where there is low HDL that may contribute to the disease despite normal cholesterol and TG levels. A more practical system classifies dyslipidaemia due to the aetiological factors (**Table 4**: Aetiological classification); categorised as primary (genetic) and secondary (lifestyle and other).

Table 4: Aetiological Classification of Dyslipidaemia

Primary Hyperlipidaemia

Hypercholesterolaemia
- Monogenic
  - Familial hypercholesterolaemia due to decreased clearance of LDL
  - Familial combined hyperlipidaemia-excess of TG and apoprotein B 100 production
  - Familial monogenic hypercholesterolaemia due to over production of apoprotein B 100
- Polygenic hypercholesterolaemia

Hypertriglyceridaemia
- Over production of VLDL-TG
  - Familial endogenous hypertriglyceridaemia without excess of apoprotein
  - B 100 production
  - Familial combined hyperlipidaemia (as above)
- Peripheral clearance defect of TG-rich Lipoproteins
  - Familial lipoprotein: deficiency (Fredrickson Type-1)
  - Familial apoprotein C-II deficiency
- Primary clearance defects
  - Familial endogenous hypertriglyceridaemia
  - Familial Type V hyperlipoproteinaemia
  - Familial combined hyperlipidaemia-clearance defect with excess apoprotein
  - B 48 production
- Primary clearance defect combined with secondary excess production of TG

Secondary Hyperlipidaemia

A. Hypercholesterolaemia
- Hypothyroidism
- Diabetes mellitus
- Cushing's syndrome
- Oral contraceptives (OCP)
- Diets rich in saturated fat
- Nephrotic syndrome
- Chronic liver disease
- Anorexia nervosa
- Acute intermittent porphyria
- Cholestasis
- Dysglobulinaemia

B. Hypertriglyceridaemia
- Diabetes mellitus
- Obesity
- Hypothyroidism
- Diets rich in carbohydrates
- Excessive alcohol consumption
- Chronic renal failure
- Cushing's syndrome
- Beta-blockers and diuretics
- Glucocorticoid and oestrogen use
- Dysglobulinaemia

C. Glycogen storage disease
- Systemic lupus erythematosus
- Bulimia
- Pregnancy
- Hypopituitarism

Source: http://secure.pharmacytimes.com/

Clinically subjects can be diagnosed to have dyslipidaemia on the basis of the following factors (Clinical classification).

1. Increase in cholesterol only (pure or isolated hypercholesterolaemia)
2. Increase in TGs only (pure or isolated hypertriglyceridaemia)
3. Increase in both cholesterol and TGs (mixed or combined hyperlipidaemias)
4. Decrease in HDL-C (isolated low HDL-C)
5. Atherogenic dyslipidaemia (increase small dense LDL-C; increase TG, Low HDL-C and increased Lp(a)

Diagnosis of Dyslipidaemia

Irrespective of the underlying mechanism or classification of dyslipidaemia, the biochemical abnormalities will manifest either as hypertriglyceridaemia or hypercholesterolaemia or a combination of both, with or without low HDL-C. Lipoprotein levels associated with various conditions are depicted in **Table 5**.

Raised triglyceride levels suggest an increase in VLDL and/or chylomicron levels while an isolated rise in cholesterol indicates a rise in LDL levels. Combination of both is often due to poor metabolic clearance of IDL, VLDL or chylomicron-remnants.

Several important studies have suggested a linear relationship between lipid levels and the risk of atherosclerotic vascular diseases or fatal and non-fatal events. Hence, there is no numeric definition for diagnosis of dyslipidaemia. The diagnosis is made/applied to subjects who have lipid levels for which treatment has proven beneficial. From the management point of view, estimation of plasma levels of TGs and total cholesterol and HDL-C are necessary as they offer a guide to detect and monitor dyslipidaemia. Further breakdown of cholesterol into LDL, HDL and VLDL cholesterol is also useful clinically. However, a detailed analysis of the TG and apoprotein content of each lipoprotein molecule is at present mainly of academic/research interest. Direct estimation of LDL cholesterol although expensive and usually vital as the calculated value of LDL-C may not correlate quite well with the actual LDL-C especially in South-East Asians due to the common dyslipidaemia characterised by elevated serum TGs with normal to mildly elevated total cholesterol/LDL-C, low HDL-C levels. If direct estimation of LDL-C is not available, then LDL-C can be mathematically derived using the Friedewald formula as given below

Table 5: Lipoprotein Abnormalities Observed with Various Conditions

Cause	VLDL	LDL	HDL
Type 1 diabetes	↑	– or ↓	– or ↑
Type 2 diabetes	↑↑	↑	↓
Hypothyroidism	↑	↑↑	↑
Pregnancy	↑	↑	– or ↑
Obesity	↑	– or ↑	– or ↑
Alcohol	↑	– or ↑	↑
Nephrotic syndrome	↑	↑↑	– or ↓
Chronic renal failure	↑	—	↓
Cholestasis	—	↑↑ (LpX)	↓
Hepatocellular disease	(IDL)	—	↓
Hyperuricaemia	↑	—	↓

VLDL = Very low density lipoprotein; LDL = Low density lipoprotein; HDL = High density lipoprotein; IDL = Intermediate density lipoprotein; LpX = Lipoprotein X.

$$\text{LDL cholesterol} = \text{Total cholesterol} - (\text{HDL cholesterol} + \text{Triglycerides}/5)$$

For example, if the total cholesterol is 200 mg/dL and HDL cholesterol is 40 mg/dL and TG is 300 mg/dL then LDL level = 200 – (40 + 300/5), i.e. = 100 mg/dL. However, this formula is only valid if levels of TGs are 400 mg. An increase in TG level from 44 mg/dL to 398 mg/dL is associated with a 73 mg/dL increase in VLDL. This, in turn, results in a spurious 73 mg/dL decrease in LDL, disqualifying many patients from necessary treatment based on LDL criteria from current guidelines.

Epidemiology of Dyslipidaemia

Epidemiological studies have established a strong correlation between premature coronary artery disease (CAD)/cardiovascular disease (CVD) and serum cholesterol levels. World Health Organization (WHO) in 2002 reported that high cholesterol level is one of the main non-communicable disease-related risk factors in India. Though there is no consistent national protocol to collect the incidence of dyslipidaemia demonstrates various lipid levels reported in different Indian studies.

The Indian Council of Medical Research (ICMR) surveillance project reported a prevalence of dyslipidaemia (defined as a ratio of total to HDL cholesterol >4.5) of 37.5% among adults aged between 15 to 64 years, with an even higher prevalence of dyslipidaemia (62%) among young male industrial workers. The INTERHEART investigators reported that the prevalence of dyslipidaemia (abnormal apolipoprotein ApoB/ApoA1 ratio) among controls without acute myocardial infarction was higher among studied participants living in the 5 South Asian countries (45%) compared with participants from the other 47 countries represented in the study (35%). Abnormal ApoB/ApoA1 ratio was the single largest contributor to the population attributable risk for acute myocardial infarction in South Asian countries. In Indian context lower lipid levels have been seen in rural population. In urban India the high triglycerides are low HDL-C and marginally elevated LDL-C is usually observed. The impact of dyslipidaemia on the burden of congestive heart disease (CHD) has been otherwise understudied at a population level in native South Asians, despite its large contribution to CHD in other world populations. The excess burden of CAD among Indian subcontinent appears to be primarily due to dyslipidaemia with a low prevalence of non-lipid factors (hypertension, smoking and obesity). Diabetes and metabolic syndrome are particularly common among Indo-Asians but do not fully explain the excess burden of CAD in this population. National Commission on Macroeconomics and Health (NCMH) in India has estimated that by 2015 approximately 62 million Indian patients will develop CAD; out of this 23 million will be less than 40 years of age. Studies have shown that the increased prevalence of dyslipidaemia was evident in males aged between 31 to 40 years. In Asian Indian subjects, the prevalence of multiple cardiovascular risk factor increase between the age group of 20 and 29 years with a rapid escalation between 30 and 39 years of age. Hence, screening for risk factors and appropriate interventions should target men and women at around 30 years of age.

Approach to Management of Dyslipidaemia

Irrespective of the cause of hyperlipidaemia/dyslipidaemia, there is uniformity and agreement regarding the management of these disorders as suggested by NCEP/ATP III, Joint European/ Joint British and Canadian guidelines. Current pharmacological therapies for the management of dyslipidaemias are outlined in **Table 6**.

Table 6: Pharmacological Agents for the Management of Dyslipidaemia

Hypertriglyceridaemias	
Fibrates	Management after diet restriction
Fibrates + Low dose resins	Required when LDL rises while on fibrates *vis-à-vis* lowered TG
Fibrates + Omega 3 fatty acids	If TG >1000 mg/dL (Type IV and IIb hyperlipidaemia)
Niacin and niacin analogue	Appropriate drug but compliance poor
Combined hyperlipidaemias triglycerides and cholesterol	
Statin	When hypocholesterolaemia is predominant
Niacin and niacin analogue	Lowers LDL and TG
Niacin + Resins	May be useful
Fibrates	When hypertriglyceridaemia is predominant
Fibrates + Resins/Niacin	If LDL rises above normal while on fibrates
Hypercholesterolaemia	
Statin	Low dose often adequate except in familial type where resins have to be added
Resin	Same as above
Fibrates	Useful in moderate rise in cholesterol
Niacin and niacin analogue	Very useful (see above)
Oestrogen replacement	Useful in postmenopausal women with moderate rise in cholesterol

LDL = Low density lipoprotein; TG = Triglyceride.

Key points in treatment of dyslipidaemia

Unlike, diagnosis of hypertension or diabetes mellitus, the diagnosis of dyslipidaemia can only be made on the basis of lipid normograms for the population under consideration. Although no consensus data is available on lipid normogram for the Indian population, considering that the projection of an epidemic of cardiovascular morbidity in coming years, the algorithm can be fairly relied upon to consider a diagnosis of dyslipidaemia and the basic approach towards its treatment (**Figure 5**).

This algorithm is suggested based upon

1. that evidences for clinical benefit for statins are robust and undisputable and yet to be confirmed for newer fibrates, cholesterol absorption inhibitors, fish oils and newer niacin formulations;
2. that much controversy remains as to what the targets of therapy should be but most agree to (a) keep the TGs to below 150 mg/dL, (b) HDL-C to more than 50 mg/dL, (c) LDL-C values being below 100 mg/dL, and (d) optional to keep the LDL-C to <70 mg/dL in patients with diabetes mellitus or vascular complications;
3. that absolute indications for intensive dietary and pharmacotherapy are: vascular diseases whether CAD, peripheral vascular disease (PVD) or cerebrovascular disease (CVD); genetic hyperlipoproteinaemias, viz. familial hyperlipidaemia and type III; and diabetes mellitus.
4. that for other patients the decision to treat and the target for therapy are based on total risk of the disease. In diabetics the targets are lower than the non-diabetics. Estimation of risk should be broadly based and include family history of CAD/CVD, age, gender, blood pressure, smoking history, alcohol intake, lipid levels (type of dyslipidaemia) and existing co-morbid conditions.

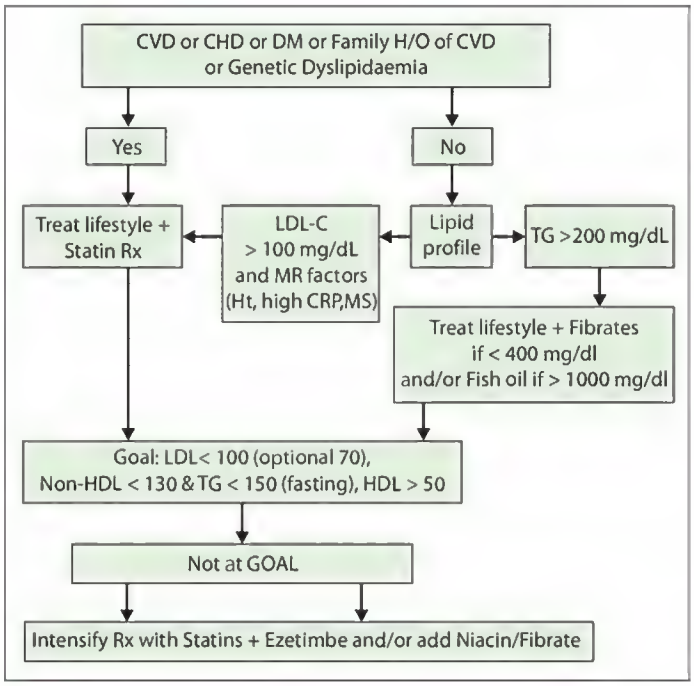


Figure 5: Suggested algorithm for the diagnosis and management of dyslipidaemia. *(Adapted from Endocrine Practice 2009; 15: 370-376).*

THERAPEUTIC CHOICES FOR DYSLIPIDAEMIA

Dietary and Lifestyle Intervention

Modification of lifestyle includes food habits, cessation of smoking, cutting-down alcohol intake, weight reduction if appropriate and regular exercises are not only very much necessary to attain normal lipid levels but are indeed the first step and cornerstone in the management of hyperlipidaemia/dyslipidaemia. Junk food rich in fat as well as refined carbohydrates, frequent snacks and consuming canned or commercially available pre-cooked food, are behavioural habits that are amenable to counselling and reinforced counselling. Alcohol supplies, empty calories and its intake in any case should not exceed 30 g per day. Aggressive weight reduction is often not feasible, so gradual reduction, attainment and maintenance of ideal body weight improves dyslipidaemia, especially TG and HDL-C. Dietary modification is initiated by reduction of saturated fat content to 10% of total calories and reduction of cholesterol intake to <300 mg per day (Step I diet) for 2 to 3 months. The saturated fat content should then be reduced to <7% of total calories and cholesterol intake to <200 mg per day (Step II diet) for up to 6 months.

Accordingly, butter, ghee, hydrogenated oil and palm oil should be eliminated from the diet. Similarly refined carbohydrates like *maida* and *maida*-based preparation can be substituted with carbohydrates with high fibre content. Dietary protein with low fat content could be selected, e.g. dried beans, peas and pulses, chicken-breast, lean meat and

low-fat dairy products. The diet should contain adequate amounts of natural fibres derived from green leafy vegetables and salads. Dietary management of dyslipidaemia in children especially in those without familial hypercholesterolaemia remains controversial. Patients who already have CAD or in the obese and dyslipidaemic subjects, weight loss is the key strategy as is eating less. Exercise is more helpful in maintaining weight loss rather than achieving it.

Pharmacological Interventions

Five groups of drugs have been recommended by the International Lipid Information Board (ILIB) to be categorised as lipid-lowering drugs (**Table 7**). Besides, the pharmacological agents mentioned in the table, fish oil supplements when used with therapeutic intention and oral oestrogen replacement therapy in menopausal women, surgical resection and probucol are tabulated in the **Table 7** and text is discussed before **Table 7**.

Table 7: Pharmacological Agents for the Management of Dyslipidaemia

Class of Drugs	Molecules	Available Strengths of pill (mg)	Dosage and Administration	Indications	Contraindications	Warnings and Precautions
Statins	Atorvastatin	10, 20, 40, 80	10 to 20 mg once daily	Hypercholesterolaemia Elevated total-cholesterol, LDL-C Prevention of stroke, Myocardial infarction (MI)	Active liver disease Pregnancy Nursing mothers Hypersensitivity	Myopathy Rhabdomyolysis Hypothyroidism Renal impairment Hepatic impairment
	Rosuvastatin	5, 10, 20, 40	5 mg to 40 mg Once daily	Hyperlipidaemia Mixed dyslipidaemia Hypertriglyceridaemia Primary dysbetalipoproteinaemia Atherosclerosis	Active liver disease Pregnancy Nursing mothers Hypersensitivity	Myopathy Rhabdomyolysis Hepatic impairment
	Simvastatin	5, 10, 20, 40, 80	5 mg to 80 mg Once daily	Prevention of stroke, MI Hypercholesterolaemia Hyperlipidaemia Hypertriglyceridaemia	Active liver disease Pregnancy Nursing mothers Hypersensitivity	Myopathy Rhabdomyolysis Hepatic impairment
Fibrates	Fenofibrate	145	160 mg to 200 mg Once daily	Hypertriglyceridaemia	Hypersensitivity Hepatic or severe renal dysfunction, Primary biliary cirrhosis Pre-existing gallbladder disease Pregnancy	Liver impairment Myopathy Pancreatitis Renal impairment
	Gemfibrozil	300, 600	1200 mg Once daily	Hypertriglyceridaemia	Active liver disease Pregnancy Nursing mothers Hypersensitivity	Liver disease Kidney disease Gallbladder disease Pregnancy
	Bezafibrate	200		Hyperlipidaemia Hypertriglyceridaemia	Hypersensitivity Hepatic or renal dysfunction Pregnancy Breast-feeding	Liver disease Kidney disease Gallbladder disease Pregnancy
Niacin (nicotinic acid)	Niaspan	500, 750, 1000	500 mg to 2000 mg Once daily	Hypertriglyceridaemia	Active liver disease Active peptic ulcer disease Arterial bleeding Hypersensitivity	Liver disease Kidney disease Pregnancy Diabetes
Bile acid sequestrants	Cholestagel	625	2.6 g to 3.8 g Divided in two or three doses	Hypercholesterolaemia Hyperlipidaemia	Hypersensitivity Bowel or biliary obstruction	Diabetes mellitus Hypothyroidism Nephrotic syndrome Obstructive liver disease Constipation
	Colesevelam	625	2.6 g to 3.8 g Twice daily with meals	Hypercholesterolaemia Hyperlipidaemia	Hypersensitivity Bowel obstruction Hypertriglyceridaemia -induced pancreatitis	Chronic liver disease Severe gout Diabetes Hyperuricaemia Peptic ulcer disease
Inhibitor of intestinal cholesterol absorption	Ezetimibe	10	10 mg Once daily	Primary hyperlipidaemia Homozygous Familial hypercholesterolaemia Homozygous sitosterolaemia	Active liver disease Pregnancy Nursing mothers	Myopathy Rhabdomyolysis Hepatic impairment

Probucol

This drug has dominant effect on lowering LDL-C and is best used as an alternate remedy in patients who had failed to respond or cannot tolerate statins. It can be administered in a dose of 500 mg twice daily. Probucol has no effect on TG levels and may even lower HDL-C levels, but surprisingly it reduces tendon xanthomas effectively, the mechanism of which is still not clearly understood and has proven even point reduction in the CRST trial. Probucol has antioxidant effects and can be used in combination with resins or statins in resistant patients. The drug is lipophilic and tends to get deposited in the adipose tissue, and hence, is not advisable to be administered to women of child bearing potential. Side effects are pre-dominantly gastrointestinal and are usually infrequent. However, prolongation of QT interval and dangerous arrhythmias can occur in occasional cases. Therefore, it is contraindicated in patient with myocardial damage, unexplained syncope (Adam-Stoke attack) or ventricular arrhythmias. As a matter of caution, electrocardiogram has to be done in every patient before and periodically after probucol therapy.

Oestrogen replacement therapy

This therapy is limited to postmenopausal women with dyslipidaemia. Oestrogen replacement therapy (ERT) is instituted only after weighing the risks for CHD and cancer. Although moderate fall in plasma levels of LDL-C and rise in HDL-C occurs, the therapy has no effect on TG levels or may even rise, especially in patients with hypertriglyceridaemia. ERT has no proven end-point reduction trial. Monitoring for gynaecological (especially breast) malignancies have to be done periodically and in women who have not undergone hysterectomy have to be given concomitant progestin therapy along with ERT. Conjugated oestrogen 0.625 mg per day and micronised oestradiol 2 mg per day is an adequate dose for treating dyslipidaemia with ERT.

Omega-3 fatty acids (omega-3FA)

The role of omega-3FA with long chain, i.e. eicosapentaenic acid (EPA) and decosahepaenoic acid (DHA) in reducing plasma TG levels by enhancing peripheral clearance of VLDL as well as lowering TG production by liver is now well documented. There may also be a modest decrease in cholesterol levels along with TG levels in plasma. Fish and other marine oils contain EPA and DHA. Currently, these are available as capsules in combination of 180 mg of EPA and 120 mg of DHA. The therapeutic dose varies from 3 to 12 capsules per day with meals, while 3 capsules per day is adequate as maintenance therapy. A trial in Japanese patients is ongoing to explore the impact of omega-3FA on cardiovascular events.

Surgical Resection of Ileum

POSCH study was the only prospective, randomised, secondary prevention trial to use partial ileal bypass as the method of reducing cholesterol levels. The trial ended after a mean follow-up of 9.7 years (range 7.0 to 14.8 years). Five years after randomisation, total cholesterol levels in the surgery group were 23.3% lower than in the control group, LDL levels 37.7% lower, HDL levels 4.3% higher, VLDL levels 8.3% higher, and TG levels 19.8% higher. Surgery reduced total mortality by 21.7% and CHD mortality by 28.0% compared with controls, but this was not statistically significant. However, patients in the surgery group had significantly lower rates of CHD mortality and non-fatal myocardial infarction combined, PVD, coronary artery bypass grafting, percutaneous transluminal coronary angiography, and disease progression as determined by coronary arteriography. Patients in the surgery group also had more adverse events, such as diarrhoea, kidney stones, gallstones, and bowel obstruction. The authors calculated a gain of 2.7 years in life expectancy in the surgery group. The follow-up study to POSCH after patients had been followed up, for a mean of 18 years (range 15.5 to 23.0 years) confirmed that lipid-lowering therapy decreased overall mortality and increased life expectancy.

CONCLUSIONS

It is well established that reducing total cholesterol and LDL cholesterol levels can significantly reduce the risk of CHD morbidity (including the need for invasive interventions) and mortality. Dyslipidaemia associated with increased CHD risk may be managed either by an individual post-event approach (secondary prevention strategy for intensive intervention and prevention of future events) or by a clusters who are at increased risk (primary prevention strategy for controlling the risk in high risk) or population-based approach (primordial prevention strategy preventing development of risk factors) with changes in diet, smoking habits and physical activity. Targeted LDL cholesterol, HDL cholesterol and TG levels as well as the multiplicative effects of other CHD risk factors should be considered when deciding on a management strategy for an individual patient. Finally, it is important to know that despite the availability of treatment guidelines, many patients do not receive adequate therapy especially in our country due to socio-economic and other reasons. Aggressive therapy of hyper-lipidaemia/dyslipidaemia can help to reduce the epidemic of premature CAD seen in Indians and people from other countries.

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18.4 Disorders of Purine and Pyrimidine Metabolism

RV Jayakumar

INTRODUCTION

Purines (adenine and guanine) and pyrimidines (cytosine, thymine, uracil) serve fundamental roles in the replication of genetic material, gene transcription, protein synthesis and cellular metabolism. Purine as well as pyrimidine triphosphates constitute the monomeric precursors of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Purines and pyrimidines are required for transcription, translation and protein synthesis.

PURINE METABOLISM

Liver is the major site of *de novo* synthesis of purines in the body, the other source being from the diet. Inside the cells, purine nucleotides are sequentially degraded by specific enzymes, with uric acid as the end product of this pathway. The steps involved in the formation of uric acid include the removal of amino acid group from the adenosine monophosphate (AMP) to produce inosine 5'-monophosphate (IMP), or from adenosine to produce inosine by adenosine deaminase. Then the IMP and guanosine 5'-monophosphate (GMP) are converted into their nucleoside forms, inosine or guanosine, by the action of 5'-nucleotidase. The next step is by the action of purine nucleoside phosphorylase which converts inosine and guanosine into their respective purine bases, hypoxanthine and guanine. Then guanine is deaminated to form xanthine, and hypoxanthine is oxidised by xanthine oxidase to xanthine, which is further oxidised to uric acid, the final product of purine degradation. The inborn errors of purine metabolism are shown in **Table 1**.

HYPERURICAEMIA AND GOUT

Hyperuricaemia is defined as a serum or plasma urate concentration greater than 7 mg/dL in males and 6 mg/dL in females. Gout is an inflammatory response to the monosodium urate monohydrate (MSUM) crystals formed secondary to hyperuricaemia. Major clinical manifestations include acute synovitis, chronic erosive and deforming arthritis, tophi, nephrolithiasis, interstitial nephritis and hypertension.

Three prerequisites for the development of gout are the development of hyperuricaemia leading to urate saturation, formation of monosodium urate (MSU) crystals and interactions between MSU crystals and leukocytes.

Epidemiology of hyperuricaemia is different from that of gout. Mean urate concentrations are age and sex related. Prepubertal in males, the mean concentration is around 3.5 mg/dL with a steep rise to 5.2 mg/dL at puberty. In females , the rise is appreciated only after menopause (up to 4.7 mg/dL). Only 10% of the patients with hyperuricaemia exhibit gout. The incidence of gout varies in population from 0.2 to 3.5 per 1000. Gout is rare in children and in pre-menopausal women. The peak age of onset in males is between 40 and 50 years. Serum uric acid concentration is the single-most determinant of the risk of developing gout. With normal renal function, its blood concentration depends mainly on breakdown of nuclear proteins and dietary purine load. Provocative factors include diuretics, alcohol, dietary excess, surgery, trauma, sepsis, stress, starvation and dehydration.

Hyperuricaemia and gout may be classified as primary and secondary. Increased overproduction of uric acid as a cause of gout is seen in only 10% to 15% of the patients (over-producers) and in 80% to 90%, uric acid excretion is impaired (under-excretors). Obesity, hypertension and dyslipidaemia are important associated disorders. A negative association exists between gout and rheumatoid arthritis.

Table 1: Inborn Errors of Purine Metabolism

Enzyme Activity	Inheritance	Clinical Features
HGPRT–deficiency (complete)	X–linked (fully expressed in males of 2-16 years)	Hyperuricaemia, gout, choreoathetosis, spasticity, mental deficiency Self-mutilation i.e., Lesch-Nyhan syndrome
HGPRT–deficiency (partial)	X-linked	Hyperuricaemia, gout, convulsion, mental retardation, spino-cerebellar syndrome
PRPPS–over-activity	X-linked	Hyperuricaemia, gout, deafness, mental retardation, polyneuropathy, dysmorphic facial features
APRT–deficiency	Autosomal recessive	Renal colic (due to calculi of 2, 8-dihydroxyadenine)
XO–deficiency	Autosomal recessive	Hypouricaemia, excessive urinary excretion of xanthine and hypoxanthine, renal colic (due to xanthine calculi)
ASL–deficiency	Autosomal recessive	Autism psychomotor retardation, axial hypotonia
AD–deficiency	Autosomal recessive	Muscular weakness and muscle cramps after exercise
PNP–deficiency	Autosomal recessive	Isolated T-cell immune deficiency
ADA–deficiency	Autosomal recessive	Severe combined immunodeficiency (T- and B-cell)

HGPRT = Hypoxanthine-guanine phosphoribosyltransferase; PRPPS = Phosphoribosylpyrophosphate synthetase; APRT = Adenine phosphoribosyltransferase; XO = Xanthine oxidase; ASL = Adenylosuccinate lyase deficiency; PNP = Purine nucleoside phosphorylase; ADA = Adenosine deaminase deficiency.

CLINICAL FEATURES

Hyperuricaemia and gout can occur in the following four phases.

Asymptomatic Hyperuricaemia

Hyperuricaemia may be an incidental finding and may never lead to gout. Conversely, during acute gouty arthritis, serum uric acid levels may not be elevated. Acute over-production of urate may occur with cytotoxic chemotherapy which is associated with a high risk of acute renal failure. Asymptomatic hyperuricaemia needs close observation but no active treatment.

Acute Gouty Arthritis

The big toe (first metatarsophalangeal joint) is the classic site for urate gout. One-third of the patients may get their first attack at another site, such as the in-step of the foot, ankle, knee or hand joints. The attack is acute, it starts in the night, the joint and surrounding tissues are swollen, red, hot, shiny, and extremely painful. There is mild fever with chills. Resolution is usual within a week even without treatment. As acute gout tends to be recurrent, a history of previous self-limiting episodes is a helpful pointer. A positive family history can be obtained from such patients.

Recurrent Gouty Arthritis

The frequency of subsequent acute attacks of gout usually increases over time. Approximately 60% of the patients have a second attack within the first year, and 78% have a second attack within 2 years. Only 7% of the patients do not have a recurrence within a 10-year period.

Chronic Tophaceous Gout

The symptom-free interval between acute episodes may last a few days to several years. In some patients, asymptomatic periods progressively shorten and in about 10 years from the first episode, chronic tophaceous phase develops. Tophi are chalky deposits of sodium urate that are large enough to be seen on radiographs and may occur at virtually any site. The most common sites include the joints of hand and feet. The helix of the ear, olecranon bursa and the Achilles tendon are the classic locations for tophi. Articular tophaceous gout can result in a destructive arthropathy and chronic secondary osteoarthritis. The duration of time between the first gouty attack and recognisable tophaceous disease is highly variable and may range from 3 to 42 years. Tophaceous disease is more likely to occur in patients with the following: a polyarticular presentation, a serum urate level higher than 9 mg/dL and a younger age at onset (i.e. 40 years or younger).

DIAGNOSIS

A definitive diagnosis requires aspiration and examination of synovial fluid to confirm the presence of monosodium urate crystals. Urate crystals are needle shaped and are negatively birefringent on polarising microscopy. The presence of crystals does not prove that gout is acute.

Serum urate concentrations are often normal during acute gout and many patients with hyperuricaemia never develop acute gout. Thus, a raised serum urate concentration favours gout, but is not diagnostic. Plain radiographs are unhelpful in patients with acute gout and might show only soft-tissue swelling. In patients with recurrent episodes, there is likely to be evidence of osseous destruction or erosive changes in the joints.

Plain radiographs are helpful to differentiate chronic tophaceous gout from rheumatoid arthritis. Erosions in gout are characteristically punched-out with overhanging sclerotic margins and are situated away from joint margins, sometimes outside the joint capsule. Rheumatoid arthritis causes marginal erosions, always within the limit of joint capsule. The absence of periarticular osteopaenia and preservation of joint space in gout also helps to differentiate the two conditions. Septic arthritis is the important differential diagnosis as the consequences of not treating it can be disastrous. The clinical features of acute gout and septic arthritis are often indistinguishable and sometimes coexist. Other conditions that can cause acute onset arthritis include reactive arthritis, pseudogout (characterised by elderly onset, predilection for knees or wrists, radiological chondrocalcinosis, and synovial fluid pyrophosphate crystals) and rheumatoid arthritis (with polyarticular presentation).

TREATMENT

Acute gout is a self-limiting condition typically lasting 7 to 10 days, but treatment ensures pain relief and speedy recovery.

Therapeutic options include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, intra-articular corticosteroids and systemic corticosteroids.

The drug of choice in most patient would be a NSAID, provided there are no contraindications (renal impairment, active peptic ulcer disease, congestive cardiac failure, known hypersensitivity, or anticoagulant therapy). The NSAID is usually continued for at least 5 to 7 days or longer if pain takes longer to resolve. To reduce gastrointestinal toxicity, the dose of NSAID should be gradually tapered as soon as improvement occurs. Parenteral preparations or suppositories are available for patients who cannot swallow tablets.

The second drug of choice is colchicine. It works by inhibiting urate crystal phagocytosis by neutrophils. Colchicine is most effective when started shortly after the onset of acute episodes, before phagocytosis establishes itself. The dose should be gradually tapered when improvement occurs and then stopped after pain completely resolves. Colchicine should be used in lower doses in patients with renal impairment.

In gout affecting medium or large joints and in those with the absence of septic arthritis, intra-articular corticosteroids are useful, especially if patients cannot take NSAIDs or colchicine. Methylprednisolone is the preparation most commonly used. The dose is typically 80 mg for large joints and 40 mg for medium joints. Pain relief can be expected in 24 to 48 hours.

In patients with polyarticular gout in whom other treatments are difficult, systemic corticosteroid is an option.

PREVENTION OF RECURRENT ATTACKS

Uricosuric Drugs

These agents decrease the serum uric acid level by increasing renal excretion. Probenecid and sulphinpyrazone are used in patients who are considered under-excretors of uric acid. Uricosuric drugs should not be given to patients with urine output of less than 1 mL per minute, creatinine clearance of less than 50 mL per minute or history of renal calculi. The physiologic decline in renal function that occurs with ageing frequently limits the use of uricosuric agents.

Probenecid

Probenecid in a dosage of 1 to 2 g per day, achieves satisfactory control in 60% to 85% of the patients. It is important to note that the drug also blocks the tubular secretion of other organic acids. This may result in increased plasma concentrations of penicillin, cephalosporins, sulphonamides and indomethacin.

Sulphinpyrazone

The dosage is 100 to 200 mg twice a day and increase it to 800 mg/day. It is a uricosuric agent that is related to phenylbutazone. Because it can act as an antiplatelet drug, it should be used cautiously in patients who are anticoagulated or have bleeding problems. Sulphinpyrazone can also cause gastrointestinal problems. Thus, caution should also be excercised in giving this drug to patients with peptic ulcer disease.

Allopurinol

Allopurinol is a xanthine oxidase inhibitor, impairs conversion of hypoxanthine to xanthine and the conversion of xanthine to uric acid. The effect of the drug depends on the dosage. Allopurinol in a dosage of 300 mg per day has been reported to reduce serum urate concentrations to less than 7 mg/dL in 70% of the patients.

Allopurinol is the drug of choice in patients with severe tophaceous deposits and in patients with a history of impaired renal function (creatinine clearance of less than 50 mL per minute) uric acid nephropathy or nephrolithiasis. The drug is also preferred as a pre-treatment agent to protect against uric acid nephropathy in patients with lymphoproliferative or myeloproliferative disorders. The initiation of allopurinol therapy can also precipitate an acute gout attack. The dosage of allopurinol should be adjusted in patients with renal impairment. Common side effects are gastrointestinal intolerance and skin rashes. Other serious events include hypersensitivity reactions, hepatitis, toxic epidermal necrolysis, vasculitis and bone marrow suppression.

Febuxostat

Febuxostat is a novel, orally administered non-purine analogue inhibitor of xanthine oxidase, used in the management of hyperuricaemia. The daily dose is 80 to 120 mg per day. It is metabolised by glucornide formation and oxidation in the liver. Adverse events include abnormal liver function test, diarrhoea, and musculoskeletal symptoms.

HYPOURICAEMIA

Hypouricaemia, defined as serum urate concentration <2 mg/per day, can result from decreased production of urate, increased excretion of uric acid, or a combination of both. Important causes are uricosuric agents such as aspirin (at doses >2 g/day), X-ray contrast materials, neoplastic diseases, hepatic cirrhosis, inappropriate secretion of vasopressin, defects in renal tubular transport such as primary Fanconi syndrome and Fanconi syndromes associated with Wilson's disease, cystinosis, multiple myeloma and heavy metal toxicity. Hypouricaemia causes no symptoms or pathology, and therefore, requires no treatment.

PYRIMIDINE METABOLISM

There are three major pathways for pyrimidine metabolism in man, *de novo* synthesis, salvage and degradation. The *de novo* pyrimidine synthesis involves series of six enzymatic reactions leading to the formation of orotic acid, orotidine monophosphate and uridine monophosphate, from which thymidine and cytidine monophosphates are formed. The pyrimidine nucleotide monophosphates are degraded to the nucleosides cystidine, uridine and thymidine by 5'-nucleotidase. Further catabolism leads to the formation of beta alanine and beta aminoisobutyrate and metabolic incorporation in the citric acid cycle.

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18.5 Iron Metabolism and Iron Overload Syndrome

Mukesh Desai

INTRODUCTION

Iron is an important element necessary for electron transport. Besides being an essential element of haemoglobin it is also an important component of several enzymes, which are necessary for several metabolic functions as shown in **Table 1**.

Table 1: Metabolic Functions of Iron

Iron Haem Proteins	Function
Haemoglobin	Oxygen carrier
Myoglobin	Oxygen storage
Cytochromes a, b, c	Energy production; converts NADH, $FADH_2$ into ATP energy
Cytochrome P450	Drug metabolism
Catalase	Degrades H_2O_2
NADPH oxidase (phagocytes)	Respiratory burst required to kill pathogen

NADH = Nicatinamide adenine dinucleotide dehydrogenase; FADH = Flavin adenine dinucleatide dehydragenase; ATP = Adenosine triphosphate; NADPH = Nicatinamide adenine dinucleatide phosphate dehydragenase; H_2O_2 = Hydrogen peraxide.

Iron must be maintained in soluble form to prevent toxicity and specialised transport systems and membrane carriers have evolved in humans to maintain iron in a 'soluble' state suitable for circulation in the bloodstream, e.g. bound to serum transferrin.

IRON METABOLISM

Since there is no mechanism for deliberate excretion of iron through the liver or kidneys, iron homeostasis is maintained primarily by the tight regulation of iron absorption in the intestine and the high degree of conservation of body iron stores.

Iron Loss and Intake

Daily excretion of iron is about 1.2 mg (faeces 0.8 mg, urine 0.2 mg, sweat 0.2 mg, hair and nails negligible amount). Iron loss through menstrual blood flow in woman is about 1 mg per day. Therefore, daily requirement of dietary iron is 1 to 3 mg and is more during periods of growth, menstruation, pregnancy and lactation.

During pregnancy, a total of 1250 mg extra iron is required: increase in packed cell volume (500 mg), foetus and placenta (500 mg), loss during labour (250 mg) and loss in breast milk (200 mg) minus 250 mg, since there is no menstrual blood loss. Therefore, during the second and third trimesters of pregnancy and while breast-feeding, an additional 4 to 5 mg of iron is required daily. Ferrous sulphate iron tablets (anhydrous, 200 mg) contain 67 mg iron, of which only 8% to 10% is absorbed. Hence, one tablet is given daily during pregnancy.

Two major sources of iron are foods containing iron and recycling of iron from senescent red cells. Most of the iron found in the plasma derives from the continuous breakdown of haemoglobin in senescent red cells by reticuloendothelial (RE) macrophages. The remaining body iron is stored, primarily in hepatocytes.

The amount of iron obtained from the diet should compensate the daily iron loss. The average Western diet contains 10-15 mg iron from which only 5% to 10% is normally absorbed. The daily requirement depends on the type of diet. A non-vegetarian diet of red meat, liver, egg-yolk is a rich source of iron. For a vegetarian, sources of iron are green leafy vegetables, dry fruits, jaggery, beans, and outer layers of cereals (which are normally discarded during refinement). Milk is a poor source of iron. Four cells play an important role in an iron metabolism as shown in **Figure 1** while the daily iron cycle is shown in **Figure 2**.

Mechanism of Iron Absorption

Dietary iron is absorbed mainly through the duodenum and upper small intestine. The absorption is regulated as per the needs of the body, i.e. increased in iron deficiency and decreased in iron overload.

Body iron status is sensed by the duodenal crypt cells through a complex mechanism involving circulating transferrin-bound iron and the transferrin receptor and iron proteins secretion is regulated by iron responsive elements (IREs) and iron binding proteins (IRPs) (**Figure 3**). Lower the intracellular iron higher the IRP secretion, the IRP binds to IRE present on 5' or 3' region of the genes of proteins involved in iron metabolism having different effect on them. Binding of IRP occur on 5' region of ferritin gene preventing translation of ferritin. Similar effect is seen on ferroportin and delta amino levulinic acid gene with their decreased production.

While binding on 3' region of transferrin and divalent metal transporter-1 (DMT-1) genes stabilises the gene and increases its expression and thus absorption of iron from gastrointestinal tract.

High intracellular iron decreases IRP, thus decreased binding to IRE on 5' region of ferritin gene allowing transcription of ferritin necessary for iron storage while decreased binding to 3' region of transferrin gene will prevent stabilisation of mRNA and allow its degradation thus decreasing transferrin production.

When body iron status is low, there is decreased iron concentration within the crypt cells. This causes an increase in mRNA expression for DMT-1.

The crypt cells migrate up the villus and mature into absorptive villus enterocytes, the DMT-1 is increased at the apical surface, increasing iron absorption from the intestinal lumen. Absorbed iron is released into the circulation via the iron export proteins.

Factors affecting iron absorption are outlined in **Table 2**.

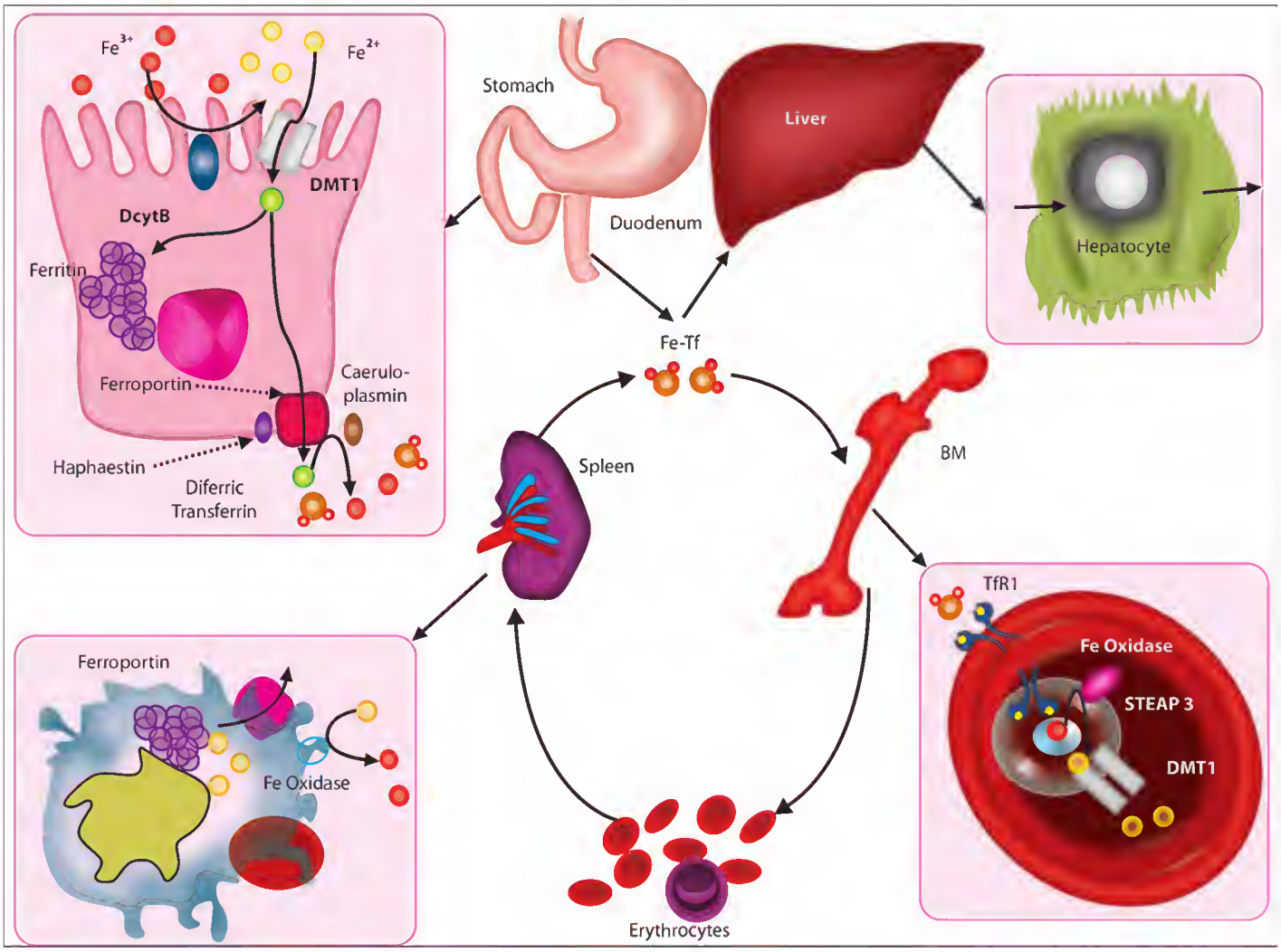


Figure 1: Overview of iron metabolism. Four cells play an important role in iron metabolism. Duodenal crypt cell for iron absorption; on brush border are enzymes DcytB (ferric reductase) which convert ferric iron to ferrous form and the DMT1 (divalent metal transporter1) which will allow absorption of iron along with other divalent metal iron like Zn, Cu and Ca. Hence co-administration of Ca^{++} with oral iron decreases absorption of iron. Once absorbed iron is released by ferroportin on the basolateral surface of crypt cell. Haphaestin acts as ferric oxidase and convert ferrous to ferric form before export. Plasma Caeruloplasmin also act as ferric oxidase and help in conversion of ferrous to Ferric form of iron. Transferrin is the carrier protein in plasma and binds two atoms of ferric iron to form diferric transferrin. Erythroblast is the major site for utilisation of iron. Only 1 mg of elemental Fe is absorbed per day. Iron thus released from duodenal enterocyte is transported as diferric soluble form bound to transferrin. Liver is the major site for storage of iron and production of Hepcidin the major regulator of Iron. Macrophages recycle senescent RBCs and very little iron is lost.

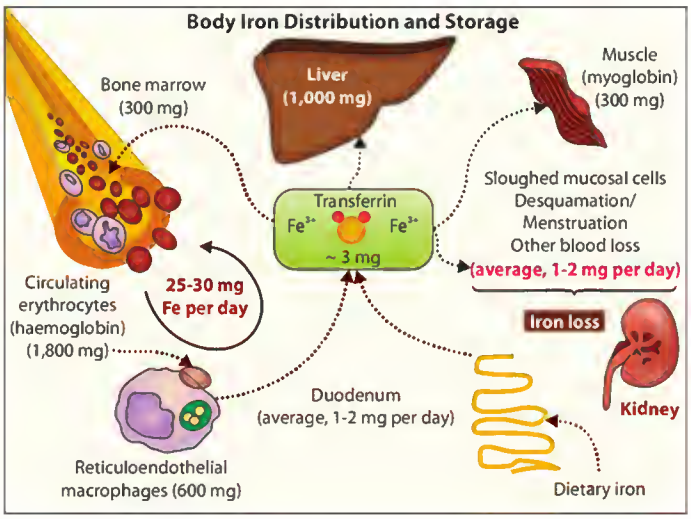


Figure 2: Body Iron distribution and storage; only 1 to 3 mg of Fe is bound to transferrin; Iron deficiency only develops once body iron stores are exhausted. Major store and distribution of Iron is in the circulating erythrocytes approximately (1,800 mg), Liver (1000 mg), RES (400 mg) and muscle (300 mg). Most of the iron is utilised to form haemoglobin.

Table 2: Factors Affecting Iron Absorption

Factors Which Increase Iron Absorption	Factors Which Decrease Iron Absorption
Haem iron	Inorganic iron
Ferrous iron (Fe^{2+})	Ferric iron (Fe^{+++})
Acids (ascorbic acid, citric acid, vitamin C, hydrochloric acid, gastric secretions)	Alkalis (antacids, pancreatic secretions)
Solubilising agents (sugars, amino acids)	Precipitating agents (phytates like bran, oats, rye, fibre and phosphates)
Iron deficiency	Iron excess
Increased erythropoiesis	Decreased erythropoiesis
Pregnancy	Infection
Hereditary haemochromatosis	Polyphenol (tea, cereals)
Protein-rich diet	Dietary calcium, milk

Specific Proteins Involved in Iron Metabolism and their Functions

Since free iron is toxic, iron must be maintained in soluble form to prevent toxicity and in human specialised transport systems

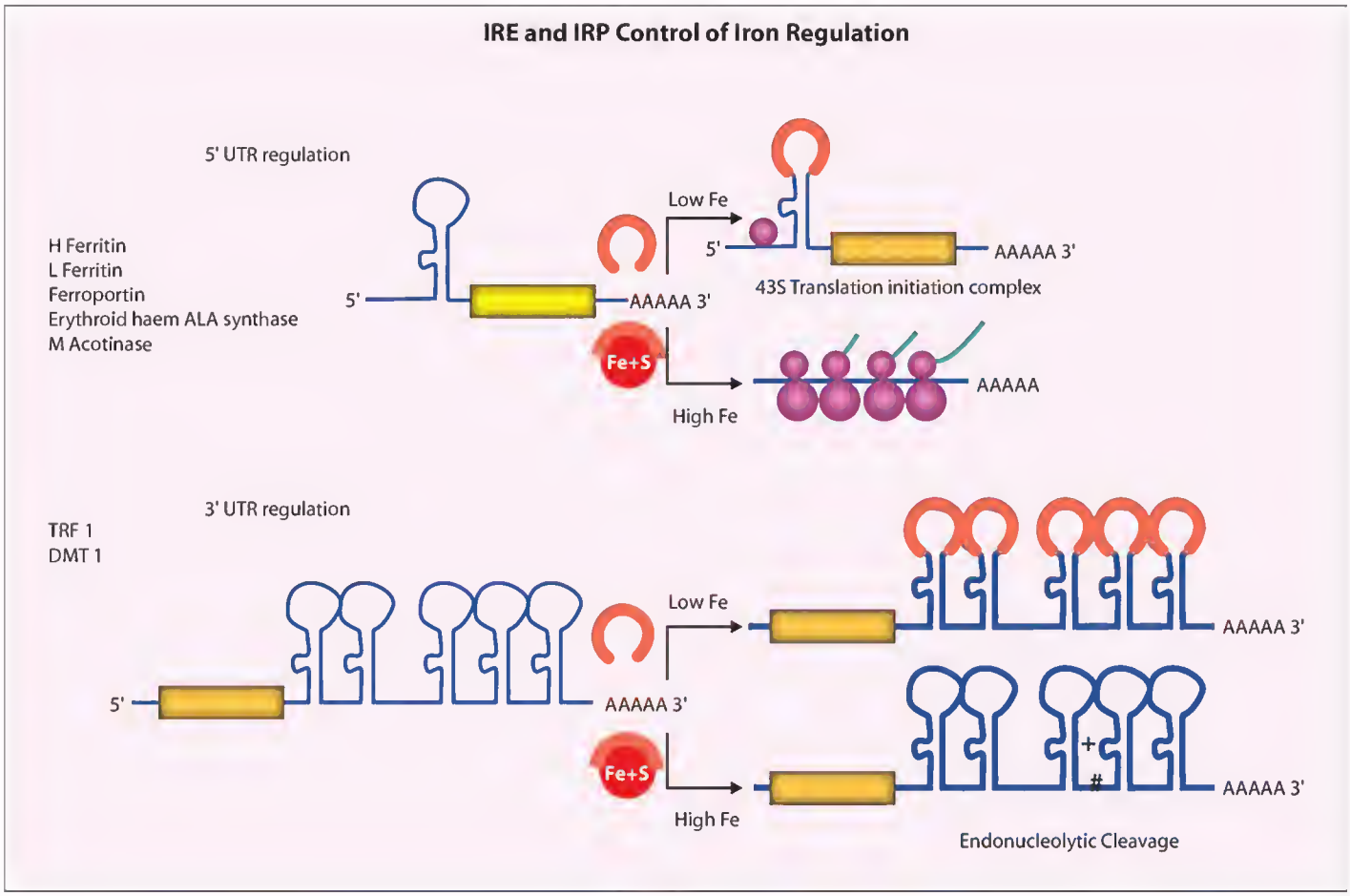


Figure 3: Intracellular regulation of Iron. Iron is regulated at both intracellular and systemic level. IRP1 and IRP2 (Iron Responsive Protein) act as cell sensor to iron availability and regulate the cellular iron by binding to IREs. The IREs are present at either the 5' UTR or 3' UTR region of mRNA of proteins important in Iron metabolism as shown in fig. In case of excess or deficiency of intracellular iron they either block or allow translation of these proteins. As for example if there is excess of iron, the IRP which is also an acotinase; an enzyme important in formation of iron sulphur cluster, rather than IRE of Ferritin mRNA. Thus allowing translation of ferritin and promoting storage of excess iron as ferritin. IRP2 disruption leads to hypochromic microcytic anaemia with late onset neurodegenerative disorder. Disruption of IRE in L ferritin gene result in hyperferritinemia with cataract syndrome, while disruption in H ferritin result in iron overload syndrome. Disruption of IRE in the ferroportin gene results in a complex disorder of iron homeostasis.

and membrane carriers have evolved to maintain iron in a 'soluble' state. **Table 3** lists the various proteins involved in iron metabolism and their functions. Rapid advances have taken place and this is an evolving field. Hepcidin is considered to be the master hormone regulating availability of iron.

Steps in the absorption of iron are outlined in **Figure 4**.

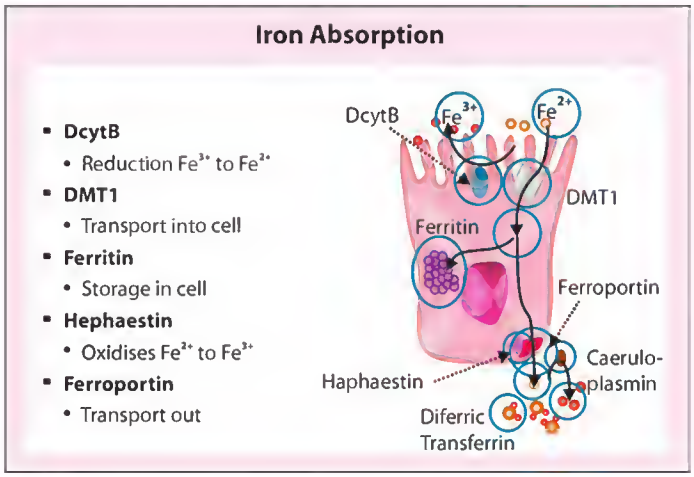


Figure 4: Duodenal crypt cell, and the steps in iron absorption and the proteins involved.

Oral ferric iron is converted to ferrous iron on the luminal surface of enterocyte brush border by DcytB ferric reductase.

Transluminal transport of ferrous iron is done by DMT-1 present in the enterocyte brush border. This step is regulated by the iron status of the body. Inside the enterocyte depending on iron status it may be sequestered in enterocyte as ferritin or transported across the basolateral membrane of enterocyte into the circulation for utilisation. Ferroportin helps export ferrous iron into circulation while reconversion of ferrous iron to ferric iron takes place with the help of hephaestin. Ferroportin is present besides on the macrophages and other RE cells and the hepatocyte and its function is regulated by hepcidin.

Distribution of Iron in Blood

Upon its release from the basolateral surface into circulation, the ferrous iron is oxidised to the ferric form and loaded onto transferrin. The aggregate binding sites of all the transferrin in the circulation comprise the total iron binding capacity (TIBC) of plasma. Normally 20% to 45% of iron-binding sites are filled (transferrin saturation). About 80% of iron passing through the transferrin compartment is from the red cells. Immature erythroid cells acquire iron from transferrin through specific transferrin receptors located on the cell surface membrane (**Figures 5 and 6**).

Table 3: Specific Proteins Involved in Iron Metabolism and Their Function

Protein	Function	Expression
Transferrin	Iron binding transfer protein fluid	Plasma
Ft (H and L subunits) (IREs 5'UTR)	Iron storage	Most cells
Transferrin receptor-1 (IREs 3'UTR)	Iron uptake receptor-mediated endocytosis of ferric transferrin	Erythroid cells, epithelial cells rapidly growing (intestinal crypt cells). Other cells including macrophages
Transferrin receptor-2	Iron uptake	Hepatocyte, circulating monocytes. Possibly senses iron status may have a role in iron regulation by controlling expression of hepcidin
DMT1 (Nramp2/DCT1) (IREs 3'UTR)	Iron import; iron release from endosome to cytoplasm	Brush border of epithelial cell of the intestinal villus. Endosomal vesicles in erythroid cells and other cell types
FP1/IR1/MTP1 (IREs 5'UTR) ferroportin	Iron export	Basolateral membrane of epithelial cell of the intestinal villus; placenta; other cell types
Duodenal cytochrome b	Ferric reductase	Brush border of enterocytes of the intestinal villus
Hephaestin	Ferroxidase	Basolateral membrane and vesicles of enterocytes of the intestinal villus
Caeruloplasmin	Ferric oxidase	Plasma
HFE (No IREs)	Uncertain. The HFE protein-β2-microglobulin heterodimer binds TfR1, reducing its affinity for transferrin	Intestinal crypt cells and tissue macrophages
Hepcidin (No IREs)	Antibacterial activity; master regulator of iron homeostasis, regulates activity of ferroportin and thus iron release from mucosal cells and macrophages	Liver, blood, urine, Iron hormone responsible for anaemia of chronic disease
Haemojuvelin	Unknown; possibly regulator of hepcidin release	Highly expressed in hepatocytes
IRP1 AND IRP2	Post-transcriptional control of target mRNAs (Ft, TfR1, DMT1, FP1/IR1/MTP1, mitochondrial aconitase, erythroid aminolevulinate synthase)	Mainly: liver, spleen, kidney, heart. Occasionally: duodenum, brain

Steps in iron transport are given below and depicted in **Figure 6**.

1. Fe^{2+}Tf bind to TfR1on RBC.
2. Fe^{2+}Tf/TfR1 complex localise to clathrin-coated pits which invaginate to form endosomes.
3. A proton pump decreases pH leading to iron release.
4. DMT1 moves iron across endosomal membrane to cytoplasm.
5. Apo-Tf and TfRl are recycled to the cell surface for further use.
6. In red blood cells most of the iron is incorporated into proto-porphyrin to make haem (mitochondria).

Reutilisation of Iron

Aged erythrocytes are phagocytosed by specialised macrophages in the spleen, bone marrow and liver. Within macrophages, the haem-oxygenase I catabolises haem, releasing ferrous iron, which may be responsible for intracellular transmembrane iron transport. Macrophages return most of the catabolised erythroid iron into the transferrin compartment of the blood stream, and the cycle recommences. Ferroportin plays an important role in the release of macrophage iron into blood and is in turn controlled by hepcidin. Thus, hepcidin is a master regulator of iron availability (**Figure 1**).

Iron Storage

Excess iron is stored in the body as ferritin or haemosiderin. The iron in ferritin is enclosed within a protein shell, apoferritin. This can take up ferrous iron and oxidise it to ferric iron, which is deposited within the iron core. In due course, ferritin is engulfed by lysosomes and catabolised to haemosiderin. Iron enters and leaves the ferritin molecule in a controlled fashion, making it available for normal physiologic functions of the cells. Minute quantities of ferritin are found in the serum, which correlate closely with the body iron stores. One microgram per litre of serum ferritin is approximately equivalent to 10 mg of storage iron.

Hepcidin

A 25 aa peptide was identified in the year 2000 with antimicrobial activity. Since it was produced by the liver it was named hepcidin *(hepatic bactericidal protein)*. It was subsequently discovered to be a master iron regulatory hormone. Factors regulating intestinal iron absorption also regulate the expression of hepcidin. Decreased iron stores, increased erythropoietic activity, anaemia and hypoxia negatively regulate hepcidin expression. Cellular targets of hepcidin are villous enterocytes, RE macrophages and hepatocytes. Iron homeostasis is dependent on regulatory feedback between body iron needs and intestinal iron absorption. Intestinal iron absorption varies inversely with liver hepcidin expression. Hepcidin decreases the functional activity of ferroportin by directly binding to it and causing it to be internalised from the cell surface and deregulated; decreases basolateral iron transfer and thus dietary iron absorption; decrease in iron export by hepatocyte and macrophage and a resultant increase in stored iron (**Figures 7 and 8**).

Hepcidin response

Transferrin receptor-2 may serve as a sensor of circulating transferrin-bound iron, thereby influencing expression of the iron regulatory hormone hepcidin. The hepcidin response is also modulated by HFE and haemojuvelin. Inflammatory cytokines including interleukin (IL)-6 and LPS increase hepcidin secretion (**Figure 9**).

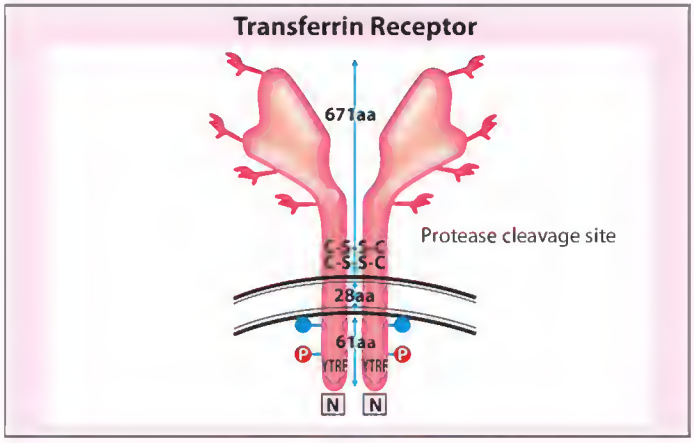


Figure 5: Transferrin receptor 1 (TfR1) which is important for the cellular uptake of Iron. TfR1 expression increases from 300,000 per pronormoblast to 800,000 per basophilic normoblast at the height if Hb synthesis. There is a precise correlation between TfR1 number and iron requirement of the body. There are 2 types of transferrin receptors. Transferrin receptor 1(TfR1) is important for absorption of iron while TfR2 is important for sensing total body iron and is important for regulation of iron. The extracellular part of TfR is shed and this sTfR can be measured. sTfR is elevated in IDA while it is normal in anaemia of inflammation (AOI). A better diagnosis of IDA in setting of AOI can be made by calculating sTfR per Log ferritin ratio. A ratio of less than 1 suggests AOI, while ratio of >2 suggest IDA. Ratio between 1 and 2 suggest IDA with AOI.

Hepcidin deficiency

It results in hereditary haemochromatosis as patient absorbs excessive iron relative to body stores implying the 'set-point' for the 'stores regulator' is altered. Ineffective erythropoiesis with increased destruction of erythroid precursors (e.g. thalassaemias) but this is coupled to increased iron absorption.

Hepcidin excess

It results in anaemia of chronic disease. Infection/inflammation induces iron sequestration in macrophages and decreases intestinal absorption. Hepcidin is a negative regulator of iron absorption in duodenum and of iron release from macrophage.

Iron Overload

Iron overload is the pathological state in which total body stores of iron are increased often with organ dysfunction because of iron deposition (**Table 4**). The iron-replete state is characterised by increased production of ferritin and decreased production of the transferrin receptor. These responses are mediated by the iron-responsive elements binding protein (IRE-BP). As the body content of iron increases, the iron saturation of

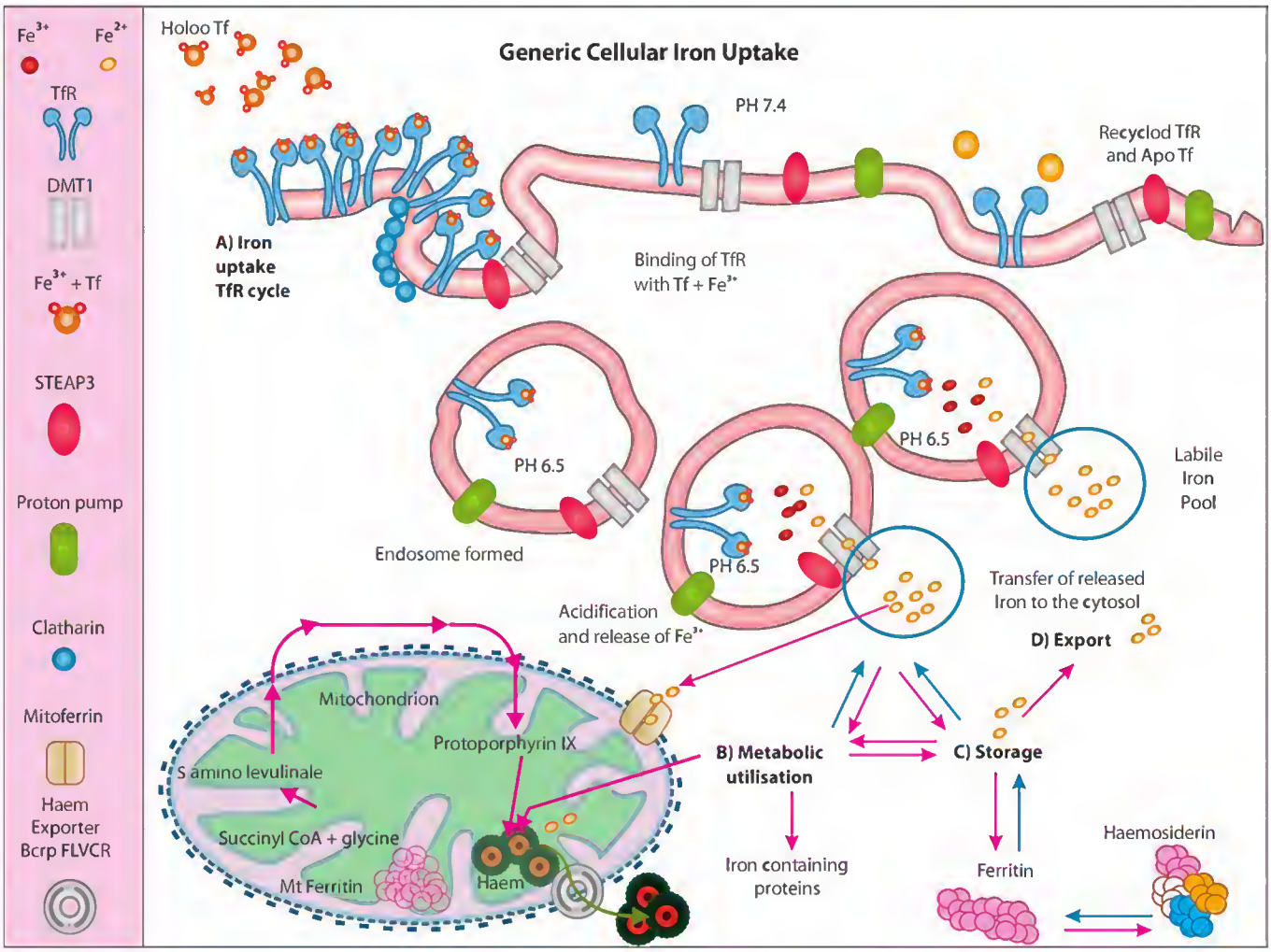


Figure 6: Cellular Iron uptake begins by holotransferrin with diferric iron atoms binding the TfR and their internalisation to form the endocytic vesicle. With progressive acidification of the vesicle by the proton pump ferric iron is released and converted to ferrous form with help of STEAP3 and exported out of the vesicle into the cytosol via DMT1. This iron in cytoplasm is called labile iron pool and available to be removed by chelation. This iron finds its way to the mitochondria, how we do not precisely know; for formation of Haem and other iron containing enzymes. The endocytic vesicle rejoins the surface of cell and the apotransferrin is released into circulation to bind diferric iron while the TfR will bind other holotransferrin to reenter the endocytic cycle. In DMT1 deficiency, there is poor iron absorption at duodenal level but iron that enters the erythroblast cannot be released from the endocyte into the circulation resulting in IDA.

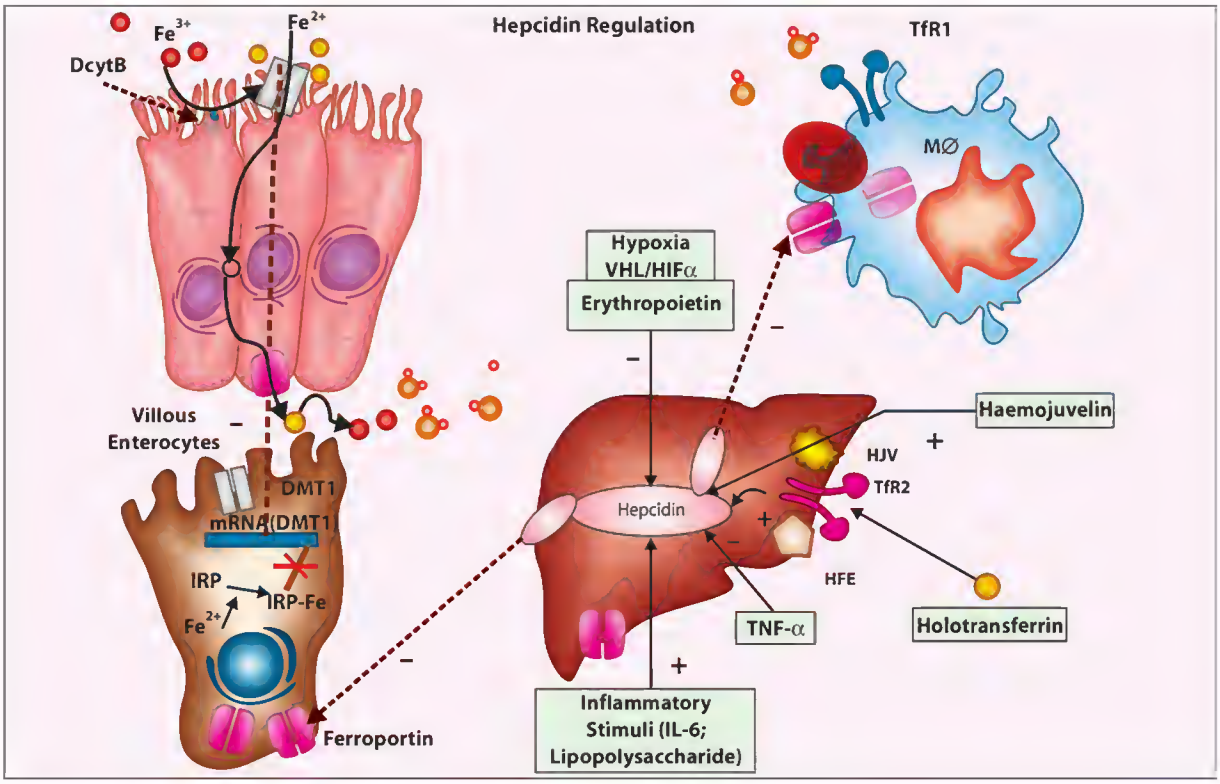


Figure 7: Hepcidin a 25 AA protein is the master regulator of iron. It is a systemic regulator and regulates body's need for iron. Hepcidin regulates iron by binding ferroportin and tagging it for ubiquitination and proteosomal degradation. This prevents export of iron from the cells like duodenal enterocyte, Macrophages and Hepatocytes. Hepcidin levels are decreased in IDA, Hypoxia and are increased by inflammatory stimuli like IL6 and LPS. Erythropoietin and TNF α negatively regulate, while HFE and HJV positively regulate Hepcidin production.

Table 4: Classification of Iron Overload

Severe iron overload

- Excess iron absorption
  - Hereditary haemochromatosis (HH)
  - Massive ineffective erythropoiesis (e.g. thalassaemia intermedia, sideroblastic anaemia, congenital dyserythropoietic anaemia)
- Increased iron intake
  - Sub-Saharan dietary iron overload
  - Excess parenteral iron therapy
- Repeated red cell transfusions
  - Congenital anaemias (e.g. thalassaemia major, sickle cell anaemia, red cell aplasia)
  - Acquired refractory anaemias (e.g. myelodysplastic syndromes, aplastic anaemia)
  - Rare genetic disorders of iron metabolism (e.g. atransferrinaemia, acaeruloplasminaemia)

Modest iron overload

- Chronic liver disease (e.g. alcoholic cirrhosis)
- Porphyria cutanea tarda
- Rare genetic disorders of iron metabolism (e.g. atransferrinaemia, acaeruloplasminaemia)

Focal iron overload

- Pulmonary haemorrhage (e.g. idiopathic pulmonary haemosiderosis)
- Chronic haemoglobinuria
- Friedreich's ataxia
- Hereditary hyperferritinaemia with autosomal dominant congenital cataract

circulating transferrin increases, the fasting transferrin saturation (serum iron, iron binding capacity) increases resulting in the off-loading of iron, particularly to cells with high levels of transferrin- receptors e.g. heart, liver, thyroid, gonads and pancreatic islets.

HEREDITARY HAEMOCHROMATOSIS

Hereditary haemochromatosis (HH) is an autosomal recessive inherited disorder with a frequency of 1 in 300 in the Caucasian population. In HH there is a gradual accumulation of iron leading to tissue damage. HH becomes symptomatic later in females (due to extra iron loss associated with menses, pregnancy and lactation) than in males. Types of hereditary haemochromatosis are outlined in **Table 5**.

Genetic Defect

The HFE protein is synthesised by the HH gene and is similar to the major histocompatibility complex (MHC) Class I protein. The role of this HFE protein and the means whereby mutations result in iron overload are still unknown, but a number of observations have been made. In the endoplasmic reticulum, newly synthesised HFE forms a 1:1 complex with β_2-microglobulin and this heterodimer is targeted to the plasma membrane. At neutral pH, the HFE/ β_2-microglobulin heterodimers form a stable complex with the transferrin receptor and decrease the affinity of the transferrin receptor for transferrin. HFE is abundantly expressed in the crypts of duodenal mucosa. This homoeostatic mechanism is disrupted when the HFE gene is mutated in HH giving a false signal that body iron stores are low resulting in increased iron uptake. There are two pathogenetic models of HFE related hereditary haemochromatosis, the crypt programming model and the HFE models as shown in **Figures 10 and 11**. The common mutations are C282Y, H63D and S65C in the HFE gene on chromosome 6.

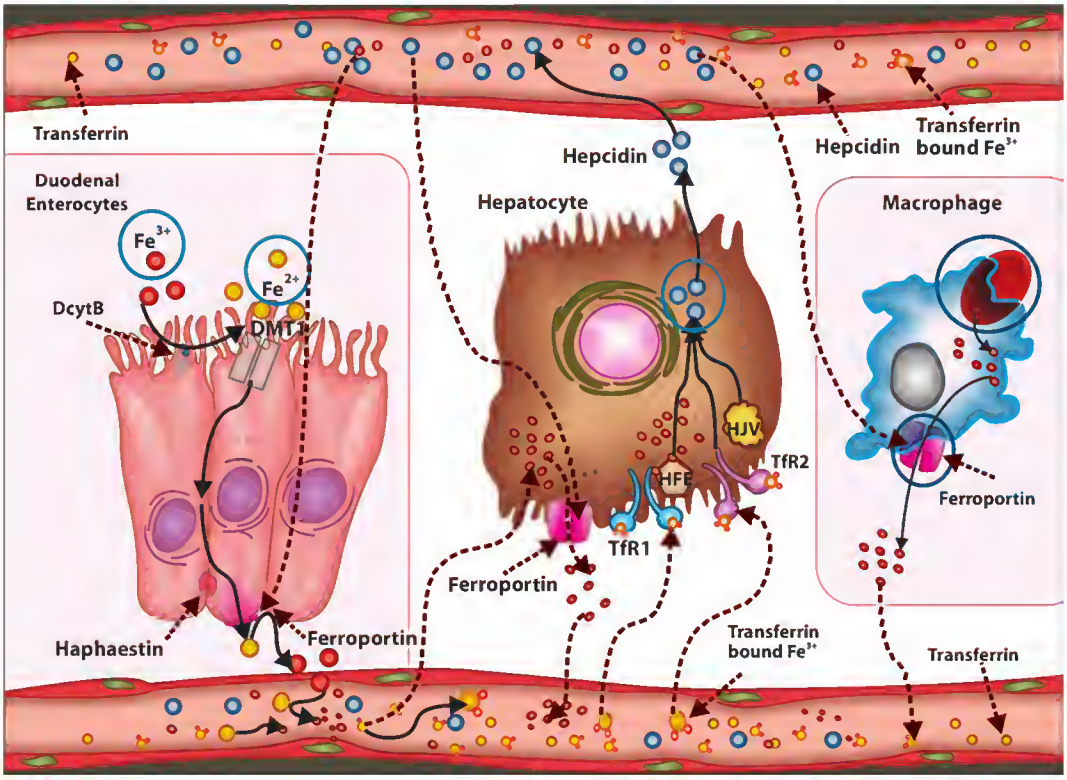


Figure 8: Overall iron regulation and iron homeostasis in the human body and the amount of investment nature has done in iron.

Table 5: Comparative Overview of the Primary Iron-Overload Disorders Classified as Hereditary Haemochromatosis in the OMIM Database

Feature	HFE-Related Hereditary Haemochromatosis	Juvenile Hereditary Haemochromatosis		TfR2-Related Hereditary Haemochromatosis	Ferroportin-Related Iron Overload
OMIM Classification	Type 1	Type 2, subtype A	Type 2, subtype B	Type 3	Type 4
Implicated gene and its chromosomal location	*HFE*, 6p21.3	*HJV* (originally called *HFE2*), 1q21	*HAMP*, 19q13.1	*TfR2*, 7q22	*SLC40A1*, 2q32
Gene product					
Name	HFE	Haemojuvelin	Hepcidin	Transferin receptor 2	Ferroportin (also iron-regulatory protein, or metal-transporter protein)
Known or postulated function	Interaction with transferrin receptor 1, probably facilitating uptake of transferrin-bound iron; possibly modulation of hepcidin expression	Unknown: possibly modulation of hepcidin expression	Down-regulation of iron relase by enterocytes, macrophages, or placental cells	Possible uptake of iron by hepatocytes	Export of iron from enterocytes, macrophages, placental cells
Pattern of inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant
Evidence of expanded plasma iron compartment (high transferrin saturation	Earliest detectable biochemical anomaly	Earliest detectable biochemical anomaly	Earliest detectable biochemical anomaly	Earliest detectable biochemical anomaly	Only in advanced stages
Main organs accumulating iron	Liver, endocrine glands, heart	Liver, endocrine glands, heart	Liver, endocrine glands, heart	Liver, endocrine glands, heart	Liver, spleen
Predominant cell distribution of iron accumulation	Parenchymal	Parenchymal	Parenchymal	Parenchymal	Reticuloendothelial
Potential for organ damage	Variable	High	High	Variable	Low
Anaemia	No	No	No	No	Maybe seen in mensturating women or after phlebotomy
Resoponse to therapeutic phlebotomy	Excellent: decrease in serum ferritin in parallel with transferrin saturation; no risk of anaemia	Excellent: decrease in serum ferritin in parallel with transferrin saturation; no risk of anaemia	Excellent: decrease in serum ferritin in parallel with transferrin saturation; no risk of anaemia	Excellent: decrease in serum ferritin in parallel with transferrin saturation; no risk of anaemia	Fair: rapid decrease in saturation with persistently high serum ferritin; substantial risk of anaemia with aggressive phlebotomy regimen
Decade of onset of symptomatic organ disease	4th or 5th	2nd or 3rd	2nd or 3rd	4th or 5th	4th or 5th

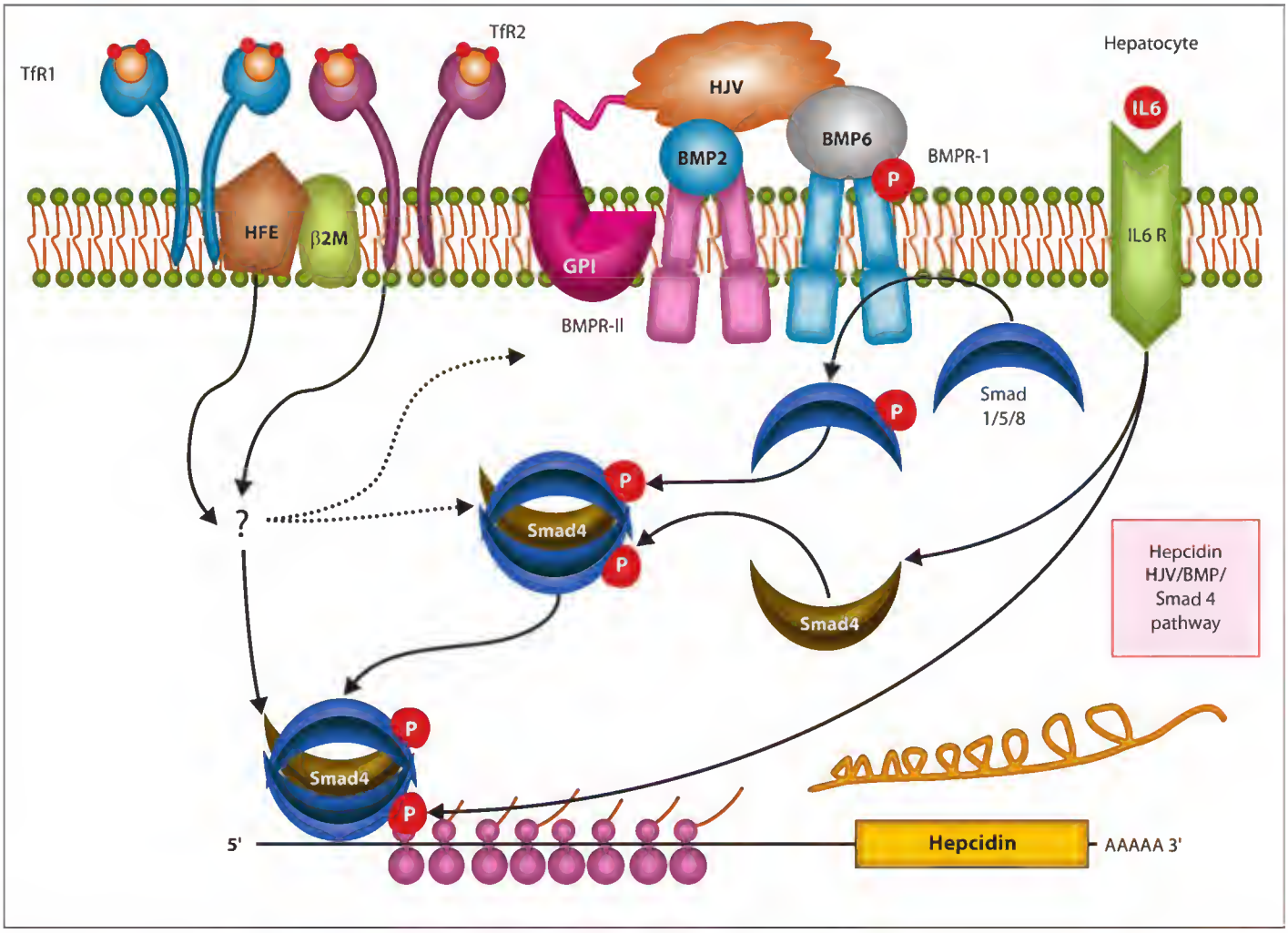


Figure 9: Regulation of Hepcidin transcription by TfR2, HFE, HJV, BMP (bone morphogenetic protein) and Smad 4. Disruption in this regulation is very often responsible for iron overload and haemochromatosis.

Clinical Features

These are mainly caused by iron deposition in various organs, as shown in **Table 6**.

The classical triad of HH is a middle-aged man presenting with diffuse hyperpigmentation, hepatomegaly and diabetes mellitus requiring insulin. The presentation occurs only when complications are irreversible and prognosis is poor. This stage is far too late and must be considered as a clinical diagnosis failure.

Signs and symptoms that may allow an earlier diagnosis include asthenia (unexplained chronic fatigue), arthralgia (most characteristically affecting second and third metacarpophalangeal joints - painful handshake) and aminotransferase elevation (especially in the absence of alcohol, NASH, viral infection, autoimmunity).

Table 6: Clinical Features of Iron Overload

Heart	Cardiomyopathy, dysrrhythmias, congestive heart failure
Endocrine organs	Growth and sexual developments are delayed in children Delayed puberty Diabetes mellitus Hypothyroidism and hypoparathyroidism Hypopituitarism
Skin	Excessive melanin skin pigmentation (bronze diabetes)
Liver	Haemosiderosis, cirrhosis, risk of hepatocellular carcinoma.
Joints	Arthropathy caused by pyrophosphate deposition
Excessive infections	Listeria, *Yersinia enterocolitica, Vibrio vulnifcus,* by ingesting uncooked seafood

Laboratory Findings

Raised serum iron and transferrin saturation (>45%, especially >60% in males and >50% in females), raised serum ferritin, lowered serum soluble transferrin receptor levels and increased iron in liver and bone marrow (Perls' Prussian blue staining) are found. Hepatic iron content of >40 µmol/g on dry weight indicates definite increase in liver iron; >71 µmol/g dry weight is highly suggestive of HH. Hepatic iron index is the ratio of µmol iron/g dry weight divided by age in years. Ratio >2 generally separates patients with homozygous HH from heterozygotes or those with alcoholic liver disease. Increased urinary iron excretion in response to iron chelator therapy are abnormal, and liver function tests, endocrine abnormalities e.g. raised blood sugar, abnormal thyroid

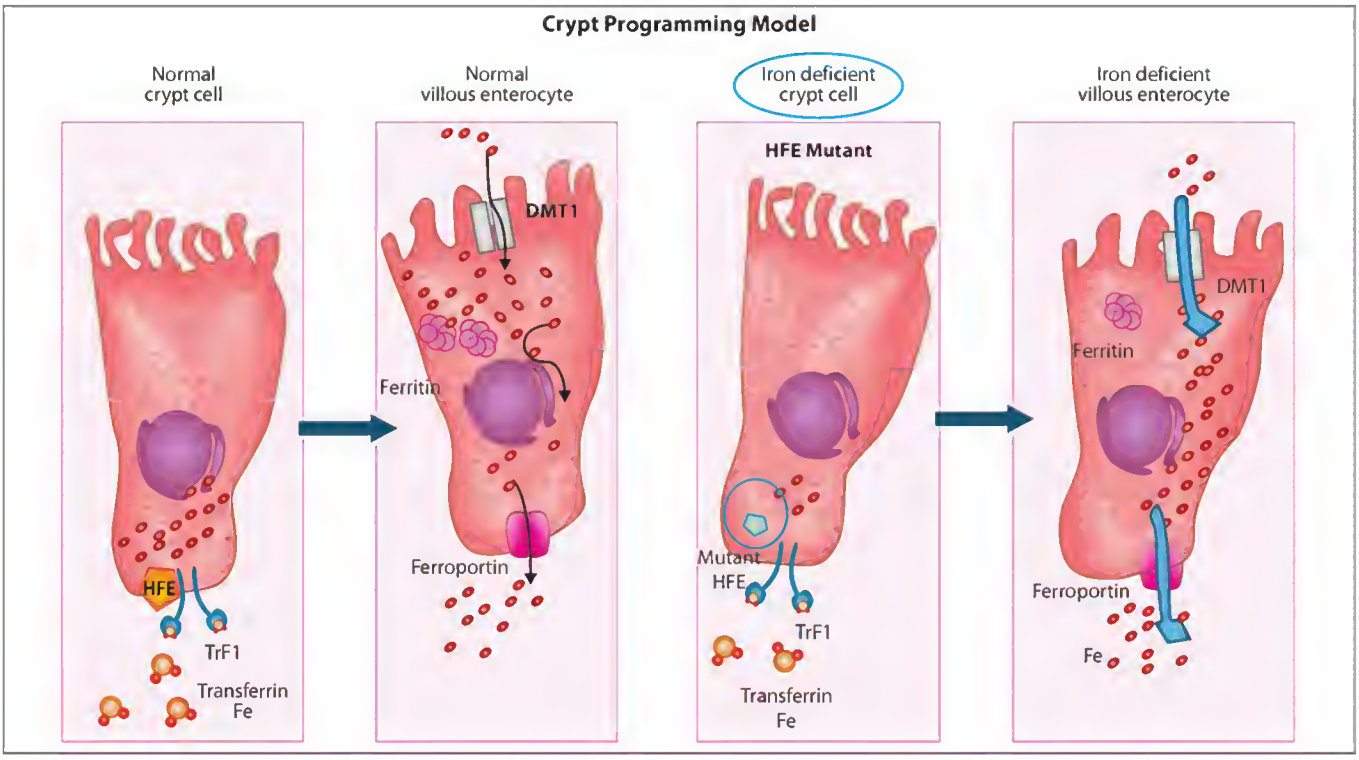


Figure 10: Crypt programming Model of HFE-Related Hereditary Haemochromatosis. Cryptprogramming model, undifferentiated duodenal crypt cells, take up iron from the bloodstream by transferrin receptor 1 (TfR1), which is located on their basolateral membranes. Interaction of TfR1 with normal HFE senses the iron status. The cellular pool of iron will programme the mature absorptive enterocytes that will be derived from these cells by modulating the activity of specialised luminal iron transporters [e.g. divalent metal transporter 1, (DMT1)] and basolateral iron transporters (e.g. ferroportin). Due to presence of C282Y mutation, HFE is unable to interact with TfR1, leading to iron-deficient crypt cells, these cells are programmed to iron starvation, hence persistently absorbing iron from the intestinal lumen and transfer virtually all of it into the bloodstream, regardless of actual erythropoietic needs.

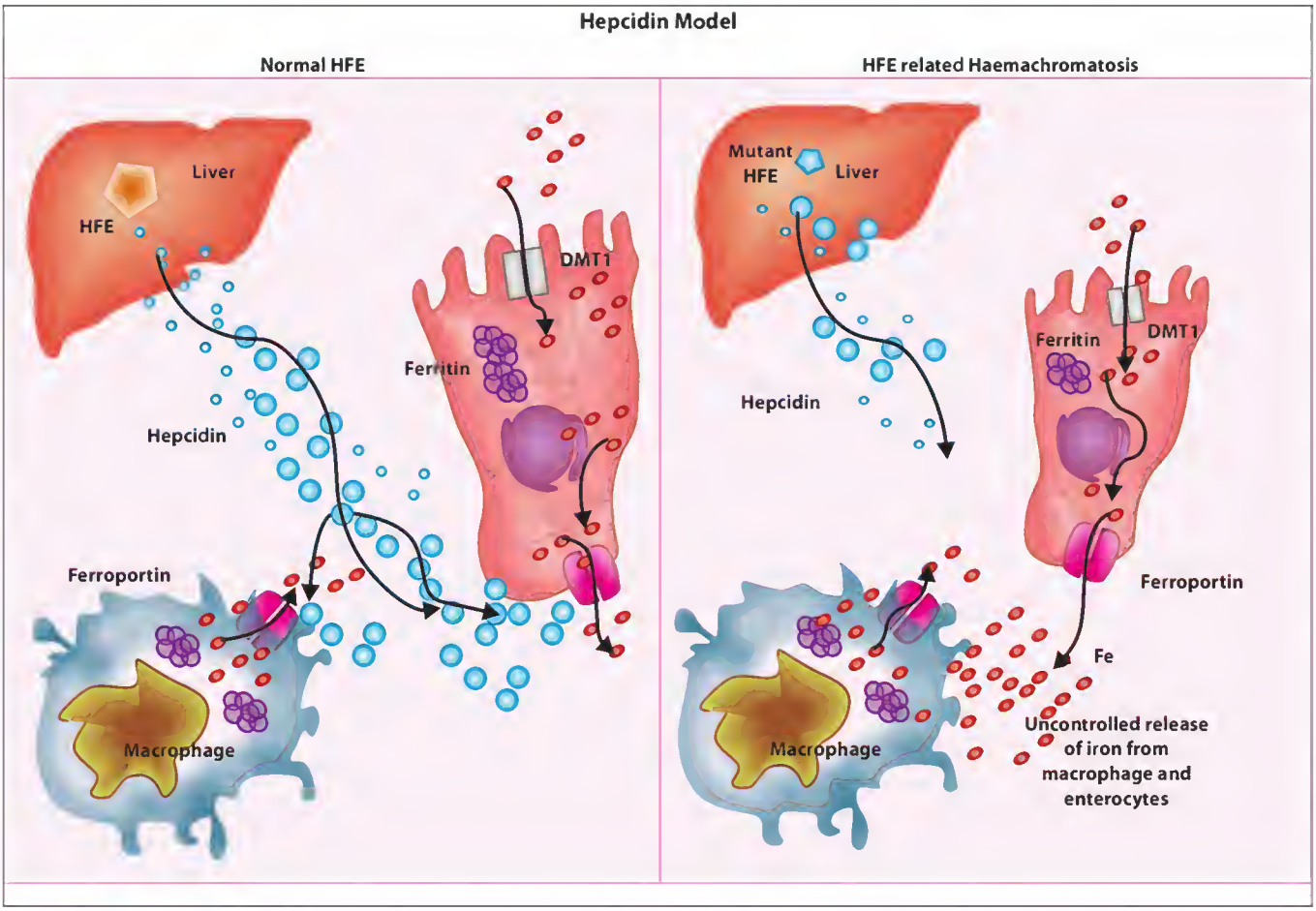


Figure 11: Hepcidin Model of *HFE*-Related Hereditary Hemochromatosis. Mutant HFE might alter signals or factors for appropriate synthesis or up-regulation of Hepcidin by hepatocytes, resulting in uncontrolled release of iron from macrophages and duodenal enterocytes.

function tests are seen. ECG and echocardiogram are abnormal. Genetic testing for HFE gene mutation C282Y (incidence >80% in HH) can be done.

Treatment

Phlebotomy greatly reduces mortality from cardiac and hepatic failure. This should be at the rate of 350 mL of blood each week or more often if the haemoglobin concentration can be maintained greater than 12 g/dL. Treatment can be measured by monitoring serum ferritin and the phlebotomy may need to be continued for over 2 years. The aim is to maintain normal transferrin saturation and serum ferritin in the low normal range, ideal is to achieve a serum ferritin around 50 ug/dL as shown in **Figure 12**. Desferrioxamine as a continuous intravenous infusion may have a limited role to treat life-threatening cardiac failure. Treatment of endo-crinopathies and infections is required. Screening for hepato-cellular carcinoma should be done.

All first-degree relatives over the age of 10 years should be tested for increase in transferrin saturation and ferritin and screened for HFE genotype.

ATRANSFERRINAEMIA

It is a rare autosomal recessive hereditary disorder. There is iron overload and hypochromic anaemia. There is reduced delivery of iron to bone marrow and reduced haemoglobin synthesis. Two mutations that have been identified are a deletion creating a frameshift resulting in a null transferrin allele and Ala 477Pro.

ACAERULOPLASMINAEMIA

It is an autosomal recessive disorder of iron overload. There is loss of function mutation in caeruloplasmin gene 3q23- q24. Caeruloplasmin has ferroxidative activity involved in the release of iron from cells. Patients have accumulation of iron in neural and glial cells of the brain, hepatocytes and pancreatic islet cells.

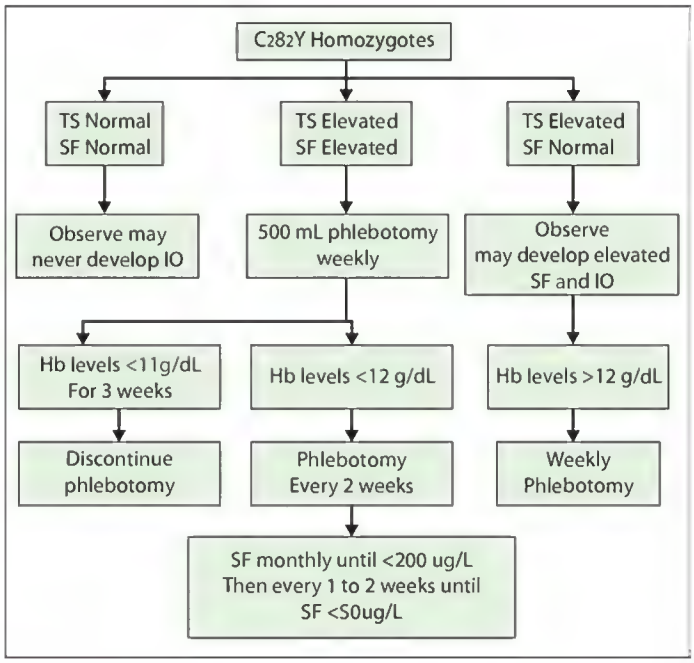


Figure 12: Strategic algorithm for C282Y Homozygous patients with hemochromatosis and the desired serum ferritin values after phlebotomy. SF (serum ferritin), TS (transferrin saturation) and IO (iron overload).

Treatment

Treatment consists of aggressive chelation with desferrioxamine and replacement of plasma or caeruloplasmin concentrate. Phlebotomy may exacerbate microcytic hypochromic anaemia and hence should be avoided.

18.6 The Porphyrias

Dhanpat Kumar Kochar, Abhishek Kochar

INTRODUCTION

Porphyrias are metabolic disorders resulting from the deficiency of a specific enzyme in the haem biosynthetic pathway. There are eight enzymatic steps in the conversion of glycine and succinyl-CoA to haem. The first and last three enzymes are located in the mitochondria whereas the other four are in the cytosol (**Figure 1**). Depending on the primary site of over production and accumulation of their respective porphyrin precursors or porphyrins, the porphyrias are classified as either hepatic or erythropoietic. Based on their clinical manifestations, porphyrias can be labelled as acute or cutaneous, but some of them have overlapping features. A definitive diagnosis requires demonstration of specific enzyme deficiency or gene defect. The important aspect including inheritance, enzyme deficiency, gene defect and excretion of precursors are shown in **Table 1**.

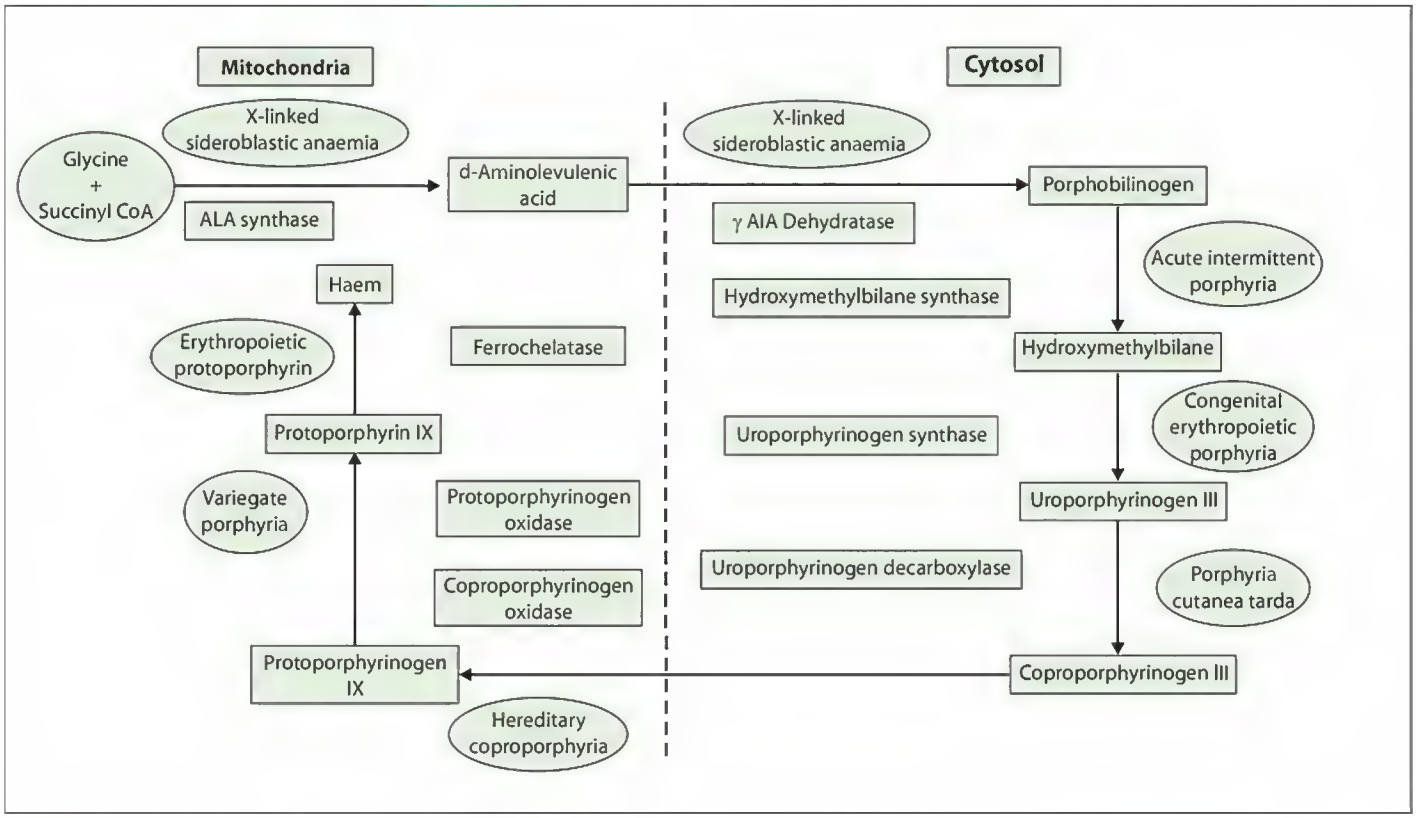


Figure 1: Haem-biosynthesis pathway with enzymes (in boxes) of each step and its associated disease (in ovals).

PORPHYRIA IN INDIA

The occurrence of acute intermittent porphyria (AIP) in India is mostly concentrated to *Maheshwari* and *Kumhar* communities of North West Rajasthan in and around Bikaner. In India, first case was reported by Wig and Malhotra in 1959. Estimated prevalence in India is 1 in 4.4 million but in Bikaner district it is around 1:12500 and around 1:400 to 1:600 in the specified communities, respectively. This prevalence is much higher than what has been described in many parts of the World. The disease has a female predilection (2:1). In their study, Wig and Malhotra have described a novel gene mutation in AIP in this region.

HEPATIC PORPHYRIAS

Acute Intermittent Porphyria

This is an autosomal dominant inherited disease resulting from the half normal level of hydroxymethylbilane synthase (HMBS) activity. In the classic form of AIP, both the 'non-erythroid' housekeeping HMBS isoform and the 'erythroid' HMBS isoform are deficient. The disease manifestation occurs due to induction of this rate limiting hepatic enzyme in heterozygotes. It remains latent or asymptomatic in majority of heterozygous having HMBS mutations and almost always before puberty. The pre-pubertal latency of the disease signifies the role of steroid hormones in clinical expression of the disease and increased frequency in women suggest a role of oestrogens or progestins. Common precipitating factors are infection, porphyrinogenic drugs (**Table 2**), steroids, alcohol, low calorie diet and occasionally pregnancy, which is usually well tolerated.

Clinical features

AIP is characterised clinically by acute episodes of a variety of gastrointestinal and neurologic symptoms and between these

episodes, the patient remains asymptomatic. Abdominal pain is constant, poorly localised and may be cramping in nature but sometimes it may be very severe and is associated with passage of red coloured (port wine) urine. Patient may have nausea, vomiting and severe constipation mimicking picture similar to intestinal obstruction. Fever, tenderness and leukocytosis are usually absent or mild because the symptoms are neurologic rather than inflammatory. Mental symptoms ranging from anxiety, insomnia, depression to disorientation, hallucination and paranoia can occur in acute attacks. Patients may have severe disabling pain all over the body, especially in lower limbs. Peripheral neuropathy is due to axonal degeneration and is primarily motor neuropathy affecting the proximal muscles of upper and lower limbs. Deep tendon reflexes are decreased or absent as neuropathy advances, however, ankle reflex may remain intact up to late in the course of illness. Sometimes 7th, 10th and 11th cranial nerves may also

Table 1: Important Features of Different Porphyrias

Disease Name	Deficient Enzyme (Activity % of Normal)	Gene Locus and Number of Mutations	Principal Symptoms (NV or P)	Increased Porphyrin Precursors and/or Porphyrins			
				Erythrocytes	Urine	Stool	Inheritance
Hepatic Porphyrias							
5 ALA dehydratase deficient porphyria (ADP)	ALA dehydratase (~ 5)	9q34 7 mutations	Neurovisceral	Zn protoporphyrin	ALA Coproporphyrin III	—	AR
Acute intermittent porphyria (AIP)	HMB synthase (~ 50)	11q23.3 272 mutations	Neurovisceral	—	ALA, PBG Uroporphyrin	—	AD
Porphyria cutanea tarda (PCT)	URO decarboxylase (~ 20)	1q34 60 mutations	Photosensitivity	—	Uroporphyrin 7-carboxylate porphyrin	Isocoprop-orphyrin	AD
Hereditary corpo-porphyria (HCP)	Coproporphyrinogen oxidase (~ 50)	3q12 36 mutations	Neurovisceral and Photosensitivity	—	ALA, PBG, Coproporphyrin III	Coproporp-hyrin III	AD
Variegate porphyria (VP)	Protoporphyrinogen oxidase (~ 50)	1q22 121 mutations	Neurovisceral and Photosensitivity	—	ALA, PBG, Coproporphyrin III	Coproporp-hyrin III Protoporphyrin	AD
Erythropoietic Porphyrias							
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen synthase (~ 1-5)	10q25.2-6.3 35 mutations	Photosensitivity	Uroporphyrin I Coproporphyrin I	Uroporphyrin I Coproporphyrin I	Coproporphyrin I	AR
Erythropoietic proto porphyria (EPP)	Ferrochelatase (~ 20-30)	18q21.3 74 mutations	Photosensitivity	Protoporphyrin	—	Protoporphyrin	AD

AD = Autosomol dominant; ALA = 5' aminolevulinic ocid; AR = Autosomal recessive; HMB = Hydroxymethylbilane; PBG = Porphobilinogen.

Table 2: List of Safe and Unsafe Drugs in Porphyria

Safe Drugs			Unsafe Drugs	
ACE inhibitors	Furosemide	Naproxen	Antidepressants	Macrolides
Acetylsalicylic acid	Gabapentin	Octreotide	Artemether	Methyldopa
Adenosine	Haloperidol	Olanzapine	Amiodarone	Nandrolone
Aminoglycosides	Hydrocortisone	Ondansetron	Azole antifungals	Phenytoin
Amphotericin B	Isoflurane	Orlistat	Barbiturates	Progesterones
Anti-D immunoglobulin	Insulin	Oxazepam	Chloroquine	Quinine (lesser than Chloroquine)
Cefotaxime	Immunoglobulins	Paracetamol	CCB's	Rabeprazole,
Ceftriaxone	Ibuprofen	Propranolol	Chlorzoxazone	Rifampicin
Chlorpromazine	Ipratropium	Propofol	Coxibs	Spironolactone
Codeine	Lactulose	Propylthiouracil	Carbamazepine	Oral contraceptive pills
Clonazepam	Lamivudine	Quinolones	(Cisapride)	Simvastatin
Clozapine	Levothyroxin	Ranitidine	(Clopidogrel)	(Sibutramine)
Dalteparin	Lithium	Rosuvastatin	Oestrogen	Testosterones
Desmopressin	Loperamide	Salbutamol	Hydralazine	Thiopental
Dexamethasone	Meropenem	Streptokinase	Isoniazid	Valproic acid
Didanosine	Metformin	Suxamethonium	IV lidocaine	(glimepride)
Estradiol patch or vaginal tablet	Morphine	Vaccines	Ketamine	(methylprednisolone)
Ethambutol	Multivitamin + iron	Vigabatrin	Metronidazole	(lamotrigine)
Enoxaparin	Nitrates		Metoclopramide	

Source: www.drugs.porphyrio.com, www.porphyrioeurope.org, www.porphyriofoundotion.com.

be involved. Patient may have generalised convulsion which may be secondary to hypertension, syndrome of inappropriate antidiuretic hormone hypersecretion leading to hyponatraemia apart from the disease itself. Patients may have urinary retention and rarely sensory loss. Progression to respiratory and bulbar paralysis and death may occur, especially when diagnosis and treatment are delayed. Patient may have postural hypotension, severe tachycardia and hypertension due to autonomic neuropathy. The disease can be disabling but is rarely fatal.

A rare homozygous dominant form of AIP occurs when patients inherit HMBS mutations from each heterozygous parent leading to very low (<2%) enzyme activity. The disease presents in infancy with failure to thrive, developmental delay and bilateral cataracts.

Diagnosis

During the acute attack, along with other features, urine is characteristically red or becomes red after keeping in sunlight for 30 minutes. The essential biochemical finding in acute attacks of AIP is increased urinary excretion of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG), which can be estimated qualitatively by Watson-Schwartz test. Levels are substantially increased in plasma and urine during an acute attack and can be measured quantitatively in blood and 24 hours urine. Study of specific HMBS gene mutation is helpful in the diagnosis of symptomatic and asymptomatic persons.

Treatment

An acute attack of AIP is treated with carbohydrate loading as intravenous glucose 300 g per day and/or intravenous hematin. The use of narcotic analgesics for abdominal pain and phenothiazines for nausea, vomiting, anxiety and restlessness are very helpful. Low-dose benzodiazepines are safe as tranquilisers. Intravenous hematin should be used in case of a severe attack or in those milder cases which do not respond within 1 to 2 days, in the dose of 3 to 4 mg/kg daily for 4 days in forms of lyophilised hematin, haem albumin or haem arginate. Rapid recovery occurs if treatment is started early. However, recovery may take months or years in patients having severe motor neuropathy. Recurrent attacks can occur during luteal phase of menstrual cycle and Gonadotropin-releasing hormone analogues are useful in such cases. Patients should not receive drugs which are likely to precipitate acute attack (**Table 2**). Hypertension may be treated by propranalol and convulsion requires use of oral gabapantine. Long-term risk of hypertension, chronic renal disease and hepatocellular carcinoma is increased in these patients and yearly hepatic imaging may be helpful. Liver transplant is being tried as a new modality of treatment.

Porphyria Cutanea Tarda (PCT)

PCT, the most common type of porphyria is due to deficiency of hepatic Uroporphyrinogen decarboxylase. It may be either sporadic (type 1) which is more common or familial (type 2 and 3). The enzyme deficiency must be substantial (~20%) for disease manifestation.

Clinical features

Blistering skin lesions appearing most commonly on the back of the hands are the major clinical features and they leave areas of atrophy and scarring when they rupture or crust. Lesions may also occur on the forearms, face, legs and feet. Skin friability and small white papules, hypertrichosis and hyperpigmentation are seen specially on face. Neurologic features are absent. The important precipitating factors include hepatitis C, human immunodeficiency virus (HIV), excess alcohol, elevated iron levels and oestrogens. The association of increased evidence of haemochromatosis gene (HFE) mutation, C282Y and H63D, in patients with type 1 and 2 PCT reflects the role of excess hepatic iron as precipitating factor. Patients of PCT characteristically have chronic liver disease and sometimes cirrhosis and have an increased risk of hepatocellular carcinoma. Hexachlorobenzene, di- and tri-chlorophenols and dioxin can precipitate the disease.

Diagnosis

Porphyrins are increased in the liver, plasma, urine and stool. The urinary ALA level may be slightly increased but the PBG level is normal. Increased isocoproporphyrins in faeces and sometimes in plasma and urine are diagnostic.

Treatment

Standard treatment is repeated phlebotomy to reduce hepatic iron load. One unit of blood can be removed every 1 to 2 weeks till serum ferittin reaches the lower limits of normal. Close monitoring of haemoglobin levels and ferritin levels is required to prevent development of iron deficiency and anaemia. Continued phlebotomy may not be needed after remission. An alternative to phlebotomy is low-dose regimen of chloroquine (e.g. 125 mg chloroquine phosphate twice a week) or hydroxy-chloroquine.

Hereditary Coproporphyria (HCP)

This Autosomal dominant porphyria results from half normal activity of coproporphyrinogen oxidase and patients may have acute attacks and cutaneous photosensitivity together or separately. An acute attack is identical but less severe than that of AIP, while the blistering skin lesions are like that seen in PCT. The diagnosis of HCP is readily confirmed by increased levels of coproporphyrinogen III in faeces, which distinguishes it from other porphyrias. An increase in the faecal coproporphyrinogen III/coproporphyrinogen I ratio is very useful for detecting latent cases. The treatment of acute attack is similar to that of AIP and PCT.

Variegate Porphyria (VP)

VP is an autosomal dominant hepatic porphyria due to deficient activity of protoporphyrinogen oxidase and can present with skin photosensitivity, acute neurovisceral crises, or both. Acute attacks are identical to those in AIP and are precipitated by the same factors as AIP whereas blistering skin manifestations are similar to those in PCT. Increased urinary ALA, PBG with coproporphyrinogen III and increased faecal protoporphyrin and coproporphyrinogen III help in diagnoses. The latter also help to distinguish VP from AIP. Plasma of the patient shows a unique fluorescence peak at neutral pH. Acute attacks are treated like that of AIP along with avoiding the exposure to sunlight.

ALA Dehydratase Deficient Porphyria (ADP)

ADP is an acute, hepatic porphyria caused due to severe deficiency of ALA-dehydratase activity (<10%). It is very rare and the clinical presentations vary according to the level of enzyme, however, neuropathy and abdominal pain

are common. There is a significant increase in urinary excretion of coproporphyrin III and ALA. The treatment of acute attack is similar to AIP.

THE ERYTHROPOIETIC PORPHYRIAS

In the erythropoietic porphyria, the excess porphyrins produced in bone marrow erythrocyte precursors are transported via plasma to the skin, where it causes cutaneous photosensitivity.

X-Linked Sideroblastic Anaemia (XLSA)

XLSA results from the deficient activity of the erythroid form of ALA synthase. These patients develop weakness since infancy and a refractory form of haemolytic anaemia. Patients have secondary hypersplenism and hypercellular bone marrow with megaloblastic erythropoiesis. The condition may respond to pyridoxine supplementation; however, blood transfusion may be needed in non-responsive patients.

Congenital Erythropoietic Porphyria (Gunther's Disease)

An autosomal recessive disorder occurring due to the deficient (not absent) activity of uroprophyrinogen III synthase causing accumulation of uroporphyrin I and coproporphyrin I isomers. Severe cutaneous photosensitivity begins in early infancy. Sunlight exposed skin becomes friable with formation of bullae and vesicles which are prone to rupture. Skin thickening, focal hypo/hyperpigmentation, and hypertrichosis of the face may occur. Haemolysis occurs due to increased levels of erythropoeitic porphyrins in blood. Increased levels of Uroporphyrin and coproporphyrin in erythrocytes, plasma, urine and faeces help in the diagnosis. The predominant porphyrin in faeces is coproporphyrin I.

Apart from supplementation of β-carotene, protection from sunlight and minor skin trauma are important preventive measures. Severe cases often require blood transfusion for anaemia. Splenectomy may reduce haemolysis and decrease transfusion requirements. Bone marrow and cord blood transplantation have proven effective in several transfusion dependent children. Recently, stem cell therapy is also being tried.

Erythropoietic Protoporphyria (EPP)

EPP is the most common erythropoeitic porphyria in children and occurs due to partial deficiency of ferrochelatase activity (<35%). Skin photosensitivity begins in childhood with pain, redness and itching occurring within minutes of sunlight exposure. It is non-blistering and is associated with elevations in erythrocyte protoporphyrin. Chronically skin may develop lichenification. About 5% of these patients may develop chronic liver disease.

The hallmark of this disease is an increase in erythrocyte protoporphyrin which is not complexed with zinc, in contrast to conditions such as lead poisoning, iron deficiency, haemolytic disorders in which zinc complexed protoporphyrin is seen. RBC's exhibit red fluorescence at 620 nm. Urinary levels of porphyrins and porphyrin precursors are normal. Avoiding sunlight exposure and wearing clothes designed for specific protection is helpful. Oral β-carotene to maintain serum level at 600 to 800 mg/dL may be very useful.

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18.7 Wilson's Disease

Sanjib Sinha, AB Taly

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disease involving a defect of copper transport by the hepatic lysosomes. It leads to excess copper deposition in liver, brain, kidneys and skeletal system, commonly affects children or young adults and runs an invariably fatal course if not adequately treated by de-coppering therapy. Among the various inborn errors of metabolism, WD is of specific interest to physicians due to availability of effective treatment. *Wilson SAK* provided detailed description of clinical and pathological changes in WD way back in 1912, but major advances in our understanding of the pathogenesis, cellular biology, and molecular genetics of the disease have occurred in the past three decades.

EPIDEMIOLOGY

The prevalence rate of WD is varied and has been reported as 12 to 29 per million in European populations. The prevalence of WD in other Asian countries has been between 33 and 68 per million but, there are no epidemiological surveys in India till date. At National Institute of Mental Health and Neurosciences (NIMHANS), we record 15 to 20 new cases of WD annually.

PATHOGENESIS

The major breakthrough regarding pathophysiology of WD came in 1948 when Cumings demonstrated excess of copper in brain and liver in these patients. It is now known that mutations in ATP-7B, a copper transporting protein, leads to abnormal accumulation of copper in hepatocytes that later spills into the circulation and eventually gets deposited in other organs. How does a copper deposition lead to tissue damage largely remains speculative?

GENETICS

Genetically WD is an autosomal recessive disorder of hepatocyte copper trafficking caused by impaired function of P-type adenosine triphosphatase (ATPase), encoded by ATP-7B gene located on chromosome 13q14 and consists of 21 exons. The ATP-7B transporter has dual synthetic and excretory roles, functioning in the transport of copper into the trans-Golgi compartment, for incorporation into the plasma protein caeruloplasmin, and into the bile, for excretion of excess stores. Defective ATP7B function results in hepatic copper accumulation and leads to hepatic and neurological manifestations of Wilson's disease. More than 400 mutations, documented from various countries including India, perhaps account for its clinical heterogeneity.

PATHOLOGY

Liver

In the early stages of the disease, diffuse cytoplasmic copper accumulation can be detected in liver by special immunohistochemical stains. Thereafter it progresses to an inter-mediate stage characterised by periportal inflammation, mononuclear cellular infiltrates, erosion of the limiting plate, lobular necrosis, and bridging fibrosis that suggests hepatitis. Cirrhosis almost invariably follows with either a micronodular or a mixed macronodular-micronodular pattern. In patients with fulminant hepatic failure, parenchymal apoptosis, necrosis and collapse might predominate, often with a background of cirrhosis (**Figures 1A and E**).

Brain

Brain shows evidence of putaminal softening, ventricular dilatation and atrophy, white matter cavitations, and central pontine myelinolysis like changes. Histological features include spongiform degeneration, astrocytosis, neuronal loss, gliosis and presence of characteristic fairly large Opalski cells, which exhibit fine granular cytoplasm and slightly abnormal nuclei (**Figure 1**).

CLINICAL PROFILE

Walshe has aptly stated that no two patients of WD may have similar clinical characteristics even among the common sib-ship, stressing its diverse manifestations. The phenotypic variability often leads to delay in diagnosis and treatment unless there is a high index of suspicion.

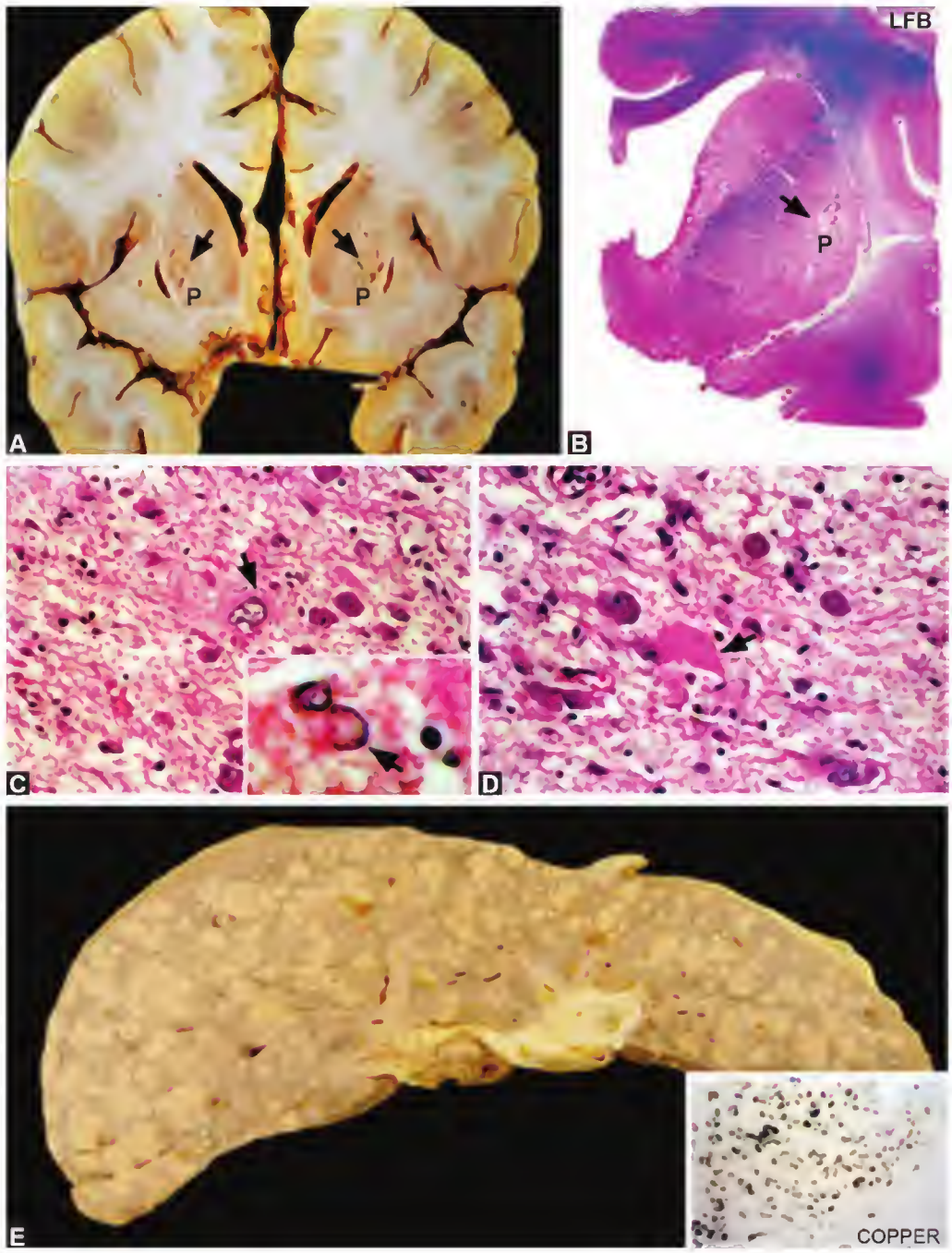
Majority of patients manifest with hepatic or neuropsychiatric symptoms (**Table 1, Figures 2A to D**). While hepatic involvement occurs early in the course of WD, it may go unrecognised and may not be the first symptom for seeking medical attention. Hepatic presentation, predominantly noted at a younger age, ranges from acute fulminant hepatitis to sub-clinical chronic liver disease. Most of these patients may not undergo investigation for WD due to its rarity in the community and low index of suspicion. Some of these patients succumb to illness while others develop neurological symptoms later in the course of disease.

Psychiatric presentation of WD includes bipolar affective disorder, schizophrenia, and psychosis with cognitive decline. A small number of patients predominantly exhibit renal dysfunction (e.g. renal tubular acidosis), and haematological symptoms (e.g. low counts, bleeding, etc.).

DIAGNOSIS

Slit lamp evaluation of Kayser-Fleischer (KF) ring forms corner-stone of clinical diagnosis. The KF ring is invariably present in all patients with neuropsychiatric form of WD but detection rate depends on the experience of clinician and ophthalmologist. In hepatic and other forms, KF ring may not be detected, and therefore, heavy reliance on this sign may lead to under recognition of the disease (**Figures 2A to D**).

The key biochemical diagnostic test includes low serum total copper, low serum caeruloplasmin and elevated 24-hour urinary



Figures 1A to E: Coronal slice of the brain from a case of Wilson's disease (WD) shows (A) bilaterally symmetrical putaminal (P) softening (arrows) extending laterally up to the external capsule; (B) whole mount preparation stained with Luxol Fast Blue (LFB) shows relative preservation of internal capsule and pale and softened neuropil in the putamen (P, arrow); (C) softened area in the putamen has bizarre astrocytes with vesicular lobulated nuclei (arrow) with inset showing Alzheimer type 2 astrocytes in the neuropil (arrow) (haematoxylin and eosin stain x 240 [Inset: H & E x 300]); (D) large opalski cell characteristic of WD has irregular eosinophilic cytoplasm and small peripherally placed pyknotic nucleus (H & E x 240); (E) slice of enlarged liver shows micro- and macro-nodular cirrhosis with inset demonstrates copper deposits within hepatocytes on rubanic acid stains (Inset: Rubanic acid x 240).

copper. It should be noted that caeruloplasmin being an acute phase reactant might be falsely normal in patients with acute presentation, especially of hepatic form. Therefore, high index of suspicion in this group of patients is required for accurate diagnosis.

One needs to carry out liver function tests, renal function tests, and haematological parameters, abdominal ultrasound, endoscopic examination, among others to assess status of various other organs involved in the disease.

Therapeutic monitoring for effective treatment can be done by 24-hour urinary copper excretion.

IMAGING

Introduction of magnetic resonance imaging (MRI) has made dramatic inroads into the pathological and anatomical correlates of clinical manifestations and has replaced computed tomography (CT) in the evaluation of WD. MRI of brain can assist in the diagnosis as well as prognosis. The MRI changes are varied in severity and topography, however, presence of central pontine myelinolysis, like changes, mid-brain tectal plate signal changes and giant Panda sign distinguishes WD from other extra-pyramidal disorders (**Table 2, Figures 3A to F**). The changes are dynamic and a significant proportion of the patients may

Table 1: Clinical Manifestations of Wilson's Disease

Hepatic
- Acute hepatitis (similar to self-limiting viral hepatitis)
- Persistently elevated serum liver enzymes
- Chronic hepatitis
- Cirrhosis (decompensated or compensated)
- Fulminant hepatic failure

Neurological
- Dystonia
- Tremor
- Dysarthria
- Drooling
- Parkinsonism or akinetic rigid syndrome
- Gait disturbances ataxia
- Pseudobulbar palsy
- Chorea
- Seizures
- Cognitive impairment
- Metabolic myopathy

Psychiatric
- Bipolar affective disorder
- Depression
- Neuroses
- Personality changes
- Schizophreniform psychosis
- Mental retardation

Haematological
- Hypersplenism and related issues
- Bleeding gums
- Haematemesis
- Pallor

Ophthalmic
- Kayser-Fleischer ring
- Sunflower cataract

Other Systems (uncommon)
- Renal tubular acidosis
- Menstrual irregularities
- Recurrent abortion
- Hyperpigmentation

Table 2: Magnetic Resonance Imaging Changes: Topographic Distribution* (n=100)

Atrophy (%)		
Cerebral	70%	—
Cerebellar	52%	—
Brainstem	66%	—
Signal Intensity Changes (%)		
Caudate	61%	—
Putamen	72%	—
Partial	—	45%
Whole of putamen	—	24%
Outer rim only	—	03%
Globus pallidus	40%	—
T2W hypointensity	—	34%
T1W hyperintensity	—	06%
Internal capsule	15%	—
Anterior	—	04%
Posterior	—	11%
Thalamus	58%	—
Lateral	—	32%
Diffuse	—	15%
Anterior	—	04%
Posterior	—	07%
Mid-brain	49%	—
Diffuse	—	19%
Dorsal (tectal)	—	12%
Periaqueductal region	—	06%
Face of Giant Panda	—	12%
Pons	20%	—
Partial (Patchy)	—	08%
Ventral	—	02%
Dorsal	—	03%
Central pontine myelinolysis-like	—	07%
Medulla	12%	—
Cerebellum	10%	—
Partial	—	04%
Middle cerebellar peduncle	—	06%
Cerebral white matter*	25%	—
Frontal	—	16%
Temporal	—	06%
Parietal	—	10%
Occipital	—	05%
Diffuse	—	02%
Cortical lesions*	9%	—
Frontal	—	06%
Temporal	—	03%
Parietal	—	—
Occipital	—	—
Diffuse	—	01%

**Some patients had more than one type of lesion [modified from Sinha et al, Neuroradiology 2006;48:613-621].*

show variable reversibility of MRI features following treatment. MR spectroscopy has provided insight into the ongoing biochemical changes.

Radiographic evaluation has documented following skeletal abnormalities osteoporosis, fractures, and arthritis and milkman pseudo fractures.

MANAGEMENT

Therapeutic Aspects

The outcome of WD was rather gloomy until 1948 when Cuming suggested use of Dimercaprol (BAL) for chelating the copper. This breakthrough in the management of WD was followed by introduction of penicillamine as de-coppering therapy in 1955 by Walshe. A number of drugs, such as zinc, trientine and ammonium tetrathiomolybdate, have been shown to have beneficial effect and frequently recommended in the management. Liver transplantation, the most definitive treatment for WD has been successfully carried out since 1982. Most patients need close monitoring and life-long supervised care. A general approach to diagnosis and management of WD is provided in **Figure 4**.

Penicillamine is the most commonly used de-coppering agent in India. A significant and paradoxical worsening, reported by few authors, can be largely reduced if penicillamine is started in a low dose and built up to the required dosage slowly (250 to 1000 mg per day). Zinc, introduced in early 1960s, is an effective agent with minimal side effects and forms an essential component of treatment in vast majority of patients. Unlike penicillamine and other de-coppering agents, zinc is cheap, easily available, has better compliance rate and can be used as an effective maintenance therapy in Indian population (150-300 mg elemental zinc per day). The experience in Indian literature on trientine dihydrochloride



Figures 2A to D: (A) Typical "Wilsonian" dystonic smile; (B) dystonia of upper and lower extremities in a young boy with Wilson's disease; (C) Kayser-Fleischer ring – naked eye appearance; (D) sunflower cataract.

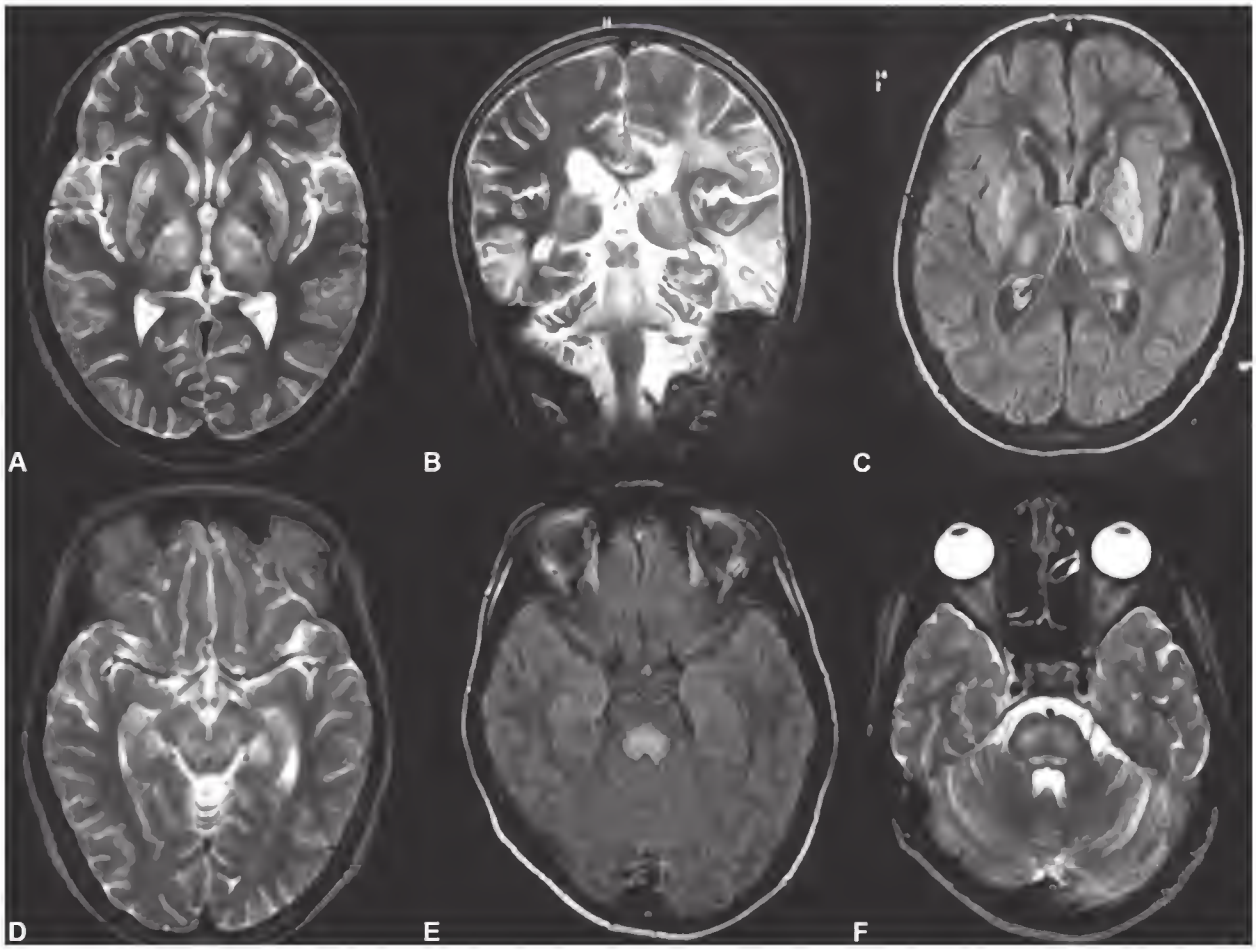
and ammonium tetrathio-molybdate in WD is rather sparse, largely due to non-availability of these drugs and their prohibitive cost.

Symptomatic treatment for hepatic dysfunction, portal hypertension, osseous changes, drooling, extra-pyramidal and psychiatric manifestations, hypersplenism is required in many patients. Surgical interventions like thalamotomy for disabling and resistant tremor in WD have been reported.

PROGNOSIS

WD has come off from the shadow of being an untreatable fatal disorder to potentially treatable disorder. It is believed that most of the patients with the currently available medications might lead a normal life. However, outcome of WD is as varied as its clinical manifestations and there are no consistent clinical imaging or laboratory parameters that can dictate prognosis.

A rapid progressive course is usually noted in the hepatic form of the disease, e.g. acute fulminant hepatic failure. In non-hepatic forms, the clinical course is usually indolent and relentlessly progressive if not treated. Most of the neurological patients do respond to therapy, even when present with severe form of the disease. Some patients have very stable initial course with dramatic response to de-coppering agents but later show



Figures 3A to F: Magnetic resonance imaging of brain in patients with Wilson's disease (WD): (A) *axial section of T2W1* showing signal changes in bilateral putamen and thalamus; (B) *coronal section of T2W1* showing signal changes involving white matter, basal ganglia and brain stem structures; (C) *FLAIR sequence* revealing signal changes in bilateral caudate, putamen and thalamus; (D) *axial T2W1 image at the midbrain level* showing the "Face of Giant Panda" sign; (E) *FLAIR axial sequence through midbrain* revealing hyperintense signal changes in the tectum; (F) *axial T2W1 through pons* showing central pontine myelinolysis (CPM)-like signal changes.

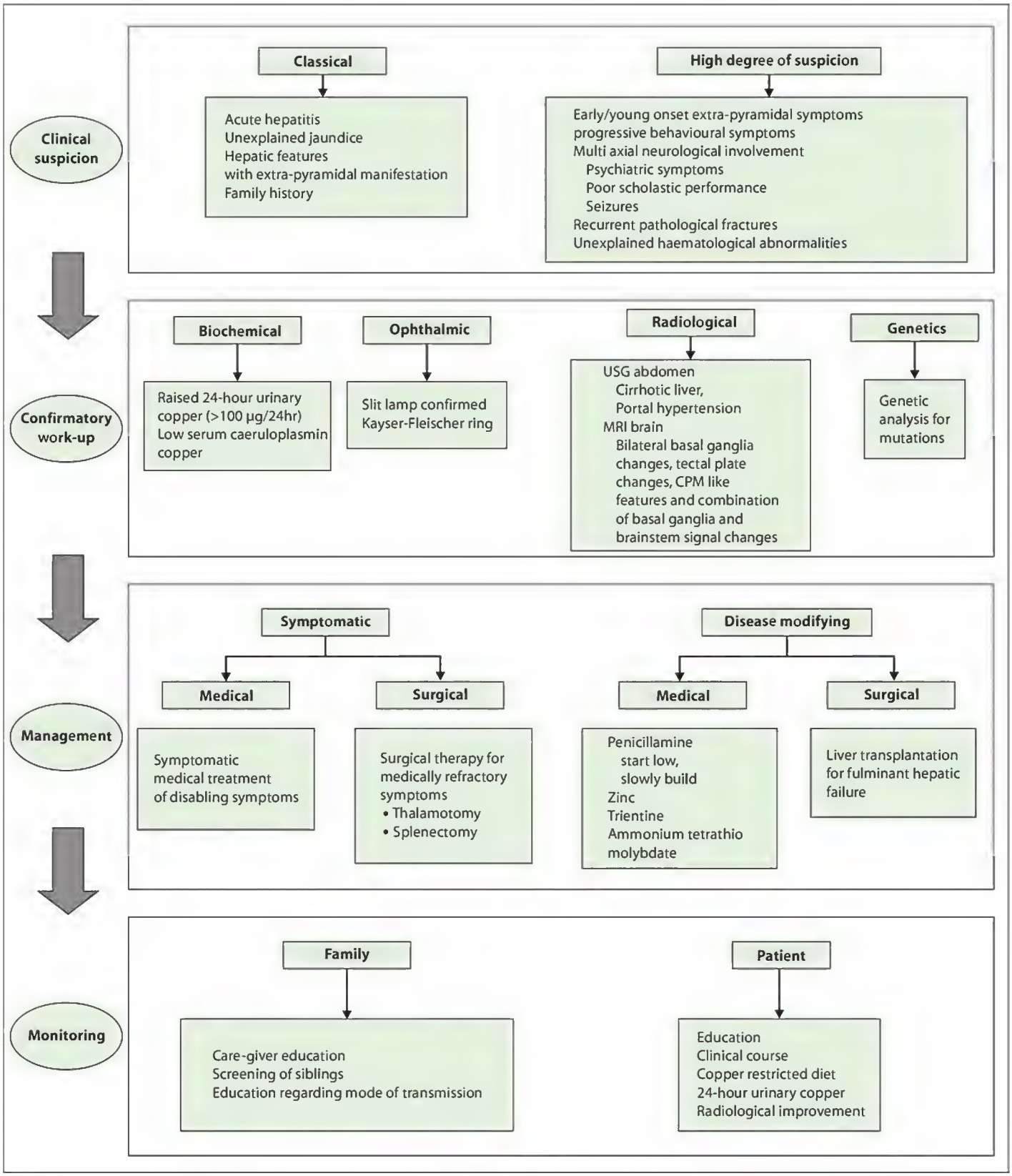


Figure 4: Flow-chart depicting a general approach for evaluation and management of patients with Wilson's disease.
Source: Modified from Taly et al. Neurology India 2009; 57: 527-40.

sudden deterioration, usually precipitated by poor drug compliance and sometimes by infections and stress. The exact reason for this delayed worsening remains a challenge. These patients probably have very delicately maintained internal milieu and any factor which tends to change the balance leads to vicious cycle of deterioration. Thus, therapeutic outcomes can be broadly classified into three categories:

1. Patients who have been diagnosed, treated and have normal life or are clinically stabilised, but still have problems with "Quality of Life".

2. Patients who have relentlessly progressive course despite specific treatment.
3. Patient who dramatically worsen and progress after long-term stable clinical course.

CONCLUSION

WD is perhaps more common than reported from India. There is a need to have epidemiological and genetic studies taking into consideration its variable presentation and high degree of consanguinity in south Indian populations. A nation-wide registry may improve awareness among medical communities and lead to early diagnosis and prompt treatment. Once diagnosis is established the patient and the care-giver need to be educated regarding compliance and long-term follow-up.

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18.8 Lysosomal Storage Disorders

Prasanta Kumar Bhattacharya

DEFINITION AND EPIDEMIOLOGY

Lysosomes are a group of subcellular organelles of diverse size and shapes, which contain numerous acid hydrolases, each of which is responsible for degradation of specific biological macromolecules derived either endogenously from metabolism or cellular structures or from breakdown of exogenous materials.

Lysosomal storage disorders (LSDs) represent a group of more than 40 distinct genetic diseases, each one resulting from a deficiency of a particular lysosomal protein or, in a few cases, from non-lysosomal proteins, that are involved in lysosomal biogenesis.

Although the incidence of LSDs in the general population is rare, it is about 1 in 5,000 live-born infants, their prevalence in certain selected populations is considerably high. Gaucher's disease and Tay-Sachs disease, for example, are reported to be 1 per 855 and 1 per 3,900, respectively in the Ashkenazi Jewish population; aspartylglucosaminuria is prevalent in 1 per 18,500 in the Finnish population and mucopolysaccharides (MPS) type III is about 1 per 24,000 in the Netherlands.

AETIOPATHOGENESIS

Most LSDs are inherited in an autosomal recessive manner, with the exception of Fabry's disease and MPS type II, which show X-linked recessive inheritance. Since lysosomes are found in most cells of the body, these disorders tend to be multi-systemic and are always progressive, although the rate of progression may vary. Organ damage arises from progressive accumulation of the substrates for the missing enzyme. There are several potential ways in which accumulated substrate might cause disease. The most obvious is enlargement of the affected cell, resulting in enlargement of the respective organ. The accumulation of undegraded substrate leads to a number of secondary biochemical and structural events, which individually or in combination, leads to the pathophysiology and clinical manifestations of these disorders. These secondary events include secondary lysosomal hypertrophy, neuronal changes, macrophage activation and cytokine release.

CLINICAL FEATURES

The clinical manifestations of the different disorders are diverse and it is not within the scope of this chapter to discuss each one in detail. Some clinical features are common for all of them. These include:

1. The symptoms arising from these disorders may start early in infancy or late in life, are usually permanent and progressive, and are unrelated with food intake or inter-current illnesses.
2. These disorders are usually associated with connective tissue diseases, skeletal abnormalities and neurological symptoms including deafness and progressive mental deterioration.
3. Visceral syndromes affecting the spleen, liver, lungs, kidneys and the heart are common.
4. Ocular disease occurs especially in mucopolysaccharidoses and neurosphingolipidoses with corneal opacities, retinal changes and macular cherry-red spots.
5. Recurrent non-immune hydrops foetalis is an uncommon but important presentation of several LSDs including Farber's disease, GMI gangliosidosis, galactosialidosis, Niemann-Pick disease type C, etc.

MODALITIES OF DIAGNOSIS

It is important to make an early diagnosis of these disorders for various reasons:

1. These being inherited genetic disorders, genetic counseling of other members of the family can be done and unexplained symptoms in relatives can be clarified.
2. Definitive treatment modalities, like enzyme-replacement therapy, bone marrow transplantation or even substrate-reduction therapies, although costly, are available for these disorders. These new treatments may halt or even reverse progressive organ damage. The substantial morbidity and premature mortality of these disorders may be preventable.
3. Several of these disorders respond to palliative treatment including renal and hepatic transplant.

Diagnostic Work-up

Early diagnosis of these disorders is critical, because those patients, who are treated before significant symptom development, have the best chance for a positive outcome. The most vital point in the diagnostic work-up is the suspicion about LSD-based on clinical clues. The LSDs can be suspected in any individual experiencing developmental delay, loss of learned skills, ataxia, seizures, weakness and dementia, more so, if the individual is regressing after a period of relatively normal development and the disorder seems progressive. Suspected patients should be referred to special laboratories for histochemical staining of biopsy material and examination of urine metabolites, including lipids and oligosaccharides, so as to narrow down the diagnostic possibilities. However, specific enzymatic assays on leukocytes isolated from fresh heparinised blood samples or on fibroblasts cultured from small skin biopsies yields better results than biopsy. These immuno-chemical tests help in patient management, especially in early detection of the disorder, prediction of clinical severity, determining the most appropriate therapeutic regimen, and for monitoring of patients who are on therapy. Molecular analysis of genes, which encode for lysosomal enzymes, especially deoxyribonucleic acid (DNA) based studies, are now available, which not only support the enzymatic diagnoses of LSD but they further help in the detection of phenotype. At present, specific enzymatic and genetic diagnoses are preferred to histopathological studies on light microscopy. Electron microscopy of biopsy material is also considered helpful in arriving at a correct diagnosis.

SELECTED DISORDERS

Table 1 summarises various enzyme deficiencies and the clinical features. The important ones are discussed in subsequent paragraphs.

Gaucher's Disease

This is the most common LSD and is also the most prevalent genetic disease among Ashkenazi Jews. It results from the deficiency of enzyme glucocerebrosidase, which normally splits glucosylceramide, to produce glucose, leading to glucosylceramide accumulation in the reticuloendothelial system.

Clinical features

Gaucher's disease is a multi-system disorder with haematological problems, organomegaly and skeletal involvement with bone pain and pathological fractures. There is hepato-splenomegaly with features of hypersplenism. The marrow cavity is widened due to deposition of Gaucher's cells (cerebroside laden macrophage with eccentric nuclei and "crumpled silk" like PAS-positive cytoplasm due to intra-cytoplasmic substrate inclusions) along with expansion of the bones, especially the lower ends of femur and humerus. Based on the presence or absence of severe neurological involvement three clinical variants are described:

1. *Type 1 Gaucher's disease (non-neuronopathic):* It is a chronic disease presenting both in young and in older persons as a slowly to rapidly progressive visceral disease characterised by hepatosplenomegaly. Younger patients have a greater degree of hepatosplenomegaly and peripheral blood cytopaenias while chronic bone disease is commoner in the older group.
2. *Type 2 Gaucher's disease (acute-neuronopathic):* It is rare, with rapidly progressive neurodegenerative course with extensive visceral involvement and death within the first 2 years of life.
3. *Type 3 Gaucher's disease (chronic-neuronopathic):* It may present with clinical manifestations that are intermediate to those seen in type 1 and 2 with presentation in childhood and death by the age of 12 to 15 years.

Tay-Sachs' Disease

It is common in Ashkenazi Jews. A history of consanguinity is usually present. There is deficiency of β-hexosaminidase A, which leads to accumulation of GM_2 gangliosides within the central nervous system (CNS) ganglion cells along with degeneration of myelin. It is clinically characterised by mental apathy, early mental retardation and visual defects leading to progressive spasticity, blindness and dementia. There are macular cherry-red spots on fundoscopy. The infantile form of the disease manifests by 6 months of age and death occurs within 3 to 4 years. The juvenile-onset type presents with ataxia and dementia with death by about 15 years. The adult-onset form starts in childhood with clumsiness, with motor and spinocerebellar signs developing in adolescence and progressing into adulthood with psychosis and dementia.

Sandhoff Disease

It is similar to Tay-Sachs' disease with additional hepato-splenomegaly and bony dysplasia.

Fabry's Disease

It is an X-linked disorder due to α-galactosidase deficiency and characterised by angiokeratomas, small vessel disease of kidneys, heart and brain, corneal and lenticular opacities. Proteinuria and progressive renal dysfunction occur in 2nd to 4th decades. Hypertension, left ventricular hypertrophy, myocardial ischaemia and infarctions and heart failure occur in the 3rd to 4th decades. Death usually results from renal failure or cardiovascular or cerebrovascular diseases in untreated patients.

Table 1: Enzyme Deficiencies and Salient Clinical Features of Few Common Lysosomal Storage Disorders

Disorder	Enzyme Deficiency	Stored Material	Clinical Manifestations				
			Clinical Types	Neurological Involvement	Visceromegaly (Liver/Spleen)	Skeletal Disease	Ophthalmic Lesions
Gaucher's disease	Glucocerebrosidase	Glucosylceramide	Type 1	–	+	+	–
			Type 2	+	+	+	Eye movement
			Type 3	+	+	+	
Tay-Sachs' disease	β-hexosaminidase A	GM2 gangliosides	Infantile Juvenile	MR, Seizures	–	–	Cherry red spot
Sandhoff disease	β-hexosaminidase A and B	GM2 gangliosides	Infantile	MR, Seizures	+	±	Cherry red spot
Fabry's disease	α-galactosidase A	Globotriao sylceramide	Childhood	Painful acroparesthesias	–	–	Corneal dystrophy
Niemann-Pick disease A and B	Acid sphingomyelinase	Sphingomyelin	Type A, neuronopathic; Type B, non-neuronopathic	MR, Seizures	+	–	Cherry-red spot
Metachromatic Leukodystrophy	Arylsulphatase A	Cerebroside sulphate	Infantile Juvenile Adult	MR, Dementia, Psychosis	–	–	Optic atrophy

MR = Mental retardation; (+) = present; (–) = absent.

Niemann-Pick Disease

It is an autosomal recessive disorder due to defects in acid sphingomyelinase. Type A is characterised by early onset progressive CNS disease with massive hepatosplenomegaly. Type B has a late and variable onset with hepatosplenomegaly and progressive hepatic cirrhosis and pulmonary disease with the presence of foamy cells in both liver and lungs. Death results in adolescence or early adulthood due to progressive lung or hepatic disease.

TREATMENT

A variety of non-specific therapeutic measures are available for most disorders. Specific therapy can be broadly divided into enzyme-based therapies and non-enzyme-based therapies.

Enzyme-Based Therapy

The enzyme-based therapies currently available are bone marrow transplantation (BMT) and enzyme replacement therapy (ERT). In BMT, which is used in at least 20 known types of LSDs, the donor bone marrow provides a constant and permanent endogenous supply of enzyme-producing cells. Unfortunately, while BMT results in varying degrees of clinical improvement, it rarely, if ever, results in complete reversal of the clinical phenotype because of: (i) inadequate tissue penetration in skeletal and neuronal tissues, and (ii) presence of extensive disease prior to commencement of BMT. Response to ERT varies considerably from disease to disease, depending on the age of onset, rapidity of disease progression and the presence or absence of neurological involvement. Within each disease too, there is considerable variation. Mildly affected patients are the most likely to respond.

Non-Enzyme-Based Therapy

Substrate reduction therapy (SRT) is a novel approach in the treatment of certain types of LSD. The imino-sugar N-butyl-deoxynojirimycin (NB-DNJ) has been shown to inhibit ceramide-specific glucosyltransferase, which catalyses the first step in glycosphingolipids biosynthesis. This results in the inhibition of biosynthesis of all glucosylceramide-based glycosphingolipids.

Future Directions of Therapy

The CNS-directed gene therapy and Chaperone therapy (also known as enzyme enhancement therapy), that have the potential to cross the blood-brain barrier are newer modes of therapy directed towards CNS manifestations of LSDs.

CONCLUSION

Increased awareness by healthcare professionals, with early diagnosis and referral to specialist centres, is increasingly important, as new treatment modalities that are now available may halt or even reverse progressive organ damage. The substantial morbidity and premature mortality of these disorders may be preventable.

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18.9 Inherited Disorders of Membrane Transport

SK Singh

INTRODUCTION

Correct localisation of substances within the cell is membrane transport. Molecular transportation takes place at the cell surface or at intracellular cell organelles. The former is responsible for localisation of various substances inside the cell against or along the concentration gradient whereas latter one prevents mixing of various proteins inside the cell organelles. While both abnormalities of membrane transport are related to disease conditions, genetically inherited only membrane transport and their relevance in disease states are described due to space constraints in the present chapter. Transportation of substance across the cell membrane is mediated by the transporters. Classes of substance that need transportation are amino acids, sugars, ions (cations, anions), vitamins and water. Defects in transportation of one or more compounds may be autosomal dominant or recessive in inheritance and these points toward genetic locus that involves alteration in membrane protein.

Pathology of many diseases have not been understood till very recently when defect in membrane transport of molecules and their role in causation of disease was recognised. Mutation in transporter molecules has been demonstrated in disorders of heart, muscle, brain, endocrine and sensory organs. Sometimes mutation of different gene that encodes interacting protein can present similar disease phenotype. In case of allelic heterogeneity, mutation of single gene leads to different diseases depending on functional inactivation, activation or presence of dominant negative effects. The number of inherited membrane transport disorders are increasing with identification of newer molecular basis of these disordes.

The defects in membrane transport that cause diseases are classified as;

1. Disorder of amino acid transport,
2. Disorder of hexose transport,
3. Disorder of anion transport.

DISORDER OF AMINO ACID TRANSPORT

In this disorder two variants are described. One involves group specific membrane receptor or carrier and the other involves substrate specific transport system. In the first variant, 5 amino acids transport disorders, cystinuria, dibasic aminoaciduria, Hartnup disease, iminoglycinuria, and dicarboxylic amino-aciduria have been described and in the second variant, the transport of only one amino acid is impaired due to existence of substrate-specific transport systems. Each of these conditions affects transport of amino acids in the kidney, gut, or both but not in other tissues.

Cystinuria

It is a common inborn error, characterised by impaired renal tubular and intestinal mucosal reabsorption, because of defective transport at brush border and excessive urinary excretion of the dibasic amino acids lysine, arginine, ornithine, and cystine. Cystine is sulphur containing non-essential amino acid that is synthesised from methionine. Because cystine is less soluble its overexcretion predisposes to the formation of renal, ureteral, and bladder stones. Such stones are responsible for the signs and symptoms of the cystinuria.

The disorder is transmitted as an autosomal recessive trait and with a frequency of 1 in 10,000 to 1 in 15,000 in many ethnic groups. There are two genetic variants of cystinuria: type 1 and non-type 1. Homozygotes for both variants have high urinary excretion of dibasic amino acids lysine, arginine, ornithine, and cystine. While heterozygote Type 1 has normal urinary level of these amino acids, non-type 1 has moderately high excretion of these amino acids (non-type 1 was previously known as type II,III). The gene for type 1 cystinuria (SLC3A1) encodes solute carrier family 3 and maps to chromosome 2p16.3. The other types of cystinuria (non-type 1) are caused by mutations in SLC7A9, which maps to chromosome 19q13 and encodes the light subunit needed for the correct processing of SLC3A1.

Clinical manifestations

Increase in urinary excretion of cystine and the other disbasic amino acids leads to cystine renal stones that account for 1% to 2% of all urinary tract calculi and it is most common cause of stones in children. Renal stone formation usually occurs in the second or third decade but may occur in the first year of life and occasionally may present as bladder calculi at birth. In the homozygous patients urinary excretion of cystine usually exceeds 500 mg per day, and stone formation occur at an early age, but heterozygotes excrete usually 100 to 300 mg per day and typically do not have urolithiasis. Clinical presentation, symptoms and signs are those of urolithiasis, haematuria, flank pain, renal colic, obstructive uropathy, infection and these complications can lead to progressive renal insufficiency.

Diagnosis

The cystine stone is pathognomonic of cystinuria. Urinary nitroprusside test should be performed on all patients with urolithiasis to exclude this diagnosis. Half the stones in cystinuric individuals are of mixed composition and the cystine core may not be detected in 10%, therefore, nitroprusside test is reliable for the diagnosis. Nitroprusside test (appearance of a cherry red colour) may be false positive in some heterozygotes for cystinuria and in patients with hypercystinuria, homocystinuria, and mercaptolactate-cysteine disulphiduria. When cystine content exceeds 1000 µmol/L (250 mg/L), cystine crystals are seen in the sediment of acidified, concentrated chilled urine. These hexagonal crystals are pathognomonic of cystine overexcretion in patients not taking sulphonamides. Qualitative urine amino acid analysis helps confirming the diagnosis of cystinuria, while quantitative chromatography can be useful for

differentiating heterozygotes from homozygotes and for following free cystine excretion during therapy. The sulphur content of cystine gives these stones their faint radiopaque appearance.

Treatment

The treatment is essentially targeted to reduce urinary concentration of cystine and to make the pH of urine alkaline as cystine crystals are soluble in alkaline but precipitate in acidic environment. These are accomplished by increasing water and fluid intake to 5 to 7 litres in 24 hours. Water is good for treatment and its intake should be distributed throughout the day and night. Alkanisation of urine to a pH of 7.5 makes the cystine stone soluble and this can be achieved by sodium bicarbonate, acetazolamide, and polycitrates. Long-term use of the alkaliser may lead to the formation of calcium oxalate, phosphate or calcium ammonium phosphate stone or nephrocalcinosis.

If the above measures fail, the alternative treatment is D-penicillamine that makes disulphide of penicillamine and cystine. Such compound is more soluble and it reduces cystine concentration in urine. The dose of penicillamine is 1 to 3 g per day. The side effects include serum sickness, pancytopaenia, agranulocytosis, immune glomerulonephritis and Goodpasture's syndrome. These side effects limit the use of penicillamine in cystinuria and is used as a reserve drug. The other drug is tiopronin (alpha mercaptopropionylglycine) given in dose of 800 to 1200 mg per day in four divided doses as safer and effective alternative. Cystine stone of less than 1.5 cm can be treated by extracorporeal shock wave lithotripsy.

Dibasic Aminoaciduria

It is characterised by a defect in reabsorption of the 3 dibasic amino acids (lysine, arginine, ornithine) but not cystine from renal tubules. It is transmitted as autosomal recessive traits. The common form (type II) is known as lysinuric protein intolerance that show defective intestinal transport of dibasic amino acids as well as exaggerated renal losses. It is associated with impairment of the urea cycle. The defective gene (SLC7A7) is mapped to chromosome 14q11.2. Multiple genes are required in the formation of this dimeric transporter that explains part of the intrafamilial variability observed in lysinuric protein intolerance.

Manifestations are related to deficiency of ornithine, arginine, and lysine. Affected patients present with hepatosplenomegaly, protein intolerance, and episodic ammonia intoxication in childhood. While adults may present with severe osteoporosis, impairment of kidney function or interstitial changes in the lungs. Plasma concentrations of lysine, arginine, and ornithine are reduced, whereas urinary excretion of lysine and orotic acid are increased. The clinical features are due to hyper-ammonaemia and insufficient amounts of lysine to support protein synthesis during growth. Patients with lysinuric protein intolerance are at increased risk during pregnancy and child birth due to bleeding tendency, and pre-eclampsia.

Type I dibasic aminoaciduria has been described, though rare in occurrence. These patients have mental retardation without hyperammonaemia and protein intolerance. Type I disease involves the same transport system as that impaired in the more common type II dibasic aminoaciduria.

Treatment

Dietary protein should be restricted in conjunction with supplementation of citrulline (2 to 8 g per day), a neutral amino acid that facilitate the urea cycle when metabolised to arginine and ornithine. Carnitine supplements improve growth by sparing lysine and by enhancing fatty acid oxidation. Pulmonary disease responds to glycocorticoids.

Hartnup Disease

Hartnup disease was named after the first reported family. There is a defect in the transport of monoamino-monocarboxylic amino acid (neutral amino acids) by the intestinal mucosa and renal tubules and this leads to neutral or aromatic aminoaciduria. Alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, glutamine, asparagine, and histidine are excreted in urine in quantities 5 to 10 times normal. This is inherited as an autosomal recessive trait, and the gene has been mapped to chromosome 5p15. Homozygotes occur with a frequency of about 1 in 24,000 births. Heterozygotes exhibit no clinical or chemical abnormalities system for neutral amino acids.

Clinical manifestations

Most of the patients remain asymptomatic but rarely those who are symptomatic present with cutaneous photo sensitivity. The skin becomes rough and red after moderate exposure to the sun, and with greater exposure, pellagra like skin rash may develop. This rash may be pruritic and a chronic eczema may appear. Skin changes have been reported in affected infants as young as 10 days of age. Some patients are also characterised by variable neurologic manifestations like intermittent ataxia and unsteady or wide-based gait. Ataxia may last a few days. It often improves spontaneously. Mental development is usually normal but episodic behavioural changes in the form of irritability, emotional instability, depression have been observed. Few patients may present with short stature and atrophic glossitis. Nutritional deficiency of tryptophan results into clinical manifestations. The manifestations is episodic and related in part to metabolic demands for tryptophan. Tryptophan metabolism leads to the synthesis of niacin and nicotinamide-adenine dinucleotide and supplies about half the daily niacin needs and renal and intestinal transport defect for tryptophan leads to niacin deficiency. Only a small fraction of patients with the chemical findings of this disorder develop a pellagra-like syndrome, implying that manifestations depend on other factors in addition to the transport defect.

Diagnosis

The diagnosis of Hartnup disease should be suspected in any patient with clinical features of pellagra without a history of dietary niacin deficiency with neurologic and psychiatric manifestations which may range from attacks of cerebellar ataxia to mild emotional lability to frank delirium accompanied by exacerbations of the skin rash. Fever, sunlight, stress, and sulphonamide therapy provoke clinical relapses.

Main laboratory finding is amino aciduria, which is restricted to neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, glutamine, asparagine, and histidine) does not occur in dietary niacin deficiency. Plasma concentration of neutral amino acids are usually normal. This is quite an unexpected finding and an

explanation for it is that these amino acids are absorbed as dipeptides and the transport system for small peptides is intact in Hartnup disease.

Treatment

Treatment is directed at nicotinic acid or nicotinamide (50 to 300 mg daily) repletion and a high-protein diet.This result in favourable outcome in symptomatic patients, but because of intermittent nature of clinical presentation, the effectiveness of these treatment measures is difficult to evaluate.Tryptophan ethyl esters bypass the absorption defect and may be an option for treatment.

Substrate-Specific Defects in Amino Acid Transport

Rarely defective renal tubular reabsorption and/or impaired intestinal absorption of a single free amino acid have been reported in families. These disorders are inherited as an autosomal recessive trait.The substrate specific defects include transportation of cystine, lysine and histidine in kidney and selective malabsorption of methionine or tryptophan in intestine.Cystine defect can lead to renal calculi, lysine transport defect in kidney and intestine. This can cause seizures, mental and physical retardation.Similar defect in histidine metabolism can also cause mental retardation while tryptophan disorder can cause calcinosis and indoluria.

DISORDERS OF HEXOSE TRANSPORT

The cells use D-glucose for energy production and for many other anabolic purposes.There are two main classes of glucose transporters in humans: active Na^+-glucose cotransporters proteins (SGLT) and the facilitative glucose transporters (GLUT). Na^+-glucose cotransporters actively concentrate glucose inside intestinal and renal cells against concentration gradient, using the electrochemical potential of Na^+ as their energy source and it does not require insulin for its action. Defects in this class of transporters cause renal glycosuria (SGLT2) and intestinal glucose-galactose malabsorption (SGLT1).Facilitative glucose transporters allow glucose to enter cells along the concentration gradient.Defects in facilitative transporters cause the glucose-transporter protein syndrome (GLUT1), Fanconi-Bickel syndrome (GLUT2) and one subtype of glycogen storage disorder (GLUT 7).

Disorders of Concentrative Glucose Transporters

Renal Glycosuria is characterised by glycosuria at normal concentrations of blood glucose. The renal tubular malabsorption is specific for glucose. Unlike generalised defect of tubular disease, phosphate and amino acids are transported normally. The genetic basis is not understood. It is a benign condition, but occasionally may present with polyuria and polydipsia due to severe glycosuria.

In normal persons, glucose is reabsorbed throughout the proximal renal tubule by a sodium-dependent, phlorizin-inhibitable transport process. Reabsorptive capacity exceeds normal plasma glucose concentration.Maximal renal absorptive capacity is exceeded at a filtered load of around 18 mmol (325 mg)/minute/1.73 m^2 body surface area, which is tubular maximum for glucose (TmG). It is achieved at 10 mmol/L (200 mg/dL) of plasma glucose concentration.

Two patterns of glycosuria are recognised: type A, characterised by a reduced tubular maximum reabsorptive capacity, and type B, showing a reduced threshold for glycosuria, with normal TmG. Homozygotes with either of these recessively inherited mutations and heterozygotes with these allelic mutations present with renal glycosuria. Renal glycosuria may not be associated with impaired intestinal transport.

Glucose-Galactose malabsorption

It is characterised by profuse, watery diarrhoea in infants on milk or foods containing lactose, sucrose, glucose, or galactose. The primary defect is in sodium-hexose cotransporter in the intestinal and in renal brush border.A specific defect in intestinal absorption of glucose and galactose can be demonstrated by oral tolerance tests that produce absence of increase in plasma glucose or galactose. Active D-glucose and D-galactose transport is absent in affected children, and partial defect is present in their parents. Treatment with a glucose- and galactose-free diet leads to the resolution of symptoms in childhood. Fructose-containing or carbohydrate-free formulas are well tolerated. Although the basic transport defect is present throughout life, most patients show an improved tolerance for glucose and galactose with advancing age.

Few patients have renal glycosuria (type B renal glycosuria) at normal plasma glucose concentrations. Urinary glucose loss is not as severe as in isolated renal glycosuria.This finding suggests the presence of multiple glucose transport proteins in the kidney.In glucose-galactose malabsorption, transport of sugars in other tissues is normal, which suggests multiplicity and tissue specificity of hexose transporters.

DISORDERS OF FACILITATIVE GLUCOSE TRANSPORTERS

The influx and efflux of glucose in mammalian cells are mediated by five different facilitative glucose transporters (GLUT-1, 2, 3, 4, and 7). Mutations of gene for two of these transporters (GLUT1 and GLUT2) have been identified.Mutation in the gene encoding the ubiquitous GLUT1 transporter causes glucose-transporter protein syndrome. Patients with this disorder present with seizures, developmental delay, and microcephaly.They have normal blood glucose concentration but low glucose in their cerebrospinal fluid. GLUT1 is the predominant glucose transporter in the blood-brain barrier. This defect is expressed in other cells, such as erythrocytes and fibroblasts, but their energy requirements is less or they express additional glucose transporters.The treatment of this disorder is ketogenic diet to deliver alternative fuels to the brain.

Mutations in the GLUT2 transporter gene which is expressed mainly in liver, pancreatic β cells and in the basolateral membrane of gut and renal tubular cells have been identified in the autosomal recessive disorder Fanconi-Bickel syndrome.

Fanconi-Bickel Syndrome (due to defect in GLUT2) is characterised by proximal renal tubular dysfunction, impaired glucose and galactose utilisation which leads to accumulation of glycogen in liver and kidney.Patients present early in life with failure to thrive and polydipsia, with prominent glycosuria and aminoaciduria, rickets, fasting hypoglycemia with ketonuria, and prolonged postprandial hyperglycaemia and hyperlipidaemia. Patients typically have protuberant abdomen due to hepatomegaly and nephromegaly (because of accumulation of glycogen in hepatocytes and renal tubular cells). The prolonged post-prandial hyperglycaemia is due to decreased sugar uptake by the liver and defective insulin synthesis and

release by the pancreatic β cell. They may not develop diabetes because pancreatic β cells have alternative glucose transporters (GLUT1 and GLUT3) that can partially compensate for the absence of GLUT2 transporters.

Treatment

There is no specific treatment available for Fanconi-Bickel syndrome. Avoidance of galactose intake, replacement of the renal losses of water and electrolytes, vitamin D and diet rich in complex carbohydrates to prevent hypoglycaemia, as for patients with other glycogen storage diseases.

DEFECTIVE ANION TRANSPORT: CONGENITAL CHLORIDE DIARRHOEA (CHLORIDORRHOEA)

This is a rare, autosomal recessive disease caused by mutation in a chromosome 7 gene. The chloride/bicarbonate transport mechanism in the distal ileum and colon is defective causing severe watery diarrhoea, beginning at birth. Absence of chloride-bicarbonate ion exchange causes profound symptoms in fetus (polyhydramnios and absence of meconium). Watery diarrhoea is apparent on the first days of life. A hypokalaemic, hypochloraemic, hyponatraemic metabolic alkalosis develops with dehydration and secondary hyperaldosteronism. Faecal fluid contains an excess of chloride ion over the sum of the accompanying cations sodium and potassium(125 to 150 mEq/L). Faecal chloride concentration always exceeds 90 mmol/L when volume and serum electrolyte disturbances are corrected, and this chloridorrhoea is diagnostic. Renal chloride transport is normal. Decreased urine chloride results from the kidney's attempts to conserve salt and water. The defective gene in this condition, called *DRA* (for downregulated in adenoma), maps to chromosome 7q and encodes an anion transporter, which is expressed only in the gastrointestinal tract. A deletion of the Val 317 codon in the *DRA* gene is responsible for the Finnish form of congenital chloride diarrhoea.

Treatment consists of adequate, lifelong repletion of electrolyte and fluid. Correction of water, sodium chloride, and potassium chloride prevents growth and psychomotor retardation and the development of progressive renal damage. Treatment of hyperreninaemia and hypokalaemia with prostaglandin inhibitors reduces renal damage but does not alter intestinal symptoms or the need for chronic sodium chloride repletion. Omeprazole may decrease stool output and improve the social life of patients.

DEFECTIVE SODIUM TRANSPORT: CONGENITAL SODIUM DIARRHOEA

This is a rare syndrome caused by defect in sodium-hydrogen exchange in small intestine and colon. Similar to chloridorrhoea, patient presents with profuse watery, secretory diarrhoea from birth with history of polyhydramnios during pregnancy. But in contrast to alkalosis in chloride diarrhoea, acidosis is present here, and faecal chloride concentration is less than sodium concentration. Treatment with oral hydration fluid is effective in improving and maintaining growth.

PRIMARY HYPOMAGNESAEMIA

In this defective intestinal magnesium transport leads to severe hypomagnesaemia and even secondary hypocalcemic tetany in infancy. Other aspects of intestinal transport are normal. Treatment includes replacement of magnesium which need to continue indefinitely.

DEFECTIVE COPPER TRANSPORT: MENKES DISEASE (KINKY HAIR SYNDROME)

This is X-linked, multi-systemic disease disorder caused by defect in cellular copper transport affecting intestine as well other organs. Menkes gene is located on long arm of X-chromosome at Xq13.3. Orally ingested copper accumulates in intestine and there is defective absorption of copper. Patient presents with growth retardation, abnormal hair, cerebellar degeneration, severe vasculopathy, fractures and foetal outcome in early age. Serum level of copper and caeruloplasmin is low but copper content of cerebellum is increased. Available treatment options are few and include parental copper administration which can help few patients in avoiding neurological complications

A large number of membrane transport defects are genetically inherited. These cannot be described in this chapter but some of them are summarised in **Table 1**.

Table 1: Genetic Disorders of Membrane Transport

Class of Substance and Disorder	Substrates	Tissues Manifesting Defect	Molecular Basis	Clinical Features
Methionine malabsorption	Methionine	Jejunal mucosa	Methionine transport protein leading to Hydroxybutyricaciduria	White hair, mental retardation, convulsions, hyperpneic attacks, edema
Familial hypercholesterolaemia	Cholesterol	Fibroblasts, lymphoid lines, leukocytes	Membrane LDL-cholesterol receptor protein	Hypercholesterolaemia, tendon xanthomas, arcus corneae, coronary artery atherosclerosis
Defect in transport of long-chain fatty acids	Long-chain fatty acids	Liver	Fatty acid transporter	Nonketotic hypoglycaemia, acute liver failure
Hypouricaemia	Uric acid	Proximal renal tubule	Urate transport protein	Hypouricaemia, hyperuricosuria, hypercalciuria
Familial hypophosphatemic rickets	Inorganic phosphate	Proximal renal tubule, jejunal mucosa	Phosphate-regulator homologue to endopeptidases PHEX	Hypophosphataemia, phosphaturia, phosphatopaenic rickets/osteomalacia
Dent's syndrome, X-linked recessive hypophosphatemic rickets and nephrocalcinosis	Chloride, phosphate	Proximal renal tubule	Voltage-gated Cl^- channel CLCN5	Proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, rickets
Hypophosphatemic rickets with hypercalciuria	Phosphate	Renal tubule	Phosphate transporter	Hypophosphataemic rickets, hypercalciuria

Contd...

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Class of Substance and Disorder	Substrates	Tissues Manifesting Defect	Molecular Basis	Clinical Features
Bartter's syndrome	Sodium, chloride	Renal tubule	Na,K,2 ≥ Cl cotransporter, apical regulated K^+ channel, basolateral Cl^- channel	Hypochloraemic metabolic alkalosis, ATP-hypercalciuria, hyperaldosteronism
Gitelman's syndrome	Sodium, chloride	Distal convoluted tubule	Na^+/Cl^- cotransporter SLC12A3	Hypokalaemic metabolic alkalosis, hypomagnesaemia, hypocalciuria
Congenital myotonia	Chloride	Muscle	Cl^- channel CLCN1	Myotonia, muscle cramps
Pendred syndrome	Iodide, chloride	Thyroid, cochlea	Na^+-independent I^- and Cl^- transporter	Deafness, ± goiter
Cystic fibrosis	Chloride	Lung, pancreas, sweat gland	Ion channel protein	Pulmonary, pancreatic destruction
Distal renal tubular acidosis (type I gradient)	Chloride, bicarbonate	Distal renal tubule, erythrocytes	Anion exchanger SLC4A1	Hyperchloraemic acidosis, hypokalaemia, acquired nephrocalcinosis, hypercalciuria, elliptocytosis
Familial goiter	Inorganic iodide	Thyroid gland, salivary gland, gastric mucosa	Iodide transport protein	Congenital hypothyroidism (cretinism), goiter
Achondrogenesis type 1B, astelosteogenesis type 2, diatrophic dysplasia	Sulphate	Osteoblasts, chondrocytes	Sulphate transporter	Skeletal dysplasia, dwarfism, deformities
Proximal renal tubular acidosis (type II HCO_3^- wasting)	Hydrogen ion	Proximal renal tubule	Proximal tubule H^+ pump carrier protein	Hyperchloraemic acidosis, bicarbonate wasting
Distal renal tubular acidosis	Hydrogen ion	Distal nephron, cochlea	H^+ ATPase ATP6B1	Hyperchloraemic acidosis, growth retardation, sensineural deafness
Liddle's syndrome	Sodium	Collecting tubule	Epithelial Na^+ channel SCNN1 (activation)	Hypertension, hypokalaemia, metabolic alkalosis
Type I pseudohypoaldosteronism	Sodium	Collecting tubule	Epithelial Na^+ channel SCNN1 (inactivation)	Hyponatraemia, growth retardation, hyperkalaemia
Hyperkalaemic periodic paralysis, paramyotonia congenita	Sodium	Muscle	Muscle Na^+ channel a subunit SCN4A	Periodic paralysis, muscle wasting, variable myotonia
Darier disease	Calcium	Keratinocytes, muscle, brain	Sarcoplasmic Ca^{2+}-ATPase ATP2A2	Keratotic skin papules, bullous lesions, psychosis
Long QT syndrome	Potassium, sodium	Heart	Voltage-gated K^+ channels KCNQ1, KCNH2, KCNE2, Na^+ channel SCN5A	Syncope, arrhythmia, sudden death
Jervell and Lange-Nielsen syndrome	Potassium	Heart, inner ear	Voltage-gated K^+ channels KCNQ1, KCNE1	Syncope, arrhythmia, sudden death, deafness
Benign familial neonatal epilepsy	Potassium	Brain	Voltage-gated K^+ channels KCNQ2, KCNQ3	Neonatal convulsions normal development
Nephrogenic diabetes insipidus (AVP-resistant)	Water	Distal renal tubule	AVP receptor	Polyuria, polydipsia, hyposthenuria
Nephrogenic diabetes insipidus	Water	Collecting tubule	Aquaporin 2 (water channel)	Polyuria, dehydration, hyposthenuria
Juvenile pernicious anaemia	Cobalamin (vitamin B_{12})	Ileal mucosa	Receptor for intrinsic factor-cobalamin complex	Megaloblastic anaemia
Folate malabsorption	Folic acid	Small bowel	Folate transport protein	Megaloblastic anaemia
Rogers' syndrome	Thiamine	Ubiquitous	Thiamine transporter SLC19A2	Megaloblastic anaemia, diabetes, deafness
Glycogen storage disease type Ib	D-Glucose	Liver microsomes	Glucose-6-phosphate transporter	Hypoglycaemia, neutropaenia, glycogen storage disease

**Source:* Modified from *Harrison's Principle of Internal Medicine* 17 edition.

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18.10 Amyloidosis

Manisha Sahay

INTRODUCTION

Amyloidosis refers to the extracellular tissue deposition of protein fibrils. Types of amyloidosis are shown in **Table 1**.

Most common are primary or AL Amyloid and Secondary or AA amyloid. The ratio of AA to AL amyloid is 2:1.

Table 1: Classification of Amyloidosis

Type	Protein	Organs	Clinical Setting
Localised			
ACal	Calcitonin	Thyroid	Medullary carcinoma of thyroid
AIAPP	Amylin	Pancreas	Type 2 diabetes mellitus, Insulinoma
ANF	Atrial natriuetic factor	Heart	Isolated atrial amyloid
Aβ	Aβ protein precursor	Brain	Alzheimer's disease, Down's syndrome
APro	Prolactin	Pituitary	Prolactinoma
APrP	Prion protein	Brain	Scrapie, Creutzfeldt-Jakob Disease (CJD)
Senile			
ATTR	Transthyretin (wild type)	Heart	Senile cardiac amyloid
Systemic			
AA	Serum amyloid A	Kidneys liver, spleen	Inflammatory disease, infection, malignancy
AL	Light chain	Kidneys, heart, nerves	Multiple myeloma
AH	Heavy chain		Other plasma cell conditions
$A\beta_2M$	β_2 Microglobulin	Periarticular, ligaments	Long-term dialysis
Inherited			
AA	Serum amyloid A	Kidneys	FMF, Muckle-Wells, TRAPS
ATTR	Transthyretin (prealbumin)	Nerves, heart	Familial amyloid polyneuropathy
A Cys	Cystatin C	Cerebral arteries	Hereditary cerebral haemorrhage with amyloid (Icelandic)
Aβ	Aβ precursor protein	Cerebral arteries	Hereditary cerebral haemorrhage with amyloid (Dutch)
AGel	Gelsolin	Eyes, cranial, and peripheral nerves	Finnish type familial amyloidosis
AFib	Fibrinogen Aα	Kidneys, liver	Hereditary non-neuropathic amyloidosis
AApoAI	Apolipoprotein AI	Kidneys, liver	Hereditary neuropathic/ neuropathic
AApoAII	Apolipoprotein AII	Kidneys	Hereditary non-neuropathic amyloidosis
ALys	Lysozyme	Kidneys, liver	Hereditary non-neuropathic amyloidosis

FMF = Familial Mediterranean fever; TRAPS = Tumour necrosis factor receptor antagonist periodic syndrome.

Primary/AL Amyloidosis

All forms of systemic amyloidosis in which the fibrils are derived from monoclonal light chains or their fragments, e.g. multiple myeloma, are considered primary amyloidosis.

AA/Secondary/Reactive Amyloidosis

This occurs secondary to various diseases (**Table 2**). In the developing world, AA amyloidosis is common due to prevalence of chronic infections. The commonest cause being tuberculosis. In 5% cases, underlying cause remains obscure. Fibrils are derived from serum amyloid associated protein (SAAP) which increases in inflammation.

Table 2: Conditions Associated with AA Amyloidosis

Chronic inflammatory diseases
- Rheumatoid arthritis and juvenile chronic arthritis
- Ankylosing spondylitis
- Psoriatic arthritis
- Reiter's syndrome
- Behçet's syndrome
- Adult Still's disease
- Crohn's disease

Chronic infections
- Tuberculosis
- Leprosy
- Osteomyelitis
- Bronchiectasis
- Decubitus ulcers

Malignancies
- Hodgkin's lymphoma
- Castleman's disease
- Renal cell carcinoma
- Hairy cell leukaemia

Inherited
- Familial Mediterranean fever
- Muckle-Wells syndrome

Dialysis-Related Amyloidosis (DRA)

DRA is a disorder caused by tissue deposition of β2 microglobulin which is a component of human leucocyte antigen.

Hereditary amyloidosis is dominant disorder (**Table 3**).

Table 3: Hereditary Amyloidosis

Protein	Clinical Picture
Transthyretin	Peripheral and autonomic neuropathy + varying degrees of visceral involvement
Gelsolin	Cranial neuropathy,renal Corneal lattice dystrophy Distal peripheral neuropathy
Apolipoprotein AI	Renal, Gastric ulcers, Polyneuropathy
Apolipoprotein AII	Renal
Lysozyme	Renal
Fibrinogen Aα	Renal and hepatomegaly

Organ-specific Amyloid

Amyloid deposition can be isolated to a single organ, e.g.cerebral amyloidosis (**Table 4**).

Table 4: Cerebral Amyloidosis

Syndrome	Precursor Protein
Alzheimer's disease	
Sporadic	Aβ peptide
Familial	Aβ peptide
Associated with Down's syndrome	Aβ peptide
Cerebral amyloid angiopathy	Aβ peptide
Hereditary cerebral haemorrhage with amyloidosis	
Dutch	Aβ peptide
Icelandic	Cystatin C
Cerebral amyloid with Prion's disease	
Gerstmann-Straussler-Scheinker disease	Prion peptide
Prion protein cerebral amyloid angiopathy	
Fatal familial insomnia	
Kuru	
Cruetzfeldt-Jakob's disease	

Age-related (Senile) Systemic Amyloidosis

Deposition of otherwise normal (wild-type) transthyretin in myocardium and other sites has been referred to as systemic senile amyloidosis (SSA).

Familial Mediterranean Fever (FMF)

FMF is common in Jews.The gene is recessive and is located on the short arm of chromosome 16 (**Table 5**).

Table 5: Comparison of Hereditary AA Amyloidosis

	FMF	Muckle-Wells	TRAPS
Race	Jews, Armenians, Turks	North European	North European
Inheritance	Autosomal recessive	Autosomal dominant	Autosomal dominant
Chromosome	16	1	12
Gene/protein	MEFV*/ marenostrin	Cryopyrin	TNF** receptor
Duration of fever	2-3 days		3 days to 3 weeks
Clinical	Abdominal pain,	Urticaria,	Rash, features
arthralgia,	arthralgia,	abdominal	
	pleurisy,	progressive	pain,
rash	deafness	arthralgia,	
			conjunctivitis
Amyloid	Very variable	30%	25%
Treatment	Colchicine	None known	Prednisolone, etanercept

**MEFV = Mediterranean fever; **TNF = Tumour necrosis factor.*

PATHOGENESIS OF AMYLOIDOSIS

All amyloids have a common conformation of anti-parallel β-sheet when studied by radiographic diffraction. This is responsible for the characteristic staining with Congo red.

1. *Proteolysis:* In AL amyloid light chains are proteolysed. In AA amyloid AA protein is a fragment of the circulating acute phase reactant SAA which is synthesised by hepatocytes, macrophages and regulated by cytokines. SAA is an apolipoprotein and is chemotactic.
2. *Increased availability* due to decreased clearance of β2 microglobulin in renal failure and dialysis leads to tissue deposition (DRA).
3. *Mutation:* In all the familial forms of amyloidosis, several mutations can occur that renders the protein amyloidogenic.

Other Constituents

Amyloid deposits contain several other components e.g., serum amyloid P (SAP), collagen IV, laminin, fibronectin, sulphated glycosaminoglycans (heparin sulphate glycoprotein) and apolipoprotein E. SAP is a normal serum glycoprotein produced in the liver.

CLINICAL MANIFESTATIONS

Skin and cardiac involvement, macroglossia, and peripheral neuropathy are rare in AA amyloidosis. **Figure 1** shows rare tongue involvement in primary amyloidosis.



Figure 1: Serratoglossia in a case of primary amyloidosis.
Courtesy: Dr Pangtey GS, LHMC, New Delhi.

Renal Disease

Renal involvement is the most common and serious problem seen in 80% in AA amyloid. The majority of patients have glomerular deposits with proteinuria, microscopic haematuria and casts. Vascular deposits result in chronic renal insufficiency. Tubular deposits cause syndromes of renal tubular acidosis or nephrogenic diabetes insipidus. The kidney size may be increased or normal. Chronic kidney disease is an important cause of death.

Non-Renal Findings

Hypofunction of endocrine glands and cardiac involvement

Hypofunction of endocrine glands can lead to endocrine deficiency syndrome and can result in cardiac involvement. Cardiac manifestations include restrictive cardiomyopathy,

systolic or diastolic dysfunction, heart failure, arrhythmia, heart block or infarction due to accumulation of amyloid in the coronary arteries.

Gastrointestinal disease

Hepatomegaly, splenomegaly, functional hyposplenism, gastroparesis, constipation, bacterial overgrowth, malabsorption and intestinal pseudo-obstruction may be seen.

Neurologic abnormalities

Mixed sensory and motor peripheral neuropathy and/or autonomic neuropathy is a prominent feature in heritable and AL amyloidoses. Central nervous system involvement is unusual with AL and AA but is common in hereditary amyloidoses.

Musculoskeletal disease

Amyloid infiltration of muscles causes pseudohypertrophy and macroglossia (AL amyloid). Arthropathy occurs due to amyloid deposition in joints e.g. "shoulder pad" sign in AL amyloid and DRA. Spondyloarthropathy, carpal tunnel syndrome, cauda equina compression and cystic bone lesions may be seen in DRA.

Haematologic abnormalities

Amyloidosis may be associated with a bleeding diathesis due to factor X deficiency , decreased synthesis of coagulation factors in patients with advanced liver disease, amyloid infiltration of blood vessels or acquired von Willebrand disease. Anaemia occurs due to renal failure or multiple myeloma and thrombo-cytopaenia due to splenomegaly. *Pulmonary infiltration* may be seen.

Skin: waxy thickening, easy bruising, subcutaneous nodules and periorbital purpura (raccoon eyes) are characteristic of AL amyloidosis (**Figure 2**).



Figure 2: Smooth and waxy papules over eyelid and raccoon eyes in case of primary amyloidosis.
Courtesy: Dr Pangtey GS, LHMC, New Delhi.

FMF: Presents with attacks of fever, abdominal pain, arthritis of large leg joints and serositis. The attacks last 48 to 72 hours.

DIAGNOSIS

Urine examination

In AL amyloid due to multiple myeloma, the dipstick which primarily detects albumin is negative while sulphosalicylic acid test for protein is positive (Bence Jones proteinuria).

Complete blood picture

It may show plasma cells. High ESR may be seen in myeloma and secondary amyloid.

Biochemistry

Serum calcium may be high and alkaline phosphate may be normal in myeloma.

Imaging

X-rays show lytic bone lesions in myeloma. In DRA radiolucent lesions, or bone cysts are seen and tend to enlarge and increase in number over time.

Ultrasonography is useful in estimating renal size.

ECHO may show speckled appearance of the myocardium.

CT and MRI are useful for detection of small lesions and for lesions of the nonaxial skeleton.

Biopsy

The diagnosis of amyloidosis should be confirmed by tissue biopsy. The abdominal subcutaneous fat is sensitive site for all systemic amyloidosis except DRA. Aspiration biopsy of subcutaneous fat with Congo red staining and examination using polarizing microscopy has a sensitivity of 57% to 85% and a specificity of 92% to 100% for AL or AA amyloidosis. If fat aspiration is negative then rectal biopsy (sensitivity – 84%), bone marrow biopsy (sensitivity – 50% to 55%), or skin biopsy (50%) or biopsy of the involved organ is done.

Light microscopy reveals diffuse extracellular deposition of amorphous pink, hyaline material (haematoxylin and eosin). These nodules stain weekly with periodic acid Schiff's (PAS) and methenamine silver stain and bind Congo red (leading to green birefringence under polarized light) and thioflavine T (producing an intense yellow-green fluorescence. Incubation with permanganate causes the fibrils to lose their affinity for Congo red in secondary, but not in primary amyloidosis.

Immunofluorescence is negative for immunoglobulins in AA amyloidosis, but is positive for monoclonal lambda or kappa light chains in AL amyloid. False negatives with immuno-fluorescence occur in 25% to 3%. Here immunoperoxidase can be helpful.

Electron microscopy fibrils are 8 to 10 nm in width, straight and unbranching and randomly orientated with pentagonal amyloid P component.

Amino acid sequencing or mass spectroscopy is the most straightforward approach to characterising the type of amyloid.

SAP scanning: Scintigraphy with technetium or radioiodine-labeled serum amyloid P component (SAP) can identify distribution of amyloid.

Paraproteins: Serum and urine protein electrophoresis followed by immunofixation is recommended. Quantitation of serum free light chains is suggested for AL patients who do not have monoclonal proteins by immunofixation.

Bone marrow biopsy demonstrates a monoclonal population of plasma cells.

Beta2-microglobulin levels: In DRA, plasma β2-micro-globulin concentration may be 30 to 50 mg/L(normal- 0.8 to 3.0 mg/L).

Chromosomal changes: Various chromosomal abnormalities may be found.

Natural History

The long-term prognosis of untreated amyloidosis is poor with median survival 4 and 31 months from the time of diagnosis with a 5-year survival of 43%.

TREATMENT

Specific Treatment

AL amyloidosis

Colchicine marginally improves survival.

Cytotoxic therapy: Regimes include prednisolone and melphalan or vincristine, carmustine, melphalan, cyclophos-phamide and prednisolone (VBMCP). Intensive chemotherapy with stem cell transplantation may be more effective. Interferon has been used in some.

Thalidomide: has been used with some success in myeloma. Its use is being explored in AL amyloid.

AA amyloidosis

Current treatment strategy in AA amyloidosis is to eliminate the supply of the precursor protein (SAA) by suppressing the acute phase response.

1. Surgical resection of the underlying cause of amyloidosis e.g. amputation of limbs affected by osteomyelitis is useful.
2. Medical:
   (a) Alkylating agents are effective for chronic rheumatological conditions, e.g. chlorambucil, cyclophosphamide with prednisolone
   (b) In RA podophylotoxin, a microtubule antagonist, along with azathioprine, chlorambucil, and cyclophosphamide may be useful.
   (c) Dimethlysulfoxide (DMSO) has been shown to be effective in some.
   (d) TNF-α antagonists offer a new approach to the management.

DRA

Increased clearance of β2-microglobulin by prolonged slow dialysis with noncuprophane high flux dialyzers should be utilised in DRA. The pathogenic effects of glycosylated beta2-microglobulin may be prevented by aminoguanidine that inhibits advanced glycation.

Hereditary amyloidoses

Liver transplantation is curative. Patients who present with advanced end-organ damage may benefit from combined hepatorenal or hepatocardiac transplantation

FMF

Colchicine has proved to be remarkably effective.

Drugs which reduce fibril formation

For example, Odo-deoxydoxorubicin (I-DOX) and Carboxy-pyrrolidin-hexanoyl-pyrrolidone-carboxylic acid (CPHPC).

Renal replacement therapy for amyloidosis

The survival on dialysis and after transplant is poorer as compared to other patients.

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18.11 Disorders of Adipose Tissue and Obesity

Shashank R Joshi

INTRODUCTION

Obesity is a chronic and increasingly common disease globally characterised by excess body fat. It develops gradually and often persists throughout life. As a preventable cause of death, obesity is second only to smoking. Like any other chronic condition, such as diabetes or hypertension, obesity worsens when strategies applied for weight reduction are withdrawn. If it is not treated for the duration of the patient's life, obesity emerges as a potent co-morbid risk factor. Obesity has been described in *Charak Samhita*: *(Sutrasthana: Ch XXI v. 3-4)* in the context of body phenotypes with obese phenotype having the following 8 defects: shortening of lifespan, hampered movement, difficulty in sexual intercourse, debility, foul smell, over sweating, excessive much hunger, and excessive thirst. The rapid spread of urbanisation and industrialisation and dramatic lifestyle changes that accompany these trends has led to the pandemic of obesity, even in developing countries. Obesity has serious public health implications. Excess weight has been associated with mortality and morbidity.

PREVALENCE

Obesity is emerging as an important health problem in India. It is estimated that 22 million Indians are obese, especially abdominally obese. Obesity is the primary driver of non-communicable diseases like diabetes, cardiovascular diseases, disabilities like osteoarthritis and even cancer.

DEFINITION AND ASSESSMENT

In the past, visual inspection of a patient gave a subjective but fairly accurate estimate of the degree of obesity. Obesity is easily diagnosed using what has been called the eyeball test. 'If a person looks fat, the person is fat'. Presently, there are three commonly used objective methods of estimating obesity in clinical practice: (i) body mass index (BMI), (ii) waist-to-hip ratio (WHR), and waist circumference (WC) and (iii) fat distribution. The typical Asian Indian population has higher proportion of fat in their body composition which is now called the "thin, fat Indian" or the Y-Y paradox which illustrates that compared to white Caucasian and African Indians have more body fat for a given BMI. Due to this the BMI, WC, WHR norms for Asian Indian population have been re-worked out.

Body Mass Index

In 1998, the US National Heart, Lung and Blood Institute established guidelines to define 'overweight' and 'obesity' and now Indian guidelines have modified these values (**Tables 1 and 2**). The parameter used is BMI (also called Quetelet Index) and is calculated using the formula:

$$\text{BMI} = \frac{\text{Weight (kg)}}{[\text{Height (m)}]^2} = \text{kg/m}^2$$

Table 1: Classification of Overweight and Obesity by Body Mass Index (BMI) for Asian Indians

	Obesity Class	BMI (kg/m²)
Underweight		<18.5
Normal		18.5 to 22.9
Overweight		23.0 to 24.9
Obesity	I	25.0 to 29.9
	II	30.0 to 34.9
Extreme obesity (Moribund obesity)	III	≥35

Table 2: BMI cut-offs for Asian Indians. *According to WHO and IOTF guidelines

Body mass index
Overweight: 23 kg/m² (as opposed to 25*)
Obese: 25 kg/m² (as opposed to 30*)
Waist circumference
Measurement method to be clearly mentioned
Action level 1: 78 cm (M), 72 cm (F), to be further reached
Action level 2: 90 cm (M), 80 cm (F), accepted
Waist-to-hip ratio
0.88 (men), 0.80 (women)
This measure of abdominal obesity could be erroneous but some studies have shown it to closely correlate to coronary heart disease

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However, the drawback of the BMI method is that it does not account for weight distribution and lean body mass. Also, very muscular or very short individuals may be classified as obese when they are not.

Waist-to-Hip Ratio and Waist Circumference

The WHR provides information about the distribution of body fat. The desired WHR for men and women is less than 1.0 and 0.8, respectively. The waist circumference cut-offs for Indians are more than 80 cm for women and more than 90 cm for men.

Body Fat Distribution (Fat Phenotypes)

On the basis of distribution of body fat, obesity may be classified into android obesity and gynoid obesity. In android obesity, fat is deposited in the abdomen (above the waist i.e. apple-shaped bodies). Android obesity is also called as abdominal obesity or central obesity. In gynoid obesity, fat is collected on the hips and buttocks (below the waist or gluteo-femoral, i.e. pear-shaped bodies). Android obesity is associated with an increased risk of metabolic complications, such as coronary heart disease, diabetes mellitus, hypertension and dyslipidaemia while gynoid obesity makes the person more prone to mechanical disorders, such as varicose veins and disorders of the joints. Since men typically carry excess weight in the upper body and women in the lower body, men rather than women, should be targeted for weight reduction.

Waist circumference correlates well with abdominal fat content. In men, there is an increased risk if the waist circumference is 85 cm or more and substantial risk if it is 90 cm or more and for women, the figures are 80 cm or more, respectively.

Aetiology

Obesity is a multifactorial condition. The factors playing a role in eating and weight control include: genetic, cultural, socio-economic, behavioural, and situational. Metabolic, Physiological and now even Viral (adenovirus). Mostly obesity is primary, that is, no obvious cause exists other than an imbalance in energy intake and energy expenditure. When energy expenditure is less than energy intake, there will be weight gain. Other causes of obesity (though not common) include genetic alterations, endocrine diseases (including Cushing's syndrome, hypothyroidism and hypogonadism), drugs and neurological disorders. The endocrinopathies associated with obesity are Cushing's syndrome, hypothyroidism, insulinoma, craniopharyngioma, Turner's syndrome, male hypogonadism and polycystic ovarian syndrome. The genetic syndromes associated with obesity are Lawrence–Moon-Biedl (LMB), Prader-Willi, Alstrom, Carpenter, Cohen, Beckwith Wiedemann. The common medications which cause weight gain are given in **Table 3**.

Table 3: Common Medications Causing Weight Gain

Psychotropic medications
Tricyclic antidepressants
Monoamine oxidase inhibitors
Specific SSRIs
Atypical antipsychotics
Lithium
Specific anticonvulsants
β-adrenergic receptor blockers
Diabetic medications
Insulin
Sulphonylureas
Thiazolidinediones
Highly active antiretroviral therapy
Tamoxifen
Steroid Hormones
Glucocorticoids
Progestational steroids

Energy Equation in Obesity

To maintain a stable body weight, energy intake must be balanced by an equivalent amount of energy expenditure, as shown in the following equation:

$$\text{E-in} - \text{E-out} = \text{E-stored}$$

where, E-in represents energy intake, E-out represents energy expenditure, E-stored represents energy stored in the body.

Energy expenditure (E-out) involves several factors as shown in the following equation:

$$\text{E-out} = \text{RMR} + \text{EE-ACT} + \text{TEF}$$

where, RMR is the resting metabolic rate, EE-ACT is the energy expenditure associated with physical activity, TEF is the thermic effect of food.

The third component of energy expenditure is the thermic effect of food, which represents the energy expended in digesting, absorbing, interconverting, and storing ingested nutrients. Overall, the magnitude of the thermic effect of food is small (about 6% to 10% of total ingested energy). Both the amount and composition of food can affect the thermic effect of food. The energy regulation is controlled by the hypothalamic nuclei, viz. lateral hypothalamus controlling hunger and the ventromedial nuclei satiety (**Figure 1**).

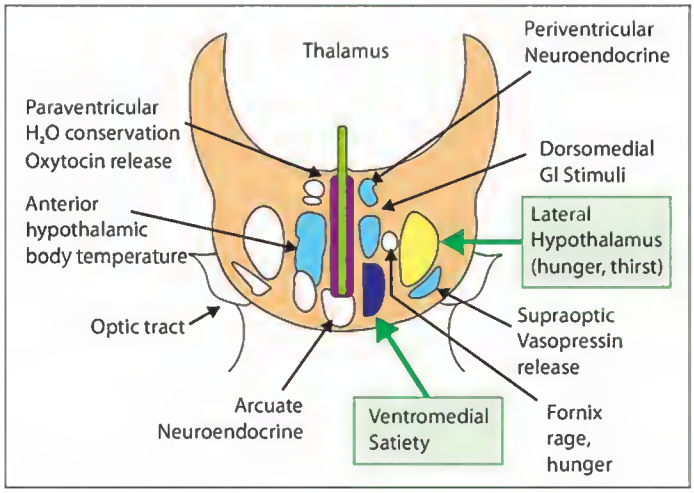


Figure 1: Role of hypothalamus in mediation of hunger and satiety.

GI = Gastrointestinal.

Goals of Weight Loss and Management

The overall goals of weight loss management are: to prevent further weight gain, to lose weight to achieve a realistic target BMI and to maintain a lower body weight over the long term (**Figure 2**). It is important that a realistic BMI rather than an ideal BMI should be aimed at in any weight loss programme. The initial goal of weight loss therapy is to reduce body weight by approximately 10% from baseline. If this goal is achieved, further weight loss can be attempted. A reasonable time period for a 10% reduction in body weight is 6 months of therapy. Not only are such reductions achievable, but importantly, modest losses of 5% to 10% of body weight has been shown to reduce health risks, such as hyperlipidaemia, hypertension and insulin resistance.

Modest reductions (5% to 10%) in weight and weight maintenance should be emphasised in any weight loss programme.

Strategies for Weight Loss and Weight Maintenance

Dietary therapy

The diet should be nutritionally adequate. It must be tailored to a person's tastes and habits. It should create a deficit of 500 to 1000 kcal per day. The fat content should be 30% or less of total calories. Emphasis should be on greater intake of fruits, vegetables and foods high in fiber. All crash diets for a few days or weeks are ineffective and are even harmful in long run. Satiety index is now used to frame modern weight loss diets. Sateity index is defined as a quantification of the duration of hunger suppression by a given amount of food (containing 1000 kJ), plus the amount voluntarily eaten when appetite returns. Protein is most satiating, followed by carbohydrates. Fat is poor at switching off appetite and very easy to store.

Exercise and physical activity

Sustained physical activity is most helpful in the prevention of weight regain. Most global guidelines recommend that adults

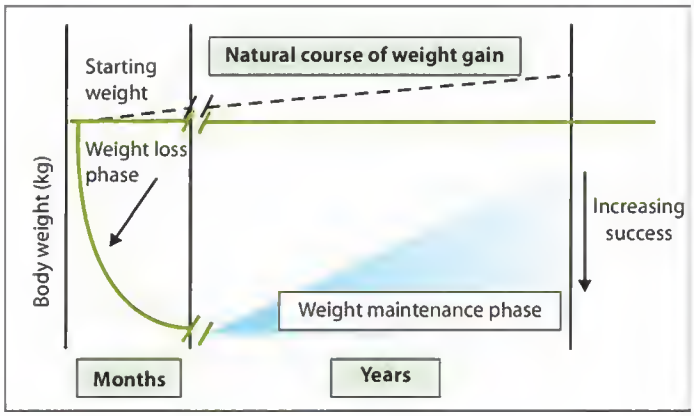


Figure 2: What is success in weight management?

participate in at least 30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week. Exercise should be initiated slowly, and the intensity should be increased gradually. The patient can start by walking 30 minutes for 3 days a week and can build to 45 minutes of more intense walking for at least 5 days a week. Exercise can be done all at one time or intermittently over the day. However, as Asian Indians have sarcopaenia and excess fat, the Indian guidelines for physical activity have been modified recently.

The Indian guidelines for physical activity are as follows: 'Physical activity is defined as any activity leading to calorie consumption'. Physical activity reduces risk for cardiovascular diseases, diabetes and other disabilities associated with obesity. Current recommendations on physical activity are being made to change the mindset of Indians so as to make them think of movement as an opportunity and not as an inconvenience. Action is needed at the individual, community and societal level to help Indians become more physically active. Work related activity should be encouraged wherever possible. Brisk walking is the preferred initial mode of exercise and does not require any special training or equipment. Brisk walking is defined as walking at an intensity wherein an individual finds speaking difficult but not impossible. The physical activity can be accumulated throughout the day in blocks as short as 10 minutes. Physical activity should be increased gradually over period of time. Dynamic yoga should be encouraged. Children should undertake at least 60 minutes of outdoor physical activity daily. Screen time (TV Television or Computer) should be less than 2 hours a day.

There is a dose-response relationship between physical activity and health, greater benefit is derived by exceeding minimum recommendations. For additional and more extensive health benefits, adults can increase their aerobic physical activity to 300 minutes (5 hours) a week of moderate-intensity, or 150 minutes a week of vigorous-intensity aerobic physical activity. Aerobic activity is a kind of physical activity in which the body's large muscles move in a rhythmic manner for a sustained period of time. Muscle strengthening activity causes the body's muscles to work or hold against an applied force or weight. Moderate physical activity are activities which lead to caloric consumption three to six times higher than basal levels (3 to 6 METs). Vigorous physical activity are activities which lead to caloric consumption more than six times higher than basal levels (>6 METs).

Behavioural therapy

Behavioural therapy forms the cornerstone of any weight loss programme. This includes food intake diaries wherein the patient records not only what and how much was eaten, but also where, with whom, how, their feelings are involved and their degree of hunger. These diaries are analysed periodically, and new modes of eating can be suggested, including not eating between meals, eating only three times a day, watching the portions of food eaten, and eating slowly with concentration. The situations that trigger eating can be avoided or controlled. Behavioural therapy is usually done in groups, with dialogue between the trained group leader (psychologist, nutritionist, physician), the other group members and the patient.

Drug therapy

Pharmacotherapy must be used in conjunction with diet and physical activity to achieve and maintain a realistic degree of weight loss. This is merely an adjuvant and most drugs are now banned except orlistat. Drug therapy should be considered for patients with a BMI greater than 27 kg/m^2 and associated obesity-related complications (i.e. hypertension, coronary heart disease, hyperlipidaemia, diabetes and sleep apnoea) or for those with a BMI greater than 30 kg/m^2.

The only approved drug for obesity is now orlistat which is a gastrointestinal lipase inhibitor (**Figure 3**). **Table 4** discusses the dosage, precautions, contraindications and side effects of the orlistat.

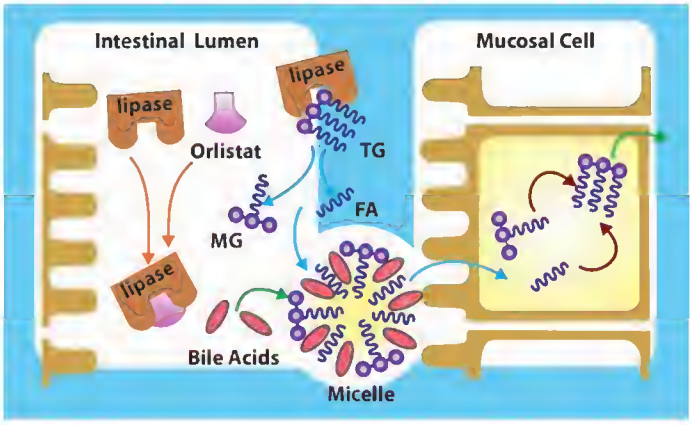


Figure 3: Orlistat prevents fat digestion and absorption by binding gastrointestinal lipases.

TG = Triglyceride; MG = Monoglyceride; FA = Fatty acid.

All other drugs which were available for obesity had or have been banned or have restricted use. Most recently sibutramine and rimonobant both have been withdrawn due to excess cardiovascular mortality and higher suicides, respectively. All the old appetite suppressants like adrenergic agents (e.g. amphetamine, methamphetamine, phenylpropanol amine, phentermine) as well as serotonergic agents (e.g. fenfluramine, dexfenfluramine, sibutramine) and thermogenic agents (e.g. ephedrine, caffeine) are all banned as they cause carcinoid related valvular heart defects and primary pulmonary hypertension. All forms of natural or alternative therapies are either hazardous, harmful or non-evident based with some questionable short-term data. The role of bariatric surgery is only restricted to morbid obesity with a BMI above 40 kg/m^2 and is currently experimental for all other indications. Surgery has no randomised controlled trials as well as long-term

evidence beyond two years and is only reserved for the severely obese morbid obese individuals. The Indian consensus on all therapies is given in **Table 5**.

Excess weight is definitely unattractive, but more importantly, it is a serious health hazard.

Table 4: Available Drug Options for Therapy: Precautions, Contraindications and Side effects

Drug	Class	Dose
Orlistat	Lipase inhibitor (Inhibits lipases, necessary for absorption of body fat)	60 mg or120 mg three times a day
Precautions		Should not be co-administered with cyclosporine
		Reduces absorption of fat-soluble vitamins. Hence, vitamin supplementation is recommended
		May increase levels of urinary oxalate. Hence it should be given with caution to patients with history of hyper-oxaluria or calcium oxalate nephrolithiasis
Contraindications		Hypersensitivity, chronic malabsorption syndrome or cholestasis
Side effects		Flatus with discharge, oily spotting, faecal urgency, fatty stools, faecal incontinence and increased defecation. These side effects increase when orlistat is taken along with a high fat meal.

Table 5: Obesity Treatment According to Body Mass Index

International (BMI)	25 to 26.9	27 to 29.9	30 to 34.9	35 to 39.9	>40
Asian Indians (BMI)	23+	25+	27+	32.5+	37.5+
Diet, Exercise, Behaviour	+	+	+	+	+
Pharmacotherapy*		With co-morbidities	+	+	+
Basic Surgery				With co-morbidities	+

*Can also be applied if waist circumference is 10 more than normal.
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CONCLUSION

Obesity is steeply increasing in India. Primary reasons are imbalanced foods and physical inactivity. Asian Indians have more body fat, more intra-abdominal and truncal subcutaneous fat and low muscle mass than white Caucasians; all conducive to the development of type 2 diabetes and cardiovascular disease. Morbidities occur at lower levels of BMI and WC in Asian Indians. Revised guidelines of BMI and WC mean that additional 15% additional population would be diagnosed as overweight/obese. More aggressive and early intervention according to revised guidelines will result in prevention of diabetes and reduction of epidemics of diabetes and CVD in Asian Indians.

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18.12 Metabolic Syndrome

Anoop Misra

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD) are important non-communicable diseases (NCDs) in developed, as well as developing countries. Asian Indians have an unusually high predisposition to develop both these NCDs. During the previous three decades, the prevalence of T2DM has doubled in India. Insulin resistance and clustering of other proatherogenic factors, which are frequently seen in Asian Indians, may be principal contributory factors for high prevalence of T2DM.

DEMOGRAPHIC, NUTRITIONAL AND LIFESTYLE TRANSITION IN INDIA

Important demographic and economic changes are occurring in South Asia. The life expectancy and the percentage of the elderly population have increased. Increasing migration from villages to cities, urbanisation and mechanisation have increased. All these factors have brought forth adverse lifestyle changes, such as nutritional imbalance, physical inactivity, stress, and increased consumption of alcohol and tobacco, leading to obesity, insulin resistance and metabolic syndrome. A complex array of factors leads to the metabolic syndrome in Asian Indians (**Table 1**).

Insulin Resistance and the Metabolic Syndrome: Epidemiological Data

Inordinate high prevalence of cardiovascular risk factors, their clustering, and high mortality due to CHD in South Asians was initially reported from UK in 1980s. Particularly abdominal obesity, hyperinsulinaemia and dyslipidaemia in South Asians were significantly more than British Caucasians. In particular, low HDL-C levels and hypertriglyceridaemia were prevalent in both genders and abdominal obesity was particularly prevalent in women. Overall, prevalence of the metabolic syndrome in migrant South Asians varies from 20% to 32% (**Table 1**).

Table 1: Associations of Insulin Resistance and Other Cardiovascular Risk Factors in South Asians

Factors With Evidence of Positive Association	Factors With Weak/No Evidence of Association
Excess body fat	C-reactive protein
Abdominal obesity	Intramyocellular triglycerides
High truncal subcutaneous fat	Leptin
Low birth weight	
High levels of procoagulant factors	

Prevalence of the metabolic syndrome as defined by the National Cholesterol Education Programme, Adult Treatment Panel III (NCEP, ATP III) and other criteria indicates ranges from ~11% to ~41% in India. While these studies show high prevalence of the metabolic syndrome in Asian Indians living in India, truly representative data from all regions of India are not available.

Definitions of the Metabolic Syndrome

The NCEP, ATP III and International Diabetes Federation (IDF) definitions of the metabolic syndrome is based on simple clinical and biochemical parameters, which could be measured in any clinic or a simple laboratory. Other available definitions of the metabolic syndrome include measures which are expensive and difficult to analyse; fasting hyperinsulinaemia, microalbuminuria etc.

The metabolic syndrome is mostly defined by modified criteria; central obesity (defined as waist circumference (WC) ≥90 cm for males and ≥80 cm for females, raised triglyceride (TG) levels: ≥150 mg/dL or on specific treatment for this lipid abnormality; reduced high density lipoprotein (HDL): less than 40 mg/dL in males and less than 50 mg/dL in females or on specific treatment for this lipid abnormality; raised blood pressure (BP): systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or on treatment of previously diagnosed hypertension; and raised fasting plasma glucose (FPG) ≥100 mg/dL or previously diagnosed diabetes. Three out of five criteria have to be present to define the metabolic syndrome.

Body Fat Distribution of South Asians: Relationship with Insulin Resistance and Other Cardiovascular Risk Factors

Excess body fat

Several distinctive features of body composition of South Asians have been recorded. Most investigators agree that South Asians have high percentage of body fat. For example; despite lower average body mass index (BMI) value, the migrant Asian Indians have higher percentage of body fat as compared to white Caucasians and Blacks.

Abdominal obesity

High prevalence of abdominal obesity is particularly the characteristic of the South Asians and uniformly recorded by several investigators. Abdominal adiposity has also been reported in those with a BMI less than 25 kg/m^2. Further, although the average WC in South Asians appears to be lower, abdominal adiposity is significantly more than the white Caucasians.

Truncal subcutaneous fat

A particularly distinctive body composition feature seen in South Asians is thick subcutaneous adipose tissue as highlighted by the investigators who used skinfold measurements in their investigations.

Other Insulin Resistance-associated Factors in South Asians (**Figure 1**)

High procoagulant tendency (high levels of plasminogen activator inhibitor-1, fibrinogen etc) has been demonstrated in South Asians with insulin resistance and other cardiovascular diseases. Low adiponectin levels have been reported in children, as well as in adults with insulin resistance and metabolic syndrome. Other associations include high levels of high-sensitivity C-reactive protein and pro-inflammatory cytokines (tumour necrosis factor-α and interleukin-6), impaired flow-mediated, endothelium-dependent dilatation, polycystic ovarian syndrome, high levels of non-esterified fatty acids and high oxidative stress.

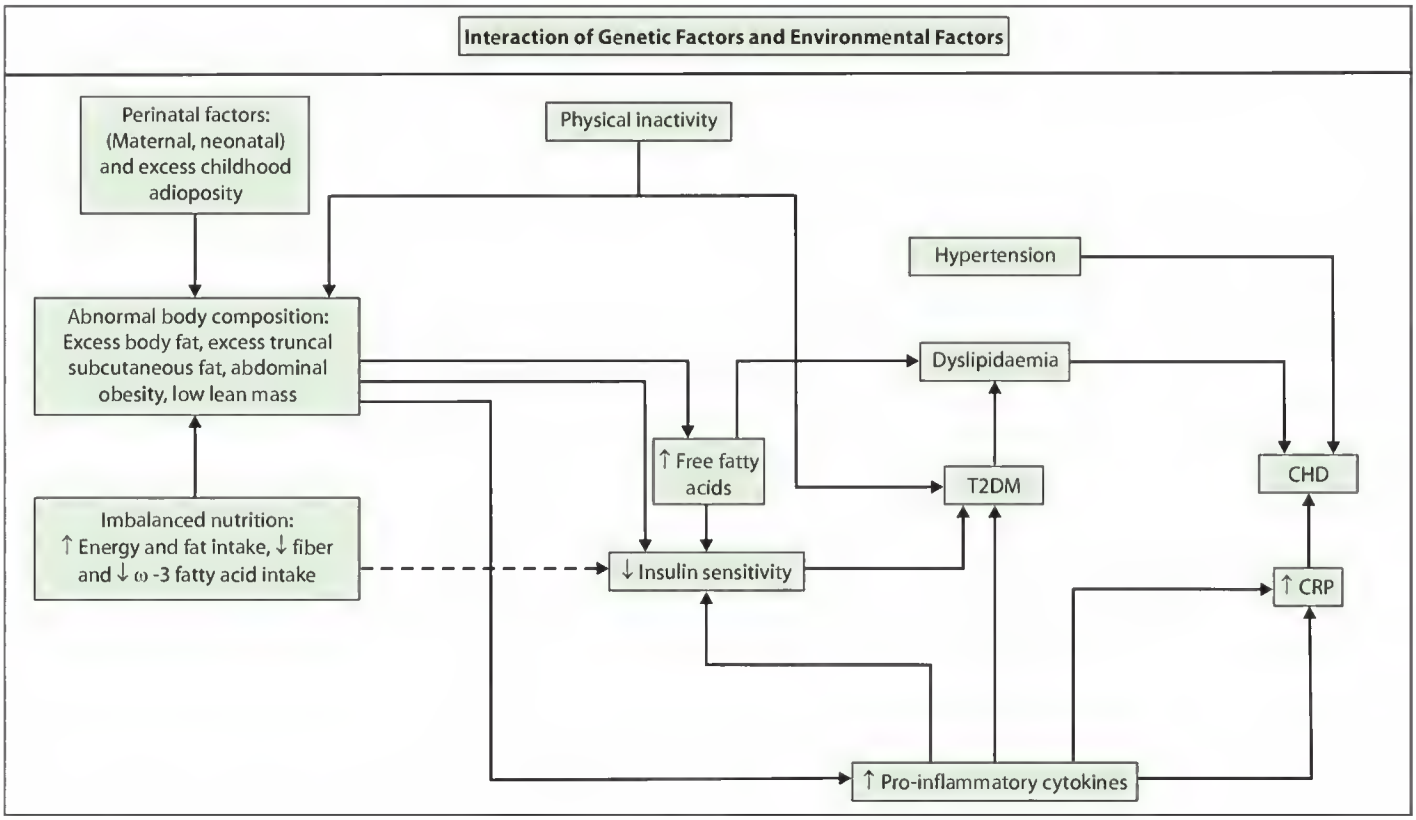


Figure 1: Complex interactions of genetic, perinatal, nutritional and other acquired factors in the development of insulin resistance, T2DM and CHD in Asian Indians.

T2DM = Type 2 diabetes mellitus; CRP = C-reactive protein; CHD = Coronary heart disease.

Prevention and Control of the Metabolic Syndrome in Asian Indians

1. Intensive efforts should be made to make South Asians aware that they are at more risk for the development of T2DM and CHD.
2. The preventive measures should be particularly vigorous for those with the family history of T2DM or premature CHD.
3. The therapeutic lifestyle changes should be encouraged from the childhood. Regular physical activity should be advised and television and internet usage should be restricted.
4. Body weight and anthropometric indices should be maintained within normal limits. The physicians should be made aware that these provisional limits for defining normal BMI and WC might be revised in the future.
   (a) Based on the recent data, and provisional recommendations of World Health Organization, BMI should be maintained between 19 to 23 kg/m^2.
   (b) The WC should be maintained below 90 cm for men and 80 cm for women.
5. Overweight individuals and those with abdominal obesity should be actively managed to lose weight by lifestyle measures.
6. Detection of one component of the metabolic syndrome should lead to search for the other components and its management.
7. Currently, no drug (e.g., metformin) is recommended for the management of insulin resistance and the metabolic syndrome. However, these guidelines may change in future, particularly for those who have prediabetes.
8. Adequate nutrition during the intrauterine period should be given to prevent early-life adverse events, which may promote insulin resistance in adulthood.
9. Research on insulin resistance and the metabolic syndrome in South Asians should be targeted on the following:
   (a) Prevalence of metabolic syndrome in various South Asian countries,
   (b) Aetiological factors of insulin resistance, particularly genetic studies,
   (c) Associations of specific macro- and micro-nutrients in South Asian diet with insulin resistance (e.g., omega-3 polyunsaturated fatty acids and dietary fibre),
   (d) Relationship with novel cardiovascular risk factors (e.g., C-reactive protein),
   (e) Intervention with insulin-sensitizers and other drugs,
   (f) Prevalence of the metabolic syndrome and morbidity correlation in children,
   (g) Best methods of imparting lifestyle and diet-related health messages in children, and
   (h) Increasing awareness of ill effects of the metabolic syndrome in populations.
10. Finally, the National Control Programmes for diabetes and cardiovascular diseases should be adequately strengthened and modified in view of the recent knowledge and guidelines.

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Section 19

Nephrology

Section Editor: Vinay Sakhuja

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19.1 Kidney—Structure and Functions

Sanjay K Agarwal

Kidneys are paired intra-abdominal organs lying opposite the upper lumbar vertebrae, and weigh 150 g each. Each kidney has an outer layer, the *cortex*, and an inner layer, the *medulla*. Both abut on to the renal pelvis; the cortex sends down columns of cortical tissue (columns of Bertin) separating the medullary pyramids (**Figure 1**). There are about 8 to 18 medullary pyramids in each kidney. They terminate in the papillary tips, which project into the calyces. The hilum of the kidney takes the vasculature to and from the kidney along with its draining system, the pelvis and ureter. The vein is the most anterior and the ureter is most posterior of the three structures. The renal arteries are frequently multiple with up to 25% persons having more than one renal artery on each side.

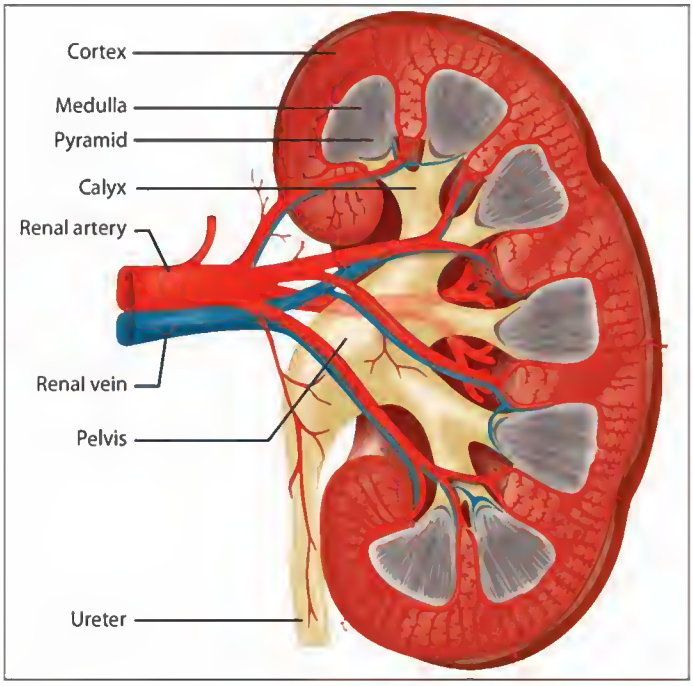


Figure 1: Cross section of kidney depicting major structures.

The renal arteries break up into arching branches known as *arcuate arteries,* which run at the cortico-medullary junction and are end-arteries, anastomosing solely through capillary channels. The *interlobular arteries* branch off the arcuate arteries and run at right angles towards the renal capsule, and branching again at right angles into afferent arterioles supplying the glomeruli; some branches go down into the medulla, first passing through the juxta-medullary glomeruli and then becoming large straight vascular channels known as '*vasa recta*' which pass down into the depths of renal pyramids (**Figure 2**). Then they bend back up to reach the arcuate veins at the cortico-medullary junction. The tips of the papillae have a special arterial supply of their own from the 'spiral arteries', branches of the interlobular arteries in the pelvis of the kidney. The afferent arterioles break up into 20 to 40 capillary loops in

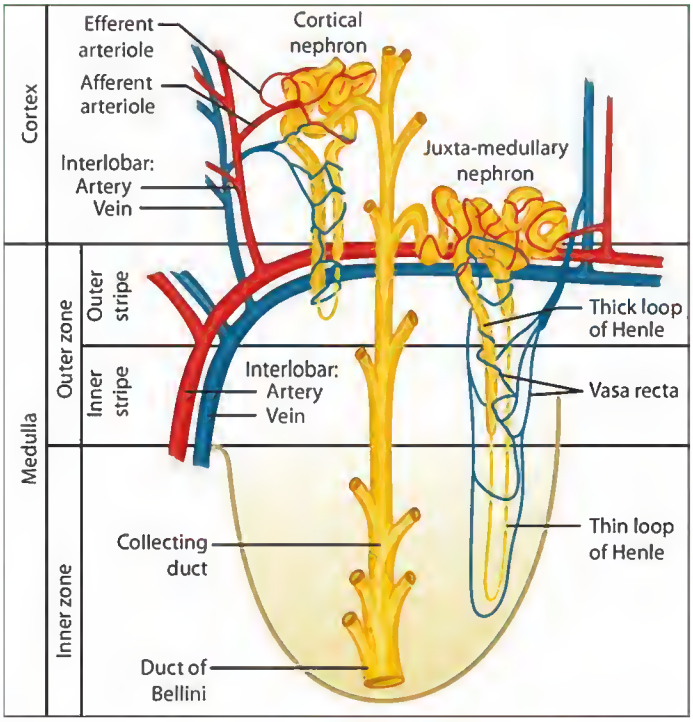


Figure 2: Distribution of renal circulation.

each glomerulus, which rejoin to form the efferent arterioles. This then splits up again to form a second capillary network, which surrounds the tubules, both proximal and distal; this network itself empties into interlobar veins.

The anatomical and functional unit of the kidney is the nephron. This consists of a glomerulus with proximal convoluted tubules (PCT), loop of Henle (LOH), distal convoluted tubules (DCT) and collecting ducts (CDs) (**Figure 3**). There are approximately 1 million nephrons in each kidney. The majority of glomeruli are in the cortex. The PCT, DCT and blood vessels constitute the bulk of the non-glomerular cortical tissue. The medulla is composed of some LOH, vasa recta and a mass of CDs. This is an important structure responsible for the water conservation.

Bowman's capsule is a specialised invagination of the PCT and is lined by parietal epithelial cells (PEC) which are flatter and less noticeable than the larger, pale staining visceral epithelial cells (VEC) which line the outer side of the capillary tuft. Electron microscopy of the glomerulus reveals that the VEC do not lie in close opposition to the glomerular basement membrane (GBM); extension of the cytoplasm of the cells, called 'foot process', come into contact with the GBM at intervals leaving many areas of the GBM surface free of the epithelial cell contact. These areas have a mean width of 240 A° and are known as 'slit pores'. The main filtration barrier is the GBM, consisting of a ramification of fibres with a mean diameter of lumen between the fibres of 52 A°.

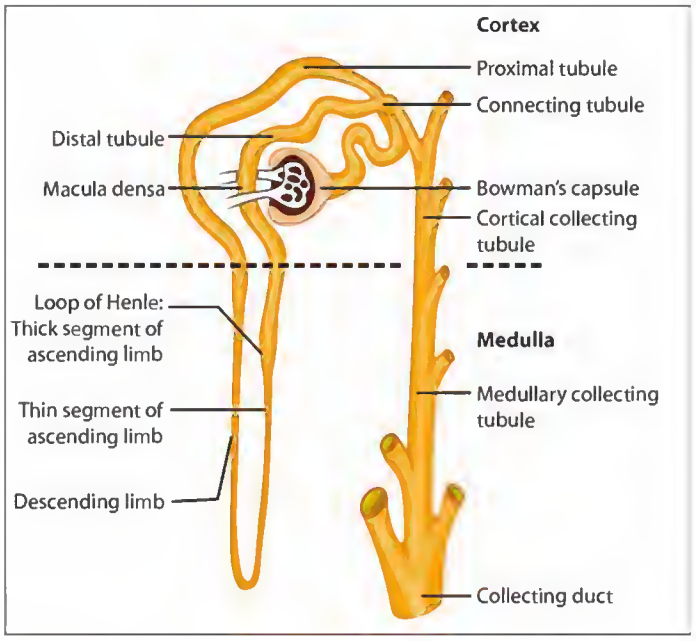


Figure 3: Various parts of the nephron.

The GBM (**Figure 4**) runs through all the capillary walls, sandwiched between the foot processes of the VEC on the one side and the endothelial cells of vessels on the other side. It is continuous with the basement membrane of the tubules. Its thickness is 3000 A° in humans. Capillary walls are lined by endothelial cells, which lie on the basement membrane from the inner side. There are fenestrations in between the endothelial cells. They are closed by a diaphragm. The endothelial cells of the glomeruli are continuous with the endothelial lining of the afferent and efferent arterioles. Studies of hereditary proteinuric syndromes have highlighted the presence of various transmembrane proteins (nephrin, fatty acid transporter tumour suppressor homolog-1 (FAT1), and FAT2, podocin and CD2-associated protein (CD2AP) that participate in the formation of the slit diaphragm (SD), which is important in preventing protein leakage. Slit diaphragms are firmly attached to the actin cytoskeleton through linker proteins, including the catenins, zona occludens 1 (ZO-1), CD2AP, and Nck,

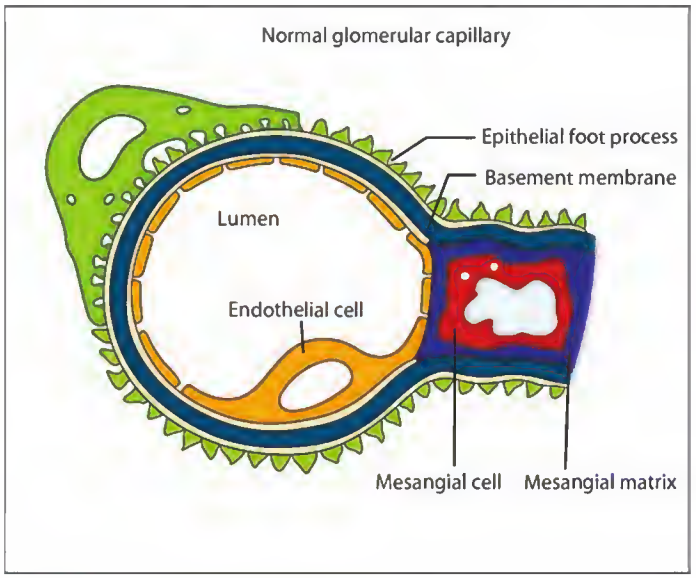


Figure 4: Glomerular basement membrane and its components.

which likely explains why genetic defects altering SD structure and function are usually associated with actin cytoskeleton re-organisation and foot process effacement.

At the point where the DCT are in contact with the afferent arteriole, the latter contains the juxta-glomerulus apparatus (JGA), a series of granular cells believed to be the source of the enzyme 'renin'. The efferent arteriolar wall is composed of smooth muscle with an endothelial lining. The structure of peritubular capillaries is such as to promote ready exchange of materials between the tubular cells and capillaries. The PCT are confined to the cortex of the kidney; these connect the glomerulus proximally with the descending limb of LOH. LOH is shaped like a 'U' tube connecting PCT and DCT, dipping down a variable distance into the medulla.

There is no clear-cut place where thick ascending limb of LOH becomes DCT. The epithelium of DCT is columnar and the surface being covered with numerous microvilli. As the CDs are approached the cell height becomes smaller, giving way to the cuboidal cells of the CDs. At the site where DCT approaches the vascular pole of the glomerulus, the nuclei of the epithelial cells become crowded, come closer and appear darker staining than in other part of DCT. This hypernuclear area is known as *'macula densa'*. The cortical collecting ducts (CCDs) are a continuation of the DCT. These run into medullary collecting ducts. Medullary collecting duct cells have a cuboidal shape; have light cytoplasm and relatively few mitochondria. They in fact resemble 'light cells' of CCDs. The collecting ducts run into the 'papillary ducts of Bellini'. In the papillary ducts, the cells are columnar in shape, have a basal nuclei and few mitochondria. The ducts of Bellini join the renal pelvis, which is covered with transitional epithelium.

FUNCTIONS OF KIDNEY

The kidneys maintain the internal environment within narrow limits in spite of great variation in intake and metabolic activity. The main functions of the kidney are regulation of body water, electrolytes, acid base balance, excretion of nitrogenous waste products, drugs and poisons, regulation of blood pressure, erythropoietin production and control of vitamin D metabolism.

Glomerular Filtration

The glomeruli filter about 180 litres of fluid each day although only approximately one and a half litres is passed as urine. Glomerular filtration rate (GFR) is defined as the amount of plasma being filtered by the glomeruli per minute. The normal GFR in Indians is approximately 75 to 79 mL/min/1.73m^2. In women, the figure is slightly lower. GFR is determined by: (1) sum of hydrostatic and colloid osmotic forces across the glomerular capillary membrane which gives the net filtration pressure; and (2) glomerular capillary ultrafiltration coefficient Kf.

Tubular Handling

The permeability of solutes across the tubules is determined by their lipid solubility and membrane pores. Pores which handle the transfer of water are called aquaporins. There are many types of aquaporins though the two important types are, aquaporin-1 (AQP1), which is found in the PCT, descending limb of the LOH, and vasa recta and aquaporin-2 (AQP2), localised to the apical membrane of the CCT and connecting tubule. Not

only does AQP2 provide the necessary pathway for water permeation that is regulated by ADH-dependent trafficking to the apical membrane, but it also has an immeasurably low permeability to urea and ions even as small as H_3O^+ or H^+.

Tubular Reabsorption and Secretion

Reabsorption can be an active process, transport against the electrochemical gradient or a passive process with transport along the electrochemical gradient. Active transport energy is provided by the action of appropriate enzymes inside the tubular cells. Being an active process, there is a limit to the maximum amount transported, which is called tubular maximum (TM). Glucose is competitively reabsorbed in the proximal tubules along with xylose, fructose and galactose. Similar to glucose, amino acids are also absorbed in the proximal tubules. Glycine, arginine and lysine have TM but many others like histidine, methionine, tryptophan, leucine and phenylalanine have very efficient reabsorption mechanism without a measurable TM. There are enzymes involved in tubular secretion with a TM of some of the substances. In addition to para-aminohippuric acid, renal tubules secrete radio-contrast media, phenol red, penicillins, probenecid and many other drugs. Many of the substances being secreted from the tubules share common mechanisms and compete with each other.

REGULATION OF BODY WATER

Water filtered from the glomerulus is 180 litres per day of which about 99% is reabsorbed. Most of it is absorbed passively in proximal tubule with sodium (**Figure 5**). Tubular fluid remains isotonic in the PCT. What happens in LOH and beyond depends upon the presence and concentration of anti-diuretic hormone (ADH). If ADH is low/shut-off, water passes through the thin part of LOH but not through the thick part of LOH. The urine in DCT is hypotonic and in the absence of ADH, urine remains dilute as it passes down in the CD. The water channel responsible for the high water permeability of the luminal membrane in response to vasopressin in aquaporin-2(AQP2). The AQP3 and AQP4 are located on the basolateral membranes and are probably involved in water exit from the cell.

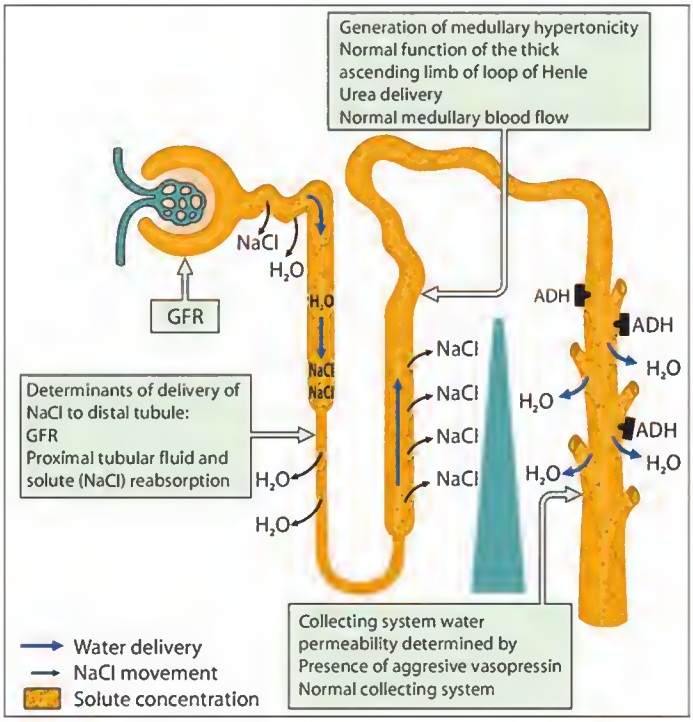


Figure 5: Salt and water handling by the tubules.

During water deprivation, the solute content of medulla is much higher than that of the cortex. Solute content increases progressively as we approach the inner medulla. Osmolarity of tissue at inner medulla is same as that of urine passed while the osmolarity of cortex is same as that of plasma. Urine in CD is also hyperosmolar. The mechanism which accounts best for the phenomenon of urine concentration, is that of *'counter-current multiplier system'*. The capillary loops of the medulla have comparatively low blood flow, and the exchange of gases and solutes occurs between the arterial and venous limbs working as a *'counter-current exchanger'*. Conserving a high content of solute and carbon dioxide (CO_2) in the deeper zones of medulla. The LOH is the site of the counter-current multiplier system.

Another important issue is the concept of 'free-water'. Free water clearance (C_{H_2O}) is the volume of blood plasma that is cleared of solute-free water per unit time. Values less than zero imply that the kidney is conserving water resulting in the production of concentrated urine. Since urine flow is determined by the rate at which plasma is cleared of solutes and water (as discussed above), urine flow (V) is given as the sum of osmolar (C_{osm}) and free water clearance (C_{H_2O}) :

$$V = C_{osm} + C_{H_2O}$$

Since osmolar clearance is given as the product of urine flow rate and the ratio of urine to plasma osmolality, this is commonly represented as

$$C_{H_2O} = V - \frac{U_{osm}}{P_{osm}} V$$

HANDLING OF SMALL IONS

In the initial part of the proximal tubule, 60% of filtered sodium is actively reabsorbed. This is an *isosmotic reabsorption*. About 25% sodium reabsorption occurs in the thick ascending limb of LOH through the apically expressed sodium-potassium-chloride co-transporter (NKCC2), which uses the sodium gradient across the membrane to transport chloride and potassium into the cell. Sodium leaves the cell actively through the basolateral sodium–potassium ATPase (Na-K-ATPase). In contrast, chloride diffuses passively through two basolateral chloride channels, ClC-Ka and ClC-Kb. Distal tubular reabsorption of sodium occurs both in the DCT and in the CD. Sodium reabsorption is dependent on aldosterone, and corticosteroid, which cause an increase in sodium reabsorption and various natriuretic factors. The mechanism of absorption of sodium in the ascending LOH is by means of a sodium pump located in the tubular cells. The 'sodium pump' is thought to receive energy by the conversion of ATP to ADP. Na-K ATPase carries out this conversion.

Potassium is reabsorbed and secreted by the renal tubule. More than half of filtered potassium is passively reabsorbed by the end of the PCT. Potassium is then added to tubular fluid in the descending limb of LOH. The major site of active potassium reabsorption is the thick ascending limb of the LOH, so that, by the end of the DCT, only 10% to 15% of filtered potassium remains in the tubule lumen. Potassium is secreted mainly by the principal cells of the CCD and outer MCD. Potassium reabsorption occurs via the intercalated cells of the MCD.

ACIDIFICATION OF URINE

Acidification of the urine is closely related to bicarbonate reabsorption. Large amounts of hydrogen ion are being secreted into the proximal tubule. Secretion of hydrogen removes most bicarbonate from the proximal tubular fluid. The hydrogen ion coming from the tubular cells is exchanged for sodium ions. The source of the hydrogen ion is carbonic acid. The bicarbonate ions inside the cells, together with sodium ions, enter the interstitial fluid and then the peritubular capillaries. Carbonic anhydrase (CA) inside the cells causes a very rapid combination of water and CO_2 to form carbonic acid. In the tubular lumen, CO_2 produced by the action of hydrogen ion on bicarbonate can diffuse rapidly into the tubular cells. Hydrogen ion also combines with buffers, and with ammonia to form ammonium ion. A little hydrogen ion remains free in solution. The combination of hydrogen ion with buffer is measured as 'titratable acidity.' This is defined as the amount of alkali in mEq required to titrate the urine to a pH of 7.4. In the distal tubule, phosphate and creatinine are the two most important buffers. Ammonia, which is produced by mechanisms in the tubular cells, diffuses into the tubular urine where it reacts with free hydrogen ion to form ammonium ion (NH_4^+). This NH_4^+ cannot diffuse freely back through the tubular cell wall and so urinary ammonium ion is a measure of part of hydrogen ion secretion.

EXCRETION OF WASTE PRODUCTS

Urea Handling

The kidneys excrete urea entirely by means of glomerular filtration. Half the filtered urea is reabsorbed by the tubules. Urea contributes to the high medullary osmolality during the formation of concentrated urine. About 40% to 50% of the filtered urea diffuses out of the proximal tubule by a passive process. In the descending LOH, urea enters the tubular fluid from the medullary interstitium and CD, so that by the time the DCT is entered the tubular fluid once again contains an amount of urea equal to that present in the glomerular filtrate. As the tubular fluid passes down the CD, a large amount of urea is lost into the medullary interstitium. In the presence of vasopressin, the DCT and CD have an increased permeability to urea so that when concentrated urine is being formed an increased amount of urea diffuses into the medullary interstitium so increasing its osmolality, and thus extracts water from the LOH.

Creatinine Handling

Creatinine, a breakdown product of muscle metabolism is excreted primarily by glomerular filtration. It is related mainly to an individual's muscle mass. As it is not significantly handled by tubules, creatinine is useful for making an estimation of GFR, though in many situations it is not critically reliable. However, it is definitely much better than urea.

EXCRETION OF DRUGS AND POISONS

The kidneys share with the liver the important job of disposing of drugs and poisons. Water-soluble drugs are primarily excreted in the urine. Kidneys are peculiarly vulnerable to toxic damage for two main reasons. First, they have a very rich blood supply in proportion to their weight, and secondly, excretion involves concentration of drugs in the renal tubules. This is why the renal tubules tend to take the brunt of the damage. In patients with kidney damage drugs excreted by the kidneys must be given with extreme caution because inadequate excretion can cause toxic blood levels; and the high blood levels in turn may be toxic to the kidneys.

REGULATION OF BLOOD PRESSURE

Hypertension is more common in glomerular than in tubulo-interstitial diseases. A well-known cause of renovascular hypertension is renal artery stenosis. A hormone called renin is manufactured in the kidneys by juxta-glomerular cells. Renin acts on angiotensinogen to ultimately produce angiotensin II, which has a vasoconstrictor effect on blood vessels. The kidneys of patients with essential hypertension excrete normal amounts of salt and water at higher-than-normal renal perfusion pressures.

CONTROL OF ERYTHROPOIESIS

The cells producing erythropoietin in the kidney are peritubular fibroblasts in the renal cortex. Erythropoietin concentrations are decreased or increased under a variety of conditions largely reflecting alterations of oxygen delivery to tissues. In addition to changes in oxygen delivery, some metabolic factors also influence erythropoietin production. In a somewhat simplified way, it is those conditions of reduced oxygen supply and increased oxygen demand that lead to increased circulating erythropoietin concentrations, whereas decreased concentrations are typical of conditions with increased oxygen supply or reduced oxygen demand.

CONTROL OF VITAMIN D, CALCIUM AND PHOSPHATE METABOLISM

Vitamin D is converted into its active 1,25 dihydroxyvitamin D in the proximal tubule by the enzyme-1α hydroxylase. Other than calcium, serum PO_4 excretion stimulates the activity of this enzyme. In addition, kidneys also control calcium and PO_4 excretion. After filtering at glomerulus, 60% to 70% of Ca is absorbed from PCT; 80% passive and 20% active. Ca is further reabsorbed in small amounts within the medullary segment of the TALOH. Active transcellular Ca transport can be stimulated by both parathyroid hormone (PTH) and active vitamin-D in the cTAL. In the early DCT, thiazide-activated Ca transport occurs. At DCT also Ca reabsorption is regulated by PTH and $1,25(OH)_2D_3$. About 10% of the filtered Ca is reabsorbed in the DCT, with another 3% to 10% in the connecting tubule (CNT) by way of mechanisms similar to those in the DCT.

Most of the inorganic PO_4 is filtered at glomerulus and 80% to 90% is reabsorbed in the PCT by way of a sodium gradient-dependent process (Na-Pi cotransport) and the rest is excreted in the urine. Most of the dietary, hormonal and metabolic factors that regulate renal tubular PO_4 reabsorption modulate the PCT expression of the type II Na-Pi cotransport protein. Some amount of filtered PO_4 is also reabsorbed in distal segments of the nephron.

CONCLUSION

Kidney is a complex, but vital human organ. The structural and functional unit of the kidney is the nephron. In addition to its excretory function, role of kidney in endocrine functions and in maintenance of blood pressure is equally important.

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19.2 Kidney Disease—A Clinical Approach

Vijay Kher

INTRODUCTION

Patients with kidney disease may have a variety of clinical presentations. Some have symptoms directly related to the kidney (gross haematuria, flank pain) while others may have extra-renal symptoms (oedema, hypertension, signs of uraemia). However, many patients are asymptomatic and are noted on routine examination to have an elevated plasma creatinine concentration or an abnormal urinalysis. Each of these groups requires a step-wise approach so as to arrive at a definitive diagnosis.

Over the last few years, there have been certain changes in the terminology of kidney disease. Acute renal failure (ARF) is now termed as acute kidney injury (AKI) to reflect the entire spectrum of severity of ARF. Similarly chronic renal failure (CRF) is now termed as chronic kidney disease (CKD). The term renal has been replaced by kidney to make it more patient friendly. The term failure has been replaced by disease as failure seemed to connote a helplessness on part of the nephrologists in managing patients with kidney disease. The term end stage renal disease (ESRD) has also been changed to chronic kidney disease stage V [glomerular filtration rate (GFR) less than 15 mL/min], as most of these patients can be given many years of good quality life with kidney transplantation or maintenance dialysis and cannot be considered as end stage.

The diagnosis of kidney disease is based on the evaluation of signs, symptoms and a series of investigations. The diagnosis is complicated by the fact that most of the signs and symptoms are non-specific and also appear fairly late in the course of the disease. A simple approach to a patient with kidney disease is to match the patient's clinical features into one of the following syndromes:

1. Asymptomatic urinary abnormality
2. Urinary tract infection (UTI)
3. Hypertension
4. Acute kidney injury
5. Rapidly progressive renal failure (RPRF)
6. Acute nephritic syndrome
7. Nephrotic syndrome (NS)
8. Chronic kidney disease
9. Urinary tract obstruction
10. Tubule function defects
11. Congenital/genetic syndromes

SIGNS AND SYMPTOMS OF KIDNEY DISEASE

The first step in evaluating a patient for kidney disease is to look for clinical features suggestive of kidney disease. These could be a change in urine output like polyuria or nocturia, which relates to loss of the concentrating ability of the kidney or oliguria (<400 mL urine in 24 hours) or anuria (<50 mL urine in 24 hours) which may be symptoms of AKI; whereas dysuria, frequency, urgency could suggest urinary tract infection (UTI), or a pathology in bladder, prostate or urethra. Oedema around eyes, haematuria, proteinuria and hypertension are suggestive of glomerular disease. Flank pain, haematuria and graveluria may suggest stone disease.

The window to kidney disease is the examination of the urine, for specific gravity, glycosuria, proteinuria and microscopic examination for red blood cells (RBCs), white blood cells (WBCs) and casts or any other cells. The urinary specific gravity and osmolality may be relatively fixed around 1010 and 290 mOsmol/L respectively, signifying the inability of the kidneys to concentrate or dilute the urine. Presence of RBCs casts with proteinuria suggests glomerulonephritis; WBCs casts in a patient with fever, chills and flank pain suggest acute pyelonephritis; eosinophiluria and eosinophilia in a patient with AKI suggests drug-induced interstitial nephritis; broad casts suggest CKD. An ultrasound is mandatory for evaluation of any patient with kidney disease as it provides information on the size and echogenicity of the kidneys as well as the morphology of the ureters, urinary bladder, urethra, prostate.

ASYMPTOMATIC URINARY ABNORMALITY

Asymptomatic patients are most commonly detected to have kidney disease following routine investigations, such as urine analysis, blood pressure measurement, biochemical analyses or as part of a health screening programme. In some patients, kidney disease is detected during clinical examination for health insurance, occupational purposes, or during pregnancy. Asymptomatic patients may be detected as a result of investigation of family members following the diagnosis of a familial renal disease. Asymptomatic patients may have either abnormal urinary excretion of protein, microscopic haematuria, abnormal imaging of kidney or urinary tract or a combination of these.

Technetium 99mm mercaptoacetyltriglycine diethylene-triamine-penta-acetic acid (DTPA) or MAG3 scan provides an excellent evaluation of function and GFR assessment of each kidney and can be used for the diagnosis and follow-up of patients with obstructive uropathy and renovascular hypertension. ^{99}Tc DMSA is useful in detecting scars in the renal parenchyma.

Routine ultrasound screening during pregnancy has resulted in prenatal detection of urological disorders. Neonatal ultrasound scanning has led to a predictable increase in the detection of urinary tract abnormalities, the most common of which is hydronephrosis.

Mild, asymptomatic proteinuria can be divided into three categories: transient, orthostatic, and persistent. Transient proteinuria is by far the most common, occurring in 4% of men and 7% of women on a single examination, with resolution on subsequent examinations. A transient increase in protein excretion may be seen with fever and exercise, as well as with

symptomatic UTI. Orthostatic proteinuria primarily occurs in adolescents; it is characterised by increased protein excretion in the upright position, but normal protein excretion when the patient is supine. Both transient and orthostatic proteinuria are benign conditions requiring no further evaluation or specific therapy. Persistent proteinuria, in comparison, is more likely to reflect some underlying renal or systemic disorder. There are three types of persistent proteinuria: glomerular, tubular, and overflow.

1. Glomerular proteinuria implies proteinuria as a result of increased glomerular permeability and usually consists of excretion of albumin.
2. Tubular proteinuria implies increased excretion of proteins due to non absorption of low molecular weight proteins which are filtered through a normal glomerular filter as in tubulo intersitital disease.
3. Overflow proteinuria is excretion of proteins which are increased in the plasma as in multiple myeloma and light chain proteinuria.

The evaluation of the patient with mild proteinuria should begin by testing the urine on at least two occasions. The urine sediment should also be examined. If the proteinuria persists, a renal ultrasonogram should be performed looking for a structural lesion, such as chronic pyelonephritis or polycystic kidney disease. A renal biopsy is generally performed if there is some sign of progressive disease, such as increasing protein excretion or a rise in the plasma creatinine concentration.

Haematuria may be grossly visible or microscopic. Gross haematuria is suspected because of the presence of red or brown urine. The color change does not necessarily reflect the degree of blood loss, since as little as 1 mL of blood per litre of urine can induce a visible colour change. In addition, the intermittent excretion of red to brown urine can be seen in a variety of clinical conditions (myoglobinuria or porphyria) other than bleeding into the urinary tract. Thus, the initial step in the evaluation of such patients is centrifugation of the specimen to see if the red colour is in the urine sediment (RBCs) or the supernatant (pigments like myoglobin as in myoglobinuria, haemoglobin in urine as in intravascular haemolysis). Although haematuria is commonly defined as the presence of more than 2 RBCs per high power field in spun urine sediment, there is no 'safe' lower limit below which significant disease can be excluded. The causes vary with age with the most common being inflammation or infection of the prostate or bladder, stones, and in older patients, malignancy. The investigations should be done as per the flow chart (**Figure 1**). If no diagnosis is apparent from the history, urinalysis, radiologic tests, or cystoscopy, then the most likely causes of persistent isolated haematuria are a mild glomerulopathy or a predisposition to stone disease, particularly in young and middle-aged patients. If haematuria is associated with nephrotic range proteinuria, it almost always suggests glomerular disease. Microscopic haematuria in itself cannot cause heavy proteinuria.

URINARY TRACT INFECTION

Infections of the urinary tract are common, distressing, and can occasionally be life-threatening. The clinical features, diagnosis, treatment, complications, and long-term significance of infection vary, depending on the site of infection and the presence or absence of structural or functional abnormality within the urinary tract. Diagnosis requires demonstration of bacteriuria and/or pyuria. In children, UTI may cause significant long-term morbidity, particularly, renal scarring, hypertension and renal impairment, which may not be evident clinically until adult life. Hence, in children even the first episode of UTI mandates a detailed work-up and evaluation.

HYPERTENSION

Hypertension is defined as an elevation of blood pressure $\geq$140/90 mmHg. This may be the first sign of an underlying kidney disease, especially in patients <35 years of age. In referral centres, 2% to 5% of hypertensive patients have renovascular hypertension. Renal ultrasound may reveal a unilateral contracted kidney suggesting an underlying renovascular aetiology and/or renal parenchymal aetiology. Another important cause of renal hypertension is reflux nephropathy, which leads to scarring of the kidneys.

ACUTE KIDNEY INJURY

AKI is a sudden and reversible loss of kidney function usually preceded by loss of blood or fluid, kidney ischaemia, hypotension or caused by drugs. It mostly recovers in 4 to 12 weeks time. The incidence of AKI is very high in hospitalised patients. An incidence of 15% has been reported among patients admitted to intensive care units, whereas among all hospitalised patients, rates of 2% to 5% have been reported. The two major causes of AKI are acute tubular necrosis (ATN, due to ischaemia or the administration of a nephrotoxin) and prerenal disease (due to heart failure, true volume depletion, or sepsis).

RAPIDLY PROGRESSIVE RENAL FAILURE

RPRF is described as insidious onset (*versus* abrupt onset in AKI) deterioration (over days to weeks) in renal function. The most important cause of RPRF is rapidly progressive glomerulonephritis (RPGN). This is characterised morphologically by extensive crescent formation and clinically by progression to end-stage renal disease in most untreated patients within a period of weeks to months. The severity of the disease is in part related to the degree of crescent formation: patients with circumferential crescents in more than 80% of the glomeruli tend to present with advanced renal failure that may not respond well to therapy. Patients should undergo early renal biopsy, which should include immunofluorescence and light microscopy and appropriate serologic assays. These include anti-neutrophil cytoplasmic antibodies (ANCA), anti-GBM antibodies, antinuclear antibodies and complement levels. The other important causes of RPRF are acute interstitial nephritis (which could be drug-induced or due to acute pyelonephritis), malignant hypertension, haemolytic uraemic syndrome and obstructive uropathy.

ACUTE NEPHRITIC SYNDROME

Acute nephritic syndrome is characterised by haematuria, proteinuria, oedema and hypertension. The prototype of this disease is acute post streptococcal glomerulonephritis. However, it can occur as a result of many bacterial or viral infections. This occurs 10 to 20 days following infection. Some of these patients may present with severe hypertension, oedema and renal failure.

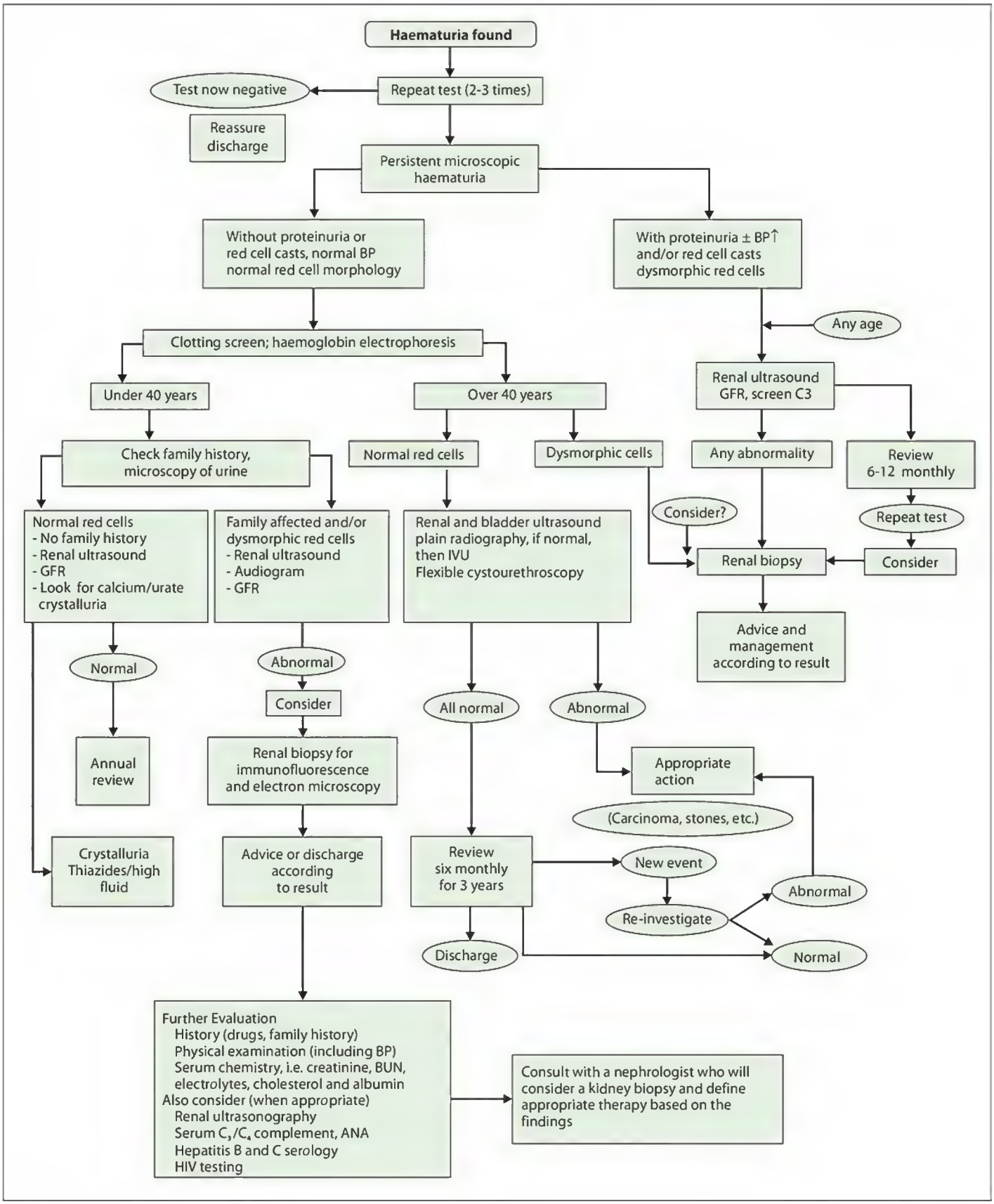


Figure 1: Evaluation of a patient with haematuria.

BP = Blood pressure; GFR = Glomerular filtration rate; IVU = Intravenous urogram; BUN = Blood urea nitrogen; ANA = Antinuclear antibody; HIV = Human immunodeficiency virus.

Most of these patients resolve completely with time. The other important renal diseases mimicking this syndrome are immunoglobulin (Ig)A nephropathy and mesangiocapillary glomerulonephritis.

NEPHROTIC SYNDROME

The nephrotic syndrome is caused by renal diseases that increase the permeability across the glomerular filtration barrier. It is classically characterised by four clinical features, but

the last two may not be seen in all patients: (i) nephrotic range proteinuria—urinary protein excretion greater than 50 mg/kg per day or urine protein-to-creatinine ratio >2, (ii) hypoalbuminaemia—serum albumin concentration <3 g/dL (30 g/L), (iii) oedema, and (iv) hyperlipidaemia. Although, oedema is generally the presenting sign of nephrotic syndrome, the diagnosis is confirmed by the presence of nephrotic range proteinuria and hypoalbuminaemia.

Primary nephrotic syndrome refers to nephrotic syndrome in the absence of an identifiable systemic disease. Within this category are patients who have a bland sediment and no glomerular inflammation on renal biopsy, i.e. minimal change disease (MCD), focal glomerulosclerosis and membranous nephropathy. Patients with primary glomerulonephritis, who have an active sediment and glomerular inflammation on renal biopsy have mesangiocapillary glomerulonephritis or mesangioproliferative glomerulonephritis. Secondary nephrotic syndrome refers to nephrotic syndrome in the presence of an identifiable systemic disease, e.g. lupus nephritis.

In children corticosteroid therapy can be initiated in patients with a high probability of having MCD without confirmation of the diagnosis by renal biopsy. In adults, a kidney biopsy is considered mandatory prior to starting any kind of immunosuppressive therapy. Children with idiopathic nephrotic syndrome treated with empirical steroid therapy can be further classified based upon their response to corticosteroid therapy: (a) steroid-responsive nephrotic syndrome—majority of the children with idiopathic nephrotic syndrome are steroid responsive. In these patients, the most likely histologic lesion is MCD, although some patients with focal segmental glomeruloscerosis (FSGS) will also respond to corticosteroid therapy. Patients who are steroid responsive have a favourable long-term outcome; and (b) steroid-resistant nephrotic syndrome—approximately 25% of all children with nephrotic syndrome will not respond to corticosteroids. The response rate is better in younger children, who are much more likely to have MCD. Some children with steroid-resistant nephrotic syndrome have genetic mutations of podocyte proteins.

CHRONIC KIDNEY DISEASE

CKD is a syndrome that results from progressive and irreversible destruction of nephrons resulting from a number of causes. It is defined as kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either: (i) pathological abnormalities or the presence of markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging studies or (ii) GFR <60 mL/min/1.73m^2 for 3 months, with or without kidney damage. This is usually progressive in nature. In most of the cases, demonstration of bilateral contracted kidneys, alongwith the clinical features of uraemia serve as the distinguishing features of chronicity. However, in CKD due to diabetes, amyloidosis and polycystic kidney disease, the kidney size may be normal or even bigger. Recently, a classification system which utilises GFR rather than serum creatinine for staging of CKD has been proposed by the National Kidney Foundation (**Table 1**).

Once a patient has been diagnosed to have kidney disease, the next step is to assess his level of renal function. Routinely a physician diagnoses kidney disease when serum creatinine and blood urea are elevated. However, the patient is said to have renal dysfunction once the GFR declines below normal. Normal GFR in an adult varies from 100 to 130 mL/min. There is an age-related decline in GFR of 1mL/min/year after the age of 30 years. The relationship of serum creatinine and urea to GFR is curvilinear and not linear, where serum creatinine and urea does not rise till the GFR declines to about 50%. Most of the patients are usually asymptomatic or mildly symptomatic at that stage. This is because of functional and structural adaptations that take place in the surviving nephrons, which compensate by increasing their functional capability. GFR can be assessed by either 24 hrs urinary creatinine clearance or estimating GFR from serum creatinine by either modification of diet in renal disease (MDRD) formula or Cockroft-Gault formula (**Table 2**).

Table 1: Definition and Staging of Chronic Kidney Disease (CKD)

Stage and Definition	Glomerular Filtration Rate (GFR) (mL/min/1.73m^2)	Clinical Plan of Action
At increased risk	>90 (with risk factors for CKD)	Screen for CKD; reduce risk of CKD
Kidney damage with normal or increased GFR	>90	Diagnose and treat; treat coexisting conditions; slow progression; reduce risk of cardiovascular disease
Kidney damage with mildly decreased GFR	60 to 89	Estimate rate of progression
Moderately decreased GFR	30 to 59	Evaluate and treat complications
Severely decreased GFR	15 to 29	Prepare for dialysis and kidney transplantation
Kidney failure	<15 (or dialysis)	Dialysis and kidney transplantation (if uraemia is present)

Table 2: Formula for Estimation of Glomerular Filtration Rate (GFR)

Cockroft-Gault Formula

CCr in Men : $\frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{P. Creatinine}}$

CCr in Women : 0.85 × value from above

[Where age in years, weight in kilograms and P. Creatinine in mg/dL]

Abbreviated MDRD Study Equation

Estimated GFR (mL/min/1.73m^2)

186 × (Scr) – 1.54 × (Age) – 0.203 × (0.742 if female) × (1.210 if African – American)

exp (5.228 – 1.154 × ln (Scr) – 0.203 × in (Age) – 0.299 if female) + (0.192 if African – American)

Once the diagnosis of CKD is established, it is important to make an attempt to find out the specific disease that caused the kidney failure. According to the recent United States Renal Data System (USRDS) data, diabetes mellitus is regarded as the leading cause of kidney failure. In India, most of the data has been generated from single centre experiences (**Table 3**). Chronic glomerulonephritis and diabetic nephropathy are

Table 3: Aetiology of Chronic Kidney Diseases in India

Disease	SGPGI, Lucknow (%)	PGI, Chandigarh (%)	Apollo Hospital, Chennai (%)
Chronic glomerulonephritis	28.6	36.6	18.2
Diabetic nephropathy	23.3	23.8	26.7
Chronic interstitial nephritis	16.5	14.3	27.0
Hypertensive nephrosclerosis	4.1	13.5	10.0
Obstructive nephropathy	6.4	—	1.2
Autosomal dominant polycystic kidney disease	2.0	3.5	2.0
Unknown	16.2	3.7	—
Miscellaneous	3.0	4.3	—

leading causes of CKD. In order to establish the underlying cause, one must look for appropriate clinical features and use suitable laboratory tests. If the kidney size is preserved then one should attempt a kidney biopsy to find out the cause but if kidneys are shrunken then the cause of kidney disease may be difficult to detect. There is increasing evidence that patients with any degree of CKD have a substantial increase in cardiovascular risk that can, in part, be explained by an increase in traditional risk factors such as hypertension, diabetes, and the metabolic syndrome. Among patients with CKD, the risk of death, particularly due to cardiovascular disease, is much higher than the risk of eventually requiring dialysis. It is important for every physician taking care of patients of CKD to identify factors which may have aggravated the degree of kidney failure, as once these factors are corrected, kidney function may improve at least partially (**Table 4**).

CONGENITAL/GENETIC SYNDROMES

This includes a varied spectrum of diseases like autosomal dominant and recessive polycystic kidney disease, congenital nephrotic syndrome (Finnish type), Alport's syndrome, Fabry's disease and juvenile nephronopthisis. The diagnosis of these entities is suspected on a positive family history, characteristic clinical features and requires a high index of suspicion. Genetic counselling is an integral part of the management of these diseases.

Table 4: Common Reversible Factors in Chronic Kidney Disease

Volume depletion
- Vomiting, diarrhoea, excessive diuresis, congestive heart failure

Urinary tract obstruction
- Nephrolithiasis, papillary necrosis, bladder outlet obstruction

Infection
- Renal or extra-renal

Vascular disease
- Uncontrolled or accelerated hypertension

Nephrotoxic drugs
- Aminoglycosides, cephalosporins, tetracycline, amphotericin, radio-contrast agents, NSAIDs, diuretics

Electrolyte and metabolic disorders
- Hyperphosphataemia, hyperuricaemia, acidosis

Catabolic states
- Surgery, burns, gastrointestinal bleed, steroids, chemotherapy

Vasculitis
- Systemic lupus erythematosus, Wegener's granulomatosis, microscopic polyarteritis

Pregnancy
- Pre-eclampsia, eclampsia

RECOMMENDED READINGS

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19.3 Acute Kidney Injury

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INTRODUCTION AND DEFINITION

The term 'acute kidney injury (AKI)' has now replaced the previously used 'acute renal failure (ARF)' that described an illness with a sudden and rapid decline in renal function, causing retention of nitrogenous waste products such as blood urea nitrogen and creatinine. The older term failed to describe the dynamic process extending across the 3 phases of initiation (or insult), maintenance and recovery and focused on the presence or absence of overt kidney failure. The new terminology considers the disease as a spectrum of injury that extends from less severe forms to more advanced injury where renal replacement therapy (RRT) may be needed.

Clinically, AKI results in a failure to maintain fluid, electrolyte and acid-base homoeostasis and may be either non-oliguric (urine output >400 mL/day), oliguric (<400 mL/day) or anuric (<100 mL/day). Lower urine volumes are associated with more severe initial injury and have implications for volume status, electrolyte imbalance and prognosis. However, conversion from an oliguric to a non-oliguric state may not necessarily ameliorate the condition.

AKI can occur in a patient with previously normal renal function or may complicate the clinical course of pre-existing kidney disease. Further, AKI may occur as an isolated process or as a part of multiorgan failure.

The Acute Kidney Injury Network definition includes the following elements as diagnostic criteria: an abrupt (within 48 hours) absolute increase in the serum creatinine concentration of $\geq$0.3 mg/dL from baseline, a percentage increase in the serum creatinine concentration of $\geq$50%, or oliguria of less than 0.5 mL/kg per hour for more than 6 hours. The diagnostic criteria are applied only after volume status has been optimised. The staging of AKI is shown in **Table 1**.

Table 1: Staging of Acute Kidney Injury

Stage	S. Creatinine Criteria	Urine Output Criteria
1	Increased 1.5 to 2 fold*	<0.5 mL/kg/hour for >6 hours
2	Increased 2 to 3 fold*	<0.5 mL/kg/hour for >12 hours
3	Increased >3 fold* or absolute value >4 mg/dL	<0.3 mL/kg/hour for 24 hours or anuria for 12 hours

** Above baseline level.*

CLASSIFICATION

AKI can be divided into pre-renal, intrinsic and post-renal categories based on the underlying causative mechanisms.

Pre-Renal Acute Kidney Injury

The appropriate physiologic response to renal hypoperfusion is pre-renal AKI. If hypoperfusion is corrected in time, the integrity of the renal parenchymal tissue is maintained and glomerular filtration rate (GFR) rapidly improves. If uncorrected, intrinsic damage ensues. Any condition characterised by hypovolemia, low cardiac output, systemic vasodilatation or intrarenal vasoconstriction can cause hypoperfusion. True or 'effective' hypovolaemia manifests with a fall in systemic arterial pressure, setting in motion corrective neural and humoral responses (activation of baroreceptors, sympathetic nervous system activation, renin-angiotensin-aldosterone system activation and ADH release). However, these compensatory mechanisms fail if the mean arterial blood pressure is less than 70 to 80 mmHg. The major causes of pre-renal AKI are shown in **Table 2**.

Table 2: Causes of Pre-Renal Acute Kidney Injury

Mechanism	Cause	Conditions
Intravascular volume depletion	Haemorrhage	Trauma, surgical, GI, post-partum,
	GI losses	Vomiting, NG suction, diarrhoea
	Renal losses	Drug-induced or osmotic diuresis, adrenal insufficiency
	Skin and mucous membrane losses 'Third-space' losses	Burns, hyperthermia, pancreatitis, crush syndrome, hypoalbuminaemia
Decreased cardiac output		Myocardial, valvular, pericardial diseases, pulmonary hypertension, pulmonary embolism, mechanical ventilation, systemic vasodilatation, antihypertensive drugs
Renal vasoconstriction		Norepinephrine, liver disease, sepsis, hypercalcaemia
Impaired autoregulation		ACEi in renal artery stenosis NSAIDs inhibition of prostaglandin synthesis in states of renal hypoperfusion

GI = Gastrointestinal; NG = Nasogastric; ACEi = Angiotensin converting enzyme inhibitors; NSAIDs = Nonsteroidal anti-inflammatory drugs.

Intrinsic Renal Failure

Acute tubular necrosis (ATN) is the commonest renal lesion in patients with intrinsic renal failure and may result from severe renal hypoperfusion (untreated pre-renal AKI) or nephrotoxic injury. Ischaemic ATN is more likely to occur in patients with trauma, major surgery, severe burns, severe hypovolaemia and overwhelming sepsis. On the other hand, nephrotoxic injury results from several drugs and toxins. **Table 3** shows the major causes of intrinsic AKI.

Post-Renal Acute Kidney Injury

Obstruction to urine flow may occur at the urethral meatus or bladder neck, both ureters or from obstruction to a single

functioning kidney. Less than 5% of AKI is consequent to obstructive causes. **Table 4** shows the causes of post-renal AKI.

Table 3: Major Causes of Intrinsic Acute Kidney Injury

Large Vessel Disease (Bilateral)
- Artery: Thrombosis, embolism/atheroembolism, aortic dissection involving renal arteries, Takayasu's aortoarteritis
- Vein: Thrombosis

Glomerular Disease
- Inflammatory: Acute or rapidly progressive glomerulonephritis, vasculitis, radiation
- Vasospastic: Malignant hypertension, scleroderma
- Haematologic: Haemolytic-uraemic-syndrome or thrombotic thrombocytopaenic purpura, DIC, hyperviscosity syndromes

Injury to Renal Tubule Acute Tubular Necrosis (ATN)
- Ischaemia
- Toxins
  - Exogenous: Antibiotics, anticancer agents, radiocontrast media
  - Endogenous: Myoglobin, haemoglobin, light chains, uric acid, tumour lysis

Acute Tubulointerstitial Disease
- Allergic interstitial nephritis (antibiotics, NSAIDs)
- Infections (bacterial, leptospirosis, fungal)
- Acute renal allograft rejection
- Infiltration (lymphoma, leukaemia)

DIC = Disseminated intra-vascular coagulation; NSAIDs = Nonsteroidal anti-inflammatory drugs.

Table 4: Causes of Post-Renal Acute Kidney Injury

Obstruction	Site	Cause
Ureteric	Intra-luminal	Stones, blood clot, sloughed renal papilla, uric acid/sulfa crystals, fungus balls, tumour
	Intra-mural	Oedema after ureteric surgery, ureteric fibrosis
	Extra-ureteric	Accidental ligation during pelvic surgery
Bladder neck	Intra-luminal	Stones, blood clot, sloughed renal papilla
	Intra-mural	Bladder cancer, infection with mural oedema, neurogenic bladder
	Extra-mural	Prostatic hypertrophy, prostate cancer
Urethral		Phimosis, congenital valves, stricture

AETIOLOGY

AKI is becoming increasingly prevalent, both in the developing and the developed countries. The incidence of AKI varies considerably depending on the selected definition of AKI and the population reported on. Differences do exist between AKI in the developed as compared to developing countries with predominantly 'hospital-acquired AKI' being reported by the former while 'community-acquired AKI' is commoner in the developing countries. In the developed world, trauma and surgery precede the onset of AKI in 60% of cases. In contrast, drugs and toxins (18% to 33%), medical disorders (30% to 35%) and gynaeco-obstetric complications (5% to 10%) account for AKI in the developing countries. In tropical countries, medical causes predominate (60% to 67%) with specific infections such as *falciparum malaria* being particularly common. Severe malaria, leptospirosis, dengue haemorrhagic fever, hantavirus nephropathy, complications of human immunodeficiency virus/acquired immunodeficiency syndrome, shigellosis and snake envenomation are frequent causes of AKI. In tropical regions, AKI related to toxicity of herbal and non-herbal products is also encountered.

PATHOGENESIS AND PATHOLOGY

A multi-phase process (hypoperfusion, injury initiation, maintenance and repair) characterises the development of ischaemic ATN. Histologic changes include effacement and loss of proximal tubule brush border, patchy loss of tubule cells, focal areas of proximal tubule dilatation, distal tubule casts, and areas of cellular regeneration that appear during the phase of recovery of renal function. The functional loss, however, is usually more prominent than the severity of the histologic changes. Necrosis is restricted to the outer medullary regions.

Increased sodium chloride delivery to the macula densa of individual nephrons (glomerular filtration with impaired proximal and loop reabsorptive function) activates the tubuloglomerular feedback mechanism causing afferent arteriolar constriction, which lowers the GFR in an attempt to reduce tubule flow rate. Backleak of filtered tubular fluid may occur across the damaged tubule epithelium.

Intra-tubular obstruction by cells and casts is also an important component of ATN. The intra-luminal casts are composed, in part, of Tamm-Horsfall protein, which is converted into a gel-like polymer in the setting of high local luminal sodium concentrations which is the characteristic of ATN.

CLINICAL AND LABORATORY EVALUATION

In patients with AKI, an in-depth history, detailed physical examination and urinalysis, careful review of all medical records and drug history, selective use of laboratory tests and renal imaging, evaluation of the response to fluid repletion and, at times, a renal biopsy, may help to uncover the cause of the renal dysfunction (**Table 5**). CKD also needs to be distinguished from AKI by features listed in **Table 6**. The use of certain indices helps in differentiation between pre-renal and intrinsic AKI (**Table 7**).

Table 5: Clinical and Laboratory Evaluation of Acute Kidney Injury

Detailed history (including drug/intervention history; review of medical records, physical examination [weight and fundoscopy])
Urinalysis: Routine and microscopic
Routine blood chemistry (BUN, creatinine, electrolytes, HCO_3, Ca, PO_4)
Complete haemogram
Special tests: Urine for eosinophila, Bence-Jones protein
Serology: ANA, ANCA, anti-GBM, complement, cryoglobulins, protein electrophoresis, ASO
Imaging: Renal ultrasound, plain radiograph of abdomen, computed tomographic urography
Renal biopsy

BUN = Blood ureo nitrogen; HCO_3 = Bicorbonote; Co = Colcium; PO_4 = Phosphote; ANA = Anti-nucleor ontibody; ANCA = Anti-neutrophil cytoplosmic ontibody; GBM = Glomerular bosement membrone; ASO = Anti-streptolysin O.

Table 6: Differentiating Acute Kidney Injury (AKI) from Chronic Kidney Disease (CKD)

Feature	AKI	CKD
Antecedent history of renal disease	Absent	Present
Prior sustained elevation of creatinine for >3 months	Absent	Present
Anaemia	Usually absent at onset	Present
Elevated serum phosphorus, decreased serum calcium, elevated serum PTH	Absent (in early phase)	Present
Neuropathy	Absent	Present
Band keratopathy	Absent	Present
Renal bone disease	Absent	Present
Small kidneys on sonography	Absent	Present (in some kidney diseases normal/ large sizes)
Tolerance to azotemia, acidosis	Absent	Present
Stability of azotemia	Absent (daily rise)	Present

Table 7: Differentiating Between Pre-renal and Intrinsic Acute Kidney Injury (AKI)

Diagnostic Index	Pre-renal (AKI)	Intrinsic (AKI)
Urinary Na^+ concentration (mEq/L)	<20	>40
Fractional excretion of Na^+ (%) (UNa × PCr/PNa × UCr) × 100	<1	>1
Urinary urea nitrogen/Plasma Urea nitrogen ratio	>8	<3
Urinary creatinine/ratio	>40	<20
Urine osmolality (mOsm/kg H_2O)	>500	<250
Blood urea nitrogen/creatinine ratio	>20	<10 to 15
Renal failure index (UNa/UCr/PCr)	<1	>1
Urine sediment	Normal	Granular casts and tubule epithelial cells

Newer Biomarkers in Acute Kidney Injury

Serum creatinine represents a poor biomarker (acute decline in kidney function may not be reflected by a rise in serum creatinine for several hours). Analytical interference (variation in reported creatinine concentrations using differing methods reflect calibration differences) and imprecision point to a need for better, alternative biomarkers (serum and/or urinary). Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and cystatin C are being evaluated in a number of studies for their utility in detecting AKI in different patient cohorts. However, it would still be premature to use them in clinical settings.

TREATMENT

Pharmacological therapies to shorten the course of AKI hitherto have been unsuccessful. The rationale for the use of loop diuretics lies in their capability to reduce energy requirements of the cells of the ascending limb of loop of Henle, ameliorating ischaemic damage. Conversion of oliguric to non-oliguric AKI facilitates the management of fluid and electrolyte disturbances and reduces the requirement for renal replacement therapy.

Significant metabolic/immunologic disturbances, induction of a pro-inflammatory state exacerbated by malnutrition mandates provision of appropriate nutritional support in an attempt to improve outcomes. Nutritional recommendations should consider the cause of AKI and prefer the enteral route. A provision of a nutritional prescription of 25 to 35 kcal/kg/day and up to a maximum of 1.7 g amino acids/kg/day, especially in hypercatabolic patients is essential. Trace elements and water-soluble vitamins should be supplemented as required. Fluid and potassium intake need to be restricted in oliguric patients.

Treatment of Complications

AKI is associated with an inability of the body to maintain homeostasis, derangements in electrolyte and water metabolism, divalent homeostasis and acid-base balance. The commonly encountered complications are shown in **Table 8**. Indications for initiation of RRT are shown in **Table 9**.

Table 8: Complications of Acute Kidney Injury

Complications	Manifestations
Metabolic	Hyperkalaemia Hypocalcaemia Hyperphosphataemia Hypermagnesaemia Hyperuricaemia Metabolic acidosis (increased anion gap)
Cardiovascular	Cardiac arrhythmias Pulmonary oedema Pericarditis/pericardial effusion
Gastrointestinal	Gastrointestinal haemorrhage
Neurologic	Altered sensorium Seizures
Haematologic	Anaemia Bleeding
Miscellaneous	Infections (pneumonia, urinary tract infection, septicaemia)

Table 9: Indications for Renal Replacement Therapy in Patients with Acute Kidney Injury

Biochemical Indications	Clinical Indications
Refractory hyperkalaemia (>6.5 mEq/L)	Urine output <0.3 mL/kg for 24 hours or
Metabolic acidosis (pH ≤7.10)	Absolute anuria for 12 hours
Electrolyte disturbances (hypercalcaemia)	Multiple organ failure
Tumour lysis syndrome (hyperuricaemia/ hyperphosphataemia)	Volume overload Pericarditis, encephalopathy, uraemic bleeding

The choice of the RRT modality should be guided by the individual patient's clinical status, medical and nursing expertise and availability of modality. Intermittent haemodialysis (IHD) is the standard form of therapy. Slow low efficiency haemodialysis is superior to IHD in haemodynamically unstable patients. Peritoneal dialysis may be used in the setting of a non-hypercatabolic AKI and in children.

PREVENTION OF ACUTE KIDNEY INJURY

AKI may develop if risk factors exist, viz. age >75 years, pre-existing CKD (eGFR <60 mL/min/1.73 m^2), cardiac failure, atherosclerotic peripheral vascular disease, liver disease, diabetes mellitus, nephrotoxic medications, hypovolaemia and sepsis.

Appropriate and adequate fluid replacement, optimisation of haemodynamic status, if necessary with inotrope/vasopressor administration, management/prevention of sepsis are essential components of prevention. Nephrotoxic medications should be stopped in patients at risk of developing AKI. Drug doses need to be adjusted depending on severity of kidney dysfunction to reduce toxicity.

Patients who are identified as being at risk of contrast induced-AKI should receive pre-procedure volume expansion with 0.9% sodium chloride or isotonic sodium bicarbonate. Low osmolar agents are associated with a decreased risk of nephrotoxicity as compared to the high osmolar agents. The dose of contrast media should be minimised. N-acetylcysteine should also be given prior to the procedure.

RECOMMENDED READINGS

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19.4 Chronic Kidney Disease

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DEFINITION AND CLASSIFICATION OF CHRONIC KIDNEY DISEASE

The world is currently facing a global epidemic of chronic kidney disease (CKD). As morbidity and mortality from infectious diseases has declined, life-expectancy has increased and chronic degenerative diseases have become more prevalent. CKD is unique amongst the chronic non-infectious illnesses in that, there is a very real window of opportunity to continue living comfortably in spite of being terminally ill. The duration of artificial prolongation of life is largely proportional to the financial resources of the patient and/or his provider. The beneficiary patient, however, is a very severe drain on the economy of his provider. In developing countries like India, it is usually the family that shoulders an immense financial burden. An insignificant percentage of the patients of CKD are supported by the government, employers or insurance companies. Whosoever is picking up the 'tab', the financial burden of the end-stage renal disease (ESRD) population is fast becoming unmanageable for the provider—be it government, family, employers, charitable organisations or insurers. It is, therefore, the need of the hour to tackle this problem not at the therapeutic end of this disease but at the 'preventable' beginning of it. The nephrology community realises this urgent need because of the severe resource crunch, not only of funds, but also of qualified nephrologists and dialysis infrastructure.

The National Kidney Foundation (NKF) of USA and the European Renal Association (ERA) have enunciated a new name for chronic renal failure; defined the stages of CKD and published the guidelines for appropriate interventions for 'preventing' CKD and its progression at each stage.

WHY RENAME CHRONIC RENAL FAILURE?

The word 'renal' is not easily understood by the lay public whereas the name 'kidney' is generally well understood. The concept of 'failure' is no longer apt for a disease which has seen much medical success by way of intervention in slowing its progression from its first stage to the final 'end-stage'.

DEFINITION OF CHRONIC KIDNEY DISEASE

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) working group has defined CKD as given below, which has been accepted and adopted internationally:

1. The presence of markers of kidney damage for more than 3 months, as defined by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR), manifest by either pathological abnormalities or other markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests; or
2. The presence of GFR less than 60 mL/min/1.73 m^2 for more than 3 months with or without other signs of kidney damage as described above.

Furthermore, 5 stages of chronic kidney disease have been defined as shown in **Table 1**.

Table 1: Stages of Chronic Kidney Disease*

Stage	Description	GFR
1	Kidney damage with normal or ↑ GFR	≥90 mL/min
2	Kidney damage with mild ↓ in GFR	60 to 89 mL/min
3	Moderate ↓ in GFR	30 to 59 mL/min
4	Severe ↓ in GFR	15 to 29 mL/min
5	Kidney failure	<15 mL/min, or patient on dialysis

**Adapted from NKF-KDOQI guidelines on chronic kidney disease. GFR = Glomerular filtration rate.*

Recently, CKD stage 5 has been further subclassified into stage 5D if a patient is on dialysis or 5T, if the patient has undergone kidney transplantation. If kidney function deteriorates post kidney transplant, the patient can be grouped into stage 5T-1 to stage 5T-4 as per the GFR criteria above.

Moreover, stage 3 CKD has been further divided into stage 3A (GFR 45 to 59 mL/min) and stage 3B (GFR 30-44 mL/min), since those in stage 3B are far more likely to progress to stage 5 than those in stage 3A.

In India, the Indian Society of Nephrology (ISN) has developed a CKD registry wherein epidemiological data of CKD patients is collected and analysed. A recent report of this registry shows that patients first presented to a nephrologist at stage 5 in 47.5%, stage 4 in 25.5%, stage 3 in 19.6%, stage 2 in 4.9% and stage 1 in 2.5%. It is very unfortunate that 50% of patients present for the first time to a nephrologist in CKD stage 5, when they cannot be offered anything more than dialysis or transplantation. It should be the endeavour of all treating physicians, particularly the internists, to pick up most of the CKD population much earlier in stages 1 and 2, when much more can be offered to slow down its progression. In fact, the target of prevention should be stage 0, i.e. the population at risk. The population 'at risk' for development of CKD is listed in **Table 2**.

Before proceeding further an important query must be answered: do these Western criteria accurately apply to the Indian population? The NKF (USA) data, upon which this classification has been made, is based on a heterogeneous population but would still have a bias towards white and black population. The people of the Indian subcontinent are ethnically different, particularly in body weight, muscle mass and dietary habits. Physicians who have evaluated the

normal Indian population for GFR, particularly of normal living donors for fitness for organ donation, have reported unexpectedly low creatinine clearance values in otherwise disease-free people. This appears to be related to low protein intake. The average per capita protein intake in the developed world is 50% higher than in the developing world (105 g vs 57.3 g).

Table 2: Population at Risk for Developing Chronic Kidney Disease

Age >65 years
Diabetes type 1 and 2
Family history of renal disease
Autoimmune disease
Systemic infections
Urinary tract infections/stones
Urinary tract obstructions
Recovery of acute kidney injury
Hypertensives
Drug abusers: Nonsteroidal anti-inflammatory drugs, analgesics/ heroin
Neoplasia
Low birth weight
Reduced kidney mass

In vegetarians, who consume neither milk nor eggs, the protein intake can be 20% to 40% less than in lacto-ovo-vegetarians. Studies have demonstrated an acute and delayed increase of GFR following oral protein loading which can also be duplicated by intravenous aminoacid loading. These studies confirm that vegetarianism results in a low GFR which can be stimulated by ingestion of a large protein meal. An infusion of amino acids mimics a large protein meal and the resultant increase in GFR has been called the 'renal reserve', which may be as high as 80% to 100% of the baseline value.

Chronically decreased GFR in the absence of kidney damage is a phenomenon much more likely to be found in our Indian population, where a large percentage of the population are vegetarian and even among those who are non-vegetarian, since meals are predominantly 'non-meat' in content and frequency.

There are other causes of chronically decreased GFR, such as unilateral nephrectomy, extra-cellular fluid volume depletion and systemic illness such as heart failure and liver cirrhosis. The patient with GFR between 60 and 90 mL/min, therefore, presents in the grey zone. When presented with this situation, the clinician can only diagnose CKD if the other markers of kidney damage, such as urinary abnormalities, pathological appearance or hypertension are also present.

AETIOPATHOLOGY OF CHRONIC KIDNEY DISEASE

Table 3 classifies CKD by aetiopathology. The relative incidence of the common causes, i.e. diabetes, hypertension, glomerulonephritis, interstitial nephritis, cystic or hereditary diseases are shown among the various races. In all races, diabetic glomerulosclerosis appears to be the commonest (**Table 4**).

Table 3: Classification of Chronic Kidney Disease by Pathology and Aetiology

Pathology	Aetiology
Diabetic glomerulosclerosis	Diabetes mellitus (type 1 & 2)
Glomerular diseases (primary or secondary)	Largely unknown
Proliferative glomerulonephritis	Systemic lupus erythematous, vasculitis, hepatitis B or C, human immunodeficiency virus (HIV) bacterial endocarditis
Minimal change disease	Hodgkin's disease
Focal glomerular sclerosis	HIV, heroin toxicity
Membranous nephropathy	Drug toxicity, solid tumours
Fibrillary glomerular diseases	Amyloidosis, light chain disease
Hereditary nephritis	Alport's syndrome
Vascular diseases	
Diseases of large size vessels	Renal artery stenosis, aortoarteritis
Diseases of medium size vessels (nephrosclerosis)	Hypertension
Diseases of small vessels (microangiopathy)	Haemolytic uraemic syndrome, vasculitis, sickle cell disease
Tubulointerstitial diseases	
Tubulointerstitial nephritis	Infections, drugs, sarcoidosis
Reflux nephropathy	Vesico-ureteric reflux
Obstructive nephropathy	Stones, prostatism, malignancy
Myeloma kidney	Multiple myeloma
Cystic diseases	
Polycystic kidney disease	Autosomal dominant or recessive
Tuberous sclerosis	
Von-Hippel-Lindau disease	
Medullary cystic disease	

Table 4: Incidence and Prevalence of Various Types of Chronic Kidney Disease*

Aetiology	Whites*	Blacks*	Asian-Americans*	Indians**
Diabetes mellitus	43.5%	42.1%	42.6%	31.2%
Hypertension	24.0%	32.9%	23.5%	14.1%
Glomerulonephritis	12.0%	10.4%	17.3%	14.4%
Interstitial nephritis	4.8%	2.0%	2.9%	7.0%
Cystic disease /hereditary	3.8%	1.5%	2.2%	2.1%
Miscellaneous	6.2%	6.0%	2.4%	15.9%
Unknown	5.7%	5.1%	5.5%	15.3%
Total	**100.0%**	**100.0%**	**100.0%**	**100.0%**

**Adapted and modified from the USRDS Data-2001; ** Data of the CKD Registry of the Indian Society of Nephrology Cumulative Report 2008.*

INTERVENTIONS IN CHRONIC KIDNEY DISEASE

The goals of proposed interventions are listed in **Table 5**. Of all these interventions, early detection and the successful delaying of progression, fall in the purview of the entire medical community. It is this one intervention which can result in reducing the incidence of CKD.

The patient may present at stages 0-1 to any doctor, except the nephrologist. If the doctor is ignorant of this disease, the moment of opportunity that presents at this stage is missed,

which can be in the form of antenatal foetal sonography; maternal antenatal care in the antenatal clinic; pre- school and yearly school health check-ups; pre-employment and pre-military health check-ups; pre-insurance health check-ups; pre-operative check-ups; periodical medical examination popularly known as 'executive health check-up' quite popular nowadays in the big metros. Diabetic clinics are one example of screening patients 'at risk'. Similarly 'hypertension' clinics are now available.

Waiting for these 'moments' of opportunity has the inherent limitation that many 'silent' cases would be undetected until the late irreversible stages are reached. It is, therefore, necessary to take the initiative to pick up those silent cases actively at the community level and the individual level.

Table 5: Proposed Interventions (Primary Prevention and Strategies for Delaying Progression to Next Stage)

Strategies for Delaying Progression to Next Stage	Goals
ACE inhibitor or ARB or both	Proteinuria <0.5 g/day and GFR decline <2 mL/min/year
Additional antihypertensive as needed	BP <130/80 if proteinuria <1 g/day and BP <125/75 if proteinuria >1 g/day
Dietary protein restriction	0.6 to 0.8 g/kg/day (caution in vegetarians)
Glycaemic control	HbA1c <7%
Cholesterol lowering therapy	LDL <100 mg/dL
Anaemia correction	Target Hb 10 to 12 g/dL
Dietary salt restriction	3 to 5 g/day (except in salt wasting states)
Smoking cessation	
Weight control	Ideal body weight
Reduce elevated Ca x PO_4	Keep Ca and PO_4 at normal levels
Avoid nephrotoxic drugs	product

Delay/treat co-existing cardiovascular abnormalities.

Prepare for impending ESRD physically, emotionally and socioeconomically by:

- *Early placement of vascular access (AV fistula) or peritoneal dialysis (CAPD) catheter.*
- *Educate patient and family about renal replacement therapy (RRT) options.*
- *Explain financial implications.*

Initiate timely RRT, i.e. renal transplant, maintenance haemodialysis or peritoneal dialysis.

Community Initiatives

The entire population of the village is screened by house-to-house visits of health care workers over a period of time. During the visit, the health care worker takes history, checks blood pressure (BP) and conducts a urine examination of every family member. Suspected cases are then sent to the referral hospitals.

The Kidney Disease Early Evaluation and Prevention (KEEP) projects of the NKF (USA) and Screening and Early Evaluation of Kidney disease (SEEK) of India are both very similar in design. These projects function by setting up kidney detection camps periodically all over the nation and inviting normal persons to come and get investigated for detection of stage 0 or 1 CKD.

An exhaustive screening of the individual should consist of history including all symptoms with relation to urine characteristics, particularly for haematuria and frothing of urine, urine flow, fluid retention, oedema, BP, diabetes, past and family history of all predisposing conditions included in stage 0.

Physical examination focussing particularly on BP, oedema, signs of congestive heart failure (CHF), per abdomen examination including genitalia should be done.

Laboratory tests should include urine for protein, sugar and microscopic examination particularly for haematuria and pyuria; serum creatinine estimation and GFR.

The level of GFR is a strong predictor of the 'time-to-onset' of ESRD as well as the risk of CKD. However, GFR cannot be measured directly, the amount of a physiological, freely filterable and non-secreted or metabolised solute, such as inulin, in the urine is an indirect marker of the amount filtered at the glomerulus. The most widely used measures of GFR are based on the 24 hours creatinine clearance or serum creatinine concentration.

Serum creatinine and creatinine clearance

Creatinine is mainly derived from metabolism of creatinine in muscle and its generation is proportional to the total muscle mass. Creatinine generation is higher in men, younger individuals and in blacks than in whites. A difference in serum creatinine according to age, gender, race, and protein intake exists. Moreover, the traditional method of serum creatinine estimation (alkaline picrate method) also detects non-creatinine chromogens compared to modern autoanalysers leading to lab variations in serum creatinine and over estimation of GFR when compared by the latter method. Substances like ketones and bilirubin may lead to spuriously elevated and decreased creatinine, respectively.

The amount of creatinine excreted in the urine is a composite of both the filtered and the secreted creatinine. Creatinine clearance over-estimates GFR by 10% to 40% in normal individuals, and is greater and more unpredictable in patients with CKD. As much as two-third of the total daily creatinine excretion can occur by extra-renal elimination in patients with severely reduced kidney function.

The normal level of GFR varies according to age, gender and body size. After the age of 20 to 30 years, the GFR declines at the rate of 1 mL/min/1.73m^2. Thus, by the age of 70, it is approximately 70 mL/min/1.73m^2. In the Indian population, a comparatively lower creatinine excretion can be expected due to relatively lower muscle mass.

The usual method of estimating GFR in clinical practice by collection of the 24-hour urinary sample with estimation of its creatinine content and using the formula given below:

Creatinine clearance = uv/p, with correction for body surface area of 1.73.

Some other major drawbacks of this method are inaccurate collection (samples thrown away, timing is wrong, urine passed with faeces is lost, most patients do not understand the collection process as also many of the laboratory or ward staff designated to do this); it is laborious, obnoxious due to smell, messy and time consuming; and it has been shown that the prediction equations described hereafter are equally accurate and much easier to use in clinical practice (**Table 6**).

Table 6: Estimating the Creatinine Clearance from Prediction Equations (The eGFR)

Cockroft-Gault equation

Cr. Cl (mL/min) = (140 – age) x weight/72 x S. Cr (x 0.85, if female)

MDRD, Serum variables

GFR (mL/min/1.73 m^2) = 170 x (S. Cr)-.999 x (Age)-0.176 x (SUN)-0.170 x (Alb)-0.318

x 0.762, if female

x 1.180, if black

Schwartz formula (in children)

Cr. Cl (mL/min) = 0.55 x length / S. Cr

The value of eGFR is illustrated in the example below:

A 62-year-old lady, height 155 cm, weight 50 kg, has a S. Cr of 1.1 mg/dL. Her eGFR by Cockroft-Gault formula is 42 mL/min.

A 24 year old man, height 170 cm, weight 65 kg, has S. Cr of 1.1 mg/dL. His eGFR is 95 mL/min.

If the eGFR had been overlooked, the lady would be considered normal, but by the CKD criteria, she is already in CKD stage 3, irrespective of her urinalysis findings

Cr. Cl = Creatinine clearance; MDRD = Modification of diet in renal disease; SUN = Serum urea nitrogen; Alb = Albumin; CKD = Chronic kidney disease; S. Cr = Serum creatinine.

Cystatin C

Cystatin C, a protein encoded by CST3 gene, has low molecular weight of 13.3 kilodaltons and is removed from the bloodstream by glomerular filtration as a single pass. Subsequently, it is metabolised in the tubules and does not appear in urine. Serum cystatin C levels are now accepted as an alternate method for estimating glomerular function. The need for an alternate method to serum creatinine arises because of the limitations of serum creatinine estimation particularly in children, small sized adults with poor muscle mass, pregnant women and renal transplant recipients. In such patients, creatinine value increases within the accepted range of 0.6 to 1.2 mg/dL are not indicative of the magnitude of fluxes in GFR and the treating physician is likely to fail to pick up an alarming reduction in GFR before it is too late to take remedial measures. The serum cystatin C levels have best been validated in these situations as an alternate method of evaluating renal function. The cost, however, is prohibitive presently as very few laboratories in India offer this test. As the substance does not come in the urine, there is no way of doing a cystatin clearance similar to creatinine clearance. Formulas for estimating GFR from serum cystatin levels are available, but beyond the purview of this text.

Guidelines for GFR Estimation

Blood urea is a poor estimate of GFR. Serum creatinine should not be used alone as an estimation of renal function. Creatinine clearance by timed urine collections or prediction equations provides additional information in defining and staging CKD. Every laboratory should supply estimated GFR by prediction equations using one of the two available adult/child formulae derived from serum creatinine, adjusting for age, sex and body mass index. Timed urinary collections of creatinine clearance may be reserved for the specific circumstances outlined in the text. Isotopic methods of GFR estimation may be used as confirmatory tests in confusing circumstances.

CLINICAL PRESENTATION OF CHRONIC KIDNEY DISEASE

The signs, symptoms and metabolic derangements of CKD may be either due to alteration of the normal homoeostatic functions of the kidney, or accumulation of the nitrogenous end-products of protein catabolism, i.e. the uraemic toxins which produce the clinical syndrome of 'uraemia' (**Table 7**).

Table 7: Clinical Presentations of Chronic Kidney Disease

Clinical Presentation	GFR (mL/min/ 1.73 m^2)	Proteinuria	Urine Sediment	Imaging Studies	Other Features
Decreased GFR	15 to 89	NA	NA	NA	Complications due to reduced GFR
Kidney failure (ESRF)	<15 or treated by dialysis	NA	NA	NA	Uraemia
Hypertension due to kidney disease	NA	±	±	Depending on aetiology	HBP

ESRF = End-stage renal failure; NA = Not available.

Clinical effects of abnormal physiology not attributable to accumulation of nitrogenous wastes are given in **Table 8**.

Table 8: Clinical Effects of Abnormal Physiology not Attributable to Accumulation of Nitrogenous Wastes

- Deranged renin angiotensin aldosterone axis
  - Hypertension
- Water and salt homoeostasis derangement
- Oedema
- Dehydration
- Congestive heart failure
- Hypertension
- Hypo- and hyper natraemia
- Potassium homoeostasis
  - Hypokalaemia
  - Hyperkalaemia
- Acid-base disturbances
  - Metabolic acidosis
- Bone, calcium and phosphorus metabolism
  - Renal bone disease
  - Extra-osseous and vascular calcification
- Erythropoietin deficiency
  - Anaemia
- Insulin metabolism
  - Hypoglycaemia
  - Hyperglycaemia
- Other endocrinopathies
  - Amenorrhoea
  - Sterility
- Growth failure

EFFECTS OF ALTERED HOMEOSTATIC RENAL FUNCTIONS

Hypertension in Chronic Kidney Disease

Secondary hypertension is a result of CKD and may result from renal vascular or parenchymal pathology. **Table 9** shows the relationship of hypertension to stages of CKD.

Table 9: Stages of CKD and Relationship with Hypertension

GFR (mL/min/1.73 m²)	With Kidney Damage		Without Kidney Damage	
	With HBP	Without HBP	With HBP	Without HBP
>90	1	1	High blood pressure	Normal
60 to 89	2	2	High blood pressure With decreased GFR	Decreased GFR
30 to 59	3	3	3	3
15 to 29	4	4	4	4
<15 (or dialysis)	5	5	5	5

HBP = High blood pressure.

Note: The 'grey' shaded areas in this table represent high blood pressure (BP) alone, high BP with low GFR (60-90 mL/min) and low GFR (60-90 mL/min) without high BP.

These categories include patients with essential hypertension with target organ renal damage (nephrosclerosis) or just low GFR associated with old age. The presence of other target organ damage, such as retinal changes, diastolic dysfunction, left ventricular hypertrophy or a history of cardiovascular events or cerebrovascular accidents, would help to differentiate one from the other. Although not strictly CKD, such patients would best deserve intervention just like CKD stages 1 and 2.

The kidneys regulate BP by renal salt and water excretion as well as by autoregulation involving the renin-angiotensin aldosterone axis. With deranged renal function, hypertension results either from renin-angiotensin and aldosterone excess or volume expansion due to failure to excrete salt and water. In addition, there may be contributions by pre-existing essential hypertension, increased sympathetic activity, altered prostaglandin/bradykinin/nitric oxide/endothelin homeostasis; parathyroid hormone/hypercalcaemia/intracellular calcium disturbance and calcification of the vasculature; drugs producing hypertension like erythropoeitin, cyclosporine, tacrolimus and steroids may also contribute. The hypertension of CKD can vary from mild to malignant and is sometimes difficult to treat. Many patients require two or more drugs having different pharmacological actions.

Water Balance

As kidneys deteriorate the ability to concentrate and dilute the urine in states of dehydration and overhydration, respectively, is lost. As a result, the patient may present with polyuria and nocturia or with oliguria and oedema. This defect results in a fixed urine specific gravity also known as isosthenuria (specific gravity = 1.010) both in dehydrated and in overhydrated states. The nocturia also causes overnight volume depletion and worsening uraemic symptoms, particularly nausea, and vomiting, known as 'morning sickness of uraemia'. A 200 mL glass of water at bed-time will help overcome this symptom.

As renal function deteriorates further and GFR approaches levels seen in stage 5, some patients become oliguric and develop oedema and CHF. Once the patient is initiated on dialysis, the urine output gradually tends to decrease with time.

Sodium

The sodium balance behaves similar to water. Most patients will have a mild-to-moderate overload of total body salt and water, until they reach CKD stage 5 when they will manifest gross sodium overload. Total body sodium overload will manifest as oedema and hypertension causing the intravascular compartment to be expanded. The patient with nephrotic syndrome will have extravascular volume overload due to total body sodium overload, but their intravascular volume is contracted when there is severe hypoproteinaemia. The fluid in this situation will accumulate in the subcutaneous tissues and the body cavities causing ascites and hydrothorax.

A few patients have true sodium deficit which is due to salt wasting states like interstitial nephritis. More often, however, this is due to non-renal factors such as fever, vomiting, diarrhoea and excessive diuretic use. Such patients present with thirst, dry mucus membranes, sunken eyeballs and fontanelles, orthostatic syncope, hypotension and tachycardia. Recognising this state is vital because correction by salt and water repletion can result in reversal of acute on chronic renal failure, a most satisfying result for both the patient and the treating physician.

Potassium

Hyperkalaemia is a life-threatening emergency but occurs only when there is oliguria. The non-oliguric patients will manifest hyperkalaemia when there is a concomitant metabolic acidosis, e.g. diabetic acidosis, biguanide misuse, renal tubular acidosis type 4 (hyporeninaemic hypoaldosteronism commonly seen in early diabetic nephropathy), large dietary overload of potassium and drugs like angiotensin converting enzyme inhibitors and angiotensin receptor blockers, potassium sparing diuretics like spironolactone, eplerenone, amiloride, calcineurin inhibitors like cyclosporine, tacrolimus, or beta-blockers and nonsteroidal anti-inflammatory drugs.

Hypokalaemia is usually iatrogenic due to diuretic use or from gastrointestinal losses. It may also be due to secondary hyperaldosteronism due to hyper-reninaemia of kidney disease.

Acid-Base Disorders

The kidneys excrete H^+ ions by the process of glomerular filtration and by tubular secretion of titrable acid and ammonia. The patient with early CKD has a normal anion gap acidosis with hyperchloraemia. Later, the chloride levels become normal and the accumulation of anions like phosphate, urate, hippurate and sulphate cause an increased anion gap and plasma bicarbonate levels between 14 and 20 mEq/L. Chronic acidosis also stimulates cytokine production and enhances malnutrition and protein catabolism. The bones in chronic renal acidosis will buffer hydrogen ion at the cost of calcium and phosphorus and this weaken the bones. In children, acidosis reduces growth hormone secretion and reduces stature. Appropriate alkali repletion is very useful in combating the effects of acidosis.

ENDOCRINE DYSFUNCTION OF CHRONIC KIDNEY DISEASE

Anaemia

Anaemia in CKD is due to deficient erythropoietin synthesis and is usually seen in CKD stage 3 and later. It is normochromic and normocytic. Anaemia seen in stages 1 and 2 is usually due to some other cause such as iron, B12, folate deficiency. It may also be a concomitant manifestation of the original multisystem disorder involving kidneys such as systemic lupus erythematous,

myeloma or haemolysis of haemolytic uraemic syndrome or paroxysmal nocturnal haemoglobinuria. Patients with adult polycystic kidney disease may not manifest anaemia as early as other CKD due to relatively high erythropoietin levels.

Deranged Carbohydrate Metabolism

Insulin, which is synthesised in the pancreas, is degraded by the proximal tubular cells of the kidneys. Prolonged insulin half-life due to impaired degradation has an effect of enhancing insulin levels, and therefore, relatively lowering blood glucose levels. The diabetic with incipient nephropathy often first presents to the nephrologist with recent onset of hypoglycaemic attacks or reduction in requirements of insulin or oral hypoglycaemic agents. Non-diabetic CKD patients often have mildly elevated blood glucose levels and impaired glucose tolerance which usually does not require therapeutic reduction of blood glucose.

Calcium, Phosphorus and Bone Metabolism

There is failure to excrete phosphorus, defective conversion of 25 $(OH)D_3$ to $1,25(OH)_2D_3$ which are the two most important physiological impairments that lead to renal bone disease.

At the cellular level there is defective bone which could be high due to increased PTH (i.e. hyperparathyroidism) or low due to decreased PTH (adynamic bone disease); or impaired matrix mineralisation as seen in osteomalacia or rickets (in children).

The commonest symptoms of bone disease, whatever their pathogenesis and histology are bone pains. The intensity of pain may be crippling enough to leave the patient bedridden and immobile, or trivial, requiring occasional pain medications. Pathological fractures may occur with trivial injury or spontaneously.

The altered calcium and phosphorus metabolism has extra-osseous manifestations. The accelerated coronary calcification due to an elevated calcium-phosphorus product has been dealt with later in this chapter. The elevated parathormone level is attributed the role of being a uraemic toxin. The manifestations of altered calcium, phosphorus and bone metabolism are first seen in CKD stage 3.

Uric Acid Accumulation and Gout

Renal dysfunction produces hyperuricaemia but this seldom causes secondary gout. The use of diuretics exacerbates hyperuricaemia. It is debatable whether there is a need to treat hyperuricaemia in the absence of clinical gout since this may also contribute to progression of CKD.

Dyslipidaemia

Dyslipidaemia is triggered by proteinuria and hypo-proteinaemia. It is mostly severe in the nephrotic syndrome but also seen in CKD manifesting otherwise.

CHRONIC KIDNEY DISEASE AND THE HEART

Recent focus on early CKD has shown that even patients of CKD stages 1 to 4 have a much higher cardiovascular morbidity and mortality. The CKD Registry of India showed that 28.7% patients in CKD stage 4 and as many as 48.5% patients in CKD stage 5 had prevalent cardiovascular disease.

The contributing factors to pathogenesis are hypertension, anaemia, uraemic cardiomyopathy, accelerated atherosclerosis associated with microalbuminuria, hyperlipidaemia (total cholesterol and high LDL+VLDL), cardiac calcification due to hyperparathyroidism, high phosphorus and high calcium - phosphorus product, high homocysteine levels and high C-reactive protein, hypoalbuminaemia and malnutrition producing a state of microinflammation.

Only a fraction of CKD patients reach stage 5 because of cardiovascular mortality and other natural causes of death. Prevention in CKD must therefore, encompass efforts to reduce cardiovascular morbidity and mortality in CKD stages 1 to 4, modifying the risk factors which lead to it.

Manifestations attributable to uraemic toxins are enumerated in **Table 10**.

Table 10: Manifestations Attributable to Uraemic Toxins

Cardiovascular system	
	Atheroma
	Arteriosclerosis
	Cardiomyopathy
	Decreased diastolic compliance
	Pericarditis
Nervous system	
	Concentration disturbances
	Cramps
	Dementia
	Depression
	Fatigue
	Headache
	Seizures
	Asterixis (flaps)
	Neuropathy
	Restless legs
	Sleep disorders
	Stupor, coma
Haematological system	
	Bleeding
	Hypercoagulability
Immunological system	
	Inadequate antibody formation
	Stimulation of inflammation
	Susceptibility to cancer
	Susceptibility to infection
Endocrinology	
	Dyslipidaemia
	Glucose tolerance
	Growth retardation
	Hyperparathyroidism
	Impotence, diminished libido
Bone disease	
	Adynamic bone disease
	Amyloidosis (β_2 microglobulin)
	Osteitis fibrosa
	Osteomalacia
	Osteoporosis
Skin	
	Melanosis
	Pruritus
	Uraemic frost
Gastrointestinal system	
	Anorexia
	Dyspepsia
	Hiccups
	Nausea, vomiting
Pulmonary system	
	Pleuritis
	Sleep apnoea syndrome
Miscellaneous	
	Hypothermia
	Thirst
	Uraemic foetor
	Weight loss

CONCLUSION

Screening for undiagnosed CKD and its early detection is aimed at reducing the incidence and delaying the progression to end-stage renal failure, postponing the need for dialysis or renal transplant. The average life expectancy of a 40-year-old patient with CKD after starting maintenance haemodialysis is 7 to 11 years. With appropriate intervention, if we are able to delay the onset of ESRD and protect him from cardiovascular morbidity between 40 and 60 years of age, the patient will have had 20 years of independent life. He can fulfil his social obligations, bring up his family, earn his own income and save enough so that he can himself afford to take care of his dialysis requirement for 3 to 5 years at the age of 60 years and above!

All this can only be possible if the whole medical community, and not nephrologists alone, get involved in the early diagnosis and screening for CKD.

RECOMMENDED READINGS

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19.5 Primary Glomerular Diseases

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INTRODUCTION

Glomerular diseases are classified as *primary* when the pathology is confined to the kidney and the aetiology is idiopathic or unknown. They are classified as *secondary* when part of a multi-system disorder.

The major clinical syndromes of glomerular disease are classified according to combinations of features like proteinuria, haematuria, oliguria, reduction in glomerular filtration rate, salt and water retention and hypertension (**Table 1**). Specific glomerular diseases tend to produce characteristic syndromes, but different glomerular diseases can produce the same syndrome. The diagnosis of a glomerular disease requires recognition of one of these syndromes followed by laboratory evaluation. Evaluation of pathologic features on a kidney biopsy specimen is often required for a definitive diagnosis.

Table 1: Major Glomerular Clinical Syndromes

Acute glomerulonephritis
Rapidly progressive glomerulonephritis
Asymptomatic urinary abnormalities: asymptomatic proteinuria, asymptomatic microscopic haematuria, recurrent gross haematuria
Nephrotic syndrome
Chronic glomerulonephritis

Glomerular diseases can be caused by a variety of mechanisms. Most glomerular diseases are immune mediated. Immune mediated glomerular injury is mainly of two types viz. *immune complex*-mediated injury and *antibody*-mediated injury. Immune complexes may cause injury through two mechanisms viz. (i) *in situ* formation of immune complexes through interaction of circulating antibodies with extrinsic antigens that have been planted within the glomerulus, as in post-streptococcal glomerulonephritis (PSGN), and (ii) intra-glomerular trapping and deposition in the subendothelial space or mesangium of *circulating* immune complexes formed in the systemic circulation as in mesangiocapillary glomerulonephritis. Glomerular lesions caused by anti-glomerular basement membrane antibody and anti-neutrophilic cytoplasmic antibodies (ANCA) are examples of antibody-mediated injury.

However, non-immune mechanisms also contribute to glomerular injury and these include *metabolic* injury as in diabetes mellitus, *haemodynamic* injury caused by hypertension or reduced renal mass, *deposition* injury as occurs in amyloidosis, *infection* related damage due to human immunodeficiency virus, *toxin* induced injury due to verotoxin and nonsteroidal anti-inflammatory drugs and finally *inherited* disorders as in Alport's syndrome.

ACUTE GLOMERULONEPHRITIS

The acute nephritic syndrome (ANS) is characterised by abrupt onset of haematuria, mild proteinuria, reduced glomerular filtration rate (GFR), oliguria and salt and water retention leading to hypertension. It can follow many bacterial and viral infections. The prototype is PSGN which is described in detail below. Many other systemic diseases may also present with an ANS. Evaluation of the serum complement level is a useful tool in differentiating these conditions (**Table 2**).

Table 2: Diseases Causing Acute Nephritic Syndrome, Classified according to Serum Complement Levels

Low Complement Level	Normal Complement Level
Post-infectious glomerulonephritis	IgA nephropathy
Mesangiocapillary glomerulonephritis	Idiopathic crescentic glomerulonephritis
Infective endocarditis	Anti-GBM disease
Essential mixed cryoglobulinaemia	Vasculitides
	Henoch Schönlein purpura
	Wegener's granulomatosis
	Microscopic polyangiitis
Systemic lupus erythematosus	

IgA = Immunoglobulin A; GBM= Glomerular basement membrane.

POST-STREPTOCOCCAL GLOMERULONEPHRITIS

PSGN follows infection with only certain strains of group A (β-haemolytic) streptococci, designated as nephritogenic. These include skin infection with *Streptococci M* types 2, 49, 55, 57, and 60 and throat infection with *Streptococci M* types 1, 3, 4, 12, 25, 18 and 49. Subclinical episodes occur about four times more commonly than clinical disease. PSGN can occur sporadically or as part of an epidemic. During epidemics, the clinical attack rate is nearly 10%.

PSGN is primarily a disease of children with peak incidence between ages of 2 and 12 years. The latent period following streptococcal infection is shorter for pharyngeal infection (7 to 14 days) than for cutaneous infection (3 to 4 weeks). The classical presentation of PSGN is with ANS presenting with haematuria (100%), oedema (80% to 90%), and hypertension(60% to 80%) with or without oliguria (10% to 20%).

Haematuria may be gross resulting in smoky urine or microscopic. Features of circulatory congestion and pulmonary oedema may at times dominate the clinical picture. Atypical manifestations include encephalopathy due to hypertension.

Laboratory Features

Haematuria is a universal finding. Red blood cell (RBC) casts and dysmorphic RBC are often seen in the urinary sediment. Subnephrotic proteinuria is present in more than 75% patients. GFR is usually decreased. Skin or throat cultures may reveal growth of streptococci. Antibodies to extra-cellular products of streptococci are markers of recent infection. These include anti-streptolysin, anti-nicotinamide adenine dinucleotidase, anti-hyaluronidase (AHase), and anti-DNAse B after pharyngitis,

and anti-DNAse B and AHase titers following skin infections. Generally, the antibody titers are elevated at 1 week, peak at 1 month, and fall toward pre-infection levels after several months. Serum levels of C3 are low at presentation and return to baseline within 8 to 12 weeks. Alternate complement pathway is activated. Prolonged hypocomplementemia suggests an alternative diagnosis. Fractional excretion of sodium is low. Circulating immune complexes and cryoglobulins are found in 60% of cases. Anaemia and hypoalbuminaemia may be seen due to haemodilution. Nephrotic syndrome is unusual.

Pathology

Light microscopy reveals a diffuse exudative endocapillary proliferative glomerulonephritis (**Figure 1**). All glomeruli are affected and usually to an equal degree. The glomerular tufts are larger than normal and hypercellular. The cell types typically present include endothelial and mesangial cells and polymorphonuclear leucocytes. Sometimes there is extracapillary proliferation leading to crescent formation. Immunofluorescence microscopy reveals granular deposition of IgG and C3 in the mesangium and along capillary walls. Electron microscopy characteristically reveals discrete subepithelial electron dense deposits. Renal biopsy is indicated only in atypical cases with rapidly deteriorating renal function or nephrotic range proteinuria.

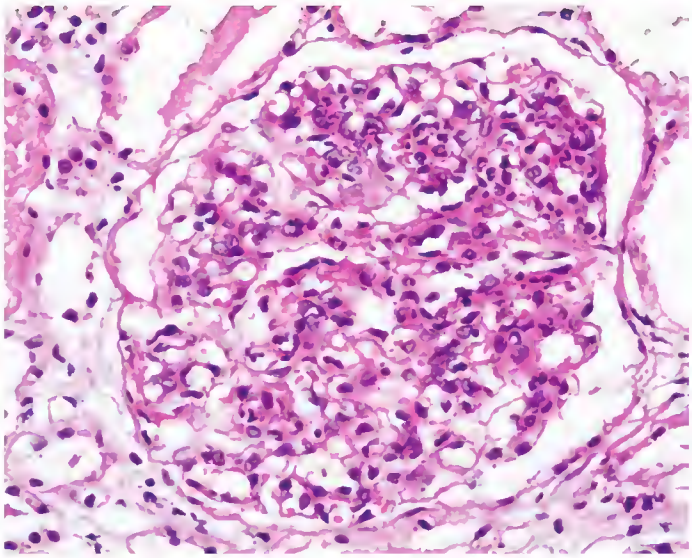


Figure 1: Glomerulus is enlarged and hypercellular due to inflammatory cell infiltration along with proliferation of endothelial cells (PSGN).

Therapy and Course

Anti-streptococcal drugs given to patients, family members and immediate contacts may limit the spread of infection. However, early anti-microbial therapy does not have any impact on the subsequent development of PSGN. Oedema responds to diuretics and salt restriction while antihypertensive agents are used to control hypertension. Most cases are expected to undergo spontaneous recovery within 1 to 2 weeks. In children the prognosis is excellent. Complete recovery occurs in 95% of cases. Bad prognostic markers include late age of onset, sporadic disease, massive proteinuria, sustained hypertension and presence of crescents on light microscopy.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

RPGN is characterised by a rapid and progressive decline in renal function over days to weeks because of underlying glomerular disease. If left untreated it leads to end stage renal failure over weeks to months. RPGN has to be differentiated from other causes of rapidly progressive renal failure (RPRF). There are many causes of RPRF including malignant hypertension and scleroderma renal crisis. In RPGN, there is an underlying glomerulonephritis which leads to RPRF.

RPGN is also known as crescentic glomerulonephritis because of the frequent presence of extensive pathognomonic crescents (**Figure 2**). Crescents are defined as the presence of 2 or more layers of cells in Bowman's space. The cells in the crescent are derived predominantly from monocytes (macrophages) that have gained entry into Bowman's space through damaged capillaries and from parietal epithelial cells lining the space.

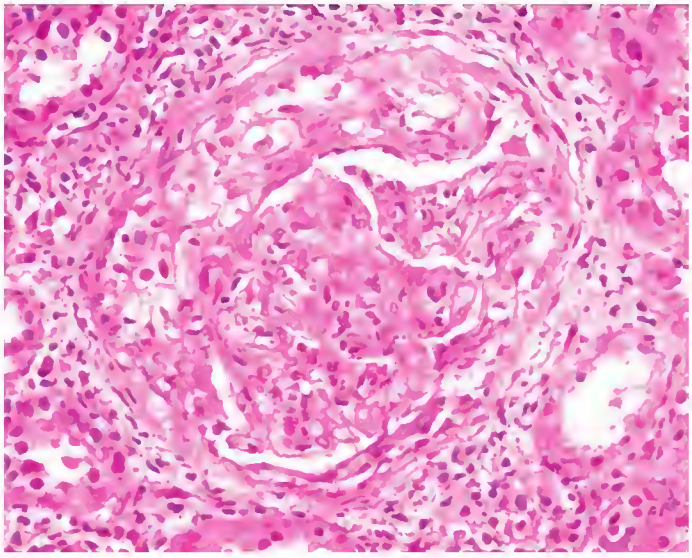


Figure 2: RPGN—Glomerular tuft is collapsed with the "epithelial crescent" on top left side.

The pattern of antibody deposition on immunofluorescence and presence or absence of ANCA is useful in classifying RPGN into three types viz., Type I (anti GBM disease), Type II (immune complex mediated), Type III (pauci-immune with ANCA positivity) (**Table 3**).

Table 3: Diseases Associated with Crescentic Glomerulonephritis

Primary glomerular diseases
Idiopathic crescentic glomerulonephritis (GN) (Types I-III)
Superimposed on other primary glomerular disease
Mesangiocapillary GN, IgA nephropathy
Associated with infectious diseases
PSGN, infective endocarditis, visceral abscess
Associated with drugs
Penicillamine, rifampicin
Associated with multisystem diseases
Systemic lupus erythematosus
Goodpasture's disease
Cryoglobulinaemia
Vasculitides
Wegener's granulomatosis
Churg-Strauss syndrome
Microscopic polyangiitis
Henoch-Schönlein purpura

PRIMARY CRESCENTIC GLOMERULONEPHRITIS TYPE I (ANTI-GBM ANTIBODY MEDIATED)

This type constitutes 5% to 10% of RPGN. It has a bimodal age distribution occurring between 20 and 30 years or 50 and 70 years with male preponderance. It is characterised by presence of either circulating or basement membrane bound anti-GBM antibodies. It may be precipitated by an influenza like illness or exposure to hydrocarbons and smoking.

Clinical Features

Mostly the onset is insidious but at times it may be abrupt. Oliguria and azotemia are early manifestations. Hypertension, if present, is usually mild. Absence of pulmonary haemorrhage differentiates this condition from Goodpasture's disease.

Laboratory Features

Urine microscopy usually reveals active urinary sediment with RBC casts and dysmorphic RBCs. Serum complement is normal. Circulating anti-GBM antibodies are detectable in plasma. Chest radiograph reveals bilateral infiltrates due to alveolar haemorrhage in those with Goodpasture's disease. Anaemia may be out of proportion to renal dysfunction due to pulmonary haemorrhage.

Pathology

Light microscopy shows extensive crescent formation in various stages of development involving more than 50% of the glomeruli. The glomerular tuft is compressed by proliferation of epithelial cells that occupy most of the Bowman's space. Crescents are cellular to begin with and later become fibrous. IF reveals smooth linear deposition of IgG on the basement membrane often accompanied by C3 deposition.

Treatment and Course

The two principles of therapy are: (1) rapid removal of circulating antibody, primarily by plasmapheresis; and (2) stopping further production of antibodies using immunosuppression. Aggressive therapy must be initiated early to prevent permanent renal dysfunction. Therapy hinges on intensive 2 to 4 litre plasma exchanges on alternate days for two weeks in conjunction with oral steroids and cyclophosphamide. Immunosuppressive therapy is required to inhibit antibody production and rebound hypersynthesis, which may occur following discontinuation of plasma exchange. Cyclophosphamide 2 mg/kg orally is instituted and continued for 6 months. Prednisolone at (1 mg/kg) is also initiated and gradually tapered over 6 months following clinical remission. With this therapy circulating antibody usually falls to undetectable levels within a few weeks. Before the availability of current therapy, the mortality rate was more than 90%, with a mean survival time of less than 4 months. Currently, with the combination of plasmapheresis, corticosteroids, and cyclophosphamide, the mortality rate has been reduced to less than 20%. Bad prognostic markers are circumferential and fibrous crescents, tubulointerstitial fibrosis and serum creatinine more than 6 mg/dL at presentation.

TYPE II (IMMUNE COMPLEX MEDIATED) CRESCENTIC GLOMERULONEPHRITIS

Clinical Features

It accounts for approximately 30% to 50% of all cases of idiopathic crescentic glomerulonephritis and most frequently affects children and young adults. Both sexes are affected equally. Patients are usually normotensive; hypertension if present is mild. Renal function may be deranged at presentation and rapidly deteriorates if left untreated.

Laboratory Features

There is active urinary sediment along with subnephrotic proteinuria. Complement levels are low. Anti-GBM antibodies and ANCA are notable by their absence.

Pathology

Crescents are present in more than 50% of glomeruli along with endocapillary proliferation. Immunofluorescence typically shows scattered deposits of IgG and IgM in the mesangium and peripheral capillary loops usually in association with C3. Electron microscopy reveals electron dense deposits in the mesangium and subepithelial region.

Course and Therapy

Spontaneous remission may often occur in children. Others should be treated with pulse methylprednisolone infusion 1000 mg intravenously for 3 days followed by oral steroids in tapering doses for 3 months. In dialysis dependent patients there may be a role for cytotoxic agents.

TYPE III (PAUCI-IMMUNE) CRESCENTIC GLOMERULONEPHRITIS

Clinical Features

Many of these patients have some form of small vessel vasculitis in which the kidneys are predominantly involved. It constitutes about 50% of all cases of crescentic glomerulonephritis.

This disorder tends to involve middle aged persons, with a slight male preponderance. Constitutional symptoms like fever, malaise, weight loss and symptoms suggestive of vasculitis like skin rash (palpable purpura), joint pain and abdominal pain may be present.

Laboratory Features

Urine analysis is similar to other types of crescentic glomerulonephritis. Anti-GBM antibodies, circulating immune complexes, rheumatoid factor and cryoglobulins are absent. Complement levels are normal. The hallmark of this condition is the presence of p-ANCA with specificity for anti-myeloperoxidase autoantibodies in the majority (70%) of patients; a small fraction (20%) may have c-ANCA with specificity for proteinase-3.

Pathology

Apart from the ubiquitous crescents, segmental or diffuse necrotising lesions are frequently seen in the glomeruli indicative of underlying vasculitis. Immunofluorescence typically reveals paucity or absence of immune deposits. Fibrin related antigens may be seen in the crescents.

Course and Therapy

Most patients are treated with pulse steroids to begin with followed by a combination of steroids along with daily oral or intermittent pulse cyclophosphamide. The dose of methyl-prednisolone is 7 mg/kg per day intravenously (not to exceed 1 g) for 3 days, followed by oral prednisone at 1 mg/kg per day (not to exceed 80 mg) for 4 weeks, and then tapered off gradually over 6 months. Relapses may occur later in the course of the

disease. The only predictor of renal survival is the serum creatinine value at the time of diagnosis. Intravenous and oral cyclophosphamide are equally efficacious. Intravenous therapy is initially administered at a dose of 0.5 g/m^2, and the oral dose is 2 mg/kg per day. Plasmapheresis should be done in dialysis dependent patients only. After induction of remission which takes 3 to 6 months, patients may be put on maintenance therapy with azathioprine. The prognosis of this condition is intermediate between type I and type II crescentic glomerulonephritis.

IMMUNOGLOBULIN A NEPHROPATHY (IgAN)

This entity was first described by Berger and Hinglais in 1968. While Henoch-Schönlein purpura (HSP) is diagnosed when purpura is associated with arthralgia, abdominal pain and concomitant glomerulonephritis, IgAN is the monosymptomatic form of HSP in which there are no extra-renal manifestations. It is the most common form of primary glomerular disease in some parts of south east Asia but accounts for only 5% of glomerular disease in India. The male to female ratio is 2:1. Familial cases have also been described. It is most commonly seen in the second and third decades of life. It is sometimes associated with other conditions like cirrhosis of liver, gluten enteropathy, dermatitis herpetiformis, Crohn's disease and seronegative arthropathy.

Clinical Features

Presentation of IgAN is highly variable, both clinically and pathologically. Clinical features range from asymptomatic gross haematuria which is often recurrent (40% to 50%) to asymptomatic urinary abnormalities (30%), nephritic syndrome, nephrotic syndrome (10%) and rarely RPGN. There may be associated loin pain during episodes of gross haematuria. Spontaneously resolving acute renal failure (ARF) can occur. ARF may be due to crescentic glomerulonephritis or due to tubular occlusion by RBCs. Episodic, gross haematuria is more common in younger people, whereas an abnormal urine sediment is more frequent in older individuals. At times episodes of haematuria immediately follow an upper respiratory catarrh, the so called 'synpharyngitic' nephritis. Patients are usually normotensive, but hypertension may occur later in a minority.

Pathophysiology

The pathogenesis of IgAN remains incompletely understood. Immunofluorscence findings of granular deposits of IgA and C_3 in the mesangium suggest that this disease is the result of the deposition of circulating immune complexes. Deposited IgA is predominantly polymeric IgA1, which is mainly derived from the mucosal immune system.

Laboratory Features

Urine analysis invariably reveals microscopic haematuria and proteinuria in the subnephrotic range. GFR is usually normal at presentation but can decline during bouts of gross haematuria. Serum IgA levels are increased in upto 50% of patients. C_3 and C_4 are usually normal. Skin biopsies may reveal dermal capillary deposits of IgA in up to 50% patients.

Pathology

Almost any glomerular lesion with the possible exception of membranous nephropathy may be seen in patients of IgAN. The most common light microscopy findings are focal, or more often, diffuse increase in mesangial cellularity and mesangial matrix with intracapillary or extracapillary proliferative lesions. Interstitial fibrosis, tubular atrophy and vascular sclerosis may be seen in advanced disease. Immunofluorescence findings are diagnostic of this disease. Immunofluorscence shows predominant IgA deposition in a diffuse granular pattern in the mesangium and occasionally in the capillary wall. Some IgG and C3 deposits may accompany IgA. Electron microscopy shows electron dense deposits in the mesangium.

Course and Therapy

Although this disease usually follows a relatively benign course, end-stage renal disease (ESRD) occurs in 15% to 20% of patients within 10 years. Currently no cure exists for IgAN. Majority of patients require management of proteinuria and hypertension with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Steroids should be used only in those with nephrotic range proteinuria. Patients with crescentic glomerulonephritis can be treated similarly to patients with idiopathic RPGN by using intravenous pulse methylprednisone followed by oral prednisone and cyclophosphamide. Poor prognostic factors are male gender, older age, hypertension, renal insufficiency at presentation, nephrotic range proteinuria, diffuse proliferative lesions associated with crescents, tubular atrophy and interstitial fibrosis.

NEPHROTIC SYNDROME

The nephrotic syndrome is characterised by heavy proteinuria (>3.5 g/24 hours/1.73m^2 in adults and >40 mg/m^2 per hour in children) leading to hypoalbuminaemia and oedema. The spot urinary protein to creatinine ratio is in excess of 3.5. Oedema is the commonest manifestation of the nephrotic syndrome. Pathogenesis of oedema may be explained by the 'underfill theory' according to which, hypoalbuminaemia lowers the plasma colloid osmotic pressure, causing greater transcapillary filtration of water throughout the body and thus the development of oedema. Oedema may also be explained by the 'overfill theory', according to which primary renal sodium retention causing an increased blood volume provokes oedema. Oedema initially develops around the eyes and ankles. With time, it becomes generalised and may be associated with an increase in weight, the development of ascites and pleural effusions. Hypertension, haematuria, and azotemia may also occur. Hyperlipidaemia (elevated total cholesterol, triglycerides, low and very low density lipoproteins) and lipiduria is also common. This results from hypoproteinaemia stimulating protein, including lipoprotein synthesis by the liver, and diminution of lipid catabolism caused by reduced levels of lipoprotein lipase.

Concomittant losses of other plasma proteins may lead to various complications. The loss of antithrombin III and plasminogen in urine, along with the increase in clotting factors, especially factors V, VII, VIII, and X, and fibrinogen increases the risk for venous and arterial thrombosis and pulmonary embolism. In children, arterial thromboses are more common whereas in adults, thromboses are more common in the venous territory. The risk of thrombosis is inversely related to serum albumin concentration. Vitamin D-binding protein may be lost in the urine, leading to hypovitaminosis D, with malabsorption of calcium. Urinary losses of Ig and a complement factor

(properdin factor B) that opsonises certain bacteria may increase the risk of sepsis due to capsulated organisms. The most common infectious complications are cellulitis, pneumonia, and peritonitis. Iron resistant anaemia may result from urinary losses of transferrin. Hypovolemia, raised intra-renal interstitial pressure and intra-tubular obstruction due to casts may lead to acute renal failure.

Examination of urine is mandatory in all cases of suspected nephrotic syndrome. Nephrotic range proteinuria will be apparent by 3+ or 4+ readings on the dipstick. The urine sediment may show red cells and/or casts. By use of a polarising microscope, one can see oval fat bodies and fatty casts.

In addition to specific therapy, supportive measures like adequate protein intake, salt restriction and use of diuretics, control of hypertension and hyperlipidaemia and minimisation of proteinuria with ACE inhibitors or ARBs should be instituted. Routine immunisations in children should be delayed until the patient is off immunosuppression for 3 months. Pneumococcal and influenza vaccination are recommended in all adults.

Although a renal biopsy is necessary for confirmation of the histologic diagnosis, the age of onset, selectivity of proteinuria, activity of urine sediment, presence or absence of hypertension, serum complement levels and presence of renal insufficiency can help to distinguish between the four primary glomerular diseases (**Table 4**).

Table 4: Differential Diagnosis of Primary Glomerular Diseases with a Nephrotic Syndrome

Histology	Age	Proteinuria	Microscopic Haematuria	Hyper-tension	↓GFR	C3
MCD	Children	Selective	–	–	–	N
FSGS	Children and Adults	Nonselective	±	+	±	N
MGN	Older adults	Nonselective	±	±	–	N
MPGN	Children and adults	Nonselective	++	++	++	–

MCD = Minimal change disease; FSGS = Focal segmental glomerulosclerosis; MGN = Membranous glomerulonephritis; MPGN = Membranoproliferative glomerulonephritis.

PRIMARY GLOMERULAR DISEASES CAUSING NEPHROTIC SYNDROME

Minimal Change Disease

Minimal change disease (MCD) is the most common cause (85%) of nephrotic syndrome in children. The incidence peaks in children aged 2 years, with approximately 80% being younger than 6 years at the time of diagnosis. It also occurs in adults in whom it accounts for 15% to 20% of all nephrotics. Almost all cases are idiopathic, but a very small minority may have an identifiable cause such as non steroidal anti-inflammatory drugs or Hodgkin's lymphoma.

Clinical Features

In children, there is a male preponderance (2:1), whereas both sexes are equally affected in adults. Onset is usually abrupt following an upper respiratory catarrh. History of atopy may be forthcoming in children. Oedema is a prominent feature. Heavy proteinuria over an extended period of time may lead to a state of protein malnutrition. Hypertension is unusual.

Laboratory Features

Nephrotic range proteinuria is almost invariably seen. Proteinuria is typically highly selective (IgG/Transferrin clearance <0.1). Microscopic haematuria is unusual. Renal function is usually normal. In children, the diagnosis can be confirmed by a complete remission induced by steroids and a renal biopsy is not required. In adults, however, since MCD is not as common, a biopsy is required before therapy.

Pathology

On light microscopy the glomeruli appear normal (**Figure 3**). Protein and lipid droplets may be seen in tubular epithelial cells. There is no significant glomerular deposition of immunoglobulins or complement on immunofluorscence. Electron microscopy reveals retraction of the epithelial foot processes along with obliteration of slit pores.

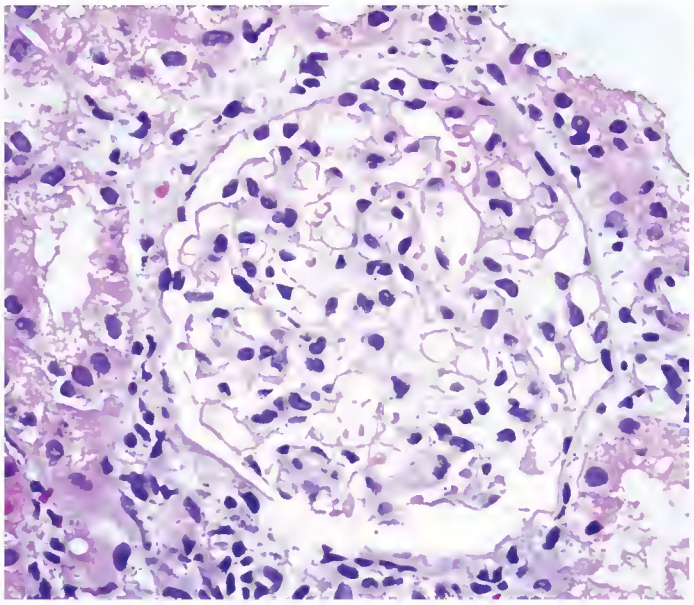


Figure 3: MCD—Glomerulus showing normal morphology on light microscopy.

Course and Therapy

Corticosteroids are the mainstay of therapy. Prednisolone is given in a dose of 60 mg/m^2 per day for 6 weeks followed by 40 mg/m^2 on alternate days for 6 weeks in children. In adults prednisolone is given at 1mg/kg per day usually not exceeding 80 mg/day and the duration of therapy may have to be prolonged to achieve remission. Approximately 90% of children respond within 2 weeks to steroids whereas the time to remission is up to 16 weeks in adults.

Depending on the response to steroids, patients may be classified as *primary responders* with no relapse, *infrequent relapsers, frequent relapsers*—initial steroid response with >2 relapses in first 6 months or >3 in a year, *steroid dependent*—relapse when steroids are being tapered or within 2 weeks of cessation of steroids and *steroid resistant*—if no reduction in proteinuria occurs by 12 to 16 weeks.

In patients who need steroids repeatedly for relapses or are steroid dependent, cyclophosphamide (2 mg/kg/day) for 12 weeks may be given to induce a prolonged remission. Cyclosporine (3 to 4 mg/kg/day) can also be used in patients with frequent relapses or steroid dependency. The prognosis is excellent for steroid responsive patients with 25 years survival in excess of 90%.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

FSGS was first described in 1957 by Arnold Rich. FSGS may be idiopathic or secondary (**Table 5**). The primary pathophysiologic process in FSGS is an injury inherent within or directed to podocytes.

Table 5: Diseases Associated with Focal Segmental Glomerulosclerosis (FSGS)

Primary (idiopathic) FSGS
Secondary
Genetic: Mutations in podocin, a- actinin 4
Reduced nephron mass: Solitary kidney, vesicoureteric reflux, renal allograft
Drugs: Heroin, Lithium, Pamidronate
Haemodynamic causes: Sickle cell disease, morbid obesity
Infections: Human immunodeficiency virus, parvovirus
Miscellaneous: Alport's syndrome, sarcoidosis, lymphoma

Clinical Features

The incidence of FSGS has been increasing in the last decade and it now accounts for 25% to 30% of idiopathic nephrotic syndrome in adults and 10% to 20% in children. The lesion is 3 times more common in males. Nephrotic syndrome is the most common clinical presentation. Less than a third of patients with FSGS present with subnephrotic proteinuria. Hypertension is seen in 50% of patients. Onset is typically insidious. Frequently, the onset of oedema follows a recent upper respiratory catarrh.

Laboratory Features

Proteinuria is typically nonselective. Microscopic haematuria is common. Serum creatinine concentration is usually normal in early stages. Serum complement levels are normal. Patients may have proximal tubular defects manifesting as renal glycosuria and aminoaciduria.

Pathology

The characteristic lesion in FSGS is focal and segmental solidification of the glomerular tuft, usually in the perihilar region (**Figure 4**). The capillaries are segmentally obliterated by accumulation of acellular matrix and hyaline deposits, along with adhesion to the Bowman's capsule (synechiae formation). Initially lesions appear in the juxtamedullary cortex. Globally sclerosed glomeruli may be seen with disease progression. Many morphologic subsets, such as a cellular variant (endocapillary hypercellularity), a collapsing variant (FSGS with mesangial hypercellularity), and FSGS with tip lesions, have been described. On immunofluroescence, granular deposits of IgM and C3 are often found in the sclerotic areas. On electron microscopy, most of the glomeruli show segmental foot process effacement.

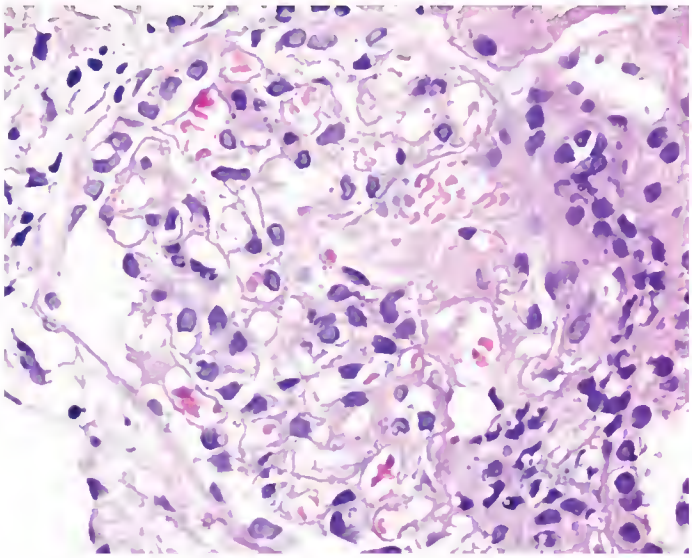


Figure 4: FSGS—Glomerulus showing a focus of sclerosis at the hilar end at 3 o'clock position.

Course and Therapy

The typical course is characterised by oedema that is difficult to manage, proteinuria that is refractory to corticosteroids and immunosuppressive agents, worsening hypertension and a progressive loss of renal function. Ten-year renal survival is in the range of 40% when nephrotic syndrome is present and up to 85% when proteinuria is subnephrotic. Corticosteroid therapy (1 mg/kg/day) may be given and may have to be extended to six months to induce remission. Lasting remission occurs in 20% to 30%, a relapsing course in 15% and a steroid unresponsive course with progressive renal insufficiency in about 60%. In steroid dependent cases cyclophosphamide or cyclosporine may be tried. Prolonged use of cyclophosphamide may lead to gonadal toxicity; therefore, persisting with cyclophosphamide beyond 3 months in patients who do not respond is unwise. Cyclosporine may be beneficial in patients unresponsive to prednisone and cyclophosphamide. Those with an older age of onset, male sex, massive proteinuria, persistent hypertension, initial abnormal GFR, hilar glomerulosclerosis, collapsing variant and severe mesangial proliferation on kidney biopsy have worse outcomes. Recurrence rate after kidney transplantation is up to 30%.

MEMBRANOUS GLOMERULONEPHRITIS (MGN)

MGN is the commonest cause of nephrotic syndrome in adults accounting for about 25% of all cases. The male-to-female ratio is 2:1 with a peak incidence in fourth and fifth decades. It can be primary (80%) or secondary (20%) (**Table 6**). Primary disease has recently been shown to be caused by antibodies to the phospholipase A_2 receptor. Onset before 20 years or after 60 years of age is more likely to be associated with secondary causes. In adults, systemic lupus erythematosus is the commonest cause, while in children hepatitis B is the commonest cause of secondary MGN.

Table 6: Diseases Associated with Membranous Nephropathy

Primary
Secondary
Auto-immune disease: Ankylosing spondylitis, dermatomyositis, mixed connective-tissue disease, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis
Infections: Filariasis, hepatitis B, hepatitis C, leprosy, Quartan malaria
Malignancies: Carcinoma (lung, colon, breast, stomach), lymphoma
Drugs: Captopril, gold, mercurials, penicillamine
Miscellaneous: *De novo* in renal allografts, sarcoidosis, sickle cell disease

Clinical Features

The onset is insidious. Most of the patients present with a nephrotic syndrome while 20% present with subnephrotic

proteinuria. Hypertension may be present but is not characteristic of the disease in its early stages. Azotaemia occurs late in the course of the disease. There is an increased propensity for renal vein and deep vein thrombosis and embolic complications.

Laboratory Features

Nephrotic range proteinuria which is non-selective is seen in over 80% of patients. Microscopic haematuria may be seen in a minority. Serum complement levels are usually normal. Screening for secondary forms may be done where appropriate. An exhaustive work-up for malignancy is not recommended. An age-appropriate health screening (mammography, sigmoidoscopy) should be performed. Other tests include antinuclear antibodies, hepatitis B serology, anti-hepatitis C antibodies and cryoglobulins.

Pathology

All glomeruli are involved. The characteristic feature on light microscopy is diffuse and uniform thickening of capillary basement membrane with patent lumina and without any proliferation of endothelial or epithelial cells. The mesangium is normocellular (**Figure 5**). On silver stain, spikes may be seen on the outer aspect of the basement membrane. Immunofluroescence reveals uniform granular deposits of IgG and C3 outlining all the capillaries but sparing the mesangium. On electron microscopy, 4 stages of MGN have been described, viz. *stage 1*: basement membrane appears normal using light microscopy, but, with electron microscopy, subepithelial electron-dense deposits are seen along the capillary walls; *stage 2:* numerous and larger deposits with spikes in between adjacent deposits are seen; *stage 3:* the spikes extend and completely surround the deposits; and *stage 4:* electron-dense deposits become more lucent giving the basement membrane a 'swiss cheese appearance'.

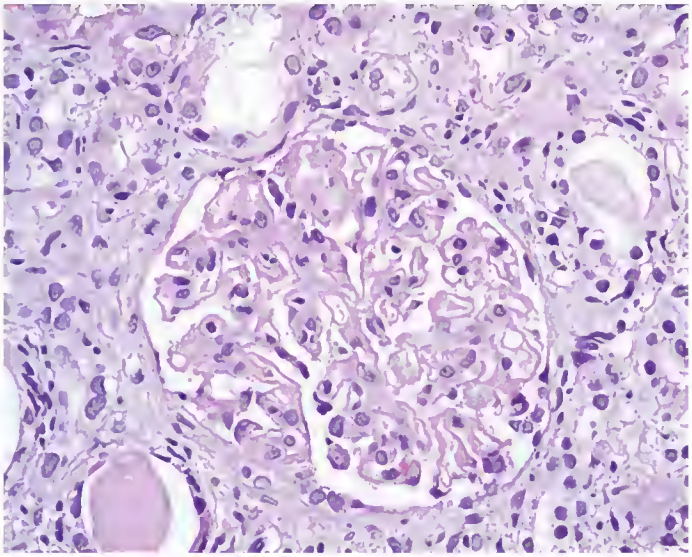


Figure 5: MGN—Glomerulus showing diffusely thickened capillary walls.

Course and Therapy

According to the course of the disease, patients may be divided into 3 groups of approximately equal size, viz. (i) one-third have a spontaneous complete remission which occurs within the first 2 years of onset, (ii) one third have persistent proteinuria with stable renal function, and (iii) one-third progress to ESRD over a decade. The incidence rate of ESRD is 14% at 5 years, 35% at 10 years, and 41% at 15 years. Poor prognostic markers are male sex, older age at onset, uncontrolled hypertension, reduced GFR at presentation, persistent heavy proteinuria and renal histology showing focal glomerulosclerosis and interstitial fibrosis.

Due to the indolent nature of the disease and tendency for spontaneous remission, not all patients need treatment; however, they must be followed up closely. Patients with persistent massive proteinuria, thromboembolism, and or renal insufficiency at presentation merit treatment. Oral glucocorticoids are not effective. The modified "Ponticelli regimen" comprising of sequential therapy in alternate months with high dose pulse methyl prednisolone for 3 days followed by oral prednisolone 0.5 mg/kg per day for 27 days in months 1, 3 and 5 and oral cyclophosphamide 2 mg/kg per day in months 2, 4 and 6 increases the likelihood of complete or partial remission. Cyclosporine may be tried in those patients in whom the above regimen cannot be used or is ineffective. Recently, mycophenolate mofetil has been used with some success. Promising results have also recently been obtained with rituximab, a monoclonal antibody against the CD20 antigen of B lymphocytes.

Anti-coagulation is indicated in those who have a thromboembolic complication and should continue until hypoalbuminaemia has been corrected.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN)

Also called mesangiocapillary glomerulonephritis, MPGN accounts for approximately 10% of adults with a nephrotic syndrome. On the basis of immunopathology and ultrastructure analysis, 3 subtypes are recognised. MPGN types I and III are variants of immune complex-mediated disease while MPGN II has no known association with immune complexes. MPGN may be either primary or secondary (**Table 7**).

Table 7: Diseases Associated with MPGN

Primary (idiopathic)
Type I, Type II (dense deposit disease) and Type III
Secondary
Auto-immune disease: Systemic lupus erythematosus, Sjögren's syndrome, cryoglobulinaemia
Infections: Hepatitis B, hepatitis C, infective endocarditis, visceral abscess, infected shunts, leprosy
Malignancies: Leukaemia, lymphoma, carcinoma
Miscellaneous: Sickle cell disease, healing phase of HUS/TTP

HUS = Haemolytic uraemic syndrome; TTP =Thrombotic thrombocytopaenic purpura.

Clinical Features

The disease affects all age groups but is unusual in children less than 5 years old with a peak incidence in the second and third decades. MPGN type I affects women more than men while the sex ratio is equal in type II MPGN. There is a preceding upper respiratory infection in as many as 50% of patients. Patients may present in one of five ways, viz. (i) asymptomatic proteinuria and haematuria detected on routine urinalysis, (ii) nephrotic syndrome, (iii) ANS, (iv) rapidly progressive renal failure, and (v) proteinuria and haematuria are often found together (nephritic-nephrotic presentation). Hypertension

is present in approximately 80% of patients at onset. A strong association is present between partial lipodystrophy and dense deposit disease. Finding of Drusen on fundus examination in a patient with glomerulonephritis suggests MPGN type II.

Laboratory Features

Nephrotic range proteinuria is seen in 50% of patients. Urine microscopy reveals an active urinary sediment. Hypocomplementemia is a characteristic finding in all types of MPGN. In MPGN type I, C3 levels are low in 70% patients and there is activation of the classic pathway of complement. In MPGN type II, C3 levels are low in 70% to 80% of patients due to activation of the alternate pathway. The pathogenesis of membranoproliferative glomerulonephritis type II is not known. C3 nephritic factor (C3 NeF) is present in more than 70% of patients. C3 NeF is an autoantibody to C3b,Bb. The binding of C3 NeF to C3b, Bb stabilises the complex, preventing degradation by its normal inactivators, resulting in complement activation and chronic consumption of C3. In type III MPGN, C3 levels are decreased in 50% of patients.

Pathology

On light microscopy, glomeruli are enlarged and hypercellular, with an increase in mesangial cellularity and matrix. Mesangial expansion leads to lobular accentuation. The capillary basement membranes are thickened by interposition of mesangial matrix into the capillary wall leading to a tram-track appearance (**Figure 6**). Crescents may be visible in 10% of biopsy specimens. On Immunofluroescence, C3 deposits are seen in a granular pattern in the capillary walls and mesangium along with IgG and IgM deposits. On electron microscopy, electron dense deposits in subendothelial sites are characteristic of this disease. In type II disease on light microscopy, the basement membranes of the glomerulus, Bowman's capsule, tubules, and peritubular capillaries are thickened. The basement membrane appears irregular and ribbon like on special stains. On immunofluroescence, C3 is deposited in an irregular granular pattern in the basement membranes on either side but not within the dense deposits or the mesangium. On electron microscopy, the basement membrane is thickened by discontinuous, amorphous, electron dense deposits in the lamina densa.

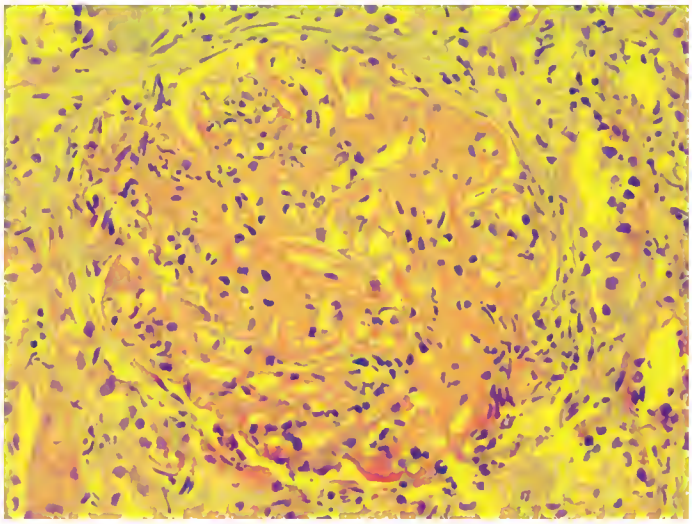


Figure 6: MPGN—Glomerulus showing lobular accentuation with increase in cellularity and mesangial matrix.

Course and Therapy

MPGN type I is a progressive disease, with 15% of non-nephrotics and 60% of nephrotics developing ESRD after 10 years. MPGN type II generally is more aggressive than MPGN type I and has a median renal survival of 5 to 12 years. The main predictors of an adverse outcome are nephrotic syndrome, hypertension and low GFR at presentation, older age, crescent formation, interstitial fibrosis and tubular atrophy. The optimal treatment of idiopathic MPGN is not clearly defined. The underlying cause of secondary forms of MPGN should be treated. Patients with hepatitis B virus–associated often go into spontaneous remission but may benefit from antiviral agents. Patients with HCV related disease and cryoglobulinaemia may benefit from antiviral treatment including interferon and ribavarin. Steroid therapy has proven to be beneficial only in children.

RECOMMENDED READINGS

1. Floege J, Feehally J. Introduction to glomerular disease. In: Feehally J, Floege J, Johnson R, editors. *Comprehensive Clinical Nephrology;* 3rd Ed, Philadelphia: Mosby-Elsevier; 2007: pp193-208.
2. Jennette JC, Falk RJ. Glomerular clinicopathologic syndromes. In: Greenberg A, editor. *Primer on Kidney Diseases;* 5th Ed, Philadelphia: Saunders Elsevier; 2009: pp148-59.
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19.6 Secondary Glomerular Diseases

OP Kalra

INTRODUCTION

Glomerular diseases may occur during the course of various systemic disorders such as collagen vascular diseases, neoplastic conditions, infectious diseases, amyloidosis, heredofamilial conditions, etc. In any patient presenting with glomerular disease, the clinician must always look for signs and symptoms of various systemic diseases which may be diagnosed for the first time on doing various biochemical and serological investigations or on renal biopsy, such as systemic lupus erythematosus (SLE), amyloidosis, etc.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is characterised by a wide spectrum of involvement of various organ systems coupled with various laboratory abnormalities, such as development of antibodies directed against various nuclear components, typically double stranded deoxyribonucleic acid (DNA). It predominantly affects women during their childbearing years. Female to male ratio is 10:1. Lupus nephritis (LN) is a frequent and potentially serious complication of SLE. Approximately 30% to 70% patients with well documented lupus have evidence of renal involvement. LN usually develops within 2 to 3 years after the diagnosis of SLE. However, renal biopsy studies show some evidence of involvement due to lupus in majority of the cases.

Aetiopathogenesis

LN is characterised by production of wide variety of autoantibodies against various nuclear components. Overactivity of B-cells associated with defects in T-cell auto-regulation play a crucial role. Certain genetic and environmental factors play a significant role in the development of disease. Patients with SLE have been found to inherit certain specific human leucocyte antigen (HLA) haplotypes (e.g., HLA-B8, DR3) with a higher frequency. Besides this, viral or bacterial peptides may precipitate the disease. Patients with clinical renal disease have been found to have high titres of auto antibodies directed against double stranded DNA (anti-dsDNA) antibodies and these bind the complement more avidly.

A few drugs have been implicated in inducing lupus-like disease in persons who are predisposed to the disease. These include procainamide, phenytoin, methyldopa, isoniazid, penicillamine, sulfonamides and few other drugs. Clinical features include mainly musculoskeletal manifestations; however, renal involvement is very uncommon. Majority of the patients have antihistone antibodies. Presence of elevated anti-dsDNA antibodies and low serum complement level is unusual. Most patients achieve remission following cessation of offending drug.

Pathology

A wide spectrum of histopathological changes may be seen which may involve every structure of the kidney. LN is a classical example of immune complex mediated glomerulonephritis. Even in the absence of clinically evident renal disease and normal renal histology on light microscopy, immunofluorescence studies may demonstrate evidence of deposition of immunoglobulins and complements. The location of immune deposits and the host response may result in a wide spectrum of renal lesions which may range from normal looking glomeruli to sclerotic glomeruli. The World Health Organisation (WHO) classification of LN has now been replaced by International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification as shown in **Table 1**.

Table 1: The 2003 ISN/RPS Classification of Lupus Nephritis (LN)

Class I	Minimal mesangial LN → Normal glomeruli but presence of mesangial immune deposits on immunofluorescence
Class II	Mesangial proliferative LN → Mesangial hypercellularity along with mesangial immune deposits
Class III	Focal LN (<50% of glomeruli) → It may be focal, segmental or global endo- or extra-capillary glomerulonephritis III (A) : Active lesions III (A/C) : Active and chronic lesions III (C) : Chronic lesions
Class IV	Diffuse LN (≥50% of glomeruli) (**Figure 1**) Diffuse segmental (IV-S) or global (IV-G) LN IV (A) : Active lesions IV (A/C) : Active and chronic lesions IV (C) : Chronic lesions
Class V	Membranous LN (may occur in combination with Class III or IV LN)
Class VI	Advanced sclerosing LN (≥90% glomeruli globally sclerosed)

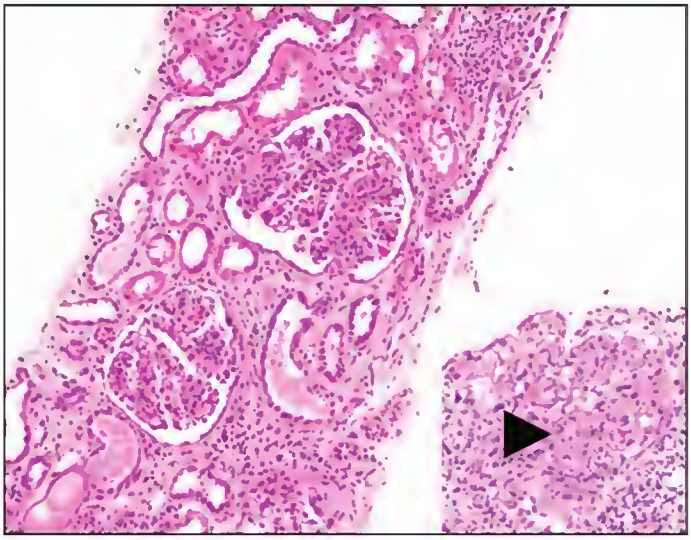


Figure 1: Lupus nephritis Class IV: There is uniformly diffuse and global endocapillary proliferation and neutrophilic infiltration. There is patchy tubulo-interstitial inflammation. (Haematoxylin-Eosin x 100). *Inset:* Higher power view of another glomerulus showing fibrinoid deposits (arrowhead) and tuft necrosis (Haematoxylin-Eosin x 200).

Cellular proliferation, fibrinoid necrosis, polymorphonuclear infiltration, karyorrhexis, haematoxylin bodies, wire loops, hyaline thrombi and cellular crescents indicate active disease; whereas lesions such as glomerular sclerosis, fibrous crescents, interstitial fibrosis and tubular atrophy suggest chronicity. High activity index and especially chronicity index have been associated with a poor prognosis. Immunoglobulin (Ig) deposits are found in all renal compartments. The predominant immunoglobulin (Ig) is IgG. The presence of IgG, IgA and IgM along with C3, and Clq in the biopsy specimens is known as 'full house' pattern and is highly suggestive of LN.

Clinical Features

Renal involvement often develops concurrently or shortly following the onset of SLE and may follow a protracted course with periods of remissions and exacerbations. The main features are proteinuria, with microhaematuria and red cell casts, hypertension and progressive renal dysfunction. Only one-third of the patients who develop LN present with renal disease as the first manifestation, some patients with LN initially show only mild urinary abnormalities such as asymptomatic proteinuria or microhaematuria. Some patients may present with full blown nephrotic syndrome, acute nephritic illness or impairment of renal function. On the other hand, a few cases may present with rapidly progressive renal failure or an established chronic renal failure. Rarely, a syndrome resembling thrombotic thrombocytopaenic purpura may develop in patients with severe disease.

The clinical course of LN is highly variable and is remarkably influenced by severity of the disease and the response to treatment. Patient may develop variable periods of remissions following treatment and later on develop flare up of disease process. When untreated or undertreated, majority of the patients with renal disease progress to develop end-stage renal disease (ESRD).

Diagnosis

The diagnosis of SLE is usually obvious in a young female presenting with multisystem disease, renal involvement and serologic markers of the disease. However, sometimes, renal disease may manifest in the absence of extra-renal manifestations. The diagnosis of SLE is often clinically established by the presence of certain clinical and laboratory features defined by the 1997 modified American Rheumatism Association criteria (**Table 2**). Development of 4 of the 11 criteria either serially or simultaneously gives 75% sensitivity and 95% specificity for the diagnosis of SLE. However, the diagnosis of lupus in an individual patient can be made without regard to the above-mentioned criteria.

Immunologic tests in lupus nephritis

Abnormal autoantibody production is the hallmark of SLE. Antinuclear antibodies are a highly sensitive screen for SLE, being found in more than 95% of untreated patients, but they are not specific for SLE and occur in many other rheumatologic diseases, chronic infections, chronic liver disease, etc. Anti-dsDNA are more specific but less sensitive marker of SLE and are found in almost three-fourths of untreated patients with active SLE. Anti-Sm antibodies although very specific for SLE are found in only about 30% of lupus patients. The presence of various patterns of antinuclear antibody (ANA), e.g. speckled, diffuse, etc. is not helpful in distinguishing SLE from other rheumatologic diseases. Besides this, certain other autoantibodies may be present such as anti-ssDNA, anti-nRNP antibodies and anti-phospholipid antibodies. Hypocomplementaemia is found at presentation in more than three-quarters of untreated patients with lupus, and is more common with evident nephritis. The concentration of C4 and Clq tends to be more depressed than C3, which suggests complement activation via the classical pathway.

Table 2: Revised American Rheumatism Association Criteria for Diagnosis of Systemic Lupus Erythematosus (SLE) (1997)

1. Malar rash: Fixed erythema, flat or raised
2. Discoid rash: Erythematous raised patches with keratotic scaling
3. Photosensitivity: Skin rash due to unusual reaction to sunlight
4. Oral ulcers: Oral or nasopharyngeal ulcers observed by the physician
5. Arthritis: Non-erosive, involving 2 or more peripheral joints
6. Serositis: Pleuritis/pleural effusion, or pericarditis/pericardial effusion
7. Renal disorder: Persistent proteinuria >0.5 g/day or 3+, or cellular casts
8. Neurologic disorder: Seizures or psychosis
9. Haematologic disorder: Haemolytic anaemia or leukopaenia (<4000/μL) on two or more occasions or lymphopaenia (<1500/μL) on two or more occasions or thrombocytopaenia (<100,000/μL) in the absence of offending drugs
10. Positive anti-nuclear antibody (in the absence of drugs known to be associated with 'drug-induced SLE')
11. Anti-ds DNA or anti-Smith antibody and/or positive anti-phospholipid antibody

Note: Diagnosis requires 4 of the 11 criteria, either serially or simultaneously.

Serial estimation of various biochemical and serologic parameters may help in predicting clinical flare of the disease. These include erythrocyte sedimentation rate, C-reactive protein, C3, C4 and anti-dsDNA antibodies level. Typically, increase of proteinuria associated with active urinary sediment, fall of serum complement and rise of anti-dsDNA antibodies indicate reactivation of disease process.

Treatment

The aims of therapy of LN include early control of disease activity, prevention of relapses and retardation of progression of renal disease with minimal adverse effects of treatment. The choice of treatment should be based on clinical presentation, laboratory parameters and renal histopathology.

In general, patients with Class I and Class II LN do not need immunosuppressive therapy directed at the kidney, however, treatment may be required for extra-renal manifestations. Patients with class III LN with only mild or moderate proliferative lesions involving a few glomeruli, with no necrotising features and no crescent formation and normal and stable GFR have a good prognosis. They may be followed closely without the need for immediate institution of immunosuppressive agents or may require a short course of high dose corticosteroid therapy. However, patients with more severe focal proliferative or segmental lesions and with necrotising features and crescent formation usually require more vigorous therapy similar to patients with Class IV lesions to avoid irreversible renal damage and progression to ESRD. In the acute phase, high dose oral or pulse steroids in conjunction with monthly pulse cyclophosphamide are the mainstay of treatment.

Typically, treatment for Class IV or severe Class III LN is initiated with intravenous pulse methyl-prednisolone in doses of 0.5 to 1g per day given for 3 or more consecutive days, followed by oral prednisolone in decreasing doses. Initial dose of prednisolone should be 0.5 to 1 mg/kg per day depending upon the severity of the disease. Cytotoxic agents should be given in conjunction with corticosteroids for induction therapy in patients with Class IV or severe Class III LN. Intravenous cyclophosphamide is given once a month for 3 to 6 consecutive months in a dose of 0.5 to 0.75 g/m^2 body surface area, ensuring that the mid-cycle leucocyte count remains above 3000/mm^3. Because of risk of bladder or gonadal toxicity and neoplasia, cyclophosphamide should not be given beyond 6 months and should be replaced by oral azathioprine 1.5 to 2.0 mg/kg body weight, which is better tolerated in the long term. In patients with impaired renal functions, the dose of cyclophosphamide should be adjusted. During the last decade, mycophenolate mofetil has been found to be a good alternative to cyclophosphamide because of its better safety profile. It can be used both for induction therapy as well as long term maintenance therapy along with low dose corticosteroids. Other treatment options for class IV/severe class III LN include low dose cyclosporine, tacrolimus, rituximab, plasmapheresis, total lymphoid irradiation, thromboxane antagonists, blockers of co-stimulatory molecules and intravenous immunoglobulins.

There is no consensus regarding therapy of membranous LN (ISN/RPS class V). The response to treatment and progression of renal injury depend on the severity of proteinuria and the degree of superimposed proliferative changes. Patients with pure membranous nephropathy with subnephrotic proteinuria show very slow progression of the disease and may do well with short course of cyclosporine with low dose corticosteroids along with inhibitors of renin angiotensin system. On the other hand, patients at high risk of progression of renal disease may benefit from intravenous pulses of cyclophosphamide, mycophenolate mofetil and prednisolone on the same lines as diffuse proliferative glomerulonephritis.

Prognosis

Availability of newer and safer immunosuppressive agents and better interpretation of the renal biopsy have significantly improved patient survival during the last two decades. Patients with ISN/RPS Class I and II LN have excellent prognosis. However, patients with diffuse proliferative and necrotising lesions fare worse than those with mesangial or mild proliferative disease. Among patients with membranous LN, disease progression is rapid among patients having nephrotic range proteinuria and proliferative disease on kidney biopsy. Besides this, higher age, black race, nephrotic range proteinuria and serum creatinine >2.4 mg/dL at presentation are associated with poor prognosis. Patients having higher scores on activity and chronicity indices on kidney biopsy also have worse prognosis.

SMALL VESSEL VASCULITIDES

The kidneys are affected by a large number of systemic vasculitides, especially those that affect small vessels. Small vessel vasculitides including Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome affect multiple organ systems including the kidneys. These diseases lead to necrotising polyangiitis and affect vessels which are smaller than arteries, including capillaries, arterioles and venules. The most common targets for these diseases in the kidneys are glomeruli, and therefore, the most common renal manifestations are those of glomerulonephritis. There is often considerable overlap in the clinical, histologic, and laboratory features of these entities; all may be associated with anti-neutrophil cytoplasmic antibodies (ANCA). Immunofluorescence typically reveals no immunoglobulin deposits. These 'pauci-immune' small vessel vasculitides can be differentiated from similar form of immune complex mediated small vessel vasculitides such as Henoch-Schönlein purpura (HSP) and cryoglobulinemic vasculitis by the absence of immune complex deposits in the vessel walls and the treatment for all is often similar involving potent immunosuppressives. Differentiation between various types of small vessel vasculitides is done by the type and the extent of involvement of various organ systems.

Wegener's Granulomatosis

Wegener's granulomatosis has been traditionally defined by the triad of systemic vasculitis associated with necrotising, granulomatous inflammation of the upper and lower respiratory tracts, and glomerulonephritis. The classic histopathologic finding is a focal segmental necrotising and crescentic glomerulonephritis (**Figure 2**). The course of the active glomerulonephritis is typical of rapidly progressive glomerulonephritis with progression to renal failure over days to months. Cyclophosphamide and steroids are the mainstay of therapy.

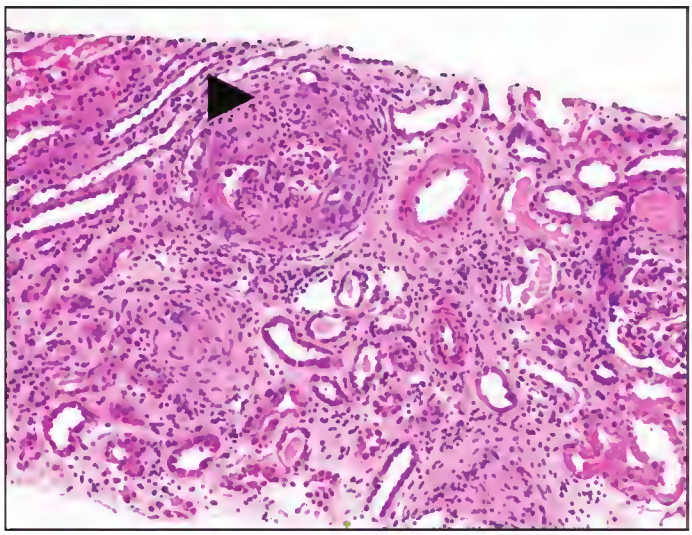


Figure 2: Glomerulus from a patient with Wegener's granulomatosis showing segmental fibrinoid necrosis associated with neutrophilic infiltrate and cellular crescents (arrowhead). Note the periglomerular tubulointerstitial oedema and inflammation (Haematoxylin-Eosin x 100).

Microscopic Polyangiitis

It is characterised by necrotising inflammation of small arteries, veins, and capillaries involving multiple viscera, including lungs and dermis and producing lesions of similar age, usually without aneurysms. Clinical manifestations include rapidly progressive glomerulonephritis, haemoptysis, mononeuritis multiplex, gastrointestinal tract and cutaneous vasculitis. Available data support a therapeutic approach similar to that used in Wegener's granulomatosis.

Churg-Strauss Syndrome

Churg-Strauss syndrome, or allergic granulomatosis and angiitis, is a rare systemic disease characterised by vasculitis, asthma, organ infiltration by eosinophils, and peripheral eosinophilia. Renal biopsies in Churg-Strauss syndrome vary from normal kidney tissue to severe glomerulonephritis, vasculitis, and interstitial inflammation. There may be a focal segmental necrotising glomerulonephritis sometimes with small crescents. Corticosteroid therapy is successful in most patients with Churg-Strauss syndrome.

Pathogenesis

Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and isolated pauci-immune crescentic glomerulonephritis are all associated with the presence in the serum of autoantibodies against certain components of cytoplasm of neutrophils: ANCA. The most common antigen specificities of ANCA in patients with vasculitis and glomerulonephritis are for proteinase 3 (PR3) and myeloperoxidase (MPO). On immunofluorescence, using normal human neutrophils as substrate, two major staining patterns are observed: cytoplasmic (c-ANCA/PR3 ANCA) has specificity for PR3 and peripheral or perinuclear (p-ANCA/MPO-ANCA) which has specificity for MPO.

ANCA testing has good sensitivity for pauci-immune small vessel vasculitis and glomerulonephritis in 80% to 90% cases. The type of ANCA helps in differentiating various types of pauci-immune small vessel vasculitides and crescentic glomerulonephritis. PR-3 ANCA/c-ANCA are most prevalent in Wegener's granulomatosis whereas MPO-ANCA/p-ANCA are most prevalent in renal-limited pauci-immune glomerulonephritis. It has been postulated that ANCA are involved in the pathogenesis of the disease process. Besides this, it has been shown that ANCA titres correlate with the disease activity.

Pathology

In majority of these cases, renal biopsy shows focal, segmental necrotising glomerulonephritis. Early mild lesions have segmental fibrinoid necrosis. In some cases, crescent formation may occur leading to rapidly progressive glomerulonephritis. Wegener's granulomatosis is associated with necrotising granulomatous lesions involving the lungs and kidneys. Besides kidneys, focal necrotizing lesions can affect blood vessels of different organ systems such as skin, upper respiratory tract, lungs, abdominal viscera, etc.

Treatment

Treatment of renal involvement due to small vessel vasculitis involves induction therapy using combined treatment with corticosteroids and cytotoxic agents, such as cyclophosphamide. In severe disease, plasma exchange may be beneficial along with induction therapy. Long-term maintenance therapy using low dose corticosteroids along with cytotoxic therapy is required in majority of the cases to decrease the frequency of relapses during follow-up.

Henoch-Schönlein Purpura

HSP is a systemic vasculitic syndrome with involvement of small vessels (capillaries, arterioles and venules) of the skin, gastrointestinal (GI) tract and joints in association with a characteristic glomerulonephritis having IgA containing immune complexes. Renal involvement in HSP is similar to IgA nephropathy and the diseases can be differentiated only by extra-renal manifestations. It is mainly a childhood disease with a peak during the first decade of life although the disease can occur at any age.

Pathogenesis and pathology

Polymeric IgA1 containing immune complexes get deposited in the skin, kidney, and other organs in association with an inflammatory reaction of the vessels resulting in a leucocytoclastic angiitis in skin, ulcerations in the GI tract and glomerulonephritis in kidney. The typical light microscopic picture is of mesangio-proliferative glomerulonephritis with variable crescent formation. Immunofluorescence typically demonstrates IgA deposits in the mesangium which may extend into the subendothelial area (**Figure 3**).

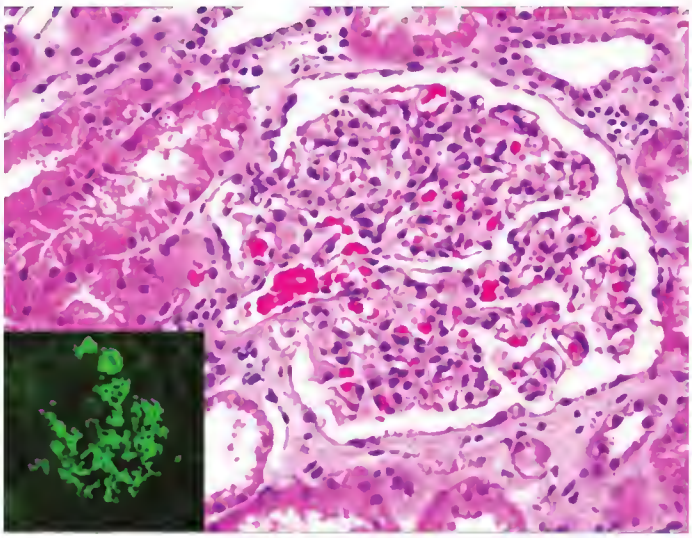


Figure 3: Henoch-Schönlein purpura with diffuse mesangial proliferative glomerulonephritis. There are only mild tubulointerstitial changes (Haematoxylin-Eosin x 100). *Inset:* Immunofluorescence shows global granular to globular staining for IgA limited to the mesangium (FITC anti-human IgA).

Clinical features

It presents with fever, malaise, fatigue and weakness and may be associated with active isolated dermal involvement or full-blown systemic disease. As per the ARA guidelines, the diagnosis of HSP may be considered in the presence of two out of four criteria—age less than 20 years at disease onset, palpable purpura, bowel angina and skin biopsy showing evidence of leucocytoclastic vasculitis. Later on, it was emphasised that presence of IgA vascular deposits is very helpful in establishing the diagnosis. Sometimes, history of infection or exposure to an allergen may precipitate the onset of illness. Skin lesions may include palpable purpura which usually occurs on the extensor surfaces of the legs and buttocks. GI manifestations may be present in the form of colicky pain, nausea and vomiting, bloody diarrhoea, haematochezia, intussusception or perforation. The onset of active renal disease usually follows the onset of the systemic manifestations by days to weeks and is characterised by microscopic haematuria, active urinary sediment, and proteinuria. Approximately 25% patients may develop nephrotic range proteinuria. Sometimes, the disease may present with rapid decline of renal function.

Course and therapy

In most of the patients, HSP has a benign course punctuated with relapses and remissions. In children, the disease is usually self limiting; however, adults have a worse renal prognosis. A poor renal prognosis is predicted by an acute nephritic presentation, older age, and especially nephrotic range proteinuria. There is no proven therapy for HSP. The extra-renal manifestations of the disease are managed by appropriate symptomatic measures. The role of immunosuppressive agents is controversial with no controlled trial showing definite benefit.

AMYLOIDOSIS

Amyloidosis is characterised by extracellular deposition of proteinaceous material having well defined morphologic and ultrastructural features usually involving multiple organ systems. Amyloid represents a family of proteins and several different types of amyloid have been identified. Amyloid fibrils are typically composed of linear, non-branching fibrils. AL amyloidosis is due to deposition of immunoglobulin light chains produced by plasma cells. On the other hand, AA amyloidosis is due to deposition of amyloid A protein in various chronic inflammatory diseases, such as tuberculosis, chronic osteomyelitis, rheumatoid arthritis, etc.

Pathology

Renal involvement occurs in both forms of amyloidosis, though it is more common in AL amyloidosis. Earliest lesions in the kidney are seen as amorphous hyaline material in the mesangial matrix and in the blood vessel walls. It is not associated with any increase in the mesangial cellularity or proliferative changes. The amyloid deposit is eosinophilic and weakly PAS positive. It stains orange on Congo-red staining and gives an apple green birefringence under polarised light (**Figure 4**).

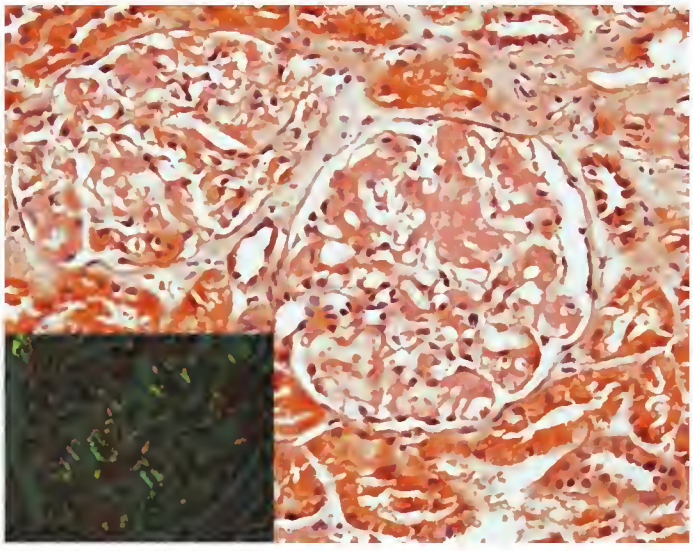


Figure 4: Amyloidosis kidney. Two glomeruli showing salmon pink staining of amorphous acellular deposits by Congo-red. *Inset:* The material was confirmed as amyloid by apple green birefringence elicited on polarisation (Congo-red x 100).

Clinical Features

The patient may present with symptoms due to involvement of kidney, heart, gastrointestinal tract, bones, peripheral nerves, skin, etc. Major renal manifestations include proteinuria and impairment of kidney function usually not associated with haematuria or hypertension. Kidney size is usually enlarged even in the presence of advanced renal failure. In some cases, proteinuria may lead to full-blown nephrotic syndrome; however, serum cholesterol is usually normal. Besides renal biopsy, histologic diagnosis can be made by examination of various tissues, such as gum, rectal mucosa, abdominal fatty tissue, etc.

Treatment and Prognosis

Development of AL amyloidosis during the course of plasma cell dyscrasias indicates severe disease with a median survival of around one year. Presence of cardiac involvement and impaired renal function indicates poor prognosis. Therapy with melphalan and prednisolone or vincristin, adriamycin and dexamethasone (VAD) therapy may result in decrease of proteinuria and retard the rate of progression of renal disease. Besides this, colchicine therapy has also been found to be useful. In a few cases, high dose chemotherapy followed by peripheral blood stem-cell transplantation may lead to significant decrease of proteinuria and improvement of renal function. In patients having AA amyloidosis, management of the underlying disease process such as tuberculosis, rheumatoid arthritis, etc. along with immunosuppressive agents may help in stabilisation of renal function. Besides this, supportive therapy, such as salt restriction, diuretics and blockers of renin angiotensin system have been found to be helpful.

INFECTION-RELATED GLOMERULAR DISEASE

Glomerulonephritis Associated with Infective Endocarditis

Embolic non-suppurative glomerulonephritis as a complication of infective endocarditis was described nearly a century ago. Although multiple renal infarcts and microabscesses have been well described complications of infective endocarditis, the role of immune complex aetiology has been emphasised during the last three decades in the aetiopathogenesis of acute glomerulonephritis. Similar disease is also seen in intravenous drug abusers with right sided endocarditis. Pathogenesis is immune-mediated as evidenced by the presence of circulating immune complexes, glomerular immunoglobulin deposits and hypocomplementaemia. Classical pathway for activation of complement is usually involved. Clinical presentation may vary from mild asymptomatic urinary abnormalities including haematuria, pyuria, and albuminuria to severe glomerulonephritis with renal insufficiency and uraemia. Kidney biopsy may reveal focal proliferative glomerulonephritis, however, few cases may develop diffuse proliferative or membrano-proliferative glomerulonephritis (**Figure 5**). The illness should be differentiated from drug-induced acute interstitial nephritis or renal artery embolism. Glomerulonephritis usually subsides with the control of infection with parenteral antibiotic therapy. In a few cases, corticosteroids and plasmapheresis have been used with variable outcome. Development of glomerulonephritis increases the morbidity and mortality in patients with infective endocarditis.

Shunt Nephritis

Glomerulonephritis has been reported following infection of ventriculo-atrial as well as ventriculo-peritoneal shunts used for the management of hydrocephalus. Common infective organisms include *Staphylococcus epidermidis*, *Staphylococcus aureus* and less frequently diphtheroids, Serratia species, etc. Patients usually present with low grade fever, arthralgias,

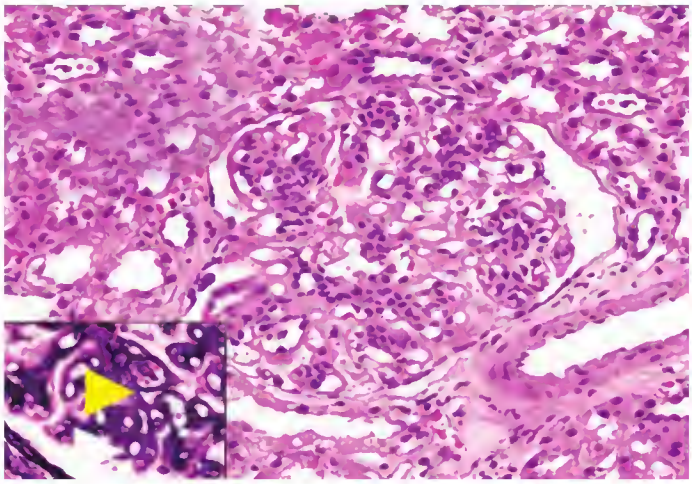


Figure 5: MPGN in a patient having infective endocarditis: Glomerulus from patient with MPGN type I showing enlarged glomerulus with increased glomerular tuft cellularity creating an accentuation of lobular pattern (Haematoxylin-Eosin x 200). *Inset:* Silver methenamine staining showing thickened capillary wall with clear region between (arrowhead) creating a tram-track appearance.

anaemia, weight loss, skin rash and hepatosplenomegaly. Renal manifestations include haematuria (microscopic or gross), proteinuria, azotaemia and hypertension. Antibiotic therapy and prompt removal of the infected catheter usually lead to remission of the renal disease in majority of the patients.

Other Infections

Glomerulonephritis may follow visceral infections involving abdominal organs, lungs or pleura. Overall clinical picture is similar to glomerulonephritis following infective endocarditis. Besides this, various other bacterial, fungal and parasitic infections are known to be complicated by glomerular involvement.

Hepatitis B and C Infection

See chapter 5 of section 14, Hepatology.

GLOMERULONEPHRITIS ASSOCIATED WITH MALIGNANT DISEASE

Besides direct involvement of renal parenchyma, neoplastic lesions involving various organ systems may be complicated by development of glomerular lesions during the course of illness. Glomerular lesions may manifest before the development of neoplastic disease, occur concurrently or after the development of neoplastic disease. Common malignant disorders associated with glomerular disorders include solid tumours involving breast, lung, stomach and colon and Hodgkin's lymphoma. Majority of the patients are above 50 years of age.

A wide spectrum of renal histopathological lesions may be seen in patients with neoplastic disorders. These include membranous nephropathy (**Figure 6**), minimal change disease, focal segmental glomerulosclerosis, IgA nephropathy, membranoproliferative glomerulonephritis, amyloidosis, etc. Sometimes, microangiopathic haemolytic anaemia may complicate the course of neoplastic disorder. Of these, membranous nephropathy has been found to be the most common lesion. The renal lesions may improve following surgical removal of the tumour or successful chemotherapy. Following recurrence of the neoplastic disease, relapse of renal lesions may occur.

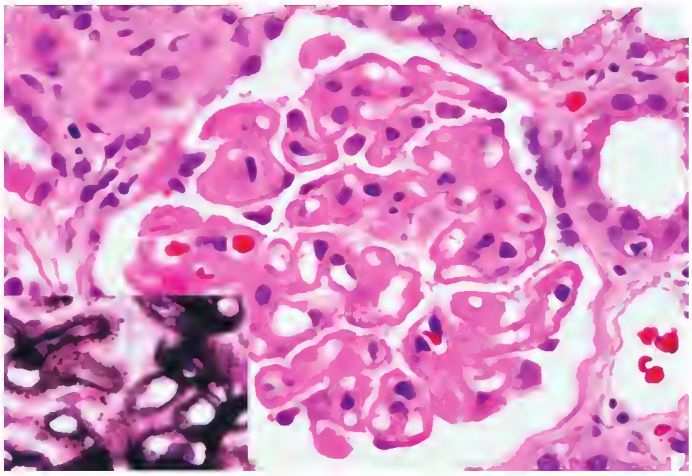


Figure 6: Membranous glomerulonephritis in a patient with placental site trophoblastic tumour: Histopathology of MGN with definite GBM thickening. There is diffuse thickening of glomerular capillary wall without any increase in mesangial cellularity. (Haematoxylin-Eosin x 200). *Inset:* MGN with spikes. Every capillary loop in this glomerulus has diffuse small spikes projecting from the epithelial side of GBM (Silver methenamine (Jones) stain x 400).

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19.7 Urinary Tract Infections

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DEFINITION AND EPIDEMIOLOGY

Urinary tract infection (UTI) is a common, distressing, and occasionally life-threatening condition. UTI may be defined as a condition in which bacteria enter, persist and multiply within the urinary tract. The clinical features, diagnosis, treatment, complications and long-term sequelae depend on the site of the infection and the presence of any structural abnormality. The infection is mostly caused by Gram-negative bacteria such as *Escherichia coli, Klebsiella, Enterobacter, Pseudomonas* and *Proteus*. *Fastidious organisms, anaerobic bacteria* and *fungi* like *Candida* may occasionally be responsible for hospital-acquired UTI. The presence of predisposing factors render the host vulnerable to complicated UTI (**Table 1**). In addition, bacterial virulence factors increase the chances of establishing infection. The incidence of UTI is 0.5 to 0.7 episodes per person per year in females of whom 25% of them have recurrences. It may manifest as acute or recurrent uncomplicated cystitis, acute uncomplicated pyelonephritis, recurrent, relapsing or complicated pyelonephritis or asymptomatic bacteriuria.

Table 1: Host Factors Predisposing to Urinary Tract Infection

Anatomical factors
Posterior urethral value
Vesico-ureteric reflux
Urethral stricture
Benign prostatic hypertrophy
Functional factors
Neurogenic bladder
Other factors
Males and females
Diabetes mellitus
Immunosuppression (post-transplant)
Calculi
Congenital abnormalities
Foreign bodies: catheters, stents
Females
Post-menopausal state (oestrogen deficiency)
Voiding habits
Spermicidal jelly
Vaginal douching
Perineal hygiene

AETIOPATHOGENESIS

The entry of uropathogens into the urinary tract is often from periurethral colonisation in females or from preputial colonisation in uncircumcised males. When host defences are weakened, urethral colonisation and mucosal adhesion of bacteria occurs. Sexual intercourse, catheterisation or instrumentation may also help transfer of bacteria into the bladder. When predisposing factors like vesicoureteric reflux or ureteral dilatation are present, infection ascends via the ureter to reach the renal parenchyma. The invasion of the normal upper tract depends on the virulence of the strain and the expression of bacterial fimbriae. Thus, ascending infections account for the vast majority of urinary infections. However, blood stream infection may sometimes result in haematogenous spread of bacteria to the renal parenchyma.

In a normal individual, a series of non-specific and specific defence mechanisms prevent adhesion and colonisation of bacteria. The non-specific mechanisms are the flushing effect of urine, normal vaginal flora and Tamm-Horsfall glycoprotein which complexes with the bacteria which are then eliminated through the urine. Circulating immunoglobulin (Ig)G and IgM in upper urinary tract are specific immunological barriers. Secretory IgA in the urinary tract, particularly the urethra, provides a barrier to the ascent of infection. In addition to humoral defences, cellular responses also play a role in preventing ascent of infection.

Only some strains of *E. coli* are capable of infecting the intact urinary tract. Bacterial virulence factors increase the chances of establishing infection of a given strain. Strains of *E. coli* causing symptomatic UTI in non-catheterised patients belong to a small number of specific O, K and H sero-groups. Adherence of bacteria to uroepithelial cells is the critical first step in the initiation of infection. For both *E. coli and Proteus*, fimbriae mediate attachment of bacteria to specific receptors on epithelial cells. Haemolysin and aerobactin produced by uropathogenic strains of *E. coli* make them resistant to the bactericidal action of human serum. The presence of O antigens, capsular K antigens, production of siderophores, haemolysins, adhesions and urease enhance the chances of a particular strain to cause infection. The virulence factors favour the release of bacterial toxins, replication and antibiotic resistance. Iron trapping characteristics of bacteria like *E. coli* also contribute to the pathogencity.

Urine flow and the act of micturition are important defence mechanisms which help to eliminate the bacteria. Other factors like low osmolality and low pH hinder bacterial growth. The presence of lactoferrin and anti-microbial peptides in the urine also help to prevent bacterial colonisation.

Infection of the parenchyma occurs when the bacteria enter and multiply in the parenchyma. In the case of vesico-uretric reflux (VUR), intra-renal reflux of urine from the renal pelvis to the collecting duct results in entry of bacteria into the renal parenchyma. This results in inflammation followed by scarring mainly at the poles of the kidney. Blood stream spread results in multiple micro abscesses which may be cortical or cortico-medullary in location.

CLINICAL FEATURES

The clinical features depend on whether the infection involves the upper or lower urinary tract. Irritative voiding symptoms are more common in lower tract infection whereas constitutional symptoms are more common in upper tract infections.

Cystitis and Urethritis

Infection of the bladder is common in women during their reproductive years. Patients with cystitis or urethritis may be

asymptomatic or present with frequency, urgency, dysuria, nocturia, urge incontinence, suprapubic pain or a sensation of incomplete bladder emptying. The urine may have an offensive smell and haematuria occurs in approximately 30% cases. Physical examination usually may reveal mild suprapubic tenderness.

About 30% of women with acute dysuria, frequency and pyuria have negative urine cultures. Sexually transmitted genital infection due to *Chlamydia*, *Neisseria* or herpes simplex virus may account for some of these cases. In addition, organisms like *Ureaplasma urealyticum* and *Myocoplasma hominis* can cause symptomatic cystitis with a sterile urine culture. These patients usually present with persistent frequency and dysuria called the 'urethral syndrome' or 'dysuria-pyuria syndrome'. Interstitial cystitis of the bladder is a condition of unknown aetiology with symptoms resembling bacterial cystitis, but negative urine cultures. The diagnosis can be confirmed by cystoscopy and biopsy.

Prostatitis and Seminal Vesiculitis

The usual symptoms of prostatic infection are frequency, dysuria, perineal or groin pain, difficulty in voiding and painful ejaculation. Per-rectal digital examination may reveal an enlarged, tender prostate or seminal vesicle. Relapsing UTI, associated with the above symptoms in men is suggestive of chronic bacterial prostatitis. A diagnosis of bacterial prostatitis is made on the basis of microscopy and culture of expressed prostatic secretions. In acute bacterial prostatitis, the patient is often acutely ill with sudden onset of fever and chills in addition to other symptoms. Per-rectal digital examination should be avoided in them during the acute stage.

Pyelonephritis

Infection of the renal parenchyma is called pyelonephritis. It may be acute or chronic. Symptoms of acute pyelonephritis include fever with shaking chills, myalgia, nausea, vomiting and loin pain which develop rapidly over a period of hours to days. Physical examination reveals renal angle tenderness. Most patients have significant leukocytosis and bacteria may be detected in the urine deposit by microscopy. Leucocyte casts confirm renal parenchymal involvement. Microscopic or macroscopic haematuria may also be present. Positive blood cultures are seen in 10% to 25% of patients with acute pyelonephritis. Emphy-sematous pyelonephritis is a particularly severe form of upper UTI seen in diabetic patients. It is characterised by accumulation of fermentative gases in the kidney, collecting system and perinephric tissues. It is mostly caused by *E. coli* and may also be associated with urinary tract obstruction.

Chronic pyelonephritis is diagnosed by radiological demonstration of clubbed calyces associated with focal or diffuse renal scarring and it may be unilateral or bilateral. It is known to develop as a result of infection and vesicoureteric reflux in early childhood. Many adults with chronic pyelo-nephritis do not have bacteriuria, remain asymptomatic for long and present later with hyper-tension or renal functional impairment.

Renal Abscess

Renal cortical abscess (renal carbuncle) occurs as a result of haematogenous spread of *Staphylococcus aureus* from a primary focus elsewhere in the body. Patients present with fever and loin pain. Bladder symptoms are absent. Clinical presentation is similar to acute pyelonephritis and imaging studies show hypoechoic or hypodense areas in the renal cortex. The diagnosis of abscess can be confirmed by aspiration and culture from the suspicious areas under ultrasound guidance.

Perinephric abscess is infection and abscess formation within the perirenal space and is often due to extension or rupture of an intra-renal abscess. A perinephric abscess usually presents more insidiously compared to renal abscess and may remain undiagnosed for a long time. Patients may complain of progressive ill health and intermittent fever for many weeks. A flank or abdominal mass may be found on examination. Surgical drainage under appropriate antibiotic cover is indicated.

Xanthogranulomatous Pyelonephritis (XGP)

XGP is a distinct form of chronic kidney infection which predominantly affects elderly women. The condition is commonly associated with renal calculi or obstructive uropathy and is usually unilateral. Infections are caused by *Proteus mirabilis*, *E. coli* or *Klebsiella* group of organisms. The renal parenchyma is replaced by foam cells which infiltrate the perinephric tissue and retroperitoneum. The kidney is enlarged, and non-functioning and may even mimic a renal tumour. Once established, treatment for XGP is partial or total nephrectomy.

MODALITIES OF DIAGNOSIS

Microscopic examination of urine is the crucial first step in confirming UTI. A properly collected early morning sample of urine is ideal. Random samples may also be used for regular testing. Pyuria is defined as presence of more than 5 WBCs/high power field (hpf) in a centrifuged urine sample. In women of child bearing age group, more than 10 WBCs/hpf is considered significant. Pyuria in the absence of bacteriuria is called 'sterile pyuria'. It indicates either infection with unusual bacterial agents like *Chlamydia*, *Ureaplasma*, tuberculosis or fungal infections or urological conditions like calculi, nephrocalcinosis, vesico-ureteric reflux, interstitial nephritis, polycystic kidney disease, tumours or renal transplant rejection.

The gold standard for diagnosis of UTI is urine culture. For bacteriological testing, a clean catch mid-stream urine sample is collected and transported to the laboratory without delay. In case of delay, the sample is refrigerated. Growth of 10^5 colony forming units (CFU) of a single bacterial strain signifies a positive culture. In the case of suprapubic aspirate, growth of even one CFU is significant. In a catheterised sample, more than 10^3 CFU is taken as significant. The growth of multiple organisms is usually due to contamination. The sensitivity pattern helps to choose the appropriate antibiotic. Rapid methods of detection of bacteriuria have been developed as alternatives to standard urine cultures. These methods detect bacterial growth by photometry or bioluminescence and provide results in 1 to 2 hours. Compared to urine cultures, these methods exhibit a sensitivity of 95% to 98%. If the bioluminescence test is negative, UTI can be ruled out with 99% accuracy.

Localisation of the infection to the bladder or the upper tract is important to decide the treatment methods. It is possible to differentiate lower and upper tract involvement by history and symptoms. A number of direct and indirect tests can also be employed to differentiate between the two. The direct approach

involves examination of the urine obtained from bladder or ureter directly by catheterisation. Indirect/non-invasive methods include detection of antibodies in serum or urine and demonstrating a reduction in the maximum concentrating ability in cases of upper UTI. Increase in urinary β2 microglobulin and LDH-5 also helps to confirm upper tract involvement. In women of the child bearing age group, detailed investigations are often not necessary for the first attack of urinary infection or when it occurs infrequently. In the case of infants or young children of both sexes and adult males, any attack of documented UTI warrants further investigations. Ideally, imaging studies are done after 4 to 6 weeks of treatment of acute infection with a view to identify predisposing factors or presence of renal damage. In the acute phase, ultrasonography is performed with a view to rule out obstruction or abscess formation. Plain radiograph of the abdomen is done to show the presence and extent of calcification of the kidneys or urinary tract and number and position of calculi. Ultrasonogram combined with plain radiograph is the preliminary imaging method in patients with recurrent infection. It can detect pelvicalyceal dilatation, calculi, pus or fluid collection, scars and enable actual measurements of the kidney. The bladder, post void residual urine and prostate can also be assessed.

Intravenous urography (IVU) provides anatomical details of kidneys, minor and major calyces, renal pelvis, ureter and bladder. It is also useful to assess post-void residual bladder urine. Conditions like medullary sponge kidney, renal papillary necrosis causing obstruction to ureters and radiolucent staghorn calculi are better diagnosed by IVU or computed tomography (CT) urogram. These procedures also give an idea about the overall kidney function. CT and CT urogram are more sensitive for detection of all types of calculi, renal/perinephric collections and presence of gas.

Isotope renography for renal imaging can be performed with either technetium labelled dimercaptosuccinic acid (DMSA), diethylene triamine pentaacetic acid (DTPA) or ethylcystine (EC). DMSA helps to identify parenchymal changes particularly scars. DTPA scans helps to measure the glomerular filtration rate (GFR), percentage of individual kidney function and level of obstruction. In case of pelviureteric junction obstruction, DTPA renogram with diuretic administration is performed to identify if the obstruction is significant. EC renogram can assess the renal function even in those with compromised renal function.

Voiding cystourethrography is a useful investigation to assess the urinary bladder and urethra, especially in children with posterior urethral valve, vesicoureteric reflux, neurogenic bladder, diverticulae and vesical fistulae.

TREATMENT

For those with symptomatic UTI infection, a 3-day course of antibiotics (cotrimoxazole or quinolones) is adequate. Such a course often eradicates vaginal colonisation also. Acute urethritis due to *Chlamydial* infection is treated with azithromycin or doxycycline (100 mg twice daily) for 7 days.

Acute uncomplicated pyelonephritis in women is treated with a 14-day course of oral quinolones or other antibiotics based on sensitivity of the organism. Parenteral quinolones, cephalosporins or aminoglycosides may be used for the first 72 hours in severe infections.

Antibiotic treatment is not necessary in asymptomatic individuals with indwelling catheters, stone, or obstruction even if urine culture is positive. In the case of asymptomatic bacteriuria during pregnancy and bacteriuria following catheter removal, treatment to re-establish sterile urine is essential.

Prostatitis is generally treated with a 6-week course of antibiotics like quinolones or co-trimoxazole, which are concentrated in the prostate.

Relapsing infection is defined as occurrence of bacteriuria with the same organism within 2 weeks of successful completion of the course of treatment. Relapse occurs due to failure of eradication of infection and occur in those with stones, renal scars, polycystic disease, chronic prostatitis or an immunocompromised state. Such patients should be investigated further and appropriate corrective measures should be taken.

Re-infection is defined as occurrence of infection with a different or similar organism after the original causative organism has been eradicated fully by the treatment. Re-infection occurs more than 2 weeks of discontinuing treatment. Meticulous perineal and perianal care helps to reduce chances of recurrence particularly in women. Maintaining high urine output, voiding after sexual intercourse or post-coital antibiotic prophylaxis with a single dose of co-trimoxazole (40 mg trimethoprim and 200 mg sulphamethoxazole) can be tried.

COMPLICATIONS

Parenchymal infections and injury to the kidney due to VUR and intra-renal reflux can lead to irreversible renal damage and scars. Severe infection in diabetics may lead to renal papillary necrosis, associated with haematuria or obstruction to the urine flow. Parenchymal abscesses may rupture into the perirenal space resulting in perinephric abscess. Infections in patients with diabetes or urinary obstruction lead to emphysematous pyelonephritis. Renal malakoplakia is a chronic granulomatous disorder characterised by an inflammatory reaction to the calcified bacterial debris. The inflammatory process results in a peculiar chronic inflammatory granuloma containing monocytes and macrophages. Chronic UTI associated with calculi may result in XGP.

PROGNOSIS AND PREVENTION

The prognosis for the first attack or infrequent UTI in adult females is favourable. In newborns and infants with developmental defects, like PUV, VUR, or both, infection induced renal scars affect renal growth. These children often develop hypertension, proteinuria and progressive renal failure in the second or third decade of life. Therefore, identification of PUV and VUR before scarring occurs is important. In children with lower grades of VUR, antibiotic chemoprophylaxis is advised while in those with grades 4 and 5 VUR, surgery is indicated. Asymptomatic bacteriuria during pregnancy may be associated with foetal growth retardation or low birth weight.

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19.8 Nephrolithiasis and Urinary Tract Obstruction

PD Gulati

INTRODUCTION AND EPIDEMIOLOGY

The term 'nephrolithiasis' is derived from the Greek words 'nephros' which means 'kidney' and 'lithos' which means 'stone'. Nephrolithiasis is common worldwide; this is the third commonest disorder of the urinary tract after urinary tract infection and prostatic hyperplasia. In USA, 13% men and 7% women develop renal stones during their lifetime. Globally, its incidence is increasing; an analysis from India shows an increase from 0.9% to 9.0% over 20 years. There is geographical variation in stone composition; in north America 75% stones are composed of calcium oxalate alone or mixed with calcium phosphate, 5% pure calcium phosphate, 5% to 10 % uric acid, 10% infection (struvite) and 1% cystine. A similar analysis from north India shows calcium oxalate 93.4% (monohydrate 80%, dihydrate 20%), mixed (calcium oxalate, phosphate, urate) 2.76% struvite (magnesium, ammonium, phosphate) 1.42%, uric acid 0.95%, cystine 0.05%.

In India, maximum prevalence occurs in Jammu and Kashmir, Punjab, Haryana, Delhi, Rajasthan, Madhya Pradesh and Gujarat (stonebelt of India); peak age is 20 to 30 years. Recurrence is common; it is 15% at one year, 30% to 40% at 5 years and 50% at 10 years.

AETIOPATHOGENESIS

Basics in Stone Formation

Normal urine contains both solvents and solutes; imbalance of their relative concentrations results in precipitation of solutes leading to *pathological crystallisation* which occurs in three stages: *Stage I* 'under saturation' when crystals remain dissolved; *Stage II* 'saturation' in which urine is saturated with crystals; and *Stage III* 'super saturation' when urine becomes oversaturated with crystals. 'Nucleation' is an important initial step, followed by crystal aggregation and stone formation; anchoring of crystals on tubular epithelium may occur, e.g. calcium oxalate anchoring on calcium phosphate (Randall's plaque).

Role of Stone Promoters and Inhibitors

Calcium, oxalates, phosphates, uric acid are stone promoters; their supersaturation is prevented by inhibitors like citrate, magnesium and pyrophosphate; citrate forms a soluble complex with calcium; magnesium and pyrophosphate inhibit calcium crystallisation. Organic inhibitors like nephrocalcin, Tamm-Horsfall protein, glycosaminoglycans and osteopontin inhibit calcium oxalate crystal growth. Small intracellular nanobacteria may also form a calcium phosphate *nidus*.

Risk Factors for Nephrolithiasis

Diet

(i) Calcium deficient diet leads to upregulation of oxalate absorption; (ii) High animal protein intake lowers urine pH favouring crystallisation; (iii) High salt intake increases urinary calcium excretion; (iv) Oxalate rich foods (vide infra) and vitamin C intake may increase stone formation since vitamin C gets metabolised to oxalate; and (v) Low potassium diet reduces citrate excretion.

Fluids

Urine output less than one litre per day, due to less fluid intake, increases stone risk; trace elements like fluorides in water, increase stone tendency by 5-fold.

Genetic factors

One in four persons with renal stone has a family history of nephrolithiasis; cystinuria and familial renal tubular acidosis are known examples.

Systemic diseases

Renal stones occur in 20% cases of primary hyperparathyroidism and in 60% of gout; patients of Crohn's disease, diabetes mellitus, hypertension are at increased risk.

Infection

Urinary infection, caused by urease producing organisms (*Proteus, Klebsiella, Pseudomonas, Ureaplasma*) makes urine alkaline (urease acts on urine to produce ammonia) and increases the risk of struvite stones. Matrix stones seen in proteus infections are composed of coagulated mucoids.

Miscellaneous

(i) pH of urine-uric acid and cystine stones are pH dependent, (ii) anatomical abnormalities like pelviureteric junction (PUJ) obstruction, horse shoe kidney, calyceal diverticulum, ureterocoele, vesico-ureteral reflux, medullary sponge kidney, make one stone prone; and (iii) medications like triamterene, indinavir act as stone nidus.

Metabolic factors

Nephrolithiasis occurs due to primary metabolic abnormality in 95% cases; systemic diseases account for only 5% cases. Calcium stones are the commonest with multifactorial aetiology (**Table 1**).

CLINICAL FEATURES

Clinical presentation depends upon size, position and type of stone. Large staghorn stones are usually asymptomatic. Common presentation is renal or ureteric colic; acute loin pain radiating to the groin with nausea, vomiting is classical; haematuria, microscopic or macroscopic, is invariably present. Stone moving down the ureter causes intermittent ureteric obstruction; presents with acute colicky pain. Urgency, frequency, strangury occur with stone at ureter ovesical junction, presence of fever indicates infection. Ureteric stone in a single kidney or bilateral ureteric stones can cause complete anuria and rapid deterioration of renal function.

Physical examination may reveal: (a) typical costovertebral tenderness; and (b) distinct tender renal lump suggesting infection-pyonephrosis or perinephric abscess.

MODALITIES OF DIAGNOSIS

Laboratory Investigations

Urinalysis reveals microscopic haematuria (78% cases), crystalluria, pyuria.

Blood investigations including complete blood counts, estimation of urea, creatinine, electrolytes, renal function (GFR), serum calcium, phosphorous, alkaline phosphatase, uric acid estimations, may reveal aetiology.

Table 1: Multifactor Aetiology of Calcium Stones

Hypercalciuria	Urine calcium excretion of >4 mg/kg per day (>200 mg per 24 hours) occurs in 60% of calcium stone formers *Idiopathic hypercalciuria* occurs in 30% to 50% cases of calcium stones; three types exist: Absorptive due to excessive absorption of calcium from the gut by 1,25 dihydroxyl vitamin D; Renal due to impaired renal tubular absorption of calcium (2% in recurrent stone formers) Resorptive due to increased resorption of bones in primary hyperparathyroidism (5% of recurrent stones)
Hyperoxaluria	Hyperoxaluria occurs in 25%. Normal urinary oxalate excretion is <45 mg per day *Dietary hyperoxaluria*: Due to consumption of oxalate rich diet and vitamin C rich fruits which increase oxaluria; grape fruit juice increases both oxalate and citrate excretion; stone tendency remains unaffected *Enteric hyperoxaluria*: Normally bile is absorbed in proximal intestine; if not absorbed, it reaches distal intestine where it binds calcium and decreases free calcium, available to bind oxalate leading to hyperoxaluria *Genetic hyperoxaluria*: (>100 mg per day) due to enzyme defect
Hyperuricosuria	In normal, urinary uric acid excretion is <600 mg per day In hyperuricosuria, excretion is >800 mg per day. It occurs in 10% of calcium stones Low urine pH precipitates urate crystals
Hypocitraturia	Normal urine citrate excretion is 600 mg per day. It occurs in 15% to 60% cases. Citrate is complexed with calcium and reduces calcium oxalate crystallisation.
Cystinuria	Normal urine cystine is 30 to 50 mg per day. It is an autosomal recessive disorder; urine excretion >250 mg per day causes stone formation.
Urine glycoprotein	Nephrocalcin, Tamm-Horsfall proteins deficiency promotes nephrolithiasis.

Specific investigations are listed in **Table 2.**

Stone analysis by X-ray crytallography/infrared spectroscopy gives chemical composition of stone and determines metabolic abnormality.

DIFFERENTIAL DIAGNOSIS

The *triad* of flank pain, haematuria and positive radiograph abdomen (KUB) is seen in 90% patients of renal stone. Atypical renal pain has to be differentiated from intestinal obstruction, acute appendicitis, clot colic of renal cell carcinoma, acute pyelonephritis and ectopic pregnancy.

Table 2: Investigations of Nephrolithiasis

Modality	Utility
Plain X-ray abdomen (KUB)	90% calcium containing stones are seen and are radio-opaque 10% radiolucent not seen like uric acid, cystine, xanthine
Intravenous urography (IVU)	Show stones—position, obstructive features and functions
Renal Ultrasound	Useful in stones more than 2 mm size May show back pressure effect
CT Scan	Plain CT: 90% accuracy and also shows radiolucent calculi CE CT: More accuracy than plain CT and shows obstruction
Renal scintigraphy	Technetium 99 mm mercaptoacetyltriglycine, with frusemide challenge, evaluates function of individual kidney and obstructive uropathy

TREATMENT

There are three major aspects of treatment of nephrolithiasis as described below:

1. Management of Acute Stone Episode

Renal stone when complicated, needs urgent intervention; uncomplicated stone can be treated conservatively with fluids and analgesics. Calcium channel blockers like nifedipine relax the ureteral smooth muscle as also tamsulosin; antibiotics are added to control the infection.

2. Prevention of Recurrent Stone Formation: Medical Treatment (Table 3)

3. Surgical Treatment

Indication

Endoscopic or surgical removal is recommended for: (a) persistent pain not relieved by analgesia, (b) stone obstructing single kidney, or bilateral ureteral obstruction and/or pyonephrosis.

Choice of intervention

1. *Extracorporeal shock wave lithotripsy (ESWL)* is ideal for renal stone of less than 2.5 cm size with 70% success. For stones of large size (staghorn/struvite), multiple sessions of ESWL with percutaneous nephrolithotomy or uretroscopic removal, are often required; ureteric colic due to residual stones in ureter ('steinstrasse'); ureteric obstruction and perirenal haematoma may occur. Pre-existent hypertension and renal insufficiency may get aggravated. ESWL is contraindicated in obstructive uropathy, abnormal anatomy of urinary tract, large stone burden and pregnancy.
2. *Ureteroscopic stone removal (USR)* using Holmium YAG laser technique carries a success rate of 95% to 100% in ureteric stones of size greater than 5 mm; however, it may be complicated by stricture or reflux.
3. *Percutaneous nephrolithotomy* gives excellent results in stones greater than 2 mm size with hydronephrosis, stone in calyceal diverticuli, horseshoe or ectopic kidney.
4. *Open surgery* is indicated for anatomic abnormality or when other options have failed. Nephrectomy is indicated for pyonephrosis.

Table 3: Prevention of Recurrent Stone Formation: Medical Treatment

General Measures	**Fluids** Increasing *fluid intake* to achieve a urine output >2.5 litres per day reduces recurrence by 50% **Diet** Low calcium intake may cause hyperoxaluria; so calcium intake should be increased Avoiding *oxalate* rich foods with optimal calcium intake *Animal proteins:* Animal foods are rich in purines—a precursor of uric acid, can cause hyperuricosuria (by increasing acid load), hypocitraturia (increased tubular absorption) and should be avoided *Fibre:* Rice bran, fruits and vegetables, decrease both calcium and oxalate excretion
Specific Measures	**Calcium stones** Calcium containing stones are the commonest; hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia all contribute **Hypercalciuria** Potassium citrate be taken 60 mEq per day orally; monitor urinary calcium, phosphorus, sodium and citrate. In case hypercalciuria persists; potassium sparing diuretic amiloride 5 mg daily can be given **Absorptive hypercalciuria** *Cellulose phosphate* (10 to 15 g daily) non-absorbable exchange resin which binds calcium in the gut and prevents absorption; contraindicated in children *Hydrochlorothiazide* (12.5 mg daily) reduces calcium excretion. **Renal leak** *Diminished calcium intake* (<400 mg per day) reduces calcium excretion **Resorptive hypercalciuria** *Orthophosphate* (250 to 2,000 mg/ day) inhibits vitamin D synthesis and decreases absorption of calcium; it increases urinary pyrophosphate **Hyperoxaluria** Restriction of *oxalate rich foods*—spinach, beets, rhubarb, tea, chocolates, nuts, peanuts, strawberry, soya food, wheat bran, possibly linked to deficiency of oxalate dehydrogenase producing *Oxalobacter* increasing gut absorption of oxalate; cranberry juice decreases oxalate and phosphate excretion and increases citrate excretion *Pyridoxine* (2.5 to 6.0 mg/kg body weight) reduces oxalate production Raise *urine pH* to >6.5; it makes calcium oxalate more soluble *Calcium supplement* (500 mg per day) controls enteric hyperoxaluria *Cholestyramine* may reduce intestinal absorption of oxalate *Probiotic* containing *Oxalobacter* formigenes may reduce oxalate excretion *Gluten free diet* in malabsorption reduces hyperoxaluria *Oestrogens* may inhibit urinary oxalate excretion by increasing osteopontin. **Hyperuricosuria** Increased *fluid intake* to achieve urine output of 2.5 litres per day Raise *urine pH* to >6.5 by giving potassium citrate (40-50 mMol per day) Avoid *purine rich foods* like meat products, kidney, liver, brain, heart, shell fish, peas, spinach, mushroom, lentils, kidney beans *Allopurinol* 100 to 300 mg per day, inhibits uric acid synthesis and reduces hyperuricosuria; *febuxostat (80 mg per day)* has less side effects **Hypocitraturia** *Potassium citrate* (60 mEq per day) gets metabolised to bicarbonate, making urine alkaline, thus preventing calcium oxalate stone formation. In *distal renal tubular acidosis* large doses of potassium citrate 120 mEq per day, are required. If hypomagnesuria is present, *magnesium citrate* 10 mg 2 to 3 times per day raises urinary magnesium and citrate and also pH.
Uric Acid Stones	Treatment is as for hyperuricosuria.
Struvite Stones	These are infection stones containing *triple phosphate* (ammonium, magnesium, calcium) which grow rapidly into large *staghorn* stones in alkaline urine (pH >7.0). Treatment is mostly surgical. Measures like *high fluid intake*, specific *antibiotics;* recently, *urease inhibitors* like acetohydroxamic acid; *chemolysis*, i.e. flushing through nephrostomy or ureteroscopically, with 10% hemiacidrin at pH 3.9, have been used
Cystine Stones	High fluid intake so as to achieve urine output >3 litres per day High citrate diet (citrus fruits), methionine rich foods (meat, poultry, dairy products) Low sodium (<50 mEq per day) reduces cystine excretion Raising urine pH to >7.5 increases cystine solubility Potassium citrate (20 to 40 mEq) corrects hypocitraturia D-Penicillamine (250 to 1000 mg) binds cystine; has serious side effects; maintain urine cystine <200 mg/L; vitamin B6 prevents toxicity Recently less toxic, tiopronin and rimatil are being used ACE inhibitor captopril forms soluble thiol cystine disulfide bond in urine

URINARY TRACT OBSTRUCTION

Definitions

Urinary tract obstruction refers to structural and functional changes in urinay tract that impede urine flow. *Hydronephrosis* refers to reversible dilatation of the urinary tract; if left untreated, it can result in progressive irreversible nephron loss.

Aetiopathogenesis

Aetiology is variable. In urinary tract obstruction, glomerular haemodynamics and tubular functions get disturbed due to release of vaso-constrictors like angiotensin II and thromboxane. In bilateral obstruction, retention of urea and water increases the circulating vasodilator atrial natriuretic peptide, which reduces the vasoconstrictor effect. Urinary concentration, acidification, renal handling of electrolytes especially potassium, are also disturbed.

Clinical Features

Patient may be asymptomatic or may have recurrent urinary infection; obstruction if prolonged and bilateral, may lead to uraemic features. Strangury, frequent micturation suggest lower ureteric stone; straining, poor stream, feeling of incomplete bladder emptying, suggest bladder neck obstruction.

Modalities of Diagnosis

Laboratory investigations

In acute obstruction, urinary sodium may be low (<20 mmol/L) with high osmolality (>500 mmol/L). In chronic obstruction, urinary concentrating ability is decreased, osmolality falls. Blood abnormalities include polycythaemia, elevated blood urea, creatinine, electrolytes, hyperchloraemic hyperkalaemic acidosis in chronic bilateral obstruction.

Imaging modalities

Renal ultrasound reveals hydronephrotic changes (fullness, ballooning of pelvicalyeal system); distended bladder with or without bilateral hydroureteronephrosis suggesting bladder neck obstruction. In latter cases, voiding cysto-urethrogram, urodynamic studies and cystoscopy may clinch the diagnosis. Plain radiograph abdomen may reveal radio-opaque calculus; intravenous urography or CT urography and retrograde pyelography indicate site of obstruction. Non-contrast CT is recommended for patients having renal impairment.

Renal scintigraphy, with frusemide challenge, distinguishes functional from anatomical obstruction.

Treatment

Obstruction in single functioning kidney or bilateral obstruction requires urgent intervention; dialysis may be needed for life-threatening hyperkalaemia/fluid overload.

If obstruction is distal to the bladder, immediate indwelling catheterisation is done followed by definitive procedure for enlarged prostate or stricture urethra. Placement of nephrostomy or cystoscopy with double J stenting will relieve upper urinary tract obstruction; definitive surgical treatment is then decided. Pyonephrosis needs drainage by nephrostomy. Post-obstructive diuresis causes volume depletion and dyselectrolytaemia; careful monitoring and adequate replacement are necessary.

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19.9 Vascular Injury to Kidney

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The kidney is a very vascular organ which receives about 25% of the cardiac output through a large network of blood vessels of varying sizes. Diseases of the blood vessels eventually affect the structure of the glomeruli, tubule and the interstitium, causing an impairment of renal functions. The kidney vasculature may be involved in many systemic diseases affecting the vascular endothelium as in hypertension, atheroembolic disease, vasculitis, haemolytic uraemic syndrome, thrombotic thrombocytopaenic purpura and scleroderma, or by diseases limited to the renal blood vessels like arterial/venous thrombosis. In this chapter some of these diseases are discussed.

ATHEROEMBOLIC RENAL DISEASE

Atheroembolic renal disease results from occlusion of small arteries and arterioles by cholesterol containing crystals, which usually slough off from unstable atheromatous plaques in the aorta and other large vessels and travel downstream into the renal arteries. The time from the precipitating event to clinically apparent atheroembolic renal disease is variable and ranges from a day to a month or two. Cholesterol embolisation usually follows invasive angiographic procedures, vascular surgery but in patients with extensive atherosclerosis it can, rarely, occur spontaneously and after administration of oral anti-coagulants or thrombolytic therapy.

Typically, it occurs in males over the age of 50 years with other risk factors for atherosclerosis like diabetes, hypertension, smoking and hypercholesterolaemia.

The symptoms and signs often result from the effects of local ischaemia and the inflammatory reaction in the organ involved. The illness may present with systemic signs like fever, myalgias and weight loss mimicking a vasculitic syndrome. These patients often have associated features of ischaemic heart disease, peripheral vascular disease, transient ischaemic attacks, retinal artery embolisation and ischaemic renal disease. Although the kidney is the most common organ involved, extra-renal cholesterol embolisation often provides clues to the diagnosis. The presentation of renal involvement may be acute with flank pain, accelerated hypertension and rapid deterioration of renal functions. More often, renal involvement is insidious and gradually progresses to chronic renal insufficiency. There may be partial renal recovery over a period of time but most patients go on to develop end-stage renal disease (ESRD) requiring dialysis support.

Skin manifestations are present in up to 60% patients and include purpura, petechiae, livedo reticularis, peripheral gangrene, ulcers and violaceous mottling of toes and feet. Involvement of other organs results in symptoms like abdominal pain, gastrointestinal haemorrhages, nausea, vomiting, hepatitis and neurological deficits. On fundoscopic examination, refractile yellow deposits known as 'Hollenhorst' plaques may be seen at the bifurcation of the retinal vessels. Common laboratory findings include normochromic normocytic anaemia, leucocytosis, thrombocytopaenia, eosinophilia, raised inflammatory markers like erthrocyte sedimentation rate (ESR), C-reactive protein and transient hypocomplementaemia. Depending on the organ involved there may be a rise of serum lactate dehydrogenase, creatinine phosphokinase and amylase. Urinalysis may show mild proteinuria, microhaematuria, pyuria and eosinophiluria. Definitive diagnosis is made on biopsy of the involved organ, showing cholesterol clefts within the vascular lumen representing atherosclerotic debris which have embolised with adjacent infarcted areas.

There is no satisfactory therapy for atheroembolic renal disease. Anticoagulation should be avoided as it may prevent thrombus organisation over unstable plaques and predispose to embolisation.

OCCLUSIVE DISEASES OF RENAL ARTERY

Thrombosis of the renal arteries may occur secondary to blunt abdominal trauma or due to non-traumatic causes such as embolic events usually arising from the heart, dissecting aneurysms, atherosclerotic plaques, vasculitis and hyper-coagulable states like factor V, protein C and S deficiencies and anti-phospholipid syndromes.

The clinical presentation depends on whether the occlusion is unilateral or bilateral, involves the major renal artery or its branches and whether it is acute or gradual in onset.

Insidious onset of occlusion may go undetected and commonly presents as impaired renal function in the elderly. Acute renal artery occlusion with renal infarction is almost always symptomatic, presenting with fever, pain in the flanks, low back or abdomen, associated with nausea vomiting, occasionally gross haematuria and hypertension. When occlusion is bilateral or to a single functioning kidney as in a renal transplant, the patient may present with oliguric ARF. Rarely, oliguria may be seen in unilateral occlusion with a normal contralateral kidney. This has been attributed to arteriolar spasm in the unaffected kidney which usually passes off in a few days. Urinalysis may reveal haematuria and proteinuria. Ultrasound Doppler studies for native renal vessels are of limited value and not useful. Imaging with contrast computed tomography (CT), magnetic resonance angiography or conventional angiography are the best means of diagnosis. Isotope renal scans may show absent or reduced perfusion.

Medical management is aimed at relief of pain, control of hypertension and where indicated dialysis. Surgical re-vascularisation is indicated in traumatic bilateral renal artery thrombosis or occlusion to a solitary functioning kidney. In occlusion due to non-traumatic causes, thrombolytic therapy is reported to be equally effective. The chances for success are

more if the obstruction is incomplete, of shorter duration and in presence of collaterals. For unilateral occlusions of a major renal artery due to any cause with normal contralateral kidneys, intra-arterial thrombolytic therapy is preferred. In unilateral segmental occlusion anti-coagulation therapy alone may be necessary. In patients with embolic disease due to atrial fibrillation, long-term anticoagulation is recommended to avoid recurrences.

MALIGNANT ARTERIOLAR NEPHROSCLEROSIS

Malignant arteriolar nephrosclerosis is used to describe the histological changes seen in patients with malignant hypertension characterised by marked elevation of blood pressure (BP) (diastolic blood pressure often >130 mmHg) associated with hypertensive retinopathy with haemorrhages, soft exudates and often papilloedema. Besides the kidneys, there may be involvement of the central nervous system, cardiac failure, and microangiopathic haemolytic anaemia. Malignant hypertension is more common in third to fifth decades of life, males, smokers and in those with underlying hypertension of some duration. It may arise *de novo* in less than 1% cases.

Renal involvement may manifest as urinary abnormalities like proteinuria which is occasionally in nephrotic range. About 20% patients have painless gross haematuria with micro-haematuria reported in about 50% patients. Patients with malignant hypertension may present with oliguric ARF or may have a progressive deterioration of kidney function with progression to ESRD.

Autopsy studies show that the kidneys are characteristically normal in size but may be shrunken in those with pre-existing hypertension of long duration or underlying chronic kidney disease (CKD). Small pin point haemorrhages may be present on the surface of the kidney giving it a 'flea bitten' appearance. The hallmark of malignant nephrosclerosis is fibrinoid necrosis of the afferent arterioles. There is infiltration of the vessel wall with fibrin, and occasionally an inflammatory infiltrate giving the appearance of necrotising arteriolitis. The fibrinoid necrosis may extend into the glomeruli which may develop segmental necrosis, proliferative lesions and even crescents. The inter-lobular arterioles reveal proliferative endarteritis. Secondary to narrowing of the lumen there is ischaemic collapse of the glomerular tuft and necrosis of renal tubules.

It has been proposed that activation of the renin angiotensin system and other neurohumoral factors leads to increased permeability of the vessel wall to plasma components like fibrin, which activates the clotting cascade leading to micro-angiopathic haemolytic anaemia and the vascular lesions. Alternatively, the vascular endothelium may be damaged secondary to the high pressure *per se*.

All patients with malignant hypertension and renal damage should receive aggressive anti-hypertensive therapy to prevent further deterioration of renal function. In patients with impaired renal function [glomerular filtration rate (GFR) less than 20 mL/minute] aggressive lowering of BP may precipitate oliguric ARF. This should not be considered as a contraindication to tight BP control as patients who have ESRD due to malignant nephrosclerosis are reported to have recovered renal function over a period of time despite being on dialysis. The mechanism of recovery of renal function after prolonged renal failure may be related to partial reversal of the vascular lesions leading to reversal of ischaemic tubular necrosis or due to hyperfiltration by the remaining nephrons supplied by the patent interlobular arteries.

BENIGN ARTERIOLAR NEPHROSCLEROSIS

Benign arteriolar nephrosclerosis is a term used to describe histological changes in the kidneys secondary to chronic hypertension. The risk factors for Benign arteriolar nephro-sclerosis include older age, black race and poorly controlled hypertension. The diagnosis is usually based on long standing hypertension being present with associated signs of other end-organ damage in the form of hypertensive retinopathy and left ventricular hypertrophy. The usual renal manifestations are proteinuria of less than 1 g per day with bland urinary sediment and mild to moderate elevation of serum creatinine. The progression of renal impairment , though slow, may lead to ESRD. The adjusted risk for ESRD is reported to increase with levels of BP.

At histology, the arcuate and other larger arteries show fibrous intimal thickening, re-duplication of the internal elastic lamina and thickening of the media. The arterioles show hyaline arteriosclerosis with accumulation of hyaline in subendothelial areas which may extend into the media. This results in narrowing of the vascular lumen leading to ischaemic atrophy of the renal parenchyma. Early in the disease process, the glomeruli may be normal. With time there is complete glomerular obsolescence, tubular atrophy and interstitial fibrosis.

Treatment is aimed at keeping the BP less than 130/80 mmHg. Most patients need a combination of drugs including a diuretic. Non-pharmacological measures like weight loss, exercise, and salt restriction should also be prescribed. The principles of management of CKD due to benign arteriolar nephrosclerosis remain the same as those for any other cause of CKD.

SCLERODERMA RENAL DISEASE

Kidney involvement in systemic sclerosis may present as slowly progressive CKD, or scleroderma renal crisis (SRC). An occasional patient may present with rapidly progressive glomerulo-nephritis.

Factors predictive of SRC are diffuse skin involvement, rapidly progressive skin disease, new onset scleroderma (less than 4 years), anaemia, cardiac involvement, high-dose steroid use (>15 mg prednisolone per day), cyclosporine therapy, and presence of anti-RNA-polymerase antibody. Conversely, patients with anti-centromere antibody (ACA) are relatively protected. Occasionally, skin involvement may be minimal or even absent. In SRC, majority of patients present with accelerated/malignant hypertension, neuroretinopathy, headache, blurring of vision, encephalopathy, seizures, pulmonary oedema, micro-angiopathic haemolytic anaemia and thrombocytopaenia. Renal involvement manifests as oliguric ARF. Urinalysis shows non-nephrotic range proteinuria, haematuria and granular casts.

The characteristic renal lesions occur in the arcuate arteries. There is proliferation of myointimal cells of the vessel wall with luminal narrowing which is indistinguishable from the changes of hyperplastic endarteritis seen in malignant/accelerated hyper-tension. Fibrinoid necrosis of the vessel wall and thrombosis are also common. Patients who have never had a renal crisis may

show on renal histology re-duplication of elastic fibres, sclerosed glomeruli, tubular atrophy and interstitial fibrosis reflecting the chronic changes of scleroderma. Aggressive management of hypertension with angiotensin converting enzyme (ACE) inhibitors has improved the cumulative 1 year survival from 15% to 76%. Angiotensin II receptor blockers, alpha-blockers and calcium antagonists are also helpful for refractory hypertension. Dialysis is required in approximately two-thirds of the patients. Approximately half of these patients will eventually recover sufficiently to discontinue dialysis. Delayed renal recovery may occur more than 24 months after the crisis and so decisions about renal transplantation should be postponed until that time. Recurrence of SRC is uncommon in transplant patients.

RENAL VEIN THROMBOSIS

Renal vein thrombosis (RVT) may occur in a number of clinical conditions (**Table 1**). The most common cause is nephrotic syndrome associated with membranous nephropathy. RVT is known to aggravate proteinuria. In nephrotic syndrome, hypoalbuminaemia (serum albumin less than 2.5 g/dL) is an indicator of an underlying hypercoagulable state and increased risk of RVT.

Table 1: Causes of Renal Vein Thrombosis

Nephrotic syndrome: Increased plasma levels of factor V, VIII, XIII, fibrinogen, thrombocytosis, decreased plasma levels of factor XII, anti-thrombin III
Neoplasms: Renal cell carcinoma, Wilm's tumour
Hypercoagulable states: Deficiency of protein C/protein S, oral contraceptives, cyclosporine
Hypovolaemia
Extrinsic compression: Lymph nodes, tumours, pregnancy
Collagen vascular diseases: Systemic lupus erythematosus
Renal transplant
Blunt trauma
Others: Acute pancreatitis, amyloidosis, tricuspid insufficiency, constrictive pericarditis

The clinical features of RVT depend on the rapidity of onset and whether RVT is unilateral, bilateral or in a solitary functioning kidney. Acute RVT presents with fever, loin pain, haematuria and renal enlargement. Deterioration of renal function has been described in bilateral RVT and in patients with a single kidney. Pain and swelling in the ipsilateral testicle may occur in males. The chronic form is usually clinically silent, but may present with increase in proteinuria and recurrent pulmonary thromboembolism.

Imaging studies are required to establish the diagnosis of RVT. Conventional ultrasonography and renal Doppler studies have a low sensitivity and may show a swollen echogenic kidney with increased resistive indices. CT and magnetic resonance imaging (MRI) often provide a definitive diagnosis, thus avoiding the need for renal venography.

Resolution of acute RVT has been demonstrated with thrombolysis, using either streptokinase or urokinase given systemically. Anticoagulants are recommended for prevention of pulmonary embolism. In nephrotic syndrome, they are continued until the serum albumin is more than 2.5 g/dL. If pulmonary embolism has occurred, initial anticoagulation with heparin for 5 to 7 days followed by oral drugs is recommended. Once oral anti-coagulant therapy is established, the prothrombin time should be kept at about one and one-half to two times normal. Patients with RVT in pregnancy are best treated with heparin alone. If anti-coagulation is contraindicated and pulmonary embolism has occurred, inferior vena cava filters may be used. Thrombectomy in the treatment of RVT has no advantage over anti-coagulation and is indicated only in presence of renal cell carcinoma.

RENAL ARTERY STENOSIS

Renal artery stenosis (RAS) is narrowing of the lumen of the main renal artery or one of its branches leading to impaired blood flow to the kidneys. It may be unilateral or bilateral. The commonest cause in the elderly is atherosclerotic renal artery disease (bilateral in half the cases) while in young females the commonest cause is fibromuscular dysplasia. Non-specific aortoarteritis or Takayasu's arteritis is a common cause of RAS below the age of 40 years in Afro-Asian countries and Japan.

The reported incidence of RAS as cause of hypertension varies between 0.6% and 5% depending on the selection criteria and modalities of diagnosis used. The activation of renin angiotensin system and resultant hyper-reninaemia play a major role in initial phase of renovascular hypertension. Over time, salt and water retention following a sustained hyper-reninaemia state take over as the mechanism for hypertension at which stage renin levels may return to normal. Stenosis in the affected renal artery leads to reduction in post-stenotic pressure and renal perfusion. The kidney tries to restore the perfusion by autoregulation but if the stenosis persists, it leads to progressive loss of kidney function and the clinical entity is called 'ischaemic nephropathy'.

Clinical clues to the presence of RAS include, abrupt onset of hypertension before 30 or after 50 years of age, accelerated/malignant hypertension, treatment-refractory hypertension, worsening of renal function after initiating ACE inhibitors, recurrent flash pulmonary oedema, unilateral small kidney and a biphasic renal bruit with systolic and diastolic components.

A number of non-invasive modalities are used for the diagnosis of RAS with varying sensitivity and specificity (**Table 2**). Renal angiography, however, remains the gold standard as it provides direct visualisation of the affected renal artery and corrective angioplasty and stenting of the stenotic lesion can be performed in the same session. Colour Doppler ultrasonography is the best non-invasive screening test with a sensitivity of about 70%. The major limitation is that it is highly operator dependent and is technically difficult in obese patients. The sensitivity also decreases in the presence of multiple renal arteries, distal lesions, and total occlusion. In functionally significant renal artery stenosis, glomerular filtration rate

Table 2: Investigations in Diagnosis of Renal Artery Stenosis

Test	% Sensitivity	% Specificity
Colour Doppler duplex sonography	Variable	Variable
Radio-isotope renography	65 to 75	65 to 85
Spiral computed tomography angiography	88 to 98	90 to 95
Magnetic resonance angiography	95 to 100	93 to 95
Conventional or digital subtraction angiography	100	100

is maintained by stimulation of the renin-angiotensin-aldosterone axis. ACE-inhibitors cause reduction in renal blood flow and GFR and their use in association with ^{99m}Tc-labeled DTPA or ^{99m}Tc-labeled MAG3 scans are useful for the diagnosis.

Management

Treatment of renovascular hypertension should include ACE inhibitors/angiotensin receptor blockers (ARBs), and address all modifiable cardiovascular risk factors like hyperlipidaemia, obesity and smoking. ACE inhibitors may cause a rise in creatinine in patients with bilateral RAS and in RAS of a single functioning kidney. Revascularisation therapy with angioplasty with/without stent placement is indicated if adequate BP is not achieved despite optimal medical therapy or if the serum creatinine rises despite adequate BP control. A favourable response to intervention is seen in patients with rapid decline of renal function. Despite revascularisation, cure of hypertension is unusual, though seen more often in fibromuscular dysplasia than in atherosclerotic renal artery disease. Renal functional recovery or stabilisation of renal function is seen in approximately 70% of the patients. Surgical revascularisation is indicated in patients with total occlusion of the renal vessel in whom renal angioplasty/stenting is not possible. Nephrectomy has a role to play when a non-functioning kidney is implicated in the cause of RVH. Revascularisation therapy is best avoided if the resistivity index on Doppler sonography is more than 80%. The likely reason for the poor response is structural alterations in smaller arteries and arterioles distal to the RAS which manifests as increased vascular resistance.

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19.10 Polycystic Kidney Disease and Inherited Tubular Disorders

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DISORDERS OF CYSTIC NATURE

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Definition

Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disorder with autosomal dominant inheritance and is a result of mutation in PKD 1 or PKD 2 gene. The disease manifests with renal and extra-renal manifestations.

Epidemiology

The incidence varies from 1 in 400 to 1 in 1000 individuals and it occurs in all races and ethnicities. It accounts for 5% of all cases of end-stage renal disease (ESRD) across the world.

Genetics

ADPKD is caused by mutations in at least 2 different genes. Mutations in the PKD 1 gene which is present on the short arm of chromosome 16 (16p13), accounts for 85% of all cases, while the PKD 2 gene which is present on the long arm of chromosome 4 (4q21), accounts for the rest. Ninety per cent of all cases are inherited in an autosomal dominant fashion, while the rest are likely to be due to spontaneous mutations.

Polycystin proteins are expressed in virtually all tissues. The PKD 1 gene codes for the protein Polycystin 1 while the PKD 2 gene codes for polycystin 2. Most mutations in either gene are single base changes, insertions or deletions of a small number of base pairs, resulting in truncated proteins and loss of function. These proteins are believed to function either independently or as a part of a complex, to regulate tubular epithelial cell gene transcription, differentiation, cell-to-cell interaction and apoptosis. Disruption of these proteins can lead to epithelial dedifferentiation, uncontrolled epithelial proliferation, apoptosis, altered polarity of tubular cells, with disorganisation of the extracellular matrix and excessive fluid secretion by the epithelial cells. They have also been localised to the primary cilia of the tubular epithelial cell which act as mechanosensors which transduce luminal signals into cellular responses that control cell proliferation, adhesion, differentiation and apoptosis.

The penetration of these mutations is 100%. However, there is marked variability in the phenotypic expression of the disease within individuals of the same family. Less than 5% of nephrons become cystic. This variability in expression and focal nature of the renal disease with its extra-renal manifestations has been explained by the 'two hit hypothesis'. This hypothesis implies that the presence of a germ line mutation is on its own not sufficient for cystogenesis, but a 'second somatic mutation' is essential to inactivate the other PKD allele.

Mutations of the polycystin 2 gene usually result in a milder form of the disease, with an older age at diagnosis and later onset of hypertension and renal failure as compared to PKD 1 mutations.

CYSTOGENESIS

Renal cysts can arise from any segment of the nephron. About 10% of all cysts retain the morphologic characteristics of the segment they arise from. They initially arise as outpouchings from the tubules, which are initially filled with glomerular filtrate, however, they separate from the tubule as they increase in size, and thereafter grow in size due to exaggerated cell proliferation due to loss of cell-to-cell interaction, associated with increased secretion of fluid within the cyst lumen which is exclusively due to transepithelial secretion of water and solutes. Hence, cysts are not dead ends of tubules which store urine generated by proximal segments of the tubules, but they are complex structures that proliferate, synthesise proteins and secrete fluid and electrolytes and show apoptosis. The cysts are present throughout the renal parenchyma and are variable in size. They tend to compress and distort the normal renal parenchyma in between as they enlarge in size.

Clinical Features

There is marked variability in the course of the disease, starting from the age at detection to its course within members of the same family and between PKD 1 and PKD 2 gene mutation carriers. The mean age at presentation is 55 years in PKD 1 and 71 years in PKD 2 disease. However, marked phenotypic variability is the hallmark of ADPKD.

One-third of adults are asymptomatic and their disease is detected during ultrasound of the abdomen conducted for an unrelated cause. With the increasing availability of sonology facilities, this proportion is likely to increase with time. The commonest presenting feature in symptomatic patients is flank or back pain, which can occur in 60% of adults. The pain is usually chronic dull aching in nature. This pain is more common in patients with large kidneys with high cyst burden. The pain could get acute in case of infection or haemorrhage into a cyst or due to renal colic due to a calculus or clot.

Hypertension is detected in 80% of adults and in up to 30% of all children with ADPKD. It is usually due to increased activity of the renin-angiotensin system. Hypertension can precede renal dysfunction by decades in adults. Hypertension in ADPKD correlates with the renal volume.

Gross haematuria can occur in 50% of adults. It is probably caused by cyst rupture into the pelvicalyceal system. More than half of all subjects with gross haematuria relate it to an inciting event such as infection or trauma. In case of associated colicky pain, infection, clot colic or renal calculus needs exclusion. There can be cyst haemorrhage within the kidney which does not communicate with the pelvicalyceal system (PCS) and could be clinically silent but for pain in the flank.

Renal concentration defects can be demonstrated in potentially all adults with ADPKD, even in the presence of normal glomerular filtration rate (GFR). Nephrolithiasis occurs in 20%

of patients. Urinary tract infections are a common occurrence in ADPKD patients. Urine cultures may be sterile in isolated cyst infections, while blood cultures would be positive in such cases. Cyst infections due to gram-negative organisms can be difficult to eradicate, requiring prolonged courses of parenteral antibiotics. Lipophilic antibiotics like fluoroquinolones, trimethoprim, clindamycin and macrolides accumulate well within the cyst, and can be used to eradicate cyst infection.

Extra-renal manifestations are common. Hepatic cysts can occur in 60% to 75% cases. Most patients with hepatic cysts are asymptomatic with normal liver function tests, unless there is haemorrhage or infection in the cysts. Hepatic cysts occur with equal frequency in either gender but they tend to be larger in women. Cysts can also be demonstrated in the seminal vesicles (60%) and prostate (10%) besides pancreas (10%) and arachnoid cysts (5%). Cysts have also been described in the ovaries, testes and the spleen. Colonic diverticuli, abdominal wall and inguinal hernias occur more commonly in ADPKD patients than the general population.

There is four-fold risk of intra-cerebral haemorrhage from an arterial aneurysm in ADPKD patients. Intracranial aneurysms can occur in up to 10% of these patients on routine magnetic resonance angiography (MRA) screening. However, most of these are small and usually do not enlarge or rupture with time. Aneurysmal haemorrhage occurs preferentially in young individuals (<50 years), in those with family history of intracranial haemorrhage, those with aneurysms larger than 10 mm in diameter and those with uncontrolled hypertension. There can also be cardiac involvement in the form of aortic root and annulus dilatation. Mitral valve prolapse can be found in 25% of all cases.

Diagnosis

Ultrasound imaging is the primary tool for diagnosis, in conjunction with family history and gene linkage analysis if needed. The Modified Ravine's criteria can be used to diagnose the disease in younger individuals with a family history of ADPKD. The presence of 2 cysts in one or both kidneys together below 30 years of age, 2 cysts in each kidney in the 30-59 years age group and 4 cysts per kidney in those above 60 years of age has a 95% sensitivity and 92% specificity for the diagnosis of ADPKD 1 in those at risk. For a child younger than 18 years any renal cyst is highly suspect for the disease. False negative ultrasound has not been reported in individuals above 30 years of age from families with ADPKD 1. Presence of hepatic cysts and cysts in other abdominal organs strengthens the diagnosis on ultrasound.

Contrast enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) of the kidney are more sensitive diagnostic tools for the diagnosis of ADPKD. Computed tomography (CT) has the advantage of identifying calcification in the cyst walls and renal calculi, besides haemorrhage within the cysts. MRI can be used to measure the volume of the kidney and predict the decline of renal function with time.

Genetic linkage analysis and mutational screening can be done in isolated cases, especially in young individuals with family history of ADPKD with normal imaging studies who wish to be kidney donors.

Treatment

There is currently no treatment available which has been proved to inhibit cystogenesis or inhibit cyst enlargement. Hence, management of these patients is purely supportive. Control of hypertension is an important measure, with the target of 135/85 mmHg or less as per the JNC VII criteria. All classes of anti-hypertensives can be used, but for diuretics. No single class of anti-hypertensive has been shown to be superior to the other, though many authors prefer to use angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs).

Complications like urinary tract infection and cyst infection should be preferably treated with lipophilic antibiotics like fluoroquinolones, trimethoprim or macrolides. Pain relief due to cyst haemorrhage, clot colic or calculus may need opioids. Occasionally, surgical excision of haemorrhagic or infected cysts may become essential.

There is faster and earlier progression to ESRD in ADPKD 1 as compared to ADPKD 2. Patients of ESRD due to ADPKD have been found to have a survival advantage over patients with ESRD due to other causes while on dialysis (haemodialysis and peritoneal dialysis). However, the survival of these patients post-transplantation is similar. Occasionally nephrectomy may become essential prior to renal transplantation in these patients due to the large size of the native kidneys or because of complications, such as stones or non-resolving cyst infection.

Animal studies show a role for vasopressin 2 (V2) receptor antagonists (Vaptans), anti-proliferative drugs (Sirolimus), statins and Somatostatin in reducing the rate of cyst enlargement. Regression of liver or renal cysts in native kidneys has been observed in renal transplant recipients on sirolimus based regimen *versus* calcineurin inhibitor (CNI) based regimen. These drugs are currently being tried in human trials.

Table 1 compares and contrasts the various inherited disorders which have a cystic presentation.

DISORDERS OF TUBULAR ELECTROLYTE HANDLING WITHOUT HYPERTENSION

Various inherited tubular disorders present with acid-base abnormalities and dyselectrolytaemia without hypertension. Gitelman's syndrome is the commonest inherited tubular disorder of these. It presents in early adulthood with metabolic alkalosis, hypokalaemia, hypomagnesaemia and hypocalciuria. It mimics thiazide diuretic abuse in its clinical presentation, while Bartter's syndrome which is a relatively rare entity, presents in early infancy with polyuria, polydipsia and failure to thrive. It mimics loop diuretic abuse in its clinical presentation. The underlying transport defect in Bartter' syndrome is at the thick ascending limb of the loop of Henle, while in Gitelman's syndrome it is at the level of the distal convoluted tubule (DCT). **Table 2** compares and contrasts these disorders which present without hypertension.

HEREDITARY TUBULAR DISORDERS WITH HYPERTENSION

Liddle's and Gordon's syndrome occur due to salt retention and due to inherited abnormalities in the distal tubule. Liddle's syndrome presents with metabolic alkalosis and hypokalaemia while Gordon's syndrome presents with metabolic acidosis and hyperkalaemia. **Table 3** compares and contrasts both the syndromes.

Table 1: Comparison of the Inherited Cystic Disease of the Kidney

	ADPKD	ARPKD	TSC	NPHP	MCK	MSK	VHL
Mode of inheritance	AD, <10% fresh mutations	AR	AD, 65% new mutations	AR	AD	AD	AD
Chromosome	PKD 1: 16p13 PKD 2: 4q21	6p21	9q34, 16p13	2q13, 9q31, 3q22, 1p36, 3q13	1q21, 16p12	Not known	3p26
Prevalence	1:400 to 1:1000	1: 20,000 to 40,000	1: 6,000 to 10,000	1: 10,00,000	1:10,00,000	1: 20,000	1: 36000
Age at onset	Adult, rarely in adolescence	Childhood	Children and adults	Childhood and adolescence	Adulthood	Adulthood	Adulthood
Symptoms at presentation	Pain, haematuria, infection, hypertension	Abdominal mass, respiratory distress, hypertension, ESRD, hepatosplenomegaly	Seizures, skin lesions, mental retardation, cardiac arrhythmias	Polyuria, polydipsia, secondary enuresis	Asymptomatic, Hyperuricaemia, gout	Asymptomatic	CNS tumours, renal cysts, Phaeochromocytoma, renal carcinoma
Kidney size	Enlarged	Enlarged	Normal or enlarged	Shrunken	Shrunken	Normal	Enlarged, if cystic
Extra-renal manifestations	Cysts in liver, pancreas, etc. intra-cranial aneurysms, mitral valve prolapse	Congenital hepatic fibrosis, portal hypertension	Angiofibromas, CNS hamartomas, cardiac rhabdomyomas	Retinitis pigmentosa, oculomotor apraxia	Can be associated with various congenital, acquired and inherited syndromes	Associated with congenital hemihypertrophy, Congenital hepatic fibrosis, Marfan's, Ehlers-Danlos, Caroli's disease	Haemangioblastomas, retinal angiomas, Phaeochromocytoma
Imaging for diagnosis	US, CT, MRI	US, MRI	US, CT, MRI	US, MRI	US, MRI	Excretory urography	CT, US, MRI
ESRD	50% by 60 years	100%	<10%	100%	100%	Rare	Occasional

ADPKD = Autosomal dominant polycystic kidney disease; ARPKD = Autosomal recessive polycystic kidney disease; TSC = Tuberous sclerosis complex; NPHP = Nephronophthisis; MCK = Medullary cystic kidney; MSK = Medullary sponge kidney; VHL = von Hippel-Lindau disease; AD = Autosomal dominant; AR = Autosomal recessive; CNS = Central nervous system; US = Ultrasound; CT = Computerised tomography; MRI = Magnetic resonance imaging; ESRD = End-stage renal disease.

Table 2: Inherited Tubular Disorders of Electrolyte Handling without Hypertension

	Bartter's Syndrome	Gitelman's Syndrome	Pseudohypoaldosteronism Type I	Primary Hypomagnesaemia
Mode of inheritance	AR : Types 1 -4, AD: Type 5	AR	AR, AD	AR
Defective protein	Type 1: NKCC2 Type 2: ROMK Type 3: CLCNKB Type 4: Barttin Type 5: NCCT	NCCT	Defective activity of α, β or γ sub-units of ENaC Mineralocorticoid receptor (MR) Type 1	Paracellin 1
Age at onset	Neonate, childhood	Adulthood	Adulthood	Adulthood
Metabolic disturbance	Hypochloraemic metabolic alkalosis, hyperaldosteronism	Hypochloraemic metabolic alkalosis, hyperaldosteronism	Metabolic acidosis, hyperaldosteronism	Metabolic alkalosis
Blood pressure	Normal or low, resistant to Angiotensin II infusion	Normal or low	Normal	Normal or low
Electrolyte imbalance	Severe hypokalaemia, hyponatraemia	Hypokalaemia, hyponatraemia hypomagnesaemia, hypocalciuria	Hyperkalaemia, hyponatraemia	Hypomagnesaemia, hypocalcaemia
Plasma renin activity	Very high	Very high	High	NA
Treatment	Liberal salt; K^+ and Mg^{2+} intake for life K^+ sparing diuretics in high doses NSAIDs	Liberal salt; K^+ and Mg^{2+} intake for life K^+ sparing diuretics in high doses	Aggressive salt repletion Control hyperkalaemia Fludrocortisone and carbenoxolone in the AD variant	Oral magnesium supplementation
Mimickers	Frusemide abuse	Thiazide abuse	—	Aminoglycoside, Cisplatin toxicity

AR = Autosomal recessive; AD = Autosomal dominant; NA = Not applicable; NSAIDs = Nonsteroidal anti-inflammatary drugs.

RENAL TUBULAR ACIDOSIS

Renal tubular acidosis (RTA) type 1 and 2 can be inherited or secondary to other causes. Normally bicarbonate is reclaimed back but in type 1 and 2 RTA, HCO_3^- is lost due to tubular defect and in lieu Cl^- is reabsorbed and serum Cl^- levels rise. Due to an excess load of HCO_3^- at the distal tubule, excessive K^+ is lost in the urine. Therefore, patients present with hypokalaemia and hyperchloraemic metabolic acidosis. The most common form of RTA, Type 4 is always acquired secondary to other causes. It is associated with hyperkalaemia and hyperchloraemic metabolic acidosis.

Type 1 RTA

Type 1 or classic distal RTA (dRTA) occurs due to either secretory or permeability defects. In secretory defects there is defective secretion of protons from the collecting duct and in permeability defects though the proton pump functions normally, however,

Table 3: Hereditary Tubular Disorders with Hypertension

	Liddle's Syndrome	Gordon's Syndrome
Mode of inheritance	AD	AD
Chromosome	16p13	12p13, 17q21
Protein	Excessive activity of α, β or γ-sub-units of ENaC	WNK 1 and WNK 4 kinases-increased activity of thiazide sensitive NCCT
Metabolic abnormality	Metabolic alkalosis, hyperaldosteronism	Metabolic acidosis
Electrolyte abnormality	Hypokalaemia	Hyperkalaemia
Plasma renin activity	Very low	Low
Treatment	Na^+ restriction K^+ supplementation Triamterene	Salt restriction Thiazide diuretics

AD = Autosomal dominant; NCCT = NaCl co-transport; ENaC = Epithelial Na^+ channel.

due to the excessive permeability the high intratubular H^+ ion concentration dissipates rapidly. In Type 1 classic dRTA the kidneys cannot acidify the urine to pH<5.5 in the presence of metabolic acidosis. Urinary PCO_2 does not rise despite HCO_3^- supplementation. The chronic metabolic acidosis leads to reduced renal production of citrate. The hypocitraturia in the presence of hypercalciuria predisposes to nephro-calcinosis and nephrolithiasis in Type 1 RTA which leads to osteomalacia or rickets. dRTA could be sporadic or hereditary. Most autosomal recessive varieties present in infancy with severe symptoms of acidosis, dehydration, failure to thrive and nephrolithiasis related kidney dysfunction. However, the autosomal dominant and sporadic varieties usually present in adulthood and are often detected incidentally during evaluation for nephrolithiasis. Sjögren's syndrome is the commonest cause of acquired dRTA in adults. Treatment is done with the help of sodium bicarbonate given in a dose of 1-4 mEq/kg body weight.

Type 2 RTA

Type 2 or proximal RTA occurs due to the excessive loss of bicarbonate from the proximal tubule. The defective acidification can exist in isolation but more commonly it coexists with generalised proximal tubular dysfunction, as a part of Fanconi's syndrome, when it is associated with glycosuria, amino aciduria, enzymuria, hypercitraturia and loss of various electrolytes like Na^+, K^+, Ca^{2+}, and PO_4^{3-}. It could occur as a part of inherited disorders like Wilson disease, cystinosis, tyrosinaemia, galactosaemia, hereditary fructose intolerance, glycogen storage disease type I, and Lowe's syndrome. Acquired forms of Fanconi's syndrome occur with heavy metal toxicity (lead, cadmium), use of outdated tetracyclines, cisplatin, aminoglycosides, ifosfamide, besides dysproteinaemias like multiple myeloma, light chain deposition disease and amyloidosis.

The presence of citrate in the urine in Type 2 RTA prevents the precipitation of calcium and oxalate within the tubules, and hence, nephrolithiasis is not a usual phenomenon. It is difficult to restore the pH to normal despite large amounts of alkali supplementation, consequent to the proportionately higher HCO_3^- loss in urine as the serum HCO_3^- begins to rise. The fractional excretion of HCO_3^- is usually more than 15% until the serum HCO_3^- falls to 15 to 17 mmol/L. At this level a new transport maximum for HCO_3^- is established and all bicarbonate is reabsorbed and the urine can be acidified to pH<5.5 because bicarbonaturia ceases. Thiazides are useful since they cause volume contraction stimulating bicarbonate reabsorption.

Type 4 RTA

Type 4 RTA is a variety of dRTA that is invariably acquired, usually always associated with moderate renal dysfunction and hyperkalaemia. It leads to hyperchloraemic metabolic acidosis and salt wasting, which is evident during salt restriction. It is usually associated with generalised distal nephron dysfunction. It can occur either due to voltage defect or but commonly due to mineralocorticoid deficiency of primary and secondary nature. Possible mechanisms are: (i) destruction of juxtaglomerular cells; (ii) decreased sympathetic denervation of the juxtaglomerular apparatus; (iii) decreased production of prostacyclin, causing a decrease in renin-aldosterone production; and (iv) primary hypoaldosteronism. Aldosterone increases Na^+ absorption and the negative intratubular potential. It also increases luminal membrane permeability to potassium and stimulates basolateral Na^+/K^+/ATPase, causing increased urinary potassium losses. Because aldosterone also directly stimulates the proton pump, aldosterone deficiency or resistance would be expected to cause hyperkalaemia and acidosis. Another major factor in decreasing net acid excretion is the inhibition of ammoniagenesis due to hyperkalaemia. Secondary mineralocorticoid deficiency is usually due to diabetes mellitus, tubulointerstitial nephritis, non-steroidal anti-inflammatory drugs use and monoclonal gammopathy. Hyporeninaemic hypo-aldosteronism usually presents in the elderly (mean age 65 years) with asymptomatic hyperkalaemia in the majority, and arrhythmia and weakness in 25% of cases. It is associated with renal insufficiency in the majority (70%), however, both hyper-chloraemic metabolic acidosis (50%) and hyperkalaemia are disproportionate to the degree of renal dysfunction.

It could occur due to resistance to the action of aldosterone either due to an intra-cellular mineralocorticoid receptor (hMR) resistance [Pseudohypoaldosteronism (PHA) type I] of autosomal dominant inheritance or due to an autosomal recessive inherited defect in the epithelial Na channel (ENaC) subunits (PHA type I). PHA type II is acquired in an autosomal dominant manner and is associated with normal renal function and hypertension, absence of salt wasting and diabetes mellitus and a kaliuretic response to mineralocorticoid administration.

Aldosterone antagonists, drugs like calcineurin inhibitors (CNIs) which interfere with the Na^+K^+ ATPase in the cortical collecting duct (CCD), or drugs like amiloride, triamterene, trimethoprim and pentamidine, which interfere with the Na^+ channel in the CCD also cause voltage defects in the distal tubule and can lead to generalised distal tubule dysfunction. Diseases associated with tubulo-interstitial nephritis and renal insufficiency like lupus nephritis, allergic interstitial nephritis, obstructive uropathy, sickle cell disease can all lead to generalised distal tubule dysfunction.

The decision to treat is often based on the severity of hyperkalaemia. Those with primary glucocorticoid and mineralocorticoid deficiency should receive both in replacement doses. Alkali therapy or loop diuretics will induce

Table 4: Heriditary Renal Tubular Acidosis

Parameter	Type 1 (Distal)	Type 2 (Proximal)	Type 4 (Distal)
Mode of inheritance	AR, AD	AR	AR, AD
Chromosome	7q33, 8q22, 17q21 (AD)	4q21	—
Defective protein	Defective H^+- ATPase in the CCD Defective HCO_3^-/Cl^- exchanger Defective Na^+/H^+ antiporter CA II deficiency	Defective basolateral Na^+-HCO_3^- exchanger in the proximal tubule	Defective α/β/γ-subunits of ENaC Defective intracellular mineralocorticoid receptor (hMR)
Age at presentation	AR: Infancy; AD: adolescence and early adulthood	Young adults	AR: infancy AD: young adults
Metabolic abnormality	Hyperchloraemic metabolic acidosis	Severe hyperchloraemic metabolic acidosis	Hyperchloremic metabolic acidosis
Electrolyte abnormality	Hypokalaemia	Hypokalaemia	Hyperkalaemia
Associations	Nephrocalcinosis, nephrolithiasis, osteomalacia	Hyperphosphaturia, hyperuricosuria, hypercalciuria, aminoaciduria, glycosuria	Hypotension, renal salt wasting, raised renin and aldosterone
Extra-renal manifestations	Sensorineural deafness inAR form, severe mental retardation in CAII defective form	Ocular phenotype with cataracts, glaucoma, band keratopathy, mental retardation	Vomiting, failure to thrive, respiratory distress in the AR variety
Treatment	Supplementation of 2 mmol/kg/day HCO_3^-, K^+, citrate is preferred	Supplementation of K^+ in large amounts, 5-15 mmol/kg/day HCO_3^-, Vit D, thiazides	High salt intake, supplement K^+

Table 5: Differences in the Various Types of Renal Tubular Acidosis (RTA)

Parameter	Type 1 (Distal)	Type 2 (Proximal)	Type 4 (Distal)
Serum K^+	Low	Low	High
Urine pH in the presence of acidosis	>5.5	<5.5	variable
Fractional HCO_3^- excretion	2 to 5%	10 to 15%	5 to 10%
Fanconi's syndrome	Absent	Present	Absent
Urine net charge	Positive	Positive	Positive
Response to therapy	Responds promptly	Poor response	Moderate response
Associations	Nephro-calcinosis	Fanconi's syndrome	Renal insufficiency

K^+ and Na^+ loss. Drugs if found to be the cause of hyperkalaemia, should be discontinued (which may not always be possible). K^+ binding resins can be utilised to reduce serum K^+ levels. In very severe cases, fludrocortisone 0.1 to 0.3 mg per day can be used with extreme caution once cardiac failure and volume overload are excluded.

Table 4 highlights the salient features of the various inherited forms of RTA.

Table 5 compares and contrasts the different forms of RTA.

HEREDITARY NEPHROGENIC DIABETES INSIPIDUS

It is a rare monogenic disease which manifests in early infancy with severe polyuria, dehydration and failure to thrive. It can be acquired by an X linked (Type 1) or AD/AR (Type 2) mode of inheritance. The X linked variant accounts for >90% of all

Tabel 6: Monogenic Diseases of Tubular Function

Parameter	Cystinuria	Hartnup Disease	Dent's Disease	Renal Glycosuria	Vit D Dependent Rickets
Mode of inheritance	AR	AR	XLR	AR	Type 1: AR
Chromosome	2p16, 19q13	5p15	Xp11	16p11	12q14
Defective protein	Dibasic amino acid transporter	Defective transport of neutral amino acids	Voltage gated Cl^- channels	Na^+-glucose cotransporter	$25(OH)D_3$ 1α hydroxylase
Incidence	1: 7000	Rare	Rare	—	
Clinical manifestations	Cystine stones, ureteral obstruction, urinary infections	Aminoaciduria Extra-renal: cerebellar ataxia, pellagra-like skin lesions	Proteinuria Hypercalciuria Nephrocalcinosis Nephrolithiasis	Usually asymptomatic Rarely polyuria due to glucose load	Rickets, osteomalacia
Treatment	Hydration - urine output >2.5 L/day Urine alkalinisation Na^+ restriction Chelation with Captopril, Penicillamine or Tiopronin D_3	Protein-rich diet Nicotinamide supplements	Na^+ restriction Thiazide diuretics	—	Physiological doses of $1,25(OH)_2$

cases and occurs due to a defect in the type 2 vasopressin receptor in the collecting duct. The rest are due to AD/AR mutations in the aquaporin 2 (AQP2) channels which causes retention of these water channels within the cytoplasm of the cell. These mutations lead to an inability to concentrate the urine despite the presence of high plasma levels of vasopressin.

It occurs in infancy and is associated with hypernatraemia due to free water loss. The hypernatraemia can be associated with seizures and higher mental function changes.

These patients can produce up to 20 litres of urine in a day, and supplementation of adequate fluids along with thiazide diuretics and salt restriction is the only solution to their problem.

MONOGENIC DISEASES OF TUBULAR FUNCTION

Occasional monogenic defects in the proximal tubular absorption of various amino acids, glucose and production of vitamin D can occur. Cystinuria is the most common among these disorders. It presents with cystine and dibasic amino acid stones. Vitamin D dependent rickets occurs due to defective production of activated vitamin D by the tubule. The features of these defects are highlighted in **Table 6**.

RECOMMENDED READINGS

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19.11 Dialysis for Chronic Renal Failure

NK Hase

INTRODUCTION

Chronic renal failure [Chronic Kidney Disease (CKD) stage 5] is an irreversible deterioration in renal function to a degree incompatible with life, in the absence of some form of renal replacement therapy (RRT), either dialysis or transplant. The kidney function is usually less than 10% to15% of its capacity. The estimated glomerular filtration rate (eGFR) is less than 15 mL/min. The number of patients suffering from CKD is growing in India. Incidence of CKD has doubled in last 15 years. The mortality among CKD patients remains 10 to 20 times higher than general populations. Hence, focus in recent years has shifted towards optimising care of these patients during earlier stages of CKD. It is recommended that all patients with CKD should be referred to a nephrologist early in the course of their disease preferably before plasma creatinine exceeds 1.2 mg/dL and 1.5 mg/dL in women and men, respectively or eGFR is less than 60 mL/min/1.73 m^2. Late referral to nephrologists (i.e. <3 months before the start of dialysis therapy) is associated with higher mortality after initiation of dialysis. The renal replacement therapies, which are well established, are chronic maintenance haemodialysis, chronic peritoneal dialysis and renal transplant. The renal transplant is the treatment of choice for end-stage kidney disease (ESKD).

DIALYSIS

Thomas Graham, Professor of Chemistry at Anderson University in Glasgow coined the term 'dialysis' in 1861. George Haas from Germany performed first successful human dialysis in 1924. Kolf and Berk from Netherlands developed the first practical human haemodialysis machine in 1943. This was rotating drum artificial kidney consisted of 30 to 40 metres of cellophane tubing in a stationary 100 litres tank. From 1943 to 1960, use of dialysis was restricted to acute renal failure (ARF). Discovery of arteriovenous shunt by Quinton and Scribner 1960 and forearm arteriovenous fistula by Brescia and Cimino in 1966 extended this therapy to chronic end-stage renal failure. Chronic maintenance haemodialysis has emerged now as one of the well-established life-sustaining therapy. In India, haemodialysis was first started in 1962 at Christian Medical College, Vellore. Subsequently, several centres in the country developed this facility. Estimates reveal that renal units in this country are offering treatment to 80 to 100 new patients with ESKD per million populations, each year.

Initiation of Dialysis

Indication for dialysis is given in **Table 1**. When dialysis was first available it was only offered to patients who are uraemic and with risk of imminent death. Current trend is to start dialysis early when patient is healthy. The advantages of starting early are improved rehabilitation, less complications, better nutritional status, improved quality of life (QOL) and survival.

Table 1: Indications for Initiating Maintenance Dialysis

Absolute Indication to Start Dialysis

- Fluid overload or pulmonary oedema refractory to diuretics
- Uraemia: Pericarditis, persistent nausea, vomiting, bleeding due to platelet dysfunction, progressive uraemic encephalopathy or neuropathy with signs of confusion, asterixis, myoclonus or seizures
- Accelerated hypertension poorly responsive to anti-hypertensive medication BUN >100 mg/mL and serum creatinine above 10 mg/dL

Other Recommendations

- K/DOQI: Dialysis should be initiated when weekly renal Kt/V urea falls below 2.0 (equivalent to renal clearance of urea of 7 mL/min, renal creatinine clearance of 9 to 14 mL/min and GFR approximately 10.5 mL/min/1.73 m^2, unless complete absence of clinical signs or symptoms of uraemia serum albumin normal and stable and adequate nutrition
- 2005 European Best Practice Guidelines: Dialysis should be initiated: (1) when GFR is <15 mL/min and there are one or more symptoms or signs of uraemia; (2) in all, before GFR has fallen to 6 mL/min/1.73 m^2 irrespective of symptoms; diabetic patients may benefit from an earlier start

Selection of Dialysis

Selecting one of the modalities is influenced by a number of factors, such as availability, convenience, comorbid conditions, socio-economic and haemodynamic stability. Most patients can be treated with either haemodialysis (HD) or peritoneal dialysis (PD). Continuous ambulatory peritoneal dialysis (CAPD) is preferred in young children, elderly patients in whom vascular access is not available and haemodynamically unstable. Home dialysis is optimal in young independent otherwise well patients who are supported by a devoted partner. Current thinking is a concept of integrated care. Rather thinking of one modality of treatment *versus* another it is best to think the patient's life span on RRT. A single patient may utilise all modalities so it is sensible to use each to its optimal benefits. Start with PD when residual kidney function is present in the beginning. Later shift patient on HD when he becomes anuric.

Principles of Dialysis

Diffusion

If two solutions of different concentrations are separated by a semipermeable membrane, solution will move from the side of higher concentration to the side of lower solute concentration. This process of solute movement on a concentration gradient is called diffusion. The rate of diffusion is greatest when concentration is highest. This is the main mechanism for removal of urea, creatinine and for the replenishment of serum bicarbonate. Other determinants of diffusion are temperature of solution, viscosity, size of molecules and membrane characteristics.

Ultrafiltration

This is the convective flow of water and dissolved solutes down the gradient caused by hydrostatic or osmotic forces. Ultrafiltration is mainly for removal of water from body.

Clinically, this movement of diffusion and ultrafiltration takes in and out of blood, across a semipermeable membrane. If blood is exposed to an artificial membrane outside the body, i.e. extracorporeal circulation, the process is called haemodialysis or haemofiltration; if exchange of molecules occurs across the peritoneal membrane, the process is called PD.

HAEMODIALYSIS

Components of Haemodialysis

Haemodialysis system can be broadly divided into a blood circuit and a dialysis solution circuit which meet at the dialyser. The blood circuit begins at vascular access. From vascular access blood is pumped through inflow bloodline called as 'arterial' line to the dialyser, back to vascular access by outflow (venous) blood line (**Figure 1**).

Vascular Access

Vascular access is lifeline for patient and achilles heel of HD. The blood access help to draw blood continuously from the patient at required rate of between 200 to 400 mL per minute and return to the patients after circulating it through artificial kidney.

Temporary vascular access

Patients requiring dialysis for a shorter period, such as those with acute reversible renal failure and patients waiting for permanent access that requires dialysis urgently, need temporary access. Temporary vascular access of choice is right internal jugular double lumen catheter inserted percutaneously. Subclavian veins should be used only when jugular vein options are not available, femoral vein should be used only in emergency when patient is breathless.

Permanent vascular access

Native arteriovenous fistula (AVF), non-dominant radio-cephalic is vascular access of choice for long-term maintenance haemodialysis. AVF has the longest life with least complications. Arm veins should be preserved in all patients likely to require dialysis. AVF should be constructed when GFR falls below 25 mL/min or within one year of anticipated need for dialysis. AVF takes 3 to 4 months for development. AVF should not be used at least one month after creation. Use before the venous wall matures can shorten the life of an AVF. If a native venous fistula cannot be created, tubal material can be grafted under the skin between the artery and the vein. Several graft materials (autologous, heterogeneous and synthetic) have been tried including saphenous vein, bovine carotid artery and polytetrafluoroethylene (PTFE). PTFE grafts are the most commonly used.

Dialyser

A dialyser, artificial kidney (filter) consists of a rigid polyurethane-shell containing hollow fibres (capillaries) or sheets (parallel plates) of dialysis membrane. Commonly used membranes have cuprophan, cellulose acetate and highly porous synthetic copolymer membranes like polyacrylnitrite (PAN), polysulphone, polymethylmethacrylate. The non-

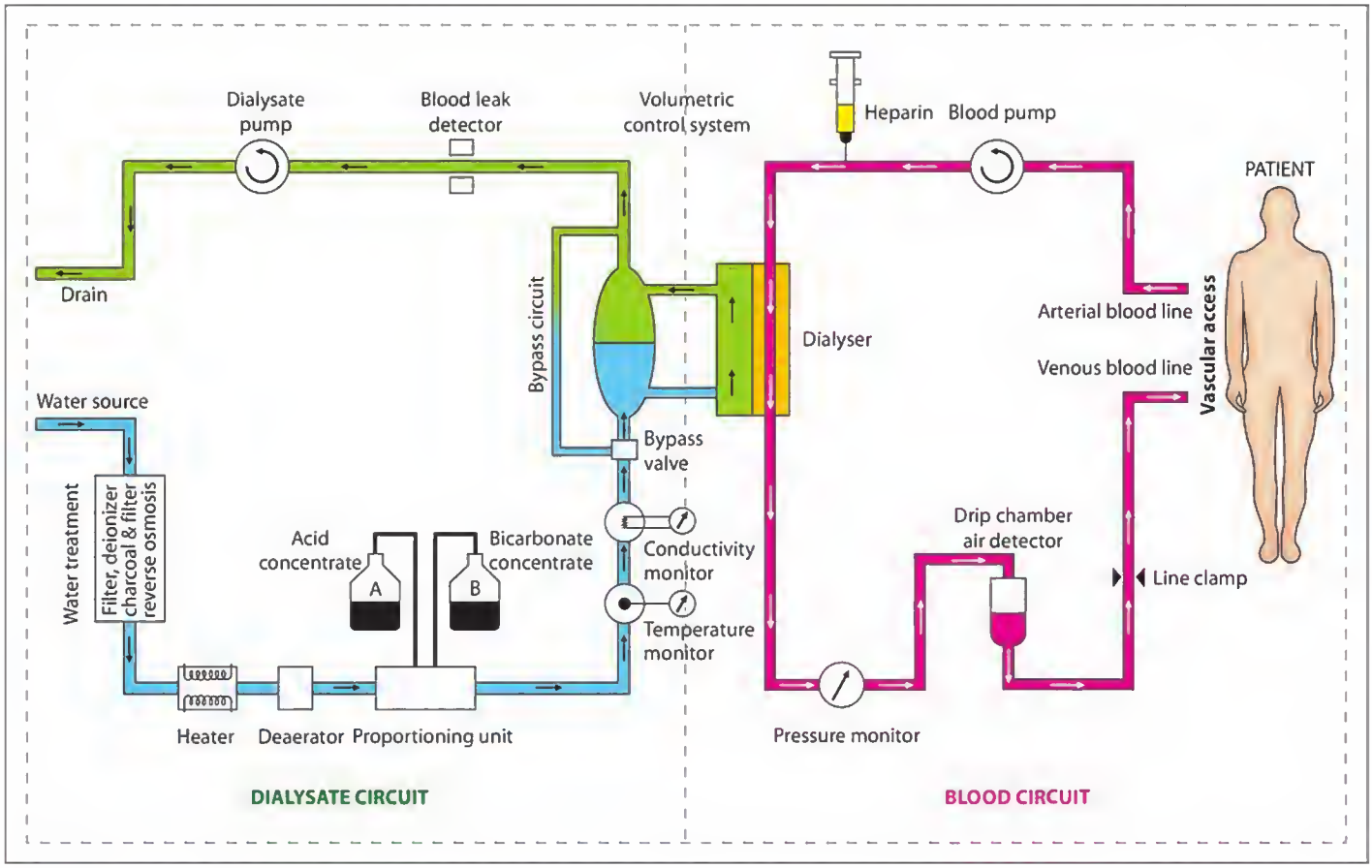


Figure 1: Components of haemodialysis.

synthetic cellulose membranes have become relatively uncommon as they activate the alternate complement pathway, lead to leuco-agglutination and cytokine release, i.e. they are bio-incompatible. The synthetic polymer membranes are preferred, they exhibit better biocompatibility, improved ultrafiltration characteristics and increased solute clearance, especially in middle-molecule weight range. Ideal dialyser should have high clearance for small and middle-molecule toxins, adequate ultrafiltration capacity, non-toxic, minimum priming volume, biocompatible, reusability and low cost. All over the world dialysers are reused.

Haemodialysis Machine

The HD machine prepares and provides dialysate to dialyser, monitors dialysate quality and controls and monitors ultrafiltration from the patients. It can be divided into four major components:

(i) Water preparation system: treated pure water is delivered to machine, is heated to body temperature by heater, deaeriated and then delivered to the proportioning systems;

(ii) Proportioning system mixes dialysate with treated water (1:34) and pumped to the dialyser. Proportionating system monitors electrical conductivity of dialysate;

(iii) Modern machines have volumetric ultrafiltration control to remove precise ultrafiltrate; and

(iv) Sodium profiling, safety monitor like conductivity temperature, blood leak and air detectors to prevent air embolism. Advance machines, have facilities to monitor blood pressure (BP), electrocardiogram (ECG), blood volume, fluid balance, access re-circulation and online monitoring for measuring urea clearance to determine adequacy of dialysis.

Dialysis Water

A large volume of water (more than 100 litres per treatment) is used to prepare dialysate from the concentrate, several methods of purifying dialysis water are employed, the most common of which is reverse osmosis. The Association for Advancement of Medical Instrumentation (AAMI) has recommended minimum standard for water used in dialysis. Bacterial colony count should be less than 100 cfu/mL.

Dialysate

Dialysis solutions are usually prepared from concentrates and contains either acetate or bicarbonate as a buffer. Acetate is now rarely used worldwide. Bicarbonate containing concentrate is preferred as they are more physiological, provide better control of acidosis and produce fewer complications and side effects. Usual composition of dialysate is sodium: 132 to 155 mmol/L, potassium 0 to 4 mmol/L, magnesium 0.25 to 0.75 mmol/L, acetate 35 to 45 mmol/L (only in acetate base dialysate), bicarbonate 27 to 40 mmol/L, dextrose 0 to 5.5 mmol/L and pH 7.1 to 7.3. Low calcium baths may be used in the acute or chronic therapy of hypercalcaemia.

Anti-Coagulation for Haemodialysis

Systemic standard heparinisation, bolus dose followed by continuous infusion of heparin 500 to 2000 units per hour to maintain the activated clotting time upto 200 to 250 seconds is standard practice, to prevent excessive bleeding, heparin must be discontinued 30 to 60 minutes before the termination of the treatment. Patients who are at high risk of bleeding, various alternatives are low dose heparinisation, low molecular weight heparin, regional citrate anti-coagulation, recombinant hirudin, prostacyclin and no anti-coagulation with saline flushes.

Complications of Haemodialysis

The most common complications during haemodialysis are hypotension, cramps, nausea, vomiting, headache, chest pain, back pain, itching, fever with chills, disequilibrium syndrome, dialyser reactions, hypoxia, seizures and cardiac arrhythmias (**Table 2**).

Table 2: Complications of Haemodialysis

Acute vascular access fistula (AVF) related	Haemorrhage, haemothorax, pneumothorax (subclavian, jugular cannulation)
Chronic arteri-ovenous fistula (AVF) related	Infection, aneurysm, steal, venous congestion, high output failure
Extracorporeal circulation procedure related	Dialyser reactions, type A anaphylactic reactions, hypoxia, hypotension, cramps, rigors, headache, fever chills, seizures, cardiac arrhythmias, haemolysis, air embolism, dialysis disequilibrium
Chronic complications	Increased anaemia, hepatitis B and C infection, metabolic bone disease, β2 microglobulin related amyloidosis, acquired renal cystic diseases, dialysis dementia becoming rare, cardiovascular calcification, malnutrition

Frequency of Dialysis

A minimum of three, 4-hour dialysis per week is desirable. Treatment time or frequency should be increased for patients with cardiovascular problems.

Home Dialysis

Done at home for 3 to 5 hours per treatment three times per week, requires special training and machine at home. Survival is generally highest in patients treated with home dialysis up to 89% at five years, 74% at 15 years in non-diabetic and 50% at 15 years overall.

Daily Haemodialysis

Daily nocturnal, daily 4 hours and short hours (1.5 to 2.5 hours) high efficiency 5 to 6 times per week are new options, patients can be monitored remotely. Patients report significantly improved QOL, symptoms and sleep pattern, have a daily Kt/v of 1.00, better BP control, less need for antihypertensive medication, lower serum phosphate, improved nutritional status and can have relaxed dietary restriction. Duration of dialysis may be an important predictor of survival independent of dialysis dose.

Dialysis Adequacy

Adequate dialysis maximises well being, minimises morbidity, improves QOL and helps patients retain social independence. Dialysis prescription should be individualised, monitored and reassessed regularly. The clinical criteria for adequate dialysis include a feeling of well-being with normalisation of BP with or without medications and control of biochemical parameters in the target ranges, i.e. haemoglobin 11 to 13 g/dL, predialysis blood urea <70 mg/dL, s. creatinine <7.0 mg/dL, Ca 10 mg/dL, PO_4 <4.5 mg/dL. Lack of malnutrition, urea reduction ratio >65% and Kt/V (fractional urea removal rate) ≥1.2 per dialysis is recommended by K/DOQI guidelines.

PERITONEAL DIALYSIS

The use of intermittent PD for chronic renal failure started in early 1960s but was handicapped by the need to pierce the peritoneum with hard catheters. The development of soft catheter by Tenckoff in 1973 allowed permanent access to peritoneum. The situation changed dramatically when Popovich and Moncrief introduced concept of a portable wearable equilibrium PD system. Two litres of dialysate were infused intraperitoneally and allowed to equilibrate for 5 hours while patient conducted his normal activities. The dialysis was then drained and replaced. There were 5 exchanges per day and 7 days a week. The name of this method was changed in 1978 to continuous ambulatory peritoneal dialysis or CAPD. Over a period of 25 years, CAPD has become one of the standard care procedure for ESRF (**Figure 2**).

Principles of Peritoneal Dialysis

The physiological basis of dialysis across the peritoneum entails the process of diffusion, connective transport and osmosis. In PD, solute and fluid exchange occurs between peritoneal capillary and dialysis solution in the peritoneal cavity. The membrane lining this cavity consists of a vascular wall, interstitium, mesothelium and adjacent fluid film. Efficiency of PD as with HD depends upon the total time on dialysis and the dwell time of each exchange, blood flow, surface area and permeability of peritoneal membrane, dialysate flow and ultrafiltration rate. Ultrafiltration in PD is osmotically mediated.

Components of Peritoneal Dialysis System

Three key components of PD are: PD catheter, PD solution and the peritoneal membrane with its associated vasculature.

Peritoneal dialysis catheters

Several types of catheters are available. Most are made of silastic rubber with two Dacron cuffs, which are placed at either end of a subcutaneous tunnel. Straight Tenckhoff catheter is usually preferred. PD catheters can be inserted surgically or percutaneously using Seldinger technique (with or without laparoscope). Regular peritoneal dialysis can be started 2 to 4 weeks after the insertion of permanent catheter.

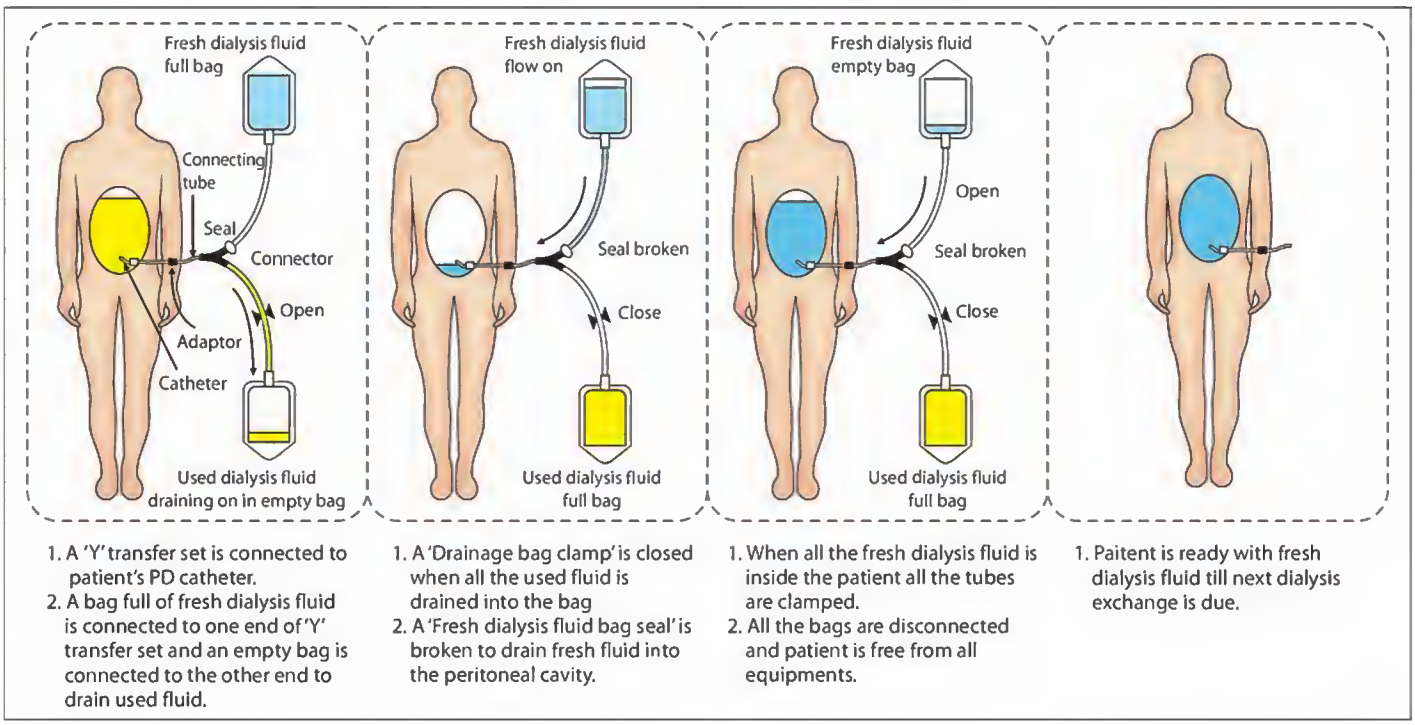
Peritoneal dialysis solutions

Standard PD fluid contains dextrose monohydrate 1.5% or, 2.5%, or 4.25%, sodium 130 to 135 mEq/L, potassium 0 to 1.5 mEq/L, calcium-1.5 mEq/L, magnesium-1.5 mEq/L, chloride-102 mEq/L and lactate 35 to 40 mEq/L. Dialysate is available in premixed, flexible, plastic bags, of 250 to 750 mL for children and 1 to 3 L for adults. Most adults tolerate 2 L volumes. Dextrose as an osmotic agent in PD has the advantages of being familiar, relatively safe and inexpensive and also is a source of calories. There is a concern however that it predisposes patient to hyperglycaemia, dyslipidaemia, obesity and long-term peritoneal damage. It is not very effective in high transporters. Alternate osmotic agents like icodextrin, aminoacids and gelatine are more expensive.

Peritoneal Dialysis Modalities

CAPD is the basic form of PD and is still in widespread use. A patient typically undergoes four manual exchanges per day (**Figure 2**). Three day-time exchanges of about 5 hours each and one overnight exchange of about 8 or 9 hours. By adjusting the dwell volume approximately most CAPD patients can achieve an adequate dose of dialysis. The simplicity of CAPD can be at home, freedom from machine, makes it most popular chronic peritoneal dialysis modality. It provides continuous therapy and steady physiologic state. The principal disadvantages of CAPD for many patients is the requirement of multiple procedure sessions each taking up 30 to 40 minutes and higher cost as compared to HD.

Automated peritoneal dialysis (APD) using cycler is now the fastest growing PD modality. APD is traditionally divided into



1. A 'Y' transfer set is connected to patient's PD catheter.
2. A bag full of fresh dialysis fluid is connected to one end of 'Y' transfer set and an empty bag is connected to the other end to drain used fluid.

1. A 'Drainage bag clamp' is closed when all the used fluid is drained into the bag
2. A 'Fresh dialysis fluid bag seal' is broken to drain fresh fluid into the peritoneal cavity.

1. When all the fresh dialysis fluid is inside the patient all the tubes are clamped.
2. All the bags are disconnected and patient is free from all equipments.

1. Paitent is ready with fresh dialysis fluid till next dialysis exchange is due.

Figure 2: Fluid exchange in continuous ambulatory peritoneal dialysis.

continuous cycling peritoneal dialysis (CCPD) and nocturnal intermittent peritoneal dialysis (NIPD). In CCPD, patient carries PD solutions in the abdominal cavity throughout the day but performs no exchanges and is not attached to a transfer set, at bed time patient hooks upto the cycler which drains and refills the abdomen with dialysate three or more times in the course of the night. In the morning, patient disconnects the cycler, the last dwell remaining in the abdomen. Patient is free to go about daily activities. In NIPD, the patient drains out fully at end of the cycling period and abdomen is 'dry' all day. Patient will perform cycler dialysis overnight. Because of the absence of a long day dwell, clearances are generally lower in NIPD than on CCPD. The main advantage of CCPD is ability to provide continuous therapy without need for on-off procedures during the day. All connections and preparations of equipment usually take place at bedtime in privacy of home, so psychological adjustment is facilitated and patient fatigue and 'burn out' may be reduced. It is also therapy of choice for most patients who require assistance in carrying out their dialysis like children, the dependent elderly and nursing home residents. The main disadvantage of CCPD is need for a cycler, the slightly greater complexity and cost.

Tidal peritoneal dialysis (TPD), a variant of APD was designed to optimise solute clearances by leaving a large volume of dialysis solution in the peritoneal cavity throughout dialysis session. It was thought that this would allow diffusive clearance to continue throughout cycling period. Initially peritoneal cavity is filled with a volume of solution selected to be as large as possible without causing discomfort. The volume used depends on patient size and habitus but is typically 2 to 3 litres. When TPD was introduced, 50% of tidal volume was common; for example if 2 L is being used, the next fill volume, the tidal volume, is 1 L, the next drain volume is about 1 L and so on. There is little evidence to suggest that TPD can provide clearance superior to that provided by cycler dialysis. However, it may decrease abdominal discomfort during inflow and outflow.

Choice and Assessment of Peritoneal Dialysis Adequacy

Inadequate dialysis and ultrafiltration failure cause patients to drop out from CAPD. Adequately dialysed patients feel well (absence of anorexia, nausea, vomiting, dysgeusia and insomnia) their BP is well controlled and they maintain a stable lean body mass. Their blood chemistry shows normal electrolytes. In order to provide adequate dialysis, total creatinine clearance (residual renal plus peritoneal) should be 50 to 60 L per week and kt/v for urea at least 2 per week. To achieve these goals, type of PD and prescription should be individualised according to residual renal function, body surface area and peritoneal membrane transport characteristic, as determined by peritoneal equilibrium test. High transporter will have poor ultrafiltration and adequate creatinine clearance, preferred mode would be multiple short dwells, like NIPD. High average transporters can be treated with standard-volume PD while low transporter will have adequate ultrafiltration but poor/inadequate solute clearance, appropriate mode will be high volume PD.

Complications of Peritoneal Dialysis

The complications observed during PD can be due to catheter malfunction; raised intra-abdominal pressure by continuous presence of dialysis solution in the peritoneal cavity; peritoneal response to unphysiologic solution and contamination; and systemic metabolic complications (**Table 3**) presents comprehensive list of problems encountered during CAPD.

Table 3: Complications during Peritoneal Dialysis

Technical complications: Catheter-related exit site infection, tunnel infection, peritonitis, pericatheter leakage, poor drainage, catheter migration rarely bowel perforation
Raised intra-abdominal pressure: Hernias, fluid leaks, rectal prolapse, vaginal prolapse, low back pain, scrotal oedema, and decrease in appetite
Unphysiologic solutions and contamination: All types of peritonitis, loss of ultrafiltration, sclerosing encapsulating peritonitis
Metabolic complications: Obesity, hypertriglyceridaemia, hyperglycaemia, hypoproteinaemia
Cardiopulmonary complications: Fluid overload, hypotension, hypertension atelectasis, hydrothorax, hypoxaemia

Peritonitis is one of the major risks of PD causing significant morbidity and mortality. It is one of the principle causes of drop out to HD. Peritonitis rates have fallen over the last 15 years from about one episode per 9 patient months (single bag system) to one episode per 24 patient months. Peritonitis is usually caused by single organism introduced by touch contamination. Peritonitis is suspected when returning fluid turns cloudy, white cell counts >100/mL with >50% polymorphonuclear leucocytes and symptoms like pain abdomen, cramps constipation or diarrhoea. Prompt empirical treatment should be started after sending fluid for Gram's stain, culture and antibiotics sensitivity. Infections with Gram-positive organism such as *Staphylococcus epidermidis*, *Staphylococcus aureus* and streptococcal species are common. Gram-negative organism causing peritonitis include *E. coli*, *Klebsiella* species, *Acinetobacter* species and *Pseudomonas* species, fungal, *Nocardia* and *Mycobacterium tuberculosis* cause peritonitis rarely. Management consists of abdominal lavage with three rapid in and out flushes of dialysate fluid. Followed by intra-peritoneal cefazolin, ceftazidime or aminoglycosides. Catheter removal is indicated if it is fungal infection or resistant, relapsing peritonitis.

Comparison of HD and PD

CAPD has a number of theoretical advantages compared with conventional haemodialysis, more independence, slow steady solute clearance, no cardiovascular instability and biochemistry destabilisation, salt and water control is generally easier, less dietary restrictions, higher haemoglobin, residual renal function is better preserved than HD. The rehabilitation rates and quality of life are better than observed in haemodialysis. Although maintenance dialysis prevents death from uraemia, patient survival remains an important issue. The survival on peritoneal dialysis is similar to that on haemodialysis. This value in older patients is slightly better than those with lung cancer and much worse than general population. CAPD is still underutilised in India because of high cost compared to haemodialysis. Major causes of death are cardiovascular disease infections and withdrawal from dialysis.

CONSERVATIVE AND PALLIATIVE CARE IN ESRF

In a country like India, cost of haemodialysis, transplant or CAPD is beyond the reach of many patients. Dialysis withdrawal is very common. Opting for conservative management is a passive suicide; patients will survive for few months. The goal of palliative conservative management is to achieve the best possible quality of life by relieving suffering,

controlling symptoms and restoring functional capability while maintaining sensitivity to personal cultural and spiritual belief and practices. Adequate calories with restricted protein, salt and water will prevent fluid overload and uraemic symptoms. Fluid overload treated with diuretics like furosemide or torsemide, treat acidosis with sodium bicarbonate to maintain HCO_3^- above 20 mEq/L. Maintain haemoglobin with iron and erythropoietin, control of hyperphosphataemia, secondary hyperparathyroidism with phosphate binders and vitamin D. The pain control may be done with simple paracetamol and tramadol. Strong opioids such as fentanyl and methadone may be used for pain control in severe cases. Constipation is treated with lactulose 15-30 mL orally or bisacodyl 30 mg orally or 10 mg rectal suppositories simple enema or glycerine rectal suppositories may also be effective. Phosphate-containing enemas should be avoided. Myoclonus, muscle twitching and seizure may be treated with clonazepam 0.5 to 2 mg orally. The terminal restlessness and agitation may be treated with midazolam 2.5 to 5 mg. For good symptom control, as required medication should be prescribed for likely symptoms in addition to regular medication for ongoing symptoms.

FUTURE HOPES

Our two kidneys work 24 hours a day, 7 days a week, so we filter 168 hours a week. It is very difficult to believe that 9 to 12 filtrations per week will do an adequate job. The kidney has synthetic, regulatory and excreting functions. Dialysis does only excretory and to some extent regulatory functions. Increasing data show that daily dialysis improves outcome, reduces anaemia and improves the QOL. Future hopes are a bionic artificial kidney, wearable human nephron filter and use of gastrointestinal tract for dialysis with oral sorbents, bio-encapsulated living cells and probiotics. Human nephron filter utilises a unique membrane-system created through applied nanotechnology. This is likely to mimic the function of a natural kidney. Animal studies using this technology are schedule to begin in the next 1 to 2 years with clinical trials to follow subsequently.

Bioartificial Kidney

The tubule assist device developed by H David Humes at the University of Michigan consists of a man made blood filter connecting a cartridge containing approximately one million human kidney cells. These proximal tubular cells can perform some of important kidney functions. Early experiments with dogs that had kidney failure demonstrated possible effectiveness of this device. Recently, phase II clinical trials with use of RAD device gave impressive results, but these need to be confirmed by a larger study.

CONCLUSION

Since the incidence of CKD is increasing, efforts should be directed to detect and treat renal failure early. Kidney failure is no longer an untreatable disease. Currently available treatment strategies, maintenance haemodialysis or PD, prolong useful life. Renal transplant is the treatment of choice. Haemodialysis and PD are prohibitively expensive and not enough donor organs are available for kidney transplantation. Therefore, it is necessary to develop affordable new approaches to replace renal function.

RECOMMENDED READINGS

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19.12 Renal Transplantation

George T John

The first successful renal transplant was reported from the United States of America between identical twins in 1956, while in India, it was done at Christian Medical College in Vellore in 1971. Currently about 3500 renal transplants are done annually in 150-odd centres all over India. This is the ideal form of treatment for chronic kidney disease—stage 5.

The issue of graft rejection is of primary concern in any transplantation. Therefore, understanding transplantation immunology is essential to be familiar with the measures taken to avoid/minimise the chance of such an occurrence. Pre-transplant evaluation selects the immunologically most suitable of the available donors. After transplantation, a balance of the immunity needs to be achieved, low enough to prevent graft rejection yet sufficiently high to protect the recipient from opportunistic infections and malignancies.

TRANSPLANTATION IMMUNOBIOLOGY

There are three phases of immune response to a transplanted allograft.

Recognition of Foreign Antigens

This occurs through the gene products (antigens) located on chromosome 6 at the major histocompatibility complex (MHC), which are called human leucocyte antigens (HLAs). When individuals differ in their histocompatibility antigens, the allografts are rejected. During maturation in the thymus, T cells that respond to self-antigens are deleted (negative selection) and those that respond to foreign peptides are selected (positive selection).

Activation of Antigen-Specific Lymphocytes

The recognition of alloantigen by T cells is the primary process that leads to activation, followed by proliferation, and then by differentiation of alloreactive T cells. This occurs by direct and indirect processes (**Figure 1**). The T-cell receptor (TCR) is a polypeptide heterodimer on the cell surface associated with the CD3 complex which is important for the expression of TCR and for the transmission of intracellular signalling. Antibody producing B lymphocytes mediate hyperacute rejection, which occurs within 24 hours in recipients with previous sensitisation to donor HLAs.

Effector Phase of Graft Rejection

Antigen presenting cells (APCs) present donor antigen on the MHC to T cells via TCR–CD3 complex. Antigen triggers T-cell receptors (TCRs) (**signal 1**). CD80 (B7-1) and CD86 (B7-2) on the APC bind to CD28 on the T-cell to provide **signal 2**. These signals activate three signal-transduction pathways—the calcium—calcineurin pathway, the mitogen-activated protein kinase pathway, and the protein kinase C–nuclear factor-κβ (NF-κβ) pathway—which activate transcription factors nuclear factor of activated T cells, activating protein 1 (AP-1), and NF-κβ, respectively. This results in the expression of interleukin (IL)-2

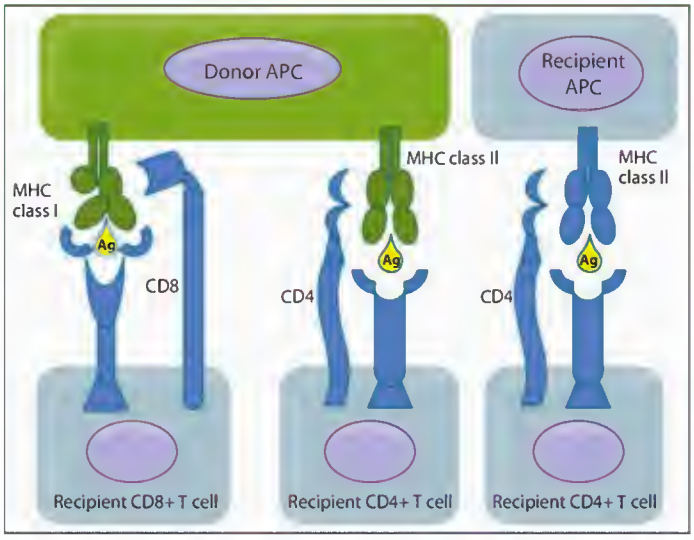


Figure 1: *Left panel:* Direct allorecognition. T-cell receptors (TCRs) on recipient T cells interact directly with intact donor major histocompatibility complex (MHC) antigens on antigen presenting cells (APCs) derived from the donor organ. CD8+ T cells preferentially interact with MHC class I antigens, whereas CD4+ T cells recognise MHC class II antigens. *Right panel:* Indirect allorecognition. Recipient T cells recognise peptides derived from donor MHC proteins that have been processed by recipient APCs and are presented in the context of self MHC expressed on APCs from the recipient.

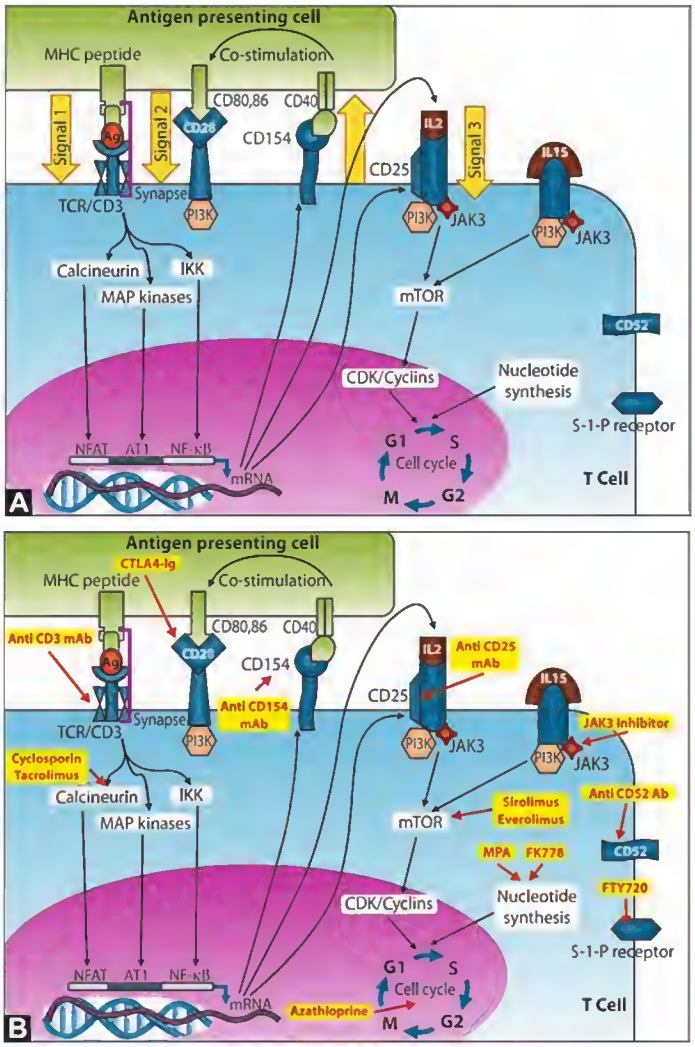
receptor α chain (CD25), IL-2 and CD154 (which further activates APCs). IL-2 and IL-15 provide growth signals (**signal 3**) through the phosphoinositide-3-kinase pathway and the mammalian-target-of-rapamycin pathway, which initiates the cell cycle. Lymphocytes require synthesis of purine and pyrimidine nucleotides for replication, regulated by inosine monophosphate dehydrogenase and dihydroorotate dehydrogenase, respectively. The CD8 cells kill with granzymes and perforins along with the engagement of Fas ligand to its target on the allograft causing apoptosis (**Figure 2A**).

Tolerance is the absence of destructive immunity against the allograft with otherwise preserved immunity. This has been achieved in experimental animal models while long-term induction of tolerance remains the holy grail of transplantation.

DRUGS OF CHOICE FOR IMMUNOSUPPRESSION

In India prednisolone and azathioprine were used in 1970s; cyclosporine and mycophenolate became available in 1990s and tacrolimus at the turn of the Century. Currently, most patients receive a triple drug regimen including tacrolimus, mycophenolate and prednisolone for maintenance immunosuppression. The sites of action of the various immunosuppressive agents are shown in **Figure 2B**.

Calcineurin inhibition with cyclosporin (CsA) and tacrolimus (FK 506; Tac) has improved results of renal transplantation remarkably. They form a complex with their specific cyto-



Figures 2A and B: (A) Shows the three-step signalling pathway for allorecognition to effector mechanisms; (B) shows sites of action of various immunosuppressive agents.

MHC = Major histocompatibility complex; TCR = T-cell receptor; JAK3 = Janus Kinase 3; MTOR = Mammalian-target-of-rapamycin; NFAT = Nuclear factor of activated T cells; MPA s = Mycophenalic acid; IKK = Inhibitor of nuclear factor-κβ kinase; CDK = Cyclin-dependent kinase.

plasmic proteins, cyclophilin and FK-binding protein respectively, which in turn bind to calcineurin. This protein which normally dephosphorylates nuclear regulatory proteins and promotes down-stream gene signalling is turned off when such a complex is formed. With therapeutic doses these drugs inhibit calcineurin by half, leaving just enough room for host defences against microbes and cancer; a delicate trade-off. For maintenance of immunosuppression, CsA or Tac are used in doses of 3 mg/kg and 0.1 mg/kg, respectively, targeting CsA trough levels of 100 to 250 ng/mL, C2 levels of 800 to 1,700 ng/mL; and tacrolimus trough of 3 to 9 ng/mL. Higher targets are achieved during the first 3 months of transplantation and lower targets are sufficient for later maintenance. Drug interactions with calcineurin inhibitors are similar; cytochrome P-450 inhibitors inhibit and augmenters increase metabolism of these drugs. Diltiazem or ketoconazole can be co-administered to reduce the dose and cost of CsA/Tac. CsA causes hirsutism and gum hypertrophy; tacrolimus causes tremor and hair loss while both drugs have nephrotoxicity. Although both drugs cause pancreatic β cell toxicity, tacrolimus is associated with a greater risk of diabetes mellitus.

Mycophenolic acid prodrugs, namely, mycophenolate mofetil (MMF) and mycophenolate sodium inhibit inosine monophosphate dehydrogenase resulting in blocking the *de novo* pathway of guanosine nucleotides producing a selective anti-proliferative action on lymphocytes which use this pathway more than other cell lines. MMF is usually dosed at 1.5-2.0 g per day in two divided doses although there is a large variation in the drug absorption and metabolism. These drugs are associated with better survival rates as compared to azathioprine-containing regimes.

Target of rapamycin (TOR) inhibitors (sirolimus, everolimus) bind to a regulatory kinase, after these form a ligand with FK-binding protein. This inhibits cytokine-dependent cellular proliferation. Sirolimus is used at a dose of 0.05 to 0.1 mg/kg per day in a single dose to achieve a target trough level of 3 to 7 ng/mL. TOR inhibitors are difficult drugs to use and have major side effects, especially when used in combination with full doses of CsA or tacrolimus. However, there is limited nephrotoxicity when TOR inhibitors are used without these agents.

Induction therapy at the time of transplantation with an IL-2 receptor blocker (basiliximab) or polyclonal antithymocyte globulin (thymoglobulin) is found to be beneficial in long-term survival of deceased donor allografts and perhaps in living donor transplant recipients.

PRE-TRANSPLANT EVALUATION FOR HISTOCOMPATIBILITY

Histocompatibility Testing and Cross-Matching

A cluster of genes on human chromosome 6 encodes for the HLAs which form the major barrier to transplantation of tissues and organs between individuals. Also, antibodies directed against HLAs as a result of repeated pregnancies, transfusions or transplantations, cause accelerated or hyperacute rejection following transplantation. The appearance of these antibodies after transplantation is associated with rejection episodes. HLAs are detected using microcytotoxicity tests or deoxyribonucleic acid-typing technology. The antibodies are detected using complement-dependent lymphocytotoxicity tests, enzyme-linked immunosorbent assay (ELISA) and fluorescence-activated flow-cytometry.

POST-TRANSPLANT MONITORING OF IMMUNE STATUS

Currently, monitoring of renal functions with urea and creatinine is the routine practice although decline in renal function is a downstream result in a cascade of events leading to rejection of the allograft. Monitoring of earlier immunological insurgencies of recipient T-cell and B-cell are possible with measurement of T-cell alloreactivity using ELISPOT test and with ELISA for donor-specific antibodies, respectively. However, these tests have not yet been shown to consistently correlate with alloreactivity. Expression of mRNA for perforin and granzyme B on histology samples correlate well with acute rejection. Frequent biopsies are difficult and mRNA for these cytotoxic mediators of cells passed into urine may become a valid non-invasive assay for rejection.

CURRENT PRACTICE

Renal transplantation is currently the best form of renal replacement therapy and is offered to children having 15 kg weight to adults up to the age of 65 years. Recipients have to be free of infection, malignancy and anti-donor-HLA antibodies.

They must have robust organ-systems to cope with the rigors of surgery and subsequent immunosuppression. Diabetics need detailed evaluation of cardiac, vascular and autonomic systems. The kidney donor source in India is still the living donor pool while in developed nations it is the brain-dead beating-heart donor. The living donors must be fully informed, consenting, medically fit, blood group compatible and without transmissible infective agents. HLA matching improves long-term survival, especially in India where profound immunosuppression needed with HLA mismatched transplantations leads to a high risk of infections. However, unmatched siblings, spouses, grandparents and paired kidney exchange donors are permitted to donate under 'The Transplantation of Human Organs Act' (THOA).

DECEASED DONOR TRANSPLANTATION

The THOA 1994 allows for deceased donor transplantations by defining the scope of brain-stem death in India. Non-governmental organisations in partnership with the state governments have expanded the deceased donor programme and a third of deceased donor organs have been made available by such initiatives. The deceased donor programme is hampered by poor awareness, lack of infrastructure to support critically ill patients and lack of co-ordinated teams for grief counselling, brain death certification, organ explantation and allocation. Until 2009, nearly 1400 deceased donor (brain-dead, beating-heart) organ transplantations have been done in India.

Altruistic donation is permitted according to the THOA but is used by some to foster paid donor transplants. The ethics of paid donor transplantation is hotly debated while the policy makers all over the world variably respond to the ever-increasing need for organs while patients remain on dialysis awaiting transplantation.

Pre-emptive transplantation (done before dialysis is initiated) from a living related donor of less than 50 years of age has the best survival advantage. It is, therefore, wise to have patients with renal failure referred to centres where a pre-emptive renal transplantation from a related donor can take place with benefits of better graft function and savings from avoiding dialysis related expenses.

Paired donor kidney exchange transplantation is being done when related donors are unsuitable for their respective recipients but suitable for a swap with an unrelated recipient, both pairs agreeing for a reciprocal donor kidney exchange. It is now possible to do renal transplantation across the ABO incompatibility barrier. Kidney donation after cardiac death is yet to be a routine practice in India. These strategies can increase the number of patients benefitting from transplantation.

TRANSPLANTATION

The donor nephrectomy can be done laparoscopically and this reduces the morbidity and the hospital stay. The recipient has the allograft implanted in the iliac fossa with anastomosis of the donor vessels to the iliac vessels and the ureter implanted into the recipient bladder using antireflux technique. Rarely, in those patients with type 1 diabetes mellitus, a deceased donor pancreas can be connected to the vascular system with the ducts usually draining into the urinary bladder simultaneously with kidney transplantation. Immunosuppression is often started 3 days prior to surgery in living donor transplants to build up drug levels. Immunosuppressive drug levels are monitored from within a week of the operation.

POST-TRANSPLANTATION COMPLICATIONS

Early surgical complications include wound infections, urinary catheter block, urinary leak and rarely vascular thrombosis. The early medical complications include acute tubular necrosis resulting in delayed graft function, acute rejection, bacterial infections of the wound, urinary tract and the lung.

Infections

The mortality and morbidity of patients in India are mainly due to infective complications. The chronological occurrence of various opportunistic infections is predictable for each environment and so it is for the tropics. The first month after transplantation shows complications of immunosuppression and surgery. The common infections are due to wound infections, lower respiratory tract infections following anaesthesia and cytomegalovirus (CMV) infections. Three to six months after transplantation is the period when tuberculosis, systemic fungal infections, CMV infections and other viral infections are seen. After six months of transplantation, nocardiosis and cryptococcal infections are also to be considered in a febrile patient. Post-transplant lympho-proliferative disorders are usually seen peaking in the first year of transplantation especially if induction therapy is used against lymphocytes and are usually a result of Epstein-Barr virus infection. Liver malignancies are generally caused by hepatitis C and B viruses. The presence of hepatotropic viruses, CMV, hyperglycaemia and polyclonal or monoclonal anti-lymphocyte antibody induction are risk factors for infections.

Rejection

Rejection processes of the renal allograft can occur from the time of surgery and for as long as the kidney remains *in situ*. The acute rejection episodes are clinically suspected if there is graft tenderness and decreased urine output and confirmed with a biopsy of the allograft. The laboratory features are more reliable and consist of decline in renal functions, leucocyturia and occasionally, haematuria. The types and severity of rejections are classified according to *Banff criteria*. Acute rejections are characterised by lymphocytic infiltration of interstitium and tubules (cellular rejection) and rarely with patchy infiltration of arterioles with or without necrosis and thrombosis (vascular rejection). Currently c4d immunostains and detection of donor-specific antibodies form the basis of diagnosing antibody-mediated rejections. Acute cellular rejections are treated with intravenous pulses of methyl-prednisolone or, if that fails, polyclonal/monoclonal antibodies are infused against lymphocytes. Vascular rejection is a more serious event adversely affecting graft survival and is usually treated with monoclonal (anti-CD3) or polyclonal anti-lymphocyte peptides.

Vascular Disorders

Vascular disorders rank high among the late complications. These are due to accelerated atherosclerosis brought about by hypertension, dyslipidaemia and renal dysfunction. These present as acute coronary syndromes, strokes, transplant artery stenosis and acral ischaemia. Transplant artery stenosis is usually seen in the context of severe hypertension and allograft

dysfunction; colour Doppler imaging is a good screening test and angiography with limited radio-contrast proves the diagnosis. Endovascular intervention with angioplasty and stenting is the current standard of care.

Recurrence of Glomerular Disorders

Recurrence of glomerular disorders is an important cause of allograft dysfunction. Focal and segmental glomerulosclerosis, mesangiocapillary glomerulonephritis (MCGN) type 1, MCGN type 2, IgA nephropathy recur in 35%, 50%, 100% and 30% of allografts, respectively. The type of immunosuppression does not alter this frequency although graft loss occurs only in a proportion of patients with recurrence. *De novo* glomerulo-nephritis is thought to be a rarer expression of rejection and is often morphologically similar to membranous nephropathy.

SURVIVAL AFTER TRANSPLANTATION

Survival after transplantation in India at 1, 5 and 10 years is about 97%, 80%, 60%, respectively. Most patients do not have the resources for further treatment if the allograft fails. So graft and patient survival are very similar in India. In developed nations with funding for transplantation, loss of an allograft would entail patient returning to the dialysis programme, waiting his turn for another deceased donor kidney.

FUTURE DIRECTIONS

Tolerance induction is the holy grail of transplantation; where specific tolerance to donor organ exists with robust immunity against other external antigens without the use of continuing immunosuppression. The underlying processes are vastly different among the different species of animals. In humans it has not been possible to consistently achieve tolerance with well-studied, non-hazardous protocols. However, the general direction has been to have a lymphocyte depleting strategy or a co-stimulatory blockade during the early phase of transplantation and calcineurin phosphatase-free immuno-suppression in the later phase. The use of stem cells in promoting tolerance pathways and in regenerating the damaged kidney is currently gaining attention.

CONCLUSION

Renal transplantation has progressed from an experimental endeavour to a highly effective therapy in the past six decades. With this success comes an increased demand for donor kidneys and a severe organ shortage. Long-term survival benefits have lagged behind the significant increments in short-term survival. Increasing the number of donor organs, improving anti-rejection therapy, tolerance induction and xenotransplantation are goals for the future.

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Section 20

Neurology

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20.1 Basic Considerations in Neurology

RS Wadia

The clinical evaluation of a patient with a neurological problem follows the standard practice of history-taking followed by physical examination and investigations as indicated by the clinical diagnosis.

THE IMPORTANCE OF HISTORY

It is important to note that in neurology the clinical examination is only useful to localise the site of lesion. The aetiology of the problem is made out by the history. In fact, at the end of history, one should be able to tentatively outline the anatomical and functional localisation as well as the pathological nature of the disease. Importantly, onset, duration and the time course of each symptom is helpful in delineating the same. Thus:

(a) Sudden onset with time of onset exactly located implies vascular aetiology,

(b) Gradual progression implies space-occupying lesion (SOL),

(c) Gradual progress over months to years is a feature of degenerative disease,

(d) Recurrent attacks with recovery occurring 2 to 4 times a week or a month suggests transient ischaemic attack (TIA),

(e) Recurrent discrete episodes over months to years suggests demyelinating disease,

(f) A disease with sudden onset which then continues to slowly progress could well be an SOL with the sudden onset being due to haemorrhage within the tumour.

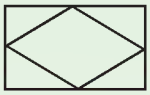
It is also to be noted that the three commonest complaints in neurology, viz. headache (all the primary headaches, migraine, tension headache, cluster headache, post exertional and coital headache), epilepsy and vertigo are very well analysed and diagnosed by history alone.

Of course while focusing on the present complaints in a neurologic examination, it cannot be over emphasised that a review of the other systems, a check on past history, a review of patient's social habits and hobbies and the family history play a vital role in neurologic diagnosis.

THE HIGHER FUNCTIONS

These include memory, orientation, intelligence, speech and abstract reasoning and are evaluated by the patient's response to examination. The mini-mental state examination (MMSE) is a rough measure of higher function, it gives a total of 32 points (**Table 1**). In disease of higher functions some terms need description. Dementia is a chronic disorder with overall reduction of higher function embracing at least two functions, e.g. memory, intelligence, orientation, speech, abstract reasoning and self-care. Although memory loss is first in cases of dementia, loss of memory alone is amnesia. In dementia memory is lost along with loss of orientation, speech and self-care. Dementia is suspected if there is a chronic disorder, MMSE score is 24 or less, and the person requires help in activities of daily living. Delirium is an acute change of higher function usually associated with fluctuating course and abnormal attention. There is usually motor restlessness, occasionally apathy. Mental retardation is the term used in children who are developing slower than normal. But these children can be noted to be developing. Mental regression is used when a child has developed some developmental milestones and then starts to lose them, stops walking and then cannot sit well, etc. Mental regression is the hallmark of metabolic disorder lipidosis, or leucodystrophy and may also be seen in chronic infections such as subacute sclerosing panencephalitis or HIV disease.

Table 1: The Folstein Mini-Mental State Examination (MMSE)

	Question	Scoring	Max. Score
1.	Where are you (state, country, city, hospital, clinic)	1 point for each	5
2.	What is the day, month, season, year, time	1 point for each	5
3.	Say these 3 words after me (yellow, apple, Ohio)	1 point for each	3
4.	Ask patient to begin with 100 and count backwards by 7's	Stop after 5, score no. correct or 1 point for each correct number	5
5.	Recall the three words given in question No. 3	1 point for each	3
6.	Ask the patient to name 'watch' then 'pencil'	1 point for each	2
7.	Ask the patient to repeat 'no, ifs, ands, or buts'	1 point if correct	1
8.	Three stage command: Take this paper in your right hand, fold it in half, and put it on the door	1 point for each correct	3
9.	Ask the patient to read silently and obey the command (print in block letters) - CLOSE YOUR EYES	1 point if correct	1
10.	Ask the patient to write a sentence	1 point if contains a subject and verb and makes sense (ignore spelling and grammar)	1
11.	Draw a clock with number and hands showing the time to be 8:20	1 points if correct numbers 1 if hands correct	2
12.	Have the patient copy this design 	1 point if all sides and angles are preserved and if intersecting sides form a quadrangle	1
		Total Score	**32**

Indian versions have been described and validated.

Minimal cognitive impairment is a new concept recently introduced. As people age they tend to be forgetful, cannot remember faces, people, and events as well as before. This is usually called benign forgetfulness. Those who have MMSE score between 25 and 27, and can otherwise look after themselves in activities of daily living are said to have minimal cognitive impairment (MCI) Patients with MCI have a six times greater risk of developing dementia and represent the early stages of dementia. Some cases of MCI may remain static and some may even improve if family circumstances improve. The importance of MCI lies in that it may represent the reversible state of dementia and a drug is likely to be more useful at this time rather than later.

LIMBIC SYSTEM

The limbic system represents the older parts of the brain and histologically does not have the six layers seen in the neocortex. It may be thought to consist of two adjoining rings: (a) Papez circuit of hippocampus going round in a ring below the corpus callosum including the fornix to the mamillary body and by the mamillothalamic tract to the anterior and dorso-medial nucleus of the thalamus; and (b) the associated areas which include amygdala, entorhinal cortex, parahippocampus and cingulate gyrus above the corpus callosum, septal area and preoptic nucleus of the hypothalamus. This limbic system subserves human emotions and is the seat of recent and short-term memory.

Memory is stored in this system with the most recent events in the hippocampal region and going backwards and round. Disruption of hippocampal fibres leads to loss of memory for a variable period as in retrograde amnesia (transient global amnesia) or transient ischaemic attack (TIA) of the limbic system or a post-ictal phenomenon or a migraine like event. Rarely a form of transient global amnesia may last beyond 48 hours, it is then invariably due to a metabolic encephalopathy.

The limbic system records immediate and short-term memory. Long-term memory is stored in the RNA of all the cells in the brain so that in very few and only advanced disorders can long-term memory be lost. Therefore, for early detection of dementia it is important to test recent memory and not past memory.

PYRAMIDAL SYSTEM

The motor movements are carried out by the upper motor neurons (UMN), i.e. the pyramidal system, and the lower motor neurons (LMN). Upper motor neurons are the descending fibre system with cells of origin in the cerebral cortex—predominantly precentral gyrus—that descends and innervates cranial nerve nuclei on the opposite side and the corticospinal tract decussates in the medulla and supplies the anterior horn cells (**Figure 1**) of the cord on the opposite side. Loss of function results in paralysis of movement and not of muscles. An acute insult causes atonic, areflexic paralysis, called neurogenic shock, which later manifests with classical signs of pyramidal dysfunction viz.:

1. A particular pattern of weakness with loss of movement
2. Increased tone with spasticity
3. Hyperreflexia of deep jerks
4. Clonus at knee or ankle
5. Absent superficial reflexes viz. abdominal and cremasteric reflexes
6. Extensor plantar (Babinski) response.

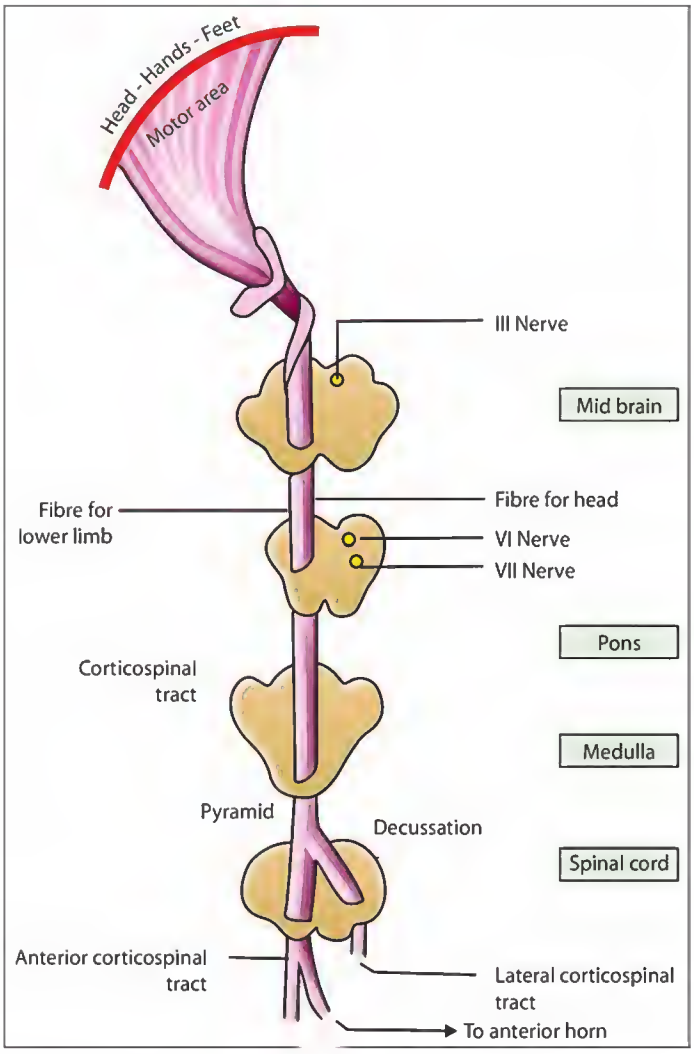


Figure 1: Schematic line diagram of motor pathways.

Generally, at least two of these signs are necessary to diagnose pyramidal disease. One alone pyramidal affection. Hyperreflexia alone, no matter how marked, should not be taken as evidence of corticospinal dysfunction. However, clonus alone is sufficient to make such a diagnosis.

The pattern of weakness is typical. In the upper limb the most affected muscles are the deltoid, triceps, and the hand muscles. In the lower limb the most affected muscles are hip flexors, knee flexors and dorsiflexors of the ankle. Hypertonia in pyramidal disease is called spasticity. It is different from that in extrapyramidal disease (rigidity) (**Table 2**).

Table 2: Differences Between Spasticity and Rigidity

	Spasticity (Pyramidal)	Rigidity (Extrapyramidal)
Muscles affected	Antigravity muscles	Agonists and antagonists equally
Nature	Clasp-knife, i.e. maximal at start of movement	Lead pipe or cogwheel
Velocity dependence	Considerable	Minor
Accompanying signs	Hyperreflexia, clonus, Babinski response	Tremors, bradykinesia, etc.

Pyramidal and extrapyramidal diseases are the main causes of hypertonia. However, there are other causes of hypertonia, viz. hysterical rigidity, gegenhalten (a plastic rigidity seen in frontal lobe disease, dementia or in some metabolic encephalopathies, e.g. hepatic) and diseases with muscle spasm, e.g. tetanus, strychnine poisoning and stiff-man syndrome.

EXTRAPYRAMIDAL DISORDERS

Extrapyramidal disorders may be divided into akinetic rigid syndrome of Parkinson's disease and allied disorders, and the dyskinesias; chorea (caudate nucleus lesion usually), athetosis (putamen lesion) and hemiballismus (subthalamic nucleus). The main lesion in the akinetic rigid syndrome is in the *substantia nigra*.

The important features of extrapyramidal lesions are shown in **Table 3**.

Table 3: Important Features of Extrapyramidal Lesions

Akinetic rigid forms

- Rigidity—Uniform increase in tone through entire range of movement (lead pipe)
- Tremor—At rest (pill-rolling type) combination of rigidity and tremor discharge causes cogwheel rigidity
- Bradykinesia (akinesia) as seen by mask face, infrequent blinking, and loss of associated arm swing while walking

Dyskinetic forms

- Chorea and choreiform movements and hypotonia
- Athetosis—Wriggling movements of fingers and hands
- Choreoathetoid movements
- Dystonia
- Hemiballismus—unilateral marked chorea

Chorea is a quasipurposive non-repetitive movement more marked at the larger joints. Dystonia is an abnormal limb position due to increased tone. It usually has a rotatory element and the limb is held in the abnormal position for some duration of time. In the akinetic rigid forms of extrapyramidal disorder unilateral affection at onset, and significant rest tremor favours idiopathic Parkinson's disease while early hallucination, early dementia and bilateral onset favours other akinetic rigid syndromes like multiple system atrophy or Lewy body disease.

CEREBELLAR DISEASE

The cerebellum and the extrapyramidal system modulate motor activity. The signs of cerebellar disease are basically three:

Ataxia

This gives rise to additional signs like dysdia-dochokinesia, past pointing, intention tremor, scanning speech and loss of balance to the same side.

Hypotonia

This causes two additional signs—the pendular knee jerk and rebound phenomenon. The jerk is said to be pendular when, on tapping the knee, it swings freely forward and backward. The number of swings is not important because a brisk pyramidal jerk will jump forward and may show 3 to 4 jerks before settling down. The cerebellar reflex swings to and fro without any jerk. Rebound phenomenon is said to be present when the patient is unable to slow his hand as we release it during power test and it goes on to strike the chest.

Inability to maintain a posture/position

This causes cerebellar tremor. The hand is held outstretched. It fails to hold a position so it goes down, then it is corrected and returns to normal, and the same cycle repeats. Cerebellar nystagmus is similar; when the eyes are looking laterally, the position cannot be held so it moves to midline and is jerked out again, and the same repeats. Its fast component is lateral whether looking left or right but is more marked on the side of the lesion. This is the hallmark of cerebellar nystagmus and is called gaze evoked nystagmus.

Acute cerebellar disease may have two more signs: skew deviation, i.e. a vertical separation of the eyes with one eye down and in, the other eye up and out. The lesion is on the side of the down and in eye. The cerebellar position of the head is with the occiput to the side of the lesion and spine concave towards the lesion. Both these signs regress after acute cerebellar injury is over.

Midline cerebellar disease is to be differentiated from lateral cerebellar disease. In midline disease, there is ataxia of stance and gait (tandem gait ataxia) without limb ataxia and tendency to fall forwards or backwards and not to one side. Midline disease frequently has no nystagmus. Cerebellar signs and symptoms are summarised in **Table 4**.

Table 4: Cerebellar Lesions—Signs and Symptoms

Head	Head tilted to affected side, rare head tremor
Eyes	Horizontal nystagmus fast component laterally more on looking to the side of lesion
Speech	Scanning or staccato (bombastic) speech
Gait	Broad based gait, drunken gait, leaning and swaying to affected side while walking in a straight line
Coordination	Intention tremors (more at end of voluntary act), past pointing, breaking of movement, dysdiadochokinesia
Muscles	Hypotonia, no wasting, no loss of motor power
Reflexes	Pendular knee jerk

MULTIPLE CRANIAL NERVE LESIONS (EXTRA-AXIAL AND INTRA-AXIAL DISEASE)

When it comes to brainstem and cranial nerve disease, the clinician often tries to recognise if the lesion is extra axial, i.e. outside the brain and catching cranial nerves, or within it, intra- axial, and causing cranial nerve palsies. Presence of long tract signs (pyramidal, spinothalamic, cerebellar) indicates an intra-axial lesion and absence suggests extra-axial lesion.

Three patterns of such multiple cranial nerve lesions are common:

(a) 2nd, 3rd, 4th, 5th and 6th cranial nerves on one side are involved in a lesion which is parasellar (by the sides of the sella) and involving the cavernous sinus, e.g. parasellar tumour, cavernous sinus thrombosis, or mucormycosis.

(b) 5th, 6th, 7th and 8th nerves on one side may be involved in a lesion at the cerebellopontine angle, e.g. acoustic neuroma or meningioma or arachnoid cyst or 5th nerve neurofibroma. To diagnose, if a cerebellopontine angle

tumour is an acoustic neuroma we go back to history. If the first symptom was hearing loss it is an acoustic. If it clearly was not, one of the other causes is more likely.

(c) 9th, 10th and 11th with or without the 12th nerve on one side are involved in a lesion near the jugular foramen.

A nasopharyngeal carcinoma entering the brain may involve any or all these three sites and may cause unilateral widespread cranial nerve palsy.

Meningitis can involve cranial nerves bilaterally and meningitides which do this are TB, syphilis, carcinomatous meningitis, sarcoidosis and some fungal meningitis.

CORD DISEASES

A cord lesion is recognised by the presence of bilateral limb signs, i.e. bilateral weakness, hypertonia, hyperreflexia or sensory loss. Of course this can occur also with brain disease, e.g. bilateral cerebrovascular disease so these signs with higher function involvement or cranial nerve disease imply brain disease. In the absence of higher function loss or cranial palsies bilateral upper motor neuron signs imply cord disease and this suspicion is increased if there is root pain, or sensory level on the trunk. When cord disease is diagnosed the first cord disease to consider is cord compression. Cord compression is diagnosed, if there is a chronic progressive disease of the cord and shows a level. The level may be a pain level—root pain—a motor level, e.g. biceps power normal, triceps weak (implying C6 lesion) or a reflex level biceps jerk absent, triceps jerk brisk (implying C5 lesion) or a sensory level. When there is a cord compression, the first tract to be involved is the pyramidal tract and next is the posterior column. So progressive pyramidal and posterior column signs without a level need also be investigated for cord compression. Spinal shock as a finding is the result of an acute cord lesion where all the reflex activity below the lesion is lost. So, though there is a cord lesion, the patient has hypotonia, areflexia, and retention of urine. One can suspect that it is spinal shock, and not a LMN nerve lesion, if the plantar is extensor or there is sensory level on the trunk.

A central cord syndrome is a lesion in the centre of the cord. It is seen in syringomyelia and intra-medullary tumour and is characterised by:

(a) Absence of root pain.

(b) Dissociated anaesthesia: Pain and temperature affected, and joint, vibration and touch sensations are preserved because pain and temperature cross the cord to go to the opposite side.

(c) Particular march of anaesthesia: In these cases first there is loss of sensation in one upper limb and adjacent trunk (half cape anaesthesia) as fibres from one side get caught; then there will be bilateral similar loss (cape anaesthesia); then jacket anaesthesia (upper limbs and trunk up to lower ribs), suspended jacket anaesthesia (sensory loss descends to umbilicus or so); and then sacral sparing. This last occurs because the spinothalamic tract is laminated so, as a central cord lesion expands, it catches first cervical, then thoracic, lumbar and sacral fibres in that order.

Root pain, i.e. pain along a nerve root often increased by coughing or sneezing is of course the hallmark of an extra-medullary cord compression.

Hesitancy (delay to initiate the act of micturition) and precipitancy (inability to hold back the act of micturition) are manifestations of cord involvement (See Chapter on Diseases of Spinal Cord).

DISORDERS OF SENSATION

Sensations in neurology are divided into superficial (touch, pain temperature) and deep (joint sense, vibration sense, sense of position, muscle sense, tendon sense and sense of deep pressure). Sensory disorders are positive or negative. Positive means paraesthesia, hyperaesthesia or allodynia. Hyperaesthesia implies a sensation, e.g. pinprick is felt more severe. Allodynia means a sensation, e.g. cold is felt as another sensation, e.g. pain.

Negative in sensation means loss of sensation and usually the superficial sensation are carried by the small nerve fibres and in the spinothalamic tract. The deep sensations are carried by large nerve fibres and in the posterior column of the cord. The patterns of sensory loss in neurology are multiple starting from peripheral nerve up, they include:

(a) Loss of sensation in a twig of nerve, e.g. in Hansen' disease in the patch of anaesthesia, or post-surgical incision, or in digital neuropathy.

(b) Mono-neuropathy means single nerve disease commonly seen in leprosy, diabetes or entrapment or pressure neuropathy.

(c) Radiculopathy shows a different distribution, e.g. an ulnar sensory loss is in the ulnar one and half fingers and the palm on that side and ending 1 inch proximal to the wrist roughly. Similarly the loss of median nerve lesion ends one inch proximal to the wrist. When the sensory loss includes ulnar hand and goes up the ulnar side of forearm it is a root lesion. Similarly a median territory hand loss extending on the forearm to the elbow or a dorsum of foot lesion extending up the leg is a radiculopathy not a neuropathy.

(d) Cord sensory losses are of various types. The sensory level of a transverse myelitis and the loss in a central cord lesion have been mentioned already. Other cord lesions are the unilateral cord lesion with touch, pain and temperature lost on one side and motor and joint vibration is lost on opposite side producing a Brown-Sequard syndrome. An anterior spinal artery occlusion causes sudden onset of major motor loss in both limbs and loss of touch, pain, temperature bilaterally but spares the posterior column as the anterior spinal artery does not supply that part of the cord. Other diseases affect the posterior column predominantly, e.g. subacute combined degeneration and may give rise additionally to a positive sign Lhermitte's sign when flexion of the neck causes a shooting pain going down the back and may be into the legs. Lhermitte's sign may be seen also in multiple sclerosis (plaque in posterior column) or radiation myelopathy or atlantoaxial dislocation.

(e) The brainstem sensory loss classically affects face on one side and spinothalamic sensory loss on the opposite side of body. This may be seen in a lesion from pons to medulla as the long sensory nucleus of the trigeminal extends from pons down to the medulla.

(f) Thalamic sensory loss is usually loss of all sensation on the opposite side of the body. This may be associated with a troublesome pain called thalamic pain on the entire

opposite body. This is central neuropathic pain and in a case of thalamic infarct may be a troublesome complaint for months or years after the infarct. Similar pain may occur with other lesions of the sensory pathways.

(g) Lastly parietal lobe lesions are characterised by mild loss of superficial sensation on the opposite side, major loss of joint sense and preservation of vibration sense. This is the only area in the body where joint sense may be lost and vibration preserved because in all other areas with deep sensation loss, e.g. peripheral neuropathy, or posterior column cord loss, or old age; vibration is lost before joint sense. Cortical sensory loss may also have astereognosis, two-point discrimination loss and may present as focal sensory epilepsy.

PERIPHERAL NEUROPATHY AND RADICULOPATHY

Peripheral nerves, i.e. the lower motor neuron extends from the anterior horn cell to the end of the nerve before the neuromuscular junction. The diagnosis of a radiculopathy is made by history of root pain and motor and sensory loss in root and not in nerve distribution (as discussed in sensory loss before). The differences between UMN and LMN lesions are given in **Table 5**.

Table 5: Comparison Between Signs of Upper Motor Neuron (UMN) and Lower Motor Neuron (LMN) Lesions

LMN	UMN
Paralysis of muscle	Paralysis of movement, especially fine movements
Weakness depending on nerve or root involved	Weakness of typical pattern in upper limb deltoid, elbow extension and, fingers. In lower limbs hip flexion, knee flexion, foot dorsiflexion
Hypotonia	Spasticity/clasp-knife rigidity
Wasting ++	Disuse atrophy at times but never severe wasting
Reflexes depressed or absent	Exaggerated reflexes ± clonus
Plantars flexors	Extensor plantar, absent abdominal reflexes

A peripheral neuropathy may be primarily due to axonal fibre degeneration or due to involvement of the nerve myelin. This is called segmental demyelination. **Table 6** shows the clinical differences in the two.

Table 6: Neuropathies—Axonal versus Demyelination

	Axonal Degeneration	Segmental Demyelination
Wasting	++	Often absent
Fasciculations	++	Nil
Site of affection	Predominant distal	Proximal and distal
Reflexes	Absent in severely affected muscles	Lost all over even in muscles not weak
Recovery	Slow, only after regeneration	Can be faster
Nerve conduction	Muscle action potential small Velocities remain near normal	Nerve conduction velocities and distal latencies slow >20% reduction

NEUROMUSCULAR JUNCTION

The clinical features to some extent depend on whether the lesion is post-synaptic, e.g. myasthenia, organophosphate poisoning, cobra bite; or pre-synaptic, e.g. Eaton-Lambert syndrome, botulism; or mixed, e.g. krait bite, antibiotic-induced myasthenia.

The common form as seen in myasthenia gravis is post-synaptic and classically causes weakness of ocular muscles (with sparing of pupils), bulbar muscles and proximal muscles of limb. The diagnosis is made partly by the distribution but mostly by the history of fatiguability, i.e. muscles get weaker with effort. Another feature is the variability of weakness from morning to evening. Classic pre-synaptic disease is often different (**Table 7**).

Table 7: Neuromuscular Junction Disease Localisation

	Post-synaptic	Pre-synaptic
Classic disorder	Myasthenia	Eaton-Lambert syndrome
Muscles affected	Ocular, bulbar and proximal limb	Limb muscles chiefly; eye, bulb spared
Reflexes	Good	Poor
Repeating reflex after exercise	Reflex reduced amplitude	Increased amplitude
Decrement test (nerve conduction)		
Slow rates (3 cps)	Decrement +	Decrement +
Fast rates (30 cps)	Decrement mild	Significant increment

Decrement implies that the amplitude of response reduces with repeated stimulation (usually only up to 4 to 5 stimuli). In increment, the response increases (and continues to increase up to 30 or more stimuli). **Figure 2** shows decrement in a case of myasthenia gravis.

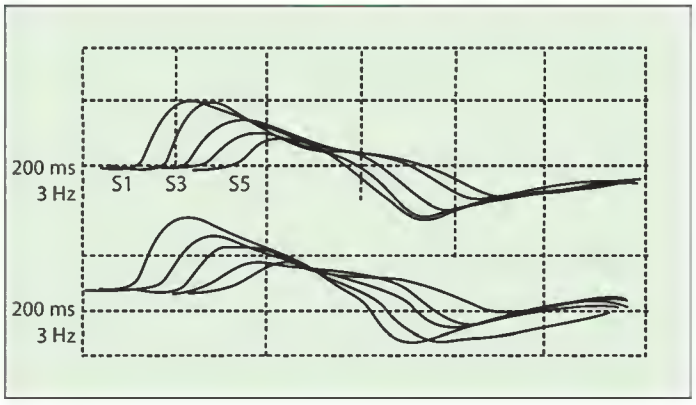


Figure 2: Decrement-reduced size of response with recurrent stimuli.

In testing decrement the ratio of response of S1 to S4 is usually calculated. A fall of 20% in S4 amplitude is considered significant for myoneural junction disease (10% for smaller muscles, e.g. face, orbicularis oculi).

MUSCLE DISEASE

Primary muscle diseases are characterised by weakness, hypotonia, preserved reflexes and normal sensations; wasting is a feature of muscle dystrophy. The weakness is usually symmetric and proximal in most cases, though hereditary distal myopathies are described, e.g. myotonic dystrophy. The acquired myopathies are all proximal.

Table 8 differentiation of causes of gradual-onset hypotonic weakness differentiates diseases of the three commonest sites of LMN-type lesion.

Table 8: Differentiation of Causes of Gradual-Onset Hypotonic Weakness

	Anterior Horn Cell Disease	Peripheral Nerves	Muscle Disease
Distribution	Proximal and distal	Distal	Proximal
Symmetry	May be absent	+ve	+ve
Fasciculation	Yes	Nil	Nil
Reflexes	Depressed equal to degree of Power loss	Depressed even with fair power	Depressed equal to degree of Power loss
Muscle percussion	+ve	+ve	Absent
Early contracture	Nil	Nil	Present
CPK and other muscle enzymes	Normal or may be elevated	Normal	Usually elevated
EMG	Neurogenic	Neurogenic	Myopathic
Nerve conduction studies	Small muscle action potential	Abnormal nerve conduction	Normal

Muscle percussion is performed by tapping a muscle directly when the deep tendon reflex is lost. Then if nerve or anterior horn cell is the cause of absent reflex the muscle contracts vigorously as reflex is lost due to nerve affection. When muscle disease is the cause, muscle percussion-induced contraction is also lost.

Weakness due to disease of muscle may be due to muscle degeneration or metabolic or inflammatory disease of muscle. **Table 9** gives features to differentiate inflammatory muscle disease from muscular dystrophy and metabolic myopathy.

Table 9: Differentiation of Inflammatory Muscle Disease from Mascular Dystrophy and Metabolic Myopathy

	Muscular Dystrophy	Inflammatory Muscle Disease	Metabolic Myopathy
Family H/o	+ve	–ve	–ve usually
Progress	Slow	Rapid	Rapid
Weakness/ wasting	Wasting more marked	Weakness > wasting	Weakness > wasting
Muscle tenderness	Absent	++	Nil
Fever, joint pain, rash	–ve	++	Nil
Reflexes	Depressed	May be increased	Depressed
Neck weakness	Rare (except myotonic dystrophy)	++	Rare
Swallowing defect	Rare	Common	Rare

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20.2 Neurological Disorders—A Clinical Approach

MV Padma Srivastava

A thorough neurological evaluation is of paramount importance and is integral for correct diagnosis virtually in every clinical encounter. Relevant history and focused clinical examination are the keys to achieve the correct diagnosis. The standard practice is to record the patient's chief complaints, and take a history of the development of the symptoms, followed by the history of illnesses and surgeries, the family history, the personal and social history, and a review of any symptoms involving the main systems. A thorough neurological examination then follows and a differential diagnosis is constructed. What is unique to neurological examination is the extreme attention to 'localisation'. In general, the history provides the best clues for aetiology and the examination for localisation.

HISTORY

The chief complaint (or the several main complaints) is the usual starting point of the diagnostic process. An example might be, a patient presenting with the triad of complaints of headache, clumsiness and double vision. The complaints serve to focus attention on the questions to be addressed while taking the history and provide the first clue to the anatomy and aetiology of the disease underlying the complaints. In this case, it may suggest the presence of posterior fossa tumour affecting the cerebellum and the brainstem. The mode of onset is critically important in determining the aetiology. For example, a sudden onset usually indicates a vascular aetiology such as stroke. A course characterised by exacerbations and remissions may suggest multiple sclerosis, whereas a slowly progressive course may indicate a neoplasm or degenerative disorder. Paroxysmal episodes may suggest the possibility of seizures, migraines, periodic paralyses, etc.

Patient may provide a clear history or at times (especially in the elderly) may give tangential information not really required. Direct questioning is often required to keep the patient or health provider focused and also to clarify the symptoms. However, it is important not to lead the patient. Patients sometimes agree with everything that the physician may suggest even if it is incorrect. Reliability of patient's history is of paramount importance. Reliability depends on the patient's intelligence, memory, language function, educational and social status. Getting information from an observer other than the patient is important for diagnosing and characterising common neurological conditions such as epilepsy or dementia. In children, the history is always the composite perceptions of the child and the parent. Patients and physicians may use the same word to mean very different things. The word 'chakkar' may not really mean 'vertigo' but may mean, seizure, syncope, dizziness, fatigue, etc. Patients may describe a limb being 'numb' when what they actually mean 'paralysis'. 'Blurred' vision may mean decreased in vision or 'diplopia' which many a time is not 'complained' as double vision. The neurologist must understand the nature, onset, duration, and progression of each symptom and the temporal relationship of one symptom to another. One must ascertain if the symptoms are getting better, are constant or getting worse? What are the aggravating and relieving factors, if any. In infant and young children, the timing of developmental milestones will be of great relevance in many neurological illnesses.

In summary, the history of the presenting illness or chief complaint should include the following information:

1. Symptom onset (acute, subacute, chronic, or relapsing).
2. Duration.
3. Course of the condition (static, progressive, relapsing and remitting).
4. Associated symptoms such as pain, headache, vomiting, weakness and seizures).

Both the absence of expected features and the presence of unexpected features may assist in the diagnosis. A patient with numbness of the feet might have a peripheral neuropathy, but the presence of the backache and loss of sphincter control suggests that a spinal cord or cauda equina lesion is more likely.

The review of history should include the elements of nervous system function that did not surface in taking the primary complaints. The history should cover following fields of cognition, personality and mood change; hallucinations; seizures and other impairments of consciousness; orthostatic faintness; headaches, special senses, speech and language function, swallowing, limb movements, strength and sensation, pain, gait and balance and sphincter, bowel and sexual functions. A positive response may help clarify a diagnosis. For example, if a patient complaining of ataxia and hemiparesis admits to unilateral deafness, this may suggest a acoustic neuroma. Headaches in a patient with paraparesis suggest a parasagittal meningioma rather than a spinal cord lesion.

Personal History

The personal history in terms of occupation, marital status, and alcohol, tobacco and illicit drug use and the medical history of the parents, siblings and children looking for evidence of familial disease is essential. Many neurological disorders are hereditary. Hence a history of similar diseases in the family members or of consanguinity may be of diagnostic importance. However, an expression of a gene mutation may be quite different from one family member to another with respect not only to the severity of the neurological dysfunction but also to the organ systems involved. For instance, the mutations of the gene for Machado-Joseph disease (SCA-3) can cause several phenotypes. A patient with Charcot-Marie-Tooth disease (hereditary motor-sensory neuropathy) may have a severe peripheral neuropathy, whereas relatives may have only *pes cavus*.

Reported diagnoses may be inaccurate. Some clinical situations such as epilepsy and other neurological conditions presumed

to have a social 'stigma' may be kept secretive and patients may show great reluctance to divulge the correct information. The history of 'seizures' in the family members will invariably be 'negative' unless relentlessly and laboriously pursued. If there is a possibility that the disease is inherited, it is helpful to obtain information from parents and grandparents and to examine the relatives at risk. Minimum data for all first and second-degree relatives should include, age, cause of death and any significant neurological or systemic diseases.

History of Previous Illnesses

The record of history should include dates and details of all surgical procedures, significant injuries including head trauma and fractures, hospitalisations, and conditions requiring medical consultation and medications. For paediatric patients, information on the pregnancy and state of infant at birth should be recorded. Seizure and worsening headaches in a patient who previously had surgery for lung cancer suggests a brain metastasis. Chronic low-back pain in a patient complaining of numbness and weakness in the legs on walking half a mile suggests neurogenic claudication from lumbar canal stenosis.

Review of Symptoms in Non-Neurological Systems

Neurological function is adversely affected by dysfunction of many systemic disorders including that of the liver, kidney, gastrointestinal tract, and blood vessels. Several neurological diseases are characterised by multi-organ involvement such as vasculitis, sarcoidosis, mitochondrial disorders and storage diseases. History of gastric surgery may lead to vitamin B12 deficiency. Sarcoidosis may cause recurrent Bell's palsy, diabetes insipidus, ophthalmoplegia and peripheral neuropathy. Disorders of the liver, kidney and small bowel can be associated with a wide variety of neurological disorders. Systemic malignancy can cause direct and indirect (paraneoplastic) neurological problems. Medications are also often the cause of neurological disturbances, particularly, anti-epileptic agents, chemotherapeutic agents, etc. Isoniazid may cause a peripheral neuropathy. Lithium carbonate may produce tremor and ataxia. Neuroleptic agents can produce a parkinsonian syndrome or dyskinesias. Special emphasis needs to be given to intake of ayurvedic medications especially those that contain heavy metals and other over the counter drugs.

NEUROLOGIC EXAMINATION

The neurological examination is one of the most unique in all of clinical medicine. Unlike many other fields of medicine in which diseases are visible, or palpable, neurology is characterised by conditions that may be detected only be applying specific examination techniques and logical deduction, except when certain cutaneous markers or other stigmata suggest the diagnosis.

Steps in the Neurologic Examination

For the purpose of simplicity, the neurological examination is divided into several steps. When mastered these steps become second nature to the examiner. These steps include the following:

- Higher mental functions
- Speech and Language
- Cranial Nerves
- Motor System
- Sensory System
- Reflexes
- Cerebellum
- Meninges
- Spine
- Gait
- Systemic examination

Tools required will include an ophthalmoscope, a reflex hammer, and a tuning fork as minimum essentials for performing the examination.

Examination of the Higher Mental Functions

This includes testing of memory, orientation and intelligence besides other aspects of patients' psychic state. Any suspicion of disorder in higher mental functions will require a very detailed assessment including detailed lobe function tests which will be out of purview of this chapter.

Memory

It is the ability to register and recall prior sensory input. Recent and remote memory functions are differently affected depending on the disease process. Past memory is relatively preserved in chronic dementing processes, with major disturbances in the attention span and recent memory. On the contrary, all aspects of memory are impaired in acute encephalopathies.

Orientation

It is an individual's cognitive sense of his status in time, place and person. These functions are affected in the same order as they are in organic disease. In other words, the sense of time is first to be impaired in organic dysfunction and the sense of person is the last to be lost. However, the order may be disturbed in psychological dysfunction.

Intelligence

It is the ability to quickly and successfully apply previous knowledge to a new situation and to use reason in solving problems. Vocabulary, fund of knowledge, calculations, abstraction and judgment are good indicators of intelligence. Due regard and allowance is given to literacy state of the individual. A mini-mental state examination is given in annexure/echapter as examination of neurological disorder.

Mini-mental state examination (MMSE)

See previous chapter on Basic Considerations in Neurology

Speech and Language

Abnormalities include aphasia, or acquired language dysfunction; dysarthria or acquired dysfunction in articulation and dysphonia or acquired dysfunction in phonation.

Dysphasia or aphasia

In dysphasia the ability to process language is impaired, resulting in an inability to understand (i.e. receptive or sensory or Wernicke's aphasia), transfer signals from the Wernicke's are to the Broca's area (i.e. conduction aphasia), or properly execute speech (i.e. expressive, motor or Broca's aphasia). The combination of Broca's aphasia and Wernicke's aphasias is referred to as mixed aphasia.

Essential Elements of Common Aphasia

Type of aphasia	Fluency	Comprehension	Naming	Localisation
Broca's	Non-fluent	Intact	Impaired	Broca's area
Wernicke's	Fluent	Impaired	Impaired	Wernicke's area
Conduction	Fluent	Intact	Impaired	Fasciculus arcuate
Global	Non-fluent	Impaired	Impaired	Non localising

Transcortical aphasia

These are caused due to the involvement of the association cortices sparing the primary language areas. They are distinguished from primary aphasia by the preservation of repetition.

Dysarthria

It is the inability to articulate spoken words. The quality of the oration in impaired but the content remains intact (e.g. slurred speech). The patient's ability to understand and synthesise speech remains intact. It results from paralysis of pharyngeal, palatal, lingual or facial musculature. It is also observed with cerebellar lesions (staccato/scanning/explosive speech) or extrapyramidal disorders (monotonous and hypo-phonic as in Parkinson's disease) etc.

Dysphonia

Dysphonia is the impairment or inability to phonate. Neurologic causes include unilateral recurrent laryngeal nerve paralysis and lesions of the vagus nerve.

Examination of the Cranial Nerves

There are 12 cranial nerves; their anatomy and examination are given in chapter 7 section 20.

Examination of the Motor System

Trophic state

Assess the size, shape and symmetry of a muscle. Atrophy, hypertrophy or abnormal bulge or depression will be important diagnostic findings. Hypertrophy with weakness is seen commonly with Duchenne muscular dystrophy.

Tone

Muscle tone is the permanent state of partial contraction of a muscle and is assessed by passive movement. The muscle may be hypertonic and hypotonic. Hypotonia is defined as decreased tone and may be seen in lower motor neuron lesions, spinal shock and some cerebellar lesions. Hypertonia may manifest as spasticity or rigidity. Pyramidal lesions result in spasticity that may manifest as a clasp-knife phenomenon. Rigidity refers to increased tone associated with extrapyramidal lesions; it may result in a cogwheel (stepwise) or lead-pipe (uniform) resistance to passive movement.

An increase in tone is noted when there is an increase in the resistance to passive movements of the limbs. The movements are either flexing or extending the limbs, rotating the limbs or shaking the hands at the level of wrists. The increase in tone is classified as follows (Ashworth Scale):

0 – Normal to decrease (flaccidity)
1 – Normal
2 – Mild increase
3 – Moderate increase
4 – Severe increase
5 – Associated with spasms

Muscle strength

The MRC grading of muscle power is the standard method of testing for muscle power.

Score	Description
0	Absent voluntary contraction
1	Feeble contractions that are unable to move a joint
2	Movement with gravity eliminated
3	Movement against gravity
4	Movement against partial resistance
5	Movement against full resistance or normal power

A central lesion usually produces greater weakness in the extensors than in the flexors of the upper extremities and the reverse in the lower extremities.

Upper motor lesions are associated with weakness, spasticity (increased tone), hyperreflexia, primitive reflexes, and the Babinski sign. Primitive reflexes include the grasp, suck and snout reflexes. Lower motor neuron lesions are characterised by weakness, hypotonia (flaccidity), hyporeflexia, atrophy and fasciculations.

Fasciculations are involuntary movements which occur as fine rippling movements under the skin, at random intervals and distribution. They are indicative of a lower motor neuron disease. They are due to denervation of whole motor units. Atrophy of the muscle groups are usually associated with fasciculations as typically seen in motor neuron disease (MND). Fibrillations are spontaneous contractions of the individual muscle fibres and are therefore not visible to the naked eye.

Examination of individual muscled groups

- The deltoid muscle is innervated by the C5 nerve root via the axillary nerve.
- Ask the patient to abduct both the arms or each arm separately to 90° and raise them above against resistance. Compare the strength of each arm. Alternately, ask the patient to raise both their arms in front of them simultaneously as strongly as they can.
- Ask the patient to extend and raise both arms in front of them. Ask the patient to keep their arms in place while they close their eyes. If there is an upper motor weakness, there will be a positive pronator drift, in which the affected arm will pronate and fall. In upper motor neuron weakness, supination is weaker than pronation in the upper extremity, leading to a pronation of the affected arm.
- The biceps muscle is innervated by the C5 and C6 nerve roots via the musculocutaneous nerve.
- Test the strength of lower arm flexion by holding the patient's wrist from above and instructing them to 'flex their hand up to their shoulder'. Provide resistance at the wrist. Repeat and compare to the opposite arm.

- The triceps muscle is innervated by the C6 and C7 nerve roots via the radial nerve.
- Have the patient extend their forearm against the examiner's resistance. Make certain that the patient begins their extension form a fully flexed position because this part of the movement is most sensitive to a loss in strength. Note any asymmetry in the other arm.
- The wrist extensors are innervated by C6 and C7 nerve roots via the radial nerve. The radial nerve is responsible for all the extensor muscles in the upper and lower arm.
- Test the strength of wrist extension by asking the patient to extend their wrist while the examiner resists the movement. This tests the forearm extensors. Repeat with the other arm.
- Finger flexion is innervated by the C8 nerve root via the median nerve. Observe for intrinsic hand, thenar and hypothenar muscle wasting. Test the patient's grip by having the patient hold the examiner's fingers tightly and instructing them not to let go while the examiner attempts to remove them. Normally, the examiner cannot remove their fingers. Note for any asymmetry in both the hands.
- Finger abduction is innervated by the T1 nerve root via the ulnar nerve.
- Test the intrinsic hand muscles by having the patient abduct and 'fan out' all of their fingers. Instruct the patient to not to allow the examiner to compress them back in. Normally, one can resist the examiner from replacing the fingers.
- Thumb opposition in innervated by the C8 and T1 nerve roots via the median nerve.
- Test the strength of the thumb opposition by asking the patient to touch the tip of their thumb with their little finger. Apply resistance to the thumb with the examiner's index finger. Repeat with the other thumb and compare.
- The hamstrings are innervated by the L5 and S1 nerve roots via the sciatic nerve.
- Test the flexion of the hip by asking the patient to lie down and raise each leg separately while the examiner resists. Repeat and compare the test flexion at the knee by holding the knee from the side and applying resistance under the ankle and instructing the patient to pull the lower leg towards their buttock as hard as possible. Repeat with the other leg.
- Ankle dorsiflexion is innervated by the L4 and L5 nerve roots via the peroneal nerve. Test dorsiflexion of the ankle by holding the top of the ankle and have the patient pull their foot towards the body as strongly as possible. Repeat with the other foot. This tests the muscles in the anterior compartment of the lower leg.
- Ankle plantar flexion is innervated by the S1 and S2 nerve roots via the tibial nerve.
- Ask the patient to 'press down' as hard as possible. Repeat with the other foot and compare. This tests the gastrocnemius and soleus muscles in the posterior compartment of the lower leg.
- The extensor hallucis longus muscle is almost completely innervated by the L5 nerve root. Ask the patient to move the large toe against the examiner's resistance towards the body. This test the extensor hallucis longus.

Involuntary movements

Involuntary movements include fibrillations, fasciculations, asterixis, tics, myoclonus, chorea, dystonia, athetosis, hemiballismus, seizures, etc. and will be described in detail in respective chapters.

Sensory System

Non-cortical sensory system

Light touch, pain, heat, cold and vibration sensations can be included in this group. Light touch is tested by touching the skin with a wisp of cotton or tissue. Pain is tested by using a sharp object such as an open safety pin. Temperature can be tested by touching the patient's skin with two test tubes, one with warm water and the other with cold water. Vibration is tested with a 128 Hz or 256 Hz tuning fork. Compare findings on the two sides, and also with corresponding areas on the examiner.

Pain and light touch sensation

The corresponding nerve root for each area tested is indicated in parenthesis:

1. Posterior aspect of the shoulders (C4)
2. Lateral aspect of the upper arms (C5)
3. Medial aspect of the lower arms (T1)
4. Tip of the thumb (C6)
5. Tip of the middle finger (C7)
6. Tip of the little finger (C8)
7. Thorax, nipple level (T5)
8. Thorax, umbilical level (T10)
9. Upper part of the upper leg (L2)
10. Lower-part of the upper leg (L3)
11. Medial lower leg (L4)
12. Lateral lower leg (L5)
13. Sole of foot (S1)
14. Peri-anal area (saddle area) (S2, S3, S4)

Alternating between pinprick and light touch, touch the patient in the above 14 areas. Touch one body part followed by the corresponding body part on the other side with the same instrument. This allows the patient to compare the sensations and note asymmetry.

Position sense is tested by asking the patient with eyes closed to report if his/her large tow is 'up' or 'down' when the examiner manually moves the patient's toe in the respective direction. Repeat on the opposite foot and compare.

Fine touch, position sense (proprioception) and vibration sense are conducted together in the dorsal column system. Rough touch, temperature and pain sensation are conducted via the spinothalamic tract.

Cortical sensory system

The cortical sensory system includes the somatosensory cortex and its central connections. This system enables the detection of the position and movement of the extremities in space (kinaesthetic sensation), size and shape of objects

(stereognosis), tactile sensations of written patterns on the skin (graphaesthesia) and tactile localisation and tactile discrimination on the same side or both sides of the body.

Stereognosia

Test stereognosis by asking the patient to close his/her eyes and identify the object that is placed in their hand. Place a key, or pen or coin in the hand. Repeat this test with the other hand using a different object.

Astereognosis refers to the inability to recognise objects placed in the hand with eyes closed. Without a corresponding dorsal column system lesion, these abnormalities suggest a lesion in the sensory cortex of the parietal lobe.

Graphaesthesia

Ask the patient to close his/her eyes and identify the number or letter that the examiner writes with the finger or back of the pen on his/her palm. Repeat on the other hand and compare.

Apraxias are problems with executing movements despite intact strength, coordination, position sense and comprehension. This finding is associated with cortical damage.

Extinction or simultagnosia

Patient must sit with eyes closed. Touch the patient on the trunk or legs in one place and then tell the patient to open their eyes and point to the location where they noted the sensation. Repeat the manoeuvre a second time, touching the patient in two places on opposite sides of their body simultaneously. Then ask the patient to point to where they felt sensation. Normally they should point to both areas. If not, sensory extinction is present.

Examination of Reflexes

The different reflex responses may be divided into three categories on the basis of their clinical significance.

Primitive reflexes

These include the glabellar tap, rooting, sucking, and palmomental reflexes. As a rule, these signs are generally absent in adults. When present, these signs signify diffuse cerebral damage, particularly the fontal lobes.

Superficial reflexes

These are segmental reflex responses that indicate the integrity of cutaneous innervation and the corresponding motor outflow. These include the corneal, conjunctival, abdominal, cremasteric, anal wink and the plantar (Babinski) reflexes. The corneal and conjunctival reflexes may be elicited by gently touching the appropriate structure with a sterile wisp of cotton. The normal response is bilateral winking. The abdominal reflex can be elicited by drawing a line away from the umbilicus along the diagnals of the four abdominal quadrants. A normal reflex draws the umbilicus toward the direction of the line that is drawn. The best known amongst these group of reflexes is the plantar reflex. The most commonly performed manoeuvre is stroking the lateral aspect of the sole with sharp object (but not noxious). The normal response is plantar flexion of the great toe. Dorsiflexion of great tow with and without fanning of toes describes the Babinski's response.

Deep tendon reflexes

These are mono-synaptic spinal segmental reflexes. When they are intact, integrity of the following is confirmed: cutaneous innervation, motor supply and cortical input to the corresponding spinal segment. These reflexes include the biceps, brachioradialis, triceps, patellar or knee and ankle jerks. The spinal roots that subserve these reflexes are:

Muscle	Spinal Roots
Biceps	C5, C6
Brachioradialis	C6
Triceps	C7
Knee	L2 to L4
Ankle	S1

Grading of Reflexes

Score	Reflexes
0	Absent
1	Hypoactive or present only with re-enforcement
2	Readily elicited with a normal response
3	Brisk with or without evidence of spread to neighbouring roots
4	Associated with a few beats of unsustained clonus
5	Sustained clonus

Individual reflexes

The biceps and brachioradialis reflexes are mediated by the C5 and C6 nerve roots. The biceps reflex is elicited by placing the examiner's thumb on the biceps tendon and striking the thumb with reflex hammer and observing the arm movement. Repeat and compare with the other arm. The brachioradialis reflex is observed by striking the brachioradialis tendon directly with the hammer when the patient's arm is resting. Note the reflex supination. Repeat and compare with the other arm.

The triceps reflex is mediated by the C6 and C7 nerve roots, predominantly by C7. The triceps reflex is measured by striking the triceps tendon directly with the hammer while holding the patient's arm with the other hand. Repeat and compare with the other arm.

The knee jerk is mediated by the L3 and L4 nerve roots, mainly by L4.

With the patient supine, lift the knee and stroke the quadriceps tendon directly with the reflex hammer. Or, with the lower leg hanging freely off the edge of the examination table, stroke the tendon. Repeat and compare to the other leg.

The ankle jerk is mediated by the S1 root. The ankle reflex is elicited by holding the relaxed foot with one hand and striking the Achilles tendon wit the hammer and noting plantar flexion. Compare with the other foot.

There are certain reflexes which are elicited when there is a suspicion of pyramidal involvement indicating heightened reflexes. These include:

Jaw jerk: Elicited by asking the patient to partially open his mouth, placing the thumb over the patient's chin and striking the thumb with the hammer. Closing movement of the jaw indicates lesion above the midbrain.

Finger flexion: Elicited by tapping the balls of the fingers with hammer.

Hoffman's response: This is elicited by holding the patient's middle finger between the examiner's thumb and index finger and using the thumb nail, press down on the patient's finger nail. A positive Hoffman's response is when the other fingers flex transiently after the click.

Wartenburg: Pull the flexed fingers of the patient outward with the examiner's hand. The thumb should extend outward.

The above three reflexes indicate upper motor neuron lesion affecting the upper extremity.

Cerebellar Signs

The cerebellum provides an important feedback loop for coordination of muscle activity by integrating the functions of the cortex, basal ganglia, vestibular apparatus and spinal cord. Midline cerebellar dysfunction results in ataxia of gait, difficulty in maintenance of upright posture and truncal ataxia. Acute neocerebellar hemispheric lesions result in additional signs. The following are the various cerebellar signs:

1. Ataxia, atonia
2. Intention tremor
3. Dyssynergia
4. Dysmetria
5. Dysrhythmia
6. Dysdiadochokinesia
7. Dysarthria
8. Nystagmus and various other eye signs
9. Pendular knee jerks
10. Rebound phenomenon

Meningeal Signs

Signs of meningeal irritation indicate inflammation of the dura, these signs are described below:

1. Nuchal rigidity or neck stiffness is tested by placing the examiner's hand under the patient's head and gently trying to flex the neck. Undue resistance implies diffuse irritation of the cervical nerve roots from meningeal inflammation.
2. Brudzinski's sign is flexion of both knees during the manoeuvre to test nuchal rigidity. This indicates diffuse meningeal irritation in the spinal nerve roots.
3. Kernig's sign is elicited by flexing the hip and knee on one side while the patient is supine, then extending the knee with the hip still flexed. Hamstring spasm results in the posterior thigh muscle and difficulty with knee extension. With severe meningeal inflammation, the opposite knee may flex during the test.

Gait and Spine

Neurological examination will be incomplete without watching the patient stand and walk. In certain situations, abnormality of gait will be the only sign. Different gait disorders can be the hemiparetic gait, the ataxic gait, the shuffling gait, the steppage gait, the spastic or scissor gait and antalgic gait. Spine must be checked for any abnormalities such as scoliosis, gibbus and also finally look for neurocutaneous markers including *pes cavus*.

Gait is evaluated by having the patient walk across the room under observation. Gross gait abnormalities should be noted. Ask the patient to walk heel to toe across the room, then on their toes only, and finally on their heels only. Normally, these manoeuvres are possible without too much difficulty. Also note the arm swing while walking. Any slowing or decrease in arm swing would indicate a subtle extrapyramidal involvement or mild weakness of upper motor neuron type.

Walking on heels is the most sensitive way to test for foot dorsiflexion weakness and walking on toes is the best way to test early foot plantar flexion weakness.

Abnormalities in heel to toe walking (tandem gait) may be due to weakness, incoordination, vertigo, sensory ataxia (poor position sense), and leg tremors.

Rhomberg's test

Perform the Romberg's test by having the patient stand still with their heels together. Ask the patient to remain still and close their eyes. If the patient loses their balance, the test is positive.

To achieve balance, a person requires the following inputs to the cortex.

1. Visual confirmation of position
2. Non-visual confirmation of position (including proprioceptive and vestibular input)
3. A normally functioning cerebellum.

If the patient loses their balance after standing still with eyes closed, and is able to maintain balance with their eyes open, then there is likely to be lesion in the cerebellum.

The full neurological examination is too lengthy to perform in practice. Instead, the experienced neurologist uses the focused neurological examination to examine in detail the neurological functions that are relevant to the history, and performs a screening neurological examination to check the remaining parts of the nervous system. This approach should confirm, refute or modify the initial hypotheses of disease location and causation derived from the history. The standard neurological examination is less effective when used to monitor the course of a disease or its temporal response to treatment. Special quantitative functional tests and rating scales are needed to measure change in neurological function over time.

General physical examination

The nervous system is damaged in numerous medical disease and a general examination is an integral part of the examination of patients with neurological disorders. For instance, atrial fibrillation, valvular heart disease, or an atrial septal defect may cause embolic strokes. Hypertension increases the risk of all types of stroke. Signs of malignancy raise the possibility of metastatic lesions of the nervous system or paraneoplastic syndromes. Some diseases, such as vasculitis and sarcoidosis, affect both the brain and other organs.

The skills of a neurologist are learned. Seeing many cases of disease teaches the neurologist which symptoms and signs should be present, and just as important, which should not be present. However, there is no substitute for experience and pattern recognition. The diagnosis of a neurological disease is a combination of science and experience and the management of neurological disease is an art.

20.3 Clinical Neurophysiology

J Kalita, UK Misra

Neurophysiological techniques help in understanding the functional aspect of central and peripheral nervous system. It involves the recording, display, measurement and interpretation of action potentials arising from the central nervous system (CNS) [electroencephalography (EEG) and evoked potentials], peripheral nerves (nerve conduction studies), neuromuscular junction (repetitive nerve stimulation) and muscles (electromyography). Knowledge about the generation of waveforms or potentials is essential for proper conduct and interpretation of the electrodiagnostic test.

ELECTROENCEPHALOGRAPHY

The EEG rhythms depend on the spontaneous intrinsic activity, which is modulated by the afferent inputs from thalamus and brainstem. The EEG abnormality, therefore, may occur either due to disruption of cortical network or sub-cortical inputs to cortical neurons. On scalp recorded EEG, the voltage of EEG signals are attenuated due to impedance of CSF, meninges, skull and scalp. The amplitude of the cortical EEG ranges between 500 to 1,500 μV whereas in the scalp it is 10 to 100 μV.

EEG Recording and Reporting

For routine EEG, electrodes are placed using '10-20' system of electrode placement (**Figure 1**). The recording electrodes interconnect into chains and the potential difference between pairs of electrodes is recorded. Electrode pairs are interconnected in different arrangements to comprehensively evaluate the whole brain activity which are known as montages. Routine EEG is recorded for 30 to 45 minutes including two activation procedures; hyperventilation and intermittent photic stimulation. Sometimes, EEG during sleep or in sleep deprived state is useful.

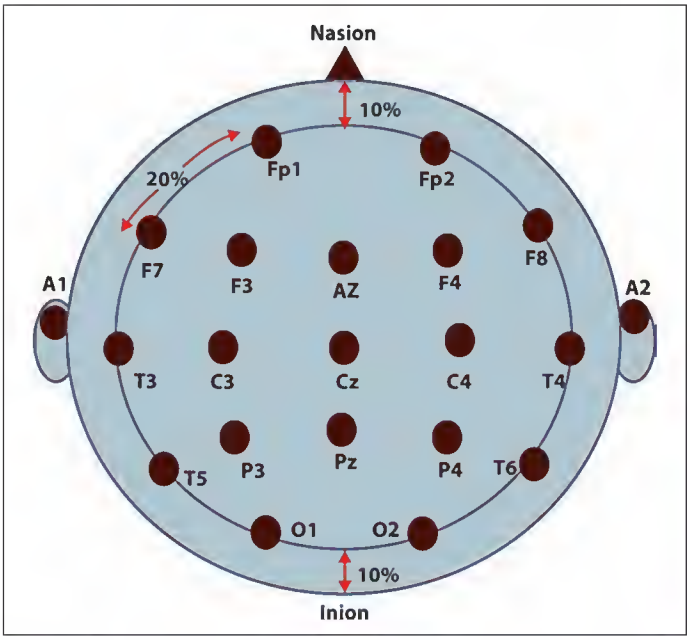


Figure 1: Schematic diagram shows '10-20' system of electrode placement for electroencephalography recording.

The EEG reporting needs knowledge of age, artifacts, sleep transient, normal variants and epileptiform and non-epileptiform abnormal discharges. The EEG report should include description of waveforms, interhemispheric coherence, reactivity and abnormal discharges (**Table 1**).

Table 1: Important Points in Electroencephalography Reporting

Waveforms: frequency, voltage, morphology, spatial distribution, modulation of frequency and voltage
Interhemispheric coherence
Symmetry: voltage and frequency
Synchrony: voltage and frequency
Reactivity: eye opening, pain, touch, sound, mental activity
Abnormal discharge: epileptiform, non-epileptiform and others

Basic EEG Rhythm

The basic EEG rhythms are named on the basis of their frequency into alpha, beta, theta and delta (**Table 2**). In normal adults, the awake pattern of EEG rhythm is of alpha range which is dominant in the occipital area. Alpha waves are sinusoidal waveform whose amplitude is reduced on eye opening (**Figure 2; Table 3**). Beta activity (10 to 20 μV) is normally present in the frontocentral area and is more marked in tense individual and those on barbiturate or diazepam.

Table 2: Electroencephalography Rhythms

Alpha: 8 Hz to 13 Hz
Beta: 14 Hz to 40 Hz
Theta: 4 Hz to 7.5 Hz
Delta: 0.1 Hz to 3.5 Hz

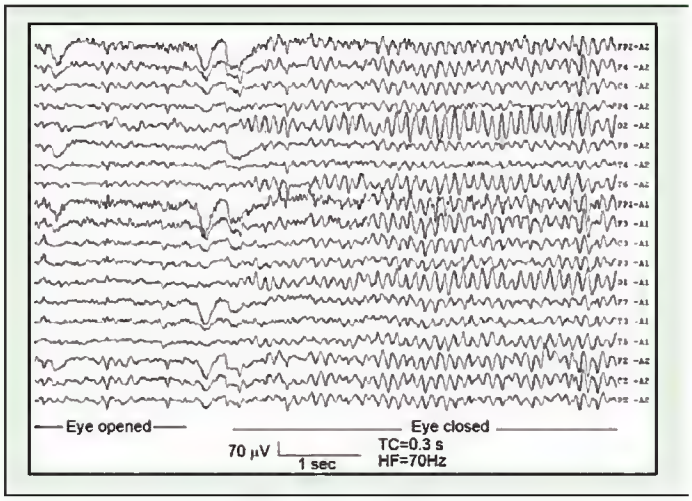


Figure 2: Electroencephalography of a normal adult individual shows posterior alpha activities. The amplitude of alpha activities is augmented when the eyes are closed.

Table 3: Characteristics of Alpha Rhythm

8 Hz to 13 Hz, 50 μV in amplitude
Maximum in posterior head region
Increased voltage in occipital, wax and wanes, varies at different time in the same individuals
Best seen in closed eyes and mentally relaxed state
Blocked by open eyes and mental effort

In normal adults, temporal theta activity may be seen. Delta activity is absent in normal adults during awake state but seen during sleep. Slow activities (delta and theta) are predominant waveforms in newborn but these are replaced by alpha and beta with the maturation of EEG; 8 Hz posterior rhythm develops by 3 years, 10 Hz by 10 years and alpha remains same till the age of 90 years.

Sleep EEG

During non-rapid eye movement (NREM) sleep, EEG tends to synchronise and during rapid eye movement (REM) sleep, it is desynchronised. The sleep spindles are 12 Hz to 14 Hz activity, which wax and wane in amplitude and are prominent in frontocentral region. It appears by 2 months of age. Vertex sharp waves are positive followed by large negative deflection of 70 ms to 200 ms duration, maximum in vertex and appear by 5 months of age. K-complexes are characterised by initial biphasic (100 ms) followed by fast activities (**Figure 3**). It appears by the age of 5 months and is prominent in frontocentral area. The EEG and clinical correlates of different stages of sleep are presented in **Table 4**.

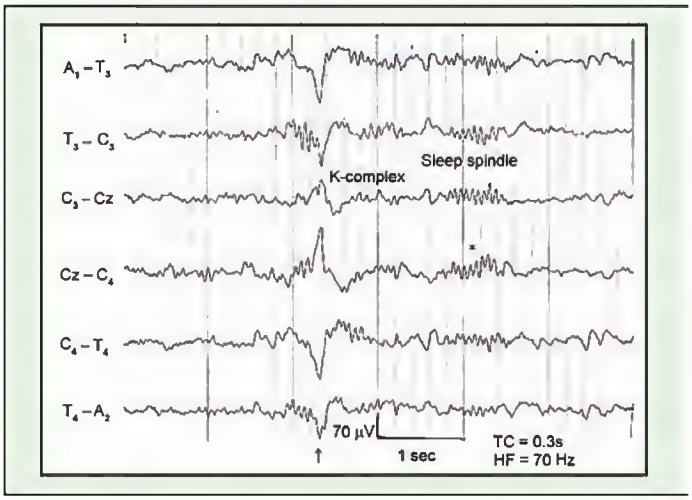


Figure 3: Electroencephalography recording during sleep shows K-complexes and sleep spindles.

Utility of EEG

EEG is crucial for the diagnosis and classification of epilepsy. Certain patterns of EEG are disease specific such as Creutzfeldt Jakob disease and subacute sclerosing panencephalitis. EEG also helps in prognostication of the patients. However, EEG is not a screening test and is not a replacement for proper history and clinical examination. While ordering EEG requisition, a precise clinical description is helpful in interpretation of the EEG.

Limitation of EEG

EEG although helps to understand the underlying brain function, but its limitations should also be appreciated which are summarised in **Table 5**.

Table 4: Clinical and Electroencephalography Correlates of Sleep

Stages of Sleep	Clinical	EEG
Non-rapid eye movement sleep		
Stage I	Drowsiness	Alpha drop out, POSTS, vertex sharp waves (VS)
Stage II	Light sleep	4 Hz, with fast waves, VS, sleep spindle, K-complex
Stage III	Deep sleep	Slowing, K-complex, some spindle and VS
Stage IV	Very deep sleep	Fast activity
Rapid eye movement sleep		Desynchronisation of EEG activity

EEG = Electroencephalography; POSTS = Posterior occipital sharp transient of sleep.

Table 5: Limitations of Electroencephalography

Surface EEG does not unambiguously determine the synaptic events contributing to EEG waveforms
EEG changes are rarely disease specific
Many focal brain dysfunctions may not be recorded by EEG, especially if deep seated or in the sulci

Abnormal EEG

The abnormal EEG may be categorised broadly into three types: (i) epileptiform discharges; (ii) periodic or quasi-periodic discharges; and (iii) non-epileptiform paroxysmal EEG abnormalities.

Epileptiform discharges

The inter-ictal epileptiform discharges are spike, sharp waves, poly or multiple spikes, runs of rapid spikes, small sharp spike and spike and slow wave complex. Ictal EEG discharges include 3 Hz spike and slow waves (absence/generalised epilepsy; **Figure 4**), generalised theta/delta (tonic seizure), periodic generalised theta or delta (myoclonic seizures), generalised electrodecremental (infantile spasm), focal periodic or dysrhythmic slow waves (*epilepsia partialis continua*), temporal, fronto-temporal or temporal low voltage wave (complex partial seizure) and localised beta (neonatal seizure).

Spike and sharp wave

Spikes are mono-, bi- or tri-phasic waveform of 20 ms to 70 ms duration whereas the duration of sharp waves is 70 ms to 200 ms.

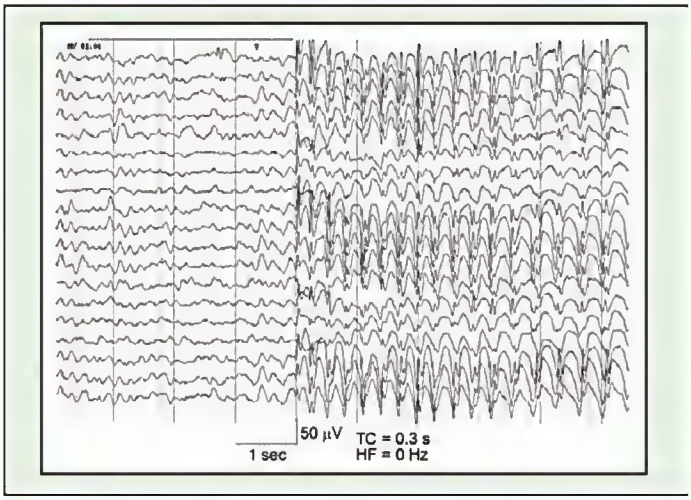


Figure 4: Electroencephalography record of a 6-year-old boy with absence seizure shows generalised 3 Hz spike and slow wave discharges during hyperventilation.

Spike and sharp waves both stand out of background. The location of spike or sharp waves suggests the possible seizure focus.

Periodic or quasiperiodic discharges

Periodic discharges are sharp or long duration (up to 150 ms), high amplitude (100 μV to 300 μV) waveforms occurring at periodic interval. These may be focal, widely scattered or generalised. Various patterns of periodic/quasiperiodic discharges are described which include: (1) burst suppression in hypoxic encephalopathy, barbiturate, nitrous oxide and cyclopropane poisoning; (2) generalised repetitive sharp transient in Creutzfeldt Jakob disease and anoxic encephalopathy; (3) periodic lateralised epileptiform discharges in herpes simplex encephalitis (**Figure 5**), temporal lobe abscess and syphilis; (4) generalised tri-phasic waves in metabolic encephalopathy; and (5) generalised periodic slow wave complexes in Lennox-Gastaut syndrome (**Figure 6**) and subacute sclerosing panencephalitis (**Figure 7**).

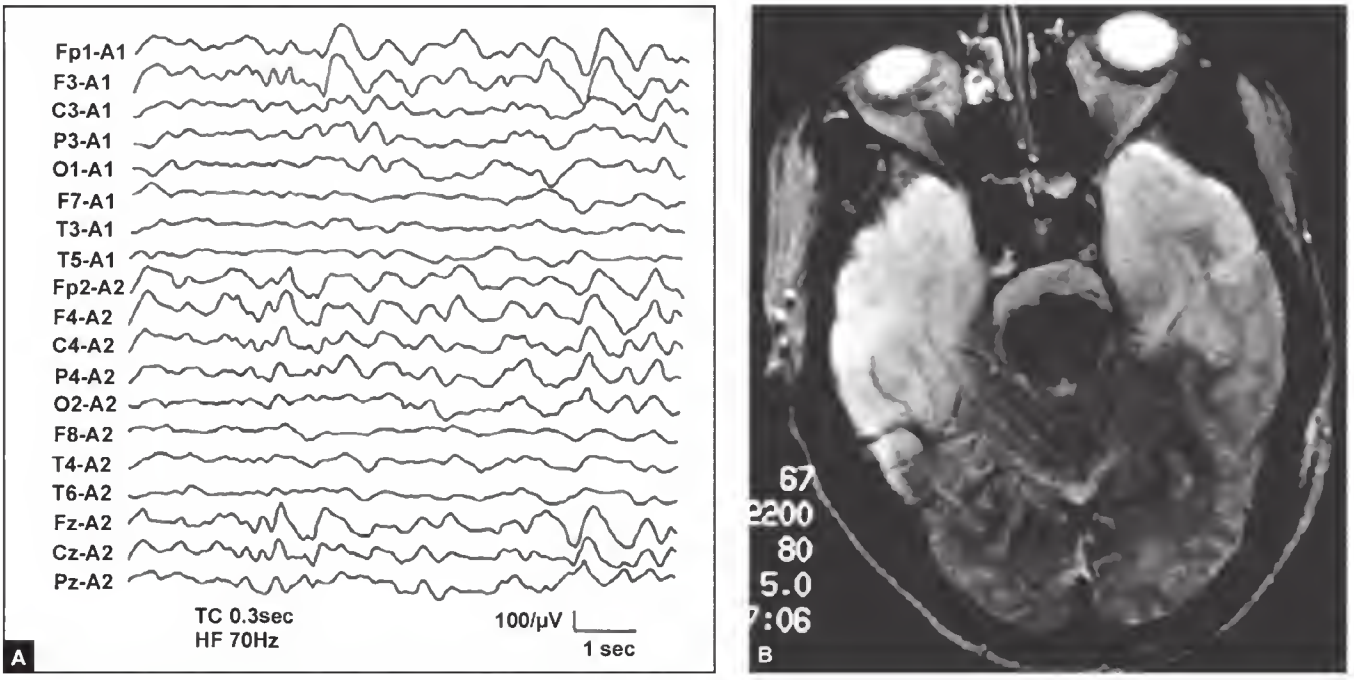
Non-epileptiform paroxysmal EEG abnormalities

Non-epileptiform paroxysmal EEG abnormalities are as follows:

1. Widespread intermittent slow activity associated with active or diffuse brain dysfunction.
2. Bilateral persistent EEG slowing associated with impaired consciousness (**Figures 8A and B**).
3. Focal persistent EEG slowing associated with focal cerebral dysfunction.

EVOKED POTENTIALS

Evoked potentials (EPs) are electrical signals generated in the nervous system in response to sensory stimuli except motor evoked potential which is recorded from the target muscle by



Figures 5A and B: (A) EEG record shows periodic lateralised epileptiform discharges (frontal predominance) with background delta slowing in a patient with febrile encephalopathy with seizure; (B) Cranial MRI of the same patient shows bilateral temporal T2 hyperintensity suggestive of herpes simplex encephalitis.

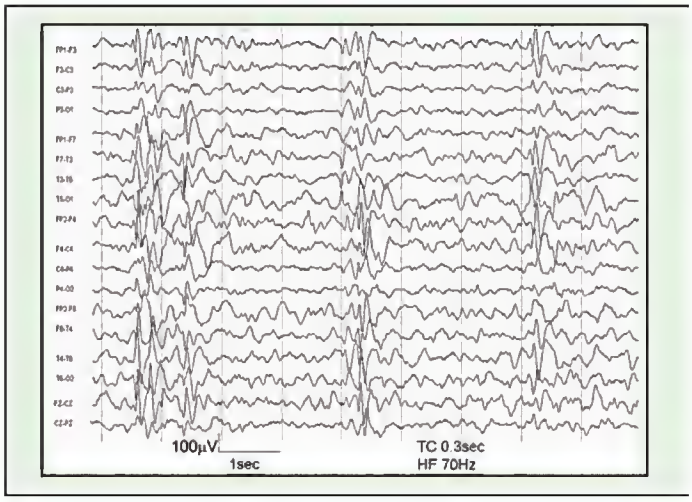


Figure 6: EEG record of a 4-year-old boy with Lennox-Gastaut syndrome shows generalised slow spike and slow wave discharges with some periodicity during sleep.

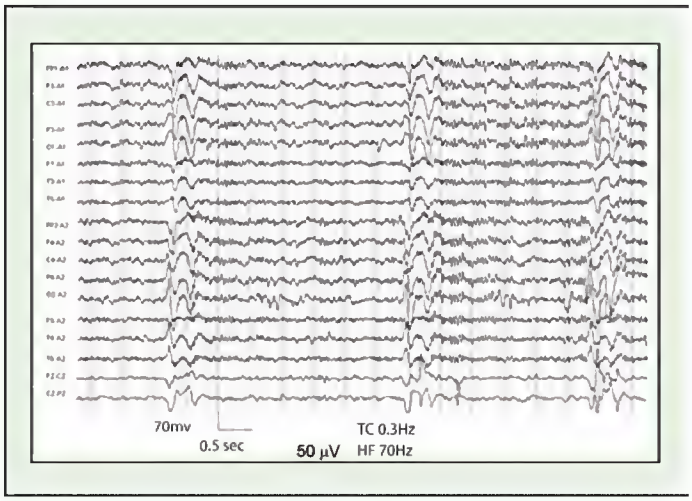
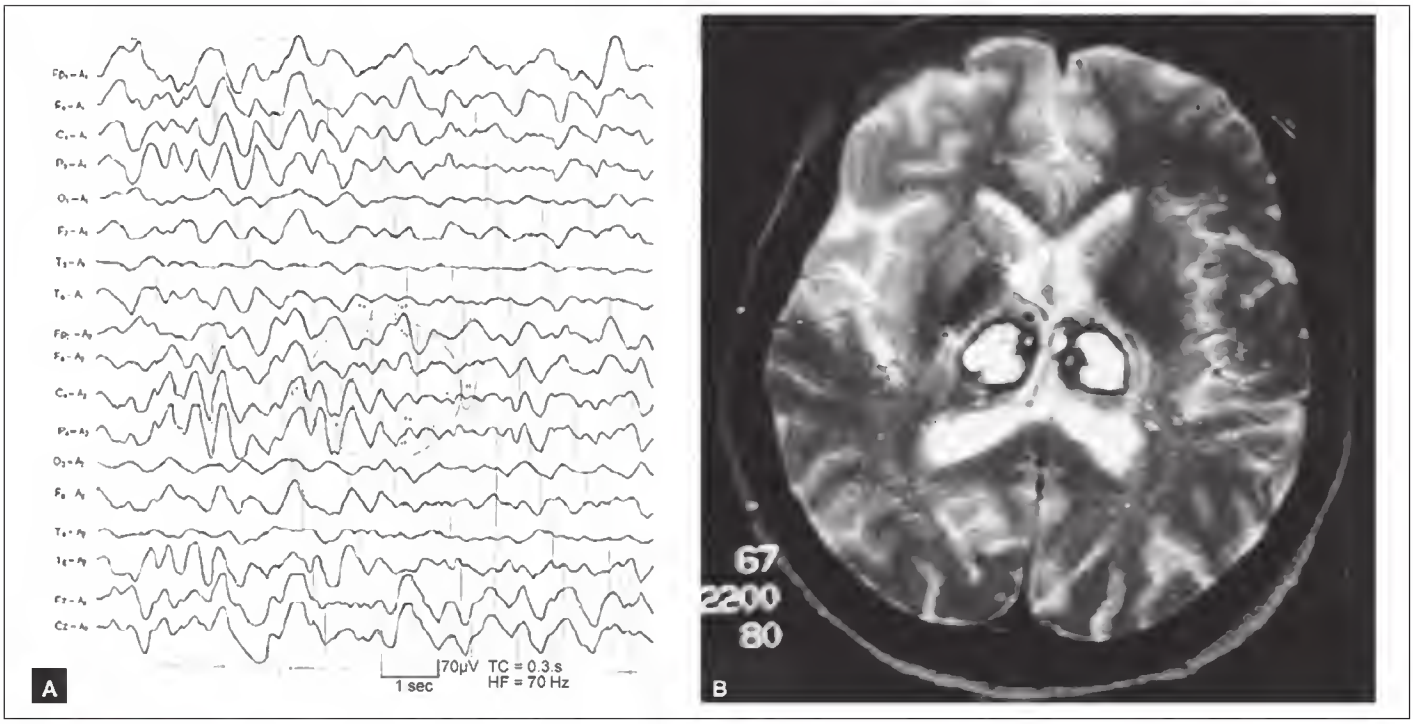


Figure 7: EEG record of an 8-year-old boy with subacute sclerosing panencephalitis shows pseudoperiodic discharges on EEG. The R complexes are coming at a rate of 2.5 to 3 interval.



Figures 8A and B: (A) EEG record of a 23-years-old lady with viral encephalitis shows delta slowing; (B) MRI of the same patient shows bilateral thalamic T2 hyperintensity with a hypointense rim suggestive of Japanese encephalitis.

applying magnetic or electrical stimuli over the motor cortex. Commonly used evoked potentials are visual evoked potential, brainstem auditory evoked potential, somatosensory evoked potential and motor evoked potentials. Cognitive and other event related potentials are yet to establish its role in the clinical practice.

Visual Evoked Potential (VEP)

VEP is obtained by averaging the responses from occipital scalp electrode in response to more than 100 sequential visual stimuli. Pattern reversal stimuli are more sensitive than flash (stroboscope) as the flash evoked VEP has great variability, insensitive to clinical lesions and provide limited information about the visual pathway. The interpretation of VEP is based on P100 latency which is an electropositive wave appearing at about 100 ms in the normal individual (**Figure 9**). Uniocular prolongation of P100 latency after full field mono-ocular stimulation suggests an abnormality anterior to the optic chiasma on that side. Bilateral P100 latency prolongation may be due to involvement of both the optic nerves, chiasma or posterior to the chiasmal lesion. Unilateral visual cortical lesion does not alter the P100 latency. VEP is abnormal in 70% to 80% patients with definite multiple sclerosis without visual symptoms (**Figures 10A and B**). VEP is abnormal in leucodystrophy, subacute combined degeneration, optic nerve tumour or tumour compressing the optic nerves and Leber's hereditary optic atrophy. VEP is normal in psychogenic blindness.

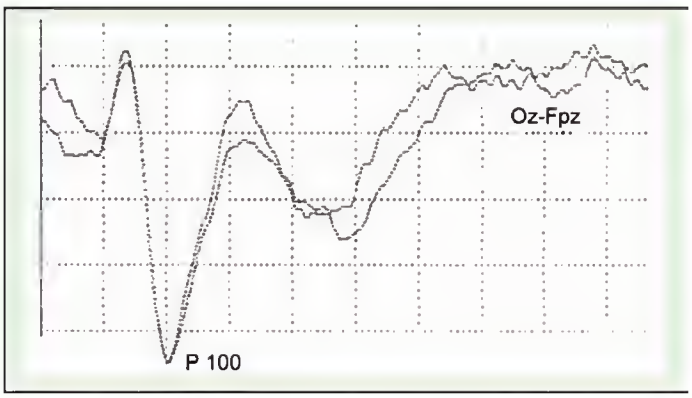


Figure 9: Pattern shift visual evoked potential in a normal individual, Sweep speed 50 ms/div, sensitivity 2μV/div.

Brainstem Auditory Evoked Potentials (BAEPs)

BAEPs refer to the series of signals generated in the auditory nerve and brainstem in response to auditory stimuli. BAEPs are recorded from the ipsilateral and contralateral mastoids or ear referred to vertex (Cz). There are 5 major waveforms (wave I, II, III, IV and V) and their absolute peak latency, peak to trough amplitudes and inter-peak latencies (IPL) of I-III, I-V and III-V are measured (**Figure 11**). BAEPs are resistant to various metabolic encephalopathies and deep anaesthesia. The generators of various waveforms of BAEPs are summarised in **Table 6**. BAEPs are abnormal in acoustic neuroma, cerebellopontine angle tumours, pontine lesion, multiple sclerosis and other demyelinating diseases.

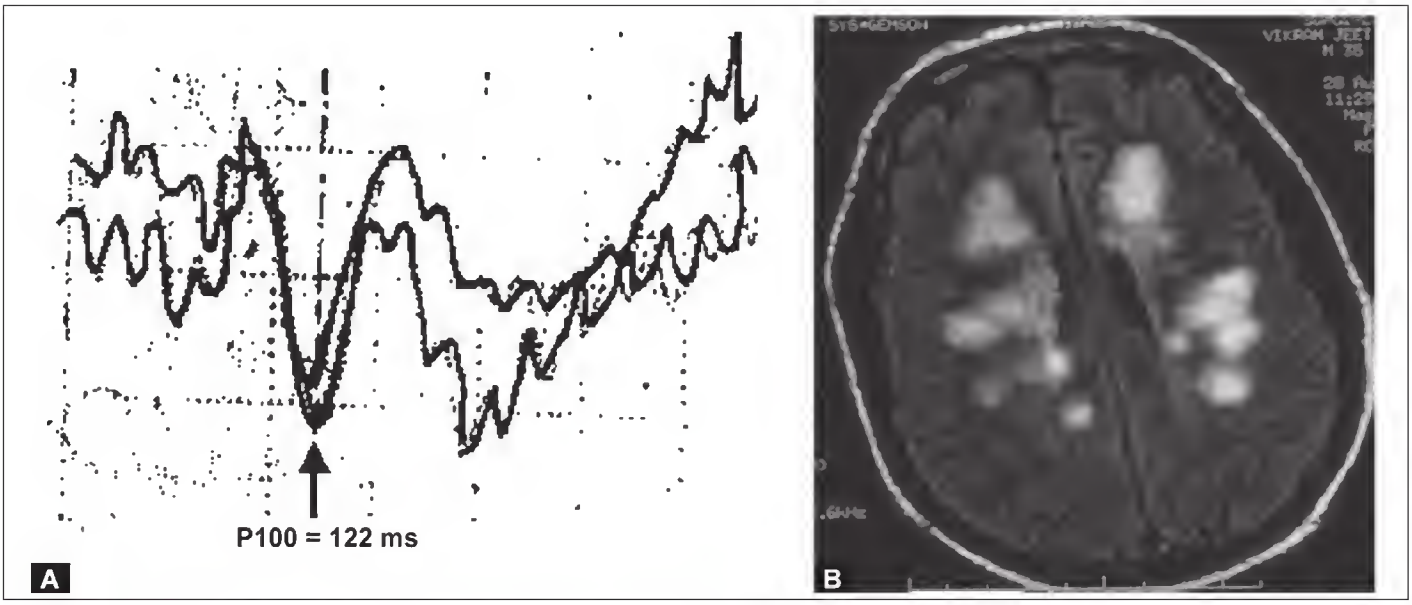
Table 6: Generators of Brainstem Evoked Potential

Waveforms	Generators
I	VIII nerve
II	Cochlear nucleus
III	Superior olivary nucleus
IV	Lateral lemniscus
V	Inferior colliculi

Somatosensory Evoked Potential (SSEP)

SSEP evaluates the integrity of sensory pathway from peripheral nerves to the cortex. Usually median, posterior tibial and or peroneal SSEPs are carried out (**Figures 12 and 13**).

Central sensory conduction time is prolonged or unrecordable in various conditions affecting the sensory pathway in the spinal cord (posterior column) and brainstem (lemniscus), thalamus



Figures 10A and B: (A) Pattern shift visual evoked potential in a 32-year-old lady with multiple sclerosis shows prolongation of P100 latency (122 ms). Sweep speed 50 ms/div, sensitivity 2μV/div; (B) Cranial MRI reveals multiple periventricular hyperintense lesions on FLAIR sequence suggestive of multiple sclerosis.

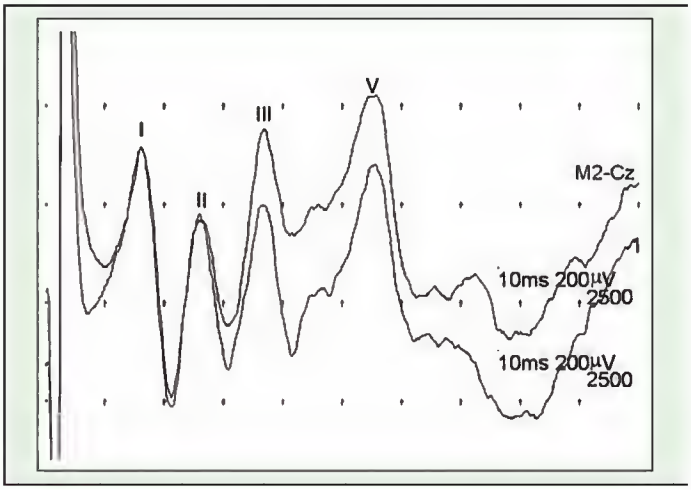


Figure 11: Normal brain auditory evoked potential.

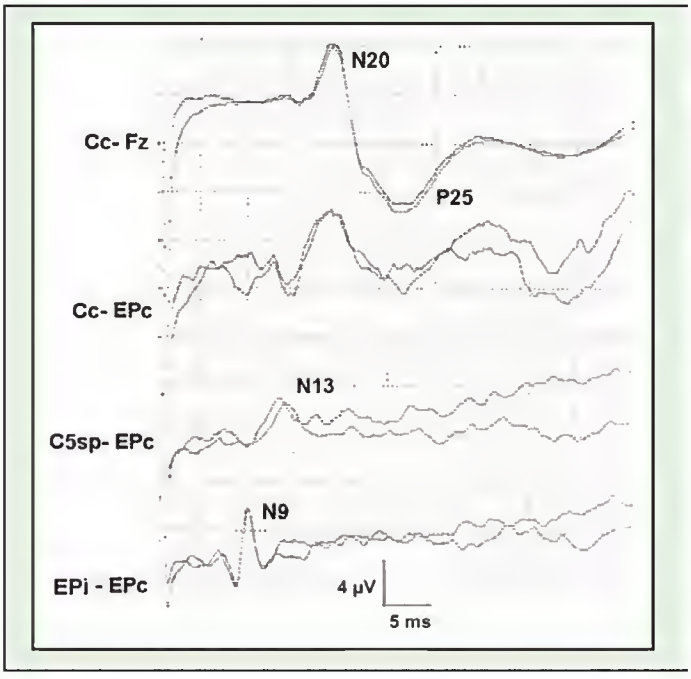


Figure 12: Normal median somatosensory evoked potential.

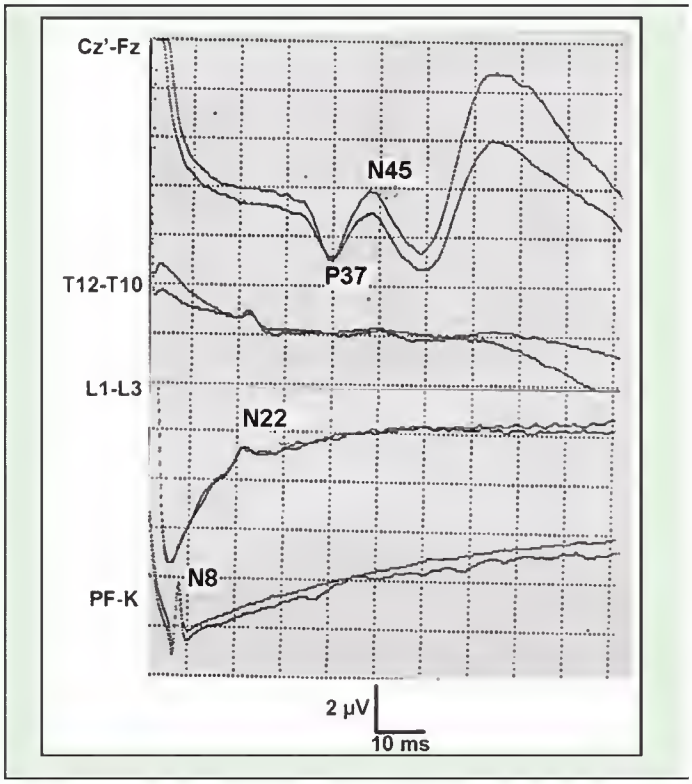


Figure 13: Normal tibial somatosensory evoked potential.

and thalamocortical pathway. 90% patients with multiple sclerosis have SSEP abnormalities. The other conditions such as hereditary ataxia, subacute combined degeneration, vitamin E deficiency, leucodystrophies, spinal sand brainstem tumours, stroke and cervical spondylosis may also result in SSEP abnormality.

Motor Evoked Potential (MEP)

MEP assesses the fast conducting motor pathways and is performed by stimulating the motor cortex using a magnetic or electrical stimulator and recorded from the target muscles (abductor digiti minimi in the upper limb and tibialis anterior in the lower limbs).

Central motor conduction time is abnormal in patients having involvement of motor pathway due to stroke, trauma, tumour, demyelinating and dysmyelinating conditions.

Repetitive transcranial magnetic stimulation has also been used for therapeutic purposes such as movement disorder and depression. Evoked potentials are also used for intra-operative monitoring and EEG for carotid endarterectomy.

NERVE CONDUCTION AND ELECTROMYOGRAPHY

Nerve conduction studies (NCS), electromyography and repetitive nerve stimulation (RNS) evaluate the functional integrity of peripheral nerves, muscles and neuromuscular junction, respectively.

Nerve Conduction Studies

Electrical stimulation of the nerve fibres results in impulses that travel along the motor, sensory or mixed nerves and produce a compound action potential. Most of the peripheral nerves can be evaluated which are accessible for stimulation.

Motor NCS

The motor NCS is done by supramaximal stimulation of the motor/mixed nerve at two points and recording from the target muscle (**Figure 14**).

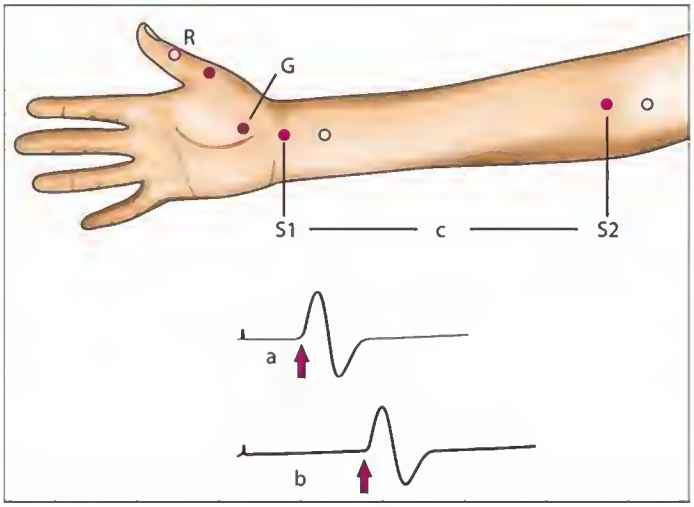


Figure 14: Schematic diagram shows method of motor nerve conduction study. The nerve conduction velocity is 'c/(b–a)' m/sec, where 'c' is the distance between proximal and distal stimulation in mm, 'a' is the distal latency in ms and 'b' is the proximal latency in ms.

R = Recording electrode; S = Stimulating electrode; G = Ground electrode.

Sensory NCS

Sensory NCS is either recorded orthodromically or antidromically. The antidromic sensory NCS is done by stimulating the sensory nerve 20% to 30% above the sensory threshold and recording from the sensory receptors, i.e. sensory innervated areas by the nerves. The reverse is done in orthodromic recording. The latency (onset/peak), amplitude (base to peak or peak to peak) and NCV are measured (**Figure 15**).

$$\text{Sensory NCV} = \frac{\text{Distance between stimulating and recording electrode in mm}}{\text{Latency in ms}} \text{ m/s}$$

The parameters of NCS should by compared with the normal laboratory values. For localising focal nerve lesion such as the carpal tunnel syndrome or other entrapment neuropathies,

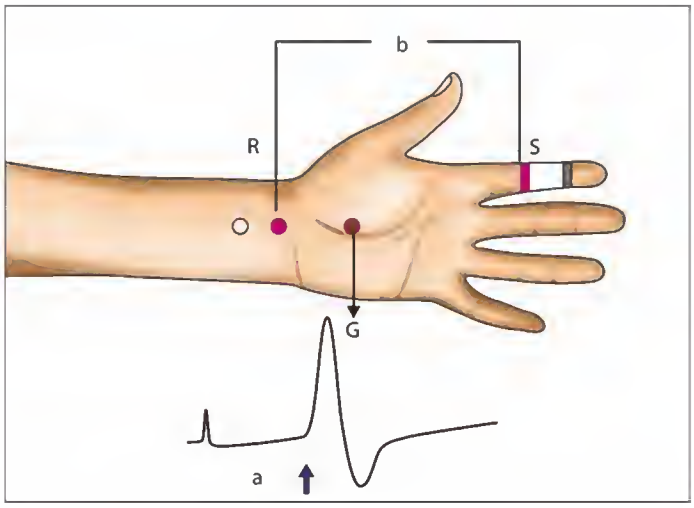


Figure 15: Schematic diagram shows method of orthodromic sensory nerve conduction. The sensory nerve conduction velocity is 'b/a' m/sec; where 'b' is the distance between the stimulating and recording electrodes in mm and 'a' is the onset latency of sensory potential.

stimulations may be applied along the nerve at a distance of 1 cm and the CMAP or SNAP is recorded (inching technique).

NCS may be affected by age, height, anomalous innervation, temperature, stimulus artefacts, electrode noise, submaximal stimulation, co-stimulation of adjacent nerves, misplacement of recording or reference electrode and error in the measurement of nerve length. In full term neonate, the NCV is half the adult value and one-third in premature baby due to incomplete myelination. NCV reaches adult value by 3 years to 5 years. Mean NCV declines by 10% by 60 years of age.

Late responses (F wave, H reflex and axon reflex)

Late responses are the potentials appearing after the motor response (M wave) following mixed nerve stimulation. There are three important late responses—H reflex, F wave and axon reflex; of these F wave is clinically more useful.

F wave: F wave is a late response resulting from the antidromic stimulation of motor neuron involving conduction to and from the spinal cord. It is elicited by supramaximal stimulation of peripheral mixed or motor nerves and recorded from the distal muscles. For clinical practice 10 to 20 F waves are adequate. The F wave parameters used in clinical practice are minimal F latency, chronodispersion, persistence, amplitude and repeated waves. Markedly prolonged F wave latency is highly suggestive of demyelinating neuropathy (**Figure 16**). It may also be prolonged in radiculopathy.

Electromyography

Electromyography (EMG) is the study of the electrical activity of resting muscle and muscle in action. Teflon coated concentric and monopolar needles are equally satisfactory. The needle is inserted slightly away from the neuromuscular junction to avoid endplate noise as well as pain. Electromyographer should know the anatomical landmark and the method of activation and relaxation of the sampled muscle. The principles used during EMG are: (a) during insertion or movement of the needle, insertional activity is produced due to injury of muscle fibres which is short lasting; (b) moving the needle for a short distance and pausing for a few seconds helps in the evaluation of spontaneous activity with the single cutaneous insertion. Relocating the needle in four quadrants of the muscle

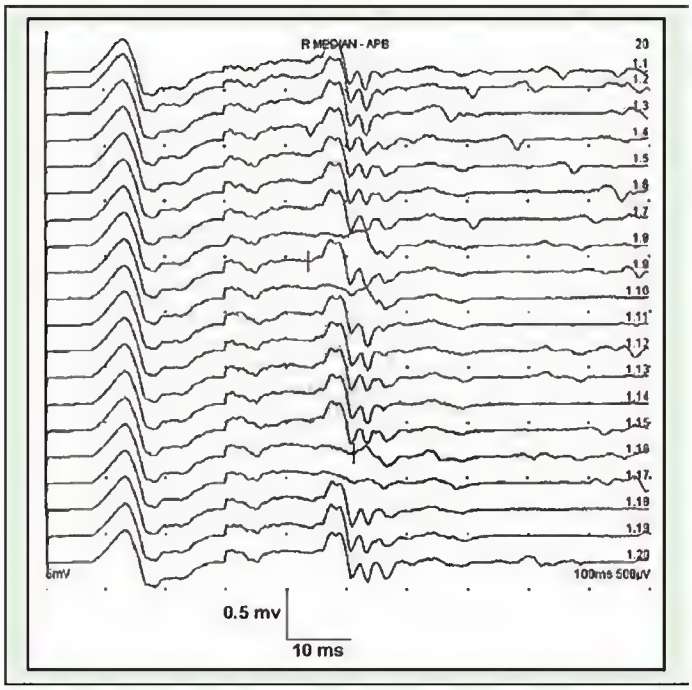


Figure 16: Median F wave study in a patient with acute inflammatory demyelinating neuropathy showing prolonged minimal latency (43.8 ms) and increased chronodispersion (8 ms).

completes the evaluation; (c) motor unit potential (MUP) is evaluated when the muscle is minimally contracted. The needle should be pushed deep or pulled out to get a sharp MUP; and (d) increasing intensity of contraction of sampled muscle shows the recruitment pattern and at the maximal contraction, interference pattern is seen.

The characteristic of insertional, various spontaneous activities and MUPs are shown in **Table 7**. The normal MUPs are usually bi- or tri-phasic and vary from 0.3 mV to 5 mV in amplitude and 3 to 13 ms in duration. The number of phases equals the number of negative and positive peaks extending to and from the baseline or the number of baseline crossings plus one. Normal MUPs have 4 or less phases and approximately 5% to 15% of MUP may have ≥5 phases which may increase to 25% in the proximal muscles. Two patterns of abnormal MUPs are found: (a) 'neurogenic—long duration, high amplitude, polyphasic with poor recruitment'; and (b) 'myopathic—short duration, low amplitude, polyphasic with early recruitment'.

Table 7: Characteristics of Spontaneous Activities on Electromyography

Potential	Morphology	Firing Rate	Firing Pattern
End plate spike	Biphasic, initial negative	5 Hz to 50 Hz	Irregular
Fibrillations	Bi/triphasic, initial positive	0.5 Hz to 10 Hz	Regular
Positive sharp waves	Biphasic, initial positive and slow negative wave	0.5 Hz to 10 Hz	Regular
Myotonia	Brief spike, positive	20 Hz to 150 Hz	Wax and waning amplitude
Complex repetitive discharges	Brief spike, positive	5 Hz to 100 Hz	Stable
Fasciculations	Like MUP	0.1 Hz to 10 Hz	Irregular
Neuromyotonia	Like MUP	150 Hz to 250 Hz	Waning

MUP = Motor unit potential.

Repetitive Nerve Stimulation

RNS helps to evaluate the diseases of neuromuscular junction (NMJ), such as myasthenia gravis, Lambert-Eaton myasthenic syndrome, botulism and congenital myasthenia. RNS is done by applying supramaximal stimulation of motor or mixed nerve and recording from the muscle supplied by that nerve. The rate of stimulation depends on the type of NMJ disorder. Low rate stimulation (2 to 3 Hz, 3 to 5 impulses) is used to evaluate the post-synaptic defect *(myasthenia gravis)* and high rate stimulation (20 to 50 Hz) for 2 to 10 seconds to evaluate the pre-synaptic defect (Lambert-Eaton myasthenic syndrome).

In low rate RNS, decrement is calculated by the baseline CMAP amplitude to that of lowest CMAP, i.e. 3rd on 4th CMAP; using the following equation:

$$\text{Decrement (\%)} = \frac{\text{Baseline CMAP amplitude} - \text{lowest CMAP amplitude}}{\text{Baseline CMAP amplitude}} \times 100$$

More than 10% decrement in any muscle is suggestive of post-synaptic NMJ disorder.

In high rate RNS, incremental response is measured as follows:

$$\text{Increment (\%)} = \frac{\text{Amplitude of highest response (last)} - \text{amplitude of 1st response}}{\text{Amplitude of 1st response}} \times 100$$

High rate RNS is painful and usually carried out in distal muscles such as abductor digiti minimi or tibialis anterior by stimulating ulnar nerve at wrist and peroneal nerve at fibular head, respectively. More than 50% incremental response in any muscle is suggestive of Lambert-Eaton myasthenic syndrome. Incremental response suggests pre-synaptic NMJ disorder. The classical findings on RNS in pre-synaptic and post-synaptic disorders are summarised in **Table 8**.

Table 8: Classical Repetitive Nerve Stimulation (RNS) Findings in Pre-synaptic and Post-synaptic Disorders

	Pre-synaptic	Post-synaptic
CMAP amplitude	Normal	Low
Low rate RNS	Decrement	Decrement
High rate RNS	Normal/decrement	Increment

CMAP = Compound muscle action potential.

Single fibre EMG may be done in patients with myasthenia gravis whose RNS test is negative.

Electrodiagnostic tests are important tools in the evaluation of neurological disorders. It is important to decide the appropriate test for appropriate clinical setting to get its highest yield.

RECOMMENDED READINGS

1. Misra UK, Kalita J. *Clinical Electroencephalography;* New Delhi: Elsevier India; 2005.
2. Misra UK, Kalita J. *Clinical Neurophysiology;* 2nd Ed. New Delhi: Elsevier India; 2006.

20.4 Neuroimaging

Rakesh K Gupta, Sunil Kumar

Neuroimaging has evolved into a super-speciality of Radiology and has found a place as a separate subject leading to degree. It is essential for the budding physicians to have at least basic knowledge of this subject. We are introducing the subject with a view to give a bird's eye view of Neuroimaging.

PLAIN RADIOGRAPHY

This is often the first imaging modality to be used for skull and spine. However, skull radiography has lost most of the indications as the changes are seen late and are indirect in nature. Computed tomography (CT) has overtaken skull radiograms in trauma, due to its superior contrast and spatial resolution. In addition, the underlying brain can also be assessed on CT. In spine, lateral and frontal radiographs of cervical, dorsal or lumbar spine are still in clinical use as it provides gross information about presence of degenerative changes, assessment of bone density and allows dynamic radiography to evaluate atlantoaxial dislocation, and spondylolisthesis. In trauma, the radiography has been superceded by CT.

MYELOGRAPHY/CT MYELOGRAPHY

Myelography, once a useful technique to evaluate intraspinal pathology, is now seldom performed, as the spinal imaging has been taken over by MRI. Myelography, if at all performed, is combined with CT to evaluate the desired region. It is helpful in patients in whom MRI is contraindicated and in some cases to demonstrate the site of a cerebrospinal fluid (CSF) leak or for diagnostic evaluation of spinal or skull base where there is poor correlation of physical findings with MRI studies. The procedure for myelography/CT myelography consists of performing a lumbar puncture and injecting water soluble, non ionic iodinated contrast medium in the strength of 180 mg I/mL for lumbar region and higher concentration up to 300 mg I/mL for cervical region if myelography is performed first. There is a waiting period of about 20 minutes to 30 minutes when a higher concentration is used.

DIAGNOSTIC ANGIOGRAPHY

Invasive diagnostic angiography has been mostly replaced by CT angiography and MR angiography for the evaluation of the blood vessels in the brain and neck. The basic reason is that it is invasive and thus associated with a small but definite incidence of complications. Special equipment, digital subtraction angiography system, is needed for these studies, which allows online visualisation of injected blood vessels. Presently, it is most often used for interventional procedures. Diagnostic angiography is reserved for cases where these studies are equivocal or where intra-cranial cross circulation is to be studied pre-operatively. It is also performed for post-operative evaluation of aneurysms, and arteriovenous malformations. In spine, it still finds a primary role in the proper evaluation of vascular malformations. The procedure is performed via transfemoral route under local anaesthesia and selective cannulation of the desired artery is done under fluoroscopic guidance. This is followed by injection of iodinated contrast medium and fast acquisition as the contrast flows through the vessel.

COMPUTED TOMOGRAPHY

The hardware of CT consists of a gantry that houses the X-ray tube and a detector assembly which typically contains 4, 16, or more rows of detectors along with a patient table which synchronises with the gantry for its movement. For usual brain studies the patient lies supine on the table that moves during scanning either incrementally or continuously while the X-rays are being emitted. The scan time is usually in seconds. The slice thickness varies from sub millimetre to 5 mm depending upon the clinical indication. The X-rays pass through the patient's head or spine and the exiting X-ray photons are detected by the detector assembly. The signals produced are processed and finally cross sectional images are reconstructed which can be viewed on a monitor. In the volume CT scanners, the data sets can be used to create three-dimensional (3D) images those can be viewed from any angle. This is very useful in analysing vascular structures such as arterial or venous systems, known as CT angiography. Different tissues in the body absorb different amount of X-rays and thus these can be differentiated, e.g. bone, brain parenchyma, CSF or water, fat and air. These have fairly constant attenuation values, called as Hounsfield units. Tissues with high Hounsfield units, such as bone, calcification, acute blood in parenchyma (haematoma), appear bright at the windows and level customised for brain parenchyma to appear greyish. At this window and level settings, fluids such as CSF, fat, and air appear dark. Hounsfield unit of water is zero. If in doubt, Hounsfield units can be quantified for tissue characterisation. Iodinated contrast media can be administered to enhance abnormal tissue with abnormal blood brain barrier. Thus a comparison with non enhanced images can help in delineating intra-cranial space occupying lesions such as tumours, granulomas, abscesses, or abnormal meninges.

Indications

Due to its high speed of scanning, wide gantry, no restrictions for the anaesthesia equipment and the monitoring systems, and its ability to show acute blood unequivocally, CT brain is most useful in patients with suspected intra-cranial bleed, and cases of trauma where a quick scan is enough to evaluate the bones, parenchyma and epidural space. Very fast contrast enhanced studies with 3D reconstruction are useful for analysing arteries or veins of the brain at a high spatial and contrast resolution obviating the need for a conventional or digital subtraction intra-cranial angiogram. This fast imaging has also been utilised to study first passage of contrast medium through the brain, i.e. perfusion imaging and analysed for parameters such as volume, regional cerebral blood flow, mean transit time and

permeability. These parameters have been found to be useful in grading of brain tumours and stroke management.

Contraindications

Patient population at risk such as pregnant women, small children, should be examined with caution. Iodinated contrast medium should also be injected with caution as it may cause renal dysfunction. Hence, it is contraindicated in patients with deranged renal function, diabetes, multiple myeloma, thyroid toxicity, dehydration, etc.

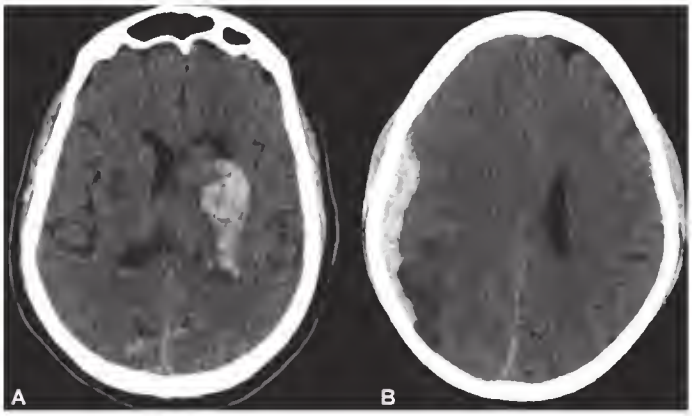
Brain

Normal appearance

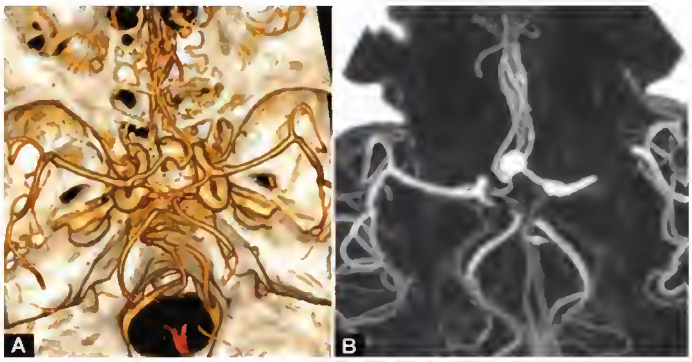
Normal brain can be easily distinguished into parenchyma, ventricular system containing the CSF, other CSF spaces such as cisterns and sulci, bony calvarium, and normally aerated paranasal sinuses. At times, certain areas of brain show physiological calcification such as pineal gland, globus pallidi, falx, etc. Grey and white matter may be distinguished on proper window settings.

Abnormal appearance

Non-enhanced CT is extremely useful in the evaluation of brain trauma, where it can show the bone injury, extradural/subdural haematoma, parenchymal haematoma (**Figures 1A and B**), and brain contusion. It can also suggest brain swelling in the form of effacement of sulci. Herniation of brain secondary to mass effect can also be detected. CT is also useful in detecting acute blood, hence it is often the first imaging modality where haematoma is to be excluded, for example, in a hypertensive patient with sudden alteration in sensorium, to confirm or exclude subarachnoid haemorrhage in a patient with sudden and severe headache, in the post-operative period after brain surgery, and similar clinical situations. CT angiography has replaced diagnostic angiography in the workup of patients with subarachnoid haemorrhage. The vascular abnormalities such as aneurysms (**Figures 2A and B**), arteriovenous malformations etc are well-delineated on CTA. Brain tumours can also be detected on CT but with inferior resolution compared to MRI especially in the posterior fossa. Presence of a mass can be inferred on a non enhanced CT by the mass effect caused by it which displaces the normal brain structures and the brain symmetry is lost. In severe cases, there is herniation of vital parts of brain through the spaces bound by rigid dural structures, which may cause irreparable damage. Non contrast studies also detect the presence of calcium in the lesion which may help in tissue characterisation. In addition, erosion or thickening of adjacent bones is also a useful indicator of the aetiology. After contrast administration, most of the tumours enhance thereby making its detection evident. The degree of enhancement may depend upon the histological grade of the tumour or its composition. The enhancement occurs due to a disruption of the blood brain barrier which allows leakage of contrast in the interstitium. Similarly, CT can detect all the non-neoplastic lesions that disrupt the blood brain barrier and enhance, thereby confirming the location and number of the lesions. Anatomical localisation is helpful as certain lesions tend to manifest in certain sites. The pattern of enhancement also helps in improved tissue characterisation as some lesions enhance homogenously, e.g. meningiomas, primary lymphomas, etc. CT is also useful in post shunt evaluation in cases of hydrocephalus. Certain congenital lesions have fatty elements which are detected easily on non-contrast study like lipomas. However, complete evaluation of a space occupying lesion is usually done with both non-enhanced and enhanced studies.



Figures 1A and B: Axial non-enhanced CT scan (A) showing a hyperdense area in left basal ganglia, suggestive of intraparenchymal haemorrhage with mass effect compressing the left lateral ventricle. Haemorrhage into subarachnoid spaces is also noted posteriorly. Axial CT scan (B) of another patient showing cresentic hyperdensity along the right fronto-parietal convexity suggesting subdural haematoma.



Figures 2A and B: Axial CT angiographic volume rendered (A) and maximum intensity projection (B) images demonstrated an anterior communicating artery aneurysm.

Spine

CT is the imaging modality of choice in spinal trauma where bony evaluation is needed for management planning. Imaging is performed in axial plane with the patient supine. As the images can be post processed for 3D models, evaluation becomes easier. Similarly CT is advocated in bony craniovertebral anomalies, in some cases of disc herniation, and in the assessment of ossified or calcified lesions. For evaluation of intradural conditions, CT myelography is performed. CT is also indicated for image-guided biopsies of the bony lesions.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is an imaging technique based on the interaction of radiofrequency induced proton shifts in a strong magnetic environment. Signal intensity is directly proportional to the field strength of the magnet used. However, in view of human safety and problems in maintaining a high degree of field homogeneity, clinical scanners currently do not exceed 3 T. Magnetic resonance (MR) scanner designed for optimal clinical study consists of a superconducting magnet of 1.5 T or 3 T (1 Tesla=10,000 Gauss) along with a moving table on which patient lies supine (although smaller strengths of 0.2 T to 0.4 T systems of permanent magnet are commercially

available, these have certain limitations). This is housed in a specially shielded room. Other cabinets and operator's console are placed separately. For imaging, radiofrequency waves are introduced after the patient lies within a coil which is matched to the region of interest to be imaged. These waves are switched on and off and the resulting signals are processed in the presence of locally varying fields which are known as gradients to form images that can be acquired in any desired plane. During the off phase, the excited protons relax and this is measured either as T2 (spin-spin or horizontal relaxation) and T1 (spin-lattice or longitudinal relaxation) relaxation. These are used to create T2 and T1 weighted images. In the normal brain, cortex, white matter, CSF, fat, air have all different appearances on T2 and T1 images. The radiofrequency waves and gradients can be combined in different ways that are known as sequences. Most commonly the sequences are used to form anatomical images but the signals can also be acquired and processed to obtain metabolite (MR spectroscopy), functional MRI (fMRI), water diffusion (diffusion weighted imaging and diffusion tensor imaging) and tissue perfusion information. Sequences can also be designed to detect the blood flow and present the information as angiograms (MR angiography). MR angiography can also be obtained after injection of a MR detectable contrast agent combined with fast imaging. These contrast agents are usually based on gadolinium compounds which shorten T1 relaxivity (enhancing lesions appear brighter). Lately, iron oxide particles based contrast agents have been introduced that work on reducing T2 relaxivity and have found uses in liver, etc. Study times typically for a MR examination vary between 15 minutes and 45 minutes depending upon the clinical protocol.

Indications

T2 and its derivatives such as fluid attenuated inversion recovery (FLAIR) are the mainstay of any imaging protocol as these bring out most of the abnormalities separately from normal brain. Usually the accompanying oedema appears bright and lesion itself may vary from hyperintense, isointense to hypointense. This is supported by a T1 weighted image which gives excellent anatomical details. Further depending upon the clinical indication protocols may consist of diffusion weighted sequences that highlight acute stroke due to restriction of water movement, MR angiography to study blood vessels in the neck or brain, contrast enhanced studies for further characterisation of the lesion, and advanced studies such as perfusion or functional imaging. Currently, MR is the investigation of choice for the evaluation all neurological disorders.

Contraindications and Safety Issues

There are three main reasons to be cautious before subjecting a patient with an implanted device for MR study. The object may move if iron is present. This may cause injury which can be quite severe depending upon its proximity to vital organs. Second problem is of heating of the device by the deposition of radiofrequency waves and cause thermal injury to surrounding areas. Lastly, the devices may be affected by the presence of varying electromagnetic fields and may stop functioning or may malfunction. Patients with implanted pacemakers, or electromagnetically activated devices such as cochlear implants etc. cannot undergo MR examination as it causes device malfunction due to the presence of a strong magnetic field and varying gradients. Similarly, objects such as bullets, pellets or other iron foreign bodies may move in the presence of a strong magnetic field. Some of devices may move just after their implantation in the patient's body and need 6 weeks to 8 weeks for local stability due to fibrosis before they are safe for MR imaging. Most of the other devices are considered safe. They may, however, produce artefacts if the scanning is done in their location. Devices made of titanium produce less obscuring of the area compared to stainless steel or other metals. Children and disoriented adults require some form of sedation to make them lie quietly without moving for the duration of the study. This needs constant monitoring and oxygenation for which specially designed MR compatible anaesthesia trolleys, laryngoscope and monitoring devices are a must. About 0.5% to 2% of patients may be claustrophobic and may not be able to undergo MRI.

Brain

Normal appearance

Normal grey matter appears slightly brighter on T2 compared to white matter and darker than white matter on T1 images. Fat appears brightest and CSF appears darkest on T1. Fat shows intermediate to bright intensity and CSF also appears brightest on T2 images. Air and bony cortex remains dark on both T1 and T2 sequences. Blood vessels with fast flow show 'flow void' or appear dark on both the T1 and T2 images whereas slow flow such as seen in some veins appears brighter. MR shows exquisite anatomical details that far surpass those seen on CT. Metallic devices have susceptibility effect and appear dark on both T1 and T2 images accompanied by a bright area. Imaging can be done in any plane without changing patient's position. In addition 3D imaging can be performed that allows thin slices and reformatting. MR spectroscopy of normal brain demonstrates three main peaks those of N-acetyl aspartate (NAA), creatine (Cr) and choline (cho). Normal brain does not show lactate or lipid peaks. These peaks are displayed on a scale based on chemical shifts and are constant in position along x-axis irrespective of the strength of the magnet. The higher field systems have better spectral demonstration due to improvement in resolution.

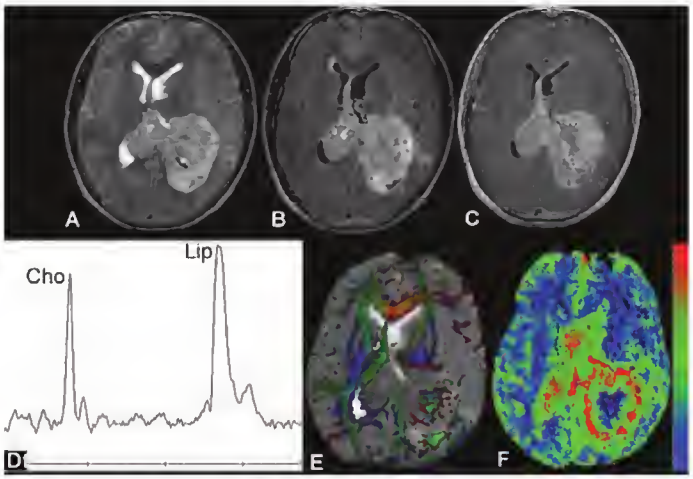
Abnormal appearance

The abnormalities are detected on MR directly accompanied by their mass effect or oedema, if any.

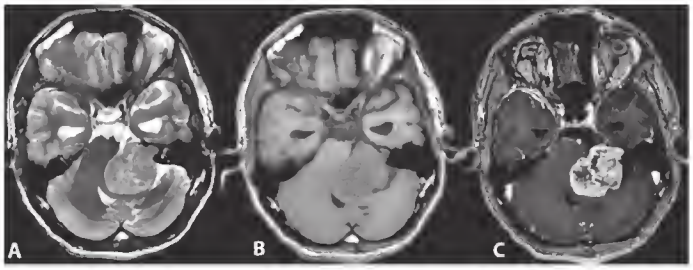
Neoplasm

Most of the tumours appear hyperintense on T2 and FLAIR and iso to hypointense on T1 images (**Figures 3A to F and 4A to C**). Accompanying oedema and necrosis within the tumour appears brighter on T2 (but less bright than CSF) and darker on T1 images (less dark than CSF). Cystic changes parallel CSF intensities on T1 and T2 images. MR can directly show the mass effect and herniation, if present. In neoplastic lesions, the contrast studies are a part of the imaging protocol which assesses the enhancement of the lesions. Contrast studies also delineate the tumour in its entire extent, and also show dural invasion, if present, as thick focal dural enhancement. The multiplicity such as those of metastases is also better evaluated on contrast studies as small cortical lesions without significant oedema may be isointense and thus not apparent on non-contrast studies. Neoplasms, especially high grade, are associated with more necrotic areas and significant mass effect whereas low grade gliomas are homogenous and usually

exhibit minimal mass effect. Further characterisation can be done by MR spectroscopy which shows elevated peak of choline and reduced peak of NAA. Lipid peak may be present in glioblastomas. High grade neoplasms also have high rCBV in comparison with low grade gliomas. fMRI may be required by the neurosurgeons to identify known functional areas in the vicinity of the lesion, as due to mass effect, these areas may be shifted. Identification of calcification is difficult on routine MR imaging sequences, however, newer sequences are being developed that can overcome this disadvantage.



Figures 3A to F: (A) Axial T2, (B) FLAIR, (C) Post-contrast, (D) H-MR Spectroscopy, (E) Diffusion tractography and (F) Perfusion weighted scans in a patient with a large left temporal lobe Glioblastoma Multiforme. T2, FLAIR and post-contrast scans show a mixed signal, heterogeneously enhancing mass in the left temporal region. MR spectroscopy shows increased choline and lipid peaks, DTI shows entrapment of normal white matter fibres by the tumour and perfusion weighted image, and reveals increased relative cerebral blood volume in the periphery of the lesion.



Figures 4A to C: (A) Axial T2, (B) T1 and (C) post-contrast T1-weighted MR images show 'ice cream cone' appearance of schwannoma that consists of a large mixed signal, heterogeneously enhancing left CP angle mass and a smaller intra-canalicular component. The ipsilateral CP angle cistern is enlarged.

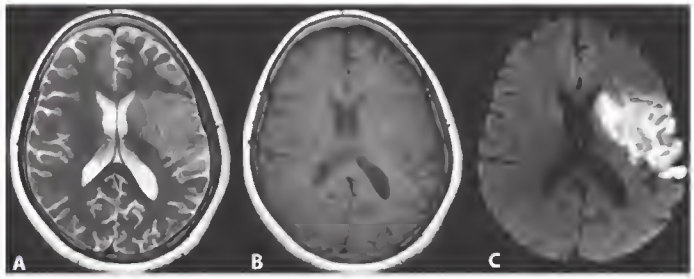
Because of its multiplanar capability, the lesions in the base of skull region including sella can be aptly demonstrated.

Trauma

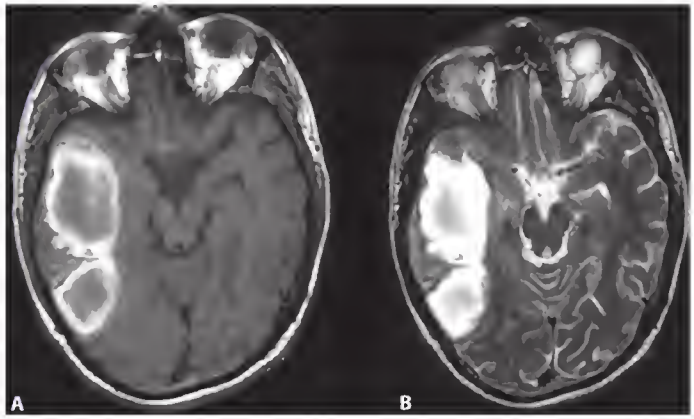
In trauma, even as CT is the primary investigation of choice, MR does have the capability to show bleed in different stages, whereas CT demonstrates it only in the acute stage. MR can additionally show small contusions or shear injury to deeper structures with clarity.

Vascular

MR is the earliest to confirm the presence of acute stroke within 2 hours on diffusion weighted images where the affected site becomes bright (**Figures 5A to C**). Other MR sequences may a take a day or more to show similar changes, though oedema or mass effect may manifest earlier. MR angiogram may show occluded intra-cranial blood vessels in the affected territory in case of a large vessel disease. In cases of embolic stroke MR angiogram of brain and neck can demonstrate the culprit plaque in the origin of internal carotid artery in the neck. Combined with perfusion imaging, diffusion imaging can show the penumbra or the region at risk if ischaemia continues. Treatment options can be chosen and initiated early based on MR imaging to maximise the recovery of the patient. Haematomas secondary to hypertension can also be documented and can be reasonably differentiated from other pathological bleeds on the basis of its appearance. Bleeds can also be categorised into acute, subacute and chronic stages based on imaging findings (**Figures 6A and B**). Other vascular conditions such as arteriovenous malformations, and aneurysms larger than 3 to 4 mm can be easily diagnosed on MRI. MR venography (MRV) can also be performed which depicts only the larger veins and venous sinuses with consistency. Diagnosis of cerebral venous sinus thrombosis can be confirmed or excluded based on MRV appearances.



Figures 5A to C: Axial T2, T1 and Diffusion weighted MR sequences show an area of (A) T2 hyperintensity, (B) hypointense on T1 weighted image and (C) with restricted diffusion in the left MCA territory suggesting acute nonhaemorrhagic infarct.

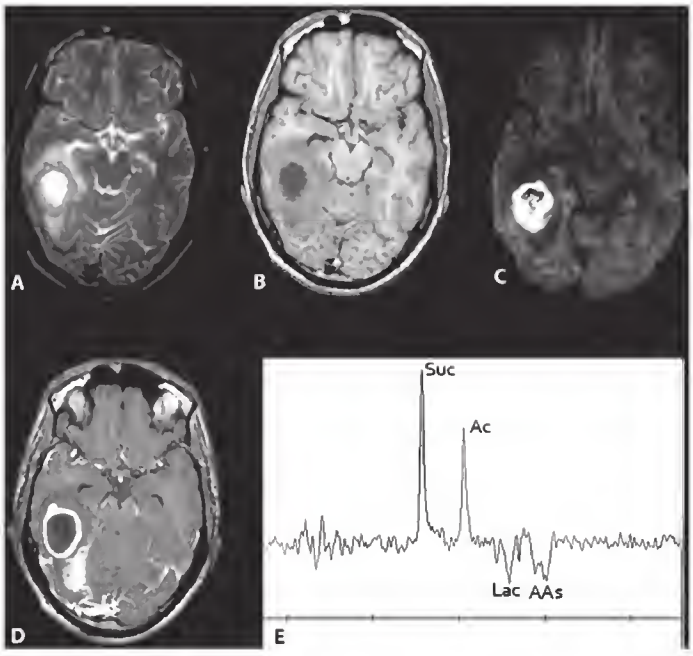


Figures 6A and B: Axial MR images show an area of hyperintensity on both (A) T1 and (B) T2 weighted sequences in the right temporal lobe suggesting subacute intraparenchymal haemorrhage.

Infections

Central nervous system Infections are common in our part of the world. If recognised, most of them are fully treatable after initiation of correct therapy, else complications ensue which can be life-threatening. In acute viral encephalitis, characteristic bilateral asymmetric signal intensity changes in inferior frontal or in temporal lobe suggest herpes encephalitis. Other viral encephalitis can have non-specific imaging features, but changes are usually bilateral and may be multifocal. In other infections, MRI can document the presence and location of the lesions which usually display ring enhancement. MR can characterise brain abscesses

by demonstrating high signal intensity on diffusion-weighted imaging (DWI) (**Figures 7A to E**). MR spectroscopy shows peaks of amino acids in addition to acetate and succinate. Common causes of seizures in this part of the world include granulomas secondary to neurocysticercosis (NCC) and tuberculomas. Both may exhibit similar MR imaging pattern, though presence of a scolex is diagnostic of neurocysticercosis. At times T2 and T1 images show a scolex; more frequently thin slice imaging is needed for its demonstration. Further characterisation may be done on MR spectroscopy where NCC shows peaks of succinate and acetate without amino acids. Tuberculosis occupies a special place in developing nations. Its common CNS manifestations include tubercular meningitis and tubercular granulomas also known as tuberculomas. Tuberculomas share the imaging features with other granulomas. However, these may be differentiated on a special imaging sequence, magnetisation transfer, on which the wall of the tuberculomas appear bright and on quantification, shows a lower magnetisation transfer ratio compared to lesions with similar MR appearance (**Figures 8A to E**). On MR spectroscopy, tuberculomas display prominent lipid peak amidst absence of normal brain peaks. Meningitis of any aetiology will show diffuse linear meningeal enhancement and may show evidence of its complications such as hydrocephalus and infarcts.

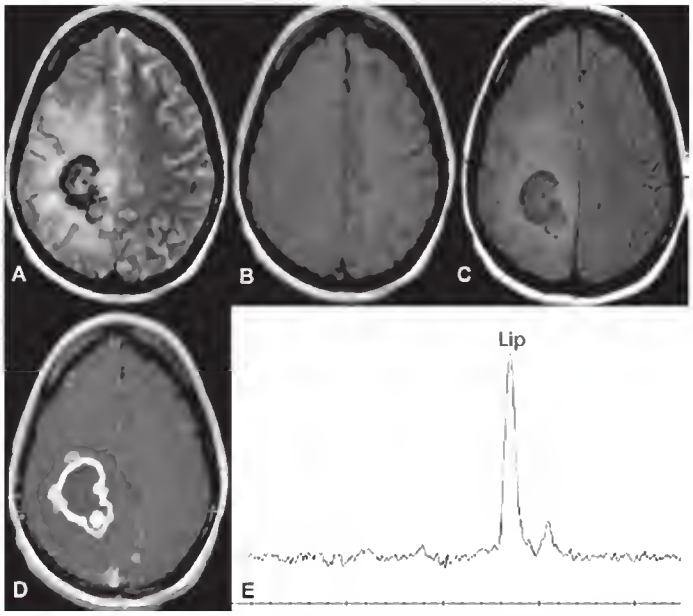


Figures 7A to E: Pyogenic abscess in the right temporal lobe of a 32-year-old man. (A) Axial T2 WI image shows a large well-defined T2 hyperintense lesion with thin hypointense rim, perifocal oedema and mass effect. (B) T1 weighted image shows isointense rim of the lesion. (C) Diffusion restriction noted on diffusion weighted image. (D) Post-contrast T1 weighted image shows rim enhancement of the lesion. (E) In vivo proton MR spectroscopy from the cystic cavity shows presence of cytosolic amino acids (Cy), lactate (L), acetate (Ac) and succinate (Suc) characteristic of an abscess.

MR is also helpful in the recognition of osmotic demyelination secondary to rapid correction of hyponatraemia which causes central pontine T2 hyperintensity. Similarly certain other encephalopathies such as hypertensive encephalopthy, ADEM may be suggested on the basis of imaging findings in the presence of appropriate clinical scenario.

Congenital

Developmental brain lesions can be in the form of structural anomalies such as holoprosencephaly, heterotopia, Dandy Walker



Figures 8A to E: (A) Axial T2, (B) T1. (C) MT-T1, (D) post-contrast and (E) MR spectroscopy scans in a patient with right parietal tuberculoma. The lesion appears hypointense on T2, hypo to isointense on T1 with a peripheral bright rim on MT-T1 sequence which enhances on post-contrast image. MR spectroscopy shows prominent lipid peak.

syndrome, abnormalities of delayed myelination or abnormal myelination, herniation of brain through bone defects—cephaloceles, changes secondary to perinatal insults, and many other conditions. Usually non-enhanced MR imaging in axial and sagittal plane will delineate all these disorders in their entirety.

Degenerative neurodegenerative diseases can also be studied by MRI and show a variety of changes. These include changes in signal intensities, or changes in volume as in dementias.

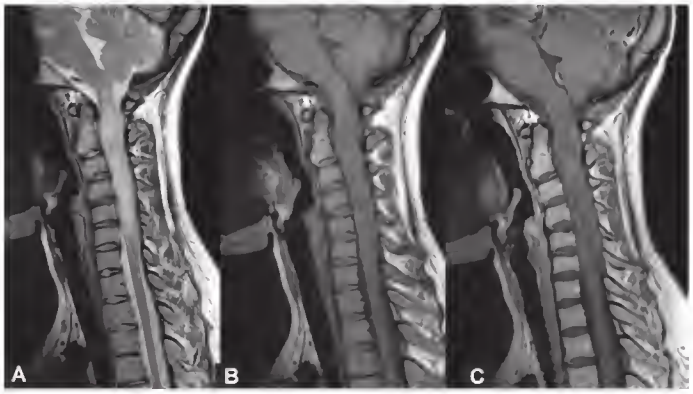
Spine

MR has revolutionised the imaging of spine and its constituents. It offers assessment of the spinal cord, intradural CSF space and epidural tissues directly in any desired plane. Usually sagittal and axial planes form the mainstay of spinal imaging. Spinal cord and nerve roots appear grey on both T2 and T1 images, and the CSF bright on T2 and dark on T1 images. The vertebrae appear relatively brighter compared to adjacent muscles on both T1 and T2 imaging. The vertebral bodies have a thin hypointensity of cortex all round. The normal dura mater may be directly seen especially in the presence of intra-canalicular fat. MR also demonstrates the normal and abnormal intervertebral discs.

Abnormal appearance

Neoplasm: MR can show marrow changes much before any bony destruction takes place. Most abnormalities of the vertebral bodies appear hyperintense on T2 and hypointense on T1 and enhance on contrast-enhanced T1 studies. These changes may occur in a single vertebra or multiple vertebrae which may be contiguous or far apart. Neoplastic conditions such as metastases and multiple myeloma may also have associated pre or paravertebral soft tissue but this is not large, usually does not exceed 8 mm in thickness, and enhances homogenously, unlike peripheral enhancement in abscess formation. Other bony tumours are less frequent in spine and usually involve posterior elements. MR can identify the tumour and define its

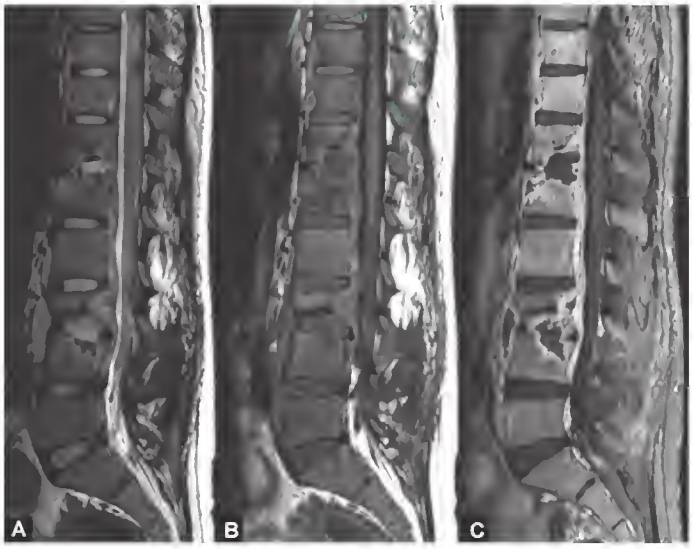
extent. Lesions extending to epidural space can also be easily delineated. Similarly intradural extramedullary lesions like meningiomas, neurofibromas, etc. and intramedullary tumours such as astrocytomas, ependymomas, etc. can be delineated in their entirety for the surgical excision (**Figures 9A to C**). Drop metastases from intra-cranial tumours such as medulloblastomas, glioblastomas, etc. are seen as small nodular enhancing areas within the CSF space.



Figures 9A to C: (A) Sagittal T2, (B) T1 and (C) post-contrast T1 weighted MR images in a patient with cervical cord astrocytoma show diffusely expanded cervical spinal cord which is hyperintense on T2 and hypointense on T1 weighted sequences with patchy enhancement following contrast administration.

Infection

In infections, solitary or more frequently two or more contiguous vertebrae are involved with hyperintensity on T2 and hypointensity changes on T1 images. Intervening disc is often involved, but this involvement may be late in tuberculosis. Infective conditions frequently cause abscess formation in the adjacent soft tissues which can be easily appreciated on T2 (these show almost fluid intensity) and post-contrast T1 imaging (abnormal soft tissue shows peripheral enhancement) (**Figures 10A to C**). On DWI, these show low AIDS-dementia complex values.



Figures 10A to C: (A) T2 weighted sagittal image shows hyperintense destructive process involving the D12-L1 and L3-L4 vertebrae and the intervening disc. There is evidence of a hyperintense pre-vertebral collection and intra-canalicular collection causing extradural compression. (B) The vertebrae and collection appear hypointense on T1 weighted image. (C) Post-contrast T1 weighted sagittal images show enhancement of the abnormal tissue along with rim enhancement of the pre-vertebral collection.

MR can also demonstrate the nerve roots along their course within the CSF space as well as through the neural canal. Root changes in arachnoiditis such as thickening, clumping, and abnormal enhancement are all documented well on MRI. In addition, CSF loculation and abnormal meningeal enhancement can also be seen in arachnoiditis.

Vascular

In spinal AVMs, MR shows serpiginous, long channels of flow void within the CSF space posterior or occasionally anterior to the cord.

Trauma

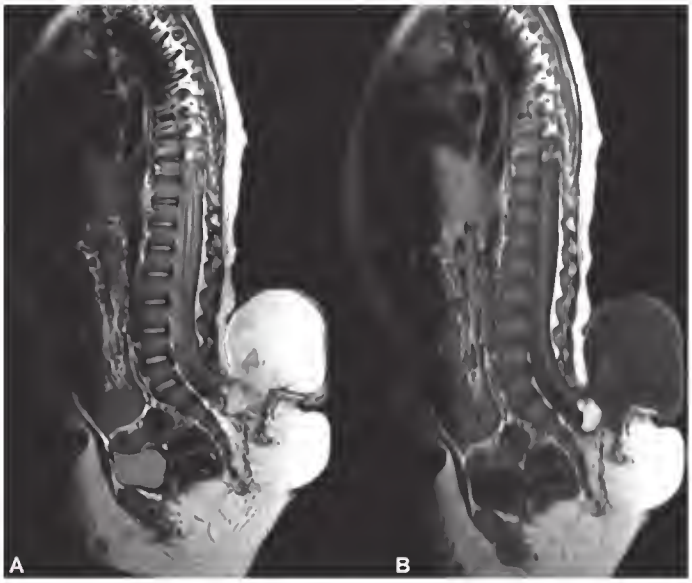
In trauma, MR is useful in the assessment of the spinal cord and informs about its integrity and presence of haematoma.

Degenerative

Normal disc can be identified by its typical appearance of hyperintensity with a thin central hypointensity on T2 images. Disc desiccation causes the entire disc to become hypointense. Disc bulges, and herniations can be differentiated on MR. MR can also show far lateral disc herniations directly that cause root compression as these exit the canal. Similarly, abnormalities of alignment are clearly shown.

Congenital

MR is especially useful in the evaluation of congenital malformations. Meningocoeles can be fully evaluated for their contents, presence of neural placode (**Figures 11A and B**) and associated Chairi II malformation or syringomyelia can be established along with intra-cranial ventricular assessment. MR is especially useful in skin covered malformations and in cases with suspected tethering where it can show low lying cord, or thick filum terminale. Any associated intradural tumours such as dermoid, epidermoids can also be seen. Diastematomyelia can be diagnosed on delineation of two cords within the same dural sheath or in different sheaths. Bone spur, if present, is easily seen.



Figures 11A and B: (A) Sagittal T2 and (B) T1 weighted MR scan in an infant with meningomyelocele. The spinal cord is tethered into a CSF filled dural sac that protrudes dorsally through a dysraphic lumbosacral spine. A small lipoma is also noted within the sac.

INTERVENTIONAL PROCEDURES

Interventional procedures have become accepted in clinical management in certain diseases as they offer much less invasion compared to operative procedures, thereby reducing complications. These procedures are frequently performed under local anaesthesia and via a percutaneous route. The most common interventional procedures are embolisation of intra-cranial and spinal arteriovenous malformations including fistulas, coiling of intra-cranial aneurysms, stenting of internal carotid plaques in the neck, and recanalisation in some cases of acute intra-cranial thrombosis. Pre-operative embolisation is also performed to reduce vascularity in some tumours such as meningiomas, glomus tumours. In the spine, vertebroplasty is performed in cases of painful benign collapse of vertebrae. This consists of injecting bone cement through percutaneous route into the affected vertebral body which seals the micro-fractures responsible for pain in these cases.

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20.5 Epilepsy

Sanjeev V Thomas

INTRODUCTION

Epilepsy is one of the oldest diseases known to mankind.The word seizure is derived from the sixth century Latin word 'seiz' that means to 'take possession of'.The word epilepsy is derived, from the Greek word '*Epilepsia*' which means to 'seiz'.

EPIDEMIOLOGY

Worldwide, there are about 50 million people with epilepsy and 90% of them live in developing countries. The prevalence of epilepsy ranges from 5 to 10 per 1000 in most countries, but it is likely to be higher in developing countries than in developed countries.The incidence of epilepsy in developed countries ranges from 24 to 53 per 100,000 population.The age specific incidence is highest at extremes of age. In developed countries it had probably reduced in young people and had increased in those aged more than 60 years.The natural history of untreated epilepsy is not readily available. It is possible that about 20% to 30% of patients are likely to have spontaneous remission while about 35% of patients may continue to get seizures in spite of treatment with two or more anti-epileptic drugs (AED). Persons with epilepsy carry 2 to 3 times increased risk (standardised mortality ratio) of death when compared to others. Sudden unexplained deaths in epilepsy (SUDEP) account for 2% to 18% of all deaths while status epilepticus accounts for 12.5% deaths.

Treatment Gap

The proportion of persons that fail to receive treatment, expressed as a percentage of those who require treatment, is termed as treatment gap.Treatment gap for epilepsy varies widely between countries and within countries. The treatment gap is highest in low income countries such as India (75%) moderate in medium income countries (~50%) and least in high income countries (<10%).Treatment gap in rural areas is twice that in urban areas.

EPILEPTOGENESIS

The term epileptogenesis refers to a long standing state in which recurrent seizures occur without any immediate provocation. It involves genetic and acquired mechanisms with several stages, the details of which are not sufficiently understood. Several genetic traits and genes associated with epilepsy have been described. Maturation of a localised lesion in the brain in to an epileptic focus involves complex synaptogenesis, neurogenesis and establishment of reverberating circuitry.

DEFINITION

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least two epileptic seizure.

CLASSIFICATION

The classifications of seizures and epilepsy syndromes have undergone several changes since the first attempt to classify them in 1960.The present classification of seizures (approved in 1981) and epilepsy syndromes (approved in 1989) were prepared before much of the knowledge on advanced imaging and molecular genetics of epilepsy had evolved.

Epileptic seizures are classified according to the ictal semiology and electroencephalographic (EEG) findings. The classification currently approved by the International League Against Epilepsy was introduced in 1981.

Partial Seizures

International classification divides seizures broadly into partial and generalised seizures with several subtypes under each category. Partial seizures have a demonstrable focal onset in clinical semiology or in EEG. In simple partial seizures, there is no loss or alteration of consciousness.They are further classified according to the phenomenology (**Table 1**).

Complex partial seizures that come as the second category under partial seizures are characterised by impairment of consciousness either from the onset or later on as the seizure progresses. Partial seizures may become secondarily generalised with typical tonic

Table 1: International Classification of Epileptic Seizures

I. Partial (focal, local) seizures
- Simple partial seizures (consciousness not impaired)
  - With motor signs
  - With sensory symptoms
  - With autonomic symptoms or signs
  - With psychic symptoms
- Complex partial seizures (Temporal lobe or psychomotor seizures; consciousness impaired)
  - Simple partial onset followed by impairment of consciousness
    - With simple partial onset (A.1 to A.4) followed by impaired consciousness
    - With automatisms
  - With impairment of consciousness at onset
    - With impairment of consciousness only
    - With automatisms
- Partial seizures evolving to secondarily generalised seizures (tonic-clonic, tonic or clonic)
  - Simple partial seizures (A) evolving to generalised seizures
  - Complex partial seizures (B) evolving to generalised seizures
  - Simple partial seizures evolving to complex partial seizures evolving to generalised seizures

II. Generalised seizures (Convulsive or Nonconvulsive)
- Absence (Petit mal) seizures
- Myoclonic seizures
- Tonic seizures
- Atonic seizures
- Clonic seizures
- Tonic clonic (grand mal) seizures

clonic convulsions and less often with either tonic or clonic convulsions. Partial onset may occasionally reveal the precise origin of the seizures in anatomical terms. Occasionally, partial motor seizures may be followed by post-ictal paresis that may last several hours. Certain specific signs or symptoms that occur during a seizure may reveal the lateralisation or localisation of the seizures. Ictal and post-ictal aphasia indicates a dominant hemispheric origin while ictal speech would favour a non-dominant hemispheric origin of seizures. Complex automatisms involving oro-alimentary structures (epigastric rising sensation, nausea and vomiting may suggest a temporal lobe origin. Experiential phenomenology such as distortion of memory, dreamy state, *déjà vu* (a feeling that a particular experience has occurred earlier) *jamais vu* (a sensation that a familiar experience is new) are some of the characteristic temporal lobe ictal semiology. While an unnatural laughing (gelastic seizures) may indicate hypothalamic origin of seizures. Seizures originating in occipital lobe often present with visual phenomenology. The common automatisms (coordinated involuntary and often semi purposive complex activities) are movements such as lip smacking, chewing, swallowing movements, scratching, picking on clothes, trying to ease oneself from the bed or surroundings. Often these movements are confined to the limbs on the side of the ictal onset. In contrast to this, posturing is involuntary tonic spasms of the muscles leading to abnormal posturing of certain body parts such as hands, legs, etc. and manifest on the contralateral side of ictal origin. Occasionally, the semiological features of a seizure may be due to selective propagation of the electrical discharges to certain areas of the brain rather than due to the focus itself. This may lead to false localisation of seizure origin.

Generalised Seizures

They are broadly categorised into convulsive and non-convulsive (absence) seizures.

Absence Seizures

Absence seizure is characterised by abrupt onset loss of consciousness, a vacant look and behavioural arrest. The person is able to maintain posture, but may have 3 per second eyelid myoclonia. Each seizure may last a few seconds and ceases abruptly when the child returns to the previously engaged activity. The EEG signature of absence is 3 per second generalised spike and wave discharges over a normal background. The EEG spikes and seizures are characteristically provoked by hyperventilation. An alteration in the T type of calcium channels in thalamus is responsible for these seizures. Childhood absence epilepsy is characterised by absence seizures that tend to start around three years of age in children who normal development. These seizures tend to respond well to ethosuximide, sodium valproate and lamotrigine.

Generalised Tonic Clonic Seizures

A typical tonic clonic seizure begins with a tonic phase characterised by loss of consciousness and tonic contraction of facial, axial and limb muscles leading to a loud cry, rolling up of eyes, rigid posturing of the extremities and apnoea. The clonic phase that follows the tonic phase is characterised by rhythmic jerking of the limbs (due to intermittent contraction and relaxation of the muscles) as in a clonus. Tongue may be bitten during the latter part of the tonic phase or during the clonic phase. There may be pupillary constriction or incontinence during this phase.

Myoclonic Seizures

Myoclonic seizures are characterised by sudden, brief shock-like contractions of agonist and antagonist group of muscles leading to a brief jerk (often less than 500 milliseconds). Myoclonus can involve any group of muscles and can occur in isolation or in a train, when it may resemble tremor or *epilepsia partialis continua*.

Tonic Seizures

Tonic seizures are usually very brief (lasting a few seconds) but longer than myoclonic seizures. They are characterised by sudden spasm of the muscles particularly the axial muscles that literally throw the subject forcibly down to the floor, resulting in deep cuts on the head or face. EMG shows a dramatic increase in muscle activity during a tonic seizure.

Atonic Seizures

Atonic seizures are characterised by sudden lapses in muscle tone resulting in lapses in posture or falls. Atonic seizures are usually very brief and occur in combination with other types of seizures as in the case of Lennox-Gastaut Syndrome.

EPILEPSY CLASSIFICATION

In contrast to the classification of seizures, classification of epilepsy attempts to classify specific epilepsies and syndromes according to their clinical presentation, seizure type, accompanying neurological deficits and EEG or imaging characteristics. Age of onset, course of illness, anatomical localisation of the epileptogenic zone and underlying pathology are taken into consideration while classifying epilepsy syndromes. The currently accepted classification of epilepsies and epileptic syndromes was approved by the ILAE in 1989 (**Table 2**).

Infantile Spasm (West Syndrome)

This syndrome manifests between 4 months and 6 months of age. A specific etiological factor can be identified in only half of the patients. Tuberous sclerosis, malformations of cortical development, trisomy 21, birth asphyxia, central nervous system (CNS) infections and inborn errors of metabolism are the common etiological factors for infantile spasm. Seizures are similar to myoclonus, but are slower in evolution. It can be flexor type, extensor type or mixed type. Flexor spasms occur as sudden contraction of the shoulder flexors, elbow flexors and flexion movement of axial muscles. The EEG in infantile spasm has typical findings—hypsarrhythmia—characterised by high amplitude slow wave (1 Hz to 3 Hz) background activity and multifocal polyspike discharges. One of the recommended treatment for infantile spasm is ACTH (150 units/m^2 for one week followed by gradual tapering and withdrawal by four weeks). Infantile spasm particularly that associated with tuberous sclerosis responds very well to vigabatrin, but the potential risk to vision has limited its use.

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is an epileptic encephalopathy that typically starts around three years of age. It characterised by multiple seizures types (tonic seizures, atonic seizures, myoclonus, generalised seizures and partial seizures) that are often refractory to AED therapy and developmental regression. The EEG shows characteristic slow spike wave discharges (1.5 to 2.5 Hz) and abnormal background activity (**Figure 1**). Sodium valproate, topiramate, lamotrigine, and clonazepam have been found to be

Table 2: International Classification of Epilepsies and Epileptic Syndromes

Localisation related epilepsies and syndromes

- Idiopathic (with age related onset)
  - Benign childhood epilepsy with centro-temporal spikes (BECT)
  - Childhood epilepsies with occipital paroxysms
  - Primary reading epilepsy
- Symptomatic epilepsy
- Chronic progressive *epilepsia partialis continua* of childhood (Kojewnikow's Syndrome)
  - Syndromes characterised by specific modes of precipitation
  - Temporal lobe epilepsies
  - Frontal lobe epilepsies
  - Parietal lobe epilepsies
  - Occipital lobe epilepsies
- Cryptogenic epilepsies

Generalised epilepsies and syndromes

- Idiopathic (with age-related onset-listed in order of age)
  - Benign neonatal familial convulsions
  - Benign neonatal convulsions
  - Benign myoclonic epilepsy in infancy
  - Childhood absence epilepsy (pyknolepsy)
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy (impulsive petit mal)
  - Epilepsy with grand mal (GTCS) seizures on awakening

Contd...

Contd...

  - Other generalised idiopathic epilepsies not defined above
  - Epilepsies with seizures precipitated by specific modes of activation
- Cryptogenic or symptomatic (in order of age)
  - West Syndrome (Infantile spasms)
  - Lennox-Gastaut syndrome
  - Epilepsy with myoclonic-astatic seizures
  - Epilepsy with myoclonic absences
- Symptomatic
  - Non-specific aetiology
  - Early myoclonic encephalopathy
  - Early infantile epileptic encephalopathy with suppression burst
  - Other symptomatic generalised epilepsies not defined above
- Specific syndromes

Epilepsies and syndromes undetermined whether focal or generalised

- With both generalised and focal seizures
  - Neonatal seizures
  - Severe myoclonic epilepsy in infancy
  - Epilepsy with continuous spike-waves
  - Acquired epileptic aphasia (Landau-Kleffner syndrome)
  - Other undetermined epilepsies not defined above
- Without unequivocal generalised or focal features

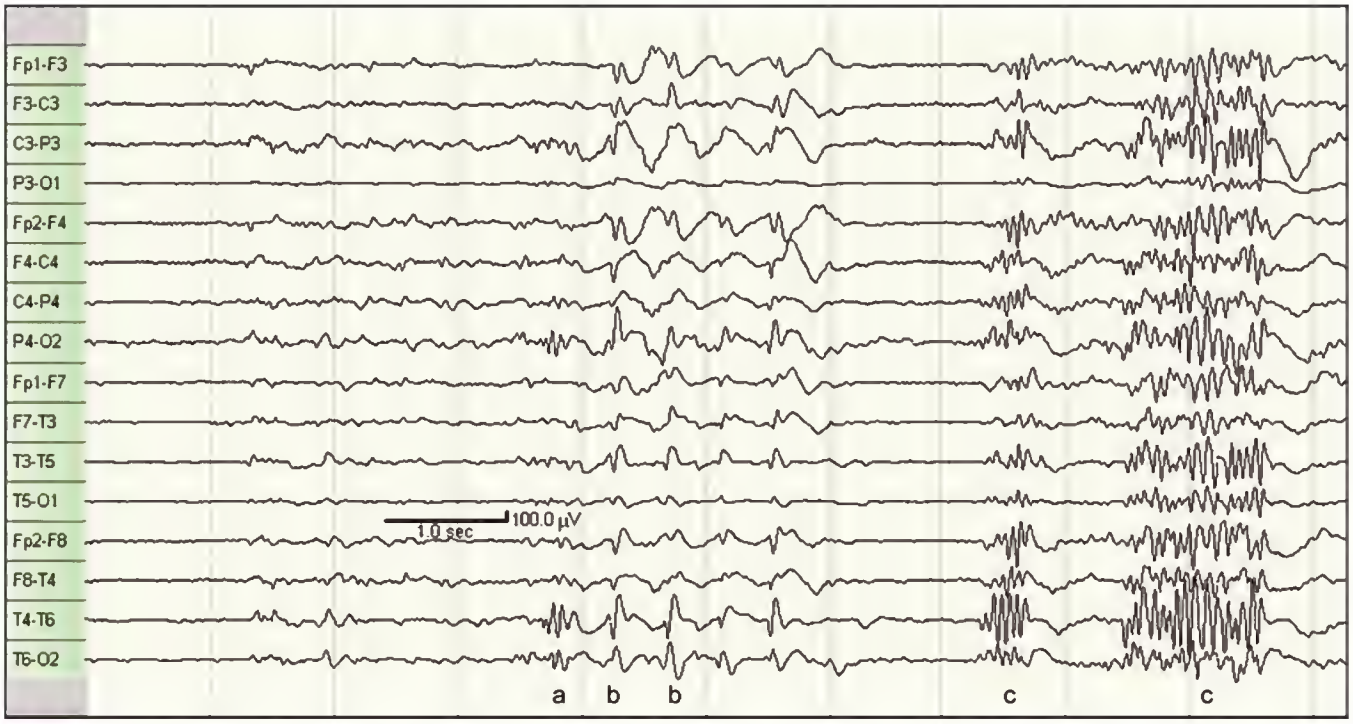


Figure 1: Lennox-Gastaut syndrome. EEG in longitudinal bipolar montage in a child (sleep state) showing (a) focal spikes (T4-T6), (b) generalised slow spike and wave discharges (2 Hz), (c) bursts of generalised paroxysmal fast activity.

effective in the management of LGS. Medically refractory cases may benefit from callosotomy, vagus nerve stimulation (VNS) or ketogenic diet. Patients tend to have a poor prognosis with persistent seizures and neurocognitive impairment.

Benign Epilepsy with Centrotemporal Spikes (BECT)

This is the most common epilepsy in childhood. It starts after three years of age and the seizures remit by adolescence. The partial seizures typical of this syndrome involve focal twitching of facial muscles, speech arrest and sialorrhoea that occur during sleep. Rarely, children can have generalised seizures during sleep. The EEG features of BECT include normal background, biphasic spike and wave discharges over centro-temporal location. These spikes have a tangential dipole with electropositivity over frontal region and electronegativity posteriorly (**Figure 2**). Most children

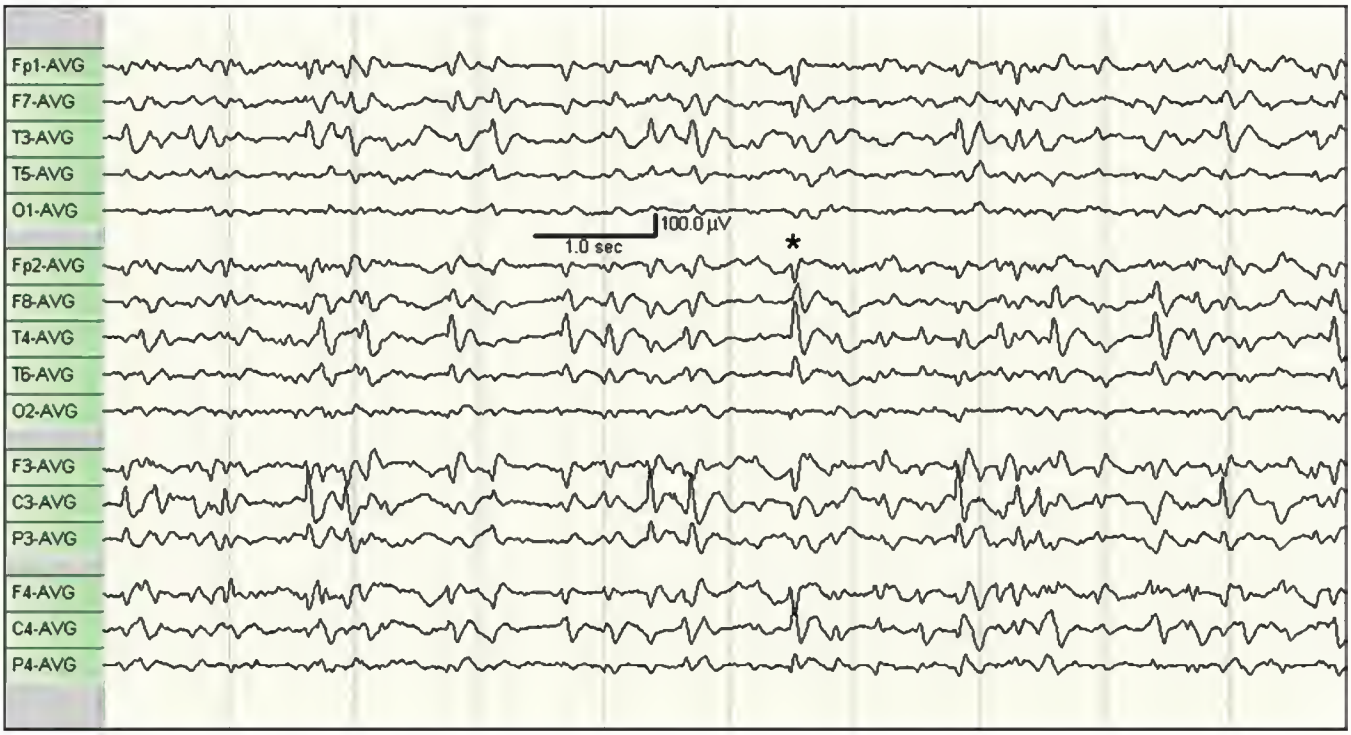


Figure 2: BECT. EEG in referential montage in drowsy state in a child showing generalised slowing of the background activity, consistent with light sleep. Spike and slow waves are profusely activated independently over both hemispheres. These spikes demonstrate typical tangential dipole with frontal electropositivity (see star in FP2-AVG derivation and electronegativity posteriorly in T4-AVG derivation). Centrotemporal spikes with extensive activation during sleep, tangential dipole and bilateral discharges are characteristic of benign childhood epilepsy with centrotemporal spikes.

respond to carbamazepine, but some may experience paradoxical worsening or an encephalopathy state. The latter group would require change of AEDs, when valproate could be an alternate AED.

Hot Water Epilepsy

Hot water epilepsy is one of the reflex epilepsies characterised by provocation of seizures by pouring hot water over head during bathing. The condition is frequently reported from Karanataka state where it accounts for 6.9% of all epilepsies.

Juvenile Myoclonic Epilepsy (JME)

This is one of the most common epilepsy syndromes in young adults. It is characterised by adolescent onset of myoclonus and generalised tonic clonic seizures without any aura. A third of affected persons give history of absence seizures in childhood. The myoclonus tends to cluster in the morning on awakening. Seizures are specifically provoked by sleep deprivation. Affected persons have normal birth, development and scholastic achievements. The EEG shows normal background activity and generalised fast (5 Hz to 6 Hz) spike wave discharges with higher amplitude frontally (**Figure 3**). Record may show photoparoxysmal response (**Figure 4**) and increased activation of spikes during sleep. JME responds well to AED therapy. JME can be distinguished from secondary generalised epilepsies and progressive myoclonic epilepsy syndromes by the normal neurological examination, normal brain imaging and typical EEG characteristics. Sodium valproate, lamotrigine, levetiracetam and phenobarbitone have been found to be effective in JME. The dosage of medications can be reduced considerably in most patients who are in remission. Nevertheless, seizures tend to relapse in about 90% patients when AEDs are withdrawn completely. Hence treatment for an indefinite period is recommended for most patients.

Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is the most common localisation related epilepsy in adults. Typically, the patients give a past history of atypical febrile seizures and thereafter several years of normalcy. By adolescence or young adult life, they manifest complex partial seizures characterised by aura (epigastric rising sensation, fear, formed visual hallucinations, etc.) behavioural arrest, posturing of extremities contralateral to the epileptic focus and automatisms ipsilateral to the epileptic focus. The seizures evolve gradually over several seconds to one or two minutes. TLE can be due to pathology in the mesial temporal structures such as amygdala, hippocampus or parahippocampal gyrus or due to pathology in the temporal neocortical structures when the seizures may simulate extratemporal origin. Magnetic resonance imaging (MRI) of the brain typically shows mesial temporal atrophy with gliosis (**Figure 5**). Developmental tumours, gliosis and arteriovenous malformations are some of the other causes of temporal lobe epilepsy. Inter-ictal EEG typically shows focal spike and wave discharges over the anterior temporal region (**Figures 6A and B**). Anti-epileptic drugs, such as carbamazepine and phenytoin are effective in controlling the seizures in a substantial proportion of patients. Nevertheless, others (particularly those with mesial temporal sclerosis) prove resistant to medical management. Those who have failed more than one appropriate AED therapy require presurgical evaluation to decide whether anterior temporal lobectomy would bring about remission. Those who demonstrate good electroclinical correlation and concordant imaging findings are likely to benefit most from surgery.

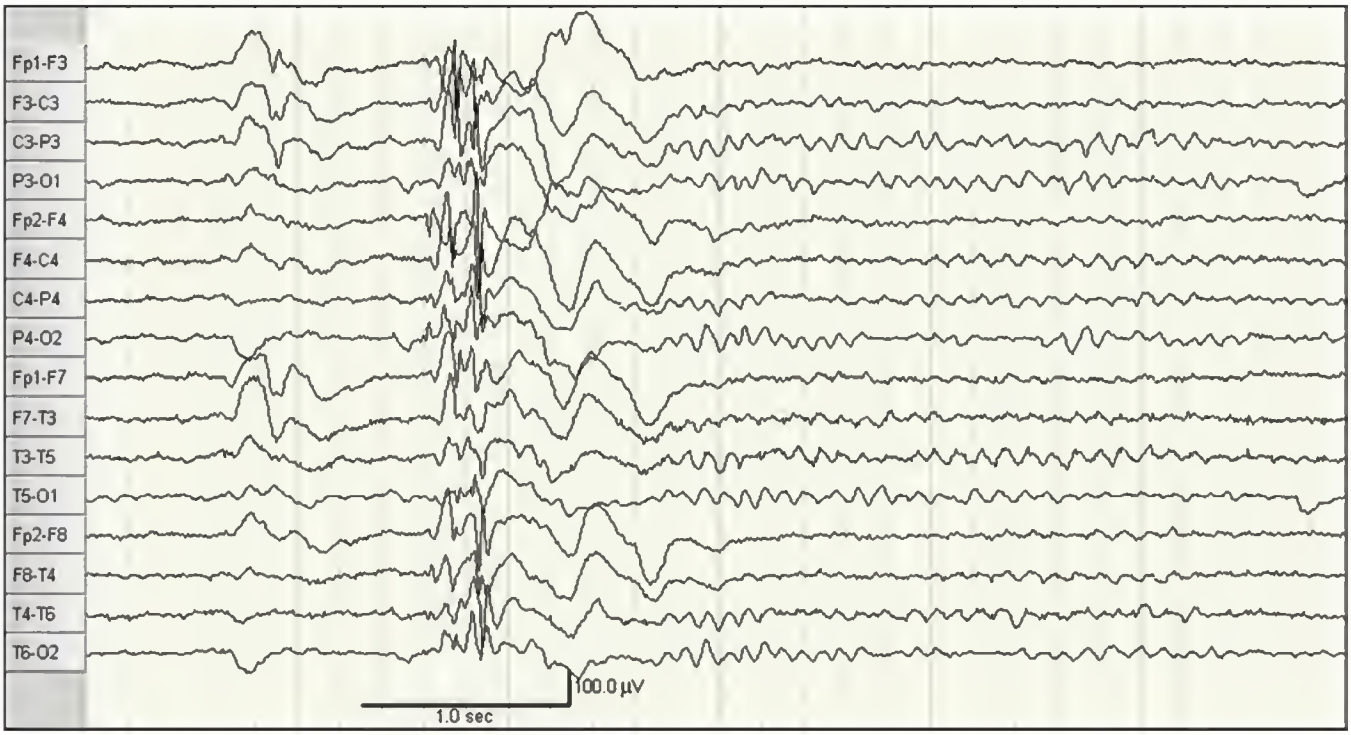


Figure 3: JME polyspike. EEG in longitudinal bipolar montage in a young adult showing generalised polyspike and slow wave activity followed by normal alpha rhythm. Generalised fast spike wave discharges (4 Hz to 6 Hz).

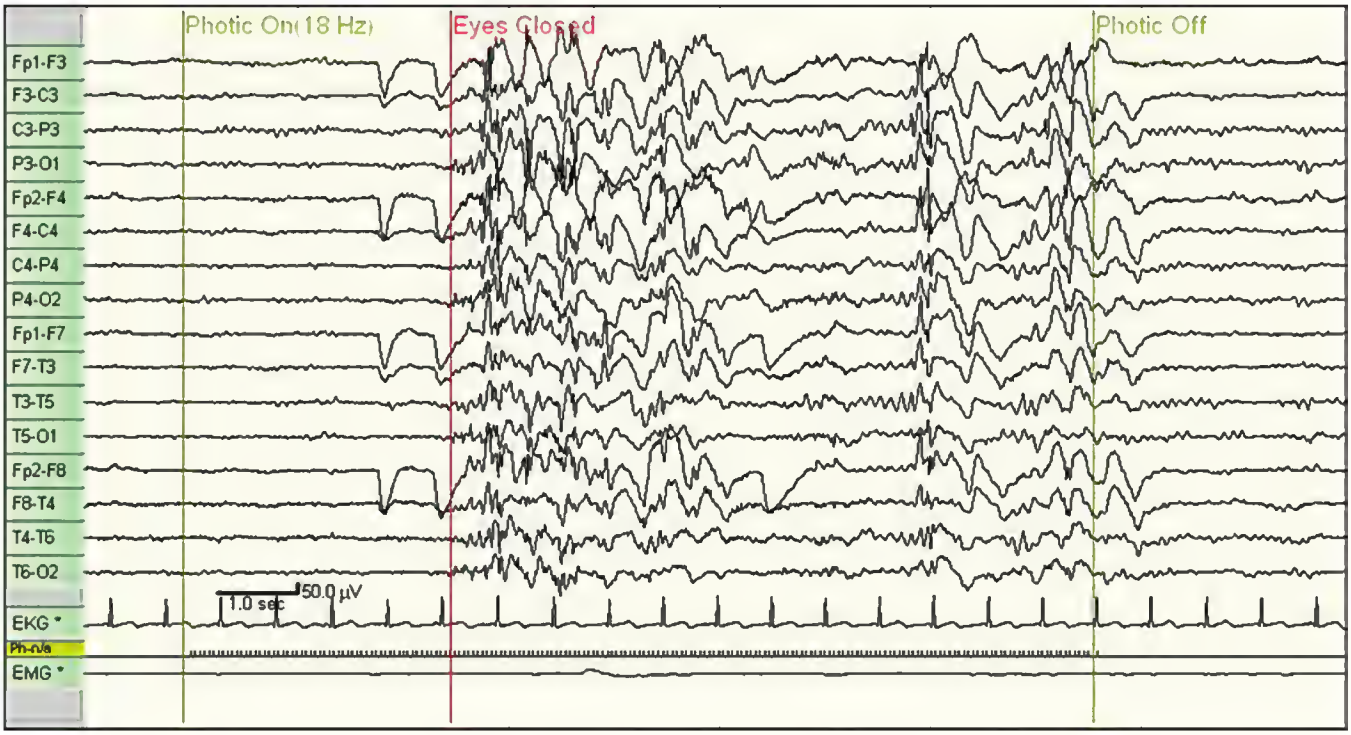


Figure 4: JME photoparoxysmal response. Continuation of previous EEG showing polyspike wave discharges with photoparoxysmal discharges at fast frequencies are typical of juvenile myoclonic epilepsy.

AETIOLOGY

Genetics

Genetic factors had been identified as aetiological factor in several types of epilepsies. Persons with epilepsy have 2 to 3 times higher family history for epilepsy when compared to persons without epilepsy. The molecular genetic basis of some of the paediatric epilepsy syndromes has been identified (**Table 3**). Mutations involving sodium, potassium, chloride channels, acetylcholine and GABA receptors have been identified in some of the epilepsy syndromes. Certain chromosomal disorders are associated with epilepsy and malformation of cortical development (**Table 4**).

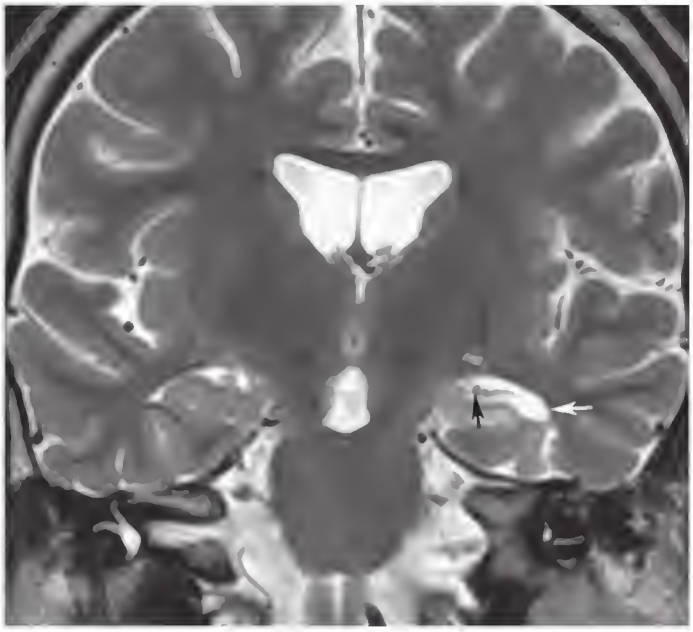
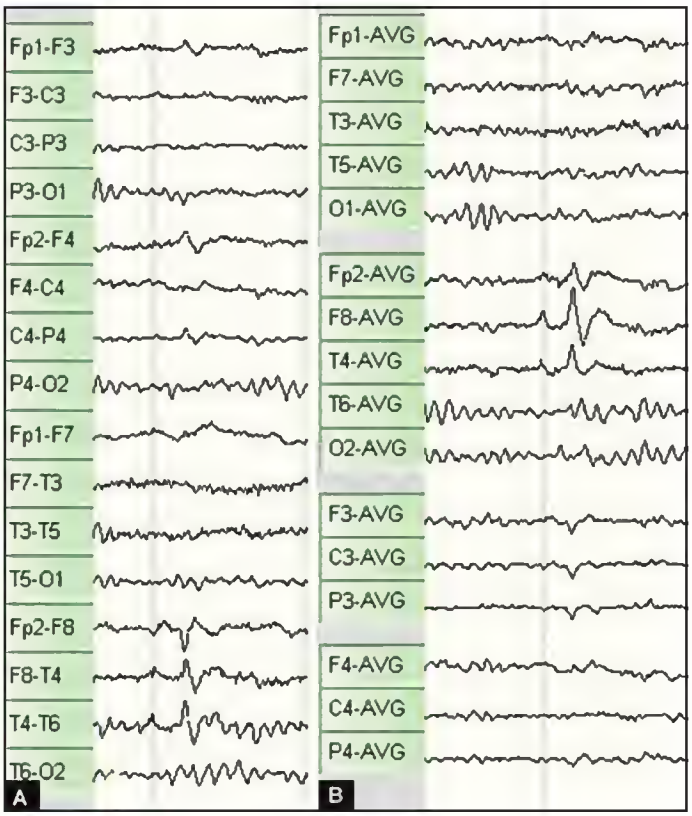


Figure 5: MTS. MRI brain T2 weighted image showing left mesial temporal sclerosis as hyperintense atrophied hippocampus (black arrow) and dilated temporal horn (white arrow).



Figures 6A and B: TLE. (A) EEG in a young adult in awake state shows spike and slow wave discharge with phase reversal across F8 electrode in the longitudinal bipolar montage. (B) The same spike when displayed in referential montage shows highest amplitude in F8-AVG derivation. These spikes are typical of temporal lobe epilepsy.

Trauma

A global survey by WHO had shown that trauma is the most frequently reported aetiology of epilepsy in more than 92% countries and it accounts for about 10% of all cases of epilepsy. Head trauma characterised by missile injury, prolonged coma, post-traumatic amnesia, depressed skull fracture or intra-cranial bleed carry higher risk of post-traumatic epilepsy.

Table 3: Selected Epilepsy Syndromes where Gene Loci have been Identified

Epilepsy Syndrome	Locus
Idiopathic generalised epilepsy	3q26; 14q23; 2q36
Adolescent onset idiopathic generalised epilepsy	8p12; 18q12; 5p
Childhood absence epilepsy	1p; 8q24
Juvenile myoclonic epilepsy	6p21; 15q14
Familial adult myoclonic epilepsy	8q23.3
Familial idiopathic myoclonic epilepsy	16p13
Benign familial infantile convulsions	19q
Benign Rolandic epilepsy	15q24
Partial epilepsy with pericentral spikes	4p15
Autosomal dominant nocturnal frontal lobe epilepsy	15q24; 3p22; 8q11.2

Table 4: Chromosomal Disorders Associated with Epilepsy

Wolf-Hirschhorn syndrome (4p-)
Miller-Dieker syndrome (del 17p13.3)
Angelman syndrome
Inversion duplication 15 syndrome
Terminal deletion chromosome 1q
Terminal deletion chromosome 1p
Ring 14 syndrome
Ring 20 syndrome

Neurocysticercosis

Epilepsy can occur due to a number of parasitic diseases such as malaria, cysticercosis, schistosomiasis and paragonimiasis. Computed tomography (CT) scan or MRI brain shows typical cysts with invaginated scolex as ring enhancing lesions or small plaques or calcifications. The control of seizures with AEDs is easier after cysticidal treatment than when left untreated.

INVESTIGATIONS

The diagnosis of seizures is made largely on the basis of detailed history obtained from an observant bystander. Nevertheless, several investigations are helpful in establishing a diagnosis of epilepsy, for certain.

Electroencephalography

Electroencephalography (EEG) is the key investigation in a suspected case of seizures. A series of electrodes are applied to the scalp according to a standard format and the electrical potentials thus gathered are amplified and displayed as an array of traces. Electrodes on left side of scalp are odd numbered while corresponding ones on right side are numbered even. The normal background activity of a subject varies according to the age and behavioural state (awake versus sleep) and the hallmark of seizures in the EEG is the occurrence of random, high amplitude spike and slow wave discharges that stand out from the background. The frequency and distribution of the spike and wave discharges are useful in making precise classification of epilepsy syndromes. These inter-ictal spike and wave discharges may occur synchronously all over the scalp in

generalised discharges. It may be confined to focal areas in the case of localisation related epilepsy. EEG may fail to reveal the spike wave discharges in some patients with epilepsy. The yield of a single EEG (presence of epileptiform discharges) is approximately 50% which increases 92% in the fourth EEG. Hence, it is important to repeat EEGs if necessary but probably is unrewarding beyond four EEGs. The yield from any single EEG can be increased by recording it after the patient has been sleep deprived. An optimal recording in the setting of epilepsy should be for 30 minutes of awake time and 20 minutes of sleep. It is important to include activation procedures such as hyperventilation, photic stimulation and mental activation. Use of special electrodes such as sphenoidal electrodes and anterior temporal electrodes (T1 and T2) are useful when the electrical focus is suspected to be in the temporal lobes. The characteristic EEG patterns for different epileptic syndromes are described in the respective sections.

Video EEG

Video EEG is a refinement on EEG, wherein a person's EEG is recorded simultaneous with videography of physical state continuously for several hours to days. The time synchronisation between EEG and video helps one to correlate the physical state of the patient precisely with the EEG activity. Video EEG recording can help physicians to make electro-clinical correlations of various types of seizures, particularly in patients evaluated for potential surgical syndromes. Video EEG is helpful to distinguish non-epileptic psychogenic seizures from genuine seizures. Video EEG is indicated when the seizure semiology is not clear from the history or when detailed seizure semiology is necessary, as in the case of potential candidates for epilepsy surgery.

Neuroimaging

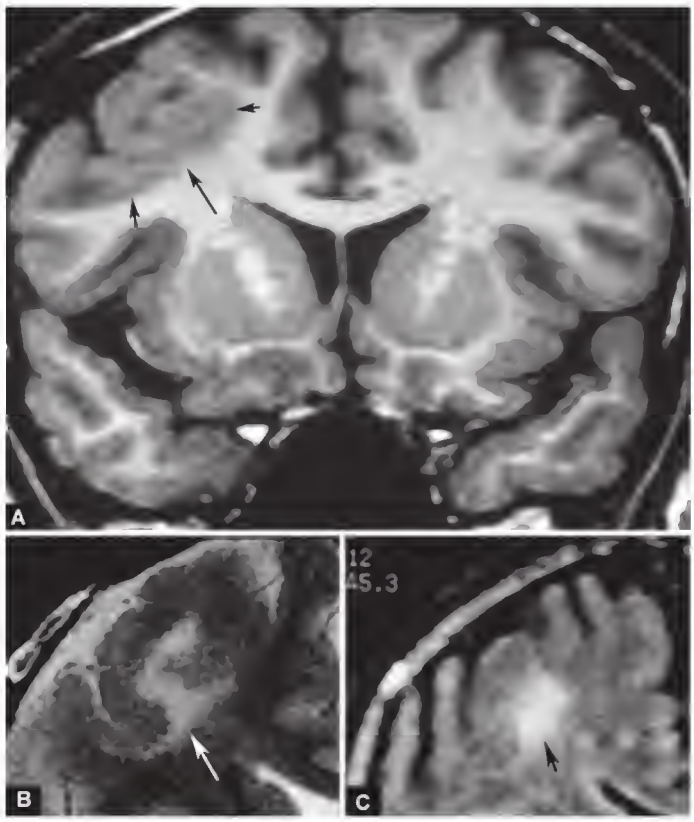
Neuroimaging is the corner stone in the classification of seizures and epilepsy syndromes. Calcifications of the brain and leptomeninges as in Sturge-Weber syndrome and tumours may occasionally be visible on good quality plain X-rays, yet a CT scan of the brain is ideal to delineate parenchymal calcifications as in neurocysticercosis, tuberculoma, tumours etc. Subtle changes like mesial temporal sclerosis and focal cortical dysplasia (**Figures 7A to C**) can be recognised only in high resolution MRI scans. Special sequences such as Fluid Attenuated Inversion Recovery images (FLAIR) can be particularly helpful to delineate these subtle changes. Ideally, all persons presenting with seizures should undergo brain imaging. Imaging is particularly indicated when the seizures have partial onset, they are medically refractory or when the semiology is changing over a period of time.

Functional Imaging

Functional imaging can contribute significantly in the evaluation of persons with epilepsy, especially when routine anatomical imaging is non-contributory.

Tc99m HMPAO SPECT

A gamma-emitting radioisotope (technetium 99) complexed to a ligand (hexamethylpropyleneamine oxime, HMPAO) is injected into the blood at the onset of a seizure. This low molecular weight compound readily passes the blood brain barrier and localises at the site of epileptogenesis proportionate to the increase in regional blood flow. The images of the resultant radiation is co-registered to an MRI or CT scan to generate images of the brain showing the epileptic focus. In order to correctly localise the focus, the T99 HMPAO needs to be injected at the beginning of the seizures. The interictal SPECT scans are not particularly useful in the evaluation of epilepsy.



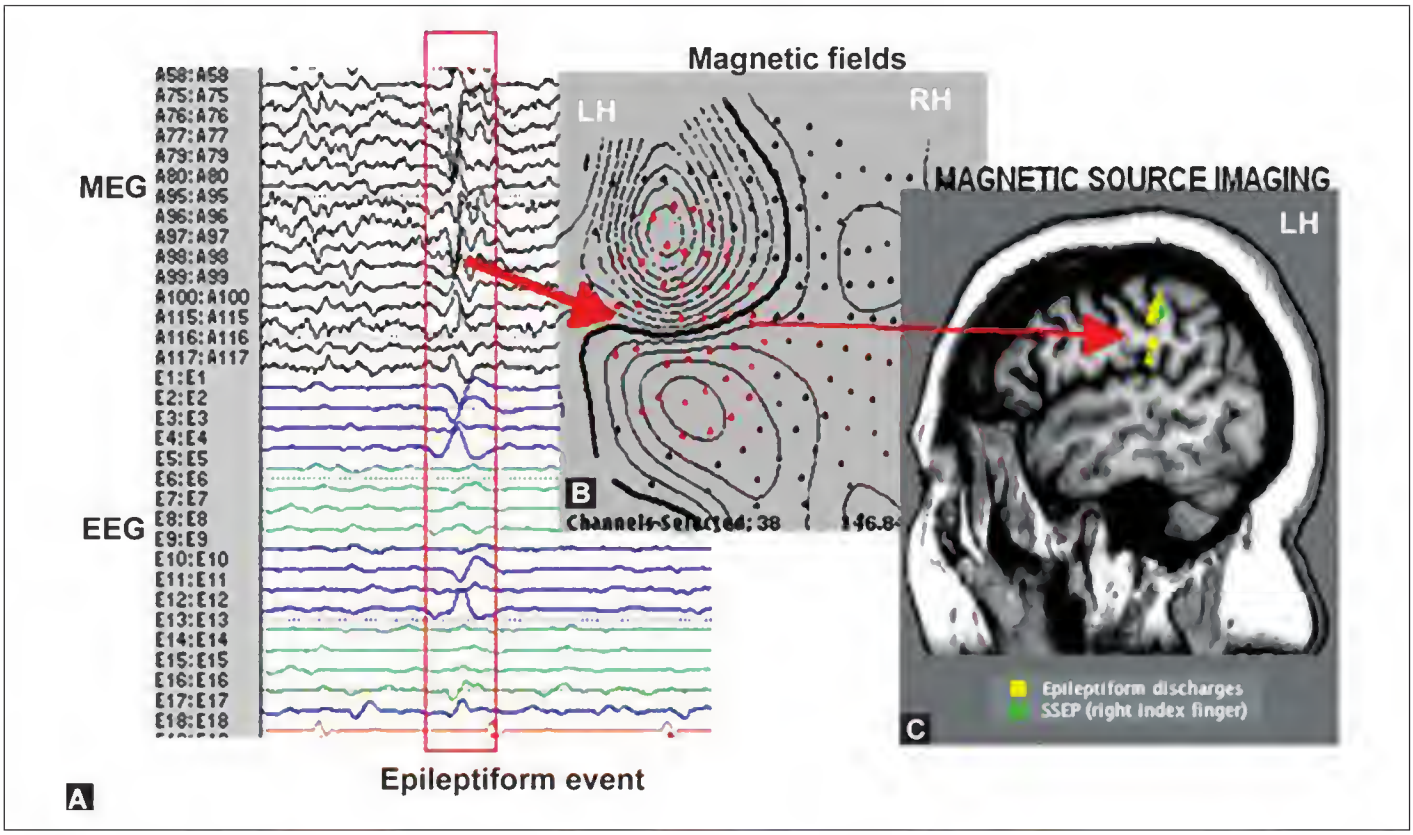
Figures 7A to C: FCD. (A) MRI brain showing abnormally thickened cortex (arrow)in T1 weighted image. (B) The abnormal pool of neurons appear as hyperintense signals in T2 weighted image, and (C) in fluid attenuated inversion recovery –FLAIR image.

Positron emission tomography

Fluorodeoxyglucose (FDG) is a glucose analogue that carries the positron emitting radioactive isotope fluorine 18 substituted for a normal OH group in the glucose molecule. When injected in the blood it is selectively taken up by neurons and glia that have increased metabolism. The positrons emitted from these focal areas indicate epileptogenic foci and can be easily visualised when co-registered with CT or MRI images. PET scans have the advantage that inter-ictal studies may reveal epileptic foci as hypometabolic cold spots even when the anatomical images are normal.

Magnetoencephalography

Magnetoencephalography (MEG) is a relatively new method of recording the magnetic field associated with electrical activity of the brain. These dipole sources are co-registered on MRI images to obtain the precise anatomical localisation. MEG has several advantages over EEG that records the electrical field of the brain. MEG can record the activity emanating from the banks of sulci, which are relatively invisible to EEG. Three-dimensional source of the dipole can be co-registered on MRI scan. Epileptic foci as well as functionally important areas like centres for language and cognitive activities can be simultaneously recorded (**Figures 8A to C**).



Figures 8A to C: MEG. (A) Magnetoencephalogram selected channels of MEG and corresponding EEG traces showing a epileptiform discharge. (B) The magnetic field related to this discharge is shown in and (C) the corresponding dipoles are marked out on the magnetic source image.

Functional MRI

Functional MRI (fMRI) is a powerful tool that can identify the precise localisation of the eloquent cortex such as language and memory centres in the brain. Most of the fMRI studies are carried out by the blood oxygen level dependent (BOLD) technique. Neural activity is associated with regional haemodynamic changes characterised by increase in regional cerebral blood flow and higher concentration of oxyhaemoglobin. Such fMRI maps closely relate to the functional areas of the brain. fMRI studies are particularly useful when a person with epilepsy is being evaluated for surgery. The spatial relationship of the epileptic foci to functionally eloquent areas would help the surgeon to tailor his surgery.

Neuropsychological evaluation

Neuropsychological evaluation includes assessment of certain global and lobar cognitive functions. A standard neuropsychological test battery would include tests for attention, frontal executive functions, memory, visuo-spatial functions, language and comprehension, higher visual and auditory functions. Memory assessment is particularly important when a mesial temporal resection including hippocampectomy is contemplated.

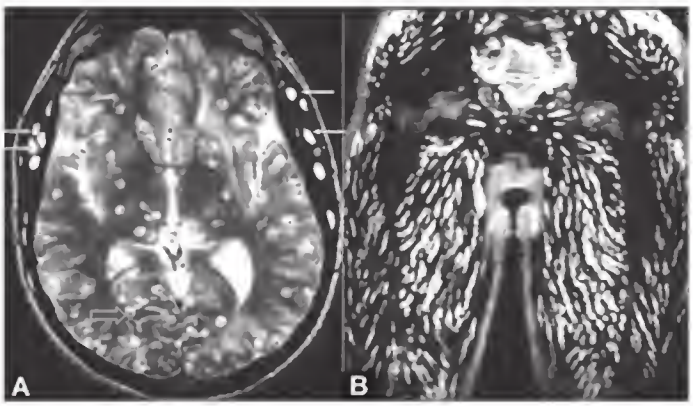
TREATMENT

Objectives

The primary objective of treatment is to prevent recurrence of seizures. The decision to initiate pharmacotherapy in a given situation depends on several issues, the type of seizure, its EEG correlate, severity of the seizures and disability or potential harms related to recurrence, age and occupation of the patient and co-morbidities (**Figures 9A and B**).

Anti-Epileptic Drugs

Introduction of phenobarbitone in 1912 marked the advent of appropriate anti-epileptic drug therapy. Since the 1990s, several new AEDs have been introduced in the market. The currently available drugs for pharmacotherapy of epilepsy are listed in (**Tables 5 to 7**). The dosage applicable to Indian population generally is about 25% less than the daily defined dose (DDD) as the average weight of adults in India is estimated as 50 kg.



Figures 9A and B: Neurocysticercosis. (A) MRI brain T2 weighted image showing widespread occurrence of cysts with central scolex in the brain parenchyma and interdiploic space and subcutaneous plane (B) MRI of gluteal region and thighs showing bullet shaped cysts in the muscular and subcutaneous plain. (Neurocysticercosis is a cause of epilepsy).

Table 5: Pharmacokinetic Properties of Commonly used Anti-Epileptic Drugs (AED)

AED	Half-Life (h)	Metabolism	Protein Bound Fraction (%)	Enzyme Induction
Phenobarbitone	100	90% hepatic	45	Inducer
Carbamazepine	8 to 22	90% hepatic	75	Inducer
Ethosuximide	60	65% hepatic	<5	Non-inducer
Gabapentin	5 to 7	95% hepatic	<5	Non-inducer
Lamotrigine	12 to 60	90% hepatic	55	Non-inducer
Levetiracetam	6 to 8	65% renal	<10	
Oxcarbazepine	8 to 10	90% hepatic	40	Mild inducer
Phenytoin	22	90% hepatic	90 to 95	Inducer
Pregabalin	6 to 7	95% renal	<5	
Tiagabine	5 to 13	90% hepatic	95	Non-inducer
Topiramate	19 to 25	30% hepatic	9 to 17	Non-inducer
Valproate	15 to 20	95% hepatic	80 to 90	Inhibitor
Zonisamide	63	70% hepatic	40	Non-inducer

Table 6: Dosage Schedule for Commonly Used Anti-Epileptic Drugs (AED)

AED	Starting Dose (mg/day)	Adult Dose (mg/day)	Dose Escalation	Paed (mg/kg/day)	DDD (mg)
Carbamazepine	200	600-1200	2-3 wks	10-30	1000
Ethosuximide	250	750-1000	2-3 wks	15-40	1250
Gabapentin	900	900-3600	2-3 days	30-90	1800
Lamotrigine	12.5	100-400	4-6 wks	5-15	300
Levetiracetam	500	1000-3000	3 wks	20	1500
Oxcarbazepine	300	900-1500	3 wks	20-40	1000
Phenobarbitone	30	60-180	2 wks	3-5	100
Primidone	125	1500	2 wks	10-25	1250
Phenytoin	100	200-450	3 wks	4-8	300
Pregabalin	150	150-600	1 wk	NA	300
Tiagabine	4	32	6 wks	NA	30
Topiramate	25	100-400	3-6 wks	5-6	300
Valproate	200	400-2400	3 wks	15-60	1500
Zonisamide	50	100-300	4-8 wks	NA	200
Stiripentol	50 mg/kg	100	4 wks	50-100	1000
Lacosamide	100	200-400	2-4 wks	NA	300
Clonazepam	0.5	2-8	4 wks	0.01	8
Clobazam	5	5-20	4 wks	0.5	20

DDD = Daily defined dose; NA = Not currently approved for use in children; Paed= Paediatric dose.

Single Seizure

The expert opinion is divided on whether to start treatment immediately after a single seizure. The overall risk of relapse after a single seizure is less than 50%. Nevertheless, the risk is higher when there is a definite epileptogenic lesion identified in the brain image or when EEG shows recurrent epileptiform discharges. The risk of relapse is relatively lower, when the interval between last seizure and evaluation is longer. The benefits as well as risk of starting treatment should be discussed with the patient along with the likely natural history of seizure for that patient so that the patient is involved in the decision making regarding treatment.

How to Start Treatment

Selection of a given AED for a patient is determined by the epilepsy syndrome, age, gender, occupation and the presence of co-morbidities. Most of the currently available AEDs have similar likelihood of achieving seizure remission when given in adequate dosage. Certain newer AEDs are not yet licensed for first line monotherapy in children. Drugs like sodium valproate may not be preferred for a young woman in reproductive age group, in view of its adverse reproductive effects and risk of teratogenicity, particularly at higher dosage. Enzyme-inducing AEDs such as carbamazepine, phenytoin or phenobarbitone may be avoided when a person is concomitantly using oral anticoagulants or oral contraceptive pills as it may adversely interact with these drugs. Topiramate may have to be avoided in patients with learning disability, speech problems and renal calcinosis as it can aggravate such conditions. Patients with severe liver or kidney dysfunction may require modification of AED dosage or selection of different AEDs (e.g. gabapentin) that may least interfere with these functions.

Drug levels are helpful, when non compliance with medications is suspected, during management of status epilepticus or when there are several co-medications that may interfere with the metabolism or bioavailability of AEDs.

Table 7: Selection of AEDs According to the Seizure Type

Seizure Type	First-Line Drugs	Second-Line Drugs	Other Drugs that may be Considered	Drugs to be Avoided (may Worsen Seizures)
Primary generalised tonic – clonic	Sodium valproate Lamotrigine Levetiracetam Topiramate	Clobazam Phenobarbitone	Primidone	Tiagabine Vigabatrin
Absence	Sodium valproate Lamotrigine	Clobazam Clonazepam Topiramate	Vigabatrin	Tiagabine
Myoclonic	Sodium valproate Levetiracetam	Clobazam Clonazepam Topiramate	Phenytoin	Lamotrigine
Tonic	Lamotrigine Sodium valproate	Clobazam Clonazepam Topiramate	Phenobarbitone	Carbamazepine Oxcarbazepine
Atonic	Lamotrigine Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate	Phenobarbitone	Carbamazepine Oxcarbazepine Phenytoin
Focal with/without secondary generalisation	Carbamazepine Lamotrigine Oxcarbazepine Phenytoin Topiramate	Clobazam Sodium valproate Levetiracetam Zonisamide	Clonazepam Phenobarbitone Primidone Gabapentin	

Rational Polytherapy

The objective of therapy is to manage epilepsy with a single drug, if possible. More than 60% of persons with epilepsy achieve remission with single drug therapy. Monotherapy carries lower risk of adverse effects, low cost, better compliance and remission rates and higher quality of life when compared to polytherapy. About a third of persons with epilepsy fail to respond to monotherapy. A second AED may be carefully selected as add on therapy. Ideally, the second drug should have a different mechanism of action, adverse effect profile or spectrum of seizure coverage compared to the first drug. Experience in India indicates that clobazam can be a good second drug to go with most other primary drugs. This AED is not approved for use in USA and certain other countries. Combinations of carbamazepine with sodium valproate or levetiracetam as well as combinations of lamotrigine with sodium valproate are found to be quite effective.

When to Stop Treatment

Epidemiological studies indicate that 60% to 70% of persons with epilepsy achieve seizure remission. According to data from general practice study of epilepsy in UK, 86% achieved 3 year remission and 68% achieved 5 year remission over a period of 9 years. About 60% of those who taper off and stop AED upon remission may relapse in the next 5 years. In children, normal growth and development, normal imaging findings and absence of inter-ictal discharges in the EEG are found to be good predictors of remission. Nevertheless, such clear markers of remission are not readily available for adults. A person who has remained seizure free for more than 3 years can be considered for AED withdrawal, provided the risk of a relapse is not excessive.

Management of Refractory Epilepsy

Large population-based studies have shown that about 20% to 30% of persons with epilepsy may prove to have seizures that do not respond to AED therapy. Their seizures may remain unabated with whatever drugs tried. Trials with newer AEDs may ameliorate seizures (50% reduction in seizure frequency) in about 20% to 40% instances. Recent studies have shown that this group of medically refractory epilepsy consists of several syndromes that respond well to epilepsy surgery.

Epilepsy Surgery

It is useful to understand the various zones relevant for surgical syndromes. A lesion responsible for the epilepsy such as gliosis or granuloma is considered as lesion zone. Seizure onset zone refers to that part of the cortex where the electrographic origin of seizure occurs. Epileptogenic zone is that part of the brain responsible for the seizure genesis. It is often overlapping or close to the lesion and needs to be excised to achieve seizure freedom. Symptomatic zone is that portion of the brain responsible for the initial ictal symptomatology. The symptomatic zone can be adjacent to the seizure onset zone or epileptogenic zone when the latter are in relatively silent areas of the brain. The functional deficit zone is that part of the brain responsible for the functional deficits associated with a seizure. The main objective of pre-surgical work up of a patient is to map out the epileptogenic zone as precisely as possible. This may require imaging, video EEG and occasionally intra-cranial recordings.

Recent studies indicate that certain epilepsy syndromes such as mesial temporal lobe epilepsy, focal cortical dysplasia, developmental tumours associated with epilepsy, Rasmussen's encephalitis selectively respond to appropriate surgical treatment. The indications for pre-surgical work up include the occurrence of frequent non-disabling seizures in spite of optimal AED therapy. The operational definition for such a condition is presence of two or more disabling partial or generalised seizures in 6 months, in spite of treatment with two or more appropriate AEDS therapy. Surgery for epilepsy could be broadly categorised as curative procedures aimed at achieving seizure remission and palliative procedures aimed at ameliorating seizure burden (**Table 8**). The primary objective of definitive epilepsy surgery is to remove sufficient amount of epileptogenic zone without compromising any eloquent cerebral functions in order to achieve permanent seizure remission. This goal can be achieved by systematically evaluating medically refractory epilepsy through several phases of non-invasive and invasive evaluation.

Table 8: Surgeries Performed to Ameliorate Epilepsy

Curative	Palliative
Anterior temporal lobectomy	Corpus callosotomy
Selective amygdalo-hippocampectomy	Vagus nerve stimulation
Lesionectomy	Multiple subpial transection
Focal cortical resection	
Lobar resection	
Multilobar resection	
Hemispherotomy/ Hemispherectomy	

The baseline non-invasive evaluation would include a good quality MRI imaging to look for structural lesions (e.g. mesial temporal sclerosis, focal cortical dysplasia or other localised lesions) and video EEG. The interictal and ictal data from the video EEG and imaging should support a coherent electro-clinical syndrome with an epileptogenic zone localised to a small area that can be resected without unacceptable adverse effects. In the case of temporal lobe epilepsy, this would involve triangulation of stable ictal semiology, focal inter-ictal epileptiform discharges, mesial temporal sclerosis and ictal onset to one temporal lobe. About 80% of patients who fulfil these criteria may achieve complete seizure freedom after standard anterior temporal lobe resection with amygdalohippocampectomy. Invasive monitoring with electrode array deployed in the subdural space (subdural strip or grid electrodes) or in the cortex (depth electrodes) may be necessary when recordings from the scalp are equivocal. Functional studies like ictal SPECT and inter-ictal PET scans can prove helpful in identifying the epileptogenic zone when the MRI fails to reveal any focal pathology. Such persons may require additional proof from invasive monitoring before they are offered epilepsy surgery. Assessment of memory by neuropsychological examination or by fMRI or intra-carotid amytal test would be necessary in persons considered for unilateral temporal lobe resection when there is suspicion that the contralateral temporal lobe is dysfunctional. Language lateralisation by fMRI, MEG or neuropsychological tests is necessary when the resection is likely to be in locations close to language areas of the brain.

Other Means

Persons with medically refractory epilepsy who are not candidates for epilepsy surgery can be offered other treatments.

Ketogenic diet

Ketogenic diet is a special diet, low in carbohydrate and high in fat, that induces a metabolic state similar to starvation ketosis. Several observational studies have shown that more than half of children with intractable epilepsy responded to ketogenic diet by reduction in seizure frequency by 50%. Ketogenic diet therapy had been found to be most helpful for children.

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a simple procedure in which the left vagus nerve is stimulated in the cervical region with a subcutaneously implanted pacemaker. The beneficial effects of VNS are not restricted to any particular seizure type but only 10% patients achieve seizure freedom.

Deep brain stimulation

Stimulation of the anterior nucleus of the thalamus (SANTE) with a stereotactically implanted electrode from a subcutaneously located pacemaker is undergoing clinical trials.

Responsive neurostimulation

In this system, a set of electrodes are implanted over the epileptogenic seizure onset zone of cerebral cortex in order to continuously monitor for onset of a seizure. As soon as an electrographic onset is detected, an electric impulse is delivered over that site to quench the electrographic seizure from progressing to a clinical seizure.

STATUS EPILEPTICUS

Status epilepticus (SE) is a common neurological emergency that occurs in about 6 to 18 persons per 100,000 population. The first operational definition of SE (American Epilepsy Society, 1993) defines SE as a single seizure lasting more than 30 minutes or the occurrence of two or more seizures, without recovery of consciousness in between. Based on more recent observations, the time duration for classifying a generalised tonic clonic seizure as status epilepticus is reduced to 10 minutes. The subgroups of patients with SE who fail to respond to standard treatment (~ 25%) are classified as refractory SE. They would require more aggressive therapy. Status epilepticus is broadly classified into convulsive and non-convulsive SE and is further sub-classified according to the seizure type.

The aetiology for SE may vary according to the age of the person and the geographic location (**Table 9**).

Sudden AED withdrawal, as in non-compliance, is the most common cause of SE in most locations. CNS infections are more frequent causes of SE in children than in adults. Cerebral malaria is an important cause for SE in endemic areas. CNS infections contribute to SE in patients with HIV infection. Alcohol excess as well as alcohol withdrawal can be important causes in communities where alcohol use is prevalent. Co-medication with certain antibiotics such as penicillins, cephalosporins, quinolones (particularly ciprofloxacin), anti-histamines and anti-depressants can predispose to SE.

Table 9: Causes of Status Epilepticus According to Age

Children	%	Adults	%
Infection and fever	35.7	Stroke	25
Medication changes	20	Medication change	18
Unknown	9	Alcohol/drugs	13
Metabolic precipitants	8	Anoxia	12
Congenital precipitants	7	Metabolic	9
Anoxia	5	Unknown	8
CNS infection	5	Infection	6
Trauma	3.5	Tumour and trauma	4.5

Convulsive SE (CSE) is relatively easy to diagnose because of the prominent motor manifestations and loss of consciousness. Nevertheless in certain situations, psychogenic status epilepticus, decerebrate spasm, tetanus, malignant hyperthermia or neuroleptic malignant syndrome can mimic CSE. Non convulsive SE may present as subtle alteration of sensorium or behavioural changes and an EEG only may reveal the diagnosis.

Management of Status Epilepticus

The first step in the management of SE is to ensure the safety of the patient. The subject should be moved to a location where there is less chance of injury. Airways should be cleared but it is unwise to force any object into the mouth of a convulsing patient as it may cause more harm. Gentle suction can be applied to remove the saliva and froth, and oxygen can be administered if it is available. Two secure intravenous cannulae can be placed for fluid resuscitation and pharmacotherapy. Blood samples may be drawn for biochemical analysis and drug levels (if available). In order to achieve early remission, it is important that the treatment is initiated early, preferably at home or in the pre-hospitalisation phase itself. Buccal or intranasal administration of midazolam or rectal administration of diazepam had been found to be an effective pre-hospital management step in clinical trials. The drug of choice for in-hospital management of SE is intravenous lorazepam. Intravenously administered lorazepam has longer duration of anticonvulsant effect (>6 hours) than diazepam (20 minutes) and carries lesser risk of respiratory depression. Lorazepam should be stored in light-proof containers, and should be restocked every 4 months to 6 months. Intravenous fosphenytoin (pro-drug of phenytoin without the propylene glycol carrier) is the best second-line therapy in SE. It is quickly dephosphorylated to phenytoin when given intramuscular or intravenous. Fosphenytoin has several advantages over phenytoin. It can be infused using standard intravenous solutions, whereas phenytoin should not be given in dextrose-containing fluids (because of drug precipitation). It can be given intramuscularly if required. Fosphenytoin can be infused at a faster rate (150 mg/minute) than phenytoin which carries some risk of cardiac arrhythmia and hypotension. The pharma-cokinetic parameters of commonly used AEDs are given in **Table 10**.

Patients who fail to respond to these two standard drugs are designated as refractory SE. They would require more aggressive management, preferably after securing endo-tracheal intubation and ventilator assistance. If ventilator support cannot be ensured it would be worthwhile administering intravenously non-sedating AEDs such as

sodium valproate or levetiracetam. Recent clinical trials indicate that these two drugs have the potential to abort SE even when the primary drugs have failed.

Table 10: Pharmacokinetic Parameters for Commonly Used Drugs for Status Epilepticus

Drug (route)	Initial Dosage	Latency (Minutes)	Duration (Hours)
Lorazepam (IV)	4 to 8 mg	3 to 10	12 to 24
Diazepam (rectal)	0.5 mg/kg	5 to 15	<1
Diazepam (IV)	10 to 20 mg	1 to 5	<1
Midazolam (IM)	0.15 to 0.3 mg/kg	5 to 10	<1
Midazolam (buccal)	0.3 mg/kg (max 10 mg)	5 to 10	<1
Midazolam (IV)	0.2 mg/kg	10 to 30	12 to 2
Phenytoin (IV)	20 mg/kg	10 to 30	12 to 24
Fosphenytoin (IV)	20 mg/kg PE	10 to 30	12 to 24
Phenobarbitone (IV)	20 mg/kg	5 to 30	48 to 72
Sodium Valproate (IV)	30 mg/kg	<20	8 to 24

Latency = Time interval between commencement of infusion and onset of action.
Duration = The duration of time from onset of infusion for which the drug may maintain adequate anticonvulsant property in the blood.
PE = Phenytoin equivalents; IV = Intravenous.

If patients have failed the above AEDs, they would require management after securing endotracheal intubation and ventilation in an ICU. Intravenous infusion of pentobarbitone, thiopentone, midazolam or propofol is another option at this stage. Most often the dosage is tailored to suppress all clinical seizures and achieve burst suppression pattern in the EEG. Such patients in SE require close monitoring of various metabolic parameters and organ functioning as they are prone to multiple organ dysfunctions.

PREVENTION OF EPILEPSY

Head trauma accounts for 10% of all epilepsy. Safety at work place and on road, especially use of helmet while driving can reduce the risk of head injury and subsequent occurrence of epilepsy. Neurocysticercosis is the most important cause of epilepsy in several parts of India and other countries (**Figure 9**). A substantial proportion of this can be prevented by controlling taeniasis.

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20.6 Disorders of Speech

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INTRODUCTION

Speech, communication and language disorders are multiple and heterogeneous (**Table 1**). Aphasia is one of them and involves a deficit in expression (motor), comprehension (sensory) or both. The modes of communication affected could be verbal, written or both and other unusual ones such as sign language in deaf mutes. At the core of aphasia lies a disturbance in language functions.

Table 1: Disorders of Speech Language and Communication

Type of Disorder	Comment
Disorders of phonation Aphonia Dysphonia	Almost always due to laryngeal dysfunction (local, non neurogenic or neurogenic paralysis of vocal cord muscles)
Disorders of articulation Anarthria Dysarthria	Non neurological local causes Neurological causes Muscles: polymyositis Neuromuscular: myasthenia gravis Neuropathic: GB Syndrome Brainstem, cerebellum, basal ganglia: CVA, neoplasia, infection, degeneration (Parkinsonism), trauma, developmental
Disorders of fluency Stammering (Stuttering) Cluttering	Usually developmental No visible underlying pathology in most
Disorder of language Aphasia Alexia/Dyslexia Agraphia	Cortical speech areas: Stroke Other causes less common Developmental: mental retardation, cerebral palsy Degenerative: Young age: Autism, Rett's syndrome, leucodystrophies and poliodystrophies Old age: Alzheimer's and other dementias

Language is an instinct whose biological substrate is also conducive to other learned traits like reading, writing and probably mathematics and music. This chapter mainly focus on aphasias, that too following cerebrovascular accidents. Other disorders will be briefly covered.

These subjects are common and contribute significantly to disability adjusted years of life (DALY's). Seminal advances in theoretical understanding and practical applications have occurred in last two decades improving prospects of rehabilitation. Research into these disorders provides crucial insight and better understanding.

EPIDEMIOLOGY AND AETIOLOGY

Aphasia occurs in about 25% of patients with stroke. Non-fluent aphasia predominates in young patients suggesting an anterior lesion, while in elderly patients fluent aphasia is attributed to more frequent posterior infarcts.

Global aphasia would suggest occlusion of internal carotid artery (ICA) or stem of middle cerebral artery (MCA) or large deep basal ganglionic plus thalamic haemorrhage. Most aphasia syndromes occur due to infarctions in left MCA territory with the exception of transcortical motor aphasia [anterior cerebral artery (ACA)] and pure alexia without agraphia [posterior cerebral artery (PCA)]. Transcortical aphasia syndromes (those with preserved repetition) suggest ischaemic infarctions in watershed territories between ACA-MCA-PCA, thereby disconnecting core speech centres in sylvian region from more peripheral association cortices in fronto-parietal-occipital regions. Haemodynamic compromises, like those in severe sustained hypotension, reduced cardiac output and proximal vascular occlusion in aorta and carotid arteries would typically predispose to lesions in watershed areas.

Aphasia associated with head injury can develop hours or even weeks after the initial event. It is most commonly associated with right side blunt orbito-frontal trauma with a contre-coup left temporoparietal injury. Trauma pathology trends to be less localised than ischaemic stroke (except gun-shot wounds), hence aphasic syndromes are often not pure or classical, but rather mixed with signs of more diffuse pathologies like altered sensorium, delirium and amnesia.

Aphasia due to tumours of left cerebral hemisphere will usually have gradual onset, poor syndromic phenotype and additional clinical deficits due to cerebral oedema and increased intracranial pressure

DEVELOPMENTAL DISORDERS

In autism spectrum disorders (more in boys) and Rett' syndrome (girls) there is normal development up to the age of 18 to 24 months, followed by rapid and severe regression of cognitive milestones. Speech communication is severely affected. Developmental dyslexias are rather common (5% or more) example of learning disability in reading and writing that persists throughout life, though somewhat overcome by extra-laborious effort and training. Verbal communication remains fine but the rules governing relationship between written symbols and their sound are not well developed in dyslexia. They remain slow readers.

Language impairment is an important diagnostic feature of dementias. Generally we presume that disease like Alzheimer's dementia are a diffuse pathology, hence language deficits likewise will also be of a general nature, rather than resembling a well defined syndrome. Yet there are a few degenerative dementing disorders whose pathology remains focal or restricted. For example, primary progressive aphasia and semantic dementia.

ANATOMICAL SUBSTRATE OF APHASIA

Approximately 90% of people are right-handed and 10% are non right-handed (left-handed and ambidextrous). The left

hemisphere controls speech and language functions in 98% of right-handed persons and also in about 50% of the non right-handed persons. These facts explain the low incidence (2% to 3%) of crossed aphasia, i.e. aphasia occurring in a right-handed person with a lesion in the right cerebral hemisphere.

The association cortex in the region of the left sylvian fissure is mainly responsible for language capability. Holistic models maintain that the entire region, or at least large portions of it, acts as a whole to support all language functions. Localisation models argue that specific language process are carried out in relatively restricted areas of this region.

Auditory perception occurs in superior temporal gyrus but recognition of meaningful words by decoding the noise takes place in Wernicke's area. The later is linked to tertiary association cortices in supramarginal and angular gyri posterosuperiorly which assign and store word meanings. All this information has to reach Broca's area anteriorly for repetition and spontaneous speech. The encoding of information into pronounceable or writable words and sentences is accomplished in Broca's area which then executes the motor programme for muscles of articulation. For reading comprehension visual stimuli from occipital cortex reach angular gyrus.

Many *subcortical structures* (posterior thalamus, basal ganglia, deep white matter, temporal isthmus, insula) mainly on left or dominant side, are an important and integral component of language circuits. Aphasic syndromes due to discrete subcortical lesions are well described, but they are generally less precise, not fitting into well established syndromes and usually recovers well in short period.

The right hemipshere has some rudimentary linguistic capability, which can be improved by training and is probably responsible for significant proportion of recovery. Emotional speech, stress, tone, melody and rhythm or prosody of speech (both in production and comprehension) and use of metaphor, humour, sarcasm and irony as means of communication are in greater control by right or non-dominant hemisphere.

CLINICAL APPROACH TO APHASIA

One must begin with patient's mother tongue and other languages, handedness and level of literacy. The handedness should be assessed by enquiring about the preferred use of a hand for many activities of daily-life in addition to eating and writing.

Associated neurological deficits like hemiparesis, facial paresis, visual field defects, hemisensory loss and amnesia should be documented. A brief examination can be completed in 5 to 10 minutes and will provide basic data about presence of aphasia, its severity and a tentative diagnosis of aphasia syndrome. More detailed assessments spanning over 1 to 2 hours in one or more sessions will be required in most subjects for comprehensive profiling and planning the rehabilitative speech therapy.

Oral Expression, Articulation and Fluency

Make your observations throughout history which try to ask questions which force the patients to utter some sentences. Like tell me about your illness, your family, the work done by you at your job.

An adequate sample of narrative speech is needed to detect the types of deficits. One can use picture description task. Aphasics produce incomplete, halting, sparse description, failing to grasp the totality of the environment despite being repeatedly pointed to the different parts of the picture.

Defective articulation and phonation are recognised during ordinary conversation. Test phrases or attempts at rapid repetition of consonant clusters bring out particular abnormality. Dysarthria is an important and common deficit in many aphasics particularly those with non-fluent speech. Pure dysarthria, however, occurs in many disorders other than aphasia. They involve basal ganglia (e.g. Parkinsonism), descending corticospinal pathway (e.g. pseudobulbar palsy), cerebellar hemispheres and connections to brainstem (e.g. stroke, demyelination, tumours), cranial nerve nuclei and trunks of 5th, 7th, 9th to 12th nerves (e.g. infective polyneuropathy), muscles of articulation in pharynx, palate, face, tongue (e.g. myasthenia gravis). Dysarthria in aphasic patients is almost always accompanied by other deficits in language communication.

Reduced verbal output can be described as reduced phrase length, speaking monosyllables or single words or short sentences. Severe non-fluent aphasics some times repetitively utter a single word intoning it differently to convey some meaning like yes!, yes?, y..y..es ?.. Other manifestations of reduced verbal output are delay in initiation of a response, increased effort or apparent strain while generating the response, pauses in between words and sentences, interruption and word finding difficulties. The non-fluent speech in Broca's aphasics is also described as *'agrammatic'*. Grammar means rule based use of many 'function words' (conjunction, articles, prepositions, auxiliaries) to join 'content words' (nouns, verbs, adjectives) into phrases and sentences. Agrammatic speech shows absence or paucity of function words. The short phrases are composed of content words only. Meaning is conveyed somehow in a manner resembling 'telegraphic language' as if to economise on words.

Circumlocution is replacing the unavailable word with round about description. *Paraphasia* exists, when instead of a word to be generated (target-word), another word is used. The distortion in the abnormal response word may be phonemic (sound related) or semantic (meaning related). *Neologism* means sound utterance of words, which do not exist in the vocabulary of the language being used by the patient. *Jargon* is a string of expression (verbal or written), which does not convey any meaning. Many of the so-called 'words' in a jargon are neologisms. Some others may be true words but are used in a jumbled up way without any context and without any grammatical rules hence no information is carried.

A small but significant minority of aphasics has *fluent but empty* speech. It is contrasting and opposite to non-fluent agrammatic speech. It appears to be fluent, effortless, with normal melody, accent, prosody and mannerisms. On close observation, however, speech is not normal. Phrases and sentences are of normal length or sometimes overly lengthy without a sense of completion. There are many paraphasias, circumlocutions and abundance of function words or grammar words whose information load is low. The content words, which really carry information, are in paucity and used flouting the rules of

grammar. Jargon is common. Such patients have profound defects in auditory and reading compression. Classical example is Wernicke's aphasia.

Auditory Comprehension

Auditory comprehension is tested at one word level, sentence level and discourse level. At one word level the examiner speaks out the word at a slow and regular rate without repetition and asks the patient to point to corresponding picture or real object or body part. We should resist the temptation to act out the command ourselves. Patient's performance is scored in terms of correct answers with respect to help or cues and time latency.

Sentence level comprehension is tested by multiple step commands : 'fold this piece of paper and put into pocket', 'pick up the piece of cloth, put it into the glass and then invert the glass on the table'. Silly questions can be asked for which only yes or no answers are possible. Example: does the stone sink in water?, is elephant larger than an ant? A short story is narrated and questions are asked based on it.

Sentence level comprehension tasks also involve picture sentence matching. There can be one sentence and many picture choices or vice-versa.

Repetition

The examiner asks the patient to repeat after him words and sentences. Initial stimuli are simple, short, common, and later they are made long, hard to pronounce and uncommon. The patient may totally fail, remain mute or come out with wrong responses. The errors may be sound disorders, incomplete responses, deletions or paraphasias. Some patient may perform fairly well on tests of auditory comprehension and also do well during daily life but fail miserably on repeating simple words or phrases (conduction aphasia). In contrast patient with transcortical sensory and mixed aphasia repeat long complex phrases mechanically or slavishly but do not follow or extract a bit of meaning from whatever they are listening and repeating.

Naming

We begin with naming objects, pictures, body parts or persons. Examiner puts his finger on the object or photo and asks the patient to name it. Many patients with aphasia fail in different manner. Some may not come out with any response. There may be delay. The response word may be altered yet be related to target word either by sound (phonemic paraphasia) or by meaning (semantic paraphasia). The response word may be phonemic jargon (non word) or semantic jargon (dictionary word but totally unconnected). Some patients may describe the word in a round about way (circumlocution). Cues or helps can be given. Phonemic cue means, uttering first one or two phonemes of the word or producing its rhythm. Semantic cue involves giving hint about synonyms or attributes of that word. In case of persistent failure, the examiner then offers the answer in two ways:

- Suggesting a wrong answer and asking if it is correct or not.
- Suggesting the correct answer and again looking if patient accepts it or not. In patients with total disruption of semantic memory of lexicon or access to it the offered correct answers are not accepted.

The naming of objects can be made category-wise. Pictures or photographs of action verbs are one important category, others being colours, geometric figures, numbers, letters, body parts.

Reading

The subject is made to demonstrate ability to recognise, match and discriminate the graphic symbols of alphabets. Then he is asked to read aloud words, phrases or paragraph without paying attention to the meaning. Reading comprehension involves word-picture or word-object matching and carrying out some commands written on a paper (e.g. touch your hair, make a fist, etc.). Somewhat difficult task is to fill in the blanks in progressively difficult sentences from amongst a choice of detractors. Large paragraphs (unseen passage) are given to read and written questions are asked based on it. A mixed list of words and non-words is provided and patient is asked to separate them out.

Writing

If the motor dexterity of writing hand is fair it is expected that patient would be able to reproduce his premorbid handwriting, at least in such mechanical tasks like copying from written stimuli, writing to dictation and serial writing of automatised sequences (like name, address, numbers, alphabets, weekdays, months). But patients with non-fluent aphasia fail in written expression too. In addition to various aspects of non-fluency (reduced output, laborious start, pauses, agrammatism), the mechanics of writing and calligraphy are also distorted. Fluent aphasics may write legibly but the written output will exhibit similar deficits of emptiness, paraphasias, jargon, circumlocution, etc. Picture naming, object naming, describing the events going on in a painted or sketched scene are further tests of written expression.

CLASSIFICATION AND SYNDROMES

The classical aphasic syndromes have been grouped on the basis of speech and language performance in stroke survivors. Their distinction depends on the presence or absence of a constellation of speech behavioural aspects. The syndromes may be artefactual, arbitrary or artificial. New ways of classifying and describing aphasic phenotypes have been proposed. Yet they serve a useful purpose (**Table 2; Figures 1A to D and Figures 2A to D**). Diagnosing an aphasia syndrome may have localising value. Prognostication can be attempted on their bases.

Classification is a useful tool for summarising the patient's symptoms and for capturing some regularities of language disruption due to the anatomical peculiarities of the brain vessels. However, there is overlap and many aphasias are unclassifiable.

DIFFERENTIAL DIAGNOSIS OF APHASIA

Aphasia is an acquired disorder in a person who had attained certain degree of speech development. Hence *developmental disorders of speech* are not aphasia. Many children with brain damage (antenatal, perinatal, postnatal) and mental retardation learn speaking, reading and related skills late or incompletely or not at all. They are not aphasic.

A *developmental suppression of the motor fluency* of speech is very common. Stuttering or stammering is not a part of the



A

Clinical: Sparse, halting speech, often misarticulated, frequently missing function words and bound morphemes. Disturbance in speech planning and production mechanism.

Anatomy: Primary posterior aspects of the 3rd frontal convolution and adjacent inferior aspects of the precentral gyrus. Prerolandic branch of middle cerebral artery. A lesion restricted to classical Broca's area causes a mild reversible non-fluent aphasia. More severe and well known type of classical Broca's aphasia requires a much larger lesion surrounding regions other than Broca's area.



B

Clinical: Poor reading and auditory comprehension, fluent speech with phonemic, morphological and semantic paraphasias. Disturbance of permanent representations of the sound structures of words.

Anatomy: Posterior half of the 1st temporal gyrus and possibly adjacent cortex.Posterior temporal branch of left middle cerebral artery.



C

Clinical: Disruption of all language processing components and severe diminution or loss of all language.

Anatomy: Large portion of the peri-sylvian association cortex. Combined lesions involving Broca's and Wernicke's area. Infarction due to occlusion of stem of left MCA or internal carotid artery.



D

Clinical: Repetition is severely impaired out of proportion to verbal expression, fluency and comprehension, literal paraphasic errors are common with frequent attempts at self correction.

Anatomy: A disconnection between Wernicke's and Broca's area due to arcuate fasiculus, a white matter tract in deep temporal lobe. Also due to lesion in superior temporal or inferior parietal region.

Figures 1A to D: Various forms of aphasia and their neuroanatomical lesions (Peri-sylvian region). (A) Broca's aphasia; (B) Wernicke's aphasia; (C) Global's aphasia; (D) Conduction's aphasia.

aphasia rubric. Early damage to the function of hearing influences the development of speech and an extreme example is *congenital deaf-mutism*.

Pure dysarthria hampers the pronunciation and intelligibility of speech but language, vocabulary, grammar, reading, writing, and auditory comprehension are intact. In severe cases, hardly any sound emanates from the articulatory apparatus and results in *anarthria*. *Disorders of phonation* occur due to diseases of the larynx, vocal cord and respiratory weakness (no enough air during expiration).

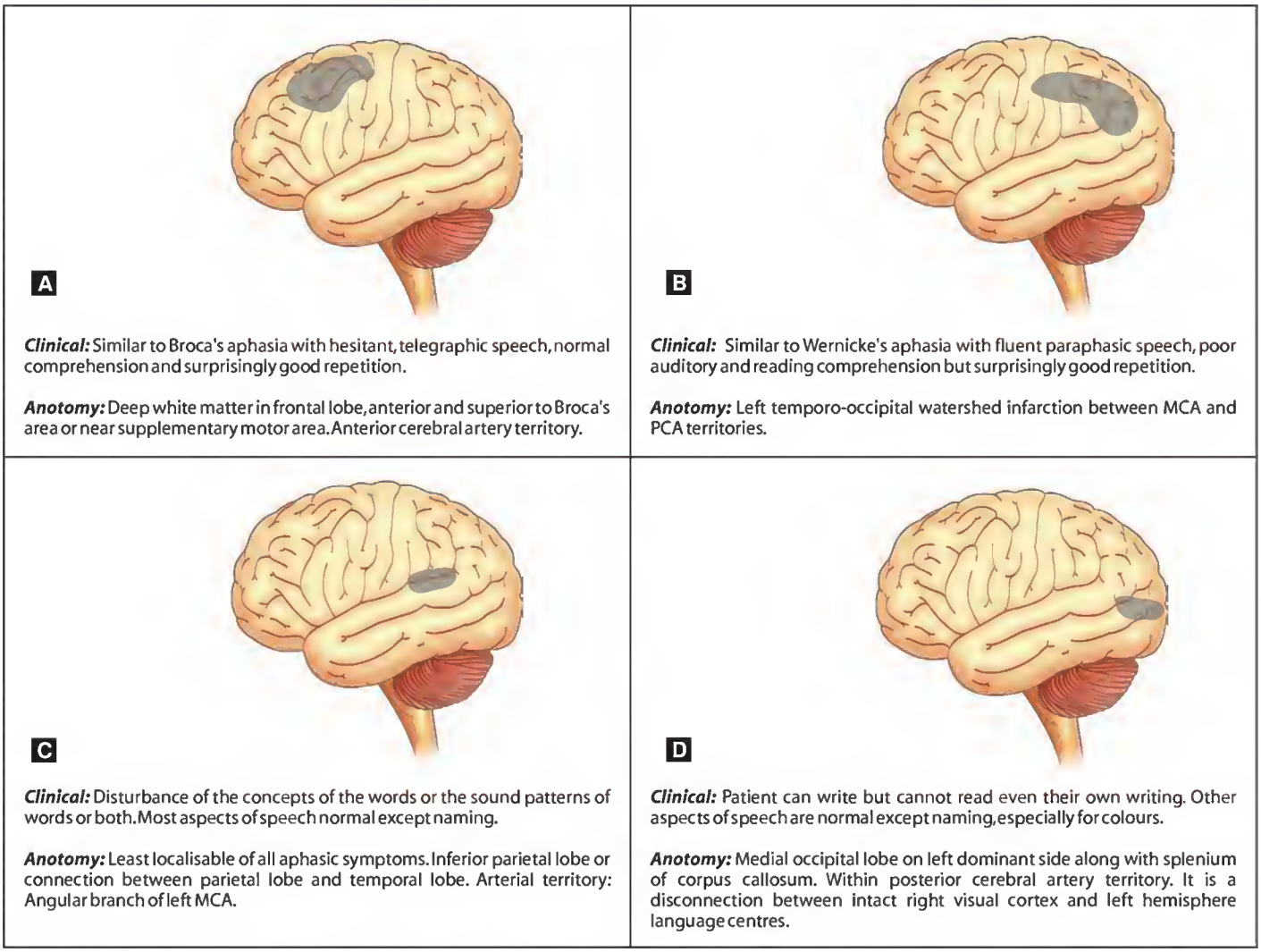
In all the above conditions, the cortical areas concerned with cerebral organisation of linguistic functions are intact. Written expression (if the patient is literate) is normal while in aphasia written and verbal deficits almost always run parallel to each other. Auditory and/or reading comprehension are also normal while in patients with aphasia these are often abnormal.

Regression of normal acquired speech and communicative ability, and other cognitive functions occur in a group of *pervasive disorders in children* such as autism, Asperger syndrome and Rett syndrome. Landau-Kleifner syndrome in children is also a disorder of acquired aphasia and epilepsy.

Patients with *conversion reaction* may become mute, speak in whispers or in a bizarre, abnormal manner. Rarely, some patients may behave as if they are not able to listen or comprehend any speech. This should raise the possibility of *malingering* or *Munchausen syndrome*.

Speech in *psychosis*, particularly *schizophrenia* is sometimes confused with aphasia. Verbal or written output may be sparse or excessive, bizarre and absurd. Responses may sound like jargon or other less severe distortions described in oral expression. Flight of ideas, pressure of speech and evasive, tangential answers may create an impression of logorrhoeic speech or Wernicke's aphasia with defects in auditory comprehension. Howsoever absurd the thoughts and speech in a patient with schizophrenia, grammar and logic are largely retained, which is not the case in those with aphasia.

One of the important prerequisites for a definition of aphasia is a *state of normal alertness or sensorium* and normal intellectual or cognitive functions. It does not mean that the two cannot coexist but in such a situation it becomes difficult to decide about the relative contribution of each of them to the clinical deficit. Patients who are stuporouse, drowsy or have an acute confusional state or delirium may be labelled as aphasic due to



Figures 2A to D: Various forms of aphasia and their neuroanatomical lesions (peripheral to peri-sylvian region). (A) Transcortical motor; (B) Transcortical sensory; (C) Anomic; (D) Alexia without agraphia.

delayed and incorrect responses. Irrelevant muttering may be mistaken as fluent jargon or vice versa. Aphasic patients with defective auditory comprehension may be wrongly considered as having *hearing impairment*. Loss of the naming function in aphasia is commonly mistaken as *loss of memory*. The contrary may also be true. Patients with amnesia, dementia and Korasokoff psychosis may involuntary fill in the gaps in their memory and be diagnosed as suffering from anomic or Wernicke's aphasia.

A patient may fail to comply with a verbal command due to *motor apraxia* and not because of a defect in auditory comprehension. Visual or tactile *agnosia* may be responsible for a naming defect rather than aphasia.

Total loss of speech or *'mutism'* is a clinical situation caused by a very wide variety of disorders, aphasia being only one of them. Congenital deaf mutism is easily identified since early childhood. Patients with severe Broca's and global aphasia may be mute for many initial days to weeks. Anarthria and aphonia (laryngeal) may resemble muteness. Frontal lobe dysfunctions are known to cause akinetic mutism. Psychogenic syndromes (conversion or dissociative states, catatonia) can also render a person totally speechless for a variable period of time.

NEUROIMAGING IN APHASIA

Clinicoanatomical correlations between lesions depicted on imaging and the aphasia profile. In the majority of patients these are along expected lines. However, about 30% exhibit misfits such as non-fluent aphasias with retro-rolandic or posteriorly placed lesions, fluent aphasias with prerolandic or anterior lesions, instance of the lesion being present in an unexpected area, discrepancies between lesion size/volume and clinical severity of and recovery from aphaisa. The most probable explanation is inter-individual variations in the anatomical substrate for language functions in brain. Factors, such as handedness, dominance, age, sex, literacy and multilingualism, may play a role in the degree of bilateral representation and other anomalous organisation of speech function.

MRI has a high sensitivity and is better for three-dimensional volumetric analysis of various discrete areas of the brain. Functional neuroimaging (fMRI), PET, SPECT) techniques are now paving the way for defining discrete neural modules or networks (not areas or centres) concerned with cognitive functions such as speech. Well-defined linguistic tasks are performed by subjects while imaging study results are compared before, during and after the task.

NEUROLINGUISTICS AND COGNITIVE NEUROPSYCHOLOGY

Linguistic analysis refers to theoretical concepts such as phonology (sound patterns, phonemes, phonetic features), morphology (word formation, morphemes), syntax (rule-based grammar, function words), semantics (lexicon, dictionary words,

their meaning) and discourse (dyadic conversation, paragraphs, long speeches).

The classical anatomicoclinical approach provided knowledge about the relationship between lesion and function. Neuropsychologist found the existence of many selective deficits, suggesting that the brain is organised into distinctive systems or modules of relative functional independence.

Linguistically oriented aphasiologists are now keen to analyse the difficulties (faced by patients) in terms of the structure and systemic features that are disrupted or retained. Details are beyond scope of this book.

Neurolinguistics has also helped in speech therapy and rehabilitation. By more precise and detailed description of the language function of brain-damaged subjects, it is possible to plan novel re-educative strategies and to monitor the recovery if performance.

It is possible to examine in detail the linguistic performance of a subject and pinpoint the boxes or arrows in the diagram, where one thinks that the functional deficit is present. The tasks are simple and not too lengthy. They ingeniously make use of reading aloud and writing to dictation words and nonwords, regular and irregular words and exception words.

Prognosis

Prognosis depends upon aetiology and site and size of lesion. Aphasia due to stroke and head injury tends to improve steadily over a period of few weeks to many months. Younger age, female sex, non right-handedness and multilingualism may be good prognostic indicators. Type and severity of aphasia matters most. Global aphasia, severe Broca's and severe Wernicke's aphasia may not improve much. Aphasic syndromes due to disconnection (conduction aphasia, alexia without agraphia) tend to improve rapidly and often completely. Aphasic syndromes may evolve from one type into another, global into severe Broca's, Wernicke's, transcortical and conduction into anomic.

By around one and half year after stroke only about quarter of aphasics regain near normal speech function while double that proportion will still be having significant difficulty in communication.

Mortality in patients with aphasia due to stroke may be about twice as high as in those without aphasia. Cardiac embolism, atrial fibrillation and a larger volume of cerebral lesion are associated with a higher probability of aphasia as well as mortality. Possibly for the same reasons and due to the presence of aphasia itself, long-term functional recovery in survivors of stroke with aphasia is poorer compared to those without it.

Management, Speech Therapy and Rehabilitation

Therapy requires teamwork involving a neurologist, psychologist, speech therapist, social worker, linguist and the relatives and colleagues of the patient. Aims of all therapies for people with aphasia should be to improve their functioning in the real social world, to enable them to cope with barriers to participation.

Speech therapy is an interactive process and it is not a mechanical application of a predefined behaviour. During therapy patient must be an active participant.

Various methods of speech therapy can be grouped into two: those reducing specific impairment and those aiming for overall functional social gain. There is no contradiction between the two. In music, one practice scales not because a performance consists of playing scales, but because doing this develops skills that results in better performance.

The intensive phase of speech therapy usually lasts a couple of months. The frequency of sessions could be twice a week to twice per day, each session lasting for about an hour. Take-home exercises are also given, which should be carried out under the supervision of family members.

The methods of speech therapy and material used are tailored according to the individual patient's needs. Psycholinguistically based therapeutics is in its infancy, but some early reports are encouraging.

For patients with very severe aphasia, *pragmatics based approaches* are recommended which relate to analysis and repair of conversation in holistic sense. The therapist follows conversational coaching approach with the help of different themes or scripts, video taps and replay and turn taking.

It is difficult to evaluate the effectiveness of formal speech therapy because so many factors influence the recovery from aphasia. Yet in recent years, a few studies have supported the utility of speech therapy, as it satisfies the stringent criteria of evidence-based medicine. Training-induced plasticity in the brain during recovery from aphasia has now been documented with the help of PET scan. It shows significant activation of the non-dominant (right) hemisphere. It is a wrong question to ask whether speech therapy (in general) is effective for aphasic patients (in general)? The right question should be: which specific modes of speech therapy can be beneficial to which particular types of patients?

Technological advances have improved the quality of life of many patients with aphasia. Audiovisual augmentative methods of communication are now possible and affordable. Computers, multimedia, speech synthesisers, touch screens and special software are being used. Melodic intonation therapy and music therapy were reported to be useful for patients with non-fluent aphasia to convey meaning through variations in tone and accent, despite a very limited repertoire of vocabulary.

Drug therapy

Randomised controlled trials have been reported with dopamine agonists (brombocriptine), nootropics (piracetam) and cholinesterase inhibitors (donepezil). There is weak evidence in favour of a mild efficacy particularly in non-fluent aphasias.

Transcranial magnetic stimulation (TMS)

It has been reported to be useful in a few case reports on chronic global aphasics. The effects are long lasting. TMS may modulate activity in the surviving left and right hemispheric neural networks for naming.

THE INDIAN CONTEXT

The burden of aphasia and other disorders of speech and communication is high in developing countries including India, as can be judged from **Table 2**, listing various aetiologies. We

Table 2: Salient Features of Major Aphasic Syndromes

Type and Aphasia	Fluency (Oral, Written)	Comprehension (Listening, Reading)	Repetition	Naming
Broca's	Severely non-fluent	Normal or mildly affected	As severely impaired as fluency	As severely impaired as fluency
Wernicke's	Fluent but empty	Severely impaired	As impaired as comprehension	As impaired as comprehension
Global	Non-fluent	Severely impaired	Severely impaired	Severely impaired
Anomic	Fluent	Mildly affected	Mildly affected	Severely impaired
Conduction	Fluent or slightly non-fluent	Mildly affected or normal	Severely impaired	Normal or mildly impaired
Transcortical motor	Mildly non-fluent	Nearly normal or normal	Paradoxically normal	Moderately impaired
Transcortical sensory	Fluent	Severely impaired	Paradoxically normal	Severely impaired
Transcortical mixed (isolation of the language Zone)	Non-fluent	Severely impaired	Paradoxically better preserved	Severely impaired

Table 3: Community Burden of Aphasia and Other Disorders of Speech and Communication

S.No.	Disease Condition	Overall Burden	Percentage with Aphasia
1.	Stroke	Prevalence 0.5%	25%
2.	Head injury	Prevalence 1.2%	5% to 10 %
3.	Dementia	10% above the age of 60 years	Almost all have variable impairment of language functions depending on severity
4.	Mental retardation	5% (all) 1% (severe)	Almost all have variable impairment of language function depending on severity
5.	Learning disabilities (e.g. dyslexia)	5%	All have variable handicap in reading and writing skills
6.	Fluency and articulation disorders: Stuttering, stammering lisping, cluttering, lalling	1%	Variable handicap in all

Table 4: Contemporary Tests and Methods of Speech Assessment

Clinical bedside examination

Screening tests

Tests of specific aspects of language behaviour
- Boston naming test
- Peabody picture vocabulary tests
- Token test (Auditory comprehension)

Functional communication
- ASHA functional assessment
- Communication activities of daily living

Comprehensive examination
- Boston diagnostic aphasia
- Porch index of communicative ability (PICA)
- Psycholinguistic assessment of language processing in aphasia (PALPA)
- Western aphasia battery

Tests for special populations
- Infants and children
- Head trauma
- Right hemisphere lesions
- Elderly and dementia subjects
- Multilingual subjects

have higher proportion of younger patients as compared to developed countries. Only a few clinicians have been working in the field of aphasiology in India. No indigenous test battery in the Indian languages has been developed, which fulfills the stringent requirements of originality, sound theoretical basis and documented standardisation and validity. Some local adaptations of the Boston Diagnostic Aphasia Examination or Western Aphasia Battery are in use. Multilingualism and illiteracy are additional challenges.

There is a paucity of speech pathologists and therapists in India. Speech therapy is laborious, time-consuming and requires motivation on the part of patient as well as therapist. Positive results may not be forthcoming in a large proportion of patients.

Physicians should be familiar with the assessment required for aphasia and its therapy (**Table 4**). Clinicians will do well if they carry a pocket book of testing cards. The tools of speech assessment can be used for therapy to some extent.

There is great need for aphasia workbooks in the Indian languages, which can be given to patients for home exercises. Computer-based and web-based programms for diagnostic evaluation and therapeutic practices have to be created in the Indian languages.

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20.7 Disorders of Cranial Nerves

Sankar Prasad Gorthi, Sundaram Venkatraman

There are twelve cranial nerves (CN I to XII) which pass to and from the brain through foramina and fissures in the bony skull. All these cranial nerves have their distribution in head and neck except cranial nerve X (the vagus) which extends down to supply other structures in the thorax and abdomen. Cranial nerves are either sensory, motor or mixed. CNs I, II, and VIII are purely sensory; CNs III, IV, VI, XI, and XII are purely motor; and the remainder are mixed. CNs III, VII, IX, and X have parasympathetic fibres. These cranial nerves have centrally situated nuclei in the brainstem. All cranial nerves (CNs) originate from the brainstem, except CNs I and II. The location of CNs III and IV nuclei are in the midbrain; CNs V, VI, VII, and VIII are in the pons; and CNs IX, X, XI, and XII are in the medulla.

Motor nuclei receive impulses from cerebral cortex through the corticobulbar fibres. These fibres originate from the precentral gyrus and descend through the corona radiata, genu of the internal capsule and reach cranial motor nuclei. Bilateral connections are present for all nuclei except for part of facial nucleus. For sensory neurons, the first order neuron cells are found in special ganglia or in sensory ganglia (Gasserian, Geniculate, etc.) or in sensory organs (nose, eye or ear). Cells in the cranial sensory nuclei are considered 2nd order neurons and their axons cross the midline to reach the thalamus. The thalamic outflow to primary sensory cortex constitutes the third order neuron.

The cranial nerves are different from the spinal nerves in that the myelin sheath surrounding them is derived from oligodendroglia whereas those for the spinal nerves are derived from the Schwann cells. Consequently, it is observed that disorders of peripheral myelin rarely affect the cranial nerves and vice versa. In addition, the cranial nerves are involved in several other disorders of the brain such as tumours, trauma, inflammation and vascular and congenital disorders. In the following section, we shall describe the cranial nerves and their disorders.

OLFACTORY NERVE

Olfactory function is very important for safety, nutrition and quality of life. Olfactory dysfunction is one of the earliest 'preclinical signs' of neurodegenerative diseases like Alzheimer's disease and Parkinson's disease.

Anatomy and Physiology

The olfactory system is made up of the olfactory neuroepithelium, olfactory bulbs, and tracts together with olfactory areas in the brain (temporal lobe and septal areas) and their connections with other brain centres. The olfactory neuroepithelium situated in the superior-posterior roof of the nasal cavity houses approximately six million bipolar olfactory receptor cells, their dendrites and also the initial part of the axons. These penetrate the cribriform plate of the ethmoid bone and enter the olfactory bulb. The axons leave the olfactory bulb and course posteriorly, as the olfactory tract in the olfactory sulcus. The olfactory tract divides into medial and lateral olfactory stria on either side of the anterior perforated substance. A small minority of the olfactory tract fibres decussate in the anterior commissure, while rest supply the ipsilateral pyriform lobe of temporal cortex and probably terminate in the amygdaloid and septal nuclei and the hypothalamus.

Clinical Evaluation of Smell

Olfactory dysfunction can be binasal or uninasal, can be complete or incomplete (Anosmia and Partial anosmia, Hyposmia, Microsmia). There may be olfactory distortions (parosmias) like dysosmia (rotten-egg like smell when sniffing a rose) or phantosmia (the presence of a smell when no stimulus is present) or olfactory agnosias (normal olfactory function but inability to process olfactory information in association cortex). Acute onset increased sensitivity to smell is hyperosmia.

Unilateral loss of smell, usually found on examination can be a helpful sign of focal neurological dysfunction. Such patients should be enquired about head trauma, recent upper respiratory tract infection, drug abuse, toxin exposure, smoking and alcohol use, seizures and radiation.

Causes of Disturbance of Olfactory Nerve

The causes of disturbances of smell are diverse (**Table 1**), but nasal and paranasal sinus disorders, upper respiratory tract disorders and head trauma account for most of them. Head trauma can cause direct damage to the olfactory bulb, olfactory nerve as it enters the skull, or direct cortical injury. Anosmia, usually bilateral, can be the first symptom of olfactory groove meningioma. Ageing, Parkinson's disease, Alzheimer's disease and Korsakoff's psychosis are important causes of hyposmia. Olfactory hallucinations occur in uncinate seizures, Alzheimer's disease, seizures, alcohol withdrawal, and depression.

Examination

Traditionally, the sense of smell is tested by asking the patient to sniff various non-irritating substances (coffee, oil of cloves and oil of peppermint), testing each nostril separately, while occluding the other nostril by a finger. Once patient detects odour, he is then asked to identify the smell (perception of smell is more important than identification of specific substance). Irritating substances are avoided as they simultaneously stimulate the trigeminal nerve fibres. University of Pennsylvania smell identification test (UPSIT) is an objective test in which 40 micro capsulated odorants with a forced choice of one of four alternative responses for each item is used.

OPTIC NERVE

The visual system consisting of both eyes and their connections to both the cerebral hemispheres accurately portrays the

environment and abstracts meaning from various items in environment. Both olfactory and optic nerves contain secondary sensory axons and are, in the true sense, tracts of central nervous system rather than a nerve.

Table 1: Causes of Dysfunction of Smell

Tumours	**Traumatic**
Olfactory groove meningioma	**Drugs/Toxins**
Frontal lobe glioma	Zinc
Deficiency states	Ciguatera fish poisoning
Vitamin B12	**Degenerative disorders**
Vascular	Alzheimer's disease
Anterior cerebral artery aneurysm	Parkinson's disease
Subarachnoid haemorrhage	Lewy body disease
Infection/Inflammation	**Systemic illness**
Creutzfeldt-Jakob's disease	Diabetes mellitus
Viral encephalitis	Renal failure
Meningitis	Turner syndrome
Kallmann's syndrome	Cushing syndrome
Leprosy	Epilepsy
Acute viral infection	**Others**
Sarcoidosis	Smoking
Rhino-sinusitis	Pregnancy
Bell's palsy	Ageing
Multiple sclerosis	Congenital or hereditary
Psychogenic	Albinism

Anatomy and Physiology

The optic nerve originates from nearly 1.2 million axons of the ganglion cells in the visual retina and travels postero-medially through the optic canal situated in the lesser wing of the sphenoid bone. At the posterior end of the optic canal optic nerves from both sides decussate to form the optic chiasma wherein one half of the axons cross the midline to join the uncrossed axons from the other eye to form the optic tract. This arrangement facilitates the left optic tract to carry visual information from the right half of the visual field and vice versa. The optic tracts encircle the cerebral peduncles on both sides to reach the lateral geniculate bodies of thalamus where few axons subserving the pupillary pathway separate and join the pretectal nucleus of midbrain. From the geniculate bodies the geniculocalcarine tract (optic radiation) reach its destination in the occipital cortex by forming the Meyer's loop anteriorly and lateral and superior to the inferior horn of lateral ventricle. From the primary visual cortex, integrated visual signals are processed in the visual association areas for interpretation and then conducted to the frontal eye fields to effect changes in visual fixation.

Cardinal Features of Optic Nerve Dysfunction

Optic nerve disorders lead to disturbance in the three chief components of vision-contrast, brightness and colour. Blurred and diminished vision suggests loss of axonal transmission. On the contrary, blurred and bright vision suggests refractory error. According to the division of optic nerve, the disorders affecting optic nerve can be divided into four groups as shown in **Table 2** and four tests are used to assess its functional integrity. In the evaluation of optic nerve the following are important: optic disc, visual acuity, colour vision (colour discrimination, and contrast sensitivity), visual fields and light reflex.

Table 2: Optic Nerve Characteristics of Various Parts and their Tests

Part of Optic Nerve	Length	Disorders	Test
Intra-ocular	1 to 2 mm	Papilloedema, anterior ischaemic optic neuropathy	Opthalmoscopy for abnormal fundus
Intra-orbital	25 to 30 mm	Thyroid opthalmopathy, optic nerve sheath meningioma	Visual acuity
Intra-canalicular	5 to 9 mm	Traumatic optic neuropathy	Visual acuity
Intra-cranial	9 to 10 mm	Pituitary tumours/ suprasellar masses	Visual fields

Papilloedema refers to swelling of the optic nerve associated with increased intra-cranial pressure. The elevated intra-cranial pressure is transmitted onto the optic nerve up to lamina cribrosa along the sleeve of the subarachnoid space leading to dilatation of retinal veins and hyperaemia. Inflammation of the optic nerve (optic neuritis) interferes with transmission of signals from retina to the occipital cortex and leads to visual blurring.

Visual defects can be classified as pre-chiasmatic, chiasmatic and post-chiasmatic. Pre-chiasmatic lesions always cause visual impairment in one eye unless the lesion is bilateral. Characteristically, chiasmatic lesions result in a bitemporal field defect as seen in pituitary tumours. Rarely, bilateral aneurysms of carotid arteries in the supra-clinoid portion can give rise to binasal field defect. The retro-chiasmatic lesions, on the other hand, give rise to a homonymous hemianopia which becomes congruous if they become closer to the occipital pole. In addition, if the lesion is in the temporal lobe in the optic radiation, the resultant field defect is upper quadrantic incongruous homonymous hemianopia. **Table 2** briefly reviews the aetiology of optic nerve diseases.

Pupillary Abnormalities

The afferent sensory signals are carried in the optic nerve to the Edinger-Westphal nucleus in the midbrain and the efferent motor signals are carried in the oculomotor nerve to the papillary constrictor muscles. The normal light reflex consists of constriction of ipsilateral as well as contralateral pupils on shining light into the eye. Inflammation of the optic nerve blocks transmission of optic signals in the afferent limb leading to poor direct and consensual papillary responses, called relative afferent pupillary defect (RAPD).

CRANIAL NERVES OCULOMOTOR TROCHLEAR AND ABDUCENS NERVES

The oculomotor nerve (CN III), trochlear nerve (CN IV) and abducens nerve (CN VI) are motor nerves of the eye ball. In addition, oculomotor nerve also provides parasympathetic innervation to the eye. Together, all these three nerves are responsible for all the eye movements.

Anatomy and Physiology

The oculomotor nerve originates from a paired nuclear complex in the periaqueductal midbrain. It is composed of several sub nuclei that innervate the following target structures in each eye:

medial rectus, inferior rectus, inferior oblique, levator palpebrae superioris, and the ciliary ganglion. Each subnucleus is paired and sends its projections ipsilaterally with two exceptions. Fibres supplying levator palpebrae superioris, initiate from cell bodies in the unpaired midline central caudal nucleus, and fibres innervating the superior rectus muscles originate from contra lateral superior rectus subnucleus. Parasympathetic preganglionic axons projecting to the ciliary ganglion originate from the Edinger-Westphal nuclei. Axons arising from oculomotor nuclei form fascicles that project anteriorly through midbrain to emerge from its ventral surface. They pass through the red nucleus and run adjacent to the substantia nigra and cerebral peduncle. The nerve travels between the superior cerebellar artery and posterior cerebral artery to enter the cavernous sinus. In subarachnoid space, the nerve lies adjacent to the posterior communicating artery and the tip of the basilar artery. Therefore, aneurysms of these arteries often compress the third nerve. In the wall of the cavernous sinus, it lies superiorly, adjacent to the fourth cranial nerve. As it emerges from the cavernous sinus, it passes through the superior orbital fissure and divides into superior and inferior branches. The superior branch innervates the superior rectus and levator palpebrae. The inferior branch innervates the inferior rectus, medial rectus, inferior oblique, and the ciliary ganglion.

The fourth nerve nucleus is located in the midbrain, inferior to the oculomotor nuclear complex and dorsal to the medial longitudinal fasciculus. The fascicles leave the nucleus and exit posteriorly and inferiorly from the most dorsal portion of midbrain after decussating in the superior medullary velum. It emerges from the brainstem at the level of inferior colliculus, runs anteriorly between the lateral midbrain and the tentorium cerebelli in the subarachnoid space and passes between the superior cerebellar and posterior cerebral arteries. Coursing around the cerebral peduncles, it enters the cavernous sinus, lying inferior to the third nerve and superior to the first division of the trigeminal nerve. From the cavernous sinus it enters the orbit through the superior orbital fissure and innervates the superior oblique muscle.

The abducens nerve nucleus is located in the floor of the fourth ventricle in the dorsal pons adjacent to the medial longitudinal fasciculus (MLF), the paramedian reticular formation, and the fascicles of the seventh nerve. The nucleus contains two populations of motor neurons, one population projects fibres to the ipsilateral lateral rectus muscle. The other group sends axons to the contralateral medial rectus via the medial longitudinal fasciculus. The nerve has a rather long course. After emerging from the caudal pons it courses superiorly along the clivus to the level of the petroclinoid (Gruber's) ligament. At this point it leaves the subarachnoid space, and enters Dorello's canal. It then travels ventrally and enters the cavernous sinus, lying adjacent to the carotid artery. It then enters the orbit through the superior orbital fissure to innervate the lateral rectus muscle.

Physiology of Eye Movements

The six extra-ocular muscles form three complimentary 'yoked' eye muscle pairs and induce eye movements. There are four major types of eye movements: saccades, pursuits, conjugate or vergent and disconjugate eye movements and these movements are executed by five neural mechanisms namely: the vestibulo-ocular reflex (VOR), optokinetic reflex (OKR), pursuit system, saccadic system, and vergence system. Conjugate eye movements are defined as movements of both eyes in the same direction by the same amount.

Vestibulo-ocular reflex maintains visual fixation during locomotion. Rapid eye movements are required to match the frequency of head rotation during locomotion. If the VOR is compromised, the visual acuity during locomotion is degraded significantly.

The optokinetic reflex generates a smooth pursuit movement that tracks a passing object for a distance and a saccade brings the eyes back to the neutral position. The VOR adapts rapidly but the OKR does not adapt rapidly. The OKR is mediated by the sensory signals originating in the retina which are conducted through the optic nerve to the pretectal region and further to vestibular nuclei and III, IV and VI CN nuclei.

Pursuit eye movements come into play in following a moving object against a stationary background. The extra striate visual cortex in the temporal lobe mediates the voluntary pursuits.

The saccadic eye movements facilitate rapid shifts of the fovea from one target to another to the tune of 900 degrees per second. The neural mechanisms controlling the saccadic eye-movements are the retinae, the somatosensory system and the auditory system that send signals to the superior colliculi in midbrain. The frontal eye fields and the superior colliculi project to the 'gaze centres' in the reticular formation of the brainstem especially interstitial nucleus of MLF for vertical gaze and the para pontine reticular formation (PPRF) for horizontal gaze. These in turn project to cranial nerve nuclei III, IV and VI.

The vergence system moves the eyes in the accommodation reflex wherein the eyes converge or diverge to perceive one image when attention is shifted from one object to another. For convergence, both the medial recti are activated and both lateral rectus muscles are inhibited. For divergence, vice versa is true. Vergence centre is not yet described.

Internuclear ophthalmoplegia (INO) is characterised by paresis of adduction in one eye and horizontal nystagmus in the contra lateral eye. Lesion in the MLF is on the side of the adducting eye. The palsy of medial rectus muscle can be either due to damage of lower motor neuron or due to MLF. If medial rectus muscle can be activated by convergence but not by lateral gaze then the lesion is likely in the MLF

Cardinal Features of Dysfunction

Lesions of these oculomotor nerves can be anywhere along their course from their nuclei in the brainstem to their target muscles in the orbit, with distinct clinical presentations. These sites can be nuclear, fascicular, subarachnoid space, cavernous sinus and orbit.

Nuclear lesions of the third (oculomotor nerve) can be complete or incomplete lesion depending upon the extent of the involvement. The classical presentation is bilateral ptosis, unilateral medial rectus paresis, and superior rectus paresis. Rostral lesions may spare the levator complex and dorsal lesions may spare the Edinger-Westphal nucleus. These commonly involve the nearby nuclei that are important for vertical conjugate gaze. Nuclear lesion of trochlear nerve (IV Cranial nerve) results in contralateral superior oblique weakness. Isolated fourth nerve

palsies due to nuclear lesions are rare. Associated findings include contralateral internuclear ophthalmoplegia, contralateral Horner's syndrome, and ipsilateral afferent pupillary defect.

Nuclear lesions of abducens nerve (VIth cranial nerve) nucleus produce conjugate, horizontal gaze palsy towards the side of the lesion. Other associated neurological signs include ipsilateral, peripheral seventh nerve palsy. Additional involvement of the MLF results in one-and-a-half syndrome, in which there is loss of conjugate gaze toward the side of the lesion (one), and impaired adduction with gaze away from the lesion (half). A combination of one-and-a-half syndrome with seventh nerve palsy is referred to as eight-and-a-half syndrome. Congenital abducens palsies are rare and they may be seen in association with other congenital anomalies. Möbius' syndrome is characterised by facial diplegia, and bilateral sixth nerve palsies. In Duane's congenital retraction syndrome there is impairment of abduction, variable impairment of adduction and narrowing of the palpebral fissure with co-contraction of the ipsilateral medial and lateral recti muscles.

Fascicular lesion is accompanied by neurological signs as the adjacent structures are commonly involved. In fascicular lesions of the third cranial nerve contralateral hemiparesis due to involvement of crus cerebri (Weber's syndrome), contralateral tremor due to involvement of red nucleus (Benedict's syndrome), and ipsilateral ataxia due to involvement of superior cerebellar peduncle (Nothnagel's syndrome) are some of the named syndromes. These lesions may spare the pupil, involve only a single division of the nerve, or result in isolated weakness of an individual muscle. Fascicular lesions of trochlear nerve are impossible to distinguish from nuclear lesions as the nerve travels a very short distance in the midbrain. Causes and associated findings are identical to nuclear lesions. Fascicular lesions of abducens nerve result in ipsilateral abduction dysfunction. A lesion in the anterior paramedian pons leads to a combination of ipsilateral facial nerve palsy, ipsilateral abduction deficit and contralateral hemiplegia, referred to as Millard-Gubler syndrome. Foville's syndrome is characterised by a combination of ipsilateral abducens and facial nerve palsies, loss of taste on anterior two-thirds of the tongue, ipsilateral Horner's syndrome, deafness, and trigeminal dysfunction. This is caused by infarction in the territory of anterior inferior cerebellar artery.

Lesion in subarachnoid space is varied and depends on the cause. Trochlear nerve in the subarachnoid space is most susceptible to injury because of its long intra-cranial course. Associated neurological signs often provide the clue to localisation. Abducens nerve lesion in subarachnoid space results in isolated abduction defect. A variety of mechanisms including ischaemia, mass lesions, trauma, meningitis, and elevated intra-cranial pressure may be responsible. Because of its unique course, the nerve may be pressed between the pons and basilar artery or clivus with increase in the intra-cranial pressure, or may get stretched along the edge of the temporal bone. Patients presenting with headache and sixth nerve palsy should be evaluated for raised intra-cranial pressure.

Lesions in the cavernous sinus and superior orbital fissure result in well described clinical syndromes like cavernous sinus syndrome and orbital fissure syndrome with features of combinations of cranial nerves III, IV and VI dysfunction. On occasion, oculosympathetic dysfunction is also observed. Exophthalmos, chemosis, and visual loss may be the other accompanying features. Sensory fibres from the opthalmic division of the fifth cranial nerve travel to join the third nerve in the lateral wall of the cavernous sinus. Hence lateral cavernous sinus lesions cause painful ophthalmoplegia and medial cavernous sinus lesions cause painless ophthalmoplegia.

Orbital lesions cause concerned cranial nerve lesion, optic neuropathy and proptosis. Orbital apex lesions of third cranial nerve result in involvement of either superior or inferior division. Superior division involvement causes ptosis and superior rectus weakness whereas inferior lesion causes weakness of inferior rectus and inferior oblique muscles. When vision is affected, the lesion is almost always in the orbital apex.

Clinical Evaluation

Oculomotor nerve assessment involves the assessment of i) eyelid position, ii) pupillary response to light, iii) extra-ocular movements, and iv) accommodation.

i. Levator palpebrae superioris muscle is responsible for lid elevation. Bilateral or unilateral drooping of the eyelids is encountered in damage to cranial nerve III. Normally, the eyelid should not drop over the pupil and eyelid position should be symmetrical on both sides.

ii. Pupillary light reflex is mediated by cranial nerve II in the afferent arc and by cranial nerve III (the parasympathetic fibres travelling in the oculomotor nerve) in the efferent arc. In the normal light reflex not only the ipsilateral pupil constricts in response to a focused beam of light but also the contralateral pupil (consensual response). If the afferent arc subserved by the optic nerve is intact but the efferent arc subserved by the oculomotor nerve is damaged then the ipsilateral pupil will not constrict but the contralateral pupil will. Pupillary dilatation and unresponsiveness occurs when the third nerve gets compressed due to an aneurysm. A normal pupil in the setting of complete third nerve palsy excludes an aneurysm. Conversely, an isolated pupillary paralysis without ptosis or opthalmoparesis is rarely caused by an aneurysm. Third nerve palsy with a normal pupillary sphincter and complete paralysis of EOM is most commonly caused by ischaemia especially associated with diabetes mellitus. All patients with ischaemic third nerve palsy improve within 4 weeks to 12 weeks of onset. Patients with complete third nerve palsy with normal pupil do not require neuroimaging if they are not progressing after the first week of onset. Patients with incomplete third nerve palsy with pupillary sparing require an MRI and or cerebral angiography to reveal an ICSOL, aneurysm, dural-cavernous sinus fistula or high grade stenosis.

iii. Cranial nerve III is assessed by observing adduction and vertical eye movements. Eye adduction is impaired because of medial rectus weakness. Weakness of inferior rectus, superior rectus and inferior oblique muscles affects the vertical eye movements.

iv. Accommodation reflex consists of convergence of eyes and pupillary constriction of both eyes. Patient's eyes converge and pupils constrict as the examiner's finger is brought from a distance towards the patient's nose.

The trochlear nerve assessment consists of assessment of direction of diplopia and head tilt. The most common cause of vertical diplopia is a fourth nerve palsy. A patient with unilateral fourth nerve palsy complains of binocular, vertical diplopia,

which worsens on down-gaze. As the superior oblique muscle depresses the eye in adduction and intorts the eye in abduction, examination of a case of trochlear nerve palsy reveals hyperdeviation on the side of the paretic muscle that is worse on down-gaze and adduction. The three step test (Parks-Bielschowsky) can be used to verify the fourth nerve palsy and is best applied with Maddox rod instruments. The three steps are: firstly, determine which eye is hyperdeviated in the primary position; secondly, measure the hyperdeviation in the lateral gaze; and thirdly, measure the hyperdeviation with head tilt. Thus, left fourth nerve palsy would result in a left hypertropia that is worse in right lateral gaze and with left head tilt.

Cranial nerves IV and VI are also tested along with cranial nerve III in the assessment of eye movements

Examination of Eye Movements

The combined action of medial rectus, superior rectus, inferior oblique (cranial nerve III) plus the superior oblique (IV) and lateral rectus (VI) muscle enables eye movements around the three axes of the eye: x, y and z. To examine eye movements draw a large 'H' in the air a few feet in front of the patient and ask him to follow your finger with his eyes in a smooth and co-ordinated fashion. The horizontal bar of 'H' will test the medial and lateral rectus muscles. The two vertical bars of the 'H' will test the motion of the superior and inferior rectus muscles and the inferior or superior oblique muscles.

Causes of Disturbance of Function

The nuclei of these three oculomotor nerves can be damaged by infection, tumour or demyelination. These nerves can become ischaemic (especially diabetes or hypertension). Meningeal infection, cerebellopontine angle tumours and mastoiditis can affect them. Carotid aneurysm, cavernous sinus thrombosis, inflammation or tumour can involve them in cavernous sinus thrombosis. Fractures of orbit or orbital tumours may involve these nerves in the superior orbital fissure. The various aetiologies can be classified into non-isolated palsies, traumatic palsies, congenital palsies, acquired non-traumatic palsies, and progressive or unresolved palsies. The various types of palsies, the corresponding clinical features, localisation of lesions and the suggested investigations are summarised in **Tables 3 and 4**.

TRIGEMINAL NERVE

This is a mixed nerve that provides sensory innervation to the face and mucous membranes of oronasal cavities and motor innervation to the muscles of mastication.

Anatomy and Physiology

The complex anatomy of trigeminal nerve extends from the peripheral nerve endings in face, sinuses, and meninges through the skull base, cavernous sinus (V1, V2 only), and trigeminal ganglion, to the intra-axial nuclei, tracts, thalamus and cerebral cortex.

Motor Portion (*Portio Minor*)

The motor nucleus is situated at the midpontine level. It receives its supranuclear control through corticobulbar fibres originating in the lower third of the precentral gyrus. These bilateral connections travel through the corona radiata, internal capsule and decussate in the pons to supply the motor nuclei.

The motor root exits from the motor nucleus, emerging from the pons anteromedial to the sensory root, passes through the posterior fossa, enters the Meckel's cave and leaves the skull via the foramen ovale. It then joins the mandibular division of the trigeminal nerve to form the mandibular nerve which supplies the muscles of mastication (masseter, temporalis and pterygoids). It also supplies tensor tympani, tensor veli palatini, mylohyoid and anterior belly of digastric muscles. The masseter, along with the temporalis and medial pterygoid muscles, closes the jaw. The lateral pterygoid, anterior bellies of the digastric and mylohyoid muscles, along with cervically innervated anterior neck muscles, work together to open the jaw. The lateral pterygoid muscles protrude the jaw and injury to one lateral pterygoid muscle causes the mandible to deviate towards the injured side.

Sensory Portion (*Portio Major*)

All the three divisions of the trigeminal nerve, ophthalmic, maxillary and mandibular join together at the trigeminal ganglion (the Gasserian ganglion) where most of the sensory cell bodies are located. Central processes of these neurons constitute the sensory root of the trigeminal nerve. These axons terminate by synapsing with second-order sensory neurons in the three major nuclear complexes within the trigeminal nucleus in the brainstem. The trigeminal nucleus extends caudally from midbrain into the spinal cord as far as the second cervical segment where it becomes continuous with the dorsal horn of the spinal cord. It has three sub nuclei: the mesencephalic nucleus, the pontine trigeminal (chief sensory, main, principal or superior) nucleus and the spinal nucleus of the trigeminal nerve.

There are two major sensory pathways that carry sensory information from face and sinuses to the cerebrum, namely: a) the discriminative touch pathway; and b) the pain and sensory pathway. The first order neurons carrying proprioceptive and tactile sensation carry information from specific areas of face and meninges to the pontine trigeminal nucleus. From this chief sensory nucleus second order neurons cross the midline in the trigeminothalamic tract and join the medial lemniscus enroute to the thalamus. The third order neurons from thalamus travel to the primary sensory cortex through the posterior limb of internal capsule and corona radiata.

The first order neurons carrying pain and temperature sensation enter the pons along with the central processes of the discriminative touch neurons. In pons, these sensory fibres descend as the spinal tract of the trigeminal nucleus to the caudal end of medulla and down up to the second cervical cord segment level. While descending, the spinal tract also gives off fibres to the nucleus of the spinal tract of the trigeminal nerve. This nucleus is divided into pars oralis (from midpons to inferior olive), a pars interpolaris (from rostral inferior olive to obex), and a pars caudalis (extends to the cervical spinal cord). The somatotopic arrangement of fibres within this nucleus gives rise to the onion-skin type of sensory loss over face. The spinal nucleus receives fibres that convey the sensations of pain and temperature from face and mucous membrane. The ascending fibres from this nucleus terminate in the thalamus. Axons of third-order neurons project to the appropriate regions of sensory cortex. The third sensory trigeminal nucleus, the mesencephalic nucleus, extends up to the superior colliculus. This receives proprioceptive impulses from masticatory muscles.

Table 3: Localisation of Lesions of Oculomotor Nerve, Trochlear Nerve and Abducens Nerve

Anatomic Localisation	Cause	Associated Symptoms			
		Oculomotor	Trochlear	Abducens	Investigations
Nuclear	Infarction, mass lesion, infection, inflammation, compression, Wernicke-Korsakoff syndrome	Bilateral ptosis, paresis of contralateral superior rectus, ataxia, abducens nerve palsy, nystagmus, altered mentation	Internuclear ophthalmoplegia, Horner's syndrome, afferent pupillary defect	Internuclear ophthalmoplegia, ipsilateral facial paresis ataxia, abducens palsy, nystagmus, altered mentation	MRI
Fascicular	Infarction, mass lesion, infection, inflammation, compression, demyelination	Contralateral hemiparesis, tremor, pupil may be spared	Internuclear ophthalmoplegia, Horner's syndrome, afferent pupillary defect	Ipsilateral facial paresis, contralateral hemiplegial, ipsilateral facial paresis, loss of taste, Horner's syndrome, trigeminal dysfunction, deafness	MRI
Subarachnoid space	Aneurysm Vasculopathic Meningitis Miller-Fisher syndrome Migraine Uncal herniation	Headache, stiff neck, pupil involved Pupil spared Headache, neck stiffness, other cranial nerve involvement Ataxia, areflexia Headache, positive family history, paediatric age group, early pupil involvement, altered mentation, ipsilateral hemiparesis	May be bilateral Usually isolated Contralateral hemiparesis or ipsilateral ataxia	Headache - usually isolated, contralateral hemiparesis, usually isolated papilloedema, petrous part of temporal bone - may be involved in mastoiditis, skull fracture, lateral sinus thrombosis, neoplasm Ipsilateral facial paresis, severe facial pain	MRI, MRA, Angiogram BP, sugar, ESR, CRP, CSF examination, MRI Nerve conduction study, CSF MRI, Urgent CT scan
Cavernous sinus	Neoplasm, fistula, thrombosis, Tolosa-Hunt syndrome, apoplexy	Pain, chemosis, proptosis, pupil involvement, ophthalmoplegia, sensory loss, bruit	Pain, chemosis, proptosis, pupil involved, ophthalmoplegia, trigeminal sensory loss		MRI, CSF, MRA
Superior orbital fissure	Neoplasm, infiltration	Superior division involvement (ptosis and superior rectus paresis)	Oculomotor, abducens, optic nerve dysfunction, proptosis		MRI
Neuro-muscular Junction		Pupils spared, frequent fluctuation, ptosis, ophthalmoparesis	Pupils spared, frequent fluctuation, ptosis, ophthalmoparesis	Pupils spared, frequent fluctuation, ptosis, ophthalmoparesis	Tensilon test and Repetitive nerve stimulation

The sensory and motor roots together form the trigeminal (Gasserian) ganglion in the Meckel's cave which lies near the cavernous sinus and internal carotid artery and gives rise to the three nerve trunks, i.e. ophthalmic division, maxillary division and mandibular division. The ophthalmic division lies in the lateral wall of cavernous sinus and enters the orbit with the third, fourth and sixth cranial nerves through the superior orbital fissure. Through numerous branches it supplies the skin of the nose, the upper eyelid, the forehead and scalp, upper half of cornea, paranasal sinuses, nasal cavity, lacrimal canal, conjunctiva, lacrimal gland, constrictor of pupil and ciliary muscle. The maxillary division enters the orbit through the inferior orbital fissure. It supplies the skin of lower eyelid, lateral nose, upper lip, cheek, lower cornea, conjunctiva and iris, palate, upper gum and teeth. The mandibular division supplies muscles of mastication (listed earlier) and skin of lower lip, lower jaw, chin, tympanic membrane, auditory meatus, upper part of ear and mucous membrane of the floor of the mouth and lower gums.

Trigeminal Reflexes

1. The corneal reflex is mediated by the afferent ciliary branch of the nasociliary nerve, its projections to bilateral facial nuclei, and facial nerve efferents.
2. The blink and lacrimal reflexes are mediated through the ophthalmic branch as the afferent arc and facial nerve as the efferent arc.
3. In the oculocardiac reflex, afferent input from pressure on the eyeball is carried via the ophthalmic branch to the efferent vagus nerve and leads to bradycardia.
4. The jaw jerk reflex is a muscle stretch reflex with afferent and efferent limbs both comprised of by the mandibular branch fibres.

The electrophysiological (EP) recording of the blink reflex, masseter inhibitory reflex, and jaw jerk reflex provides a means to evaluate the physiologic function of the trigeminal system. Patients with classical trigeminal neuralgia usually have normal or only mildly abnormal trigeminal reflexes, whereas those with symptomatic trigeminal neuralgia typically have reflex abnormalities.

Clinical Evaluation

Sensory evaluation

Exteroceptive sensations (touch, pain, temperature) are tested on the face, testing each division separately, comparing it with the opposite side. Lesions distal to Gasserian ganglion result in sensory loss in the territory of the individual branch, while lesions at or proximal to Gasserian ganglion cause ipsilateral loss over face. Lesions within the brainstem may result in onion-skin pattern of sensory loss. Presence of dissociated sensory loss over the face characterises lesions affecting the spinal tract and nucleus of the trigeminal nerve and differentiates it from lesion affecting the main sensory nucleus.

Table 4: Types of Palsies of Oculomotor Nerves (Cranial Nerves III, IV and VI)

Types of Palsy	Oculomotor	Trochlear	Abducens
Type 1: Non-isolated	Third nerve palsy is considered nonisolated in the presence of the following features: 1. Orbital disease 2. Myasthenia gravis 3. Multiple cranial nerve palsies (including bilateral third nerve palsy) or radiculopathy 4. Brainstem signs (e.g. hemiplegia, cerebellar signs, other cranial nerve deficits) 5. Systemic, infectious, or inflammatory risk factors for third nerve palsy (e.g. history of previous malignancy, giant cell arteritis, collagen vascular disease) 6. Severe headache	Fourth nerve palsies are considered non-isolated in the presence of the following features: 1. Other neurologic or neuro-ophthalmological signs 2. Evidence to suggest myasthenia gravis such as ptosis, or fatiguability of the of the motility deficit 3. Evidence for systemic inflammatory disorders such as giant cell arteritis	Sixth nerve palsies are considered non-isolated in the presence of the following features: 1. Other neurologic or neuro-ophthalmological signs 2. Evidence to suggest myasthenia gravis such as ptosis, or fatiguability motility deficit 3. Evidence for systemic inflammatory disorders such as giant cell arteritis
Type 2: Traumatic	A clear temporal relationship to significant previous head trauma and no progression	Isolated, unilateral, or bilateral fourth nerve palsies, which have a clearly established temporal relationship to previous head trauma and do not progress, are considered traumatic in origin. Patients have no neurologic deficits other than those associated with the initial traumatic event	Isolated unilateral sixth nerve palsy, which has a clearly established temporal relationship to significant previous head trauma and does not progress, is considered traumatic in origin
Type 3: Congenital	Patient born with an isolated third nerve palsy or noted to have a third nerve palsy within the first 3 months of life	Congenital fourth nerve palsy, in addition to the features described above for fourth nerve palsy in general, may show the following: 1. Large vertical fusional amplitudes (greater than 6 to 8 prism diopters) 2. Facial asymmetry or sternocleidomastoid muscle hypertrophy 3. Long-standing anomalous head position that may be present in old photographs	Patients born with sixth nerve palsy or noted to have a sixth nerve palsy within the first 3 months of life
Type 4: Acquired, Nontraumatic isolated palsy	Type A: Third nerve palsy with a normal pupillary sphincter with completely palsied extra-ocular muscles Type B: Third nerve palsy with normal pupillary sphincter and in completely palsied extra-ocular muscles Type C: Third nerve palsy with subnormal pupillary sphincter dysfunction and partial or complete extra-ocular muscle palsies	Vasculopathic fourth nerve palsy occurs in patients greater than 50 years of age with or without known hypertension or diabetes, or in younger patients with known vasculopathic risk factors. Patients without vasculopathic risk factors and not classified as any of the above has non-vasculopathic fourth nerve palsies	Vasculopathic sixth nerve palsy occurs in patients older than age 55 or those with known vasculopathic risk factors (e.g. hypertension or diabetes). Patients without vasculopathic risk factors defined above are considered to have non-vasculopathic sixth nerve palsy
Type 5: Progressive or Unresolved Palsy	Patients with third nerve palsy that worsen acute stage (>2 weeks) or who develop new neurologic findings are considered to have progressive third nerve palsy. Patients without resolution of third nerve palsy after 12 to 16 considered unresolved	Fourth nerve palsies that worsen after the acute stage (greater than 1 week) as defined by a significant in the measured ocular vertical deviation are considered to be progressive, and patients without improvement in the measured ocular vertical deviation after 6 to 8 weeks are considered unresolved	Sixth nerve palsy that worsens after the acute stage (>2 weeks) as defined by a significant increase in the measured ocular deviation or a new neurologic finding develops is considered progressive or non-isolated. Patients without resolution in the measured horizontal deviation after 12 to 16 weeks are considered unresolved
Type 6: Cranial nerve palsy with signs of aberrant regeneration			

Motor evaluation

A lesion of this part results in weakness and wasting of muscles of mastication; other muscles are difficult to examine.

Reflex evaluation

Corneal reflex and jaw jerk are important reflexes conveyed by the trigeminal nerve. Blink reflex and corneomandibular reflex are partly carried by the trigeminal nerve.

Cardinal Features of Dysfunction

Nuclear lesions of trigeminal nerve

Nuclear lesions affect other brainstem structures as well and are diagnosed by 'the company they keep'. Hemiparesis (due to involvement of basis pontis), contralateral sensory loss (due to spinothalamic tract involvement), ipsilateral tremor (due to involvement of brachium conjunctivum), internuclear ophthalmoplegia (due to involvement of medial longitudinal fasciculus), Horner's syndrome (due to involvement of the descending sympathetic fibres) are some of the common findings pointing at a lesion in the brainstem. Infarction, small brainstem haemorrhage, demyelination, metastatic tumours, arteriovenous malformations, syringobulbia can cause nuclear lesions. Lateral medullary syndrome characteristically affects the spinal nucleus, while lesions of mesencephalic nucleus cause apparently no neurological dysfunction except a depression of jaw jerk.

Preganglionic trigeminal nerve lesion

Common causes of lesion at this site are tumours (meningioma, Schwannoma, and metastasis), meningitis (infectious, inflammatory, and carcinomatous), trauma, and aneurysm. Cerebellopontine angle tumours involve the trigeminal nerve roots by extension of the pathological process and cause ipsilateral facial pain, paresis of masseter, paraesthesia, depressed corneal reflex, tinnitus, deafness and ataxia. Rarely nystagmus, facial and other lower cranial nerves involvement may be associated. Trigeminal neuralgia is characterised by sudden, excruciating, lancinating, usually unilateral and paroxysmal pain, often in maxillary or mandibular divisions. It is more common in females, especially older ones and is slightly more common on the right side. Pain usually lasts for a few seconds, may recur several times a day and is triggered by nociceptive facial stimulation. Many cases are probably due to compression or irritation of the entry of trigeminal nerve roots (aberrant vessel, demyelinating plaque, infarction, and tumour).

Lesions of the Gasserian Ganglion

This leads to severe, paroxysmal, usually hemifacial (sparing the angle of mandible) paraesthesia and pain. Vascular malformations, tumour, infections, granulomas are some of the common causes. Sjögren's syndrome, rheumatoid arthritis, SLE and dermatomyositis can cause bilateral sensory trigeminal neuropathy.

Lesions in Middle Cranial Fossa

Variable degree of trigeminal involvement is seen in middle cranial fossa lesions; Gradenigo's syndrome (ophthalmic division and abducens nerve involvement, usually secondary to otitis media), cavernous sinus and superior orbital fissure syndromes are some of the common causes.

FACIAL NERVE

Anatomy and Physiology

This nerve is motor nerve to the mimetic muscles of the face. It also has secretory fibres to the salivary and lacrimal glands and mucous membrane of the oral and nasal cavities. In addition, there are somatic pain fibres from the external auditory canal and a small strip of skin between the mastoid process and pinna and taste fibres from the ipsilateral anterior two-thirds of the tongue. Seventy per cent of the facial nerve fibres arise from the motor neurons of the facial nucleus, the remaining 30% are mixed sensory and autonomic fibres forming nervus intermedius. The motor nucleus is located in the ventrolateral portion of the caudal pons. Fibres course medially, curving around the sixth nerve nucleus, forming the facial colliculus in the floor of the fourth ventricle. It makes its exit from the lower part of pons between the olive and restiform body. Fibres for voluntary and reflexive facial movements are different. The sensory root (nervus intermedius of Wrisberg) contains bipolar neurons in geniculate ganglion, the distal axons of which supply taste fibres to the anterior two-thirds of the tongue and the proximal axons terminate in the nucleus solitarius. Visceral fibres from superior salivatory nuclei course in nervus intermedius and course along the greater superficial petrosal nerve to synapse in the sphenopalatine ganglion. The postganglionic fibres from sphenopalatine ganglion, in turn, supply lacrimal and palatine glands. After leaving the pons, motor and sensory roots course in the cerebellopontine angle for about 24 mm, entering the internal auditory canal where it lies anterosuperior to the vestibulocochlear nerve. From the internal auditory canal to the stylomastoid foramen, the facial nerve has a tortuous course which is nearly 33 mm long. Facial nerve has six segments; intra-cranial (24 mm), in the internal auditory canal, labyrinthine, tympanic (12 mm), mastoid (15 mm to 20 mm), and intraparotid. After it leaves the internal auditory canal, the facial nerve travels the fallopian canal (labyrinthine segment), running at a right angle to the petrous pyramid. Here the nerve is most susceptible to vascular and traumatic insults. The tympanic portion courses behind the cochlea and semicircular canal and ends at the beginning of the stylomastoid segment. Stylomastoid segment gives branches to stapedius muscle and the chorda tympani. Facial nerve exits through the stylomastoid foramen entering the parotid gland where it divides in upper and lower trunks. Upper trunk gives rise to frontal, zygomatic and buccal branches. Lower trunk has mandibular and cervical branches. Upper face has bilateral representation, while the lower face has contralateral representation.

Causes of Facial Nerve Lesion

Congenital

This is frequently associated with other birth defects including limb deformity, pectoral aplasia, microtia and external auditory canal atresia. Craniofacial syndrome and Möbius' syndrome are some of the examples of congenital facial palsies.

Toxins

Thalidomide embryopathy causes peripheral facial palsy. Exposure to chlorocresol and ethylene glycol may cause facial palsy.

Traumatic

Peripheral facial palsy in the context of trauma should raise suspicion of basilar skull fracture. Sphenoid electrode insertion for long term video EEG monitoring can cause facial palsy in about 20% cases.

Pregnancy

Facial palsy occurs three times more often in pregnant women as compared to non-pregnant women. Most cases of facial palsy occur in the third trimester. Neonatal outcome is unaffected.

Bilateral facial palsy

Guillain-Barre syndrome, Lyme's disease, sarcoidosis, HIV seroconversion phase, acute lymphoblastic leukaemia, CIDP and leprosy are some of the common causes of bilateral facial palsy.

Bell's palsy

It is an acute, acquired, nontraumatic, unilateral, infranuclear facial palsy. There is flaccid paresis of all facial mimetic muscles on the involved side. Affected side is smooth, the brow droops, and the cheek balloons on expiration. There is lagophthalmos and Bell's phenomenon (on attempted closure, the globe turns

up and out). Lower lid is everted with excess tearing. Various facial reflexes are lost. Lesions proximal to the geniculate ganglion affect taste sensation, lacrimation and stapedial reflex, while distal lesions cause only muscle weakness. Bell's palsy is most common in the third decade; it's incidence in the general population is about 20 cases per 1, 00,000 population. A typical patient complains of facial palsy which evolves over 24 to 48 hours, preceded by retroauricular pain. Herpes simplex virus is often blamed as the culprit. About 80% to 85% patients recover completely within three months.

Clinical Testing

Assessment of facial nerve involves five important functions: (1) functions of facial expression; (2) taste function with sugar or salt solution. Protruded tongue is touched using a stick soaked in sugar or salt solutions on one side, and patient was asked to point out at the appropriate taste written on paper before he returns his tongue into mouth. Rinsing with water between testing two different applications is a must; (3) somatic sensation from the external ear; (4) function of Stapedius muscle (hyperacusis); (5) secretomotor innervation of the lacrimal and salivary glands (Schirmer's test).

VESTIBULOCOCHLEAR NERVE

Anatomy and Physiology

The nerve is unique in that it subserves two entirely distinct sensory functions, i.e. hearing (cochlear component) and balance (vestibular component). The acoustic and vestibular systems via the eighth nerve and their diverse central connections in the brainstem, cerebellum, reticular formation, and cortex allow localisation and interpretation of the body with respect to gravity, motion, and posture. The sensory receptors for both components of cranial nerve VIII are hair cells and they are situated on the inner wall of the membranous labyrinth, which is a coiled delicate tubular structure containing endolymph. The membranous labyrinth lies inside the bony labyrinth which consists of interconnected tunnels within the petrous temporal bone.

The hair cells of the vestibular apparatus and cochlea are connected through the primary sensory neurons to the nerve cell bodies in the Scarpa's (vestibular) and spiral ganglia respectively. The central processes form the eighth cranial nerve that travels through the internal auditory meatus accompanied by the VII cranial nerve and enters medulla at its junction with pons.

The Vestibular System

The vestibular apparatus consists of the utricle, the saccule, and the three semicircular canals. Fibres are projected to the vestibular nuclei, which lie in the floor of the fourth ventricle. These nuclei consist of four separate nuclear groups viz. superior, lateral nucleus of Deiter, the medial nucleus of Schwalbe, and the descending nucleus. The superior and medial vestibular nuclei receive efferent fibres primarily from the cristae and cerebellum. Cerebellar afferents primarily synapse on the lateral vestibular nucleus.

The Cochlear System

The cell bodies of the afferent auditory neurons lie in the spiral ganglion in Rosenthal's canal, which follows the pathway of the bony spiral shelf from the apex of the cochlea towards its base. The fibres are arranged in a tonotopic manner throughout their extent till the brainstem. The cells synapse with the inner hair cells of organ of Corti. The cochlear efferent supply originates in the superior olivary complex of brainstem. The fibres of the auditory nerve bifurcate in the brainstem, and enter both the dorsal and ventral cochlear nuclei. From here, fibres are projected tonotopically, via the three striae, to inferior colliculus, medial geniculate body and auditory cortex.

Clinical Evaluation

Specialised books should be consulted for a detailed account of the following tests.

1. Function of vestibular nerve is assessed by examination of eye and postural movements. It is important to assess movements of all extraocular muscles and look carefully for nystagmus.
2. Caloric test: A caloric test can be conducted by irrigation of the external auditory canal with warm (44°C) and cold water (30°C). The head has to be elevated and should form an angle of 30 degrees from the horizontal plane, irrigation should be done for 20 seconds and after a latent period of 1.5 minutes to 2 minutes nystagmus is observed which is towards the opposite side with cold water irrigation and towards the same side after irrigation with warm water (COWS—cold opposite and warm same side).
3. Hearing test: Rinne's and Weber'.
4. Electro-oculography (EOG).
5. Electronystagmography.
6. Computerised dynamic positionography.
7. Auditory function: Pure tone audiometry, speech audiometry, tympanometry, BAER, etc.

Sensorineural Deafness

This term refers to a deficit in perceiving either tones or speech that is due to a lesion central to the oval window. This is therefore due to lesion of cochlea (sensory), cochlear nerve, nuclei (neural), or the central auditory pathways.

Tinnitus

Tinnitus and head noises are common complains which bring a patient to audiologists and otolaryngologists. The patient experiencing tinnitus may describe the sound as ringing, roaring, hissing, whistling, and rustling.

Vertigo

Vertigo refers to hallucination of movement. The most common complaint is of dizziness, a term that represents a wide range of symptoms. Peripheral causes of vertigo are peripheral vestibulopathy (labyrinthitis, vestibular neuronitis), benign positional vertigo, post-traumatic vertigo, vestibulotoxic drug-induced vertigo, Meniere's disease, other focal peripheral diseases (e.g. bacterial infections, degeneration of hair cells, genetic anomalies of labyrinth, cupulolithiasis, tumours of eighth nerve, otosclerosis, fistula of labyrinth and rarely focal ischaemia etc.).

GLOSSOPHARYNGEAL AND VAGUS NERVES

Glossopharyngeal nerve carries visceral and general sensation from the pharynx, carries subconscious sensation from the carotid sinus and body, and innervates the stylopharyngeus

muscle and the parotid gland. Vagus nerve carries visceral sensation from the larynx, pharynx, and thoracic and abdominal viscera and sends motor signals to pharyngeal, laryngeal and visceral muscles. Both these nerves mediate the complex interplay between upper aero-digestive tract functions. Dysfunction of these two nerves may lead to dysphagia, dysphonia, dyspnoea, or a combination of these symptoms.

Anatomy and Physiology

The glossopharyngeal nerve is comprised of general somatic afferent, general visceral efferent, special visceral afferent, and parasympathetic fibres that supply the tongue and pharynx.

The vagus nerve contains motor, sensory, and parasympathetic fibres. It emerges from the posterolateral sulcus of the medulla, in close association with the glossopharyngeal nerve.

Clinical Evaluation

Motor function

Pure glossopharyngeal motor paralysis may be negligible. Mild dysphagia may occur and the palatal arch may be somewhat lower on the affected side. The striated muscles of the pharynx, soft palate, and larynx are innervated by the vagus nerve. The soft palate and the uvula are examined at rest and with phonation. Pharyngeal function is evaluated by noting the character of the voice, ease of respiration and cough, and observing pharyngeal contractions during phonation. Unilateral palsy results in ipsilateral flattening of the palatal arch on phonation, ipsilateral palate fails to elevate, and uvula is retracted to the nonparalysed side. Nasal twang to speech and dysphagia may occur. Ipsilateral cord may assume cadaveric position. With bilateral vagal lesions, the palate droops bilaterally with no palatal movement on phonation. Voice is of nasal quality. There is profound dysphagia, more for liquids. Nasal regurgitation and respiratory embarrassment are other features.

Sensory function

In glossopharyngeal nerve dysfunction assessment, taste sensation is tested over posterior third of the tongue and is lost ipsilaterally in nerve lesions. Pain and soft touch is ipsilaterally lost over posterior third of the tongue, soft palate, tonsils and pharyngeal region. The vagus nerve sensory dysfunction cannot be tested adequately, as the area of supply overlaps with other cranial nerves, and some of the structures are inaccessible.

Reflex function

Pharyngeal and palatal reflexes are absent on the side of the lesion. In cases of vagus nerve dysfunction, ipsilateral gag reflex is depressed as the efferent fibres are carried in the vagus nerve.

The gag reflex prevents the entry of foreign objects into the alimentary and respiratory passages. Both cranial nerves IX and X are assessed by testing the gag reflex. The right and left side of the pharynx should be lightly touched with a tongue depressor. The IX nerve acts as the sensory afferent and the X nerve as the motor efferent.

LESIONS OF THE IX AND X NERVES

Nuclear and Intramedullary Lesions

This may occur in syringobulbia, demyelination, vascular disease, motor neuron disease and malignancy. These lesions cause involvement of other cranial nerves and brainstem structures.

Extramedullary Lesions

Cerebellopontine angle syndromes: Acoustic tumours may involve the nerve here. The involvement is associated with tinnitus, deafness, and vertigo. Lesions within the posterior fossa like primary or metastatic tumours, infections, carcinomatous meningitis, sarcoidosis and Guillain-Barre syndrome are some of the causes of lower cranial nerve dysfunction.

Jugular Foramen (Vernet's) Syndrome

This syndrome consists of ipsilateral sternomastoid and trapezius weakness, dysphonia, dysphagia, impaired gag reflex, palatal droop and vocal cord paresis on the affected side, with loss of sensation over the posterior tongue and palate. Unilateral, dull aching pain, localised behind the ear is often associated. Glomus jugulare tumours, skull base fractures, and metastasis can involve the glossopharyngeal, vagus, and accessory nerves which travel through this foramen.

Lesions within the Retropharyngeal and Retroparotid Space

Neoplasms, vascular compression, abscesses, adenopathy, trauma can involve the nerve in these spaces. This results in Collet-Sicard's syndrome (involvement of 9th, 10th, 11th, and 12th cranial nerves) and Villaret's syndrome (involvement of 9th, 10th, 11th, and 12th cranial nerves, sympathetic chain and occasionally 7th cranial nerve).

Lesions of the Vagus Nerve

Tumours, aneurysms, trauma and enlarged lymph nodes can injure the vagus nerve in the neck and in the thorax. This results in complete vocal cord paralysis with unilateral pharyngeal anaesthesia.

Lesions of the Superior Laryngeal Nerve

Trauma, surgery, and tumour may damage this nerve. This results in mild hoarseness of voice.

Lesions of the Recurrent Laryngeal Nerve

Aneurysm, enlarged lymph nodes, mediastinal lymph nodes and surgical intervention can damage this nerve, more so on the left side. Unilateral insult causes transient hoarseness of voice, while bilateral palsy results in severe bilateral approximation of the cord resulting in airway limitation, stridor, and severe limitation of voice.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is characterised by severe sharp, lancinating pain in the region of the tonsil, radiating to the ear. Patient usually describes an abrupt pain in the throat or ear that lasts for a few seconds and is triggered by chewing, swallowing, yawning etc.; occasionally the pain may be associated with syncope (bradycardia and hypotension causing the fall). This is often idiopathic, and occasionally tumour, vascular compression, trauma and demyelination may cause this syndrome.

ACCESSORY NERVE

The spinal accessory nerve, primarily a motor nerve, innervates two major muscles, the sternocleidomastoid and the trapezius, in the neck and back. The lower motor neuron cell bodies are located within the rostral spinal cord. The accessory nucleus is a column of cells located in the anterolateral grey area of

the upper cervical spinal cord segments, which anatomically correlate the location of the nucleus ambiguous above and the dorsolateral part of the ventral horn of the spinal cord below.

Clinical Evaluation

Sternomastoid muscle

This muscle flexes the head and turns it from side to side. When one muscle contracts, the head is rotated and drawn to the ipsilateral shoulder so that the occiput is pulled toward the side of the contracting muscle. When both sternomastoids contract simultaneously, it results in flexion of neck.

Trapezius muscle

The muscle retracts the head and also elevates, rotates and retracts the scapula. It also assists in raising the abducted arm above the horizontal.

HYPOGLOSSAL NERVE

Anatomy and Physiology

The hypoglossal nerve is the motor nerve of the tongue. Its fibres arise from the hypoglossal nucleus, situated in the paramedian medulla, beneath the hypoglossal trigone of the floor of the fourth ventricle.

Clinical Evaluation

Observe the tongue at rest, after protrusion, and assess the strength while the tip of tongue is pushed against the cheek and rapidity of tongue movements. Unilateral lower motor neuron lesions cause paresis, atrophy, furrowing, and fasciculation. The tongue deviates to the paretic side on protrusion due to unopposed action of the normal contralateral genioglossus muscle. Dysphagia and dysarthria are minimal. Protrusion of tongue requires the action of the extrinsic muscles, whereas lateral movements of the nonprotruded tongue are accomplished by the intrinsic muscles. Bilateral lower motor neuron lesions of the tongue result in bilateral atrophy, weakness and fasciculation. The tongue cannot be protruded voluntarily. Marked dysarthria, dysphagia, and breathing difficulties may be associated.

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20.8 Ischaemic Cerebrovascular Diseases

PM Dalal

INTRODUCTION

'Stroke' is defined as rapid onset of focal neurological deficit, resulting from diseases of the cerebral vasculature and its contents. The term 'transient ischaemic attacks' (TIA) implies complete recovery of such a deficit within 24 hours. Cerebral or subarachnoid haemorrhage is consequent to rupture through some acquired or inherent weakness of the vessel wall (see chapter on Haemorrhagic Cerebrovascular Diseases). Stroke represents third most common cause of death in developed nations. For India, community surveys have shown a crude prevalence rate for 'hemiplegia' in the range of 200 per 100,000 persons, nearly 1.5% of all urban hospital admissions, 4.5% of all medical and around 20% of neurological cases.

PATHOGENESIS

The normal functions of the brain are dependent upon a relatively constant supply of oxygen and glucose derived from the blood perfusing it (55 mL to 70 mL of blood/100 g of brain/min). The principal source of energy is almost exclusively oxidation of glucose. If the blood flow is critically reduced below 15 mL/100 g/min, the resulting ischaemia with hypoxia, when sufficiently prolonged, may cause death of neurons and glia (cerebral infarction).

The mean arterial blood pressure, cerebrovascular tissue resistance, local metabolic products (pH, PaO_2, $PaCO_2$), together with several known and unknown factors, help to maintain the critical threshold of blood flow for energy metabolism. Furthermore, the blood flow varies in different areas of the brain and a self-regulatory mechanism ('autoregulation') determines the regional flow to meet local metabolic needs.

In regions of cerebral ischaemia, there is 'paralysis of autoregulation' and the microvasculature is non-reactive to pressure changes, to vasoactive agents and to other forms of stimuli. The cerebral vasculature in this ischaemic zone becomes permeable to protein and fluid leaks in the vicinity (extracellular cerebral oedema). Such vascular events also lead to local haemoconcentration and vascular stasis.

To protect the brain from ischaemia, several collateral pathways exist. The four major extra-cranial arteries (carotid and vertebral arteries) form good-calibre, low-resistance anastomoses at the base of brain ('Circle of Willis'). In addition, extra-cranial anastomoses exist between the cervical branches of the ipsilateral external carotid, subclavian and vertebral arteries. Such arterial anastomoses help to maintain cerebral blood supply even with occlusion of major extra-cranial arteries or various intra-cerebral arteries. These post-Willisian anastomoses further protect the brain tissue from the effects of occlusion of single cortical branches (**Figure 1**). However, in the presence of generalised arterial disease or multiple skipped stenotic lesions (atherosclerosis), anomalous or congenital variations, these collateral pathways may prove inadequate and predispose to cerebral ischaemia resulting in brain infarction.

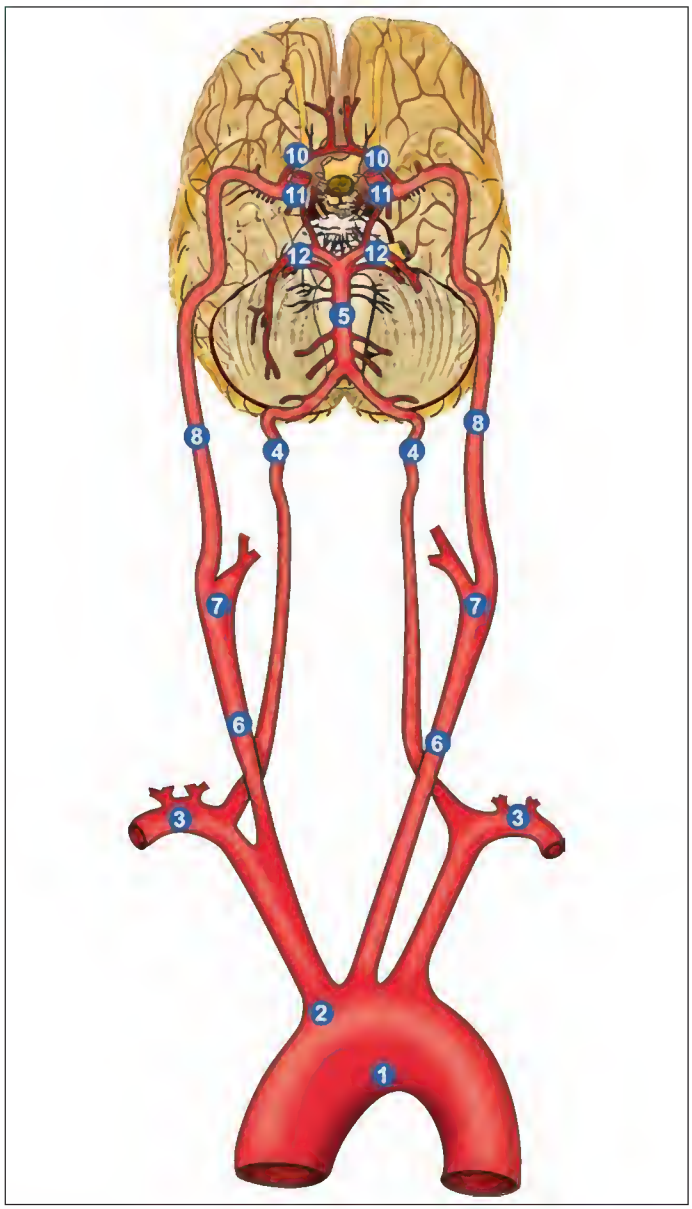


Figure 1: Cerebral collateral circulation. Aortic arch (1), Brachiocephalic artery (2), Subclavian artery (3). The four major cerebral vessels, i.e. the carotid system (6,7 and 8), and the vertebro-basilar system (4 and 5), unite at the base of the brain to form a hexagonal 'Circle of Willis'. These vessels form a network of extensive anastomoses between themselves, in the neck (pre-Willisian anastomoses). Their cerebral branches: the anterior cerebral (10), the middle cerebral (11), and the posterior cerebral arteries (12) anastomose with themselves distal to the circle of Willis (post-Willisian anastomoses).

GENERAL CLASSIFICATION

Table 1 outlines the classification of cerebrovascular diseases. Three types of major strokes are now recognised. These are ischaemic, haemorrhagic and lacunar strokes. Ischaemic variety with cerebral infarction results from atherothrombosis or brain embolism to cerebral vessels. The term transient ischaemic attack implies cerebral ischaemia with complete recovery of focal neurologic deficit within 24 hours, resulting from platelet-fibrin microemboli ('embolic hypotheses) or 'haemo-dynamic crisis.' Haemorrhagic stroke with bleeding within the central nervous tissue occurs due to ruptured cerebral aneurysm in the young and hypertensive intra-cerebral bleeding in the elderly. Lacunar strokes are deep, small cerebral infarcts located in basal ganglia or deep white matter, resulting from diseases of small penetrating vessels.

Table 1: Classification of Cerebrovascular Diseases

Ischaemic strokes
- With cerebral infarction
  - Cerebral thrombosis with or without atherosclerosis
  - Cerebral embolism (congenital heart disease and acquired valvular disease, cardiomyopathy, myocardial infarction, endocarditis, prolapsed mitral valve, etc.)
  - Lacunar strokes (deep, small cerebral infarcts)
  - Cerebral venous thrombosis and cortical thrombophlebitis
  - Arteritis (syphilitic, tuberculous, rheumatic, Takayasu's disease, collagen diseases, etc.)
  - Blood diseases (polycythaemia, sickle cell anaemia, procoagulant states like protein C and protein S deficiency, raised anticardiolipin antibodies or circulating lupus anticoagulants, hyperproteinaemia, etc.)
  - Arterial hypotension and anoxic encephalopathy
  - Dissecting aneurysms of brachiocephalic vessels
  - Angiographic complications
  - Infarction of undetermined cause (e.g. AIDS-related syndromes)
- With cerebral ischaemia
  - Transient ischaemic attacks (platelet-fibrin microemboli associated with atheroma or cardiac diseases, etc.)
  - Local embolism from proximal atheromatous plaques and paradoxical embolism
  - With cardiac arrhythmias (atrial fibrillation, complete heart block, sick-sinus syndrome, etc.)
  - Arterial hypotension or haemodynamic crisis (e.g. massive gastrointestinal bleeding)
  - Vasospasm with migraine or subarachnoid haemorrhage
  - Undetermined source

Idiopathic and rare types
- Drugs and oral contraceptives, disseminated intravascular coagulopathy, consumption coagulopathy, cerebral malaria, Behcet's syndrome, cerebral amyloid angiopathy, hyper-homocysteinaemia/homocystinuria, hyperviscosity syndrome, paraproteinaemia, etc., cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)

Haemorrhagic stroke
- Discussed in Chapter on Haemorrhagic Cerebrovascular Diseases

Stroke of undetermined origin
- Multi-infarct dementia in lacunar syndromes or leucoaraiosis
- Moyamoya disease
- Fibromuscular dysplasia
- Binswanger's subcortical arteriosclerotic encephalopathy
- Winiwarter-Buerger disease (thromboangitis obliterans - cerebral form)
- Aortic arch syndrome (non-inflammatory)
- Unclassified syndromes

ISCHAEMIC CEREBROVASCULAR DISEASES (CEREBRAL ISCHAEMIA AND INFARCTION)

General Considerations

If, for any reason, such a cardiac arrest or prolonged hypotension [systolic blood pressure (BP) falls below 70 mm Hg] occurs, brain tissue is significantly deprived of its nutrition for more than three minutes, ischaemic-hypoxic cerebral injury or infarction results. Such infarcts are either pale (ischaemic infarction in thrombosis) or may show petechial haemorrhages in the cortical mantle (haemorrhagic infarction in brain embolism). The sylvian region is commonly involved in middle cerebral artery occlusion (mid-field infarct) whereas with internal carotid artery lesions; the cerebral infarction is mostly located in the distal territory (end-field infarction).

A mid-field infarct is produced by occlusion of a small penetrating vessel, and if located in the territory of major anatomical pathways, it may prove catastrophic. On the other hand, an end-field infarct resulting from occlusion of a major vessel in the neck with good collateral circulation may be asymptomatic. Obstruction to venous return can also result in haemorrhagic infarction (e.g. cortical cerebral venous thrombosis). Acutely infarcted brain tissue is soft and swollen, frequently herniates downwards and may compress the vital centres within the brainstem, with fatal outcome. Like infarction elsewhere in the body, cerebral infarcts heal by gliosis leaving a firm scar or a cystic cavity.

Aetiopathology and Pathophysiology

Cerebral infarction is usually attributed to partial or total occlusion of its regional microvasculature by thromboembolism (**Figure 2**). Cerebral atheroma is by far the most common underlying intimal vascular pathology, whereas thrombosis associated with arteritis (syphilitic, rheumatic, tuberculosis) is not an uncommon aetiology for 'strokes in the young' in India.

Experimental studies on pathophysiological events leading to infarction have shown that there is a dense central core, surrounded by a less dense zone of ischaemia ('penumbra') and neuronal death occurs in this central focus unless perfusion is quickly restored. On the other hand, cells in the zone of penumbra remain viable for about three hours ('therapeutic window') and can be salvaged by reperfusion or neuro-protective agents. Major factors, which enhance neuronal injury, are an increase in intra-cellular cytosolic calcium concentration from failure of ionic-pump functions or 'leaks', changes in Na^+/K^+ gradients, acidosis, release of free radicals and other unknown factors, which in turn disrupt the blood-brain barrier (BBB) and microvascular function. Energy depletion from brain hypoxia is one of the key events that fails to maintain normal concentrations of cellular adenosine triphosphate (ATP), leading to delay in re-synthesis of macromolecular proteins essential for endothelial cell structure and function. Energy failures also induce proteolysis and lipolysis, production of arachidonic acid and platelet activating factors, cell adhesion molecules, nitric oxide and free radicals, post-ischaemic hypo-perfusion or hyper-perfusion injuries resulting in further neuronal damage ('ischaemic cascade hypothesis'). Thus, development of cerebral infarct is not merely the result of ischaemia but the end-result of several highly complex 'ischaemia-modifying factors.' For

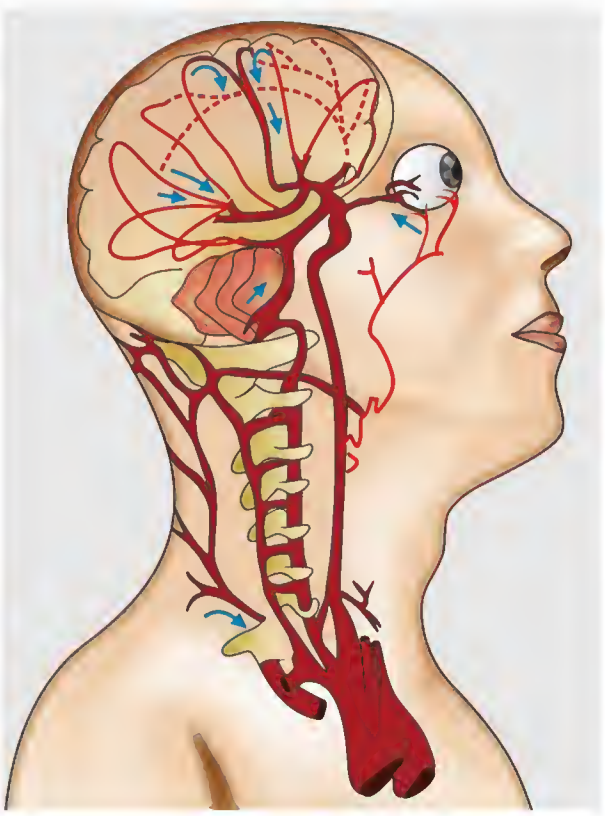


Figure 2: Arrows denote the alternative route of blood supply in the event of a major block in the neck vessels (e.g. carotid or the vertebral arteries), via costo-cervical and the thyrocervical anastomoses. Likewise, leptomeningeal anastomoses over the cerebral hemispheres (arrows) will try and limit the size of an infarct from an isolated branch occlusion (Diagrammatic presentation).

example, exposure of vascular endothelium to raised homocysteine (>100 µmol/L) levels leads to reduced nitric oxide, increased levels of adhesion molecules and expression of procoagulant factors like plasminogen activator inhibitor (PAI-1), tissue plasminogen activator (tPA), protein C (PC) and thrombomodulin (TM), which in turn promote platelet aggregation, leucocytes adhesion and thrombosis.

Clinical Features

Obesity, feeble or absent peripheral arterial pulsations, vascular bruits, unequal or raised blood pressure, postural hypotension and retinopathy may be detected during general physical examination.

In about 60% of the patients, prodromal warning symptoms of TIA may precede. Such episodes of TIA are usually brief (lasting for a few minutes to less than an hour) and may come singly or in successive spells over a number of hours or days or months, and leave no significant residual signs. TIAs may not be always related to posture or the level of BP, and may disappear altogether. However, in some cases (10% to 15%), an evolving or a full-blown stroke may follow the last ischaemic spell.

When the stroke evolves in a stepwise manner, ('thrombosis in evolution') the symptoms may appear in each limb in succession or simultaneously. This stuttering or intermittent progression is typical of atherothrombosis. Not infrequently, the stroke may announce itself abruptly as a single major catastrophic event (accomplished infarction or completed stroke). The other clinical manifestations depend on the site of arterial occlusion. The specific neurovascular syndromes, which result from there, are described below.

Internal carotid syndrome

The cervical portion of the internal carotid artery near the carotid sinus is a common site for athero-stenosis (**Figures 1 and 2**) and about 60% of all thrombotic lesions are located here. Often, these lesions may be asymptomatic because of collateral anastomoses (external carotid-ophthalmic anastomoses or from superficial and deep cervical anastomoses or from the opposite carotid artery through the anterior segment of the Circle of Willis). Warning symptoms precede a major ictus in nearly 50% of the subjects. Such symptoms include brief episodes of confusion, with speech difficulty (aphasia, dysarthria, dyslexia), sensory paraesthesia with or without motor weakness of the opposite side. Ipsilateral amaurosis fugax (transient monocular blindness), fleeting or semi-permanent, alternating with or accompanied by a contralateral hemiplegia or sensory deficit, is pathognomonic of carotid artery syndrome; however, these events occur in only 15% to 20% of the patients.

The clinical manifestations of acute carotid artery occlusion are almost indistinguishable from those of middle cerebral syndrome. Feeble internal carotid or superficial temporal artery pulsations, dilated pupil and poorly pulsating retinal vessels on the side of the suspected carotid lesion and ocular or cervical bruits on the ipsilateral side may suggest the correct diagnosis. Carotid duplex Doppler sonography and angiography are helpful in defining the extent and degree of stenosis.

In patients with an old or silent occlusive carotid artery lesion on one side, a new lesion on the opposite side may prove catastrophic. Here, the physical finding of bilateral hemiplegia (quadriplegia) with coma can be mistaken for basilar artery syndrome.

Asymptomatic cervical bruit

A carotid bruit may be heard in the neck in about 5% of asymptomatic elderly patients (55 years to 80 years). Unless haemodynamically significant, it is very difficult to correlate the mere presence of a bruit with a subsequent TIA or stroke in that territory. The role of prophylactic endarterectomy to prevent a future stroke (estimated at 6% within next 3 years) has not been established by clinical trials. In such cases antiplatelet therapy may be prescribed.

Middle cerebral syndrome

The cortical branches supply lateral surface of the cerebral hemisphere, except for the regions supplied by the anterior and posterior cerebral arteries. The areas of supply include the sensory-motor cortex, the motor and sensory speech centres, auditory area and optic radiation. The penetrating branches (lenticulo-striate arteries) supply the putamen, globus pallidus, genu and posterior limb of the internal capsule.

The clinical picture of middle cerebral artery occlusion is variable. Contralateral hemiplegia, hemianaesthesia with or without homonymous hemianopia and aphasia (dominant hemisphere) are common manifestations. Occlusion of the superior division presents as contralateral hemiparesis with sensory deficit and expressive aphasia (Broca's aphasia), whereas Wernicke's aphasia

(sensory aphasia) is frequent with lesions of the inferior division of dominant side. Monoplegic symptoms with lesion of single cortical branches are not uncommon.

Occlusion of penetrating branches (lenticulo-striate arteries) has been repeatedly blamed for a dense sensorimotor hemiplegic syndrome ('capsular-hemiplegia'), but significant sensory loss seldom occurs with such a lesion and 'pure motor hemiplegia' is common.

Anterior choroidal syndrome

This artery supplies the posterior limb of the internal capsule, which carries the corticospinal and sensory fibres for the contralateral limb. This syndrome, which represents a true 'capsular-hemiplegia' (dense hemiplegia, hemianaesthesia and homonymous hemianopia), is rare.

Anterior cerebral syndrome

The cortical branches mainly supply the medial superior surface of the frontal lobe and the parietal lobe up to the paracentral lobule. The penetrating branches supply the anterior limb of the internal capsule and part of the head of caudate nucleus.

An anterior cerebral artery occlusion proximal to the anterior communicating artery, in subjects with a symmetrical Circle of Willis, is frequently asymptomatic. Occlusion, distal to the anterior communicating artery, manifests itself by a sensorimotor paralysis of the opposite lower extremity with mild weakness of the opposite shoulder. Mental changes, ictal and urinary incontinence, gait disturbances, apraxia, grasp and sucking reflexes may accompany the above findings.

Occlusion of an unpaired anterior cerebral artery (supplying both the hemispheres) results in a cortical type of paraplegia, with sphincter incontinence and a mental state in which the patient is alert but mute (akinetic mutism). Aphasia and hemianopia are never seen.

Occlusion of the penetrating branches and of the Heubner's artery is frequently blamed for ataxic tremors of the contralateral limbs (frontal ataxia). Apraxias, idiomotor dyspraxia of the limbs and gait may also be present.

Posterior cerebral syndrome

This artery supplies the medial and inferior aspects of the occipital and temporal lobes. Its branches also supply the midbrain, cerebral peduncle, most of the thalamic and sub-thalamic regions.

Embolic occlusion of the posterior cerebral arteries is not uncommon. Contralateral homonymous hemianopia is a significant finding and this results from infarction of the primary visual area (calcarine cortex); the central vision is frequently spared, even in cases with bilateral disease (gun-barrel vision). Other manifestations of visual dysfunction include illusory or distorted vision, visual-object agnosia and various forms of dyslexia without dysgraphia. The pupillary reflexes are well preserved. Contralateral hemiplegia from lesion of the cerebral peduncle (peduncular hemiplegia) and thalamic syndrome (Dejerine-Roussy syndrome) may also be present. In the thalamic syndrome, there is varying degree of sensory loss to all modalities and spontaneous burning or agonising pains are frequent (analgia dolorosa). Memory loss (amnesia) suggests lesion of the medial temporal cortex. Contralateral involuntary choreoathetosis or ataxic tremors are rarely observed.

Vertebro-basilar syndrome

After traversing through the bony vertebral canals both vertebral arteries unite intra-cranially to form the basilar trunk. Their short paramedian and long circumferential branches supply the entire brainstem, cerebellum and the vestibular apparatus. TIA manifest as episodes of vertigo, dizziness, diplopia, dysarthria, dysphasia, incoordination of gait and limbs and bilateral signs of sensorimotor deficit. Occipital headaches may be present. Ipsilateral 3rd nerve palsy with contralateral hemiplegia (Weber's syndrome) or with crossed cerebellar ataxia (Claude's syndrome) is diagnostic of midbrain localisation. Homolateral paralysis of the 7th nerve with contralateral hemiplegia and hemianaesthesia (Millard-Gubler syndrome) is suggestive of a pontine lesion. Palatal paralysis and ataxia of limbs, with impairment of posterior column sensation on same side of the body accompanied by diminution of pain and thermal sense on the opposite limbs (Wallenberg's syndrome) indicate lateral medullary infarction from a distal vertebral artery lesion.

Quadriplegia with bilateral conjugate, lateral gaze palsy and 'mute state' with fully preserved consciousness has been described ('locked-in syndrome') in infarction of the basis pontis (sparing the tegmentum), from a mid-basilar occlusion.

Occlusion of isolated cerebellar branches may produce dizziness, nausea, vomiting, nystagmus and appendicular or truncal ataxia without sensorimotor deficit in any limb. Such a syndrome should be differentiated from cerebellar haemorrhage where emergency surgical decompression may prove life-saving.

Aortic arch syndrome

The intriguing clinical syndrome is characterised by diminution or absence of the arterial pulsations in the vessels of the arms and the neck; the seat of the disease, irrespective of its aetiology, being located near the origins of the great vessels arising from the aortic arch.

Several aetiological factors like congenital anomalies, trauma with or without aneurysm, chronic dissecting aneurysm, mediastinal tumours, thrombophilia syphilitic aortitis and atheromatosis appear to be one of the causes of this syndrome, and that an arteritis of undetermined origin is responsible for a good number of female cases. Likewise, it has been a prevalent impression that nearly all the cases of aortic arch syndrome reported from India are a form of arteritis of rheumatic, syphilitic or undetermined origin. It has now been appreciated that the primary lesion in such cases, particularly in men, may not always be an arteritis.

Laboratory and Other Investigations

Complete haemogram with platelet count, erythrocyte sedimentation rate, bleeding, clotting and prothrombin time are routine screening tests for the diagnosis of anaemia, polycythaemia and bleeding diathesis. Tests for sickle cell, anticardiolipin antibodies, or circulating lupus anticoagulant, C-reactive protein are performed when indicated. Blood sugar, urea, lipids, uric acid and electrolytes are other baseline

investigations. In thrombotic strokes, at any age, where common risk factors are not present, protein C and protein S deficiency and homocysteinaemia should be looked for. Genetic and chromosomal studies are rarely indicated.

Chest radiograph and serial electrocardiograms are essential. In cardioembolic studies, two-dimensional echo (transthoracic or trans-oesophageal) is of great value whereas Holter monitoring should be done when indicated.

Electroencephalography (EEG) is not of diagnostic value but examination of cerebrospinal fluid (CSF) within 7 days of the ictus is helpful in the diagnosis of cerebral haemorrhage (80%) and in nearly 90% of subarachnoid haemorrhagic (SAH) cases. Red cell and leucocyte counts per mm^3 of CSF in three citrate bulbs will differentiate a traumatic tap. VDRL of blood and CSF, fluorescent treponemal antibody absorption tests (FTA-ABS) and HIV test are necessary for the diagnosis of syphilis and AIDS-related vascular syndromes.

Duplex sonography and transcranial Doppler studies have assumed significant role in evaluation of extra-cranial and intra-cranial carotid arteries, in assessing the degree of narrowing (stenosis) and location of superimposed thromboemboli, if any. This is an investigator-oriented test and individual variations in defining degree of stenosis are common. Nonetheless, serial evaluation by same investigator using well standardised diagnostic set up is useful. The nature of lesions (stenosis, etc.) may need to be verified by magnetic resonance (MR) or computed tomography (CT) angiography. If surgical intervention is planned, it would be more meaningful to define available collateral circulation and precise degree of narrowing by digital subtraction angiography (DSA). There is a correlation between intima-media thickness (? early athero lesions) and elevated lipid levels and here serial follow-up evaluation to judge regression by statin therapy is often recommended.

Computerised cranial tomography is the single-most important non-invasive investigation to distinguish an ischaemic infarction and cerebral haematoma from other conditions simulating strokes (e.g. subdural haematoma, tumour). It also provides an estimate of the extent and location of supratentorial cerebral infarction, including small (0.5 cm) lacunar infarct. It can also detect surrounding oedema and haemorrhagic infarction. However, it may not differentiate early (within 1 to 3 hours) ischaemic lesion from normal tissue. Brainstem lacunaes are difficult to detect by conventional CT.

In subjects having TIA or reversible ischaemic neurologic deficit (RIND), carotid Doppler sonography helps to detect carotid artery lesion, but magnetic resonance angiography (MRA) or DSA will clearly define the cerebral vasculature, the extent and degree of ulcerated atheromatous lesions, and will help in eventual medical or surgical management. The hazards of DSA in comatose patients with dense neurologic deficit and decompensated cardiac status should be carefully weighed.

Magnetic resonance imaging (MRI) (T2 weighted, diffusion and perfusion weighted studies) of brain, and visualisation of cerebral arteries by MRA in hyperacute (within 1 to 3 hours) ischaemic strokes defines the extent and severity of arterial and cerebral lesions, which are usually not well seen on routine CT evaluation. Thus, MRI with MRA helps a great deal in taking therapeutic decisions like thrombolytic therapy. The DSA is performed when surgical intervention is contemplated. SPECT of brain with specific radio-pharmaceutical agent can be performed to study cerebrovascular reactivity in regions of hypoperfusion.

Course and Prognosis

In subjects who survive stroke, some degree of recovery is the rule. Chances of significant recovery are remote when no improvement is noted within first 6 weeks to 8 weeks. About 20% to 25% of the patients with massive cerebral infarction and brain swelling die during the acute phase. Here, old age, presence of severe neurological deficit with coma and pyrexia, intercurrent infections, poorly controlled hypertension, diabetic states and basilar artery thrombosis are of grave prognostic significance.

Recurrent episodes are frequent but there is no way to predict the same in a given subject. However, control of 'risk-factors' is beneficial (*see stroke prevention*).

Differential Diagnosis

The principal hallmarks of cerebral infarction resulting from thromboembolism include prodromal warning symptoms with rapid onset of focal neurologic deficit, stuttering or intermittent progression, a constellation of symptoms and signs diagnostic of a well-defined neurovascular syndrome, relative preservation of consciousness, clear CSF, some degree of recovery, and evidence of vascular disease elsewhere in the body.

In distinguishing cerebral haemorrhage from cerebral infarction, the following collective criteria may prove helpful: moderately severe to intense headache (throbbing, pulsating or pounding) in a known hypertensive subject, accompanied by nausea and vomiting; altered state of consciousness (drowsiness progressing to deepening coma) with irregular respirations; neck stiffness accompanied by dissociated eye movements, or forced gaze deviation; blurred disc margins or pre-retinal haemorrhage, with changes suggestive of hypertensive retinopathy and hemiparesis on one side with shivering movements or even frank convulsions on the non-paralysed side or quadriparesis (paucity of withdrawal movements to pinch stimuli in each limb), with an extensor plantar response on both sides. Presence of blood in the CSF will settle the diagnosis in majority. It should be noted that nearly 30% survive a small intra-cerebral bleed. However, haemorrhagic cerebral infarction in a hypertensive subject and occult intra-cerebral bleed (haematoma or slit haemorrhage) may show a clear CSF at the onset. Here, CT scanning is invaluable in arriving at a diagnosis.

Subdural haematoma and other mass lesion may mimic a stroke. A history of headache or seizures, papilloedema, raised spinal fluid pressure and xanthochromia with elevated protein content, midline shift of a calcified pineal gland on skull radiograph, or shift of midline on echoencephalography, suppressed alpha activity or high-voltage slow waves on EEG and abnormally high local concentrations of radioisotope in brain scan, all point to the true nature of the lesion. CT or cerebral angiography helps to settle the diagnosis, but isodense subdural haematoma can often be misdiagnosed as an infarct.

A history of head injury, careful cranial examination for marks of injury, blood-stained CSF and characteristic radiographic

findings like fracture easily differentiate post-traumatic conditions from strokes.

Post-epileptic hemiplegia (Todd's paralysis) with complete recovery may simulate transient cerebral ischaemia. Clinical history suggestive of seizure disorders with EEG abnormalities in a young subject proves helpful in arriving at a correct diagnosis.

Posterior fossa tumours, the administration of sedatives or tranquillisers, multiple sclerosis, vestibular disorders and hysteria may simulate vertebro-basilar artery disease, but seldom present diagnostic problems. Here, meticulous history with serial clinical observations proves more helpful.

Transient Ischaemic Attack (TIA Syndrome)

The term transient ischaemic attack implies complete recovery of focal neurologic deficit in stroke syndrome within 24 hours. In RIND, the paresis may persist for more than 24 hours with nearly complete recovery within a week. During a follow-up of nearly five years 30% of TIA patients develop a full-fledged stroke.

Among proposed theories for TIA, the 'embolic hypothesis' and 'haemodynamic crisis' are gaining support. It is suggested that platelets begin to adhere over exposed collagen of denuded intimal surface and triggers the release of phospholipids and arachidonic acid, cyclooxygenase enzyme converts arachidonic acid into a potent platelet aggregator (thromboxane-A_2). Acetylsalicylic acid (aspirin) blocks this enzyme activity and thereby helps in prevention of TIA. Dipyridamole blocks enzyme phosphodiesterase to achieve effect similar to aspirin. Furthermore, endothelial cells release prostacyclin (PG_2), which also prevents aggregation of platelets.

Repetitive (5 to 10 attacks/day), short-lived (<15 min), typical spells of hand and arm weakness suggest proximal arterial narrowing with poor collateral circulation producing transient focal ischaemia. On the other hand, a single spell of speech difficulty with or without arm involvement lasting for about 12 hours suggests embolic ischaemic attack with some degree of infarction. The specific type of TIA points to the particular artery involved.

Treatment of Ischaemic Cerebrovascular Disease

An outline of diagnostic evaluation and the emergency management of an acute stroke case (acute hemiplegic syndrome) are described in **Figure 3**.

Medical Management

The goal of therapy is to avoid development of cerebral infarction and, if already present, to restrict its progression or recurrence. Treatment is divided into three phases: phase I—saving life and speedy recovery; phase II—rehabilitation to achieve adaptation (physical, occupational, social) for a gainful employment; and in phase III—emphasis is laid on prevention of the recurrence of stroke.

Phase I

General measures and intensive care: In acute stage of cerebral ischaemia (ASCI), maintenance of vital signs (temperature, pulse, respiration, BP), patency of airway, fluid and electrolyte balance, and prevention of complications like pulmonary aspiration, seizures, thrombophlebitis, and bedsores are mandatory. Here, general medical and meticulous nursing care is of paramount importance. Hyperglycaemia or hypoglycaemia should be appropriately treated. Acute stroke is now recognised as a medical emergency and specialised care in intensive stroke units is generally recommended.

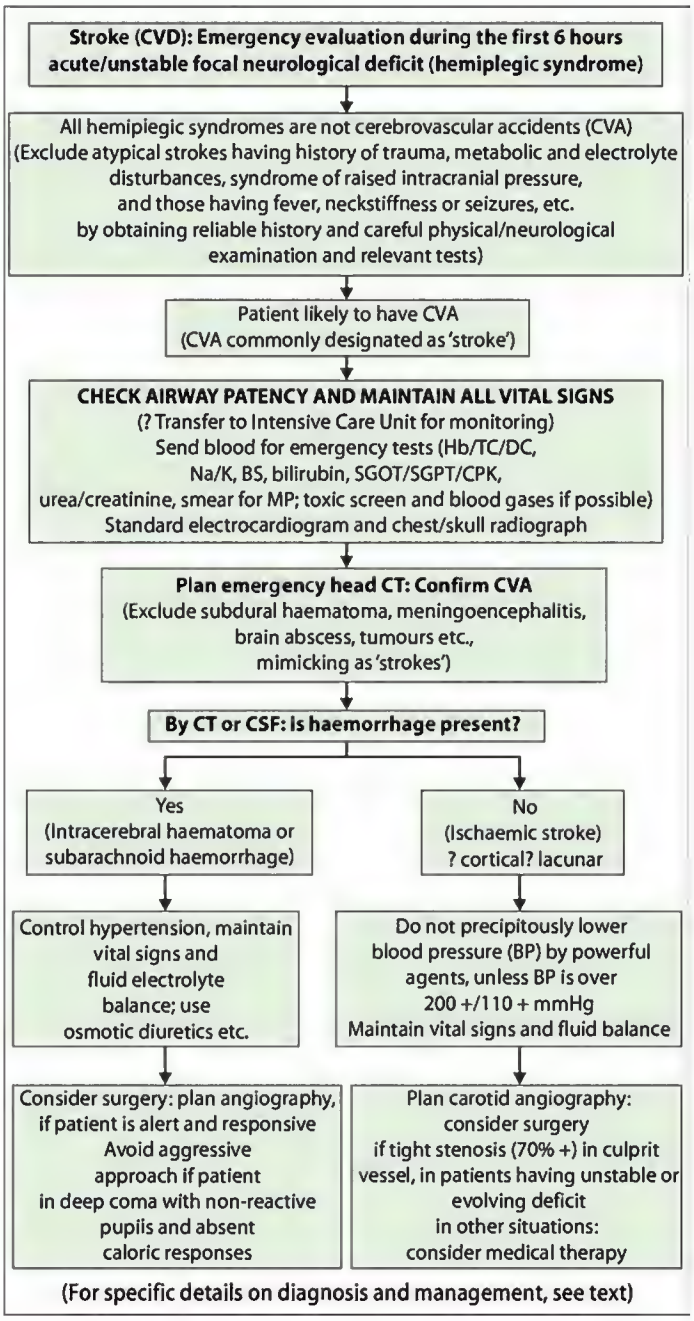


Figure 3: Diagnostic evaluation and emergency management of an acute stroke.
Courtesy: Modified from US National Stroke Association recommendations for the emergency evaluation and treatment of stroke.

CVD = Cerebrovascular disease; Hb = Haemoglobin; TLC = Total leucocyte counts; DLC = Differential leucocyte counts; Na = Sodium; K = Potassium; BS = Blood sugar.

Ventilation: Cerebral hypoxia in ischaemic and haemorrhagic strokes carries grave prognosis because it predisposes to cerebral oedema and raised intra-cranial pressure (ICP) and may precipitate brain herniation. Therefore, every effort should be made to keep the airway patent by preventing accidental aspirations and gentle care of pulmonary secretions with utmost sterile precautions. Here, administration of oxygen (4 to 6 litres/minute) preferably through an oxygen tent, is now routinely advocated. Ventilator support is indicated with O_2

saturation less than 90% or raised $PaCO_2$ or in comatose subjects having signs of cerebral hypoxia secondary to hypoventilation. Ear oximetry monitoring is helpful.

Blood pressure control: In acute stroke, 'cerebral autoregulation' is lost and blood flow in the infarcted areas is solely dependent on mean arterial BP. In the presence of severe hypertension (e.g. BP over 220/120 mm Hg) parenteral therapy with titratable agents such as intravenous (IV) labetalol or enalapril which reduce BP smoothly are recommended. Calcium channel blockers are best avoided because they produce marked fall in BP in some patients. On the other hand, raised BP levels in patients with hypertensive and non-hypertensive stroke often falls unpredictably within 24 hours to few days, worsening perfusion in ischaemic penumbra leading to irreversible injury. Therefore, any significant hypotensive episode should be promptly treated to prevent extension of cerebral infarction.

Fluids, electrolyte balance and blood glucose: Ischaemic tissue with break in the 'blood-brain barrier' (BBB) retains fluid, predisposing to cerebral oedema. Thus, a phenomenon of 'cerebral squeeze' sets in and this compresses the adjacent viable neuronal tissue; the swollen brain may also herniate transtentorially onto the vital brainstem areas and thereby impair level of responsiveness and increase the neurological deficit. Irrespective of stroke subtype, hyper-glycaemia (plasma glucose more than 200 mg/dL or 10 mmol/L) is associated with increased mortality or reduced functional outcome, and insulin therapy may be desirable. Likewise, IV 5% dextrose in water is best avoided in early stages of massive cerebral infarction with brain swelling. Judicious restriction of fluid intake (parenteral) in first 48 hours is often advocated. On the other hand, excessive use of diuretics may precipitate cerebral hyponatraemia.

Measures to improve cerebral blood flow: Haematocrit is one of the chief determinants of whole-blood viscosity. It is postulated that lowering the haematocrit value to 30% to 33% with haemodilution therapy improves cerebral blood flow and oxygenation of infarcted tissues. However, results of recent randomised trials have failed to show consistent beneficial effects of haemodilution therapy.

Reduction of increased intra-cranial pressure and cerebral oedema: With raised ICP, the head should be elevated by 30°. If associated with increasing drowsiness, intubation and hyperventilation to keep partial pressure of carbon dioxide (PCO_2) at 25 to 30 mm Hg would be helpful. In hypertensive crisis (BP more than 240/130 mm Hg), sodium nitroprusside is often used but parenteral use of labetalol or enalapril and frusemide are preferred. The BP should be carefully monitored and lowered gradually. In the first week of massive cerebral infarction with evidence of cerebral oedema hyperosmolar solution (e.g. intravenous mannitol) is prescribed to reduce vasogenic brain oedema but its effect is short-lasting and rebound cerebral oedema may prove harmful. Furthermore, in patients with incipient left ventricular failure, pulmonary oedema may be precipitated. Here, IV infusion of 10% glycerol may be helpful. On the other hand, restriction of IV fluids and frusemide induced diuresis are more effective in brain oedema with signs of herniation. High dose of corticosteroids can reduce cerebral oedema but their role in the treatment of vasogenic oedema is doubtful. Decompressive craniotomy, in massive cerebral or cerebellar infarction causing brainstem compression, is often advocated.

Specific therapy

Antiplatelet drugs: Acetylsalicylic acid (aspirin) prevents platelet aggregation by blocking production of platelet-derived thromboxane-A_2 but it also suppresses release of prostacyclin from vascular endothelium. It is widely used in primary and secondary prevention of strokes. In the treatment of TIA, RIND and in secondary prevention of strokes, the optimal dose is still debated. Low-dose therapy (100 mg/day or less) may be as effective as higher dose (325 mg/day or more). Other antiplatelet drugs like sulphinpyrazone or dipyridamole used alone do not offer any specific advantage. However, in female 'non-responders' aspirin combined with dipyridamole (up to 200 mg twice a day) may prove more effective on account of its synergistic activity.

Ticlopidine (a thienopyridine derivative) inhibits platelet aggregation by interfering with ADP-induced transformation of glycoprotein IIb/IIIa receptors on platelet membrane. It has shown more than 30% reduction in 'stroke risk' when compared to aspirin therapy. It is equally beneficial to men and women. Patients with diabetes mellitus, those on anti-hypertensives and those with elevated creatinine levels benefit more with ticlopidine (250 mg b.i.d.) than aspirin. However, the drug is relatively toxic (i.e. reversible neutropaenia, diarrhoea). Clopidogrel (75 mg/day) is reported to be safer than ticlopidine. In a recent trial (MATCH study), combination of clopidogrel (75 mg) and aspirin (75 mg) showed no real benefit in outcome of vascular end-points. Newer antiplatelet agents like abciximab are potent antagonists of platelet glycoprotein IIb/IIIa receptors but hazards like symptomatic intra-cranial bleeding are a major concern.

Anticoagulants: Parenteral heparin and long-term oral anticoagulants have been extensively tried in acute ischaemic strokes, particularly in elderly subjects having non-rheumatic atrial fibrillation (NRAF) or from cardioembolic source. Though such treatments can prevent extension of thrombus, its value in completed stroke is doubtful and its use is often fraught with dangers. Judicious use in recurrent TIAs, thrombosis in-evolution, cardiogenic embolisation to the brain in patients not responding to anti-platelet therapy, and in patients who are not fit for carotid surgery has been suggested.

To minimise the risk of haemorrhagic complications, it is necessary that the ischaemic infarction is confirmed by investigations like CT scan and CSF and not on the basis of clinical acumen alone. If a subject worsens under anticoagulant therapy, diagnostic re-evaluation should be done and even a second CT with or without CSF examination (under manometric control) may have to be carried out to ascertain the cause of worsening (extension of infarct *versus* intra-cranial bleeding due to anticoagulation).

During the stage of heparinisation activated partial thrombo-plastin time is kept up to two times the control, and 3000 to 5000 units of heparin are often given on 6 to 8 hourly basis. In practice, an IV bolus of 100 units/kg followed by continuous infusion (1000 units/hour for 24 hours), under constant supervision for bleeding parameters, preferably in an acute care unit is advocated. Of the many oral anticoagulant drugs, coumarin sodium (2 to 5 mg/day) is generally well tolerated. Prothrombin index (ideally INR) of 2.0 to 3.0 is usually maintained for months or longer, keeping

a close watch on haemorrhagic complications. Newer synthetic short-chain (low molecular weight) heparins or heparinoids are safer and effective but expensive. In the presence of actively bleeding ulcers, malignant hypertension, hepatic failure and poor patient compliance, anticoagulant treatment is contraindicated.

The current evidence suggests that aspirin is the treatment of choice when compared to anticoagulants for patients with non-cardioembolic stroke. However, anticoagulant therapy significantly benefits high-risk patients with atrial fibrillation in the elderly subjects, whereas aspirin may still be the drug of choice in stroke prevention in low risk group in the younger age.

Thrombolytic therapy

Intravenous thrombolytic therapy: Spontaneous recanalisation with better survival by intrinsic thrombolysis is well documented. Increasing experience with several 'clot-selective' thrombolytic agents have demonstrated significant and sustained neurological improvement when treatment is initiated within the first four and half hours of ictus, in MRI-positive and CT-negative ischaemic infarcts (i.e. when 'window of therapeutic opportunity' is open).

Intra-arterial thrombolytic therapy: Recent advances in superselective microcatheter (Tracker-18 or Microsoft stream catheter) techniques permit the investigator to reach at exact site of occlusive lesion and infuse a thrombolytic agent directly on to the clot surface thereby achieving higher rate of successful recanalisation.

Neuroprotective agents: Cerebral ischaemia induces release of excitatory aminoacid neurotransmitters like glutamate and glycine, which promote calcium entry into neurons through receptor-mediated membrane channels or by voltage-dependent calcium channels. Cell destruction most likely occurs from production of nitric oxide and subsequent formation of other free radicals. Clinical trials with several neuroprotective agents, including dihydropyridine compound (nimodipine), have not shown overall beneficial effects. Results of other trials are awaited.

Managing raised homocysteine (tHcy) level: Elevated levels of tHcy have been reported as significant and an 'independent risk factor' for myocardial infarction and stroke, though precise mechanisms linking raised tHcy to vascular disease have not been established. It has been suggested that raised tHcy harms endothelial cell functions, increases oxidative stress and thereby risk to thrombosis. Treatment with vitamins (B6, B12, folic acid) reverses the raised levels of tHcy and thereby possibly prevents progression of vascular disease.

Statins and stroke: Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins have also been considered beneficial in prophylaxis against myocardial infarction, stroke and other vascular events.

Data from SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) suggest that statins reduce a risk of recurrence of stroke and that stroke prevention may be independent of their effects on lowering low-density lipoprotein.

Surgical management: Thromboendarterectomy with or without reconstructive vascular surgery within a few hours or days after an acute ischaemic brain infarction is considered risky, because early reperfusion may convert pale infarct into a haemorrhagic one.

Recent well-designed controlled studies (NASCET—North American Symptomatic Carotid Endarterectomy Trial) have confirmed beneficial results of carotid artery endarterectomy (CAE) in tight cervical stenosis (70% to 99%). Patients who benefit the most from surgery are those with highest risk-factors. During immediate post-operative period higher doses of aspirin and control of all risk-factors are mandatory. The benefit by carotid endarterectomy in symptomatic lesions with mild stenosis (30% to 69%) or in asymptomatic cases is controversial.

Stenting and angioplasty in symptomatic carotid stenosis: Though CAE appears well established in tight symptomatic carotid stenosis (>70%), stenting with or without embolic protection devices are getting accepted as alternative mode of treatment in cases with CAE is not feasible or difficult. It has been reported that fewer complications occur with stenting as compared to CAE (e.g. neck haematoma, cranial neuropathy, etc.).

Stem cell therapy in acute stroke: Ethical and moral issues have prevented experimental trials on stem cell therapy in humans with acute ischaemic stroke. Animal experiments in various models do suggest that this avenue of therapy needs to be explored. However, reliable and verifiable reports are yet not available.

Phase II

Neurorehabilitation: As soon as the subject shows signs of neuronal recovery with some volitional movements, active physiotherapeutic measures should be started for early rehabilitation.

Phase III

Stroke prevention: In 80% of stroke-survivors, the chances of recurrence are high during the first few weeks and nearly 10% in the first year. Modification of risk-factors has shown decline in stroke morbidity and mortality. The prevention strategies are: control of hypertension, stop smoking or tobacco use, antiplatelet anticoagulants, CAE, treating hyperlipidaemia and diabetes mellitus, correcting all other treatable or modifiable risk-factors, and regular physical exercise and keeping ideal body weight. The risk of stroke doubles for every 7.5 mmHg rise in diastolic BP and a 25% relative risk reduction in stroke risk is reported in patients who are able to lower their diastolic BP by more than 6 mmHg.

CEREBRAL EMBOLISM

General Considerations

Local occlusion of an intra-cranial artery by a circulating fragment, which may be composed of broken bits of thrombi, platelet-fibrin masses, cholesterol debris, tumour cells, fat globules, gas bubbles, bacteria and parasites or other foreign bodies, is known as cerebral embolism.

Aetiopathology and Pathophysiologyc

Detachment of intra-cardiac thrombi or vegetations during atrial fibrillation is most frequent source of cerebral embolism. Atheromatous debris from aortic arch is another common source. Thrombosed pulmonary veins in bronchiectasis, lung abscess and such infections may be a source of embolisation. Paradoxical embolism is not uncommon. Recurrent embolism can occur from unidentifiable source and here subacute bacterial endocarditis, non-bacterial marantic endocarditis and atrial myxoma should be considered.

Twenty-five per cent of all systemic emboli reach the brain and 60% of them lodge in the middle cerebral arterial territory. In urban centres cerebral embolism accounts for 25% to 30% of all ischaemic strokes; young subjects of either sex are frequently affected. Acute carotid embolism in the neck with fluctuating paresis (RIND) has also been described.

On account of sudden impaction of an embolic plug, sufficient time is not available for compensatory mechanisms to protect the cerebral cortex from ischaemia; hence, the ictus announces instantaneously with varying degree of neurological deficit. The embolic plugs frequently break and migrate distally and thereby restore circulation in its ischaemic territory; haemorrhagic (red) cerebral infarction is, thus, the consequence of reperfusion of blood in an ischaemic (pale) area. If the circulation is restored within an hour, before the death of nerve cells the neurological recovery may be equally dramatic.

Clinical Features

Cardiac arrhythmia and obvious heart disease may be noted on general physical examination. Ophthalmoscopy may reveal embolic fragments with sludging or stasis of blood in the retinal veins. Ipsilateral carotid arterial pulsations may be feeble.

There are no warning prodromal symptoms but in some subjects focal seizures may precede the ictus. The stroke develops fully within few seconds or minutes; stuttering or intermittent progression is rare. The clinical manifestations depend on the site of occlusion, and the specific neurovascular syndromes resulting therefrom are in no way different from those described for thrombotic arterial disease. Coma indicates massive cerebral infarction.

The presence of severe neurological deficit with coma at the onset of the ictus, fever and other intercurrent infections, cardiac failure, uncontrolled hypertension or diabetes mellitus, advanced age and basilar artery embolism, all carry a grave prognosis. Nearly 30% of all patients with acute brain embolism die from the initial ictus and around 80% of comatose patients succumb to the illness. In those who survive an acute insult some degree of recovery is common. If no improvement is noted in the first 6 to 8 weeks, chances of subsequent or significant recovery are remote. Recurrence of a cerebral embolic episode is reported in 40% of patients, and nearly 40% of them die from a second embolic stroke.

Laboratory Findings

In general, the findings are similar to those outlined under atherothrombosis. In septic infarcts, the white cell count may be very high; in haemorrhagic cerebral infarction, the CSF is often blood-stained. Atrial fibrillation, tachyarrhythmia and other ECG abnormalities are frequently detected. In early stages (within hours), cerebral angiographic findings are characteristic and may show migratory occlusive lesions of isolated branches in absence of atheromatous disease. A repeat arteriography after a few days may be entirely normal and this suggests, 'vanishing emboli'. two-dimensional echo or transoesophageal echocardiography helps to define myocardial infarction or valvular lesions or vegetations. Holter monitoring may document cardiac dysrhythmia.

Diagnosis

The following points should help to arrive at the correct diagnosis; history of abrupt onset of a full-blown neurologic deficit without intermittent progression, developing within a few minutes; absence of warning symptoms; presence of potential source of embolism; evidence of previous or concurrent episodes of embolism to other parts of the body; and clear spinal fluid (in almost all cases).

CT or MRI may show hyperdense arterial occlusive lesion and also helps to settle the diagnosis by excluding atherothrombotic brain infarction, intra-cerebral haemorrhage and subdural haematoma and other non-stroke conditions.

Treatment

General nursing and intensive medical care, as outlined for cerebral thrombosis, are the sheet-anchor of therapy. Vasodilator drugs do not help. Current enthusiasm for infusion of thrombolytic agents to lyse an embolus has not been very encouraging as haemorrhagic complications far outweigh the potential benefits. Since the stroke is complete, anticoagulant medication is of little help. Furthermore, in massive cerebral infarction or in the presence of severe hypertension, anticoagulant therapy may convert pale infarct to a haemorrhagic one. On the other hand, long-term anticoagulant treatment (keeping INR around 2.0) is routinely advocated to prevent recurrent embolism in elderly subjects with irregular cardiac rhythm. Specific treatment for the underlying cardiac or similar disease should be given (e.g. bacterial endocarditis). An active rehabilitation programme is initiated as soon as some volitional movement is noted.

Prophylaxis in Cardioembolic Stroke

Cardioembolic strokes are common in subjects having non-valvular atrial fibrillation, post acute coronary syndrome (e.g. mural thrombi, ruptured chordae tendinae, ventricular aneurysm, etc.), valvular rheumatic heart disease, cardiomyopathy, septal defects and patent foramen ovale (PFO). In atrial fibrillation, the stroke recurrence risk is as high as 12% per year. To prevent recurrent brain embolism, long-term oral anticoagulant therapy keeping INR around 2.0, is advocated in elderly patients having irregular cardiac rhythm. Thus, choice of antithrombotic therapy depends upon the aetiology of stroke. Oral anticoagulation treatment is the preferred choice for inferred cardioembolism in setting of atrial fibrillation, while the varying rates of haemorrhage with oral anticoagulants continue to favour antiplatelet therapy in other setting of inferred aetiology. Insufficient data exist to determine whether antithrombotic therapy combined with antihypertensives, statins or other agents will further reduce the risk of stroke in synergistic or supplemental fashion.

LACUNAR STROKES

When exposed to chronic hypertension, the small cerebral vessels and penetrating vessels in particular, show thickening and fibrosis of their walls leading to luminal narrowing, lipohyaline changes (lipohyalinosis) and microinfarction (lacunar infarcts). The weakness in the vessel wall segment may predispose to formation of microaneurysms, which may bleed or become occluded by thrombosis.

Lacunae are deep, small (150 mm to 300 mm), multiple wedge-shaped infarcts in the subcortical white matter seen mostly in hypertensive, diabetic and elderly subjects. These are commonly located in the basal ganglia, thalamus, corona radiata, internal capsule, brainstem, cerebellum and mainly in the territory of

small penetrating vessels. Cortical grey matter, hypothalamus, midbrain and medulla oblongata are relatively spared.

Lacunae can be asymptomatic, but may produce dense neurological deficit if located in the regions of major pathways. On the basis of clinico-pathological studies, Fisher described many lacunar syndromes, i.e. pure motor hemiplegia (infarction in the posterior limb of the internal capsule or basis pontis), pure hemisensory syndrome (thalamic infarct), homolateral ataxia and crural paresis, clumsy-hand dysarthria syndrome and other brainstem symptom complexes. Earlier, these syndromes were considered pathognomonic of ischaemic cerebrovascular disease but these have also been described with small cerebral bleed; here, CT is often desirable to rule out such micro-bleeds. It is not uncommon to have TIA or RIND precede lacunar stroke. Some degree of recovery is always common. Progressive intellectual deterioration and loss of cognitive functions (dementia) in association with slow hesitant gait and pseudobulbar signs may result from multiple lacunae (multi-infarct dementia) and should be differentiated from Alzheimer's disease and similar conditions. Here, CT or MRI is important diagnostic test where lacunar infarcts are often visible as small, punched out, hypodense areas.

Aspirin is commonly prescribed. Treatment of underlying diseases like hypertension, diabetes mellitus and hyper-lipidaemia is essential. Anticoagulant therapy is considered controversial.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a syndrome characterised by recurrent ischaemic attacks with subcortical microinfarcts (non-arteriosclerotic, non-amyloid angiopathy) associated with subcortical dementia and migraine in young adults. Here, MRI shows widespread white matter disease and genetic dysfunction is presumably located on chromosomes 19q12. Similar syndrome where gene polymorphism is associated with specific cerebral small vessel pathologies is under investigation.

Arteritis

The clinical features of syphilitic and other forms of arteritis involving various cerebral arteries are in no way different from the neurovascular syndromes described under cerebral thrombosis. With specific serological tests, the diagnosis of meningovascular syphilis is not difficult. Specific treatment with antisyphilitic drugs is advocated.

STROKES OF UNDETERMINED ORIGIN

Strokes in Young in India

Several reports suggest that in about 20% of non-cardioembolic strokes in young (<45 years), the commonly believed risk-factors (e.g. hypertension, diabetes mellitus, tobacco use, etc.) are absent. Here, altered haematocrit level and disturbed equilibrium in coagulation and fibrinolysis have been postulated. Among procoagulant states: protein C/protein S deficiency, hyperhomocysteinaemia, raised anticardiolipin antibody or circulating lupus anticoagulant factor, etc. should be checked for. The possibilities of subacute central nervous system infection and autoimmune vasculitis need critical evaluation. Thus, strokes in young demand meticulous evaluation and specific tests to ascertain its aetiology for correct diagnosis and long-term management. Comprehensive cardiovascular evaluation should not be ignored. CT, MRI of brain and imaging of extra-cranial and intra-cranial vessels often helps to define the anatomical lesion and possibly its pathology. General medical management of ischaemic stroke in the young is similar to strokes in elderly and specific therapies should be prescribed for specific aetiologies. However, despite extensive investigations in 10% of cases the underlined aetiopathology remains uncertain or speculative.

Moyamoya Disease

It is an angiographic entity characterised by an unusual combination of progressive occlusive lesion at the intra-cranial carotid bifurcation with an extensive or profuse abnormal anastomotic network of dilated arterioles and capillaries at the base of the brain. The characteristic angiographic appearance is often described as puff of cigarette smoke drifting in the air. The carotid occlusion is non-inflammatory subintimal fibroplasia near arterial cushions. It is mostly reported in children and young adults among Japanese and other Asians. Headaches, convulsions and SAH are frequent clinical manifestations. As yet, there is no specific treatment.

Fibromuscular Dysplasia

Fibromuscular dysplasia is a segmental, non-atheromatous, non-inflammatory angiopathy of unknown cause. It involves the intima, media and sometimes the adventitia of renal, aorto-iliac, splenic and internal carotid arteries and vascular bruits are usually present. It has a characteristic angiographic appearance where irregular beading on stenotic areas alternate with dilated aneurysmal segments. Young or middle-aged women, taking contraceptive pills, may present with migraine type headache or TIA. Surgical dilatation of the narrowed segments reduces these symptoms in many.

Other Cerebrovascular Diseases

Binswanger's subcortical arteriosclerotic encephalopathy, leucoaraiosis, Winiwarter-Buerger disease are some other causes of strokes. Cerebral venous thrombosis during pregnancy and puerperium is commonly seen throughout India and will need special evaluation and demands acute intensive medical management. Recent studies have shown a significant decline in the incidence of stroke mortality, through the relative distribution of cerebrovascular disease lesions (ischaemic and haemorrhagic) in hospital cases has not changed over the years. Thus, a higher percentage of stroke survivors with varying degree of residual disability will pose major socio-economic challenge in occupational rehabilitation of these victims. Stroke prevention needs no emphasis.

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20.9 Haemorrhagic Cerebrovascular Diseases

MV Padma Srivastava, Ajay Garg

INTRODUCTION

Spontaneous intra-cerebral haemorrhage (ICH) is the deadliest most disabling and least treatable form of stroke. Following a major haemorrhage, 35% to 52% are dead within a month and less than 20% were living independently after 6 months. The hospital mortality rates of ICH who are comatose and mechanically ventilated is 60%. ICH constitutes 15% of all strokes in the West and 20% to 30% in Asian populations. The lack of proven and accepted medical or surgical treatment for ICH leads to great variation among physicians concerning both surgical and medical management.

The percentage of haemorrhagic strokes may vary between different regions within India and there is increasing literature suggesting higher percentage of haemorrhagic strokes (30% to 40% of all strokes), in North-Eastern regions including Kolkata, Death at 1 year for ICH varies by location of ICH, 50% for deep haemorrhage; 57% for lobar; 42% for cerebellar and 65% for brainstem bleeds. The most important risk factor for ICH is poorly controlled chronic hypertension. Advanced age is an additional risk factor for ICH, with the rate doubling with each decade of life until 80, when the incidence plateaus at nearly 25 times that of previous decade

AETIOLOGY

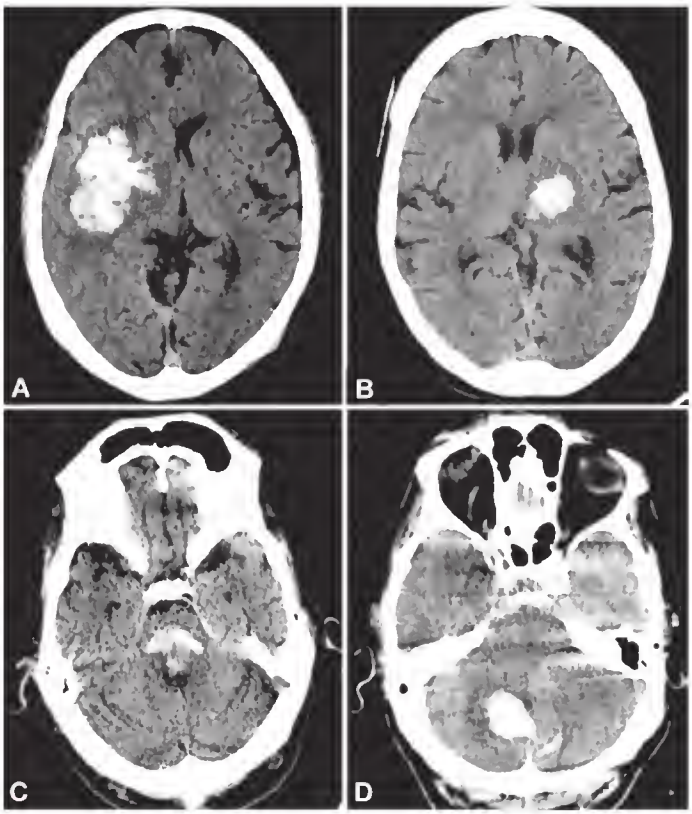
The various aetiological factors for ICH are listed in **Table 1**.

Table 1: Causes of Intra-Cerebral Haemorrhage

- **Abnormal blood vessels**
  - Vascular malformations
    - Arteriovenous malformations
    - Saccular aneurysms
    - Cavernous angiomas
    - Septic and mycotic aneurysms
  - Lipohyalinosis and microaneurysms
  - Amyloid angiopathy
  - Cerebral tumours
  - Cerebral venous thrombosis
  - Vasculitis
  - Moyamoya syndrome
  - Haemorrhagic transformation
- **Sytemic bleeding tendency**
  - Haemophilia
  - Leukaemia
  - Thrombocytopaenia
  - Anticoagulants
  - Antiplatelet agents
  - Thrombolytic agents
- **Illicit drugs**
  - Amphetamines
  - Cocaine
- **Hyperperfusion syndrome**
- **Trauma**

CHRONIC HYPERTENSION

The most common sites of hypertensive haemorrhage are deep grey matter (putamen, globus pallidus, and thalamus) (65%), subcortical white matter (10% to 20%), pons (10% to 15%), and cerebellum (8% to 10%) (**Figures 1A to D**). Haemorrhages have been associated with microscopic changes in blood vessels, but the exact mechanism is debated. Miliary aneurysms (Charcot-Bouchard aneurysms) are found on the lenticulostriate branches of the middle cerebral artery and paramedian branches of the basilar artery in nearly 50% of hypertensive patients over 66 years of age. Destruction of the tunica media through a process variably described as lipohyalinosis and fibrinoid necrosis on the other hand, is found in vessels within the area of ICH. An anatomic factor that may contribute to hypertensive ICH is that perforating vessels are small perpendicular branches directly off major arteries that are subject to much higher shear stress than cortical feeders, which reside at the end of the circulatory tree. It is likely that hypertension-induced ICH is the result of some combination of altered flow dynamics and histopathologic changes within the vasculature.

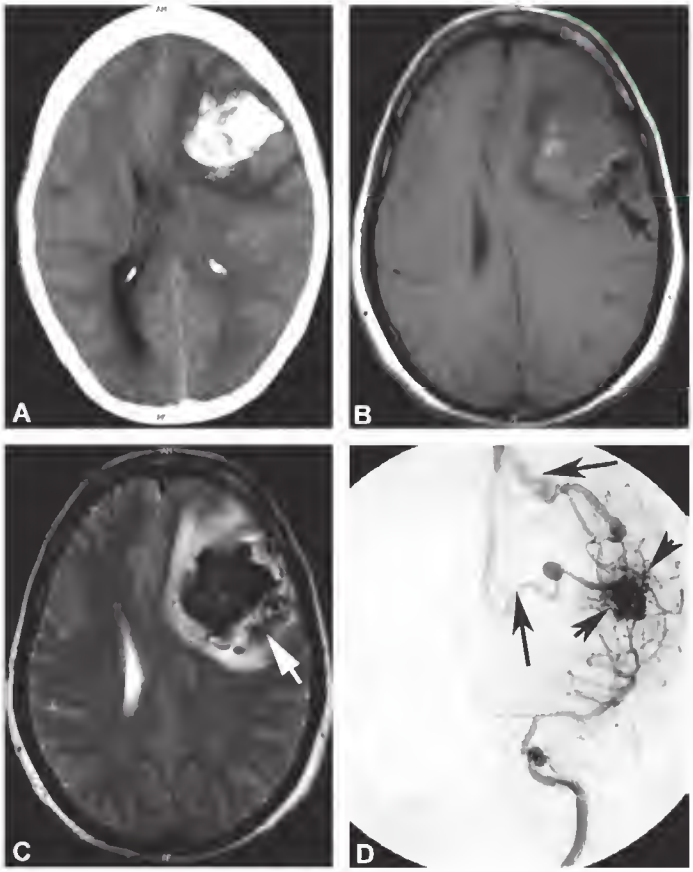


Figures 1A to D: Hypertensive haematomas. (A) Axial non-contrast CT scans show hyperdense acute intra-cerebral haematomas in the region of right external capsule/lentiform nucleus, (B) left thalamus, (C) pons and (D) right cerebellar hemisphere.

VASCULAR MALFORMATIONS

Up to 25% of ICH are attributable to bleeding from rupture of aneurysms and arteriovenous malformations (AVMs). Rupture of an aneurysm produces ICH in 5% to 25% of cases. If the aneurysm is adherent to the brain parenchyma, haemorrhage may be directed into the substance of the brain rather than purely into the subarachnoid space. In some cases the bleeding is actually limited to the parenchymal component, and no subarachnoid blood is found on computed tomography (CT) scan. Anterior communicating aneurysms may produce flame-shaped haemorrhages in the base of the frontal lobes.

Over half of patients with AVMs present with some type of haemorrhage; 60% of which are parenchymal in location. Lesions are found throughout the cerebrum, brainstem, or cerebellum. AVMs characteristically rupture during the 2nd to 4th decades of life. Symptoms of AVM-induced ICH depend on location. Multiple calcified vascular channels may be seen within a haematoma on CT scan, suggesting the presence of an underlying AVM (**Figure 2A**). Magnetic resonance imaging (MRI) (**Figure 2B and C**) and four-vessel cerebral digital subtraction angiography are useful adjuncts in diagnosis and planning management (**Figure 2D**).



Figures 2A to D: (A) Axial non-contrast CT scan show hyperdense acute intra-cerebral haematoma in the left frontal lobe with surrounding hypodense oedema. (B) The haematoma is iso-hyperintense on T1-weighted image and (C) hypointense on T2-weighted image suggesting acute-early subacute stage. Note that hypointense flow-voids on the posterolateral aspect of haematoma on both T1-WI and T2-WI (short arrows in B and C), pointing to arteriovenous malformation as cause of haematoma. In intra-arterial digital substraction angiography, (D) left internal carotid angiogram show nidus of the arteriovenous malformation (short arrows in D) with early draining veins into superficial and deep venous systems (long arrows in D).

CEREBRAL AMYLOID ANGIOPATHY

This is characterised pathologically by the deposition of amyloid in cerebral vessels, primarily small and medium-sized arteries of the cortex and leptomeninges. The classical birefringent amyloid material is seen on histological examination in the media and adventitia, which stains positive for Congo red. The incidence of these histopathological changes at post-mortem increases steadily with age, occurring in as many 60% of unselected autopsies of individuals older than 90 years. The incidence of haemorrhage secondary to amyloid angiopathy also increases with age and is rare before the age of 55 years. The mechanism of rupture of affected arteries is thought to be either a weakening of the vessel wall or the formation of microaneurysms at the sites of amyloid deposition. It is strikingly restricted to vessels of the leptomeninges and grey matter, and usually stops abruptly when a penetrating vessel reaches a junction of the cortex and subcortical white matter. Haemorrhages in cerebral amyloid angiopathy are almost exclusively lobar and often superficially close to the surface, with the site of rupture usually being at the grey-white matter junction.

CAVERNOUS ANGIOMAS (CAVERNOMAS)

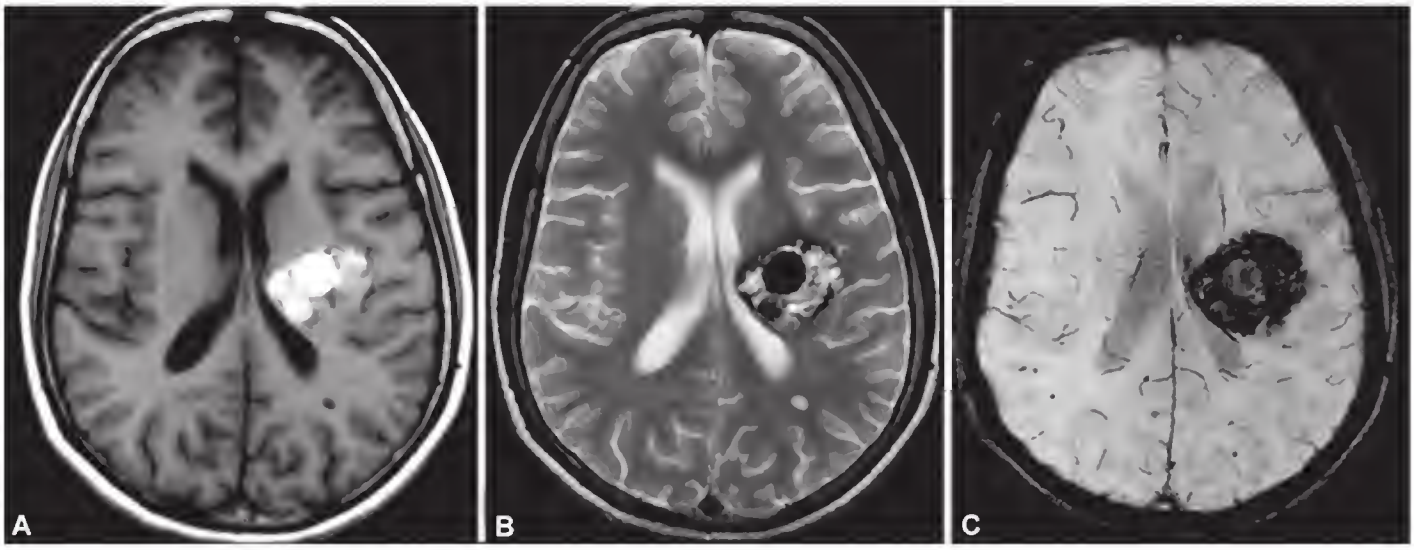
These are of unknown aetiology, but it has been suggested that at least part of the lesion forms as a localised reaction to small haemorrhages. These are mainly diagnosed from the characteristic MRI appearance of a central nidus of irregular bright signal intensity on T2-weighted imaging, surrounded by a peripheral hypointense ring resulting from haemosiderin deposition due to previous episodes of bleeding (**Figures 3A to C**). No abnormalities are seen on angiography. Cavernomas are predominantly supratentorial, most commonly affecting the temporal, frontal and parietal lobes. The most frequent infratentorial site is the pons. Cavernomas may present with seizures, intra-cerebral haemorrhage or progressive neurological deficit. The last of these is more likely to occur in brainstem cavernoma. The majority of cavernous angiomas are asymptomatic and are frequently found on MRI performed for other reasons. The outlook in the vast majority of asymptomatic cases is benign.

OTHER CAUSES

Approximately 10% of ICHs are attributable to coagulopathies, resulting from anticoagulation, platelet inhibition, thrombolytic therapy or underlying systemic disease (**Figure 4**). Warfarin, heparin, aspirin, dipyridamole, tissue plasminogen activator, streptokinase, and urokinase have all been implicated as causes of ICH. Additionally, ICH occurs in 1% to 2% of patients receiving anticoagulants for systemic indications. Systemic disease such as renal and hepatic failure, thrombocytopaenia and the leukaemias produce coagulopathic states that may also result in ICH. Haemorrhage from an underlying neoplasm is rare. This occasionally appears in malignant tumours, including glioblastoma multiforme, lymphoma, and metastatic tumours such as malignant melanoma, choriocarcinoma, renal cell and bronchogenic carcinoma. Benign tumours are almost never associated with ICH.

Infections may also result in ICH. Fungal infections predispose to cortical and subcortical haemorrhage by direct infiltration of the vessel wall by the organism. In its extreme form, herpes simplex may produce acute, necrotising encephalitis that preferentially affects the temporal and frontal lobes.

ICH may occur following reperfusion (e.g. following carotid endarterectomy or acute thrombolysis), 1 or 2 days after head



Figures 3A to C: Cavernoma. (A) Axial T1-weighted image show a iso-hyperintense lesion in the left corona radiata. (B) The lesion is of mixed signal intensity with hypointense rim in T2-weighted image and (C) blooms in susceptibility-weighted image, suggesting cavernoma.

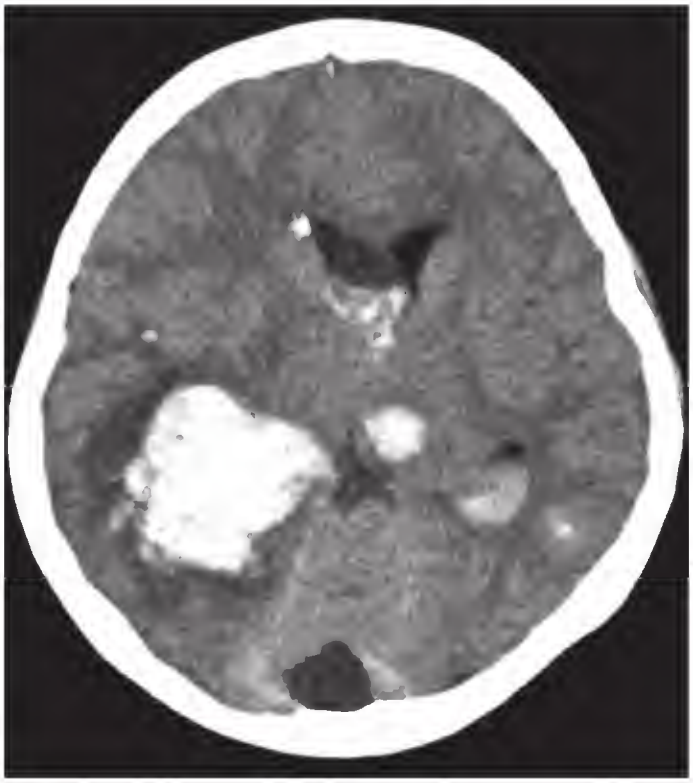


Figure 4: Haemophilia. Axial non-contrast CT scan show multifocal hyperdense acute haematomas of different sizes in both cerebral hemispheres with intraventricular extension.

trauma as a result of venous sinus occlusion, and consequent to the use of drugs such as cocaine, amphetamines, pseudoephidrine and phenylpropanolamine. Sinus thrombosis is associated with a variety of medical conditions, including pregnancy, dehydration, local or systemic infection, sickle cell trait, oral contraceptive use and hypercoagulable states.

CLINICAL FEATURES

The focal signs and symptoms accompanying ICH reflect the location of the haemorrhage and are indistinguishable from ischaemia occurring in the same vascular territory. Lobar haemorrhages frequently produce contralateral weakness or sensory loss, language disturbance, hemianopia or lesser field disorders, and parietal lobe signs. Their relationship to the cortex makes them more likely to be complicated by seizures. Seizure are more frequent in ICH, occurring in as many as a quarter of individuals, although they are also seen in about 5% of patients with ischaemia, particularly early after onset.

Occasionally, very small haematomas present with symptoms indistinguishable from transient ischaemic attacks (TIAs). However, majority of ICHs cause complete stroke.

Putaminal haemorrhages typically cause contralateral hemiparesis with variable degrees of sensory loss, ataxia and with larger haematomas, a homonymous hemianopia.

Thalamic haemorrhages can result in contralateral sensory loss and weakness, while if they extend to or compress the superior midbrain, they may result in depressed signs. Pontine haemorrhages often result in reduced consciousness, pinpoint pupils, bilateral weakness and pontine cranial nerve dysfunction, and may be severely disabling.

Cerebellar haemorrhages are particularly important to identify clinically as they may require surgical intervention, which can be life-saving. The onset can be deceptive, with initial non-specific brainstem symptoms (e.g. vertigo or double vision), followed a few hours or even days later by progressive clinical features, including gait, trunk or limb ataxia, nystagmus, headache, vomiting and coma from brainstem compression. Hemiparesis will be rare. The clinical course of cerebellar haemorrhage can be difficult to predict at onset. An abrupt deterioration may occur after a period of clinical stability. Moderate degrees of quadrigeminal cisternal compression predicts poor outcome unless the haematoma is evacuated early in the course. Severe mass effect on the cistern carries a poor prognosis.

INVESTIGATIONS

Plain CT scan of the brain remains the mainstay of diagnosis of ICH. Blood is easily seen and appears hyperdense on non-contrast enhanced CT scans. MRI is also very sensitive investigation to ICH provided the appropriate sequences are used. However, interpretation of haemorrhage on images is more complicated than with CT. Following haemorrhage, a

series of events occurs that can be detected using MRI; these include initial deoxygenation of the blood within the haemorrhage; its subsequent chemical breakdown from haemoglobin into methaemoglobin, and finally the formation of iron-containing haemosiderin deposits. Therefore, MRI can be used to distinguish between previous cerebral infarction and haemorrhage at a time when the appearances on CT are identical.

Certain radiological features characterise particular underlying causes of ICH. An AVM may be seen on MRI as a cluster of vascular channels with flow voids (**Figures 2B and C**). Cavernous angiomas appear as small areas of high signal on T2-weighted images surrounded by a ring of low intensity due to haemosiderin deposition (**Figure 3C**). Haemorrhage secondary to tumours can contain complex mixtures of increased and decreased signals related to the presence of viable tumour, necrotic tissue, calcification and haemorrhage occurring at various time points. Cerebral vasculitis may be suggested by the concurrent appearance of both ischaemic and haemorrhagic lesions. Angiography (conventional four vessel; magnetic resonance angiography (MRA) or CT angiography) will be required to exclude a treatable source of recurrence, such as aneurysm, AVM, etc.

TREATMENT

Treatment of Acute ICH

1. Potential treatments of ICH include stopping or slowing the initial bleeding during the first few hours after the onset.
2. Removing blood from the parenchyma or ventricles.
3. Management of raised intra-cranial pressure (ICP) and decreased cerebral perfusion.
4. Good general supportive management.

Patients with ICH require considerable attention to the ABCs of resuscitation and rapid correction of deranged parameters. Up to 50% of these patients may require mechanical ventilation. Recent evidence indicates that many haematomas undergo enlargement over the first few hours suggesting that aggressive correction of coagulopathies might be helpful.

Consensus on Managing Blood Pressure

Early after ICH, there appears to be no compelling need to treat hypertension aggressively unless there are signs of systemic complications especially in the setting of large bleeds with raised ICP. However, new data suggest that modest (15%) reduction of blood pressure (BP) does not lower cerebral blood flow (CBF) in patients within 24 hours of ICH. Thus, modest reduction in blood pressure of very hypertensive patients (MAP >130 mm Hg) is indicated. Further studies to validate the level of BP lowering are in progress.

Choice of Antihypertensives

The most appropriate antihypertensive agent to use in ICH patients is one that has a short half-life and moderate efficacy with minimal cerebrovascular effects. Drugs should be administered so as to avoid sudden large drops in blood pressure. Vasodilators, especially those that dilate veins, can raise ICP by increasing cerebral blood volume and should be avoided. Sodium nitroprusside and nitroglycerin increase. ICP and lower cerebral blood flow in patients with reduced intra-cranial compliance. Labetalol, a combined alpha blocker and beta blocker, does not alter ICP or CBF; thus making it a popular agent making it a popular agent. However, large doses may be required to counteract the sympathetic nervous system stimulation associated with ICH. Other useful agents include hydralazine, and the calcium channel blockers, nicardipine and angiotensin converting enzyme inhibitors, enalapril.

Management of Increased Intra-Cranial Pressure

ICP is considered a major contributor to mortality after ICH. ICP may be managed through osmotherapy, controlled hypertension and barbiturate coma. Elevated ICP is defined as intra-cranial pressure more than or equal to 20 mm Hg for more than 5 minutes. A therapeutic goal of all treatments of raised ICP is less than 20 mm Hg and cerebral perfusion pressure (CPP) of more than 70 mm Hg. Patients with suspected elevated ICP and deteriorating level of consciousness are candidates for invasive ICP monitoring. Intraventricular ICP monitors and intrapare-nchymal fiberoptic ICP devises are two commonly used methods of monitoring ICP.

The CPP-guided therapy focuses on maintaining a CPP of more than 70 mm Hg to minimise reflex vasodilation or ischaemia. Despite long standing debates, no controlled trial has demonstrated the superiority of approaches. A balanced approach begins with simple and less aggressive measures, such as head positioning, analgesia and sedation and then progresses to more aggressive measures.

Head of bed elevation

Elevation of the head of the bed to 30 degress improves jugular venous outflow and lowers ICP.

Osmotic therapy

The most commonly used agent is mannitol, an intravascular osmotic agent, that can draw fluid from both oedematous and non-oedematous brain tissue. It also decreases ICP through cerebral autoregulation. Mannitol decreases blood viscosity that results in reflex vasoconstriction and decreased cerebrovascular volume. The first medical line of defence is osmotherpay. However, it should not be used prophylactically. Mannitol 20% (0.25 to 0.5 g/kg every 4 hours) is reserved for patients with type B ICP waves, progressively increasing ICP values, or clinical deterioration associated with mass effect. Due to rebound phenomenon, mannitol is recommended for only few days to a week. To maintain an osmotic gradient, frusemide (10 mg 2 to 8 hourly) may be administered simultaneously with osmotherapy. Serum osmolarity should be measured twice daily in patients receiving osmotherapy and targeted to less than or equal to 310 mOsm/L.

Hypertonic saline

Solutions have been shown to reduce ICP in some cases of refractory raised ICP to mannitol and hyper-ventilation. Exact dose, concentration and mode are not clarified.

Cerebrospinal fluid (CSF) drainage

When an intraventricular catheter is used to monitor ICP, CSF drainage is an effective method for lowering ICP, particularly in the setting of hydrocephalus. The principal risks associated with ventriculostomy are infection and haemorrhage. In addition to the mass effect of the haematomas, secondary hydrocephalus may contribute to elevated ICP. Ventricular drains should be

used in patients with or at risk for hydrocephalus. Use prophylactic antibiotics and preferably remote catheter early but not later than 7 days.

Neuromuscular blockade

Muscle activity may further raise ICP by increasing intrathoracic pressure and obstructing cerebral venous outflow. If the patient is not responsive to analgesia and sedation alone, neuromuscular blockade is considered.

Hyperventilation

Hyperventilation is one of the most effective methods to reduce raised ICP. However, it has fallen out of favour primarily because of the simultaneous effect of lowering CBF. And it is also transient in its effect. In fact, after a patient has been hyperventilated for more than 6 hours, rapid normalisation of arterial partial pressure of carbon dioxide can cause a significant rebound increase in the ICP.

Barbiturate coma

High-dose barbiturate treatment acts by depressing cerebral metabolic activity. This results in reduction in CBF, which is coupled to metabolism, and a fall in ICP. The use of barbiturates in the treatment of refractory ICP requires intensive monitoring and is associated with a significant risk of complications.

Surgery

Evacuation of haematoma; VP shunts, etc.

MANAGEMENT OF GLUCOSE LEVELS

Evidence indicates that persistent hyperglycaemia (>140 mg/dL) during the first 24 hours after stroke is associated with poor outcomes, and thus, it is generally agreed that hyperglycaemia should be treated in patients with acute stroke. The management for ICH and ischaemic strokes are similar.

Fluid Management

The goal is euvolaemia. If hypovolaemia is thought to contribute to hypotension, central venous pressure (CVP) should be maintained between 5 mm Hg and 12 mm Hg. Electrolytes should be checked and substituted; acidosis and alkalosis should be corrected according to blood gas analysis.

Prevention of Seizures

Seizure activity can result in neuronal injury and destabilisation of an already critically ill patient and must be treated aggressively. Additionally, non-convulsive seizures may contribute to coma in less than or equal to 10% of neurocritical care patients. In patients with ICH, prophylactic AED may be considered for a month and then tapered and discontinued if no seizure activity occurs during treatment.

Management of Body Temperature

Normothermia should be maintained. Acetaminophen or cooling blankets may be used to treat hyperthermia. Use antibiotics if infection is suspected.

Other Medical Management Issues

Pulmonary embolism is a common threat during the recovery period, particularly for bedridden patients with hemiplegia. Pneumatic devices decrease the risk of pulmonary embolism during hospitalisation. Randomised trials of medical therapy for ICH comparing steroid versus placebo, haemodilution versus best medical therapy and glycerol versus placebo did not reveal significant benefit for the use of these agents. Depending on the patients clinical state, physical therapy, speech therapy and occupational therapy should be instituted as soon as possible.

Recommendations for Initial Medical Therapy

Class I evidence

1. Monitoring and management of patients with ICH should take place in an intensive care unit setting because of the severity and complexity of the condition.
2. Appropriate anti-epileptic therapy should be used for treatment of clinical seizures in patients with ICH.
3. Sources of fever should be treated and antipyretic medications should be administered to lower temperatures in febrile patients with stroke.
4. Early mobilisation and rehabilitation are recommended in patients with ICH who are clinically stable.

Class II evidence

1. Treatment of elevated ICP should include a balanced and graded approach that begins with simple measures such as elevation of the head of the bed and analgesia and sedation and followed by aggressive treatment as outlined above.
2. Evidence indicates that persistent hyperglycemia (>140 mg/dL) should be treated in patients with acute stroke.
3. Blood pressure management: The blood pressure has to be lowered by 10% to 15% and rather slowly.
4. A brief period of prophylactic anti-epileptic therapy soon after ICH onset may reduce the risk of early seizures in patients with lobar haemorrhage.

Recommendations for Prevention of Deep Vein Thrombosis and Pulmonary Embolism

Class I

1. Patients with acute primary ICH and hemiparesis should have intermittent pneumatic compression for prevention of venous thromboembolism.
2. Treatment of hypertension should always be part of long-term therapy because such therapy decreases the risk of recurrent ICH.

Class II

1. After documentation of cessation of bleeding, low-dose subcutaneous low-molecular weight heparin or unfractionated heparin may be considered in patients with hemiplegia after 3 to 4 days from onset.
2. Patients with an ICH who develop an acute proximal venous thrombosis, particularly those with clinical or sub-clinical pulmonary emboli, should be considered for acute placement of a vena cava filter.
3. The decision to add long-term anti-thrombotic therapy several weeks or more after placement of a vena cava filter must take into consideration the likely cause of the haemorrhage, associated conditions with increased arterial thrombotic risk and the overall health and mobility of the patient.

Potential New Treatments for ICH

Potential new treatments for ICH include stopping or slowing the bleeding during the first several hours, removing the

bleeding during the first several hours, removing the blood after the bleeding has stopped and delivering agents that limit the effects of blood.

HOW OFTEN DOES ICH GROW?

Before the 1990, the accepted wisdom was that bleeding in ICH occurred over minutes and then remained stable.

In a study where repeated CT scans were done was surprisingly seen, the haematomas continued to grow significantly) an increase of more than 33% in volume), after the first CT in 38% of patients; 26% within 1 hour and 12% between 1 and 20 hours. This growth occurred in all locations and was associated with clinical deterioration on the NIH stroke scale (NIHSS) and Glasgow coma scale (GCS) scores.

The only consistently identified risk factor for early haematoma growth is the interval between symptom onset and the initial CT; the earlier the CT, the more likely it is that a follow-up CT will show enlargement. Other risk factors that have been identified include liver disease, a history of cerebral infarction, hypertension, hyperglycaemia, irregular haematoma shape, depressed level of consciousness, alcohol use, and reduced fibrinogen levels, but these have not yet been confirmed.

The pathogenesis of early haematoma growth is poorly understood. The reasonable and conventional notion is that haematoma growth results from persistent bleeding or re-bleeding from a single arterial or arteriolar rupture. Several lines of evidence also suggest that early haematoma enlargement may also result from secondary bleeding into perilesional tissue in the periphery of the clot.

RATIONALE FOR ULTRA-EARLY HAEMOSTATIC THERAPY FOR INTRA-CEREBRAL HAEMORRHAGE

The three most consistently identified predictors of poor outcome after ICH are haematoma volume, the presence of intra-ventricular haemorrhage and depressed level of consciousness. Of these, haematoma volume has been identified as the single most powerful predictor of 30-day mortality after ICH. Given the evidence that ongoing bleeding can occur for several hours after onset, it is plausible that ultra-early haemostatic therapy might minimise haematoma volume and improve outcome.

In patients with normal coagulation, the most feasible haemostatic agents for ultra-early ICH therapy include the antifibrinolytic amino acids, aminocaproic acid and tranexamic acid, aprotinin and activated recombinant factor VII (rFVIIa).

Since these drugs primarily inhibit fibrinolysis, these are more suitable for clot stabilisation than for the promotion of clot formation. Clinical trials indicate that these agents reduce the frequency of rebleeding after aneurysmal sub-arachnoid haemorrhage but increase the frequency of delayed cerebral ischaemia and other thrombotic complications resulting in no overall benefit on the outcome.

Aprotinin is a polypeptide that inhibits the action of several serine proteases including plasmin and kallikrein. Aprotinin primarily inhibits the initiation of both coagulation and fibrinolysis induced by contact of blood with a foreign surface but it has no effect on platelet function. Its main indication is for reducing peri-operative bleeding including cardiac surgery rather than treating spontaneous internal bleeding.

FVIIa is an important natural initiator of haemostasis and exerts its primary effects locally in regions of endothelial disruption and vascular injury. Pharmacological doses of rFVIIa amplify this process. In 9 years of clinical use for the treatment of haemophilic patients with inhibitors, rFVIIa has been associated with a low risk of systemic coagulation or thromboembolic complications and has a good record for treating intra-cranial haemorrhages. Preliminary clinical trials indicate that rFVIIa also promotes haemostasis in patients with normal coagulation systems. It is rapidly acting and has a relatively short half-life of 2.5 hours which corresponds well with the duration of high risk for continued bleeding in the acute stage of ICH.

Trials of recombinant activated factor VII were not contributory or at best inconclusive.

SURGICAL THERAPY

The four recognised surgical procedures to evacuate an ICH are simple aspiration, craniotomy with open surgery, endoscopic evacuation and stereotactic aspiration. Their use in clinical practice is inconsistent. In some countries, e.g. the Netherlands, these are rarely performed; in others, e.g. in USA, these are undertaken in about 20% of patients with ICH and in others, e.g. some centres in Germany and Japan, they are offered to 50% or more of patients. Such wide variation in practice reflects uncertainty about the effectiveness and risks of surgery due to lack of appropriate evidence.

CEREBELLAR HAEMATOMA

Indications of surgery are less controversial than supratentorial ICH. The selection criteria include, impaired consciousness with preserved brainstem reflexes, and perhaps large haematomas (>3 cm to 4 cm in diameter) and vermis haematomas distorting the quadrigeminal cistern even in alert patients, because delayed decline in consciousness and death can be extremely rapid. Trials in cerebellar haematoma showed benefit in small haematomas, in patients put on less invasive surgical procedures like endoscopic aspiration and stereotactic aspiration. Over a period the consensus has been developed as below.

Consensus Guidelines

Surgery for Primary Intra-cerebral Haemorrhage

Recommendations for surgical approaches

Class I:

Patients with cerebellar haemorrhage more than 3 cm who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should have surgical removal of the haemorrhage as soon as possible.

Class II:

1. Although stereotactic infusion of urokinase into the clot cavity within 72 hours of ictus apparently reduces the clot burden and risk of death, re-bleeding is more common, and functional outcome is not improved; therefore, its usefulness is unknown.
2. Although theoretically attractive, the usefulness of minimally invasive clot evacuation utilising a variety of

mechanical devices and/or endoscopy awaits further testing in clinical testing; therefore, its current usefulness is unknown.

3. For patients presenting with lobar clots within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered.

Class III:

The routine evacuation of supratentorial ICH by standard craniotomy within 96 hours of ictus is not recommended. Possible exception is for patients presenting with lobar clots within 1 cm of the surface.

Recommendations for timing of surgery

Class II:

No clear evidence at present indicates that ultra-early craniotomy improves functional outcome or mortality rate. Operative removal within 12 hours particularly when performed by less-invasive methods, has the most supportive evidence, but the number of subjects treated within this window is very small.

Class III:

Delayed evacuation by craniotomy appears to offer little if any benefit with a fairly high degree of certainty. In those patients presenting in coma with deep haemorrhages, removal of ICH by craniotomy may actually worsen outcome and is not recommended.

Recommendations for decompressive craniectomy

Class II:

Too few data currently exist to comment on the potential of decompressive craniectomy to improve outcome in ICH.

THE ICH SCORE

In an attempt to develop a standard clinical grading scale for ICH analogous to those for traumatic brain injury, SAH or ischaemic stroke, Hemphil *et al* developed the ICH score. The factors included for ICH score were:

GCS score—3 to 4 (2 points), 5 to 12 (1 point), 13 to 15 (0 point); age >80 years—yes (1 point), no (0 point); infratentorial origin of ICH—yes (1 point), no (0 point); ICH volume >30 cm^3 (1 point), <30 cm^3 (0 point), and intraventricular extension—yes (1 point); no (0 point). All 26 patients with an ICH score of 0 survived and all 6 patients with an ICH score of 5 died. Thirty-day mortality increased steadily with ICH score ($p < 0.005$). The ICH score is a simple clinical grading scale that allows risk stratification on presentation with ICH. The use of a scale such as the ICH score could improve standardisation of clinical treatment protocols and clinical research studies in ICH.

The time is nearing when ICH will join ischaemic stroke and SAH as a cerebrovascular disease with scientifically proven therapies.

RECOMMENDED READINGS

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3. Mendelow AD, Gregson BA, Fernandes HM, *et al*. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Hemorrhage (STICH): a randomized trial. *Lancet*. 2005;365:387-97.

20.10 Cerebrovenous Thrombotic Disorder

D Nagaraja, N Karthik

Cerebral veno-sinous thrombosis (CVT) involves the thrombosis of the cortical veins and the draining venous sinuses, either alone or in combination. This distinct cerebrovascular condition frequently affects young adults and children. About 75% of the adult patients affected by CVT are women, but this trend is not seen among children or elderly persons. CVT is an important cause of maternal morbidity and mortality in India. Puerperal CVT has been reported to be about 10 to 12 times more frequent in India than in the West.

AETIOLOGY AND PATHOGENESIS

There are a number of causes of CVT. In about 80% to 85% of patients with CVT in developed countries, a direct cause or pro-thrombotic risk factor can be identified. In a patient with such an underlying risk, a precipitating factor such as delivery, dehydration, infection or injury may result in CVT. In all these situations, the common underlying pathogenetic mechanisms include hyper-coagulable state, decreased fibrinolytic activity, slowing of circulation, damage to the endothelium and other unknown mechanisms

Despite new diagnostic technologies, the exact cause of puerperal CVT is still unclear and several predisposing factors are being continuously described. Observational studies have shown a higher platelet adhesive index, platelet adhesive number, serum triglyceride, phospholipids, fatty acid level and elevated plasma fibrinogen levels compared to controls. Elevated Factor VIII:C independently increases thrombotic risk. A population based case control study showed that FVIII:C of greater than 150% is associated with an adjusted odds ratio of 4.8 for a first episode of CVT compared to levels under 100%. In addition, the presence of moderate to severe anaemia has been observed in most patients, with about 56% having haemoglobin less than 10 g/dL. Various genetic thrombophilic conditions such as those associated with factor V Leiden, prothrombin variant G20210A and MTHFR C677T mutations have been identified as risk factors for venous thrombosis. Factor V Leiden mutation resulting in resistance to activated protein C is the most common genetic risk factor for venous thrombosis in Caucasian population. It has been reported to be present in about 4% to 5% of the normal white population, but absent from the indigenous populations of Asia, Africa, America and Australia. The second commonest genetic polymorphism in Caucasians is a variant in the prothrombin (factor II) gene comprising a G to A transition in the 32-untranslated region at nucleotide position 20210. In the European general population, with CVT its frequency is seen as high as 50%. Another polymorphism involves the gene that encodes methylene tetrahydrofolate reductase enzyme (MTHFR) (677C >T) which results in substitution of alanine to valine and produces a thermolabile enzyme with reduced activity. With regard to venous thrombosis, a meta-analysis showed that the MTHFR 677TT genotype was associated with a 20% higher risk of venous thrombosis compared to the 677CC genotype.

Oral contraceptives, especially third-generation contraceptives that contain gestodene or desogestrel have an increased risk of CVT. However, it plays an insignificant role in developing countries. Anti-phospholipid antibody syndrome has been recognised as an important cause of CVT. Anti-cardiolipin antibodies have been detected in 23% of patients with CVT compared to controls from India suggesting it to be an important risk marker. CVT can occur after trauma, neurosurgical procedures. Local infections in the head and face area are notorious to cause sinus thrombosis (cavernous, transverse and sigmoid sinus thrombosis). Meningitis can predispose to more generalised thrombosis of the veins/sinuses.

Recently hyper-homocysteinaemia has been identified as independent risk factor for CVT. Over 50% of the patients with CVT are observed to have elevated homocysteine. Various genetic mutations involving homocysteine have been studied. Only MTHFR C677T mutation has been found to influence homocysteine levels in 5% to 10% of patients and controls. Folate deficiency and to lesser extent B12 deficiency was found to influence high levels of homocysteine in over 50%. Unlike in Caucasians, factor V Leiden, factor V A4070G, prothrombin G20210A, factor VII G353A gene mutations do not have any significant role in Indian patients with CVT. Elevated factor VIII elevated anti-phospholipid antibodies are the other common risk factors associated with increased CVT risk. Often, more than one risk factor may co-exist in CVT.

CLINICAL FEATURES

The presenting features of CVT usually depend upon the sinuses involved, speed of occlusion, involvement of the cortical veins and the presence of collaterals. The common symptoms of CVT include headache, seizures, vomiting, focal deficit and fever. The most frequent but least specific symptom of sinus thrombosis, present in over 90% of adult patients, is severe headache. It is gradual in onset, usually increasing over a period of days to weeks, severe in intensity and often bilateral with associated vomiting. However, it can also be catastrophic such as in sub-arachnoid haemorrhage. Seizures, the next commonest symptom, occur in about 40% to 70% of patients. They may be focal but more commonly generalised. Life-threatening status epilepticus or clusters may be seen in 20% patients. Neurological signs develop in 50% of patients with sinus thrombosis and include monoparesis, hemiparesis or paraparesis. At times, patients may show only extensor plantar response. Unlike puerperal CVT, symptoms develop less rapidly in the non-puerperal group.

Based on the clinical symptoms and signs, the following distinct syndromes can be seen in patients with CVT:

1. Syndrome of dural sinus and cortical vein thrombosis (commonest)
2. Syndrome of deep venous system occlusion
3. Syndrome of cavernous sinus thrombosis

4. Syndrome of increased intra-cranial tension without motor weakness.

INVESTIGATIONS

Cranial Computed Tomography

It is a useful initial technique to diagnose CVT and rule out other acute cerebral disorders. However, it can be entirely normal in 10% of patients. The findings include 'direct signs', i.e. primarily caused by the thrombosis of veins and sinuses and 'indirect signs' when they are secondary to the effects of thrombosis.

1. Direct signs of CVT

a. *Cord sign:* In a non-contrast enhanced computed tomography (CT), the fresh clot in the cerebral veins and sinuses appears hyperdense; and is referred to as cord sign. It is commonly seen in cortical veins, straight sinus and vein of Galen. False positive cord sign may be in children and in conditions with haemo-concentration (**Figure 1A**).

b. *Dense delta sign:* It is seen in non-contrast enhanced CT. In the axial section, the superior sagittal sinus appears as a hyperdense triangle (**Figure 1B**).

2. Empty delta sign

In contrast enhanced CT, a triangular shaped hypodensity surrounded by hyperdense rim is observed. This is most commonly seen in the posterior part of the superior sagittal sinus, straight sinus and transverse sinus. It is the most frequent direct sign of CVT.

3. Indirect signs of CVT

Indirect signs are more frequent. Venous stasis and hyperaemia caused by occlusion of the straight sinus and superior sagittal sinus may lead to intense enhancement of the falx cerebri and tentorium. Non-contrast enhanced CT may show irregular hyperdense or mixed density lesions suggestive of haemorrhagic infarctions which are either small or large, single or multiple. These may not confirm to known arterial territories. Non-haemorrhagic infarctions are also common. In addition, diffuse oedema of the brain may be seen.

CT venography is a promising technique for creating images of the cerebral venous system using helical CT technology. The appearance of dural sinus thrombosis at CT venography is that of a filling defect within the thrombosed dural sinus, alone or in association with a venous infarct.

Magnetic Resonance Imaging

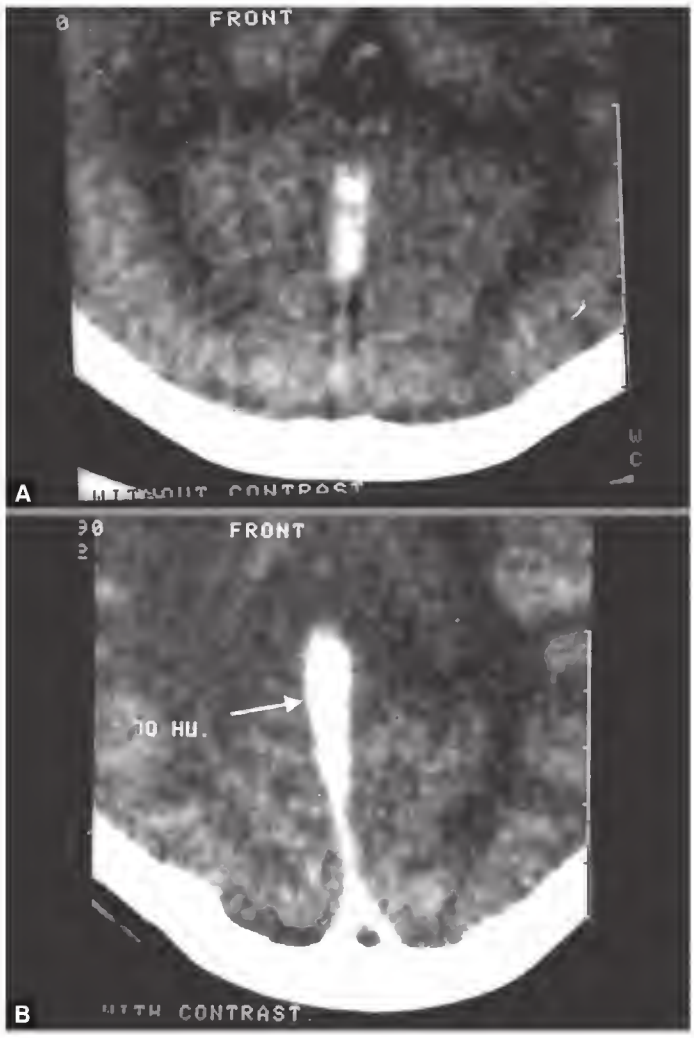
The introduction of magnetic resonance imaging (MRI) has made the diagnosis of CVT possible non-invasively. The following are the changes seen in the MRI.

1. Thrombosed sinus with occlusion

Early thrombus, which contains deoxyhaemoglobin is isointense on T1-weighted and hypointense on T2-weighted image. This is usually seen during the first five days of CVT. Subacute thrombus, which contains methaemoglobin, shows a hyperintense signal on T1-weighted and T2-weighted MRI.

2. Venous infarct

Acute venous infarcts may often be haemorrhagic and appear iso- to mildly hyperintense on T1-weighted and hypointense on T2-weighted image.



Figures 1A and B: (A) Cord sign CT scan without contrast; (B) Delta sign CT scan with contrast.

3. Diffuse cerebral oedema

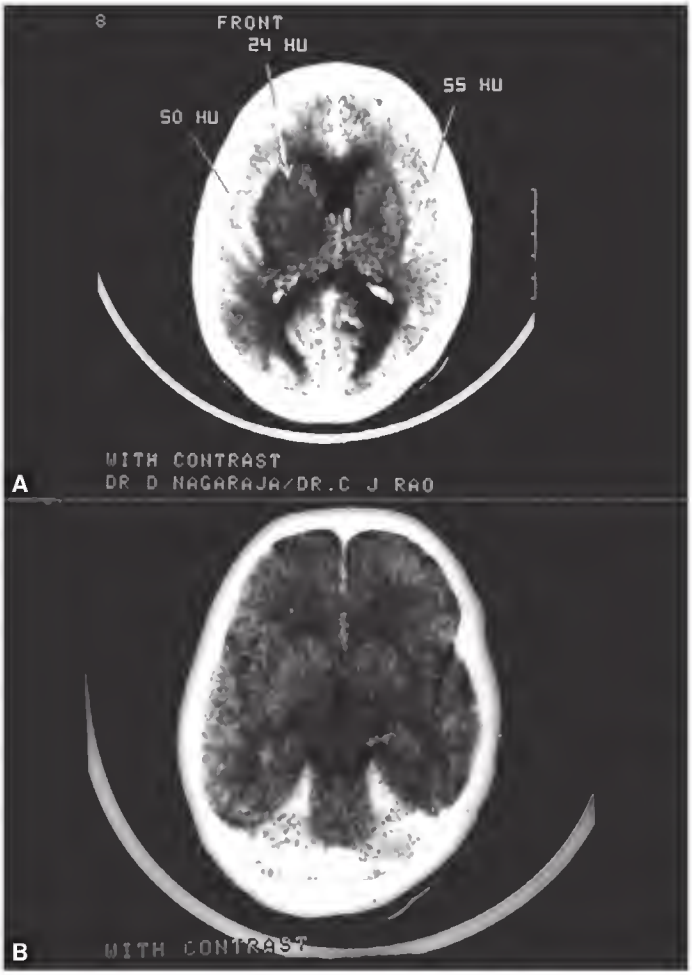
Venous congestion of the brain leads to sulcal effacement and slit-like ventricles.

Magnetic Resonance Venography

It shows either reduction in rate of flow from the involved sinus which is not aplastic or hypoplastic on source images, presence of frayed appearance of flow signal from the sinus after recanalisation. The combination of an abnormal signal in a sinus and a corresponding absence of flow on magnetic resonance venography confirms the diagnosis of thrombosis (**Figures 2A and B**).

Digital Subtraction Angiograph (DSA)

DSA is the gold standard for the diagnosis of CVT. It provides better details of the cerebral veins and hence is useful in the diagnosis of rare cases of isolated thrombosis of the cortical veins without sinus thrombosis. The characteristic angiographic signs are non-filling of the cortical veins or dural sinuses (**Figure 3**), slowing of circulation and stagnation of the contrast medium in the capillary and venous phases. Angiography also shows dilated and tortuous ('corkscrew') veins, which are evidence of thrombosis downstream in the sinuses.



Figures 2A and B: (A) Contrast scan—Bilateral deep venous infarction with peripheral enhancement; (B) Contrast scan—Intense tentorial enhancement.

Other Laboratory Investigations

Other studies include a complete haematological profile, coagulation work-up including prothrombin time, activated partial thromboplastin time, pro-coagulant profile (antiphospholipid antibody, serum homocysteine, Protein C/Protein S, antithrombin III), blood sugar, liver and renal function tests, cardiac evaluation and systemic screening for malignancy.

MANAGEMENT

Combination of acutely increased intra-cranial pressure and large venous infarcts is potential for cerebral herniation. But, these patients can make a remarkable recovery. The priority of treatment in the acute phase is to stabilise the patient's condition and to prevent or reverse cerebral herniation. Raised intra-cranial pressure should be tackled with aggressive osmotic agents such as mannitol with supportive ventilation as and when required. Surgical removal of the infarct or decompressive hemicraniectomy may be attempted in patients not responding to the above regime as a last resort. In addition, it is imperative to evaluate and treat possible causes of sinus thrombosis, such as infections. Anti-epileptic medications should be given to all patients of CVT irrespective of the occurrence of seizures as convulsions can further worsen the intra-cranial hypertension.

Anticoagulation

Prior to the introduction of heparin therapy, the outcome of CVT was uniformly poor with a high mortality. The most obvious rationale is that heparin may arrest the progression of thrombotic process and prevent pulmonary embolism. The ideal dose of heparin that would be beneficial without increasing the risk of intra-cranial haemorrhage is still debated. There is no increased risk of cerebral haemorrhages after treatment with heparin with conventional doses of heparin at 1,000 units per hour, but regular monitoring of APTT is required. Medium dose (5,000 units 8 hourly) and low dose (2,500 units 8 hourly) have been found to be effective (medium better than low) with better safety profile. As such, there is no necessity of monitoring of APTT with low and medium dose regimens. As per recent guidelines, patients with CVT without contraindications for anticoagulation should be treated either with body weight-adjusted subcutaneous low molecular weight heparin or dose-adjusted heparin. Concomitant intra-cranial haemorrhage related to CVT is not a contraindication for heparin therapy. The optimal duration of oral anticoagulant treatment after the acute phase is unclear. Oral anticoagulation may be given for 3 to 6 months. If CVT was idiopathic or secondary to transient risk factor, hereditary thrombophilia with a target INR of 2.5 for 6 to 12 months in patients with mild hereditary thrombophilia with a target INR of 2 to 2.5. In puerperal CVT, anti-coagulation is recommended for a period of 6 to 12 weeks as the recurrence of CVT beyond this period is rare. Recurrent sinus thrombosis occurs in 2% of patients, and about 4% of patients have an extra-cranial thrombotic event within one year. Indefinite anticoagulation should be considered in patients with two or more episodes of CVT or in those with 'severe' hereditary thrombophilia.

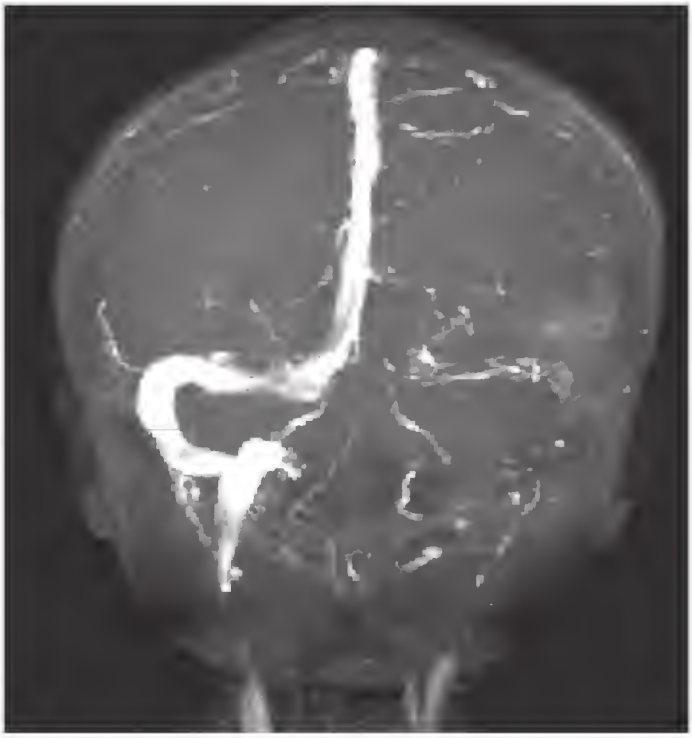


Figure 3: Digital subtraction angiogram showing non-visualisation of left transverse and sigmoid sinus.

Thrombolysis

Rationale of thrombolytic therapy is to obtain a rapid recanalisation of vessels affected and thereby stop the clinical deterioration. Endovascular thrombolysis can be attempted with instillation of thrombolytic enzyme, usually urokinase, into the sinus, sometimes in combination with mechanical thrombo-aspiration. Thrombolysis may be used systemically. The results are not well validated.

COURSE AND PROGNOSIS

More than 80% of all patients now have a good neurologic outcome. In the present era, mortality has fallen from 20% to 50% in the pre-CT period to less than 10%. Puerperal CVT has poorer outcome than non-puerperal cases. Similarly, the symptomatic CVT group has a less favourable outcome. Poor prognostic factors include prolonged deep coma, massive haemorrhagic infarction with midline shift and brainstem compression, rapidly progressive course and involvement of the deep venous system. Deaths in CVT are usually caused by mass effect with herniation. With low morbidity only a small proportion is left with neurological sequelae. Recurrence of CVT is also rare unless associated with inherited pro-thrombotic state.

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20.11 Bacterial Meningitis and Brain Abscess

Ravindra Kumar Garg

BACTERIAL MENINGITIS

Bacterial meningitis is defined as bacterial invasion and subsequent inflammation of pia-arachnoid matter and exudation in cerebrospinal fluid (CSF) of the subarachnoid space. Bacterial meningitis is a potentially life-threatening condition if left untreated. The grave potential for severe neurological damage or even death necessitates prompt medical attention and evaluation.

Epidemiology

Bacterial meningitis has an annual incidence of 4 to 6 cases per 100,000 adults. At present about 1.2 million sporadic cases of bacterial meningitis occur annually worldwide with approximately 135,000 deaths. Bacterial meningitis is much more common in developing and poor countries than developed nations. In developed countries, previously *Haemophilus influenzae* was the most common cause of community-acquired meningitis; following the introduction of effective vaccination, the frequency of meningitis caused by this organism has declined by 82%. At present *Streptococcus pneumoniae* and *Neisseria meningitidis* are responsible for approximately 80% of all cases. In India *Salmonella* species have also been reported to cause meningitis.

Pneumococcal meningitis is often associated with distant infection, such as pneumonia, otitis media, mastoiditis, sinusitis or endocarditis. The triad of pneumococcal pneumonia, meningitis, and endocarditis is a rare but serious condition, known as Austrian syndrome. Predisposing conditions include splenectomy or asplenic state, multiple myeloma, hypogammaglobulinaemia, alcoholism and liver cirrhosis.

Meningococci are transmitted through respiratory droplets. Most cases of invasive disease occur in children and young adults. Meningococcal infection is possibly the most common cause of bacterial meningitis in India and vast majority of cases are sporadic.

Listeria monocytogenes is associated with exceptionally high mortality. *Listeria* meningitis is more frequently seen in neonates, the elderly, alcoholics, diabetics, and in patients with immunocompromised states. Meningitis due to Gram-negative bacilli is unusual except at the extremes of life. *Escherichia coli* are cultured from 30% to 50% neonatal patients of bacterial meningitis. *Klebsiella* species, *Escherichia coli*, and *Pseudomonas aeruginosa* may be isolated in CSF following head trauma or neurosurgical procedures.

Pathogenesis

The common bacteria causing meningitis are transmitted via air-borne route. Bacteria after colonising the nasopharyngeal mucosa secrete immunoglobulin (Ig)A protease enzymes that breakdown the protective mucous barrier allowing bacterial attachment to the epithelium. The outer adhesive bacterial pili (finger-like projections) also play an important role in the attachment of the encapsulated bacteria to the nasopharyngeal mucosa. After attachment bacteria invade the adjacent intravascular space and gain access to the blood stream and finally enter into the CSF through the choroid plexus of the lateral ventricles, and other points where blood-brain barrier is weak. Once bacteria reach the CSF these rapidly multiply because host humoral defence mechanisms in CSF are deficient. Alternatively, bacterial meningitis can occur by haematogenous spread of bacteria, through congenital neuroectodermal defects, craniotomy sites, middle ear diseases, paranasal sinus infections and skull fractures (**Table 1**).

Table 1: Six Stages in the Pathogenesis of Community-acquired Bacterial Meningitis

Nasopharyngeal colonisation
Nasopharyngeal epithelial cell invasion
Invasion of meningeal vessels
Intravascular multiplication and bacteraemia
Crossing of blood-brain barrier; bacterial entry into CSF
Survival and multiplication in CSF

The innate inflammatory immune response of the host is of crucial importance for the early containment of bacterial infection. The innate immune responses are mediated by toll-like receptors which are pattern recognition receptors that are expressed in microglia (the resident macrophages of the brain). When Toll-like receptors interact with bacterial antigens, an intense inflammatory immune response starts which has the potential to cause immunopathological changes in the host tissue. Experimental studies demonstrated that Toll-like receptors-2 deficient mice were highly susceptible to *Streptococcus pneumoniae* meningitis because of reduced bacterial clearing.

In central nervous system (CNS), in addition to multiplication, bacteria expose microbial antigens to host cells, which subsequently trigger an inflammatory response. This inflammatory response is mediated by cytokines such as tumour necrosis factor-alpha (TNF-α), interleukins (IL), and prostaglandins. Secretion of IL-1 family of cytokines along with TNF-α leads to excessive production of several other pro-inflammatory mediators. Under influence of these chemicals, a large number of neutrophils are recruited in to the subarachnoid space. Activated neutrophils and other inflammatory cells release many potentially cytotoxic agents including oxidants and matrix metallo-proteinases that cause extensive damage to the brain tissue. Matrix-metallo-proteinases, in fact, lead to degradation of components of the blood-brain barrier. This in turn results in several acute complications of bacterial meningitis like cerebral oedema formation, increased intra-cranial pressure and ischaemia.

Pathology

The important pathological feature of bacterial meningitis is a purulent exudate which is present in the basal cisterns and extends throughout the subarachnoid space. The underlying brain (although not invaded by bacteria) becomes congested, oedematous and ischaemic because of extensive disruption of blood-brain barrier. The inflammatory exudates may affect vascular structures crossing the subarachnoid space producing an arteritis or venous thrombophlebitis with resultant cerebral infarction. Similarly, cranial nerves passing through the purulent basal exudates may suffer direct damage. Hydrocephalus can result from obstruction of CSF flow in the ventricles and subarachnoid space. Transtentorial herniation is caused by diffuse swelling of the brain parenchyma, or hydrocephalus.

Clinical Features

The characteristic symptoms and signs of bacterial meningitis are headache, fever, nuchal rigidity, photophobia, vomiting and lethargy or an altered level of consciousness. The sensitivity of the classic triad of fever, neck stiffness, and altered mental status is low, but almost all such patients present with at least two of four symptoms: headache, fever, neck stiffness, and altered mental status. Other signs of meningeal irritation (Brudzinski's and Kernig's signs of the neck and legs) are also present in majority of the patients. Seizures occur in approximately 23% to 40% of patients, typically in the first week of illness. Focal neurological signs complicate bacterial meningitis in 15% to 28% of patients, and are caused by cortical vein thrombosis, cerebral artery spasm, subdural empyema or rarely brain abscess. In the elderly and in the immunocompromised or neutropaenic patients, classical signs and symptoms of meningitis may be minimal or absent. These patients may present with a mild confusional state.

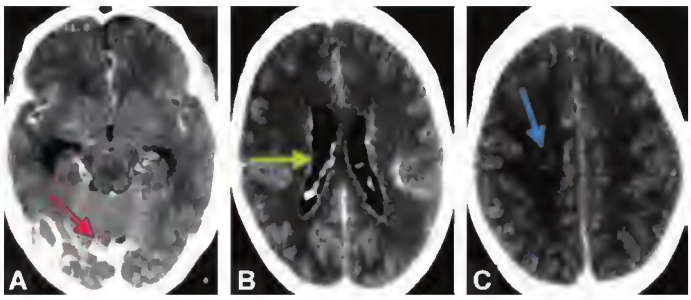
The most frequent cranial nerve abnormality is the involvement of the 8th cranial nerve, which results in hearing loss. Sensorineural deafness, unilateral or bilateral can appear early or late in the course of illness, and is usually permanent. Involvement of the 6th and 7th cranial nerves occurs early or late in the course of the disease and is probably never persistent. The presence of bilateral 6th nerve palsies suggests raised intracranial pressure. Papilloedema is rare (less than 1% of patients), its presence usually suggests another diagnosis such as intracranial space-occupying lesion. Abnormalities of 7th and 8th cranial nerves may also develop even in a few adequately treated individuals. The incidence of hearing loss is greater in patients with *Streptococcus pneumoniae* meningitis than in patients with *Neisseria meningitidis* infection.

Other clinical signs indicative of elevated intra-cranial pressure and cerebral herniation are coma, unilateral or bilateral fixed and dilated pupils, decorticate or decerebrate posture, abnormal respiration (Cheyne-Stokes breathing, hyperventilation, apnoea or respiratory arrest) and loss of oculo-cephalic reflex. These signs are often of ominous prognostic significance.

Diagnosis

If bacterial meningitis is suspected, lumbar puncture is an essential procedure. CSF changes are characteristic of bacterial meningitis. Opening CSF pressure is often elevated usually in the range of 200 mm Hg to 500 mm H_2O. The CSF appearance may be turbid because of the presence of blood cells, bacteria, and protein. In untreated bacterial meningitis, the white blood cell count is markedly elevated, usually in the range of 1,000 cells/mm^3 to 5,000 cells/mm^3. Bacterial meningitis usually leads to a neutrophil predominance in CSF. The CSF glucose concentration is less than 40 mg/dL in approximately 50% to 60% of patients. A ratio of CSF to serum glucose of less than or equal to 0.4 is 80% sensitive and 98% specific. The CSF protein concentration is invariably elevated. Gram's staining of CSF sediment is extremely important as it permits rapid and accurate identification of the causative micro-organism. The CSF culture is positive in approximately 70% to 85% of patients. The probability of CSF culture being negative is increased if patient has received prior antimicrobial therapy. Blood culture is also performed and can be positive in 80% of cases of *Haemophilus influenzae* meningitis and less than 50% of patients with pneumococcal and meningococcal meningitis. Polymerase chain reaction (PCR) has been utilised to amplify deoxyribonucleic acid (DNA) from patients with meningitis caused by the common meningeal pathogens. A rapid aetiologic diagnosis is possible with the use of counter-current immunoelectrophoresis and such other serological techniques. These tests detect capsular antigen in CSF and are useful if CSF microscopy is negative, especially, if patient has already received antibiotics.

Neuroimaging, before lumbar puncture, should be performed if patient has focal neurological deficit, seizures, papilloedema, coma, or in immunocompromised state. CNS complications of bacterial meningitis detectable by neuroimaging are: meningeal enhancement, cerebral oedema, transient dilatation of ventricles, ventriculitis, hydrocephalus, subdural effusion or empyema, cerebral infarct, brain abscess, and cerebral venous sinus thrombosis (**Figures 1A to C**). Neuroimaging in uncomplicated bacterial meningitis is often normal.



Figures 1A to C: Cranial contrast-enhanced computed tomography of brain in a patient with pneumococcal bacterial meningitis showing: (A) meningeal inflammation (red arrow); (B) ventriculitis (green arrow); and (C) a small brain abscess (blue arrow).

Differential Diagnosis

Several infective and non-infective CNS disorders, presenting with headache, fever, focal neurological deficit and with an altered state of consciousness, are included in the differential diagnosis of acute bacterial meningitis. These conditions include cerebral malaria, heat stroke, viral encephalitis and viral meningitis. In India and other endemic countries distinction between cerebral malaria and acute bacterial meningitis is often difficult, particularly in children. If a patient of suspected bacterial meningitis is HIV-positive, the differential diagnosis should also include cryptococcal meningitis, tuberculous meningitis, and toxoplasma meningoencephalitis.

Treatment

Antibiotic therapy should be immediately started soon after diagnosis is suspected or confirmed with characteristic CSF findings, without waiting to determine the aetiological organism. Delay in initiation of antimicrobial therapy can result in poor outcome.

Empirical antibiotic therapy

Choice of empirical antibiotic is determined on the basis of the patient's age and underlying health status. With the worldwide increase in the occurrence of penicillin-resistant pneumococci, combination therapy with vancomycin plus a third-generation cephalosporin (either ceftriaxone or cefotaxime) has become the choice of empirical antimicrobial therapy. For patients with penicillin or cephalosporin hypersensitivity, the recommended treatment is chloramphenicol plus vancomycin. In young infants (less than 3 months old) and older adults, in whom *Streptococcus agalactiae* and *Listeria monocytogenes* are prevalent, treatment with broad-spectrum cephalosporins is supplemented with ampicillin. Patients who have had recent neurosurgery, head trauma and immunosuppressed patients with or without nosocomially acquired infection need broader antibiotic coverage such as combination of ceftazidime and vancomycin (**Table 2**).

Table 2: Empirical Antimicrobial Therapy in Bacterial Meningitis

	Likely Organisms	Choice of Antimicrobials
Children less than 3 months	*Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*	Ampicillin + Cefotaxime *or* Ampicillin + Aminoglycoside
3 months to less than 18 years	*Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*	Vancomycin + Third-generation Cephalosporin
18 to 50 years	*Streptococcus pneumoniae*, *Neisseria meningitidis*	Vancomycin + Third-generation Cephalosporin
Above 50 years	*Streptococcus pneumoniae*, *Listeria monocytogenes*	Vancomycin + Third-generation Cephalosporin + Ampicillin
Immunocompromised adults	*Listeria monocytogenes*, Gram-negative bacilli	Ampicillin + Ceftazidime
Penetrating head trauma, ventricular shunt, neurosurgical trauma	*Streptococcus pneumoniae*, *Staphylococcus*, *Listeria monocytogenes*, Gram-negative bacilli, *Pseudomonas aeruginosa*	Vancomycin + Ceftazidime *or* Vancomycin + Cefepime

Pathogen-specific therapy

Once a bacterial pathogen is isolated and *in vitro* susceptibility testing is performed, antimicrobial treatment should be modified. As a result of increase in penicillin-resistant *Streptococcus pneumoniae*, adult patients with pneumococcal infection should receive ceftriaxone plus vancomycin unless organism is demonstrated to be cephalosporin-sensitive. Penicillin-sensitive species can be treated with continued cefotaxime, ceftriaxone, or chloramphenicol, or even switched to penicillin-G. For penicillin-resistant species, vancomycin is continued and rifampin may be added. Penicillin is the drug of choice for meningococcal meningitis. Generally, high-dose intravenous penicillin-G should be administered every 4 to 6 hours for patients with invasive meningococcal disease. Acceptable alternatives to penicillin-G are ampicillin, cefotaxime and ceftriaxone. Most reported strains of *Neisseria meningitidis* are moderately susceptible to high-dose penicillin-G, cefotaxime, and ceftriaxone. Chloramphenicol is indicated for patients with anaphylactic allergic reactions to penicillin. Chloramphenicol has also been used routinely in under-developed countries, but single-dose ceftriaxone is an efficacious, easy to use, and low-cost alternative (**Table 3**).

Role of corticosteroids

Theoretically, control of inflammatory changes with the help of corticosteroids may prove effective in decreasing many of the pathophysiologic ill-effects of bacterial meningitis. Several clinical studies have demonstrated the benefit of adjunctive dexamethasone in infants and children with *Haemophilus influenzae* meningitis, and adults with pneumococcal meningitis, in which mortality and incidence of adverse outcome have found to be declined. In children, administration of corticosteroids led to reduction in incidence of severe hearing loss in *Haemophilus influenzae* bacterial meningitis. However, a recent meta-analysis of existing data suggests that the benefit of dexamethasone for all or any subgroup of patients with bacterial meningitis remains unproven and dexamethasone does not seem to significantly reduce death or neurological disability. Use of adjunctive dexamethasone in adults with meningitis caused by other bacteria, and in infants and children with pneumococcal meningitis, is controversial.

To be effective, dexamethasone should be administered concomitant with or just prior to the first antimicrobial dose for maximal effect on the subarachnoid space inflammatory response. In adults, the dexamethasone was administered in dosage schedule of 0.15 mg/kg every 6 hours for 2 to 4 days with the first dose administered 10 to 20 minutes before, or at least concomitant with the first dose of antimicrobial therapy. Dexamethasone was usually given for four days regardless of microbial cause or clinical severity.

Table 3: Pathogen-specific Antibiotic Therapy for Bacterial Meningitis in Adults

Pathogen	Antimicrobials	Dosage	Duration (Days)
Streptococcus pneumoniae	Ceftriaxone *or* Cefotaxime + Vancomycin	4 g/day (12 hourly) 12 g/day (4 hourly) 2 g/day (6 hourly)	10 to 14
Neisseria meningitidis	Penicillin-G *or*	20 to 24 million U/day (4 hourly)	5 to 7
	Ceftriaxone	4 g/day (12 hourly)	
Haemophilus influenzae	Ceftriaxone *or* Cefotaxime	4 g/day (12 hourly) 12 g/day (4 hourly)	7
Listeria monocytogenes	Ampicillin + Gentamycin	12 g/day (4 hourly) 6 mg/kg/day (8 hourly)	14 to 21
Gram-negative bacilli	Ceftriaxone *or* Cefotaxime	4 g/day (12 hourly) 12 g/day (4 hourly)	21
Pseudomonas aeruginosa	Ceftazidime + Intraventricular Gentamycin	8 g/day (8 hourly)	21

Other supportive management

Careful management of fluid and electrolyte balance is an important supportive therapy. Both over- and under-

hydration are associated with adverse outcomes. The patient requires analgesics for headache and backache and careful nursing in a darkened room if photophobia is prominent. Symptomatic treatment of pyrexia is appropriate in majority of the patients. In children, prophylactic anticonvulsant can also be used. In patients with signs of raised intra-cranial pressure, an intracranial pressure measuring device may be inserted. Intravenous mannitol may be required to reduce the elevated intra-cranial pressure. In a few patients treatment of shock or disseminated intravascular coagulation may be needed.

Duration of antibiotic therapy and response to treatment

Usually, 5 days of antibiotic therapy is sufficient for most of the immunocompetent patients of bacterial meningitis. However, authorities on the subject suggest at least 7 days treatment for *Haemophilus* and meningococcal meningitis. Patients with pneumococcal meningitis require antibiotic therapy for at least 10 to 14 days. A prolonged antibiotic therapy is worthwhile in patients with persistent fever, seizures, coma, and in patients who are immunocompromised. In *Listeria monocytogenes* and streptococcal meningitis, antibiotics should be given for 14 to 21 days. For Gram-negative bacilli a minimum treatment of three weeks is needed. In a responsive patient, the CSF becomes sterile 1 to 2 days after antibiotic treatment. The fever usually disappears within few days but may persist for several weeks. Dead bacteria may be seen on Gram's stain of CSF for several days. In bacterial meningitis which has responded well to antimicrobial therapy, repeated lumbar puncture is not routinely required. Repeat CSF analysis should be performed if patient has not responded after 48 hours of appropriate antimicrobial therapy.

Prognosis and Complications

Mortality from bacterial meningitis varies from 5% to 25%, depending on the causative organism, age of the patient, and the predisposing illness. The mortality rate is higher among patients with pneumococcal meningitis than among those with meningococcal meningitis (30% versus 7%). Risk factors for an unfavourable outcome are advanced age, presence of otitis or sinusitis, absence of rash, a low score on the Glasgow Coma Scale on admission, tachycardia, a positive blood culture, an elevated erythrocyte sedimentation rate, thrombocytopaenia, and a low CSF white-cell count. The case fatality rate for *Haemophilus influenzae* meningitis has been reported about 5%. *Listeria monocytogenes* meningitis is associated with a high mortality rate.

A study (in adults with pneumococcal meningitis) reported meningitis-associated intra-cranial complications in 75% of patients, and systemic complications in 38%. Diffuse brain oedema and hydrocephalus were the most frequent intra-cranial complications. The incidence of arterial thrombosis and cerebral venous thrombosis were also very high. Approximately 10% of cases developed spontaneous intra-cranial haemorrhages. Few patients developed acute spinal cord dysfunction due to myelitis. Hearing loss was reported in 20% of all patients and 26% of survivors. Sterile subdural effusion is a common complication of *H. influenzae* meningitis but is relatively uncommon in other bacterial infections of the meninges. In up to 30% of meningitis survivors, long-term neurologic sequelae develop, including hearing loss and other focal neurologic deficits.

Meningococcal meningitis may be characteristically associated with prominent purpuric or petechial rash affecting extremities in about 50% of patients. Neurological and other systemic complications are relatively infrequent. The most important non-neurological complication of meningococcal meningitis is disseminated intravascular coagulation induced by the endotoxins liberated by the bacteria.

Prophylaxis

During an outbreak of meningococcal disease, individuals at risk should be treated by administration of antibiotics known to eradicate meningococcal carriage. Rifampicin is used for the prevention of secondary cases of meningococcal meningitis. The recommended dose is 600 mg every 12 hours for 2 days in adults. Prophylactic treatment is given to close household contacts and hospital personnel. Ciprofloxacin can also be used for prophylaxis in single oral dose of 500 mg daily in adults.

Recurrent Bacterial Meningitis

Three factors, that play an important role in the predisposition of recurrences of bacterial meningitis, include tears in the dura, fracture of the cribriform plate or paranasal sinuses and a nasal meningocoele. These lesions produce a connection between the external environment and the subarachnoid space. Through these defects, bacterial pathogens can readily gain access to meninges and brain, leading to recurrent meningitis. About 50% of patients with repeated attacks of bacterial meningitis have persistent CSF rhinorrhoea for months to years. Abrupt cessation of nasal discharge of CSF followed by global headache and fever suggest recurrence of meningitis. In patients with recurrent bacterial meningitis, *Streptococcus pneumoniae* is the usual pathogen. CSF rhinorrhoea can be diagnosed by measuring glucose concentration of nasal secretions. Usually nasal mucus secretion contains little glucose but in case of CSF rhinorrhoea, the glucose amount of nasal secretion approximates that in CSF. Treatment of recurrent bacterial meningitis consists of use of the pneumococcal vaccine, along with prophylactic oral penicillin. Fistulous connection between subarachnoid space and nasal sinuses requires surgical repair. The prognosis of recurrent meningitis is better as mortality is much lower than in other forms of bacterial meningitis.

BRAIN ABSCESS

Definition

A brain abscess may be defined as localised suppurative necrosis of the brain parenchyma and a circumscribed collection of purulent exudate in the brain, due to bacterial and other infections.

Incidence

The advent of antibiotics and improved treatment of ear and sinus infections has led to a reduction in intra-cranial abscess formation, but incidence in western world still lies at 2 to 3 patients per million per year.

Pathogenesis

In brain abscess, bacteria reach the brain parenchyma by spreading from a contiguous cranial site of primary infection. These sites most often are in the middle ear, mastoids or

paranasal sinuses. Infection may spread either directly through the skull bone (osteomyelitis), or through emissary vein producing a suppurative thrombophlebitis. The area of brain involved is usually adjacent to the area of primary infection. For example, infection from frontal sinusitis can extend to frontal lobes and infection originating from middle ear or mastoid air cells can lead to either temporal lobe or cerebellar abscess. There may also be direct extension of infection from a contaminated compound skull fracture or other deep penetrating head injury. Occasional cases are associated with osteomyelitis of skull or dental infections. Brain abscess may also be a complication of neurosurgical procedure.

About one-third of all brain abscesses are haematogenous in origin and primary septic focus is either acute bacterial endocarditis or pyogenic infections of lung or pleura. Pulmonary infections commonly associated with this disease are lung abscess and bronchiectasis. Haematogenous spread of bacteria to the brain may occur in patients with congenital cyanotic heart diseases or with pulmonary right-to-left shunt. Fallot's tetralogy is the commonest congenital heart disease responsible for brain abscess. Metastatic or haematogenous brain abscess are often multiple and found at grey and white matter junctions in the territory of middle cerebral artery. *Listeria* abscesses tend to involve brainstem.

Pathology

Formation of brain abscess is usually preceded by the development of a small area of infarct secondary to occlusion of a small vessel or because of thrombophlebitis of surface vessels. Infarcted or necrotic brain tissue favours bacterial invasion and multiplication. Thus, formation of brain abscess begins with an area of focal cerebritis with subsequent focal softening and liquefaction. As the process continues there is formation of an encapsulated abscess cavity along with variable amount of oedema surrounding the abscess.

Improved anaerobic and aerobic bacteria culture techniques enable us to identify the causative organism in over 80% of patients. Mixed infection is seen in approximately 30% to 60% of patients. Microaerophilic and anaerobic organisms are the main pathogens isolated from brain abscess, the most common being the bacteria of *Streptococcus intermedius* group especially *Streptococcus milleri*, and anaerobic *Bacteroides* species. Methicillin-resistant *Staphylococcus aureus* is of increasing concern as an aetiological organism. Isolates from brain abscesses in immunocompromised patients frequently differ from those recovered from abscesses in immunologically intact individuals. *Enterobacteriaceae*, *Pseudomonas aeruginosa*, or *Listeria monocytogenes* may be isolated from brain abscess in immunosuppressed patients. Fungi including *Cryptococcus neoformans*, *Candida*, *Mucor*, *Aspergillus* species and *Cladophialophora bantiana* may be associated with brain abscess in diabetics and other immunocompromised patients, as well as in patients abusing intravenous drugs. *Nocardia asteroides*, although most commonly isolated from immunocompromised patients, may cause brain abscess in patients without known impairment of immune function. The most common cause of focal intracranial infection in patients with AIDS is *Toxoplasma gondii*, followed by *Cryptococcus neoformans* and *Mycobacterium tuberculosis* (**Table 4**).

Table 4: Most likely Pathogen Depending on Primary Source of Infection in Brain Abscess

Site	Likely Pathogen
Middle ear	*Streptococcus milleri, Bacteroides fragilis, Escherichia coli, Proteus, Streptococcus pneumoniae,* often mixed
Paranasal sinuses	*Streptococcus pneumoniae Streptococcus milleri*
Haematogenous	*Streptococcus pneumoniae Streptococcus milleri, Staphylococcus aureus*
Head trauma	*Staphylococcus aureus, Pseudomonas*
Lung abscess	Anaerobic bacteria
Immunocompromised patients	*Toxoplasma, Streptococcus pneumoniae, Aspergillus, Candida, Nocardia, Listeria monocytogenes*

Clinical Features

Symptoms and signs of brain abscess usually develop over 2 to 3 weeks. Infrequently, the onset is more gradual, but features may develop acutely in the immunocompromised patient. Early symptoms include headache, lethargy, intermittent fever and focal or generalised seizures. Fever is present in less than 50% of patients. Focal neurological deficit may develop depending on the site of lesion. For example, lesions in the frontal cortex may produce hemiparesis or monoparesis while lesions in the occipital cortex cause homonymous visual field defects. Patients with cerebellar abscess may present with dysarthria, nystagmus and limb incoordination. Nuchal rigidity is present in 25% patients. Papilloedema and 6th cranial nerve palsy are infrequent. As the abscess expands increased intra-cranial pressure becomes more pronounced producing headache, vomiting, psychomotor slowing, lethargy and increasing confusion. If untreated, eventually, brain herniation and death may occur as a result of expanding mass.

Diagnosis

The diagnosis of brain abscess is established with the help of neuroimaging. The CT scan usually demonstrates a lesion with a low-density necrotic centre, a well developed contrast-enhancing capsule (in the form of 'ring' enhancement) and surrounding cerebral oedema (**Figure 2**). The enhancing lesions caused by pyogenic abscesses are commonly located at the grey-white matter junction. Frequently, the capsule of abscess is difficult to visualise via conventional imaging techniques, and double contrast CT is needed to clearly define the capsule of the abscess. CT, in addition, may also reveal opacification of the mastoids and sinuses. On non-contrast magnetic resonance imaging, pyogenic abscess show an isointense-to-slightly hyperintense capsule on T1-weighted images and is hypointense on T2-weighted images. The ring enhancement on post-contrast images is usually thin, smooth, and often thinner along the medial margin. However, a greater thickness, irregularity, and nodularity of the wall of the lesions are often suggestive of tumour or a fungal infection. Magnetic resonance diffusion-weighted imaging along with apparent diffusion coefficient and proton magnetic resonance spectroscopy can provide additional information for differentiation of brain abscess from other necrotic lesions. Differential diagnosis of ring enhancing lesions on CT is tabulated in **Table 5**.

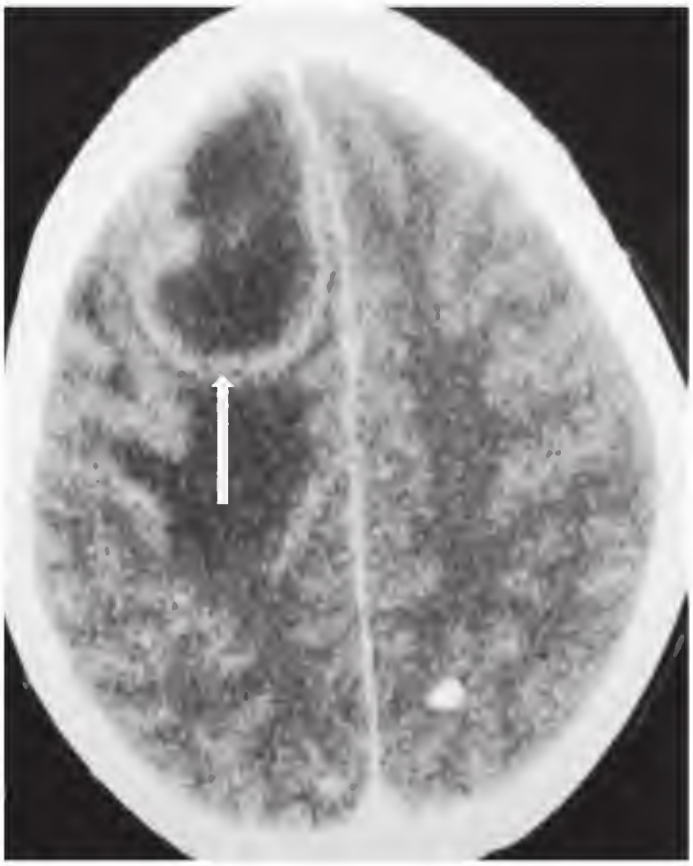


Figure 2: Cranial contrast-enhanced computed tomography of brain showing a brain abscess (white arrow) and marked perilesional vasogenic oedema in the right frontal region.

Table 5: Differential Diagnosis of Ring Enhancing CT Lesions

Large (>20 mm)
Brain abscess
Brain tumours (e.g. gliomas, secondaries)
Tuberculous abscess
Fungal abscess
Small (<20 mm)
Common
Cysticercus granuloma
Tuberculoma
Uncommon
Old infarct
Focal encephalitis
Sarcoidosis
Microabscesses
Vasculitis
In Immunocompromised Patients
Toxoplasmosis
Primary CNS lymphoma
Fungal granuloma
Tuberculoma and tuberculous abscess

Treatment

The treatment of brain abscess usually requires appropriate antibiotic therapy and surgical drainage. Broad-spectrum antibiotic treatment is started as soon as clinical diagnosis is made. Empirical antibiotic therapy should provide coverage against staphylococci (usually with vancomycin to cover methicillin-resistant *Staphylococcus aureus*) and Gram-negative bacilli (with a third-generation or a fourth-generation cephalosporin, such as ceftazidime or cefepime, respectively). Because vancomycin is less active against methicillin-susceptible *Staphylococcus aureus*, nafcillin or cefazolin is preferred for the treatment of documented methicillin-susceptible *Staphylococcus aureus* infection. Ceftazidime should be used in place of ceftriaxone or cefotaxime if *Pseudomonas aeruginosa* infection is suspected. Once bacteria are cultured, therapy should be changed according to the antibiotic sensitivities. Antibiotics should be administered intravenously and treatment is continued for 6 to 8 weeks.

Because the most immediate threat from brain abscess is the mass effect, surgical aspiration of pus often diminishes the risks of increased intra-cranial pressure. Burr-hole aspiration of pus is a simple and safe method. Persistent reaccumulation of pus despite repeated aspiration may require surgical excision of the abscess. Mannitol or corticosteroids may be essential, at least, initially to control cerebral oedema. Corticosteroids should be used cautiously if at all and should be tapered off rapidly as they may interfere with capsule formation and host defence against organisms.

Prognosis

Mortality from brain abscesses ranges from 30% to 65%, mortality is lower in patients who receive dual treatment with antibiotics and surgery. About 50% of survivors have neurological sequelae like recurrent seizures and focal neurological deficit.

RECOMMENDED READINGS

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20.12 Neurotuberculosis

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INTRODUCTION

Tuberculosis is one of the oldest known diseases affecting almost every organ system of the human body. Despite worldwide infection control programmes and powerful antibiotics, tuberculosis of the central nervous system (CNS) is still more than a historical relic. There is increasing prominence of extrapulmonary infection, worrying prevalence of drug-resistance mycobacteria and there is increasing association of acquired immunodeficiency syndrome (AIDS) epidemic with tuberculosis. All these facts suggest that CNS tuberculosis will remain a significant clinical entity in coming years.

Tuberculosis can affect any part of the nervous system including the meninges, brain and spinal cord. Tuberculous meningitis (TBM) is by far the most common manifestation, accounting for 70% to 80% of all cases of neurotuberculosis. Various forms of neurotuberculosis that are commonly encountered in clinical practice are given in **Table 1**.

Table 1: Spectrum of Neurotuberculosis

Tuberculous meningitis	Basal Spinal
Tuberculoma	Intra-cranial Parenchymal Extraparenchymal Spinal
Tuberculous abscess	
Tuberculous encephalopathy	With meningitis Without meningitis
Spinal affection secondary to skeletal tuberculosis	

EPIDEMIOLOGY

Neurotuberculosis is not distributed uniformly around the world. In the less developed countries, the disease remains a common disease of childhood. The epidemiological data regarding prevalence of neurotuberculosis is very scarce in the developing countries. It accounts about 15% of extrapulmonary tuberculosis and 0.7% of all clinical tuberculosis. Neuro-tuberculosis is the most serious form of tuberculosis; even with prompt and adequate treatment, mortality rate goes up to 27%.

In the developed countries, the rates of extrapulmonary tuberculosis declined only minimally in spite of reduction of incidence of pulmonary tuberculosis, and rates of CNS infection remained similarly constant, representing approximately 5% of extrapulmonary cases reported.

Since the epidemic of HIV infection, there are increased occurrences of both reactivated and newly-acquired infections. Extrapulmonary tuberculosis including CNS tuberculosis, is considerably more frequent in the setting of HIV infection than otherwise. In parts of Africa and Asia, more than 50% of HIV-infected patients have tuberculosis during the course of their illness. Thus, HIV-infected individuals with active disease may come to serve as reservoir for the spread of primary tuberculous infection into their community.

AETIOLOGY

Virtually all tuberculous infections of the CNS are caused by the human tubercle bacillus, *Mycobacterium tuberculosis*. Infections caused by *M. bovis* acquired from the ingestion of contaminated milk are now quite rare, as are infections caused by other non-tuberculous mycobacteria (NTM) pathogenic for human, except in immunocompromised patients, where infection of *M. avium* and *M. intercellulare* are common.

PATHOGENESIS

Like all other forms of tuberculosis, CNS infection begins with inhalation of infectious particles. On reaching the alveoli, airborne droplet nuclei, each containing small number of organisms, multiply either within the alveolar space or within the alveolar macrophages. For first 2 to 4 weeks, when there is virtually no inflammatory response, haematogenous dissemination of the organism is believed to occur in every case.

Two to four weeks following infection, cell-mediated immunity to bacteria develops. A tubercle is formed, consisting of macrophages, lymphocytes and other cells surrounding a necrotic caseous centre. Fate of these tubercles and subsequent course of infection are a function of both the immunologic capacity of the host and other incompletely understood genetic factors. When there is robust immunity, minute caseous foci are formed only to be eliminated completely by the surrounding macrophages leaving no residua. Less efficient but still effective immune response results in larger caseous foci which, despite fibrous encapsulation, continue to shelter viable mycobacteria, which may cause reactivated disease if host's immune vigilance lessens. In the presence of profound immunodeficiency, primary tubercle continues to grow, the caseous centre may liquefy, organisms proliferate and tubercle ultimately ruptures, discharging organisms into the surrounding tissue.

When these events occur within the brain and meninges and the so-called Rich's foci ruptures discharging the organism in the subarachnoid space, tuberculous meningitis results. The vascular choroid plexus are common sites for tubercle formation and also common site for rupture of a tubercle as also foci located on the surface of the brain. Those tubercles located deep in the brain or spinal cord parenchyma will enlarge to form tuberculoma or tuberculous abscesses.

PATHOLOGY

Meningeal Exudate and Meningitis

The primary pathological event is the formation of thick tuberculous exudates within the subarachnoid space. These exudates diffuse with particular prominence at the base of the

brain irrespective of the location of the discharging focus. The exudates accumulate around the interpeduncular fossa, enveloping the optic nerves at the chiasma and extending over the pons and cerebellum, often into the sylvian fissures and rarely up along the cerebral hemispheres. Thus, other cranial nerves such as III, IV, VI, VII, and VIII may be involved in the subarachnoid space in varying degrees.

In appearance, the exudate is gelatinous and frequently nodular. Microscopically, it consists of polymorphonuclear leucocytes, red blood cells, macrophages and lymphocytes within a fibrin network. Typical tubercles, occasionally with large zones of caseation necrosis develop within the exudate. In untreated cases, a large number of tubercle bacilli can be detected at the margins of caseous necrosis. With treatment fibroblasts and elements of connective tissues replace the exudates.

Vasculopathy

Accompanying the tuberculous exudate is a characteristic inflammation affecting the medium and small sized blood vessels traversing it. The adventitial layer of vessels develops changes similar to those of the adjacent tuberculous exudate. The intima of the vessels may eventually be affected similarly or these may be eroded by a fibrinoid-hyaline degeneration. Thus, the lumen of the vessel may be completely occluded. Ischaemic cerebral infarction, thus, results which is a common sequel of tuberculous arteritis, most often in the distribution of middle cerebral artery (reflecting the presence of tuberculous exudate within the Sylvian fissure) and the lateral striate arteries as they penetrate the base of the brain. Infrequently haemorrhagic infarcts have been described. The vascular lesions cause various types of neurodeficits, seizures and cognitive disturbances.

Border-Zone Encephalitis

TBM is appropriately characterised as a meningo-encephalitis because it affects not only meninges but also parenchyma. There are pathological changes in the brain immediately underlying the infected meninges. Frequently there is only a glial reaction; occasionally the changes may be of inflammatory nature with peri-vascular cuffs of small mononuclear cells, and later on gliosis. It is seen most frequently in the Sylvian fissure.

Hydrocephalus

It results from profound disturbances in the circulation of the CSF due to blockage of CSF pathway by the dense basal exudates. There is also interference in the absorption of the CSF by the arachnoid granulations. All these result in communicating hydrocephalus. Isotope cisternoventriculography with iodine-labelled human albumin has been used to confirm it. Sometimes, the obstruction may be at the level of aqueduct of Sylvius or foramen of Monroe leading to obstructive hydrocephalus.

Tuberculoma Formation

If a tubercle situated deep in the brain parenchyma or spinal cord enlarges at the expense of the parenchyma, a tuberculoma is formed. Its centre gets liquefied by the caseous necrosis. Initially solitary lesion or a cluster of microscopic foci are formed in the cortical or subcortical region. Lesions may coalesce later forming larger lesions, even tuberculous abscess.

Tuberculous Encephalopathy

This entity is apparently independent of other pathology. It consists of cerebral oedema occasionally with peri-vascular demyelination or haemorrhagic leucoencephalopathy. These changes occur deep in the white matter of the brain at a distance from vascular abnormalities or exudates. Some observers hypothesise that it is a purely allergic phenomenon, mediated by tissue hypersensitivity to either bacillary antigens or possibly to a myelin-related antigen of brain tissue itself.

Spinal Meningitis

Spinal meningitis is a common asymptomatic accompaniment of cranial meningitis. In most cases, there is extension of basal exudates downwards. However, tuberculous spinal arachnoiditis can present first time as spinal cord disorder and may move upwards often asymptomatically into the cranial cavity.

CLINICAL FEATURES

Tuberculous Meningitis (TBM)

The clinical picture of TBM is quite variable, with substantial differences among patients of different ages. The clinical manifestations depend upon a variety of factors related both to the organism and the host like pre-existing malnutrition, coexistence of HIV infection, BCG vaccination, etc.

Among children, majority of cases (75% to 85%) are below the age of 5 years. The onset of the disease may be acute, i.e. within 6 days, sub-acute or gradual, taking more than 3 weeks to develop. Among adults, the disease typically presents in a somewhat indolent fashion. The classical form of the disease evolves through a prodromal stage, a stage of meningeal irritation, leading to a stage of diffuse or focal cerebral involvement. Nausea, vomiting, anorexia, abdominal pain, constipation and behavioural changes are among most commonly reported symptoms. Headache is reported in less than 25% of children than in adults (50% to 75%) (**Table 2**). Some degree of fever is usual, but it may be of low grade and absent in 10% to 15% of children and 25% to 30% of adults. As the disease progresses, signs of meningeal irritation will develop, though it is less commonly seen in infants, instead fullness of fontanelle is seen. Seizures may present at any stage of the disease. Ten to twenty per cent of subjects may have seizures during the initial period, later it may be seen in up to 50% of cases. Psychobehavioural changes are frequently observed at onset in adults. Signs and symptoms of raised intracranial pressure like enlargement of head in children and papilloedema may be seen early in the disease.

Table 2: Clinical Presentation of Patients with Tuberculous Meningitis

Feature	Among Children	Among Adults
Headache	20% to 50%	50% to 60%
Nausea/vomiting	50% to 75%	8% to 40%
Apathy/behavioural changes	30% to 70%	30% to 70%
Seizures	10% to 20%	0% to 13%
Prior history of tuberculosis	55%	8% to 12%

Focal neurological signs, which are common in the later part of the disease, most frequently consists of unilateral or, less commonly, bilateral cranial nerve palsies. Most frequently affected is the sixth cranial nerve followed by III, IV, VII and less commonly II, VIII, X, XI and XIIth. Visual impairment may be there due to optochiasmatic

arachnoiditis, tuberculoma compressing the optic nerve, secondary optic atrophy from papilloedema or ethambutol toxicity. Fundoscopic examination may reveal papilloedema, disc pallor or choroid tubercles, which are seen in 10% of cases with TBM and it is a very useful clue to diagnosis. There may be isolated pupillary involvement without other features of III nerve palsy. Rarely, there may be internuclear ophthalmoplegia and horizontal gaze paresis due to intrinsic brainstem lesion. Other common findings include hemiparesis, monoparesis and aphasia due to ischaemic infarction in 10% to 45% of cases. Less frequently neurological signs include a variety of abnormal movements like chorea, hemiballismus, athetosis, myoclonus and cerebellar ataxia. Persistent movement disorder may persist even after recovery from meningitis, especially among children.

In untreated cases, there may be deterioration of the consciousness from drowsiness to deep coma and brainstem dysfunction. Rarely intra-cranial bleeding may complicate TBM. Intraventricular haemorrhage may result from rupture of tuberculous mycotic aneurysm and parenchymal haemorrhage from moyamoya phenomenon of tuberculous arteritis.

In order to assess severity of the disease and guide to prognosis, it is useful to stage patients clinically at the time of diagnosis, based on the British Medical Research Council classification.

Stage 1 (early disease)

Patient has meningeal signs only, consciousness is undisturbed and no focal neurological signs are present.

Stage 2 (medium severity)

Consciousness is disturbed but the patient is not comatose or delirious. Focal neurological signs and cranial nerves palsies are present. Raised intra-cranial pressure may occur secondary to hydrocephalus. In infants, fontanelle bulges and head enlarges, and in adults there is papilloedema.

Stage 3 (advanced disease)

Patient is deeply comatose with evidence of brainstem dysfunction, decerebrate or decorticate posturing, fixed dilated pupils, irregular pulse and respiration. Untreated patients progress the three stages and usually die.

Children may develop a rare but clinically distinct entity called tuberculous encephalopathy. The distinctive feature of which is a young child or infant with pulmonary TB who develop a diffuse cerebral disorder in which drowsiness comes early with convulsions, without focal neurodeficit.

In BCG-vaccinated children atypical localised form of meningeal tuberculosis has been reported. Others may have transient, recurrent and mild serous meningitis.

Tuberculoma

Approximately 1% of tuberculosis patients develop CNS tuberculoma. In one-third of cases tuberculoma may be multiple. Clinical presentation depends on site, size and pathological stages of the lesions. In children, tuberculoma is most commonly seen in the posterior fossa, in contrast to adults where these are mostly found in supratentorial compartment.

Clinical manifestations include that of slowly progressive space-occupying lesions with or without features of raised intra-cranial pressure or meningeal irritation. Patient may present first time with seizure. There may be involvement of cranial nerves like III, VI, VII or II. They can present like pituitary space occupying lesions with cranial nerve dysfunction, which may resolve completely with anti-tuberculosis therapy. There may be focal neurodeficit like hemiparesis, paraparesis or lateralised ataxia. Multiple tuberculoma or large solitary tuberculoma may present with features of encephalopathy. Constitutional systemic symptoms are present in less than one-third of cases.

Spinal Tuberculosis

This may be due to involvement of spinal meninges, of spinal cord secondary to vasculopathy or tuberculoma, or of the bony elements of the spine (caries) with secondary involvement of the cord (Pott's paraplegia).

Tuberculous spinal meningitis may be due to secondary spread of cranial meningitis or from spinal caries, or may be primary spinal meningitis presenting with single or multiple level ascending or transverse radiculomyelopathy. Symptoms include fever, spinal pain, radicular pain, paraesthesia, combined upper and lower motor features in lower limbs and bladder disturbances. Chronic spinal arachnioditis may be indistinguishable from spinal cord compression.

Vertebral involvement accounts for more than 50% of all skeletal tuberculosis. Thoracic and lumbar spines are most commonly involved due to paucity of movement. Multiplicity of vertebral body involvement (up to 50%) and posterior element lesions are frequently seen, which may lead to sudden paraplegia due to 'concertina' collapse of the involved vertebrae or vascular thrombosis. In about 70% of cases, paraplegia recovers completely if treated promptly.

DIAGNOSIS

Cerebrospinal Fluid Analysis

Typically the fluid is clear or slightly opalescent with raised opening pressure. A cobweb may develop when the CSF is allowed to stand for short time, though it is not a specific finding. A moderate lymphocytic pleocytosis up to 500 cells/mm^3 is characteristic of TBM. However, counts of more than 1000/mm^3 and predominantly polymorphonuclear leucocytes may be found in the early part of the illness. There is moderate elevation of CSF protein (100 to 500 mg/dL) and depression of glucose (<40mg/dL). Hypoglycorrhachia has been correlated with more advanced stage of clinical disease and a rise in CSF glucose after therapy indicates better prognosis.

In tuberculoma, the CSF may be normal or may show a lymphocytic pleocytosis with increased protein levels. In spinal meningitis, there may be spinal block with CSF xanthochromia, very high protein levels (>1 gm/dL) and lymphocytic pleocytosis.

Identification of tuberculous bacilli in the CSF confirms diagnosis though it is difficult. A variety of techniques have been proposed.

Direct smear

Detection rate is 15% to 20%. It may be increased by centrifuging large volume of CSF and preparing a thick smear of the deposit, and examination of cobweb.

Culture

Traditional culture in Lowenstein-Jensen media is a time consuming procedure. Newer radiometric (BACTEC 460 TB) and non-radiometric, semi-automated and fully automated liquid

systems have decreased the time to a positive result to 1 to 3 weeks with good rates of positivity (80% to 95%).

Polymerase chain reaction (PCR)

PCR technique held promise in the confirmation of diagnosis of TBM. It has a high specificity (98%) but low sensitivity (56%). Three regions of the *M. tuberculosis* genome are targeted: IS 6110 sequences, MBP 64 gene codes and 541 bp regions.

Real-time PCR combines rapid cycle DNA amplification with fluorimetry. In cultured samples it has 100% specificity and can detect as few as 10 organisms. Nested real-time PCR may further improve the sensitivity.

Indirect tests that are helpful in the diagnosis of TBM include adenosine deaminase level in CSF, radiolabelled bromide partition test, CSF tuberculostearic acid level, and mycobacterial antigen and antibody detection by ELISA (**Table 3**).

Table 3: Newer Diagnostic Tests for Tubercular Meningitis

Test	Sensitivity	Specificity	Time Required
Radiolabelled bromide partition test	90% to 94%	88% to 96%	48 hours
CSF ADA level	73% to 100%	71% to 99%	<24 hours
CSF tuberculostearic acid level	95%	99%	<24 hours
CSF mycobacterial antigen	79% to 94%	95% to 100%	<24 hours
CFS mycobacterial antibody	27% to 100%	94% to 100%	<24 hours
PCR	83% to 100%	80% to 100%	<24 hours

CSF = Cerebraspinal fluid; ADA = Adenocine deaminase activity; PCR = Palymearse chain reactian.

Radiology

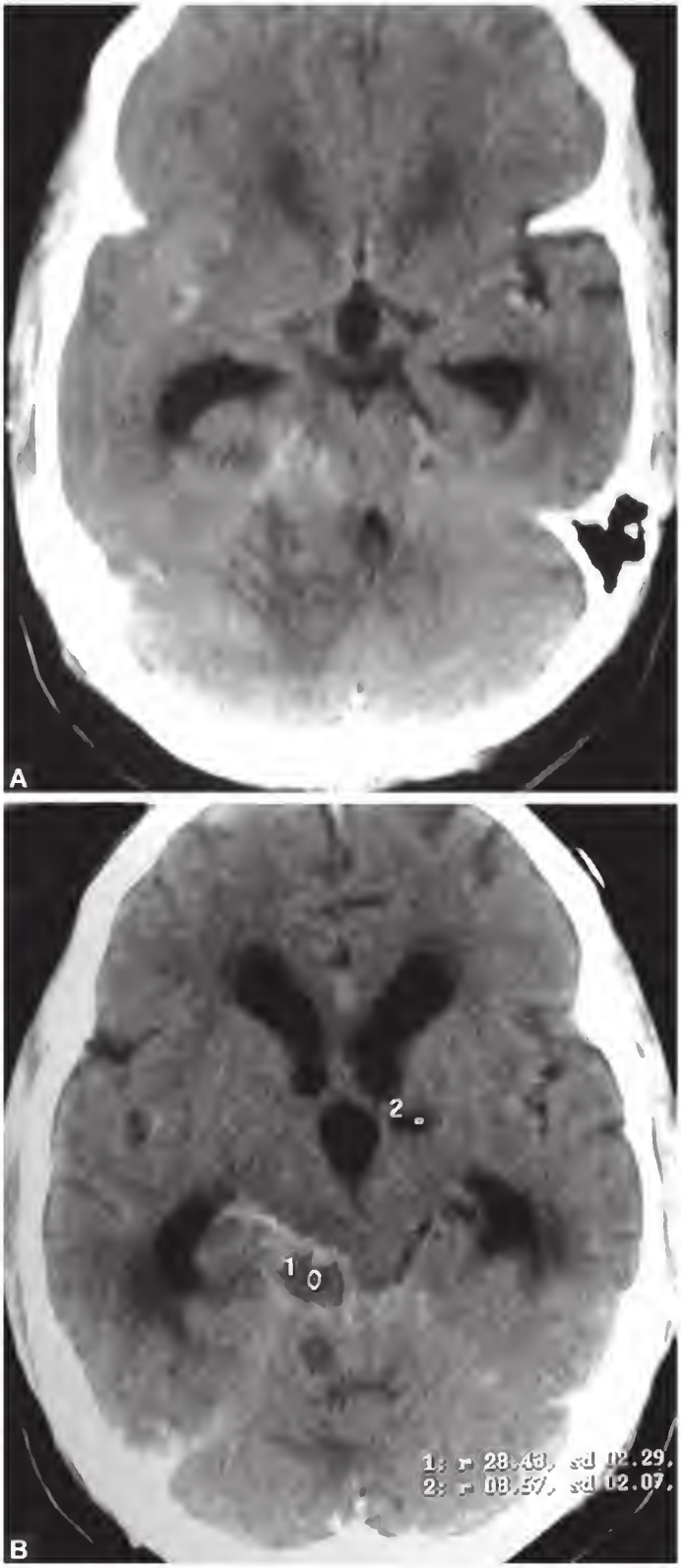
Contrast-enhanced CT scan and MRI are invaluable in the diagnosis of neurotuberculosis but none of the radiological changes are pathognomonic. MRI is better than CT scan in detecting diffuse and focal meningeal granulomatous lesions, small tuberculoma and focal infarcts.

Tuberculous meningitis

Meningeal enhancement is frequently seen, most commonly in the basal subarachnoid cisterns, Sylvian fissures and around brainstem. There may be associated hydrocephalus or infarction. Hydrocephalus is the single-most common abnormality (50% to 80%), which can be of either communicating or obstructive type (**Figures 1A and B**).

Tuberculoma

The radiological features of tuberculoma on CT vary according to its stage. Mature lesions appear as a well-defined round or oval ring enhancing mass with occasionally a target sign. The immature tuberculoma are iso/hypodense on plain CT and show ring or nodular contrast enhancement. In many cases, solitary tuberculoma may be indistinguishable from abscess, tumour and cysticercus granuloma (**Figure 2**). On MRI, solid caseating granulomas are isointense on T1 and iso/hypointense on T2-weighted images. Occasionally, there may a central hyperintense area with hypointense rim on T2-weighted images. Non-caseating granulomas are usually hypointense in T1 and hyperintense in T2-weighted images, with homogeneous contrast enhancement. Conglomerated lesions are often seen in gadolinium-enhanced MRI.



Figures 1A and B: CECT brain showing basal enhancing exudates with obstructive hydrocephalus.

Magnetic resonant spectroscopy (MRS) can provide biochemical information from a tissue. MRS of a tuberculoma usually shows presence of lipid/lactate peak with increased choline:creatine ratio, but usually less than two.

Magnetisation transfer imaging with contrast is a more sensitive imaging modality in tissue characterisation and helpful in differentiating tuberculoma from cysticercus granuloma.

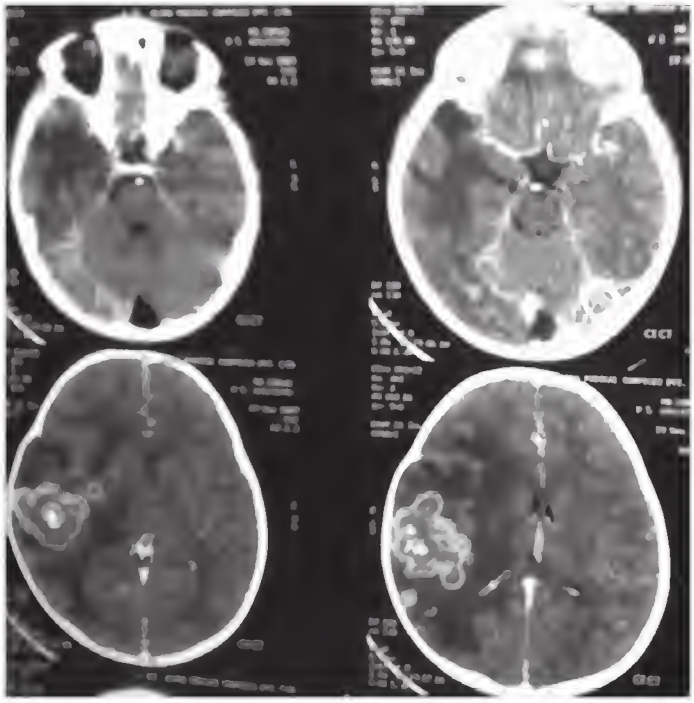


Figure 2: CECT brain showing tuberculoma as large mass like lesion with extensive perifocal oedema, mass effect and midline shift and also basal exudates.

Spinal disease

Non-invasive MRI has replaced conventional myelographic techniques in detecting spinal diseases. Abnormalities on MRI have included obliteration of the subarachnoid space, clumping of nerve roots, oedema of cord, central and ecentric cavitation of the cord, and extensive signal abnormalities within the substance of the cord. Intramedullary tuberculoma are hypointense in both T1- and T2-weighted images with marked gadolinium enhancement.

MANAGEMENT

It is very important to start treatment at the earliest to prevent neurological sequelae and mortality. Often treatment is started empirically, before confirming reports are available.

Chemotherapy

Available antituberculosis drugs are divided on the basis of efficacy and toxicity into first-line [isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z) and streptomycin (S)] and second-line (para-aminosalicylic acid, ethanolamine, cycloserine, kanamycin, capreomycin and amikacin) agents. Newer second-line drugs like fluoroquinolones (ciprofloxacin or ofloxacin) and macrolides (azithromycin and clarythromycin) are used in multidrug resistant (MDR) cases or when first-line drugs are not tolerated.

Isoniazid and rifampicin are bactericidal and other first-line drugs are bacteriostatic. Isoniazid, pyrazinamide and ethambutol have good CSF penetration and others have poor CSF concentration (**Table 4**).

Treatment Regimens

World Health Organization (WHO) recommends use of 4 drugs (HRZE) for 2 months followed by 2 drugs (HR) for 6 to 7 months for the treatment of TBM. The same drug regimen is prescribed for tuberculoma and spinal disease.

Table 4: Recommended Dosage of First-Line Anti-Tuberculosis Drugs

Agent	Usual Daily Dose	Adult Daily Dose
Isoniazid	5 to 10 mg/kg	300 mg
Rifampicin	10 to 12 mg/kg	450 to 600 mg
Pyrazinamide	25 to 30 mg/kg	1 to 1.5 g
Ethambutol	15 to 25 mg	800 mg
Streptomycin	15 to 20 mg	0.75 to 1 g

In spite of WHO recommendations, universal consensus regarding duration of treatment has not developed. The current UK guidelines recommend 12 months of anti-tuberculosis treatment (ATT) in uncomplicated cases of TBM (including tuberculoma without meningitis) extending to 18 months if pyrazinamide is omitted. The American Thoracic Society's recent recommendation is a course of 2 months of HRZ, followed by 4 months of HR for adults and 10 months HR for children. In a recent study from South India by Venugopal and co-workers, it has been seen that directly observed treatment, short-course (DOTS) intermittent regimen is an effective treatment for neurotuberculosis.

A paradoxical worsening of clinical and laboratory parameters has been noted by many clinicians immediately after starting ATT, including enlargement of tuberculoma. Addition of corticosteroids may lessen this paradoxical response.

Multidrug-Resistant Neurotuberculosis

Drug resistance may be primary or secondary. Exact incidence of MDR of neurotuberculosis is not known due to difficulty in isolating mycobacteria from the CSF. In other forms of tuberculosis, prevalence of resistance to any drug is 13% to 25% and of MDR is about 13%. Most case reports of MDR TBM from India are among immunocompromised patients due to HIV infection. There is no standard protocol for the treatment. Every attempt should be made to isolate the organism and test for sensitivity. At least two agents to which the organism is sensitive are to be continued for a full 18 to 20 months.

Corticosteroids

Despite a substantial literature accumulated over the past 40 years, the place of corticosteroids in the treatment of TBM remains unclear. It is most beneficial when complications appear. These include raised intra-cranial pressure, cerebral oedema, stupor, focal neurological signs, spinal block, hydrocephalus and basal opto-chiasmatic arachnoiditis (**Table 5**).

Table 5: Corticosteroids in Neurotuberculosis

Indications	
Clinical	Stage 2 or 3 disease Raised intra-cranial pressure Focal neurodeficit suggesting vasculitis Tuberculous encephalopathy
Radiological	Cerebral or perilesional oedema Hydrocephalus Infarcts Opto-chiasmatic arachnoiditis
CSF	Rising CSF protein suggesting spinal block
Doses	Adults: Prednisolone—60 mg per day or 1 mg/kg per day, or Dexamethasone—8 to 16 mg per day Children: Dexamethasone—0.3 to 0.6 mg/kg per day
Duration	3 to 6 weeks, then slowly tapered over 2 to 4 weeks or longer depending upon the clinical response and experience of clinicians

Surgery

Surgical intervention in TBM is primarily directed at relief of hydrocephalus by ventriculo-peritoneal shunt. Progressive hydrocephalus refractory to medical treatment or deterioration of level of consciousness are indications for urgent CSF diversion. The use of temporary external ventricular drainage in conjunction with prophylactic antibacterial agents has been advocated as a safer and convenient alternative to indwelling shunt in TBM.

Surgical excision in tuberculoma is indicated when the anterior optic pathway is compressed with resultant visual impairment or for large tuberculoma with great rise of intra-cranial pressure not permitting for effective medical therapy. Surgery is also useful in tuberculous spondylitis to decompress the cord and to stabilise the spine.

PROGNOSIS

The most firmly established prognostic factor is clinical stage of disease at the start of treatment. There is two-fold increase in mortality when treatment is started at advanced stage of the disease as opposed to the early stage. Other poor prognostic factors include extremes of age and co-existence of miliary disease. The sequelae are common among children seen in 25% to 50% of cases, and include mental regression, behavioural changes, seizures, visual and auditory loss, other cranial nerve palsies, movement disorder, hemiparesis/paraparesis/quadriparesis and various endocrinopathies due to hypothalamic-pituitary damage.

PREVENTION

Large-scale studies demonstrated efficacy of BCG vaccination in preventing pulmonary tuberculosis varying from 0% to 80% and in preventing TBM is 52% to 84%.

The provision of adequate nutrition, housing, and basic healthcare are essential components of disease control programme.

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20.13 Neurosyphilis

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Syphilis, a chronic systemic disease caused by *Treponema pallidum*, is usually considered to involve the central nervous system (CNS) late in the course of the disease. In fact, CNS syphilis represents a continuum encompassing early invasion (within the first few weeks or months of infection) to a prolonged period of asymptomatic involvement in the latent phase; and, only in a small per cent of cases, progressing to late neurological manifestations.

EPIDEMIOLOGY

Reports from South-West Asia and Africa estimated the prevalence of syphilis to range from 0.35% to 15%. Data on prevalence of syphilis in India are scanty and seroprevalence has been estimated to be 1.4% and 2.4% in Kerala and Aurangabad, respectively. In the last decade, there has been a 50-fold increase in syphilis in Eastern Europe and epidemics continue to occur with a 7 to 10 year cycle in the USA.

AETIOPATHOGENESIS

Treponema pallidum, a spirochete, is a thin delicate organism with 6 to 14 spirals and tapered ends. Humans are the only known natural host for *T. pallidum*. Virulent strains of *T. pallidum* are grown and maintained only in rabbits, as none of the pathogenic treponemes has been successfully cultured. Nearly all cases of syphilis are acquired by sexual contact with an infectious lesion. Less common modes of transmission include non-sexual personal contact, infection in-utero, and blood transfusion.

T. pallidum rapidly penetrates the intact mucous membranes or microscopic skin abrasions and enters the lymphatics and blood within few hours to produce systemic infection and metastatic foci long before the appearance of primary lesion. The incubation period (from inoculation to appearance of primary lesion) varies from an average of 3 weeks, up to 6 weeks. The primary lesion (chancre) usually persists for 4 to 6 weeks and then heals spontaneously. The generalised parenchymal, constitutional and mucocutaneous manifestations of secondary syphilis usually appear 6 to 8 weeks after the healing of primary lesions. In some patients, it may appear several months after the chancre has healed and some patients may enter the latent phase without secondary lesions. In the latent asymptomatic phase, the disease is apparent only by serology. In the pre-antibiotic era, about one-third of patients with untreated latent syphilis developed clinically apparent tertiary disease; today specific treatment and coincidental therapy for early and latent syphilis have eliminated tertiary syphilis, except for sporadic cases of neurosyphilis, infected with or without HIV.

Neurosyphilis spans all the stages of disseminated disease. CNS invasion occurs during the first few weeks or months of infection and cerebrospinal fluid (CSF) abnormalities are detected in as many as 40% of patients during the secondary stage. Syphilis characterises the most chronic form of meningitis and pathological changes are sequelae of the chronicity of the meningeal reaction. Meningeal, meningovascular and parenchymatous syndromes are perhaps best viewed as a continuum of disease, rather than as discrete disorders. All these disease processes are different clinical expressions of the same fundamental pathological events, especially meningeal invasion, obliterative endarteritis, and parenchymal invasion. Factors which transform the intermediate stage of asymptomatic syphilitic meningeal infection to the late form of parenchymal neurosyphilis are unknown.

CLASSIFICATION OF NEUROSYPHILIS

The classification of neurosyphilis is given in **Table 1**.

Table 1: Classification of Neurosyphilis

Asymptomatic neurosyphilis
Symptomatic neurosyphilis
Meningeal
Meningovascular
Parenchymal
General paresis
Tabes dorsalis

CLINICAL FEATURES

Asymptomatic Neurosyphilis

The diagnosis of asymptomatic neurosyphilis is made in patients who lack neurologic symptoms and signs, but have CSF abnormalities. The CSF abnormalities include mono-nuclear pleocytosis, increased protein concentration or a reactive Venereal Disease Research Laboratory (VDRL) slide test. In primary and secondary syphilis such abnormalities may be found in up to 40% of untreated patients and *T. pallidum* can be isolated in up to 30% of the patients. In patients with untreated asymptomatic neurosyphilis, the overall cumulative probability of progression to clinical neurosyphilis is about 20% in the first 10 years; the likelihood is highest among patients with the greatest degree of pleocytosis or protein elevation in the CSF.

Symptomatic Neurosyphilis

In the antibiotic era, symptomatic neurosyphilis may present not as one classic syndrome, but as mixed, subtle or incomplete forms of disease. The onset of symptoms usually comes one year after infection for meningeal syphilis, at 5 to 10 years after for meningovascular syphilis, after 20 years for general paresis and after 25 to 30 years for tabes dorsalis.

Meningeal Syphilis

This condition may be concurrent with or follow secondary syphilis. Patients often present with headache, nausea, vomiting, neck stiffness, cranial nerve involvement (usually 7th and 8th), seizures and changes in mental status. There may be involvement

of the brain or spinal cord. Rare complications of acute syphilitic meningitis include hydrocephalus, myelitis or lumbosacral radiculitis.

Meningovascular Syphilis

Meningovascular syphilis accounts for 3% to 17% of all cases of neurosyphilis. This reflects diffuse inflammation of pia and arachnoid, together with evidence of widespread arterial involvement. These patients usually present with prodromal symptoms consisting of headache, vertigo, insomnia and psychological disturbances, weeks to months before the onset of the ischaemic deficit. Most patients develop ischaemia in the middle cerebral artery territory and not uncommonly multiple bilateral infarctions. Two types of arteritis have been described in patients with meningovascular syphilis. 'Heubner arteritis' is the most common form and involves the large and medium sized arteries. It is characterised by inflammation of the intima, thinning of media and interstitial proliferation. 'Nissl arteritis' is characterised by endothelial and adventitial proliferation, involving small vessels preferentially. Computed tomography (CT) or magnetic resonance imaging (MRI) demonstrate multiple small infarctions in different vascular distributions involving both the white matter and the cortex and conventional angiography reveals segmental stenosis with occasional beaded appearance in the basal artery and focal stenosis and aneurysmal dilatations in more peripheral ones. The findings are diffuse, accounting for the multiple bilateral infarcts.

Parenchymal Neurosyphilis

General paresis

This encephalitic form reflects widespread parenchymal damage and typically presents as progressive dementia beginning 15 to 20 years after original infection. The disease manifestations can be remembered by the mnemonic *PARESIS* (**Table 2**).

Table 2: General *PARESIS* Mnemonic

P	:	Personality
A	:	Affect
R	:	Reflexes (hyperactive)
E	:	Eye (Argyll Robertson pupils)
S	:	Sensorium (illusions, delusions, hallucinations)
I	:	Intellect (decrease in recent memory, orientation, calculation, judgement, insight)
S	:	Speech

Tabes dorsalis

Tabes presents with symptoms and signs of demyelination of posterior columns, dorsal roots and dorsal root ganglia. Tabes is characterised by lightening pains, autonomic dysfunction and sensory ataxia. Affected patients have normal strength with hyporeflexia in the legs and a positive Romberg's sign. Pupils are abnormal in more than 90% of the cases. Other associated features include optic atrophy, ophthalmoplegia, ptosis, gastric or other visceral crisis (pharyngeal, laryngeal, genitourinary, intestinal, rectal), impotence, faecal incontinence and pain and temperature loss leading to trophic changes such as Charcot's joints and perforating foot ulcers. The small irregular Argyll Robertson pupil, a feature of both tabes dorsalis and general paresis, reacts to accommodation but not to light.

DIAGNOSIS

Cerebrospinal Fluid

The diagnosis of neurosyphilis is based on clinical evidence and is supported by CSF abnormalities, particularly CSF pleocytosis and reactive CSF VDRL tests. The CSF pleocytosis in neurosyphilis is lymphocytic and is generally mild. Mild elevations of CSF protein concentration ranging from 45 to 200 mg/dL are also common, with higher values in early neurosyphilis compared to late neurosyphilis. The CSF VDRL is considered to be the gold standard for diagnosis of neurosyphilis. The accepted sensitivity of CSF VDRL ranges from 30% to 70%, though it is considered to be very specific. False-positive results may be seen when CSF is visibly blood tinged. Thus, a reactive CSF VDRL establishes the diagnosis of neurosyphilis, but a non-reactive test does not exclude the diagnosis. In contrast to CSF VDRL test, CSF treponemal antibody tests, such as CSF fluorescent treponemal antibody absorption test, are more sensitive but less specific for the diagnosis of neurosyphilis. Thus, a non-reactive CSF treponemal antibody may exclude the diagnosis of neurosyphilis but a reactive test does not establish the diagnosis.

T. pallidum can be identified in the CSF by inoculation of CSF into rabbits. However, rabbit inoculation is too cumbersome and expensive to be used clinically. Polymerase chain reaction (PCR) or reverse transcriptase PCR can be used to detect *T. pallidum* in CSF. Detection of *T. pallidum* in CSF is more common in early syphilis compared to late syphilis.

Neuroimaging

Neuroimaging in patients with asymptomatic neurosyphilis usually shows no abnormalities. Imaging in syphilitic meningitis



Figure 1: Contrast enhanced T1-weighted MRI image showing enhancement of meninges in the region of right third nerve (CSF VDRL positive).

involving brain and spinal cord may show enhancement of meninges, cranial nerves or spinal roots (**Figures 1 and 2**). CT or MRI of brain may show one or more areas of infarction in meningovascular syphilis. Cerebral gummas usually enhance, as may the associated meninges. Angiography may show segmental arterial narrowing, focal narrowing and dilatations or 'beading' and occlusion. Syphilitic vasculitis more commonly affects the supraclinoid segment of the internal carotid artery.

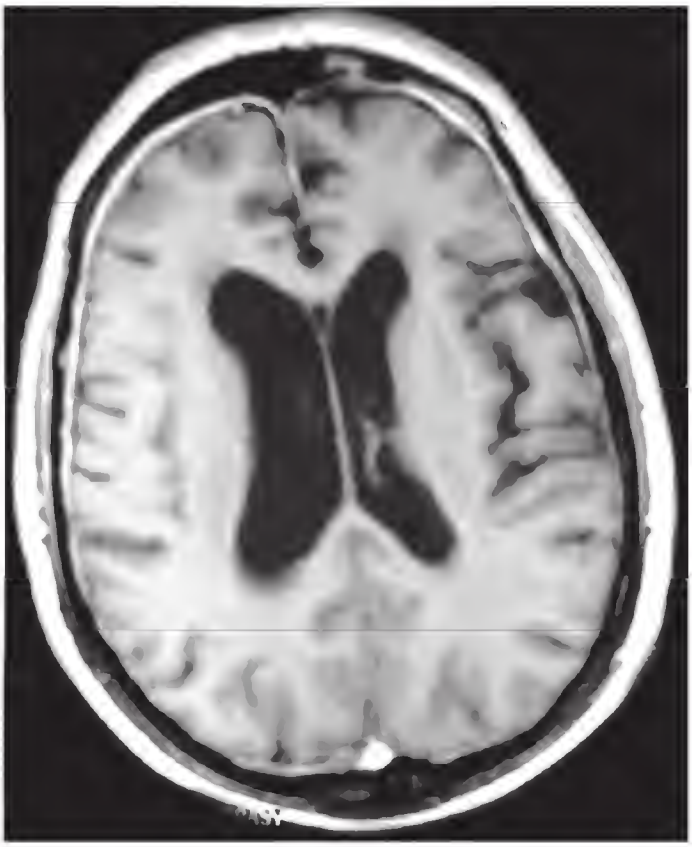


Figure 2: Contrast enhanced T1-weighted MRI image showing diffuse enhacement of pachymeninges and brain atrophy in a patient of general paresis.

TREATMENT

The Centre for Disease Control (CDC) recommend high dose intravenous penicillin G as first-line therapy and prevention for neurosyphilis and intramuscular procaine penicillin with oral probenecid as an alternative in adults, but not in children (**Table 3**).

The success of neurosyphilis therapy is judged by resolution or stabilisation of clinical abnormalities and by resolution of CSF abnormalities. CDC guidelines state that CSF WBC (white blood cell) counts should decline at 6 months and all CSF abnormalities should resolve by 2 years after the treatment. Careful follow-up after neurosyphilis therapy is mandatory for all patients. CSF should be re-examined 3 months after therapy. If CSF WBC countis normal and the CSF VDRL is non-reactive at 3 months, no further LP is required. For those with persistent CSF abnormalities at 3 months after therapy, CSF should be re-examined at 6 months after therapy and every 6 months thereafter until CSF WBC and CSF VDRL reactivity normalise. Failure of the CSF WBC count to decrease 6 months after therapy or failure of CSF VDRL to decline four-fold (or to non-reactive if initial titer is <1:2) 1 year after therapy is an indication for re-treatment. Serum VDRL or rapid plasma reagin test should be obtained at 3, 6 and 12 months after therapy and every 3 to 6 months thereafter until they are non-reactive.

Table 3: Treatment of Neurosyphilis

Recommended Regimen

Adults	:	Aqueous crystalline penicillin G, 18-24 MU IV per day given as 3 to 4 MU IV q 4h or as a continuous IV infusion for 10 to 14 days
Children	:	Aqueous crystalline penicillin G, 200,000-300,000U/kg/day IV, given as 50,000 U/kg IV q4-6h for 10 days

Alternative Regimen (adults only)

Procaine penicillin, 2.4 MU IM once daily plus, probenecid 500 mg p.o. q.i.d., both for 10 to 14 days

Experimental Regimen (adults only)

Ceftriaxone: 2 g IV once daily for 10 to 14 days

Alternative Drugs in Patients Allergic to Penicillin

Doxycycline	:	100 mg p.o. b.i.d for 2 weeks
Tetracycline	:	500 mg p.o. q.i.d for 2 weeks
Erythromycin	:	40 mg/kg/day (max 500 mg/dose) p.o. in divided doses for 2 weeks

NEUROSYPHILIS AND HIV

Syphilis is most common in individuals who are at risk of HIV infection or who are already infected with HIV. Patients who have both HIV infection and syphilis may be more likely to fail therapy for early syphilis and to develop early neurosyphilis. Neurosyphilis may be more difficult to diagnose in the setting of concomitant HIV infection. HIV infected patients may be more likely to fail therapy for neurosyphilis.

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20.14 Acute Viral Infections of Central Nervous System

Nadir E Bharucha

ACUTE VIRAL INFECTIONS

Acute viral infections of the central nervous system (CNS) have a sudden onset and run a short course over days to weeks. They result in meningitis, encephalitis, myelitis, radiculitis or combinations of these. Certain features of viral infections are noteworthy. This includes tropism—viruses may infect specific cells and anatomical areas of the nervous system, e.g. anterior horn cells are affected in poliomyelitis, the dorsal root ganglion cells in varicella zoster infection and the neurons in rabies. Certain viruses (e.g. herpes simplex and varicella zoster) have the ability to remain latent in the nervous system and get reactivated months to years later. Most viruses replicate in extraneural tissues before invading the CNS and involvement of the nervous system is usually only an occasional complication of the systemic viral infection. The majority of viruses enter the nervous system via the haematogenous route, except herpes simplex and rabies viruses. Often the viral agent cannot be identified during the acute illness and the diagnosis can only be made retrospectively. Viruses may affect the CNS by means other than direct invasion; peri-venous encephalomyelitis usually follows a systemic viral infection or vaccinations and is an allergic reaction to viral antigen.

ACUTE VIRAL MENINGITIS

Viral meningitis is inflammation of the meninges due to a viral infection and in the majority of cases is a benign, self-limiting illness. Cerebrospinal fluid (CSF) examination shows an increase in lymphocytes and proteins with normal sugar.

'Aseptic meningitis' is a non-specific term indicating any form of meningitis where the CSF is bacteriologically sterile, accompanied by a lymphocytic pleocytosis and normal sugar content. Viral meningitis is a common but not the only cause of aseptic meningitis.

Aetiology

The most common viruses causing meningitis are the enteroviruses (poliovirus, coxsackie, ECHO, enterovirus [EV]-70), arboviruses, HIV and herpes simplex viruses (HSV 1 and 2). Others are the lymphocytic choriomeningitis virus (LCMV), Epstein-Barr virus (EBV), influenza, adenovirus and the mumps virus. Enteroviruses are the commonest cause of viral meningitis.

Clinical Features

All age groups are susceptible, but it is more common in those below 30 years of age. There is often a prodromal phase with fever, headache, myalgia and malaise. Many enteroviral infections give rise to a skin rash or gastrointestinal symptoms. Upper respiratory symptoms may accompany adenovirus and influenza infections. Measles and chickenpox usually present with their classical skin lesions before invading the CNS. Mumps meningitis may be accompanied by parotitis or pancreatitis.

With the onset of meningitis there is fever, headache, photophobia, nausea, vomiting and neck stiffness. The sensorium is usually clear and focal neurological signs are rare.

Investigations

Routine blood investigations are usually normal. CSF examination shows a clear fluid with mildly raised pressure, moderately increased proteins, normal sugar content and pleocytosis ranging from 50 to 500 cells/mm^3. The pleocytosis is mainly lymphocytic although very early in the disease there may be a predominance of neutrophils. High CSF cell counts in thousands is seen in LCMV and mumps and CSF glucose may be mildly reduced in LCMV, mumps, HSV-2, varicella-zoster virus (VZV). Culture of the virus from the CSF, blood, urine or stool is only rarely possible. CSF PCR is now being increasingly used to identify replicating viruses in the acute stage and is useful for diagnosing HSV, VZV, CMV and EB viruses. Demonstration of virus-specific IgM antibodies in serum also suggest acute infection and if such antibodies are found in the CSF, acute CNS infection may be presumed. However, seroconversion does not occur immediately and in most instances, the diagnosis is made retrospectively by measuring the viral antibody levels in the acute and convalescent phases. A four-fold increase in specific antibody titres in acute and convalescent serum or CSF is considered to be positive and even IgM antibodies may persist for months in the serum and CSF.

Differential Diagnosis

It is important to exclude other causes of aseptic meningitis. These include partially treated pyogenic meningitis, tuberculosis, fungal infections, syphilis and carcinomatous meningitis. Parameningeal foci of infection such as, brain abscess and subdural empyema can present with aseptic meningitis, though usually have focal signs. Subarachnoid haemorrhage is an important clinical consideration.

Treatment

Acyclovir may be used in HSV-1 and 2, EBV and VZV infection and HAART in HIV meningitis. But viral meningitis is usually a self-limiting illness and specific treatment with anti-viral drugs is usually not required. Symptomatic care, like relief of headache, bed rest, provision of adequate nutrition and maintenance of fluid and electrolyte balance is usually sufficient.

ACUTE VIRAL ENCEPHALITIS

In viral encephalitis there is inflammation of the brain parenchyma resulting in an acute febrile illness, with evidence of meningeal involvement and signs and symptoms of diffuse and/or focal neurological deficits. If the spinal cord is also involved, the term encephalomyelitis is used. Viral encephalitis is a far more serious illness than viral meningitis.

Aetiology

A large number of viruses can cause encephalitis, but the more common ones are shown in **Table 1**.

Table 1: Common Viruses Causing Acute Encephalitis

Arboviruses	Japanese, St. Louis, Western equine, California
Herpes virus	Varicella-Zoster virus, Epstein-Barr virus, Cytomegalovirus
Rhabdovirus	Rabies
Enteroviruses	Coxsackie, ECHO Virus
Influenza	Parainfluenza
Others	Mumps, measles, rubella, lymphocytic choriomeningitis

Pathogenesis and Pathology

Microscopic examination reveals perivascular and parenchymal infiltration with mononuclear cells, glial nodules and neuronophagia. Inclusion bodies may be seen in the cytoplasm or nucleus of brain cells. These, though characteristics, are not specific enough to identify the particular virus involved, except the Negri bodies of rabies. The CNS may be involved diffusely or there may be predominant involvement of localised areas.

Clinical Features

There is often a prodromal period, lasting for a few days, of mild fever, bodyache, headache and malaise. In addition, there may be specific signs and symptoms which could help identify the causative virus, e.g. skin rashes with coxsackie and echoviruses and herpangina with certain enteroviruses. Upper respiratory symptoms are common with influenza and respiratory viruses. Mumps may present with parotitis or pancreatitis. The characteristic skin lesions of chickenpox, measles and rubella are usually evident before the patient develops the rare complication of encephalitis.

After the prodromal phase there may be a short afebrile period before signs and symptoms of encephalitis commence. This biphasic pattern is commonly seen in arboviral encephalitis.

The onset of encephalitis is usually acute with fever, headache, photophobia, nausea, vomiting and signs of meningeal irritation. Diffuse CNS inflammation results in confusion, disorientation, agitation, stupor and sometimes coma. Convulsions are common. Focal neurological deficits may manifest as aphasia, hemiparesis, sensory deficits, visual field defects, ataxia, ocular palsies and other cranial nerve palsies. Spinal cord involvement may result in myelitis with varying degrees of paraparesis.

Hypothalamic involvement can give rise to diabetes insipidus and autonomic instability. Syndrome of inappropriate ADH secretion (SIADH) is also a common manifestation. Brainstem involvement can compromise the respiratory centre. In severe cases, cerebral oedema can raise the intra-cranial pressure and precipitate brain herniation.

Investigations

Examination of the blood is usually unremarkable except for the occasional finding of atypical lymphocytes in EBV infection, increased serum amylase in mumps, and hyponatraemia in SIADH. CSF examination reveals a lymphocytic pleocytosis with moderately raised protein and normal sugar content. Serological tests, using acute and convalescent serum, can help identify the causative virus if there is a four-fold increase in specific antibody titres. Viral culture from serum and CSF is sometimes possible. Nucleic acid amplification using the PCR is likely to become useful in the future.

CT or MRI scans of the brain may show non-specific diffuse or focal changes with cerebral oedema. The EEG usually shows a bilateral slowing with disappearance of the normal waveforms and occasional high-voltage spike-and-wave discharges. When these studies show focal changes in the frontotemporal areas of the brain, one should consider the possibility of HSV encephalitis.

Diagnosis

Other conditions that may mimic viral encephalitis should be ruled out (**Table 2**). These include non-infectious encephalopathies, septic encephalopathy occurring as a remote effect of systemic sepsis, post-infectious acute disseminated encephalomyelitis and infectious inflammatory encephalitis of non-viral aetiology. The epidemiological setting is important in making a diagnosis because certain types of encephalitis, especially those due to arboviruses, tend to cause epidemics, affecting a large number of people in a restricted geographical area. The prodromal symptoms and signs can also help in identifying the causative virus.

Table 2: Differential Diagnosis of Acute Viral Encephalitis

CNS Infections and Related Conditions	Other Primary CNS Disorders	Metabolic, Toxic and Other Systemic Diseases
Bacterial e.g. partially treated meningitis, parameningeal infections, brain abscess, tuberculosis, neurosyphilis	Structural brain lesions e.g. those caused by vascular disease, trauma or tumour	Acute sodium and carbohydrate imbalance, porphyria, phaeochromocytoma
Fungal e.g. *Cryptococcus, Candida*	Acute psychotic disorders	Salicylate, heavy metal, barbiturate intoxication
Protozoal e.g. cerebral malaria, toxoplasmosis	Seizures, e.g. postictal or complex partial	Sarcoidosis, collagen vascular disorders, neoplasm, infective endocarditis
Metazoal e.g. cysticercosis	Status epilepticus, neoplasm	
Acute post-infectious encephalomyelitis		Systemic infections, e.g. typhoid, septicaemia, Hypertensive encephalopathy

Treatment

Vital parameters should be closely monitored and supportive and symptomatic treatment should be initiated. Raised intra-cranial pressure may be decreased using mannitol in a dose of 0.5 gm/kg of 20% solution intravenously over 20 minutes every 4 to 6 hours. Steroids may also be used to decrease the cerebral oedema. Anticonvulsants are probably best given prophylactically and the drugs of choice are phenytoin and carbamazepine.

Antiviral therapy with acyclovir significantly improves prognosis in HSV encephalitis. It can also be of use in severe encephalitis due to VZV and EBV.

SPECIFIC ACUTE VIRAL INFECTIONS

Poliomyelitis

Poliomyelitis is caused by the poliovirus, an RNA virus belonging to the picornavirus (enterovirus) family. There are three serotypes, 1, 2 and 3. It can cause acute asymmetrical flaccid paralysis which may produce a permanent disability. Poliomyelitis-like syndromes can also be caused by coxsackie viruses A and B, enterovirus 70, and viruses usually associated with an encephalitic illness, such as the Japanese encephalitis and West Nile viruses. Prophylactic vaccination is the most effective means of preventing poliomyelitis.

Post-polio syndrome

Some patients, years after the acute attack of poliomyelitis, develop progressive weakness and atrophy in the paralysed limb and sometimes also unaffected parts of the body. The pathogenesis is not clear but may be due to a delayed dysfunction of surviving enlarged motor units coupled with ageing, overuse or disuse.

Japanese Encephalitis

This arboviral encephalitis, caused by a flavivirus, is one of the most common causes of epidemic encephalitis in India.

Epidemiology

Japanese encephalitis is endemic in China, Thailand, Korea and many other parts of South-East Asia. In India, sero-conversion was first detected in areas of Tamil Nadu in 1955. Following this, there have been frequent epidemics in different parts of the country, viz., Tamil Nadu, Karnataka, Andhra Pradesh, Puducherry, Goa, Maharashtra, Madhya Pradesh, Uttar Pradesh, Bihar, West Bengal, Assam and Manipur. Epidemics usually occur in the summer and monsoon months.

Clinical features

Children and young adults are mainly affected, except in populations with little resistance. The incubation period ranges from 5 to 15 days. A large number of subclinical cases occur and it is only the occasional patient (1:300 to 1:1000) who manifests signs and symptoms of encephalitis.

The onset is abrupt. About 90% of patients experience severe rigors initially. Other features of viral encephalitis then manifests. Seizures are common in children and focal neurologic deficits occur. Involuntary movements like chorea, myoclonus and tics are also seen. Hyperthermia may occur. A lower motor neuron type of muscle weakness and wasting has been noted rarely. The mortality rate ranges from 20% to 40% and may even be greater. In those who survive, there may be sequelae such as seizures, persistent paralysis, ataxia, mental retardation and, rarely, Parkinsonism.

Investigations

There may be peripheral leucocytosis. CSF examination shows lymphocytic pleocytosis, with elevated proteins and normal sugar. During the acute illness, a probable diagnosis can be made if there is a significant increase in specific antibody titre in serum or CSF to the particular virus, as compared to antibody titres to other flaviviruses. Recently, a specific and sensitive serologic test (using ELISA) has been developed which detects IgM antibody in the CSF during the acute phase of the illness. The diagnosis can be confirmed if there is a four-fold increase of antibody titres between acute and convalescent sera or CSF. Viral culture is usually not successful.

Treatment

No specific antiviral drugs are available and only supportive care such as reduction of cerebral oedema, control of seizures and circulatory and respiratory support can be given.

Prevention

There is an effective inactivated vaccine that should be given to high-risk groups, especially children, in the inter-epidemic period. Two doses of 1 mL each (0.5 mL for children less than 3 years) are given subcutaneously at an interval of 7 to 14 days. A booster dose of 1 mL is given after a few months (but before 1 year). Protective immunity develops one month after the second dose. Vaccination may be repeated after 3 years.

Other preventive measures include vector control methods, vaccination of animal reservoirs such as pigs and use of mosquito nets.

Rabies

Rabies is a fatal zoonosis that affects only the CNS. It is found worldwide except Antarctica, being spread by mammals to man, dogs being important vectors in Asia and Africa but more commonly by bats in developed countries. It was known to ancient Babylonians 4000 years ago. Its name derives from 'rabhas' (Sanskrit) to rage or 'rabere' (Latin) to rave. It affects 30,000 to 70,000 people per year throughout the world. The RNA rhabdovirus of the genus Lyssavirus is responsible. There are several serotypes. The organism is transmitted either by a bite or a scratch, by inhalation or organ transplant.

Clinically, there are 5 stages – an incubation period (average 20 to 60 days), a non-specific prodrome, the encephalitic phase (furious rabies), coma and death. Typically there is local pain or paraesthesia or fasciculation related to the entry of virus into the peripheral nervous system. Hydrophobia and aerophobia are due to brainstem involvement and there is abnormal autonomic activity. Dumb rabies or paralytic rabies is much less common and can masquerade as the Guillain-Barre syndrome. Diagnosis can be confirmed by identification of the virus in saliva or in the nerve endings around hair follicles in a full thickness nuchal skin sample or by the presence of antibodies in serum and CSF. There is no treatment apart from symptomatic care. The only survivors are those who have been immunised. Rabies can be prevented by pre-exposure prophylaxis and post exposure wound care and active and passive immunisation according to established guidelines.

Herpes Simplex Encephalitis

The HSV commonly cause infection but rarely produce encephalitis. Herpes simplex encephalitis is the commonest fatal cause of sporadic encephalitis. All age groups are affected but it is most common in children and young adults.

Pathogenesis and pathology

HSV-1 accounts for more than 95% of cases. It is a double-stranded DNA virus and is the causative agent of herpes labialis (cold sore). Encephalitis may be a manifestation of primary infection by the virus, in young people. In such cases, the virus first infects the face or mouth and then presumably enters the CNS via the olfactory bulb. But the virus also has the ability to remain latent in sensory ganglion cells (especially of the trigeminal nerve) and probably also in the CNS itself. It is postulated that the majority of cases of herpes simplex encephalitis occur as a consequence

of reactivation of the latent virus. The incidence of herpes simplex encephalitis is thought to be more in patients with AIDS and in other immunosuppressed patients.

There is predominant involvement of the medial temporal lobes, other parts of the limbic system and orbital surface of the frontal lobes. There is haemorrhagic necrosis in these areas with mononuclear cell infiltration and often intranuclear (Cowdry type A) inclusion bodies in neurons and glial cells.

Clinical features

The onset is usually abrupt, with fever and headache. Early in the course, there may be behavioural changes, confusion and hallucinations, suggesting an acute psychotic illness. But soon there is a progressive decline in the level of consciousness associated with myoclonic jerks and focal, complex partial or generalised seizures. Motor weakness is less commonly seen. Mortality is high. Among those who survive, many have residual dementia with prominent impairment of retentive memory. In young children HSV-1 encephalitis more often presents as diffuse encephalitis without the typical localisation seen in older children and adults.

Investigations

CT of the brain often shows areas of low absorption, oedema and contrast enhancement in the temporoparietal cortex. MRI is more sensitive than CT and shows hyperintensity and cerebral oedema in the frontotemporal, cingulate or insular regions on T2-weighted images. Cortical and meningeal contrast enhancement is also seen. If possible, MRI brain should be the first investigation.

CSF findings are similar to that seen in other forms of encephalitis. The CSF may also show a significant number of RBCs (>500 cells/mL) but this finding is common to other forms of encephalitis with haemorrhagic necrosis. CSF may be normal in 5% of patients with HSV encephalitis. EEG may show epileptiform high voltage periodic lateralising discharges. Serologic studies are usually unhelpful in the acute stage since a rise in specific antibody titre is delayed. Viral isolation from CSF and blood is usually unsuccessful. Probably the most sensitive and specific early non-invasive method for the diagnosis is the demonstration of HSV DNA in CSF using the PCR. The sensitivity of the test is about 95% in the first week (possibly less in the first 24 to 48 hours), but becomes less over the subsequent weeks.

Treatment

The drug of choice is acyclovir which is given as an intravenous infusion over 1 hour at a dose of 10 mg/kg every 8 hours for 14 days in PCR proven cases. The patient should be well hydrated to avoid the transient renal insufficiency that may result due to crystallisation of the compound in the renal parenchyma. Treatment should be prolonged to 21 days in immunosuppressed patients to reduce the possibility of relapse.

When acyclovir is given early in the disease, the mortality can be reduced from 70% in untreated patients to less than 30%, and surviving patients have markedly decreased residual symptoms.

Other Herpes Virus Infections

HSV-2

About 50% of infants delivered by the vaginal route to mothers suffering from a primary attack of genital herpes (caused by HSV-2) develop a meningoencephalitis that is often very severe. The incidence is much less if the mother is having a reactivation of genital herpes. HSV-2 also produces encephalitis in immunocompromised patients.

About 25% of patients with acute genital herpes develop transient symptoms and signs of viral meningitis. Moreover, the virus may invade the sacral spinal cord resulting in bladder and bowel disturbances and impotence. Transverse myelitis is a rare complication of HSV-2 infection. In some patients there may be recurrent attacks of aseptic meningitis. Indeed HSV is thought to be the commonest cause of Mollaret's meningitis. Acyclovir may be useful in selected cases such as those with recurrent aseptic meningitis.

Varicella-zoster virus

VZV causes varicella in children and herpes zoster in adults. The commonest neurological complication of varicella is a self-limiting cerebellar ataxia. Less common complications include meningoencephalitis, transverse myelitis and Reye's syndrome. VZV is a much commoner cause of encephalitis than HSV. The neurological syndromes associated with herpes zoster include cranial and peripheral nerve palsies, cerebral vasculitis and encephalomyelitis. Both HSV1 and VZV have been associated with Bell's palsy. Treatment is with acyclovir 10 mg/kg 8 hourly for 7 days together with prednisolone 60 to 80 mg/day for five days if there is cerebral vasculitis.

Epstein-Barr virus

Neurological complications are very rare. Encephalomyelitis, aseptic meningitis, and cranial and peripheral neuropathies can all occur. Diagnosis depends on recognition of the clinical syndrome of infectious mononucleosis and its laboratory correlates. Serum EBV, IgG and IgM antibodies are elevated and EBV DNA will be identified in CSF by PCR.

Cytomegalovirus

CMV often causes an encephalitis, mass lesions and myeloradiculitis in immunocompromised patients, including those with AIDS. Diagnosis is made by CSF PCR. If the foetus is infected by the virus in utero, congenital malformations and mental retardation occur. Treatment is by ganciclovir and should be continued in HIV as long as the CD4 count is depressed.

Human herpes virus 6, 7, 8

Human herpes virus types 6, 7 and 8 are being found increasingly in specific situations such as renal transplant. Human herpes virus 6 is thought to be associated with multiple sclerosis.

Chikungunya

Chikungunya, meaning which bends up, is a viral illness producing fever, rash and joint pains, carried by *Aedes aegypti*, like dengue and yellow fever. It recently reached epidemic proportions in central and southern India. It rarely produces neurological manifestations, but affects all levels of the neuraxis, meninges, brain, spinal cord and peripheral nervous system. Residual defects may be severe and there is no specific treatment.

Encephalitis Lethargica (von Economo's Disease)

This is a type of encephalitis which mainly affects the thalamus and midbrain. There was a pandemic around the time of World War I, but sporadic cases continue to be reported. Many of these

patients, months or years later, develop a slowly progressing Parkinsonism which is often associated with episodes of oculogyric crisis (tonic deviation of the eyes to one side, usually upwards, for minutes to hours). The symptoms of Parkinsonism can be relieved by levodopa.

SLOW VIRAL INFECTIONS OF THE CNS

These diseases are characterised by a long incubation period ranging from months to years. Once the disease manifests, it progresses slowly and insidiously over several months without fever and the other usual features of an infection. Because of these characteristics, slow viral infections behave more like degenerative and hereditary diseases. The reason for such an atypical course is not well understood. Slow viral infection may be classified as those caused by conventional viruses and those by non-conventional agents (prions).

SLOW VIRAL INFECTIONS CAUSED BY CONVENTIONAL VIRUSES

Subacute Sclerosing Panencephalitis (SSPE)

SSPE, formerly called inclusion body encephalitis, is a subacute form of encephalitis caused by the measles virus. The disease mainly affects young children between 5 and 15 years of age, but rarely young adults may also be involved. Most patients have had measles at an unusually young age, usually before the age of 2 years. The incidence of SSPE has greatly decreased after the introduction of measles vaccination.

Pathogenesis

It is postulated that measles virus, lacking M protein in its membrane, is able to remain dormant in brain cells and this subsequently results in death of neurons.

Clinical features

The onset of the disease is insidious and usually manifests as behavioural disturbances and poor performance in school. The child then becomes clumsy and begins to have involuntary movements, especially myoclonic jerks. Visual disturbances are common. There is no fever. Symptoms and signs of pyramidal and extrapyramidal system lesion are seen and dementia then supervenes. Death is almost invariable within 1 to 2 years.

Investigation

High antibody titres to the measles virus are present in the blood and CSF, but characteristically, there are no antibodies against the M protein of the measles virus. The CSF is acellular with mild increase in proteins and shows a marked increase in oligoclonal gamma globulin. The EEG shows a 'burst suppression' pattern with periodic bursts (every 5 to 85) of high voltage sharp slow waves followed by a period of suppression with attenuated waveforms. In the later stages, the CT and MRI may show cortical atrophy and multifocal changes in the white matter as a result of demyelination.

Treatment

The disease is almost always fatal, but antiviral drugs like inosiplex and intrathecal interferon have been reported to prolong survival. Clonazepam can be used to control the myoclonus.

Rarely, subacute measles encephalitis, unlike SSPE occurs shortly after measles in children with defective cell-mediated immunity. Also rare is progressive rubella panencephalitis, which occurs several years after congenital rubella and is similar to SSPE, but rubella antibodies, not measles antibodies, is found in serum and CSF.

Progressive Multifocal Leucoencephalopathy (PML)

PML is a rare disease caused by a papovavirus, named after the initial patient, JC virus. It usually occurs in patients with haematologic malignancies, AIDS, other immunosuppressed states or chronic debilitating diseases, in whom there is defective cell-mediated immunity, and now with a variety of drugs (natalizumab).

Clinical features

The disease usually presents with visual field defects especially hemianopia and impairment of higher functions with dementia and personality changes. As the disease progresses, motor and sensory deficits occur. Fever and seizures are not common. Death usually occurs within 6 months.

Investigations

MRI is useful in detecting the demyelinating lesions in the white matter. These lesions are typically T2 hyperintense, minimally enhancing and located periventricularly in the centrum semiovale, parieto-occipital region and cerebellum. CSF is usually normal. Serological tests are unhelpful because nearly 90% of the adult population is seropositive for the JC virus, but PCR can be used with high specificity to identify JC virus in the CSF.

Treatment

PML is almost always fatal but if the immunosuppressed state can be reversed, e.g. by treating HIV, the disease process may be arrested. Cytosine arabinoside has been tried but its usefulness is unproven. Plasmapheresis has been tried for natalizumab-induced PML.

PRIMARY HIV INVOLVEMENT OF THE CNS

HIV can directly involve the nervous system, resulting in many neurological syndromes (**Table 3**).

Table 3: Manifestations of Primary HIV Involvement of the Nervous System

CNS Syndromes	Neuropathies	Myopathies
Aseptic meningitis AIDS dementia complex Vacuolar myelopathy Vasculitis	Inflammatory demyelinating polyneuropathy (acute and chronic) Distal symmetric sensori-motor polyneuropathy Mononeuritis multiplex Progressive radiculopathy	Polymyositis Nemaline rod myopathy

Meningitis

Many patients, at or soon after sero-conversion, develop signs and symptoms of meningitis. This is usually benign and self-limited.

AIDS Dementia Complex (ADC)

ADC is a form of subacute encephalopathy and manifests insidiously with impairment of memory, poor concentration, behavioural changes and difficulty in writing. Tremor, ataxia, defective ocular movements, paresis, hyperreflexia, and bowel and bladder disturbances then supervene.

There is a moderate increase in CSF proteins and IgG and there may be mild lymphocytic pleocytosis. Antibodies to the virus are present in high titres in the serum and CSF, especially in the latter. The virus may be cultured from the CSF. CT shows mild cerebral atrophy and multifocal white matter changes are detected by MRI in a large number of patients. The EEG shows a generalised slowing or may be diffusely disorganised.

Histopathology shows multinucleated giant cells throughout the cortex and white matter with reactive gliosis. The giant cells contain HIV particles and viral antigens. The endothelial and glial cells may also contain viral antigens but the neurons are rarely infected. Neuronal injury probably is a consequence of cytokines and neurotoxins released by infected immune and glial cells.

In addition to symptomatic care, early treatment with HAART may slow the progress of the disease and produce cognitive improvement.

Differential diagnosis

As shown in **Table 4** patients with AIDS are prone to opportunistic infections and neoplasms that also cause CNS manifestations. These should be excluded because many of them can be treated effectively. Sometimes, stereotactic brain biopsy may be required to arrive at a definite diagnosis.

Table 4: Opportunistic Infections and Neoplasms Affecting the Nervous System in Patients with AIDS

Opportunistic Infections		Neoplasms
Viral	**Non-viral**	
Cytomegalovirus	*Cryptococcus*	Primary CNS lymphoma
JC Virus	*Toxoplasma*	Metastatic systemic lymphoma
HSV-1, 2	*Mycobacteria*	Metastatic Kaposi's sarcoma
Varicella-zoster virus	*T. pallidum*	
	Aspergillus	
	Nocardia	
	Mucormycosis	

AIDS = Acquired immunodeficiency syndrome; HSV = Herpes simplex virus; CNS = Central nervous system.

Vacuolar Myelopathy

Ten to thirty per cent of patients with AIDS develop a vacuolar myelopathy, characterised by a progressive spastic-ataxic paraparesis with urinary incontinence. Most also have evidence of AIDS dementia. Pathologically there is vacuolar degeneration of the white matter of the lateral and posterior columns, especially affecting the thoracic spinal cord. It resembles B12 deficiency, there may be coexisting B12 deficiency, but B12 deficiency is not responsible. There is oedema of the myelin sheath of nerve fibres and the HIV virus can be isolated from the spinal cord of those affected. There is no effective treatment for vacuolar myelopathy, unlike HIV encephalopathy.

Neuropathies

Seropositive individuals may also develop acute inflammatory demyelinating polyneuropathy (AIDP, GBS) which is similar to that seen in seronegative patients. But, unlike these patients, the CSF shows a monocytic pleocytosis, in addition to a raised protein level and normal sugar. Chronic inflammatory demyelinating polyneuropathy (CIDP) runs a more chronic course. As in seronegative patients, plasmapheresis and high dose immunoglobulin therapy are likely to be useful in the management. Both AIDP and CIDP are rare forms of neuropathy in HIV-infected patients. They occur only when the CD4 count is over 400/mm^3.

The most common form of neuropathy in HIV-infected patients is a painful, distal, symmetric sensory neuropathy. It occurs when CD4 count is low, usually less than 200/mm^3. Patients initially complain of paraesthesiae and pain in the feet. Examination shows impaired pain and temperature sensation with loss of ankle jerks. Symptomatic relief of pain can be achieved with analgesics, tricyclic anti-depressants and duloxetine, and anti-convulsants, such as carbamazepine, gabapentin and pregabalin.

TROPICAL SPASTIC PARAPARESIS (TSP)

TSP is a chronic neurological disease characterised by a slowly progressive spastic paraparesis and variable sensory abnormalities. It is strongly associated with the HTLV-1 virus although environmental toxins and nutritional factors may occasionally play a role. The disease is prevalent in Japan (where it is also called HAM or HTLV-1-associated-myelopathy), Seychelles, the Caribbean Islands, parts of South America and Western Africa.

Clinical Features

The disease mainly affects those in the third and fourth decades of life with a greater prevalence among women. Patients present with a gradually progressive spastic paraparesis with hyperreflexia and positive Babinski sign. Sensory symptoms like paraesthesias are common in the distal lower limbs, and sensory deficits particularly of position and vibration sense are frequent. Bladder symptoms supervene and constipation is common. Spasticity and weakness may also be present in the upper limbs but are much less than in the lower limbs. Pathologically, there is degeneration of the lateral columns, especially the corticospinal tracts. To a lesser extent, degenerative changes may also be seen in the posterior columns and the spino-cerebellar and spino-thalamic tracts.

Investigations

The CSF may show a mild pleocytosis but proteins are usually raised. High titres of antibodies to the virus can usually be detected in the serum and CSF and the virus can also occasionally be cultured from lymphocytes in the CSF and blood. MRI may show evidence of demyelination in the spinal cord.

Treatment

Patients often show a favourable response to oral or parenteral steroids. Zidovudine may retard progression of the disease by limiting viral replication.

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20.15 Slow Virus Infections and Prion Diseases

SK Shankar

The term 'prion' was coined by Stanley Prusiner in 1982 to describe the atypical infectious proteinaceous agent causing transmissible spongiform encephalopathies, a group of infectious neurodegenerative diseases with long incubation periods and invariably fatal outcomes affecting a broad spectrum of host species. In humans, prion disease results from infectious modes of transmission: new variant Creutzfeldt-Jakob disease (vCJD) following consumption of infected beef; iatrogenic CJD following blood transfusion or cadaveric tissue grafting; inherited modes following non-conservative germ line mutation of the prion protein (PRNP) gene open reading frame - familial CJD, Gerstmann-Straussler-Scheinker disease (GSS), fatal familial insomnia (FFI), or by mechanisms not well understood-sporadic CJD (sCJD). The clinical symptoms associated with each of the forms vary dramatically. The disease associated prion-protein (PrPsc) is a partially protease resistant, misfolded β pleated , insoluble, disease specific isoform of the host encoded native cellular prion protein (PrPc), accumulating in neural and reticuloendothelial tissues.

CREUTZFELDT-JAKOB DISEASE

The global incidence of CJD varies from 0.3 cases per million to 1.1 cases per million population. sCJD accounts for 80% to 85% of cases, occurring world wide and affects people in the middle and old age. Inherited (familial) form of CJD (fCJD) accounts for about 10% to 15% of cases. The CJD Registry at National Institute of Mental Health and Neurological Sciences (NIMHANS), Bangaluru has recorded 124 cases over 45 years (1968–2009), with an approximate incidence of 0.124 cases per million population. Majority of the patients presented between the age of 55 years and 65 years and another peak at a younger age (35 to 45 years), with male preponderance. The disease in India appears to be manifesting a decade earlier compared to the West. Among the cases recorded in the Registry, 10 of the 25 cases where the history was available were vegetarians, confirming that CJD can occur in vegetarians and represents the sporadic form occurring due to genetic mutation. In India, there have been no authentic cases of iatrogenic CJD (iCJD) following blood transfusion or corneal transplantation.

Replication of the prion protein occurs in lymphoid tissues like spleen and lymph nodes, well before neuroinvasion. Prions are lymphotropic in sheep scrapie and vCJD, but less so in sCJD and bovine spongiform encephalopathy. PrPc, encoded on chromosome 20 in humans is absolutely essential for transportation of PrPsc to the central nervous system (CNS). Haemopoietic cells transport prions from the site of entry to the lympho-reticular system, where they replicate. Recent studies have documented deposits of PrPsc in nerves and muscle of humans, and a human case of CJD with myositis and deposition of PrPsc in muscle and brain has been reported.

The dynamic prion pathogenesis probably has distinct phases of infection like peripheral replication, transmigration from the periphery to CNS and neurodegeneration. The infective PrPsc initiates a thermodynamically controlled cascade causing conformational change of native PrPc into the insoluble, fibrillary form. The PrPc and PrPsc are not neurotoxic and the precise cause of neuro-degeneration is not clear. In cases of fCJD, two important codon mutations at 178 and 200 have been identified. Polymorphism at PrP codon 129 is critical to determine the clinical phenotypes; valine at codon 129 results in classical CJD while methionine substitution at the same site presents as FFI.

Infectious Form of CJD

Iatrogenic CJD has been reported following corneal transplantation, accidental use of contaminated neurosurgical instruments and electroencephalography (EEG) electrodes, dura mater grafts and parenteral administration of pituitary growth hormone derived from contaminated cadaveric sources. The clinical features differentiating iCJD from sCJD are an early age of onset (10 to 40 years), long incubation period of 4 to 30 years, prominent cerebellar symptoms, and terminal dementia.

OTHER FORMS OF HUMAN TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

Gerstmann-Straussler-Scheinker Disease (GSS)

It is a rare autosomal recessive disorder (not a single case reported from India), with diverse clinical symptoms like ataxia, spastic paraparesis, extrapyramidal signs and dementia. Immunopathologic hallmarks are a variable degree of spongiform change in the brain, multicentric PrP immuno-reactive plaques in the cerebellar molecular layer, neurofibrillary tangles in cerebral cortical neurons, and β amyloid plaques resembling Alzheimer's disease.

Fatal Familial Insomnia

This phenotype of CJD shares similar mutation at codon 178 with fCJD, in addition to methionine at codon 129. The age of onset of FFI varies from 25 to 61 years and the duration of illness 7 to 33 months. Sleep disturbance is an early feature followed by automatism, endocrine and motor system involvement. On EEG, classical periodic complexes are rare. Pathologically, severe neuronal loss and astrogliosis in ventral and dorsomedial thalamus, minimal neocortical spongiosis and absence of PrP plaques are the features.

Kuru

Identification of Kuru heralded the study of spongiform encephalopathies and their association with prion disease. It is a neuro-degenerative disorder confined to the Fore tribe of Papua New Guinea in the South Pacific and has disappeared with discontinuation of ritualistic cannibalism. The disease was more common among females, manifesting with progressive cerebellar degeneration, ataxia, tremor and terminal dementia. Histopathologically, mild spongy change, severe Purkinje and

granule cell loss, presence of periodic-acid-schiff positive, PrP immuno-reactive amyloid plaques with radiating spikes in the granule cell layer of cerebellum were characteristically found.

NEW VARIANT OF CJD

With the recognition of bovine spongiform encephalopathy (BSE) in cattle following changes in the practice of commercial production of cattle feed, a distinct and fatal form of CJD has been recognised, manifesting at a young age (16 to 48 years, mean 28 years). The clinical presentation is dominated by psychiatric symptoms like personality changes, depression, sensory parasthesias and dysesthesias affecting face, hands, legs and feet followed rapidly by cerebellar ataxia, myoclonus, chorea, pyramidal and extrapyramidal signs and terminal akinetic mutism. Duration of clinical illness is longer (9 to 30 months, average 14 months). EEG does not show the characteristic triphasic waves. The characteristic magnetic resonance imaging (MRI) feature is hypointensity on T1W images in posterior thalamus (pulvinar sign). Molecular genetic analysis of cases of vCJD revealed methionine homozygosity at codon 129 of the PrP gene. Not a single case of vCJD has been reported from India.

ANIMAL PRION DISEASES

Scrapie in sheep, BSE in cattle, chronic wasting disease in mule, elk and deer and feline spongiform encephalopathy are the animal forms of this disease; lower medulla oblongata being the classical site of involvement in addition to other areas. Not a single case of BSE has been reported from India, though rare occurrence of scrapie has been recorded from Northern India.

Clinical Features

Majority of the cases of CJD reported are of the sporadic variety. Rapidly progressive dementia is the commonest manifestation (100%) associated with myoclonus (91%), and motor disturbances (extrapyramidal, cerebellar, pyramidal and anterior horn cell symptoms). The clinical features suggesting CJD are often preceded by a prodromal period with non-specific clinical signs like fatigue, sleep and memory disturbances, behavioural changes, vertigo and ataxia. Visual complaints are reported in 54% and psychiatric features in 25% of the cases. Masters and Richardson, reviewing the clinical spectrum of human prion diseases, subclassified CJD into: Heidenhain variant with visual symptoms and significant occipital cortical pathology, striatal variant resembling Huntington disease, thalamic variant including FFI, cerebellar variant resembling Kuru, clinical forms with oculomotor disturbances resembling progressive supranuclear palsy and panencephalitic form with white matter demyelination (reported from Japan). Recently, cases are being reported presenting with non-convulsive status epilepticus, deafness and dysesthesia of the arm. Because of expanding clinical forms, an occasional case may escape clinical recognition. The clinical syndrome of vCJD has not changed from the initial description. The duration of illness of CJD reported from India varied from 3 months to 3 years, majority dying within 6 months and presenting a decade earlier than patients reported from the West. Occasional cases of probable familial CJD are noted in India.

Diagnosis

The ability to diagnose the disease early is vital for therapeutic intervention in animals destined for human consumption and humans participating in tissue and blood donation programmes. There is a demand for diagnosing prion disease in the asymptomatic stage. EEG, cerebrospinal fluid (CSF) analysis and MRI examination form the trio for premortem diagnosis of CJD in the symptomatic stage. The diagnostic EEG feature is pseudo-periodic sharp triphasic waves with a sensitivity of 64% and specificity of 84% using standardised set of criteria to define positive and negative tracings. Diagnostic sensitivity of EEG is found to correlate with PrP genotype in the patients.

CSF usually shows mild elevation of protein without pleocytosis. Detection of 14-3-3 protein is the single most useful laboratory test for the diagnosis of sCJD, correlating with the clinical settings. Estimation of neuronal specific enolase (NSE), S-100b and tau protein have yielded good results, though slightly inferior to 14-4-3. The sensitivity tends to increase as the illness progresses, being negative in the early stages. Sensitivity is higher for classical than for atypical cases of CJD and is also influenced by molecular genotype of the disease.

Demonstration of bilaterally symmetric hyper intensities in the basal ganglia on T2W images in association with rapidly progressive dementia are fairly diagnostic of CJD. Diffusion-weighted imaging (DWI) and fluid attenuation inversion recovery (FLAIR) imaging are superior in detecting cortical abnormalities with or without striatal hyper intensities. MRI abnormalities are found at an early stage of illness, especially DWI. In contrast to the lower sensitivity of EEG and CSF analysis in the diagnosis of vCJD, hyperintensity of posterior thalamus (pulvinar sign) is exceptionally useful with its diagnostic accuracy further enhanced with the use of FLAIR imaging. Pulvinar sign is very rarely reported in cases of sCJD and iCJD.

DIAGNOSIS ON BRAIN BIOPSY AND AUTOPSY (Figures 1 to 5)

Demonstration of spongiform encephalopathy, neuronal loss, gliosis and PrPsc protein in various morphological forms, especially around the spongy vacuoles and in plaques by immunohistochemistry is the gold standard for diagnosis of CJD and other prion diseases. The degree and extent of the cardinal pathological features vary depending on the duration of illness.

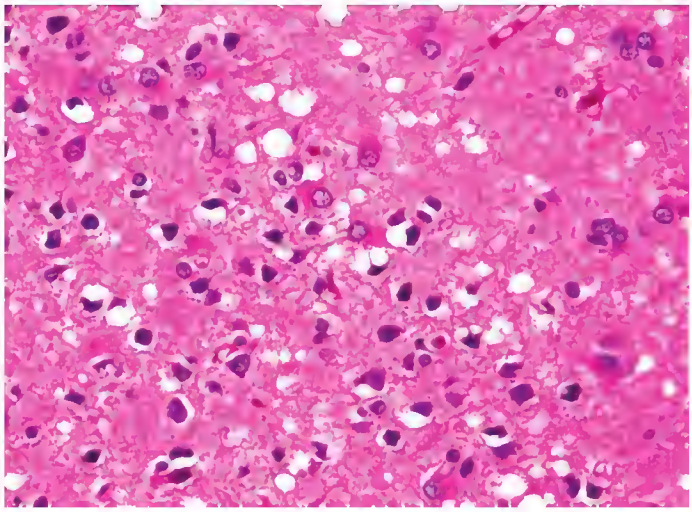


Figure 1: The cerebral cortex showing multiple vacuoles in the neuropile abutting the neurons and reactive astrocytosis (Haematoxylin and Eosin x 100).

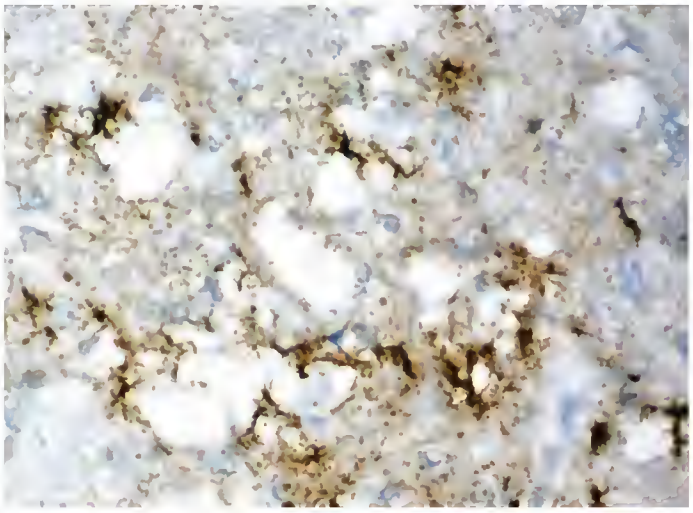


Figure 2: Immunostaining with KG-9 antibody prion protein labelling the edge of the vacuoles and the septae establishing diagnosis (Immunoperoxidase x 300).

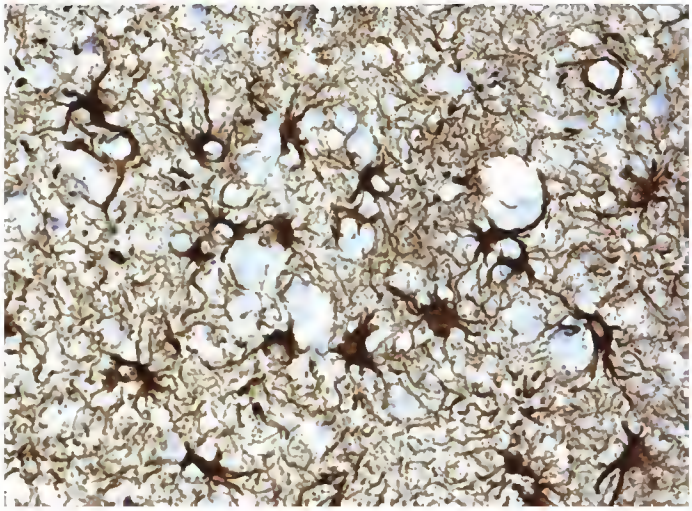


Figure 3: GFAP immunolabelling of reactive astrocytes, some of the processes encircling the vacuoles (Immunoperoxidase x 300).

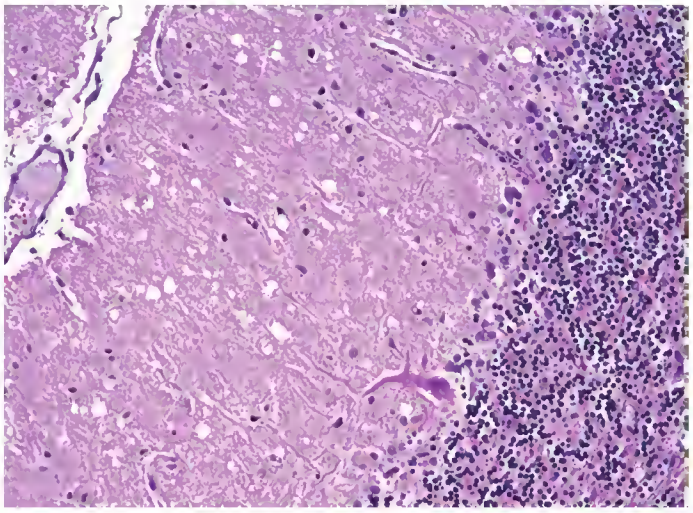


Figure 4: Cerebellum in a case of CJD showing neuropil vacuoles in the molecular layer (Haematoxylin and Eosin x 60).

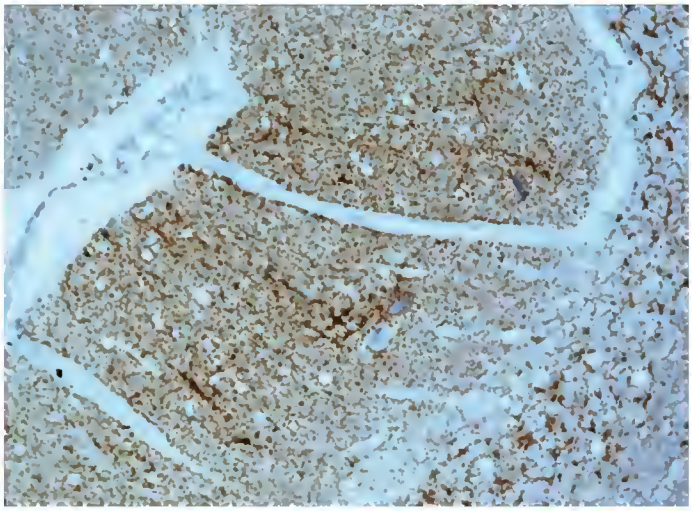


Figure 5: Immunostaining with KG-9 antibody to PrPsc labelled the neuropile of cerebellar molecular layer. In some places linear labelling is seen reflecting deposition of PrPsc along the dendrites (Immunoperoxidase x 60).

Western-blot analysis utilising a small bit of fresh brain tissue is a sensitive method to detect PrP, even before the evolution of characteristic pathological features. Facilities for western-blot and molecular genetic analysis of CJD cases are not available in India, while immunohistochemistry on formalin-fixed paraffin-embedded brain tissue is carried out at NIMHANS, Bengaluru. National Prion Disease Pathology Surveillance Centre at Case Western Reserve University, Cleveland, Ohio, USA (http://www.cjdsurviellance.com) assists in diagnosis. Biopsy of extraneural sites like tonsils and vermiform appendix (sites rich in lymphoreticular tissues) are of diagnostic use only in cases of vCJD and not other forms.

TREATMENT

Till date no treatment is available. Compounds that work *in vitro* have no significant beneficial effects when administered at the onset of symptoms in animals or after clinical manifestation in humans. Until we have a precise understanding of the physico-chemical nature of the infective agent, the molecular and biochemical mechanisms leading to neurodegeneration or the physiological function of PrPc, the search for therapeutic interventions will continue.

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20.16 Fungal and Parasitic Diseases of Nervous System

Ashok Panagariya, Bhawna Sharma

CENTRAL NERVOUS SYSTEMS FUNGAL INFECTIONS

Fungal infections of the central nervous systems (CNS) were considered rare but are increasingly recognised in recent times. The internist is intimidated when confronted with the challenge of managing patients with CNS fungal infections. A high index of suspicion is vital for an early diagnosis and timely appropriate management may prove life saving. Fungal infections although traditionally thought to be of relevance in the immunocompromised subjects not uncommonly, may also be encountered in the immunocompetent populations. Myriad clinical presentations of the CNS fungal infections often mimicking other common diseases may pose diagnostic dilemmas.

Pathogenic fungi include yeasts, filamentous fungi and dimorphic fungi. Yeasts are unicellular organisms and include the relatively common *Cryptococcus* and *Candida*.The filamentous fungi (moulds) are characterised by branching hyphae, which are either septate or aseptate and include the more common *Aspergillus* and the *Zygomycetes* (including Rhizopus, Rhizomucor and Mucor). Dimorphic ('endemic') fungi are filamentous at 25°C and yeasts in the host tissue which include Blastomyces, Histoplasma, Coccidioides and Paracoccidioides. *Cryptococcus, Aspergillus, Zygomycetes (Mucor),* and *Candida* species are universally distributed. *Cryptococcus* and *Mucor* account for the common CNS mycosis.

Most fungi are of low virulence and are non-pathogenic. Pathogenic fungi invade the brain usually in the setting of predisposing risk factors (**Table 1**). Pathogenic fungi enter the host usually through inhalation and initiate a self limiting asymptomatic or mild pulmonary infection. If the fungemia overcomes the host's immune defence system in a predisposed individual, it may cross the blood-brain barrier and enter the CNS. Local extension into brain due to a contiguous infection of paranasal sinuses, ear and orbit is another important portal of entry. The other routes of fungal invasion include indwelling arterial lines or venous catheters that can be infected by *Candida* leading to fungaemia. Less common routes of infection are skin (*Sporothrix*), oral and gastrointestinal tract *(Candida)* and nasal sinuses (*Aspergillus* and *Zygomycetes*). Finally, direct inoculation of fungus into skull fracture wounds or during neurosurgical procedures also predisposes to CNS fungal infections. CNS mycosis may present with a number of clinical syndromes (**Table 2**).

DIAGNOSIS OF CNS FUNGAL INFECTIONS

Cerebrospinal fluid (CSF) sampling is indicated in all patients with suspected CNS mycosis. CSF reveals lymphocytic pleocytosis (*Cryptococcus, Candida*), neutrophilic predominance (*Aspergillus, Blastomycosis*) or eosinophilia (Coccidioides). CSF examination usually shows low glucose and high protein. CSF culture for fungal meningitis is far less sensitive compared to bacterial meningitis. Larger volume of CSF and centrifuged sediment analysis increase the diagnostic yield of fungal staining and culture. Most fungal examinations are time consuming. CSF antigen testing is available for *Cryptococcus* and *Histoplasma*, with high sensitivity and specificity rates (90%).

Table 1: Predisposing Risk Factors for Central Nervous System Fungal Infections

Prolonged antibiotic use
Diabetes mellitus
Cancer chemotherapy
Human immunodeficiency virus
Malignancy
Intravenous drug abuse
Neurtropaenia
Hereditary immune deficiency disorders
Indwelling catheters
Surgery
Trauma

Table 2: Clinical Syndromes of Central Nervous System Fungal Infections

Meningitis/encephalitis
Meningovascular syndromes
Focal infection/mass lesions
Infarction or haemorrhage

The spectrum of radiographic characteristics ranges from no abnormality on MRI and CT to meningeal enhancement, abscesses, intraventricular or intraparenchymal granulomas, gelatinous pseudocysts and/or hydrocephalus. If non-invasive methods fail brain biopsy may help in establishing the definitive diagnosis.

Fungaemia is seen with a few species, including *Candida*, *Histoplasma* and *Cryptococcus*, however yield from blood culture is usually poor and time consuming.

Only common CNS fungal infections relevant in the Indian context are being described here.

CRYPTOCOCCOSIS

Cryptococcus neoformans, an encapsulated yeast-like fungus is the most common CNS mycosis. It is found in mammal and bird faeces, particularly in pigeon droppings. CNS infection can be meningeal or less commonly parenchymal. Disseminated disease occurs commonly in immunocompromised while cryptococcomas (granulomas) occur in imm unocompetent hosts. Cryptococcal meningitis is thought to be a reactivation of the dormant lesion in the lung similar to Ghon's focus of pulmonary tuberculosis.

Headache is the most common symptom. Other symptoms more typically seen in bacterial meningitis like neck stiffness

or photophobia are distinctly uncommon. Basal meningitis may cause obstructive hydrocephalus (**Figure 1**). Focal lesions like cryptococcomas or infarction present with focal neurological deficits or seizures. The commonest parenchymal sites are the mid-brain and the basal ganglia. Infarctions in basal ganglia, internal capsule and thalamus may rarely occur.

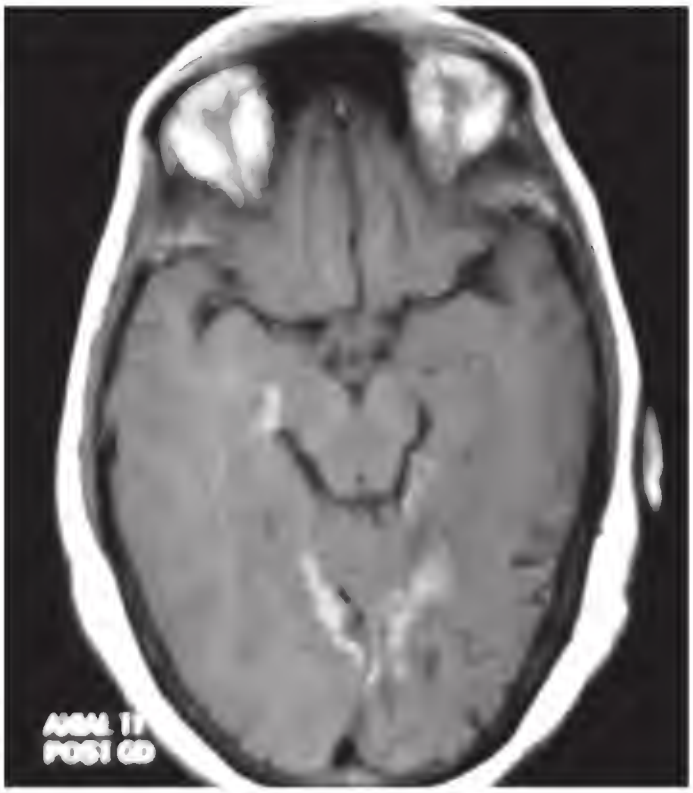


Figure 1: Axial T1W contrast image showing enhancement of basal cisterns and tentorium in a patient of cryptococcal meningitis.

CSF in cryptococcal meningitis shows a lymphocytic pleocytosis with exceptionally high protein levels. CSF may, however, be normal in exclusively parenchymal disease. CSF India ink preparation shows the polysaccharide capsule of the cryptococcus as a clear 'halo' surrounding the organism. CSF staining and culture may yield positive results if adequate samples are obtained. Cryptococcal latex antigen detection test relies on agglutination tested at differing titres of CSF and has a sensitivity of 90%. Imaging may reveal meningeal enhancement, abscesses, cryptococcomas, gelatinous pseudocysts and hydrocephalus.

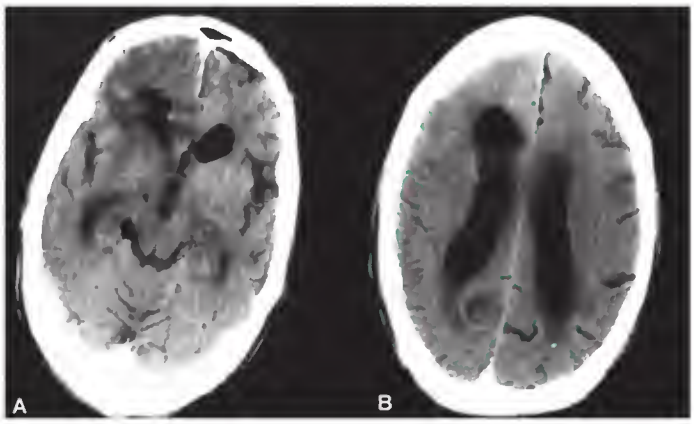
Treatment comprises of combination chemotherapy with conventional amphotericin B and flucytosine for 2 to 4 weeks and then switching to fluconazole for 8 weeks. Lifelong flucanazole therapy is indicated in patients with AIDS.

ZYGOMYCOSIS

These filamentous fungi (*Mucor* and *Rhizopus)* grow profusely on decaying vegetables, fruits, animal excreta and bread rich in carbohydrates. Unlike most other mycoses in which cerebral involvement is secondary to a primary focus in the lung (aerosol entry), this mycosis occurs most commonly from an infection of the facial skin, nasal and paranasal sinus mucosa or nasopharynx and leads to vascular invasion and thrombosis. The basifrontal area is involved by direct venous invasion through the orbital plate and cavernous sinus. A black regional discharge, such as from the nose, indicates necrosis of the underlying tissue and should suggest the diagnosis of mucormycosis.

ASPERGILLOSIS

Aspergillus is a ubiquitous fungus in soil, water, decaying vegetation and organic debris. *Aspergillus fumigatus, A. terreus,* and *A. flavus* cause CNS infection. Spread to CNS occurs haematogenously or by direct inoculation into the CNS during surgical procedures or from contiguous structures. CNS aspergillosis can present as solitary or multiple lesions, meningitis and less commonly mycotic aneurysm, dural abscess, myelitis and invasion of carotid or vertebral arteries. Patients usually present with fever, altered mental status, focal neurological deficits and less often signs of meningeal irritation. Imaging reveals several patterns: solid enhancing lesions (aspergilloma) or ring-like enhancing lesions, infarction/haemorrhage, mycotic aneurysms and rarely pneumocephalus (**Figures 2A and B**).



Figures 2A and B: Axial CT head plain images showing ventricular pneumocephalus in a diabetic patient with aspergillosis.

TREATMENT OF CNS FUNGAL INFECTIONS

Amphotericin B is an effective agent for most CNS mycoses. Amphotericin B is a polyene antibiotic that binds to ergosterols in the fungal cell wall and disrupts the cell wall integrity leading to increased permeabilty, K^+ leakage and cell death. Depending on its concentration, it can be fungistatic or fungicidal. It is used in a dose of 0.3 to 1.5 mg/kg body weight per day intravenously daily as a 1 to 4 hour infusion. It has poor penetration of blood-brain barrier, reducing its ability to achieve effective fungicidal levels in the brain. Side effects include renal toxicity, hypokalaemia, hypomagnesaemia, normocytic normochromic anaemia and 'flu-like' allergic reaction during or after intravenous infusion. Lipid-based amphotericin B compounds although costlier have lesser adverse effects. Most CNS fungal infections require long treatment periods of 4 to 10 weeks often guided by CSF culture reports.

Oral flucytosine, a cytosine analogue, commonly used as an adjunct to amphotericin B in case of invasive infections with *Cryptococcus*, *Candida* and *Aspergillus,* is usually well tolerated but may rarely cause bone marrow suppression, especially with concomitant use of amphotericin B.

Azoles (ketoconazole, fluconazole, itraconazole, voriconazole) although broad-spectrum are weak antifungals. They have good bioavailability on oral administration and are usually well tolerated.

Hydrocephalus may require an external ventricular drainage or shunt surgery. Surgical interventions comprise of exenteration of the infected facial, nasal and intra-cranial tissues in cases of mucormycosis and aspergillosis and drainage of cerebral abscesses.

Fungal infections are difficult to eradicate and have a high relapse rate, especially in immunocompromised states despite best antifungal regimens. The cure rate for cryptococcal meningitis is about 75% and 25% for aspergillosis and zygomycosis. The past few years have seen major advances in the development of newer antifungal agents including a novel class of drugs, the echinocandins and improved azole molecules with better efficacy.

CNS PARASITIC INFECTIONS

Parasitic diseases of the CNS are not only common in the developing countries but their incidence is also rising in the developed world due to increased international travel and increase in the number of immunocompromised hosts.

Parasites involving the CNS fall into two major categories – protozoa and helminths. Protozoa are unicellular microbes, e.g. plasmodium, toxoplasma, acanthemoeba while helminths are multicellular, macroscopic organisms, e.g. *Taenia*, *Echinococcus*. Cerebral malaria and cysticercosis are by far the most common CNS parasitic infections.

Parasitic infections do elicit immune responses in the body but immunity against parasites is weaker as compared to other pathogens. This is due to complex structure and antigenic diversity of the parasites. Also intra-cellular parasites lodging in body cavities or vesicular cysts escape humoral immunity.

NEUROCYSTICERCOSIS (NCC)

NCC is the most common parasitic disease of the nervous system and is the main cause of acquired epilepsy in developing countries. In India 40% of adult onset focal seizures are due to NCC. It is absent in Israel and Muslim countries, where pig rearing is unacceptable for religious reasons.

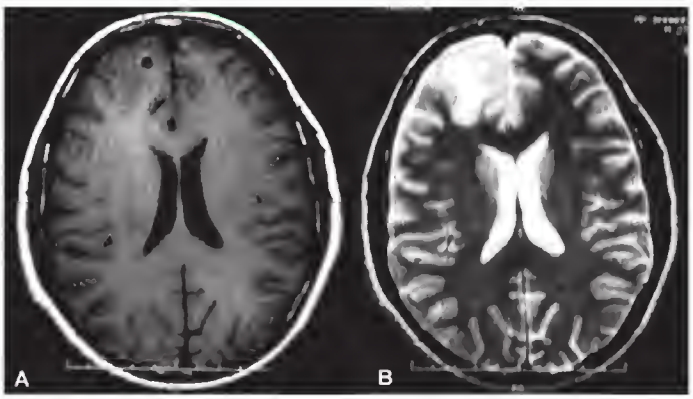
Taenia solium has a two-host biological cycle, with man as the definitive host carrying the intestinal tapeworm and pig as the intermediate host harbouring the larvae or cysticerci. Humans, like pigs, can become intermediate hosts if fresh vegetables, uncooked food or water contaminated with human faeces is ingested or by direct ingestion of poorly cooked pork infected with cysticercus. Cysts evaginate in the small intestine, enter the bloodstream and reach the tissues, especially CNS, where they reside as cysticerci.

Parenchymal cysts evolve through following four stages—vesicular, colloidal, granulonodular and calcified. Vesicular stage harbours the live larva with scolex and translucent liquid around without any evidence of host reaction. As the cyst degenerates it passes through transitional stages of colloidal and granulonodular stages which have perilesional oedema. Finally, when the cyst dies, it can disappear or become an inactive calcified nodule. Uncommonly cysticerci may present with diffuse encephalitic form, leptomeningitis or may be located in the subarachnoid space or ventricular system (multilobulated racemose forms).

It affects people of all ages and both sexes. The clinical manifestations depend on the number and topography of lesions and the viability of the parasite. Following syndromes have been described with cysticercosis: subclinical, parenchymal, subarachnoid, intraventricular, spinal, and ocular.

Many individuals with NCC remain entirely asymptomatic. Most patients with parenchymal cysticercosis present with focal seizures and less commonly with focal neurological deficits like motor or sensory deficits, ataxia, involuntary movements, brainstem dysfunction and neuropsychiatric changes. Headache and increased intra-cranial pressure is more common with extraparenchymal disease. Hydrocephalus may occur with intraventricular cysts or arachnoiditis. Spinal NCC is relatively rare. Ocular cysticercosis is associated with variable degrees of uveitis, endophthalmitis, and impaired vision. Cysticerci may lodge in skeletal muscle and present as pseudohypertropic myopathy.

Neuroimaging forms the cornerstone of diagnosis. When the larva is viable, the CT shows circumscribed, rounded, hypodense lesion of 4 to 20 mm size without perilesional oedema or contrast enhancement. On MRI, the vesicular larva appears CSF isointense on all sequences. Both MRI and CT may show a high intensity, 2 to 4 mm mural nodule pathognomonic of cysticercus. Colloidal and granulonodular stages are degenerating stages and, therefore, have irregular perilesional oedema and ring enhancement in the former and solid enhancement in the latter (**Figures 3A and B**). Calcified cyst is seen as punctuate hyperdensity on CT and hypointensity on both T1 and T2 MRI without any oedema or enhancement. Other causes of inflammatory granuloma like tuberculoma must be differentiated (**Table 3**).



Figures 3A and B: Axial T1W and T2W images showing a single small round cystic lesion in right frontal lobe with perilesional oedema in Neurocysticercosis.

Table 3: Neurocysticercosis versus Tuberculoma

	Neurocysticercosis	Tuberculoma
Size of the lesion	Usually <20 mm	Often >20 mm
Margin of lesion	Thin smooth wall	Thick irregular wall
Perilesional oedema	Mild to moderate	Moderate to marked
Focal neurological deficit	Usually none	Often present, persistent

Subcutaneous calcified nodule may be visible on X-ray corroborative with NCC. Serological tests have a limited value due to poor sensitivity and specificity. Recent advances include the upcoming serological assays for identification and sequencing of specific antigens of cysticercus but such tests

need further validation. A brain biopsy may be required when other modalities fail to reveal the cause.

In patients with a single ring-enhancing lesion presenting with seizures, treatment with an anticonvulsant drug alone is advocated, as most of these cysts resolve spontaneously. Seizure management requires appropriate anti-epileptic drugs. A number of controversies surround the appropriate treatment of NCC. Asymptomatic viable NCC or calcified NCC do not require specific anti-parasitic treatment. There is considerable controversy whether the colloidal or granulonodular stages require anti-parasitic drugs as the cyst is already dying. Potential harms with anti-parasitic treatment comprise of neurological worsening in case of multiple parenchymal NCC or subarachnoid cyst rupture leading to arachnoiditis. A recent Cochrane review shows minimal benefit of anti-parasitic treatment in terms of somewhat quick resolution of cyst but no better seizure control. Cysticidal treatment should be avoided in ocular, brainstem and spinal NCC. Options for cysticidal treatment comprise of albendazole or praziquantel. Albendazole is preferred because it has better penetration into subarachnoid cysts and does not pharmacologically interfere with corticosteroids and anticonvulsants. The dose of albendazole is 15 mg/kg body weight per day divided in 3 oral doses for 7 to 28 days along with dexamethasone. Praziquantel in 3 oral doses of 25 mg/kg body weight at 2-hour intervals, followed 5 hours later by dexamethasone 10 mg intramuscularly has also shown good therapeutic results.

TOXOPLASMOSIS

CNS toxoplasmosis is an AIDS-defining condition that occurs in *T. gondii*-seropositive patients due to reactivation. In an immunocompromised host *T. gondii* reactivation leads to variable clinical features – headache, acute confusional state, focal neurological deficits, focal seizures, personality change or, movement disorders according to the site of involvement. Details are available in chapter Toxoplasmosis of section Infectious Disease.

ECHINOCOCCOSIS (HYDATID DISEASE)

Echinococcosis is a zoonotic parasitic disease. Patients present with headache, vomiting, papilloedema, focal/generalised seizures, hemiparesis, dysarthria, and cranial nerve palsies. Hydatid disease rarely may affect spinal cord. Imaging reveals large rounded cystic lesions which are CSF isointense without perilesional oedema or contrast enhancement (**Figure 4**). Serological tests and hydatid cyst at other sites may further aid the diagnosis.

Surgical resection of the cyst is the treatment of choice. The size of the cyst can be shrunken by pre-treatment with albendazole. Details are available in section Infectious Diseases of chapter Tapeworm and Hydatid Diseases.

AMOEBIC MENINGOENCEPHALITIS

Free-living amoebae rarely invade the CNS, but intra-cranial amoebic infections are fatal. Three amoebic parasites are known to invade CNS (*Naegleria fowleri*, *Acanthamoeba* and *Entamoeba*) and cause primary amoebic meningitis (PAM) or granular amoebic meningoencephalitis (GAM). It is suspected when there is a history of water exposure (swimming/diving in

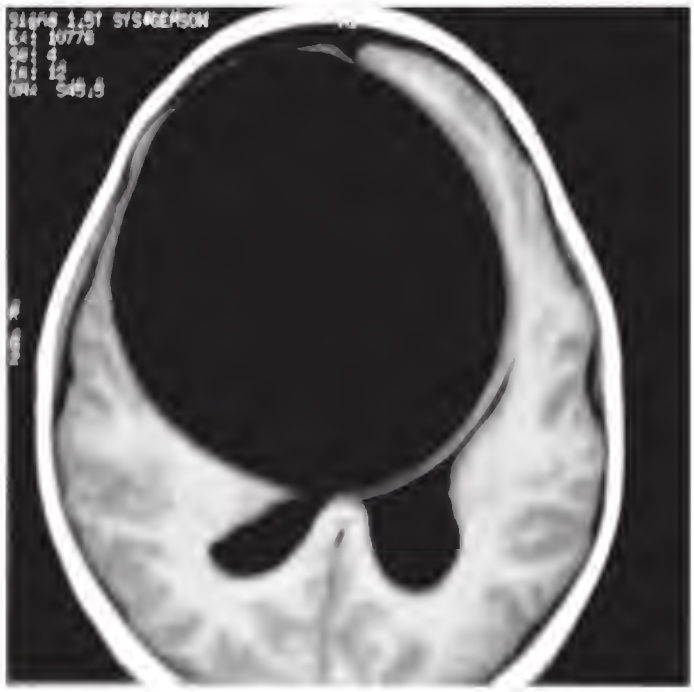


Figure 4: Axial T1 W image showing a large round CSF isointense cystic lesion without perilesional oedema in a patient with CNS hydatid disease.

warm fresh water ponds contaminated by free-living amoebae). Trophozoites penetrate the nasal mucosa and ascend along the olfactory nerves to invade the brain. It causes acute purulent meningitis, necrotising haemorrhagic encephalitis, brain oedema and necrotic vascular invasion.

A patient of PAM is typically a previously normal child presenting with a clinical picture compatible with acute pyogenic meningitis (high-grade fever, headache, stiff neck, seizure, altered mental status). The disease rapidly progresses to coma and death due to raised intra-cranial pressure and cerebral herniation. GAM affects all ages with a male predilection in immunocompromised hosts. Clinical picture resembles that of brain abscess or chronic meningitis.

CSF examination typically reveals polymorphonuclear and rarely eosinophilic pleocytosis with increased protein and low glucose levels. Motile trophozoites may be seen on CSF wet mount preparation. Imaging is usually normal in PAM and reveals multiple enhancing lesions in GAM. Outlook remains poor with a mortality rate greater than 80%. Many drugs, including amphotericin B, rifampin, tetracycline and trimethoprim have been tried in anecdotal cases with variable results.

CEREBRAL MALARIA

Cerebral malaria is caused by *Plasmodium falciparum* and rarely by *P. vivax*. *Cerebral malaria* is a neurological emergency that requires urgent intervention. It is a diffuse severe bihemispheric dysfunction with paucity of localising signs caused by the parasitic sequestration within the vasculature of the brain.

The pathogenesis of cerebral malaria is not completely understood. Sequestration of parasitised RBCs caused by cytoadherence of RBCs to the endothelial cells of the capillary and post-capillary venules is traditionally believed to play a key pathogenetic role. The parasitised RBCs adhere to microvascular endothelial cells leading to brain ischaemia. Also such cyto-

adhesion causes cytokine (e.g. TNF alpha and interleukins) production and complement activation leading to an increase in blood brain barrier permeability causing perivascular haemorrhages and diffuse cerebral oedema.

Incubation period is usually 10 to 18 days. The case definition of cerebral malaria by World Health Organization (WHO) requires (1) impairment of consciousness, (2) presence of asexual forms of *P. falciparum* in peripheral blood film or bone marrow smear, and (3) exclusion of other causes of encephalopathies. Impaired consciousness should at least last for 30 minutes. The fever may be classically intermittent, irregular or continuous. Patients typically have a diffuse encephalopathy with bilateral pyramidal signs, decrebrate and decorticate posturing occuring in severe cases. Generalised seizures occur in approximately half the patients. Focal deficits and nuchal rigidity is reported in some cases while papilloedema is rare.

The key to the diagnosis is a high index of suspicion in patients with febrile encephalopathy in malaria-endemic areas. Demonstration of *P. falciparum* on thick and thin smear examination of the peripheral blood after staining with Giemsa or Field stain establishes the diagnosis. Cerebral malaria occurs when more than 10% of the peripheral RBCs are parasitised. At least 3 smears prepared at intervals of 6 to 8 hours should be declared negative before excluding the diagnosis of malaria. Recently, rapid antibody-based serologic tests and PCR test for the detection of plasmodium DNA have been introduced.

Brain imaging is usually normal in cerebral malaria but may show diffuse cerebral oedema, white matter abnormalities and cortical or subcortical infarcts in the watershed zones. CSF in cerebral malaria often shows a mild degree of lymphocytic pleocytosis (10 to 50 cells/μL), mild increase in protein and normal glucose.

In a malaria-endemic zone, treatment should be started in a suspected case without waiting for laboratory confirmation of the diagnosis. Management includes specific anti-malarial chemotherapy and supportive therapy for multiorgan dysfunction. In patients with a very high parasitic burden, an exchange transfusion has been recommended.

Due to widespread resistance of *P. falciparum* to chloroquine, the drug of choice is intravenous quinine sulphate or parenteral artemisinin derivatives. Intravenous quinine is administered by slow infusion in a loading dose of 20 mg/kg body weight in 5% dextrose over 4 hours, followed by a maintenance dose of 10 mg/kg body weight infusion every 8 hours. For treatment details, refer to chapter on Malaria in the section Infectious Diseases.

The mortality from cerebral malaria varies from 20% to 33%; in children the case fatality rate can be up to 40%. Recovery is usually complete in early treated cases. Approximately 5% of cases, mostly children, are left with residual neurological dysfunction. Recombinant human erythropoietin has shown beneficial effect in experimental cerebral malaria and will soon enter into large clinical trials.

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20.17 Raised Intra-Cranial Pressure and Hydrocephalus

Daljit Singh

Normal intra-cranial pressure (ICP) is the pressure of the brain contents within a closed intra-cranial cavity, i.e. skull. In adults, it varies from 5 mm Hg to 15 mm Hg. It is a dynamic pressure influenced by several factors including blood pressure, respiration and position of the person. Nevertheless, it provides a very important parameter in deciding the treatment of several neurological disorders.

In simple words, ICP is a reflection of the volume of brain, blood and cerebrospinal fluid (CSF) in the skull. Any change in any content would lead to displacement of blood or CSF from the skull into internal jugular vein or spinal canal, respectively. This enables the autoregulation to maintain constant ICP (Monro Kelly doctrine) as well as cerebral blood flow. In other words; the changes in the volume can maintain the constant ICP up to a point beyond which any change in the volume will result in rise of ICP (**Figure 1**).

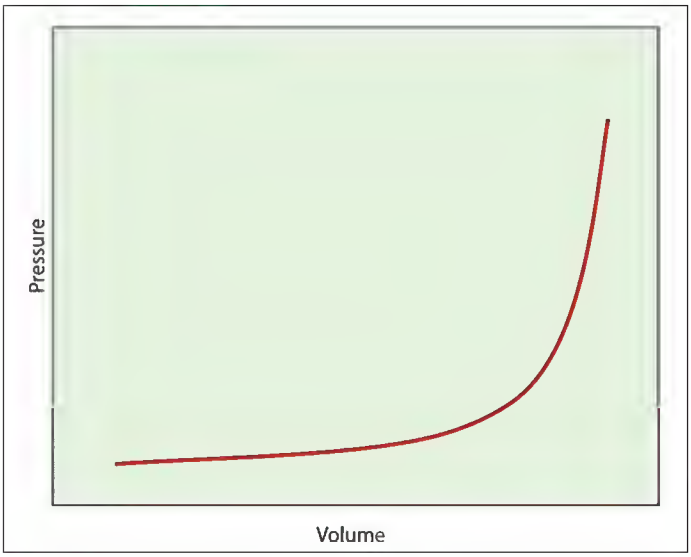


Figure 1: Pressure volume curve depicting a constant intra-cranial pressure initially followed by a rapid rise.

The change of volume or pressure within the cranial cavity is dependent upon the size of skull, age of patient, status of fontanels, condition of sutures and condition of brain. Old age can accommodate a large amount of displacement due to atrophy whereas children can do the same with the help of suture diastases or open fontanelles. Adults are most susceptible to changes in ICP.

There can be features of raised ICP in several diseases of brain as well as systemic disorders. Several drugs and chemicals are also known to produce raised ICP, e.g. lead, mercury, tetracylines, etc. Anaemia polycythaemia and hypoxia due to any cause can result in changes in ICP.

Normal capacity of the adult skull is around 1400 cc. CSF is constantly secreted at 500 to 700 cc (per 24 hours). At a given time, the brain has around 75 cc of blood and 75 cc of CSF of which 35 cc remains in the ventricles. CSF is produced at the rate of 0.35 cc per minute. Intra-cranial circulation of blood is about 750 to 1000 litres per day. Cerebral perfusion pressure (mean arterial pressure—ICP) is maintained constant by autoregulation. Failure to maintain a constant blood flow or cerebral perfusion pressure results in failure of auotoregulation.

Lundberg described three wave patterns in ICP; A waves are pathological with a level of 50 to 100 mm Hg; B waves are rhythmic variations related to respiration and are of shorter duration; and C waves are Traube-Hering-Mayer waves with a frequency of 6 waves per minute. These are of little clinical significance.

An understanding of the basics of ICP plays an important role in the management of hydrocephalus. In hydrocephalus, ICP can be raised due to ventricular enlargement as well as due to other associated conditions, e.g. oedema, infarction, impaired cerebral blood flow, impaired autoregulation, etc. Therefore, while treating hydrocephalus, the clinical impact of each one of these contributory factors should be kept in mind.

HYDROCEPHALUS

Hydrocephalus is a clinical syndrome of raised ICP with ventriculomegaly. It should be differentiated from ventriculomegaly without raised ICP, which is a condition of large ventricles and is usually asymptomatic. However, both these terminologies are wrongly interchanged by most clinicians. It is important to understand that hydrocephalus requires treatment whereas only ventriculomegaly does not.

Pathogenesis

The reported incidence of hydrocephalus ranges from 0.2 to 3.5 per 1,000 births.

CSF is produced in the lateral ventricles by the choroid plexus. The production is an active process regulated by an osmotic gradient as well as by the enzyme carbonic anhydrase. After production, CSF flows from the lateral to the third ventricle via the Foramen of Monroe. There are two foramina, one on each side. From the third ventricle, CSF flows to the fourth ventricle via the aqueduct of Sylvius, which is usually 8 to 12 mm in length. The fourth ventricle is a small chamber which holds some amount of CSF and has four openings for the CSF to egress from it. The paired laterally placed foramina of Luschka, a single median foramen of Magendie and a central hiatus which opens into the central canal of spinal cord.

The CSF, after flowing out of the fourth ventricle, ascends up to the brain surface, bathes the brain parenchyma and is absorbed with the help of arachnoid Pacchonian granulations along the mid line by the superior sagittal sinus. This entire concept is known as *bulk flow of CSF.*

It is important to understand that besides this, CSF is also absorbed by capillaries in the subarachnoid space and 2nd, 7th, 9th and 10th cranial nerves.

The flow of CSF inside as well as outside the ventricles is regulated by the cardiac cycle. The flow is out of the ventricle in systole and towards the ventricle in diastole. This *pulsatile flow of CSF* has added a newer understanding in the pathogenesis of hydrocephalus (**Figure 2**).

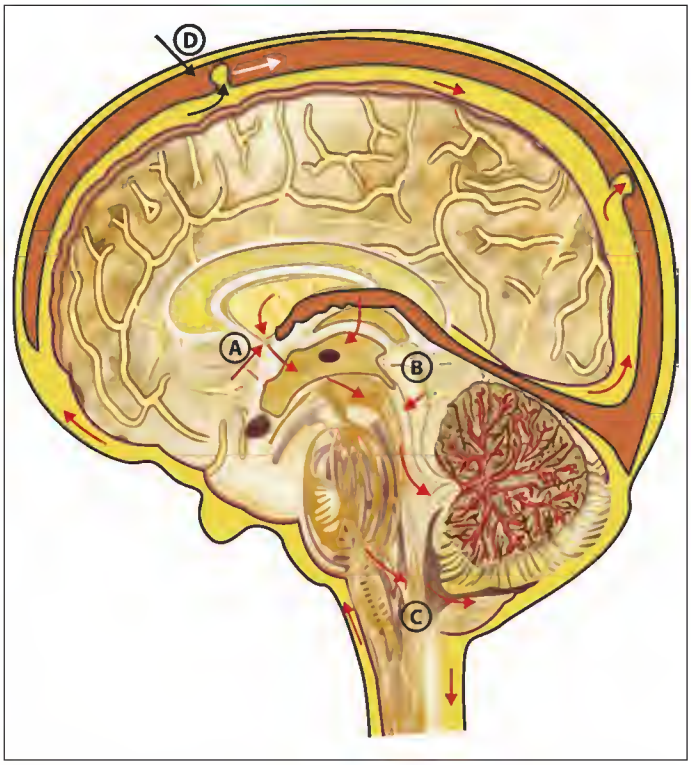


Figure 2: The cerebrospinal fluid flow in the brain and types of hydrocephalus. Sites A to C, non-communicating and site D, communicating hydrocephalus.

Classification

Hydrocephalus is classified in several ways, however, none is accurate. For simplicity, it is divided *functionally* into *communicating (Non-obstructive)* and *non-communicating (Obstructive)*. It can be further classified as *acute and chronic*. There are special categories of hydrocephalus, namely normal pressure hydrocephalus (NPH), otic hydrocephalus, hydrocephalus ex vacuo, double compartment hydrocephalus, latent hydrocephalus of adults, benign external hydrocephalus, and arrested hydrocephalus.

Dandy described the functional divisions of hydrocephalus, i.e. communicating and non-communicating which are still used by many. Whereas obstructed hydrocephalus refers to obstruction to the flow at any level from the lateral to the fourth ventricle outlet, communicating hydrocephalus results due to poor absorption at the level of the subarachoid space.

Clinical Findings

The presentation of hydrocephalus is variable. It depends upon the age of the patient and ability to withstand the change in the volume of CSF and pulsatility of the blood vessels.

Acute hydrocephalus will present with headache, vomiting, nausea, respiratory difficulties (cheyne-stokes) and papilloedema. Besides children may present with wide and tense fontanelles, irritability, lack of interest, and rejection of food. Neurogenic pulmonary oedema can be an associated fatal condition due to refractory raised ICP. Decerebration and decortication can occur if hydrocephalus remains untreated. Altered sensorium or loss of consciousness may be terminal in such cases.

Chronic hydrocephalus presents with an enlarged head, Macewen's sign (crackpot sign), impaired gaze of eyes, upward gaze paresis (sunset sign), Perinaud's syndrome, sutural diastasis, visible scalp veins, and impaired mentation. Many a time the only presentation can be a generalised seizure, which is ischaemic in origin.

Bradycardia, hypertension, arrhythmia and asystole can be associated findings. False localising signs, e.g. unilateral or bilateral 6th nerve palsy are not uncommon.

A classical triad of urinary incontinence, gait ataxia and memory impairment is seen in normal pressure hydrocephalus, however, the classical presentation is seen in ony 50%.

Radiologically, such patients may show beaten silver appearance of skull, ballooning of third ventricle into sella or empty sella syndrome. However, such appearances are rarely seen these days.

Diagnostic Criteria

Computed tomography (CT)/Magnetic resonance imaging (MRI)

The CT or MRI provide adequate information about aetiology and type of hydrocephalus. Cine Mode MRI can show the flow of CSF via the aqueduct and is helpful in establishing aqueductal stenosis.

Early hydrocephalus can be picked up by the presence of enlarged temporal horns of more than 2 mm. Temporal horns are normally not visible or may be slit-like. Absence or invisibility of the Sylvian and inter hemispheric fissures adds to the features of raised ICP. Similarly, absence of CSF in subarachoid spaces (sulci of brain) suggests obstructive hydrocephalus.

The ratio of frontal horn diameter (FD) and inner diameter of brain at that level (ID) of more than 50% is suggestive of hydrocephalus. Similarly the ratio of FD maximal bi-parietal diameter (BPD) of more than 30% (Evans ratio) is suggestive of hydrocephalus (**Figure 3**).

Presence of periventricular lucencies suggest transudation of fluid from the ventricle and is mostly seen in obstructive hydrocephalus.

There can be unilateral dilatation of a ventricle in obstructed foramen of Monroe, triventriculomegaly in aqueductal obstruction or quadri-ventriculomegaly (pan-ventriculomegaly) in outlet obstructions. Enlargement of all ventricles with excessive CSF in subarachoid spaces suggests communicating hydrocephalus or ex-vacuo dilatation.

Intra-operative ultrasonography can pickup congenital hydrocephalus in most of the cases.

Aetiology

Hydrocephalus is commonly associated with congenital diseases, e.g. neural tube defects (meningomyelocoele) Chiari malformation, Dandy-walker syndrome, primary or secondary aqueducatal stenosis, neonatal infections and post

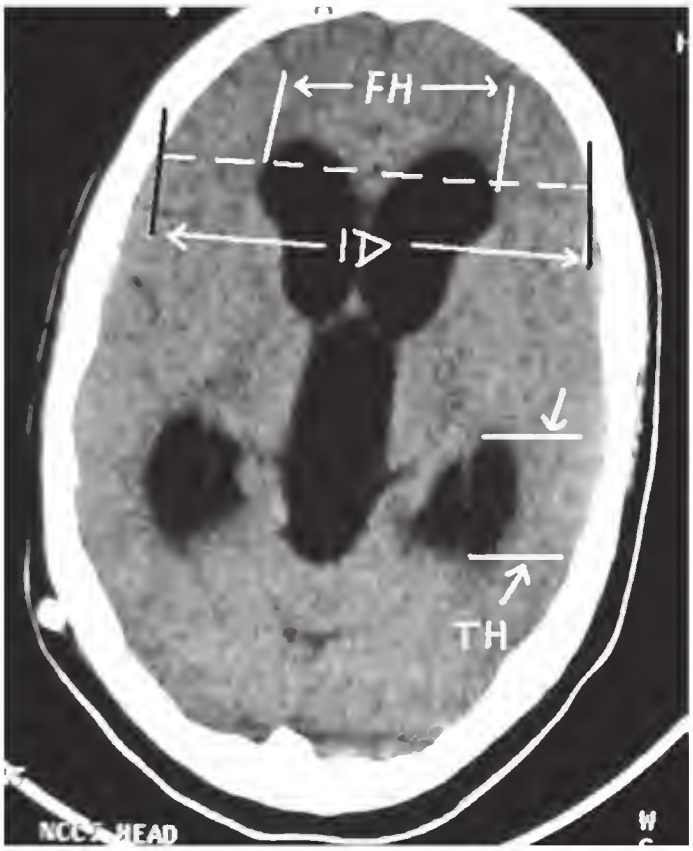


Figure 3: CT diagnostic criteria for hydrocephalus.

TH = Temporal horns; FH = Frontal horns; ID = Inter hemispheric diameter at frontal horns.

haemorrhagic. Secondary hydrocephalus can occur in tuberculosis or brain tumours at various locations in relation to CSF pathways. Posterior fossa tumours, e.g. medulloblastoma, ependymoma are common causes of hydrocephalus in children. Spinal tumours, Craniopharangioma and colloid cyst are some of the other conditions associated with genesis of hydrocephalus. Choroid plexus papilloma and early tubercular meningitis can result in excessive CSF production, resulting in hydrocephalus (**Figure 1**).

Treatment

There is a lot of debate and controversy regarding the optimal treatment of hydrocephalus. Similarly, there are controversies regarding optimal time of surgical intervention.

Medical Treatment

Acetazolamide, a carbonic anhydrase inhibitor can be used in a dose of 25 mg/kg per day in three divided doses and increased up to 100 mg/kg per day with a strict watch on electrolytes, and arterial blood gases. Acetazolamide may act for non-communicating hydrocephalus, tubercular meningitis, and as a temporary adjunt before surgical intervention.

The other diuretics, e.g. frusemide 0.5 mg/kg and mannitol 0.25 to 0.5 gm/kg 6 hourly act as additional agents to lower ICP. It has no role to play in decreasing the size of ventricles. Steroids (dexamethasone) 0.25 to 1gm/kg per day can be recommended for a short time in post infective hydrocephalus just to resolve the exudates in the prepontine and subarachnoid spaces. Controlled ventilation, without producing hypocarbia, can reduce ICP as well.

Surgical Interventions

Lumbar drainage

Tapping of CSF from the spinal subarachoid space can help in relieving ICP, particularly in communicating hydrocephalus. An lumbo-peritoneal shunt can be inserted in selected cases of hydrocephalus. Post tapping headache and tonsillar herniation can be sequelae of such procedures.

Ventriculo-peritoneal shunt (VP shunt)

The most accepted surgical procedure in the treatment of hydrocephalus is VP shunt. The CSF from the ventricles is drained via a silicon tube into the abdomen. A subcutaneous tunnel carries the shunt from the ventricle to the abdomen. At time ventriculoatrial shunt can be used to achieve the same target. As ventriculoatrial shunt may lead to hydrocephalus and endocarditis, hence, it has been abandoned by most neuro-surgeons.

VP shunt may require repeated revisions due to block, infection, or disconnection and can be associated with intestinal perforation, and cyst formations in the abdomen. Over drainage of shunt can lead to slit ventricle syndrome, subdural effusion and haematoma. One commonly used shunt in India is the Chhabra shunt. Flow regulated shunts (Medtronics) allow the controlled flow of CSF and are considered superior to other types of shunts.

The success rate of Chhabra shunt is 70% to 90%. It should be remembered that post-tubercular hydrocephalus can have associated vascilitis, cerebritis and brain oedema. All these associations can be a deterent of good recovery after a VP shunt.

Endoscopic third ventriculostomy (ETV)

ETV is an excellent procedure for hydrocephalus where internal shunting is done within ventricular system. An ostomy is made inside the third ventricle which drains CSF into the prepontine cistern bypassing the aqueductal obstruction. The procedure is simple and has no associated complications of shunt. The success rate varies from 60% to 100% depending upon the initial cause of hydrocephalus. ETV can be performed successfully in all types of hydrocephalus including post-tubercular and NPH.

Other endoscopic procedures include monroplasty, aqueductoplasty, stenting, and septostomy. Each of these procedures has its own indications. Choroid plexus fulguration (burning) can be done whenever there is excessive CSF production.

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20.18 Dementia

PS Mathuranath

INTRODUCTION

Some of the most complex functions performed by the brain are cognition and behavioural functions. The cognitive functions, which are commonly known as intellectual and cortical functions, would include many domains, such as memory, language, orientation, attention, praxis, executive functions (such as planning, logic, judgement, insight, abstract thinking, etc.), and calculation. Dementia is a term that is used to refer to a collection of symptoms, some of which are listed in **Table 1**, resulting from the derangement of cognition and/or behavioural brain functions due to diseases. By a broad definition, an acquired impairment in more than one of these functions, that progresses over time, resulting in a decline in the occupational and functional abilities of the subject, and is not related to or occurring exclusively during delirium. It is important to emphasise that, by definition, impairment in cognitive functions present since birth is not dementia.

Table 1: Symptoms that could Occur in Dementia

Cognitive Symptoms	Behavioural and Psychological Symptoms
Amnesia	Behavioural symptoms
Episodic amnesia	Agitation
Language impairment (Aphasia)	Irritability
Non-fluent aphasia	Anxiety
Fluent aphasia	Apathy/Indifference
Visuospatial disorientation	Disinhibition
Disorientation to time	Aberrant motor behaviour
Disorientation to place	Appetite and eating changes (food faddisms)
Apraxia	
Impaired calculation	Stereotypes
Impaired attention	Psychotic symptoms
Impaired executive functions	Delusions
Impaired judgement	Hallucinations
Impaired planning	Depression
Impaired insight	Euphoria/elation
Perseveration	Illusions

EPIDEMIOLOGY, CLASSIFICATION AND CLINICAL FEATURES

Dementia is largely a disease affecting the elderly. Its prevalence in those over 60 years of age ranges between 5% and 20% in the developed nations. Both prevalence and incidence of dementia nearly doubles every 5 years in the population above 65 years, reaching a prevalence of nearly 35% in those above 85 years. A simple classification of dementia based on the aetiology is shown in **Table 2**.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the commonest type of dementia. It usually occurs after the age of 65 years, and is, therefore, considered senile dementia. Increasing age, presence of the epsilon 4 allele of

Table 2: Classification of Causes of Dementia

Primary Degenerative Disorders
- Alzheimer's disease (AD)
- Frontotemporal degenerations (FTLD)
  - Frontal variant (fvFTD)
  - Primary progressive aphasia (PPA)
    - Progressive non-fluent aphasia
    - Semantic dementia (SD)
- Huntington's disease (HD)
- Lewy body dementias (LBD)
  - Dementia with Lewy bodies (DLB)
  - Parkinson's disease with dementia (PDD)
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)

Vascular Dementias†
- Multi-infarct dementia
- Subcortical arteriosclerotic encephalopathy (Binswanger's disease)
- Multiple subcortical lacunar infarctions
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)
- Amyloid angiopathy

Other Causes of Dementia

Infections
- Acquired immunodeficiency syndrome† (AIDS)
- Subacute sclerosing panencephalitis (SSPE)
- Progressive multifocal leucoencephalopathy (PML)
- Whipple's disease†
- Neurocysticercosis†
- Chronic meningitis†
- Neurosyphilis†
- Creutzfeldt-Jakob disease (CJD)

Metabolic/Nutritional
- Vitamin deficiencies† (Vitamin B12, thiamine, niacin)
- Thyroid disorders†
- Corticosteroid homeostasis†
- Chronic hepatic encephalopathy†
- Hypercalcaemia†
- Hypoparathyroidism
- Chronic renal failure and dialysis
- Wilson's disease†
- Lafora body disease
- Metachromatic leucodystrophy
- Adrenoleucodystrophy
- Spinocerebellar ataxias

Toxic and Structural
- Drugs†
- Alcohol†
- Heavy metals†
- Primary† and secondary tumours
- Paraneoplastic syndromes†
- Chronic hydrocephalus†
- Normal pressure hydrocephalus†
- Chronic subdural haematoma†

† Potentially reversible or preventable (partial list).

apolipoprotein E (Apo E ε4) on chromosome 19, female gender and Down's syndrome are well-established risk factors for AD. Although not convincingly established, low education, head injury in the past, homocysteinaemia, and a family history of dementia are also believed to increase risk for AD while use of nonsteroidal anti-inflammatory drugs (NSAIDs) and statins are believed to reduce the risk for AD. Neuronal loss and deposits of intraneuronal amyloid plaques and intercellular neurofibrillary tangles characterise the histopathology. The amyloid plaques consist of aggregates of Aβ42, which is the toxic degradation product of the amyloid precursor protein. The neurofibrillary tangles consist of aggregates of hyperphosphorylated tau proteins. Typically, AD presents with loss of memory for recently acquired information (episodic memory). Confabulation for the lost information is not uncommon. This is usually followed by disorientation to time and then place. As the disease progresses, other domains like language and praxis get involved. Remote memory acquired years before, often remains preserved till late stages. Variance in the clinical presentation can occur very rarely. These include an occipital variant presenting with visual symptoms, a temporal variant presenting with language impairment, and a frontal variant presenting with behavioural symptoms. Impairment of episodic memory, however, remains the central feature in all forms of AD. In early stages, there is very mild dependence for activities of daily living. In the moderate stages, patients become more and more dependent for activities of daily living and self-care with advancing loss of cognitive domains. In severe stages, they are almost completely dependent for all activities of daily living. The average duration from presentation to death could vary from 8 to 14 years.

FRONTOTEMPORAL LOBAR DEGENERATION

Unlike AD, frontotemporal lobar degeneration (FTLD) is a syndrome consisting of heterogeneous group of diseases. It is the commonest pre-senile dementia syndrome, and affects individuals 60 years of age or less, sometimes as young as 35 to 40 years of age. It represents a form of a focal lobar degeneration of the brain whose presentation is determined by the region of the brain maximally affected. Thus, broadly two variants of FTLD are recognised—the behavioural variant called the frontal variant of frontotemporal dementia (fvFTD), and the aphasic variant called the primary progressive aphasia (PPA). PPA could further be of two types, progressive non-fluent aphasia (PNFA) and progressive fluent aphasia or semantic dementia (SD) (**Table 2**). fvFTD is the commonest type of FTLD, that is characterised by loss of insight, dysexecutive syndrome and behaviour and personality changes that are either dominated by apathy or by disinhibition. PNFA and SD initially present with non-fluent or fluent aphasia, respectively and over time may progress to involve other frontal functions. No specific risk factors have been identified for FTLD so far. Mutations on the tau gene on chromosome 17 are seen in some of the familial forms of fvFTD, while mutations in progranulin gene on the same chromosome has also been shown to cause fvFTD. Pathology in these cases is often non-specific and variable and could include Pick bodies, ballooned neurons, and focal microvacuolation. The course is progressive and survival is shorter than that in AD.

OTHER DEGENERATIVE DEMENTIAS

These are degenerative diseases where dementia is a co-morbidity accompanying involvement of other systems in the nervous system usually manifesting with subcortical features like motor problems (Parkinsonism, ataxia, etc.) (**Table 2**).

Lewy body dementias (LBD) are senile dementias characterised pathologically by the presence of cortical and sub-cortical Lewy bodies which clinically manifests as progressive cognitive decline accompanied by symmetrical Parkinsonism. LBD is further classified into two subtypes—dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD). DLB is clinically characterised by progressive memory loss, with bilateral appendicular akinetic-rigid parkinsonism occurring within one year before or after. Other characteristic features include visual hallucinations, and significant fluctuations of symptoms. Pathology shows loads of cortical Lewy body. PDD is characterised by onset of dementia in a patient with Parkinson's disease. The most consistent risk factors for PDD in patient's with Parkinson's disease include higher age, more severe parkinsonism (particularly rigidity), presence of postural instability and gait disturbance and presence of some mild cognitive disturbance at the time of onset of Parkinson's disease.

Corticobasal ganglionic degeneration (CBD) is a pre-senile dementia where asymmetrical Parkinsonism is usually accompanied by progressive cognitive deficit, alien limb phenomenon, apraxia, and often acalculia. Dementia is also a feature of progressive supranuclear palsy (PSP), which is characterised by bilateral parkinsonism with axial rigidity, frequent falls, eye-movement abnormalities, particularly vertical (up and down) gaze palsy, and pseudobulbar palsy. Huntington's disease (HD), which is linked to chromosome 4, is characterised by behavioural and personality changes which occurs along with chorea. Dementia is an accompaniment in some of the spinocerebellar ataxias (SCA).

VASCULAR DEMENTIA

Vascular dementia (VaD) is also a syndrome where the dementia is a result largely of clinically overt or covert cerebrovascular insults to the brain. Thus, it could result from many mechanisms (**Table 2**). The area of the brain insulted, dictates the clinical presentation and manifestations. Presence of cerebrovascular risk factors (like hypertension, diabetes, hypercholesterolaemia, history of strokes, or myocardial infarctions, etc.) in history and subcortical features (motor deficits, urinary incontinence, release reflexes, etc.) on examination are common in vascular dementia. Neuroimaging as well as histopathology show evidence for lacunar, infarcts or leucoareotic changes.

OTHER CAUSES OF DEMENTIAS

Many other diseases could also result in dementia. They are listed in **Table 2**. The dementia in many of these conditions is either partially or fully reversible with timely and appropriate intervention. Thus, early diagnosis is the key to the management of dementia in such conditions. Some of the common and typical conditions are briefly described below.

Infections and Toxins

AIDS-dementia complex (ADC) is probably the most significant one in this category. It occurs in the late stages of AIDS and probably represents the end stage of the disease. Extensive neuronal infiltration by the HIV is thought to be the cause for it and response to antiretroviral agents is limited. Before the advent of ADC, neurosyphilis was perhaps the most significant

infectious cause for dementia. Dementia is seen in both, meningovascular syphilis and in general paresis of insane. While the former presents with sensorial and cognitive changes, the latter usually presents with behavioural changes. Its importance lies in early diagnosis of the condition as both the conditions are eminently treatable and dementia can be reversed. Chronic meningitis, especially tubercular, could rarely present with dementia. Creutzfeldt-Jakob disease (CJD), a prion disease, is a less common cause of dementia in the elderly that is rapidly progressive and results in mortality in 12 to 18 months. Neurocysticercosis, a parasitic infection and subacute sclerosing panencephalitis, a late sequel of childhood measles infection, are causes of dementia seen in the younger age groups. Yet another common situation that could masquerade as dementia, especially in the elderly, is the multitude of medication-related effects due to drugs that they may be taking for comorbid conditions. In particular these are CNS depressants like benzodiazepines, conventional antipsychotics, and anticholinergics.

Metabolic and Nutritional Diseases

Vitamin B12 deficiency is associated with progressive psychosis and subtle cognitive and often behavioural impairment, especially in the malnourished population. Although the cause-effect relationship with dementia is ill-established, treatment of the condition has been shown to reverse some of the symptoms. Pellagra presents with dementia and dermatitis and is mostly seen in the malnourished and the alcoholics. It is an eminently treatable condition. Hypothyroidism and many of the endocrine, liver and renal diseases can have dementia as one of the manifestations. Appropriate treatment often helps in reversing the dementia. Wilson's disease is yet another potentially reversible cause of dementia in the younger age group.

Structural Diseases

Normal pressure hydrocephalus (NPH) is a typical example. NPH presents in the elderly with urinary incontinence, gait apraxia and dementia and responds to ventriculo-peritoneal shunting. Subdural haematomas following subtle falls and midline brain tumours such as, paramedian meningiomas can occur in the elderly and manifest as dementia. They are effectively treated surgically if diagnosed early.

EMERGING CONCEPTS IN DEMENTIA

Mild cognitive impairment (MCI) is thought to be the condition preceding overt manifestation of dementia. Amnestic variety of MCI, the most investigated form of MCI, is characterised by the presence of memory symptoms, objective memory impairment on testing, and relative preservation of other cognitive domains, activities of daily living, and occupational abilities. Most subjects with amnestic MCI have been shown over time to progress to AD. Vascular cognitive impairment (VCI) is a condition similar to MCI, but with associated vascular risk factors. Thus, VCI could be expected to progress to VaD. The importance of being able to define and diagnose such conditions is that they can help in early diagnosis of dementia and, therefore, provide an opportunity for effective intervention. It must be emphasised, however, that our understanding of these conditions is still preliminary.

APPROACH TO DIAGNOSIS

Figure 1 illustrates an algorithmic approach to dementia. Delirium and depression are the commonest conditions that could be mistaken for dementia. Delirium is characterised by sensorial, motor and autonomic hyper- and/or hypo-activity, which distinguish it from dementia. Depression, which could precede or be comorbid with dementia, is a more difficult condition to differentiate from dementia. Fluctuation over a period of time, a global impairment across many cognitive domains, and frequent 'do not know' answers on neuropsychological tests helps to differentiate depression from dementia. The next step will be to review the comorbid conditions and the medications that the patients may already be taking. The final step is to establish progression of the symptoms over time and impairment of activities of daily living. Once dementia is diagnosed, risk factors should be identified, and the type of dementia characterised following the steps shown in the algorithm.

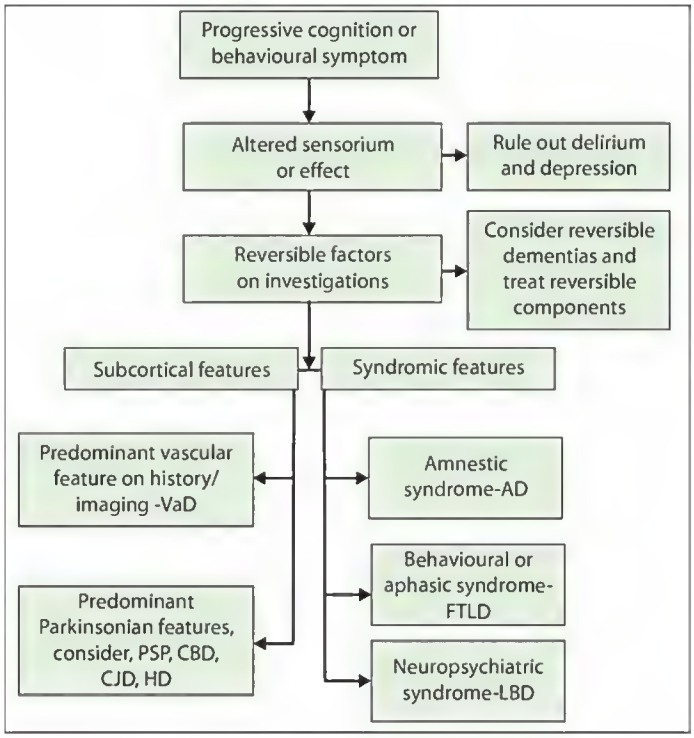


Figure 1: Algorithm for approach to diagnosis of dementia.

INVESTIGATIONS

The purpose of investigations in dementia is three-folds to confirm diagnosis, type, impairment, and severity; to look for partially or completely reversible aetiologies and comorbidities; and to gather information for appropriate treatment and rehabilitation and to follow-up. In addition to the standard tests, many other investigations could also be done aimed at specific aetiological causes that may be suggested by the history and clinical examination. A brief discussion on the major recommended investigations is provided below.

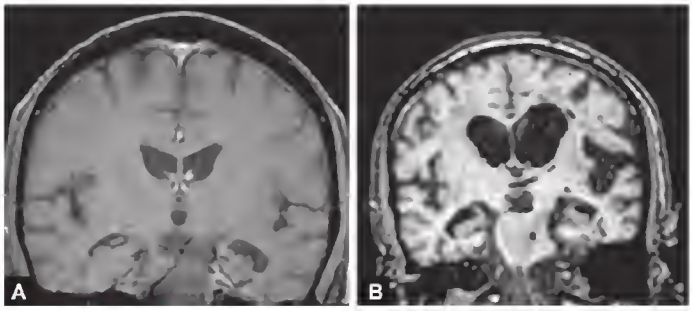
Blood Investigations

Haemogram and peripheral smear to look for anaemia, vitamin B12 deficiency, markers of acute/chronic infections and malignancies; renal and liver function tests to rule out acquired metabolic causes of dementia; thyroid functions and serum

calcium and phosphorus levels for endocrinal causes of dementia, serum VDRL, and serum vitamin B12 assay complement the evaluation of all patients with dementia.

Neuroimaging

A plain and contrast-enhanced CT scan of the head is sufficient in most cases to visualise tumours, CNS infections and major infarcts. MRI of the brain is finding an increasing role in the classification of degenerative and vascular causes of dementia (**Figures 2A and B**). It is also useful in the diagnosis of infectious causes of dementias.



Figures 2A and B: (A) Coronal MRI sections of Alzheimer's disease showing hippocampal atrophy and (B) primary progressive aphasia showing asymmetrical temporal neocortical atrophy resulting in widened Sylvian fissure on that side.

Electroencephalography (EEG)

Although not mandatory, EEG is a useful investigation in atypical or rapidly progressive forms of dementias like CJD.

Cerebrospinal Fluid Examination (CSF)

Like EEG, CSF examination through a lumbar puncture is presently not mandatory but useful in detecting covert, but reversible causes of dementia such as chronic neuroinfections. However, with increasing research for CSF biomarkers, such as CSF-tau and CSF-amyloid β protein in degenerative dementia like AD; it may become a mandatory investigation in future for the diagnosis and classification of dementias.

Neuropsychological Tests

A battery of neuropsychological tests for memory, orientation, language, visuospatial skill, etc. help in quantifying the impairment through standardised methods and minimise the subjective element involved in the clinical diagnosis of dementia. They also help in typing and staging the disease, planning the rehabilitation and following up the progress. Like any other investigation, it requires technical expertise of trained psychologists in administration of tests and interpretation of results. Mini-mental status examination is a useful bedside screening test for dementia.

MANAGEMENT

There are four basic principles in the management of dementias: treat all reversible causes and potentially treatable comorbidities; disease modifying pharmacological treatment; symptomatic pharmacological treatment; and non-pharmacological management and family counselling.

Removing potentially offending drugs, such as, anticholinergics and CNS depressants in the existing prescription, promptly treating infections, metabolic and electrolyte derangement and nutritional deficiencies and addressing comorbidities, such as depression, constitute the most important steps in the treatment. Disease modifying pharmacotherapy with appropriate agents in cases of reversible dementias (e.g. antituberculosis therapy in chronic tubercular meningitis presenting with progressive cognitive decline) is imperative. Disease modifying treatment for degenerative dementias are still under research and may become available in the near future.

In degenerative dementias, currently the essence of treatment is judicious use of symptomatic pharmacological treatment. They are broadly of two types—cognitive symptom-modifying agents that have been shown to slow down the disease progression and agents useful for the behavioural and psychological symptoms of dementia (BPSD). There are many agents useful in treating the cognitive symptoms and currently atypical antipsychotics are the ones usually recommended in the treatment of BPSD. Some of these agents are listed in **Table 3**.

The non-pharmacological measures include environment modification and counselling. Personal and extra-personal environment modifications are important since majority of dementia patients are older individuals. Personal environment modifications include minimising sensory deprivation (treat earwax and cataract, provide hearing aids), practical advise on avoiding falls and fractures, exercising caution in prescribing drugs (as dementia patients may be highly sensitive to many CNS active drugs when used in standard doses), treating constipation, maintaining personal hygiene (including oral and dental), ensuring adequate undisturbed sleep at night, etc. Extra-personal environmental modifications include clean-levelled flooring, well-lit rooms and toilets, grab-rails in toilets, rooms and stairways, regularising meal and sleep timings, etc. Many other forms of therapy, such as reality therapy, cognition therapy, reminiscence therapy, music therapy, behaviour-modification therapy, etc. may also have a role to play.

Family counselling for dealing with dementia patients and their maladaptive and aggressive behaviour is an important aspect of the management. Since caring for a patient with dementia is a stressful activity and the carers are more likely to be untrained family members than professionally trained carers, attending to the needs and minimising the stress of the caregiver constitutes an important activity in facilitating the management of the patient. Counselling should also include advice to the patient and family on the need for organising financial (e.g. operating joint bank accounts) and legal (e.g. making a will or power of attorney) issues since the patients with dementia could progressively lose the ability to manage their own affairs or make competent judgment.

There are two broad models of care in dementia. Home-based care model is useful in mild or moderate dementia. This can be supported by clinic care (visit to the doctors), respite care at home (when professional carers relieve the carer in the family for some time by taking over the care responsibilities) and day-care centre (when respite care is provided during a part of the day by a professionally run centre where the patient can be sent). The other is the community-based care model, which is

Table 3: Some Pharmacological Agents Useful in the Management of Dementia

Agents	Action/Type	Current Recommendations
Useful for cognitive symptoms		
Donepezil hydrochloride	Acetylcholinesterase inhibitor	Useful in all stages of dementia. Started at 5 mg/day and increase to 10 mg/day after 4–6 weeks
Rivastigmine	Acetylcholinesterase and butyryl-cholinesterase inhibitor	Useful in early and moderate stages. Started at 1.5 mg and increased every 3–6 weeks by 1.5 mg up to a maximum of 12 mg/day
Memantine	NMDA receptor antagonist	Useful in moderate and advanced stages Usually used as an add-on therapy. Started at 5 mg/day and increased by 5 mg every 3–6 weeks to 10 mg twice per day
Galantamine	Nicotinic receptor agonist	Useful in moderate and advanced stages. Usually used as an add-on agent. Initiated at 8 mg/day and increased every 4 weeks up to 24 mg/day
Useful in BPSD		
Quetiapine	Strong 5-HT_2 and D_2 blocker	Useful in delusions, hallucinations, aggression etc. Initiated at 25 mg/day and gradually increased by 25 mg up to a maximum dose of 400 mg
Olanzapine	Moderate D_2, 5-HT_2 and Muscarinic M1 blocker	Useful in delusions, hallucinations, aggression, etc. Initiated at 2.5 mg/day and can be increased up to 10 mg/day
Risperidone	5-HT_2 and D_2 receptor blocker	Useful in delusions, hallucinations, aggression etc. Initiated at 0.5 mg/day and can be increased up to 2 mg/day
Clozapine	Moderate D_2, 5-HT_2 and strong muscarinic M_1 blocker	Useful in delusions, hallucinations, aggression, etc. Should be used only in recalcitrant case. Initiated at 6.25 mg/day and increased by 6.25 mg once a week up to a maximum of 50 to 100 mg/ day
Escitalopram	Short-acting SSRI	Useful in depression, stereotype, etc. Initiated at 2.5 mg/day and increased up to 10 mg /day
Clonazepam	Short-acting benzodiazepine	Useful in anxiety, insomnia, aggression etc. Initiated at 0.25 mg/day and increased up to 2 mg/day.

useful for patients with advanced dementia, who are difficult to manage without constant medical or para-medical supervision. Thus, this involves institutionalisation of the patients at professionally run institutions that have adequate medical support.

THE INDIAN SCENARIO IN DEMENTIA

Increasing population and life-expectancy in India is resulting in an increase in the individuals at risk for dementia. Urbanisation, migration of the youth, and fragmentation of joint families in India is increasing the cognitive stress and decreasing the support to the growing number of people at risk for dementia and, thereby, perhaps increasing its incidence. Population-based studies from different parts of the country have shown that the prevalence of dementia (and AD) in those ≥60 years of age ranges from 0.8% (and 0.1%) in rural North India to 3.5% (and 1.31%) in urban South India. An increasing prevalence with advancing age has also been demonstrated by Indian studies. The only incidence data available so far is from rural north India, which is reported to be 4.7 per thousand person years. Data from most population-based studies suggest that AD is the commonest cause of dementia in India. Published hospital-based audits suggest, however, that patients with vascular dementia seem to be seen in the tertiary care hospitals more often than any other form of dementia. The prevalence of AD has been shown to be higher in women (1.8%) as against that of men (0.7%) in most studies. Prevalence rates were not very different in the illiterates and the literates in Indian studies, thus not supporting low education as a potential risk factor. Although the frequency of ApoE ε4 allele was lower in the Indian population, the risk of AD conferred by it in Indians (odds ratio 3.4) has been found to be comparable to that in the Western population.

Studies from Western India have suggested that there is low awareness of this condition in the population and in health professionals. Unpublished data from some of the tertiary care hospitals with specialised dementia care suggest that there is perhaps a higher frequency of psychosis in Indian patients when compared to western patients with AD. They have also shown that unlike in the west, the majority of the carers of dementia patients in India are family members, usually the spouse or the daughter-in-law. Furthermore, there is also evidence that the burden of care perceived by the carers of dementia patients in India is relatively lower than those of the patients in many western nations. While home-care model is popular and perhaps more widely practiced in India, availability of institutions providing day-care respite or community-care models are almost non-existing, thereby putting families with advanced dementia patients under severe duress. Availability of professional respite care providers is also scanty.

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20.19 Extrapyramidal Disorders

BS Singhal

Extrapyramidal disorders relate to dysfunction of the basal ganglia. They result in disturbance of movement and posture without significant paralysis. The term 'movement disorders' is often used synonymously with extrapyramidal or basal ganglia diseases.

Movement disorders can be broadly divided into akinetic rigid syndromes (Parkinsonism) in which there is paucity of movement (akinesia or bradykinesia) often accompanied by an increase in muscle tone (rigidity) and hyperkinesias or dyskinesias which are associated with excessive abnormal involuntary movements (**Table 1**).

Table 1: Classification of Extrapyramidal Disorders

Akinetic rigid syndromes	
Idiopathic Parkinson's disease	
Secondary Parkinsonism (definable cause)	
Drugs	Phenothiazines, haloperidol, pimozide, metoclopramide, reserpine, lithium
Toxins	Manganese; 1-methyl, 4-phenyl tetra-hydropyridine (MPTP); carbon disulphide
Hypoxia	Carbon monoxide, cyanide
Viral	Encephalitis lethargica, Japanese B encephalitis, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis
Vascular	Atherosclerosis
Metabolic	Wilson's disease, hypoparathyroidism, GM1 gangliosidosis
Head injury	Punch-drunk syndrome
Brain tumour	
Parkinson-plus syndromes	
Progressive supranuclear palsy	
Multiple system atrophy (olivopontocerebellar atrophy, Shy-Drager syndrome, striatonigral degeneration)	
Corticobasal degeneration	
Diffuse Lewy body disease	
Familial basal ganglia calcification	
Huntington's disorder (juvenile variant)	

IDIOPATHIC PARKINSON'S DISEASE (PARALYSIS AGITANS)

This is the most common akinetic rigid syndrome. Parkinson's disease (PD) affects 1% of adults over the age of 60 years, with increasing frequency in older age groups. It affects both sexes equally.

Clinical Features

The symptoms start insidiously and tend to be unilateral or asymmetrical at the onset. The initial manifestations may be tremor, slowness, stiffness or clumsiness of an arm or, less commonly, of a leg.

Tremor, rigidity, akinesia and postural disturbances are the major clinical abnormalities. The tremor has a frequency of 4 to 6 Hz, is present mainly at rest (resting tremor) and is suppressed on voluntary movement. Distal muscles are affected more than the proximal, and the rhythmic tremor at the wrists and fingers has been termed 'pill-rolling' tremor. It disappears during sleep and is aggravated by emotional excitement or fatigue. This tremor may also be seen in the legs or lower jaw. Some patients also have fast action tremor at 8 to 12 Hz, mainly on sustained posture or action.

Akinesia and rigidity result in significant impairment of movement. There is lack (akinesia) or paucity (bradykinesia) of movement. Rigidity is present over the entire range of movement (lead-pipe rigidity). The face is expressionless ('mask-like'). Glabellar tap is often positive. There is a generalised slowing of motor activity. Motor acts like dressing, feeding and walking show a marked slowing. All recreational and work tasks, household chores and self-care functions become impaired. Handwriting becomes smaller (micrographia) and eventually may become illegible. Rapid, repetitive and alternating movements, such as finger-tapping, opening and closing of the fist, pronation-supination of the forearm and foot-tapping are performed slowly and clumsily. The combination of tremor and rigidity gives rise to 'cog-wheeling,' which is best appreciated on passive slow rotatory movement of the wrist.

The voice becomes soft (hypophonic), monotonous and stuttering, and the speech is more rapid than normal. In advanced cases, the speech is barely more than a mutter. Increased salivation and seborrhoea (greasy skin on face and forehead) are commonly seen but early and prominent bulbar symptoms suggest Parkinson-plus syndrome.

Postural instability and gait difficulty are a major problem in PD. The head usually tilts forwards and the body becomes stooped, often with pronounced kyphosis. The arms become flexed at the elbow and wrists. Flexion also occurs in the joints of the legs (**Figure 1**). A tonic extension of the great toe (striatal toe) has often been misinterpreted as an extensor plantar response. Rising from a sitting position may take several attempts, with frequent fall back into the chair. To assess postural instability, the physician performs the pull test. There is retropulsion.

The gait is slow and shuffling. With asymmetric involvement of lower limbs, there could be a noticeable limp. The associated arm swing is reduced. Patients may have a tendency to advance rapidly with short steps (festinating gait) as though they are chasing their centre of gravity. Sometimes, the feet may appear to be glued to the floor, the so-called freezing phenomenon. When combined with postural instability, freezing may result in forward falls. This is a late feature and its early occurrence suggests a diagnosis other than true Parkinson's disease. The salient clinical features are summarised in **Table 2**.

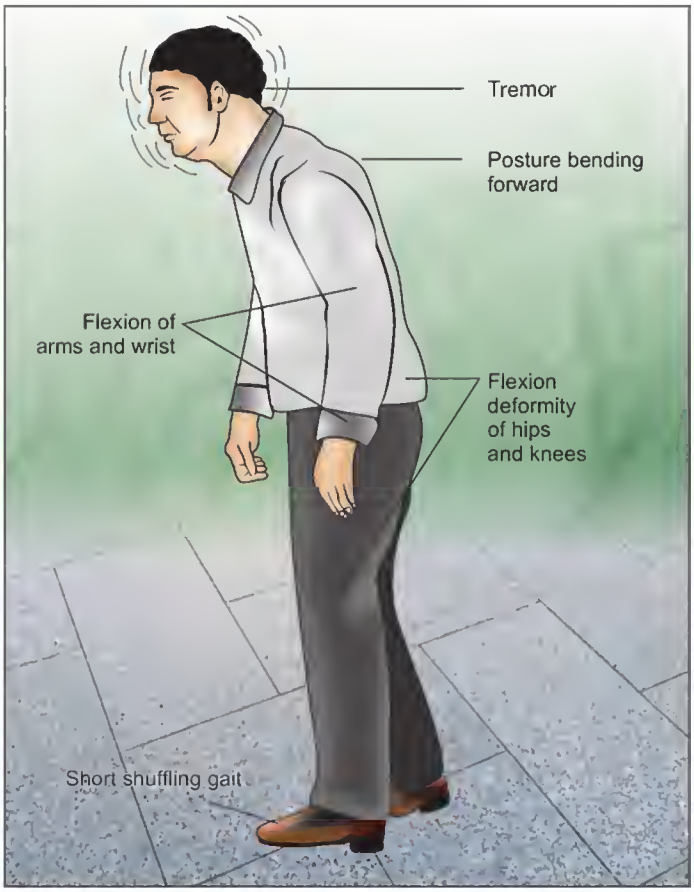


Figure 1: Typical posture of Parkinsonism.

Table 2: Parkinsonism - Clinical Features

Mask face
Slurred, indistinct speech
Festinant gait, stooped posture
Tremors—resting or postural
Rigidity—lead pipe or cog wheel

Non-motor symptoms

Although PD is recognised mainly by its motor manifestations, Non-motor symptoms (NMS) are also frequently encountered and can significantly impact the quality of life of PD patients.

NMS include autonomic and sensory disturbances, depression, anxiety, cognitive impairment and sleep disturbances.

Autonomic and sensory disturbance

Autonomic dysfunction, such as constipation, frequency of micturition and nocturia, and mild to moderate degree of orthostatic hypotension may occur. Anti-parkinsonian medications aggravate orthostatic hypotension. If autonomic features are very prominent and early, one must consider the possibility of Shy-Drager syndrome.

Subjective sensory dysfunction such as undefined muscle pain, abdominal discomfort, dysaesthesia in feet and painful neck movements, may be present.

Mood and cognitive disturbances

Depression and anxiety are frequently seen in Parkinson's disease and they often coexist. They significantly affect the quality of life in Parkinson's disease patients and must be appropriately treated.

Cognitive disturbances suggestive of frontal lobe dysfunction are common. Frank dementia is uncommon, and its presence in the early stages suggests conditions like Alzheimer's disease and multi-infarct dementia.

Sleep disturbances are common in PD. Fragmented sleep and REM sleep behaviour disorder (RBD) may precede or follow the onset of PD. Sleep disturbances lead to excessive daytime sleepiness and poor daytime functioning.

Pathology

The most consistent pathological finding is degeneration of the nigrostriatal tract. The degenerating neurons contain Lewy bodies. Though seen in other conditions, Lewy body is a highly sensitive marker for PD. Besides the nigrostriatal tracts, PD also affects other parts of the brain like the olfactory centre, lower brainstem, thalamus and cerebral cortex.

Neurotransmitters

Depletion of the dopaminergic neurons of the substantia nigra results in reduction of striatal dopamine, which is thought to be the main biochemical abnormality in PD. Normally equilibrium exists between acetylcholine and dopamine. With dopamine deficiency, there is acetylcholine hyperactivity; this may be a mechanism for parkinsonian symptoms. Norepinephrine, serotonin, somatostatin, substance P, and the enkephalins are also found to be depleted in varying degrees. Freezing has been attributed to degeneration of the noradrenergic pathways from the locus caeruleus. Depression may be related to reduced production of serotonin in the raphe nuclei. Degeneration of cholinergic neurons in the nucleus basalis of Meynert may be responsible for the dementia.

Aetiology

The cause of PD is not known. Environmental factors have been implicated. MPTP, a toxic product of heroin, was found to cause an acute clinical syndrome which was identical to PD, possibly even with formation of Lewy bodies. Chronic exposure to an MPTP-like toxin in the environment has been suggested. In Guam, Parkinsonism - ALS - dementia complex has been linked to the intake of cycad plant. Genetic factors may play an important though poorly understood role.

Disturbances in oxidative phosphorylation are seen, particularly a reduction in the activity of complex I of the mitochondrial electron transport chain. Free ion levels which may lead to formation of toxic free radicals are also increased. With normal aging, the population of viable nigral neurons gradually diminishes. Ageing may thus play a contributory role.

Genetics of PD

Although PD usually occurs sporadically, families with autosomal dominant and autosomal recessive PD have been identified, especially among patients with an early onset of disease.

The first gene mutation linked to PD was the gene for the protein alpha synuclein (SNCA) labelled PARK I. Since then, many other genes linked to PD have been identified. Mutation of the leucine rich repeat kinase 2 (LRRK2) gene is common in autosomal dominant PD. Mutation of the Parkin gene is

commonly associated with early onset autosomal recessive Parkinsonism (PARK2). These patients have a higher proportion of dystonia, hyperreflexia and severe treatment-related motor complications.

Investigations

Conventional laboratory studies do not help in the diagnosis of PD. Computed tomography (CT) and magnetic resonance scans are normal or show only variable degrees of atrophy.

Imaging

Positron emission tomography (PET) scans using fluoro-deoxyglucose (FDG) or dopamine transporter (DAT) and single photon emission computed tomography (SPECT) scans have been used to study dopaminergic terminals and help to differentiate PD from other Parkinson's plus syndromes.

Treatment

Pharmacotherapy is the mainstay of management. However, at every stage of the disease, the role of exercise and physiotherapy should be emphasised. The stiffness and slowness of movement require graded exercises-walking, fixed-bicycle or fixed-wheel exercises and deep breathing. **Table 3** lists the commonly available drugs used in the treatment of Parkinson's disease.

Table 3: Currently Available Drugs for Treatment of Parkinson's Disease

Drugs	Average Daily Dose Range	Side Effects
Levodopa preparations		
Carbidopa/levodopa [10/100;25/100;25/250]	300 to 1000 mg (of levodopa)	Anorexia, nausea, vomiting, agitation, confusion, psychosis, postural hypotension, arrhythmias, dyskinesias
Benserazide/levodopa [25/100; 12.5/50]	600 to 800 mg (of levodopa)	
Controlled-release carbidopa/levodopa [50/200]	200 to 800 mg (of levodopa)	Gastrointestinal and cardiac side effects are less with addition of decarboxylase inhibitors (carbidopa, benserazide)
Amantidine	100 to 200 mg	Anorexia, confusion, psychosis, pedal oedema, livedo reticularis
Anticholinergics		
Trihexylphenidyl	4 to 8 mg	Dry mouth, blurred vision, sphincter disturbances, psychosis, palpitations, nausea, vomiting
Procyclidine	7.5 to 15 mg	
Benztropine	1.0 to 1.5 mg	
Dopamine agonists		
Bromocriptine	5 to 10 mg	Nausea, vomiting, postural hypotension, psychosis, confusion
Ropinirole	3 to 12 mg	Hallucinations, cognitive decline
Pramipexole	1.5 to 4.5 mg	Somnolence, does not have ergot like side effect of bromocriptine
Apomorphine (subcutaneous injection)	1 to 6 mg	Nausea, vomiting, confusion, psychosis
COMT inhibitors		
Entacapone	400 to 800 mg	Diarrhoea, may aggravate dyskinesias, discoloured urine
Tolcapone	200 to 400 mg	Diarrhoea, dyskinesias, hepatotoxicity
MAO-B inhibitor		
Selegiline	5 to 10 mg	Hallucinations, confusion, postural hypotension
Rasagiline	0.5 to 1 mg	Somnolence, giddiness, orthostatic hypotension

Treatment of early PD

Levodopa combined with decarboxylase inhibitor (carbidopa or benserazide) is the most effective anti-parkinsonian drug. Most motor symptoms respond well to levodopa. However, the long-term side-effect of levodopa include motor fluctuation (shortened duration of benefit of each dose) and dyskinesias (involuntary movement). Hence, in the early stage of the disease, it is better to delay the use of levodopa and initiate treatment with other drugs like selegiline or amantidine or the newer dopamine receptor agonists (pramipexole or ropinirole). This is even more applicable when the onset of PD occurs at a younger age. The use of anticholinergic drug like trihexyphenidyl should be restricted only to young-onset PD patients with significant tremors. In PD patients over the age of 70 years, treatment should be started with levodopa. The golden rule for all anti-parkinsonian drugs is 'start low and go slow'.

On-off phenomenon

With prolonged use of L-dopa, as the disease progresses, one faces the problem of severe dyskinesia and on-off phenomenon, where the patient switches from a mobile state with aggravated dyskinesia to a helpless akinetic state.

Apomorphine is a dopamine agonist which has a rapid onset of action (5 to 10 minutes) and can 'revive' a patient from the akinetic spell. It is given subcutaneously.

New anti-Parkinson's drugs

Newer anti-Parkinson's drugs are available for patients in whom conventional drugs either are ineffective or have adverse side effects.

Dopamine receptor agonists

Besides the commonly used bromocriptine, the new dopamine agonists include ropinirole and pramipexole. Both of them are non-ergot compounds, hence the ergot related side effects of bromocriptine do not occur. Both of them have been found to be effective either as monotherapy in early onset Parkinson's disease (prior to starting levodopa) or as adjunctive therapy to levodopa in advanced Parkinson's disease. The incidence of somnolence in pramipexole treated patients is reported to be higher than patients on other drugs.

Catechol-O-methyl transferase (COMT) inhibitors

Tolcapone and entacapone are the COMT inhibitors used in Parkinson's disease. By inhibiting the COMT enzymes, which metabolise levodopa in the gut and liver, they increase the levels of levodopa in the brain and prolong the efficacy time of a levodopa dose. Entacapone is the COMT drug commonly used as reports of hepatotoxicity with tolcapone have restricted its use in clinical practice.

Rasagiline

This is new MAO-B inhibitor. It has been shown in clinical trials to be effective in early onset PD as well as in the later stages of disease.

Treatment of specific symptoms

Action tremor: The following drugs can be used: propranolol, primidone, and benzodiazepines, particularly diazepam, in the same way as for essential tremors.

Orthostatic hypotension: The following measures are employed—review of the drug regime, salt and fluid repletion, elevation of the head end of the bed; this promotes sodium retention and reduces nocturnal diuresis, elastic stockings, use of drugs like indomethacin, clonidine and propranolol, and if severe, one may have to use mineralocorticoid (fludrocortisone) starting at 0.1 mg daily. Sudden change of posture and prolonged standing should be avoided.

Depression: The treatment is usually initiated with a serotonin-reuptake blocker - fluoxetine 20 mg once daily or sertraline 50 mg once daily increasing to 100 mg twice daily. Tricyclic anti-depressants like amitriptyline may also be used.

Psychosis: Bromocriptine, amantidine, anticholinergics, selegeline and levodopa may all cause psychosis. Visual hallucinations are common.

Antiparkinsonian drugs are slowly discontinued, beginning with selegeline followed by anticholinergics and then dopamine agonists. The dose of L-dopa could also be reduced if required. Antipsychotic medication may have to be given. Phenothiazines and butyrophenones are not used as they increase the parkinsonian state. Newer atypical drugs used to treat hallucinations and psychosis in PD include clozapine, risperidone, olanzapine and quetiapine.

Clozapine is a new antipsychotic with the least extrapyramidal side effects. It is started as 12.5 mg at bedtime and slowly increased. Important side effects are agranulocytosis and sedation.

Sialorrhoea: Centrally acting anticholinergics like trihexiphenidyl can reduce saliva production and ameliorate other aspects of PD. If the central side-effects of these drugs prove intolerable, a peripherally acting anticholinergic agent like propantheline (15 to 30 mg 6 hourly) is helpful.

Constipation: It occurs in 80% of patients with PD. It is exacerbated by anticholinergics. These should be withdrawn if possible. A high-fibre diet is recommended. Bulk-forming agents like dietary fibre and stool-softening agents like dioctyl sulphsuccinate may be given. Cisapride has been found to speed colonic transit and ameliorate constipation.

Freezing: There are no suitable medicines to treat this symptom. Low-obstacle visual cues and rhythmic routines may minimise freezing episodes.

Advanced Parkinson's disease

Advanced PD is characterised by two types of motor fluctuations: (1) wearing off, in which the duration of benefit of each levodopa dose becomes progressively shorter, and (2) dyskinesias, characterised by abnormal involuntary movements of the face, trunk and limbs during the 'on' phase. Besides careful adjustment of PD drug dosages, two procedures may be of benefit in advanced PD.

1. Surgery – Deep brain stimulation (DBS).
2. Continuous enteral infusion of levodopa (Duodopa).

Surgery in Parkinson's disease

Stereotactic surgical procedures are nowadays being increasingly used for advanced Parkinson's disease with severe on and off phenomena and disabling dyskinesias in which medical therapy has failed to provide relief.

The procedures currently employed are ablative procedures like thalamotomy and pallidotomy and also DBS. Subthalamic nucleus stimulation (STN stimulation), globus pallidus stimulation (GPI stimulation) and ventral intermediate (VIM) thalamic nucleus stimulation are all different types of DBS procedures.

The above procedures require neurosurgeons with expertise in stereotactic techniques. Thalamotomy directed to the VIM nucleus is indicated for asymmetric, severe medically intractable tremor. Unilateral pallidotomy is indicated for advanced Parkinson's disease with motor fluctuations and drug induced dyskinesias along with significant bradykinesia and rigidity. Bilateral pallidotomy may have unacceptable side effects.

DBS of VIM thalamic nucleus is an alternative to thalamotomy for severe contralateral tremor in Parkinson's disease and essential tremors.

DBS of subthalamic nucleus is very effective. It is the surgical procedure of choice in many centres. It has been found effective in reducing almost all motor manifestations of PD with a high safety profile. DBS procedures are expensive.

Human foetal mesencephalic cell transplants have been tried in idiopathic Parkinson's disease who are poorly controlled with medicine and have motor fluctuations. Clinical trials have failed to establishes efficacy of this procedure and are currently not recommended in PD.

Continuous Enteral Infusion of Levodopa

In patients with advanced PD in whom DBS is not possible or is refused, the option of duodopa can be given to them. This is levodopa in a gel form which is infused continuously by a pump at a constant rate directly into the small intestine through a jejunostomy tube. Continuous enteral infusion has proved beneficial in reducing motor complications of advanced PD.

ATHEROSCLEROTIC PARKINSONISM

In patients with multi-infarct state, especially lacunar infarcts, some features of Parkinsonism may be present. Gait disturbance and freezing can be a prominent feature.

POSTENCEPHALITIC PARKINSONISM

Between 1916 and 1927, there was a worldwide epidemic of encephalitis lethargica. One-third of the patients were left with chronic neurological deficits, the most common being Parkinsonism. Parkinsonism was seen at any time from the acute stage of encephalitis to over 20 years later. Besides parkinsonian features, oculogyric crises were a common and unique phenomenon of the disease. Various forms of dystonia, chorea, myoclonus, pyramidal signs, behavioural changes and sleep-cycle alterations were also present. Sporadic cases of postencephalitic Parkinsonism continue to occur even today.

Other viral encephalitis like Japanese B encephalitis may be associated with Parkinsonism.

PARKINSONISM-PLUS SYNDROME

Atypical features, such as absence of tremor, early gait and postural abnormality, additional neurologic deficits and poor response to L-dopa suggest that the patient may not have idiopathic PD. The additional neurologic abnormalities are supranuclear ophthalmoparesis (progressive supranuclear palsy), dysautonomia (Shy-Drager syndrome), ataxia (olivopontocerebellar atrophy), laryngeal stridor (striatonigral degeneration) and dementia (diffuse Lewy body disease).

PROGRESSIVE SUPRANUCLEAR PALSY (PSP) (STEELE-RICHARDSON SYNDROME)

The patients present with frequent falls, axial and nuchal rigidity, and pseudobulbar symptoms like dysarthria and dysphagia. Tremor is usually absent. The pathognomonic feature is vertical supranuclear gaze palsy. The patients have fixed stare and poor convergence. In later stages horizontal gaze is also affected.

MULTIPLE SYSTEM ATROPHY (MSA)

MSA encompasses three entities, viz. Shy-Drager syndrome, striatonigral degeneration (SND) and olivopontocerebellar atrophy (OPCA). In the Shy-Drager syndrome autonomic disturbances in the form of orthostatic hypotension, sphincter disturbance and impotence predominate. In SND, besides the parkinsonian features the patients have laryngeal stridor and pyramidal features. Rest tremor is usually absent and findings are usually symmetrical. Cerebellar signs are most prominent in the OPCA variety of MSA.

PARKINSONISM-DEMENTIA-AMYOTROPHIC LATERAL SCLEROSIS COMPLEX

The disease complex was largely prevalent among the Chamorro population of Guam Islands. Besides parkinsonian features and progressive dementia, the majority of patients also have motor neuron disease. The aetiological hypotheses include a toxic agent from the cycad plant and disturbance in minerals like calcium and magnesium.

HYPERKINETIC MOVEMENT DISORDERS

Dystonia

Dystonia tumor and myoclonus is explained in details in chapter 20, Section 20.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

NMS is a life-threatening complication of neuroleptic therapy. Its incidence has been estimated at 0.5% to 1.0% of those taking neuroleptics. It can affect all ages and both sexes, but is most frequent in young men. Almost all the neuroleptic drugs can cause the syndrome, but it is more common with more potent dopamine antagonists and long-acting preparations. Most cases occur within two weeks of initiating therapy or of increasing the dose.

Clinically, NMS is characterised by extreme rigidity, fever, autonomic disturbance and a depressed or fluctuating level of consciousness. It develops over a period of 1 to 3 days. Occasionally, tremor, dystonia or other dyskinesias are prominent. The diagnosis is supported by finding an elevated serum creatine kinase level.

In the management of NMS, emphasis is placed on prevention. Factors which increase the likelihood of NMS include initiation of neuroleptic therapy at high doses, rapid increases in dosage, coexisting dehydration, organic brain disease and the concurrent use of other drugs like lithium and tricyclic anti-depressants. The neuroleptic drugs should be withdrawn as soon as the diagnosis is suspected. NMS is a neurological emergency requiring intensive care. Measures include maintenance of fluid and electrolyte balance and reduction of temperature - if needed by body cooling. Respiratory support and dialysis for rhabdomyolysis may be required. Bromocriptine is given orally in doses ranging from 7.5 to 60 mg/day. The oral dose of dantrolene sodium varies from 50 to 200 mg/day; the initial intravenous dose is 2 to 3 mg/kg/day. The drug is continued for 12 to 48 hours after the fever is controlled. Hepatotoxicity can occur with dantrolene. Without specific treatment, death may occur in about 25% of the cases.

TARDIVE DYSKINESIA (TD)

Refers to the development of a movement disorder after chronic exposure to dopamine-receptor antagonists. TD affects about 10% to 20% of patients exposed to neuroleptics for more than a year. Patients most at risk are women over the age of 50 years. It is characterised by stereotyped orolingual and masticatory movements taking the form of lip smacking and lip pursing, tongue protrusion, and licking and chewing movements. The muscles of the upper face are usually spared; the trunk and limb musculature may also be affected. The pathophysiology of TD is thought to be denervation super-sensitivity of striatal dopamine receptors or affection of GABA pathways.

Tardive dyskinesias are irreversible in about 40% of cases. Even those who improve do so several months after the neuroleptic drugs are stopped; elderly patients are the least likely to improve. Early detection to prevent the development of more severe manifestatio ns is important. Neuroleptic drugs may be used on a long-term basis only if absolutely necessary. Once TD is present, the causative drug should be withdrawn if possible. If TD is disabling, pre-synaptic dopamine blockers like reserpine and tetrabenazine may be used with some success. Occasional patients may benefit from a trial of baclofen or clonazepam.

RECOMMENDED READINGS

1. Jankovic J, Tolasa E. *Parkinson's Disease & Movement Disorders*; 5th Ed. Wolters Kluwer, Lippincott Williams & Wilkins; 2008.
2. Jankovic J. Neurologic Clinics; *Movement Disorders*; Vol. 27, No. 2. Elesvier Publication; 2009.

20.20 Hyperkinetic Movement Disorders

Mohit Bhatt

INTRODUCTION

Hyperkinetic movement disorders refer to diseases characterised by excessive involuntary body movements that may span from subtle and barely noticeable to severely disabling. Based on the phenomenology hyperkinetic movement disorders can be classified as dystonia, chorea, myoclonus, tremor and tics. Inheritance plays an important aetiological role in hyperkinetic motor disorder but there are important treatable secondary causes that need attention. Identifying the type of hyperkinetic movement disorder, distribution pattern and associated neurological signs and medical condition helps in arriving at an accurate diagnosis.

DYSTONIA

Definition

Dystonia is defined as an involuntary movement that produces muscle spasms leading to twisting movements or abnormal sustained posture of the affected body part or region. Slow writhing movements in the affected part often described as athetosis are dystonic in nature. Dystonia may result in irregular alternating or tremulous movements. Dystonic tremor is jerky, with a variable amplitude and can be task or position specific. Dystonia is a manifestation of co-contraction of agonist and antagonist muscles. One of the interesting aspect of dystonia is its fluctuating nature. Certain posture or positions of body part can alleviate dystonia. Touching a body part (sensory trick, gesteantagoniste) can reduce dystonic spasm. It is best to ask the patient about sensory tricks as they can be variable and at times quite unusual. Dystonia can go into natural remission lasting minutes to days and even years and then recur.

It is important to classify dystonia as it helps to elucidate the possible diagnosis, plan investigation and prognosticate. Dystonia can be classified on the basis of following:

1. ***By distribution of body parts***
   (a) *Focal dystonia:* involvement of one body part, e.g. hand or neck; (b) *segmental dystonia:* involvement of two contiguous body parts, e.g. neck and arm; (c) *generalised dystonia:* involvement of two or more contiguous body parts and trunk.
2. ***By age***
   This helps prognosticate patients. Onset of symptoms before 25 years of age often indicates that the disease will spread or generalise and most likely be disabling. While adult onset dystonia or onset after 25 years of age indicates that the disorder is likely to remain anatomically restricted, e.g. Writer's cramp.
3. ***By aetiology***
   Clinically this is the most useful classification for dystonia and includes: primary dystonias, dystonias plus syndrome, secondary dystonias, *heredodegenerative dystonias* and paroxysmal dystonias.

When approaching a patient with dystonia, one has to decide if the dystonia is primary (inherited) wherein dystonia is the only clinical manifestation or secondary to structural brain lesion or a degenerative process. The most obvious clue to secondary dystonia is the presence of other neurological symptoms and signs, e.g. seizures, cognitive decline, pyramidal signs. Further, 'Red flags' for secondary dystonia include abnormal birth history and delayed developmental milestones, progressive neurological course, bulbar involvement and exposure to drugs. Patients with primary dystonia have normal scans and metabolic profiles, while secondary dystonias are associated with abnormal imaging and/or biochemical abnormalities, e.g. abnormal copper metabolism and magnetic resonance imaging (MRI) in Wilson's disease.

Primary dystonias are inherited and occur at a specific age group. If either of this rule is broken one must suspect presence of a secondary dystonia.

Primary Adult Onset (45 years and above) Dystonia

These are focal dystonias involving the cranio-cervical region and best treated with botulinum toxin injection. Classic examples of this are: (a) dystonic torticollis: turning of head to one side, (b) blepharospasm: involuntary spasms of eye closure, and (c) oromandibular dystonia: involvement of mouth, jaw and tongue.

Primary Adult Onset (25 to 45 years) Limb Dystonia

Patients have dystonia of usually the upper limb. Dystonia is observed during a particular task, especially repetitive tasks, e.g writing, money counters dystonia, typist's dystonia and musician's dystonia. The disability tends to increase for a few years and then plateau. Rest alleviates symptoms briefly. This form of dystonia is resistant to treatment but a small percentage of patients do experience partial relief with local botulium toxin injection.

Primary Young Onset (<25 years) Dystonia

This is often known as Torsion dystonia or Oppenheim's dystonia. It affects children in their teens with onset usually in the lower limb. Over 2 years or so the movements become generalised, though cranial and bulbar regions are rarely affected. Sixty per cent of patients have mutations in the DYT_1 gene on chromosome 9q. GAG deletion in DYT1 gene which codes for protein TORSIN –A expressed in the dopaminegic areas of the brain is responsible for symptoms in this condition. This mutation is expressed in all ethnic groups but highly prevalent in Ashkenazi-Jewish population because of founder effect. Inheritance is autosomal dominant with a gene penetration of only 30%. Therefore, not all carriers will express the disease and beyond 26 years of age it is unlikely that a carrier of DYT 1 gene may ever suffer from the disease. Expressions can vary from severe generalised dystonia to just focal limb dystonia.

Dystonia-Plus Syndromes

There are two types of syndromes: (a) dopa responsive dystonia (DRD), and (b) myoclonus dystonia syndrome.

Dopa responsive dystonia (DRD, Segava Syndrome) is a rare autosomal dominant disorder that can be effectively treated with L-Dopa in small doses. If not recognised it can lead to severe disability. The dose of L-Dopa required to ameliorate symptoms is usually quite small (levodopa 200 to 400 mg/day) and usually does not need to be escalated over time. Patients present in the young age with leg dystonia, spasticity and Parkinsonism. Fluctuations are common and females are more affected (ratio 4:1). Clinical manifestations can be quite variable and diagnosis is difficult. As a rule it is recommended that all patients with young onset (<25 years) dystonia be given a trial with L-Dopa.

Heredodegenerative Dystonias

Degenerative diseases associated with dystonia are presented in **Table 1** based on the neurological signs accompanying the dystonia.

Table 1: Degenerative Diseases Associated with Dystonia

Dystonia with Parkinsonism
- Parkinson's disease
- Multiple system atrophy
- Progressive supranuclear palsy (PSP)

Dystonia with eye movement disorder
- Niemann-Pick type C
- Ataxia telangiectasia
- Spinocereballar ataxia

Dystonia with bulbar involvement
- Neuronal brain iron accumulation (NBIA) (including PKAN and neuroferritinopathy)
- Neuro-acanthocytosis
- Wilson's disease

Dystonia with ataxia
- Spinocerebellar ataxia
- Wilson's disease
- Huntington's disease

Dystonia with peripheral neuropathy
- Metachromatic leucodystrophy
- Spinocerebullar ataxia
- Neuro-acanthocytosis

Treatment of Dystonia

1. Medical
   (a) Trihexyphenidyl, benzodiazepines and tetrabenazine
   (b) Botulium Toxin: For focal dystonias
2. Surgical: Deep brain stimulation of globus pallidusinternus
3. In all patients with young onset primary dystonias, a trial with L-Dopa for 3 months is essential, before classifying the dystonia as L-dopa non-responsive. Usually a dose of 300 to 600 mg/day of levodopa is required.

CHOREA

Chorea is defined as brief quasipurposeless involuntary movements that flit and flow from one body part to another. Patients with chorea often appear restless and fidgety. Chorea is often generalised but can remain focal, e.g. face or one side of the body (hemi-chorea). In clinical practice the terms chorea and choreoathetosis are often used interchangeably. However, athetoid movements are slow, distal and more accurately defined as dystonia. Therefore, the terms like athetosis or choreoathetosis are best avoided. A clinician should be able to differentiate chorea from dystonia at bedside.

Severe proximal chorea resulting in wild flinging movement of limbs is known as ballism. Hemiballism refers to ballism restricted to one side of the body. Vascular injury involving the subthalamic nucleus is the commonest cause for hemiballism. Diseases characterised by chorea are listed in **Table 2**.

Table 2: Diseases Characterised by Chorea

Inherited/ Degenerative	Huntington's disease Wilson's disease Neuroacanthocytosis Benign hereditary chorea
Autoimmune (post-infection)	Systemic lupus erythematosus Antiphospholipid syndrome Hashimoto's chorea Sydenham's chorea
Infections	HIV Encephalopathy Creutzfeld-Jakob disease (CJD)
Drugs	Dopamine receptor blockers Levodopa Oral contraceptives Anticonvulsants
Structural Lesions	Basal ganglia (caudate) lesions
Metabolic	Hyperthyroidism Hyperglycaemia Sodium disturbances Calcium, manganese and iron deposition disorders

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant degenerative disease characterised by behavioural disturbance, dementia and chorea, described by Huntington in 1872. It has a prevalence of 4 to 8 per 100,000 world over. HD is rare in the first two decades of life and when present it manifests with Parkinsonism and rigidity (Westphal variant). In later age group initial symptoms are variable and include features of dementia, psychiatric problems or chorea. Presence of a strong autosomal dominant pattern of inheritance helps clinch the disgnosis. Lack of inhibition leading to inappropriate behaviour, disorganisation, lack of executive function, apathy, depression and paranoia present in variable combination. Chorea may be subtle at the onset but steadily progresses making the diagnosis obvious.

Eye movement abnormality often assists in the diagnosis and includes: (a) slow hypometric saccades, (b) impersistence of gaze, (c) difficulty in initiating saccades. Patients blink or use head thrust to look from one point to another.

Bizarre gait is another common feature of HD. With advanced disease chorea gives way to Parkinsonism and dystonia. Genetic testing clinches the diagnosis.

Genetics of HD

This is a triplet-repeat disorder. A mutation in the Huntington's gene on chromosome 4 leads to enlargement of the polyglutamine portion to be added to the Huntington's protein. The protein aggregation leads to cell death. The number of repeats in this gene determines when the disease will manifest. Higher the number of CAG repeats younger is the age of manifestation of HD.

Treatment for behavioural problems

1. Selective serotonin reuptake inhibitors for depression
2. Benzodiazepines for anxiety and insomnia
3. Psychological therapy

Treatment for movement disorder

1. Tetrabenazine
2. Amantadine and valproate
3. Dopamine blocking agents

Sydenham's Chorea

Thomas Sydenham was an English Physician of great repute who described this condition in children. This is now known as Syndenham's chorea and is an immune-mediated disorder that follows streptococcal infection (rheumatic fever). Patient develops chorea weeks or months (<6) after streptococcal infection. It is more common in young girls. Associated dystonia may dominate the movement disorder in some children. Behavioural disturbance is often associated with the movement disorder. Antibodies against streptococcal antigen bind to basal ganglion leading to clinical manifestation. Usually, complete remission occurs within few weeks or months of onset of chorea and only seldom are drugs are required for a long period to suppress chorea. Tetrabenazine, valproic acid and occasionally with dopamine antagonists are used in such cases.

Relapses of chorea are seen in 20% of cases while a small number develop chronic persistence of chorea. Patients with refractory chorea may benefit from immunoglobulin or plasma exchange. As in rheumatic carditis penicillin prophylaxis well into adult life is required to prevent another bout of streptococcal infection and recurrence of the disease.

MYOCLONUS

Myoclonus is a brief electric shock like jerk. Physiological myoclonus is experienced by all as hiccups or jerks while falling asleep (hypnic jerk). Myoclonus results from brief activation of a group of muscles. This activation can be from the cortex, subcortical structures like brainstem; spinal cord or nerve, root and plexii. Analogus to the phenomenon of 'positive myoclonus', a brief cessation of muscle activation produces loss of muscle tone produces negative myoclonus as seen in liver flaps (asterix).

Clinically it may be possible to localise the origin of myoclonus. Cortical origin manifests as small amptitude distal limb jerk and is often focal. It may be stimulus sensitive, i.e gently tapping the affected body part triggers the myoclonic jerk. While subcortical myoclonus is large amptitude and generalised.

Various causes of myoclonus are presented in **Table 3**.

Electrophysiology and Myoclonic Jerks

Myoclonic jerks are caused by brief (<50 ms) bursts of muscle activity. It is not possible to generate voluntary contraction for such brief periods. This gives a myclonic recording on EMG evidence of organicity. Further, voluntary motor activity is preceded by a slow wave called Bereitschaft potential (BP) on electroencephalogram (EEG). Consistent presence of a Bereitschaft potential prior to myoclonic jerk helps to diagnose a psychogenic myoclonus.

Table 3: Causes of Myoclonus

Primary myoclonus	Hypnic jerks, hiccups
	Benign infantile myoclonus with feeding/sleep
	Essential myoclonus
Myoclonus with epilepsy	West's syndrome
Lennox-Gastaut syndrome	—
Epilepsia partialis continua	—
Progressive myoclonic	Lafora body disease
Epilepsy and ataxia	Unverricht-Lundborg disease
	Neuronal ceroidlipofuscinosis
Sialidosis	Myoclonus epilepsy with ragged red fibres (MERRF)
Symptomatic myoclonus	Liver failure
With encephalopathy	Renal failure
	Drug intoxication (alcohol, lithium)
	Post hypoxia (Lance-Adams syndrome)
Without encephalopathy	—
Plus dementia	Alzheimer's disease
Creutzfeldt-Jakob disease	—
Plus Parkinsonism	Cortico-basal degeneration
	Multiple system atrophy
Other	Whipple's disease
	Coeliac disease
Paraneoplastic	—

Symptomatic Myoclonus

1. Generalised myoclonus with encephalopathy may be a manifestation of metabolic disease. Acute hepatic encephalopathy may manifest with generalised or focal myoclonus (flaps). Once the metabolic condition improves the myclonic jerks abate.
2. Post-hypoxic myoclonus (Lance-Adams syndrome): This is a result of hypoxic brain damage due to cardiac or respiratory arrest. It is characterised by generalised multifocal non-progressive, stimulus sensitive cortical myoclonus, often accompanied with ataxia and encephalopathy. Presence of severe myclonus in such a setting is a poor prognostic sign. It is resistant to most medical treatments.
3. Subacute sclerosing pan encephalitis (SSPE): Reactivation of measles virus can cause progressive encephalopathy, periodic slow myoclonic jerks, abnormal EEG. Myoclonic jerks are periodic and are time locked to periodic slow complexes on EEG in a 1:1 ratio. Successful vaccination against measles has reduced this disease. It is always fatal, therefore, the need to vaccinate all children against this virus infection. Anecdotal reports suggest benefit of isoprinosine and interferon alpha.

Spinal Segmental Myoclonus

Spinal cord lesions like demylenation, tumours or traumatic injury produce segmental myoclonus. It can be stimulus sensitive and imaging studies localise abnormal region often helps. Jerking of the affected segment is continuous and often will continue even in sleep.

Treatment

Drugs that are used for myoclonic jerks include clonazipam, primidone, piracetam, levetiracetam and sodium valproate.

Often combination of the above drugs is required to control the myoclonic jerks.

TREMOR

Definition

Tremor is defined as rhythmic sinusoidal oscillation of a body part, usually due to alternating activation of agonist and antagonist muscles. Tremor seen when body part is at rest is called rest tremor, while tremor triggered by movement is called a kinetic tremor. Postural tremor seen in certain postures i.e. out stretching of hands and action tremor, seen during movement are types of kinetic tremors. Therefore, to study tremor in a patient first look for tremor when limbs are at rest then ask the patient to stretch out their limbs and lastly make them do alternating action like finger-nose-finger movements. Most tremors manifest in the arms but some tremors are localised to jaw, chin, or legs or generalised. Disorders associated with tremors are presented in **Table 4**.

Table 4: Disorders Associated with Tremors

Rest Tremors	
	Parkinson's disease (typically 3 to 5 Hz)
	Drug Induced
Postural Tremors	
	Essential tremor
	Hyperthyroidism
	Task specific tremor
	Neuropathic tremor—IgM paraproteinemia
Kinetic Tremors	
	Cerebellar disease
	Holme's tremor
	Wilson's disease

Focal Tremor Syndromes

1. Orthostatic tremor is characterised by fine high frequency (16 Hz) leg triggered on standing, resulting in sense of imbalance and unsteady feeling. Walking alleivates the symptoms. It is usually seen after 50 years of age, and drugs like clonazepam helps.
2. Head tremor is also known as titubation. Direction of head nods may be either of Yes – Yes or No – No pattern. Common causes for head nodding is Parkinson's disease, as part of Essential tremor or dystonia and rarely seen with 3rd ventricular tumours (Bobble Head Doll syndrome).
3. Jaw tremor is seen with Parkinson's disease and as an adverse effect of dopamine blocking drugs.
4. Palatal tremor is usually caused by lesions in the brainstem (Gullian-Mollaret triangle).

Disorders Mimicking a Tremor

1. Chin tremor or geniospasm is an inherited (autosomal dominant) disorder. The movements respond well to botulium toxin injections.
2. Oculomasticatory myorhythmia: These are characterised by rhythmic contraction of facial and ocular muscles is and are diagnostic of Whipple's disease.

TICS

As the name suggests tics are brief involuntarty stereotypic movements or vocalisations. An important characteristic of tics is patient's ability to suppress them for short periods. Patients feel a sense of subjective discomfort during suppression of tics. The discomfort is released by flurry of tics. Tics are common and 15% of population will have tics at some time. In a smaller proportion it is the beginning of chronic tic disorder.

Simple motor tic: Eye blinking, eyebrow raising, winking, forehead raising, pouting, nose wrinkling, shoulder raising.

Complex motor tic: Head shaking, touching self, touching others, kicking, jumping, hopping, copropraxia, echopraxia.

Simple vocal tic: Grunting, sniffing, coughing, humming, whistling.

Complex vocal tic: Saying words or parts of words, coprolalia, echolalia, pallilalia.

Clinical Features Associated with Tic Disorders

Copropraxia: production of obscene gestures

Echopraxia: coping the movements of others

Coprolalia: saying obscene words

Echolalia: coping the words of others

Pallilalia: repetition of the same phrase, word, or syllable (e.g. 'My name is Mohit…t…t…t…t')

The most important tic disorder is Tourette's syndrome named after the French Neurologist Gilles de la Tourette. It affects 14 % of population under the age of 18 years. Beyond 18 years, symptoms wane reducing its prevalence in adult life. Diagnosis of Tourette's syndrome requires presence of multiple motor and vocal tics, and these tics for one year and in a person under 18 years of age.

Tics in Tourette's syndrome and tics can be treated with tetrabenazine, clonazepam, clonidine and botulium toxin.

20.21 Cerebellar Disorders

Pramod Kumar Pal

INTRODUCTION

The functions of cerebellum include control of muscle tone, coordination of movements, and control of posture and gait. It also co-ordinates the movements of eye and body with respect to gravity and movement of the body in space. Recent evidence suggests that cerebellum probably plays a role in learning.

Cerebellum and or its connections to other parts of the central nervous system (CNS) may be affected in several ways. The aetiology can be congenital (hereditary or non-hereditary) or acquired (**Table 1**). The most common disorder is degeneration of cerebellum and/or its connections, often affecting other parts of the nervous system.

Table 1: Classification of Cerebellar Ataxias

Hereditary ataxias
- Autosomal recessive ataxias
- Autosomal dominant ataxias
  - Spinocerebellar ataxias (SCA)
  - Episodic ataxias (EA)
- Mitochondrial disorders

Non-hereditary ataxias
- Idiopathic late onset cerebellar ataxia
- Multiple system atrophy
- Symptomatic ataxias

Congenital or developmental disorders, cerebellar malformations
- Non-genetic
- Genetic

CLINICAL MANIFESTATIONS OF CEREBELLAR DISORDERS

Ataxia, a term attributed to disturbances of coordinated muscle activity, is the hallmark of disorders of cerebellum, its afferent or efferent connections. Manifestations include truncal ataxia, unsteadiness of gait and stance and ataxia of intended limb movements. The ataxic limb movements are irregular, jerky, tend to overshoot the target (past-pointing), often accompanied by rhythmic side-to-side movements as the target is approached (intention tremor). There is impaired judgement of the distance to the target (dysmetria), movements tend to be broken down at various joints (dyssynergia) and inability to perform rapid alternating movements (dysdiadocokinesia).

In neurodegenerative disorders other areas of the nervous system may be variably involved resulting in pyramidal signs, peripheral neuropathy, ophthalmic changes, bulbar and brainstem dysfunction, posterior column dysfunction, extrapyramidal manifestations, dysautonomia and cognitive decline.

DIAGNOSTIC APPROACH TO CEREBELLAR DISORDERS

The first step in the evaluation of cerebellar disorder is to distinguish focal from non-focal cerebellar disorders. In the former, symptoms are usually acute to subacute in onset, cerebellar signs are usually unilateral in early stage and there may be signs of raised intra-cranial tension or systemic manifestations (e.g. in cerebellar abscess). Non-focal cerebellar disorders (e.g. degenerative ataxias), are usually insidious in onset, chronic in evolution, and may have a positive family history.

The next step is to identify disorders with a highly characteristic phenotype that can be diagnosed easily on clinical grounds and confirmed by specific laboratory tests, e.g. Friedreich's ataxia (FA), ataxia telangiectasia, cerebrotendinous xanthomatosis, etc.

Finally it is important to look for extra-neural manifestations in patients with cerebellar ataxias, which may provide clues to the aetiology.

An outline of important steps in eliciting history and neurological examination in a patient with cerebellar dysfunction is given in **Table 2**. Further diagnostic tests will depend on the mode of inheritance, age at disease onset, rate of progression, accompanying symptoms, etc.

HEREDITARY ATAXIAS

In hereditary ataxias, an autosomal recessive (AR) inheritance is characterised by several affected members in one generation with healthy parents. Presence of consanguinity in parents strongly favours such inheritance. Typically these disorders manifest in childhood, adolescence or early adulthood. Presence of ataxia in subsequent generations, particularly if both sexes are affected, is highly suggestive of autosomal dominant (AD) transmission. The onset of symptoms is usually later than in AR disorder, though early onset can be seen in subsequent generations due to anticipation (discuses later in the chapter). Finally there are ataxic syndromes, which may have mitochondrial inheritance. However, a negative family history does not always rule out a hereditary disorder. An erroneous conclusion of 'sporadic' disorder may occur in the following situations: (i) unreliable history, (ii) social stigma attributed to a positive family history, (iii) mild symptoms of degenerative disorders in relatives ignored by informants, (iv) family members not examined and (v) strong anticipation in index patient (onset of symptoms at early age even before a parent is symptomatic).

Classifications

Classifications of hereditary ataxias have undergone changes over past several decades. Greenfield (1954) was the first to classify heredoataxias based on pathological criteria. In 1970 Konigsmark and Weiner classified olivopontocerebellar atrophics (OPCAs) into five categories based on genetic, clinical and pathologic data. The genetic loci ascribed for autosomal dominant cerebellar ataxias (ADCAs) are increasing steadfastly, and till date include SCA1 to SCA31, dentato-rubro-pallido-luysian atrophy (DRPLA), and episodic ataxias (EA-1 to EA-7). An updated classification of ADCAs described by Harding based on SCA genetic loci (symptomatic classification of SCAs) is given in **Table 3**. A genetic classification of AR ataxias is given in **Table 4**.

Table 2: Clinical Examination in Cerebellar Disorders

Neurological examination

a. Cerebellar signs: Ataxia of gait, stance, impaired tandem walking, dysdiadochokinesia, incoordination in upper limbs (finger-to-nose test) and lower limbs (heel-knee-shin test), rebound phenomenon, hypotonia and hyporeflexia (if pure cerebellar syndrome, sometimes with pendular knee jerks), dysarthria (scanning, slurred, explosive or a combination), and nystagmus.
b. Determine if the disorder is 'pure' cerebellar or mixed with other neurological signs
c. Whether the cerebellar signs are:
   Bilaterally symmetrical
   Unilateral
   Bilateral, but asymmetrical
d. Other neurological signs often associated with ataxic syndromes:
   Abnormalities of ocular movements:
      Jerky pursuit
      Hypometric and sometimes hypermetric saccades
      Impaired optokinetic nsytagmus
      Vertical gaze palsies (often supranuclear)
      Downbeat nystagmus associated with anomalies of craniovertebral junction
   Head thrust sign
   Reduced visual acuity, optic atrophy, retinal degeneration, macular degeneration
   Papilloedema in ataxic disorders resulting from space occupying lesions in cerebellum
   Extrapyramidal features, such as tremor (rest or action), rigidity, bradykinesia, 'bulging eyes' (as a result of facial dystonia), choreoathetosis and dystonia, myoclonus, etc.
   Deafness
   Bulbar signs, pyramidal signs, sensori-motor peripheral neuropathy, impaired proprioception, etc.
   Autonomic dysfunction
   Mental retardation and cognitive decline
e. Does the neurological syndrome fit in to a well defined disease entity (such as Friedreich's ataxia, or SCA7 characterised by dominant cerebellar ataxia with retinal degeneration?

General physical examination

a. Musculoskeletal abnormalities-kyphosis, scoliosis, pes cavus, contracture of tendoachilles, etc.
b. Telangiectasias (conjunctiva, oral mucous membrane, external ear lobe, eyelids, exposed part of neck, antecubital and polpliteal spaces)
c. Ichthyosis
d. Neurocutaneous markers
e. Neck-to-body ratio and low hair line especially in sporadic ataxias where craniovertebral anomalies are suspected

Systemic examination

a. Cardiac abnormalities (e.g. hypertrophic cardiomyopathy in Friedreich's ataxia)

Autosomal Dominant Cerebellar Ataxias

As discussed earlier, most of the ADCAs are now labelled as SCAs. The types of nucleotide repeat abnormalities in SCAs are shown in **Table 3**. The most common abnormality found in SCAs is abnormal cytosine-adenine-guanine (CAG) repeat. CAG encodes glutamine, and therefore CAG triplet repeat expansions result in expanded polyglutamine proteins, known as ataxins, which cause a toxic gain of function. These abnormal proteins result in neuronal loss with gliosis in a specific pattern according to the genetic mutation. 'Anticipation' is common in these disorders, characterised by an earlier age of onset and more aggressive disease in subsequent generations due to further expansion of the CAG triplet repeat and increased polyglutamine number in the mutant ataxin. Certain clinical findings can give a clue to the type of SCA genotype. Direct genetic testing is currently available for a large number of SCAs including SCA1, SCA2 to SCA8, SCA10, SCA12, SCA14, SCA17, DRPLA and some of the episodic ataxias (EAs). The most common genetically defined SCAs worldwide as well in India are SCA1, SCA2, and SCA3. In India, SCA2 has been reported to be the most common SCA in Northern and Western India, and SCA1 in Southern India. The clinical features of the common SCAs are discussed below.

SCA1

The frequency of SCA1 varies from 6% to 27% of the ADCAs. SCA1 results from mutated Ataxin-1 protein as a result of increased CAG trinucleotide repeats of the SCA1 gene located at chromosome 6p23. The clinical features are quite variable, with age of onset from 4 to 74 years (average around 4th decade) and anticipation is common. Pancerebellar involvement results in gait, trunk and limb ataxia, dysarthria and less frequently nystagmus. Ophthalmologic signs are prominent later in the disease, include slow or absent saccades and gaze paresis. Other manifestations are upper motor neuron signs (spasticity-most common in lower extremities, exaggerated stretch reflexes-especially knees, extensor plantar responses), extrapyramidal signs (later in disease include dystonia and chorea), sensory or sensory-motor polyneuropathy (especially large fibre), and bulbar dysfunction (vocal cord paralysis and stridor). Most patients are disabled by five years, bedridden by 10 years, and death by 10 to 20 years after onset of symptoms.

SCA2

SCA2 is a common ADCA (13% to 18% of the ADCAs), caused by mutated Ataxin-2 due to extra CAG trinucleotide repeats in reading frame of ataxin-2 gene located on chromosome 12q 24.1. There is clinical overlap with SCA1 and SCA3 and significant intrafamilial variability. The age of onset of symptoms is variable, ranging from 6 to 67 years (average around 20 years), and anticipation is also common. Apart from progressive limb and gait ataxia, and dysarthria, SCA2 is characterised by slow saccades (almost 100%) and polyneuropathy. Extrapyramidal features are often seen and include tremor, titubation, dystonia, chorea and myoclonus. Occasionally, dopa-responsive young-onset Parkinsonism may be the presenting or dominant feature in the family. Other features may include bladder dysfunction (~40%), pyramidal signs (~ one-third), fasciculations and amyotrophy (approximately 20%), and dysphagia. MRI findings of atrophy of pons, cerebellum, middle cerebellar peduncles, and medulla can be appreciated in **Figure 1**.

SCA3

SCA3, also known as Machado-Joseph disease (MJD) is another common ADCA (23% to 63%). It results from mutated ataxin-3, due to extra CAG trinucleotide repeats of ataxin-3 gene on chromosome 14q32.1. Male parent transmits the mutant allele about 73% of time. Anticipation is common, and clinical features are variable among different families, as well as within the same family depending on the CAG repeat lengths. Apart from cerebellar signs, patients can have extrapyramidal, pyramidal

Table 3: Autosomal Dominant Cerebellar Ataxias

Type	Notation	Locus	Mutation/Gene
ADCA			
Type I	SCA1	6p23	CAG>39 (Ataxin-1)
	SCA2	12q24.1	CAG>32 (Ataxin-2)
	SCA3	14q32.1	CAG>54 (Ataxin-3)
	SCA4	16q22.1	Mutation at PLEKHG4; (Puratrophin-1)
	SCA8	13q21	CTG repeats, noncoding
	SCA9	?	?
	SCA12	5q31-33	CAG>66 (Protein phosphatase 2A
	SCA17	6q27	CAG>44
	SCA27	13q34	Point mutation at Fibroblast Growth Factor (FGF) 14
	SCA28	18p11.22-q11.2	Unknown
Type II	SCA7	3p14.1-p21.1	CAG>37 (Ataxin-7)
Type III	SCA5	11q13	Mutation of β-III Spectrin (SPTBN2)
	SCA6	19p13	CAG>19 (α_{1A} voltage-dependent calcium channel subunit-CACNA1A)
	SCA10	22q13	ATTCT repeat (Ataxin-10)
	SCA11	15q15.2	Tau tubulin kinase 2 (TTBK2)
	SCA14	9q13.4	Protein kinsae C gamma (PKC γ)
	SCA15	3p24.2-3pter	Inositol 1,4,5-triphosphate receptor, type 1 (ITPR1)
	SCA22	1p21-q23	
	SCA26	19p13.3	
	SCA30	4q34.3-q35.1	
	SCA 31	16q22.1	Pentanucleotide (TGGAA) n repeat insertion
Other			
	SCA13	19q13.3-q13.4	Potassium channel, voltage-gated, shaw-related subfamily, member 3 (KCNC3)
Dentato-rubro-pallido-luysian atrophy		12p13	CAG>48 (Atrophin)
Episodic Ataxias (EA)			
	EA-1	12p13	Missense point mutation in the potassium voltage-gated channel gene KCNA-1
	EA-2	19p13	Stop codon nonsense mutation of the α_{1A} voltage-dependent calcium channel subunit gene CACNA1A
	EA-3	1q42	
	EA-5	2q22	Mutation at CACNB4β4
	EA-6	5p13	Missense mutation of SLC1A3 gene (EAAT1 protein)

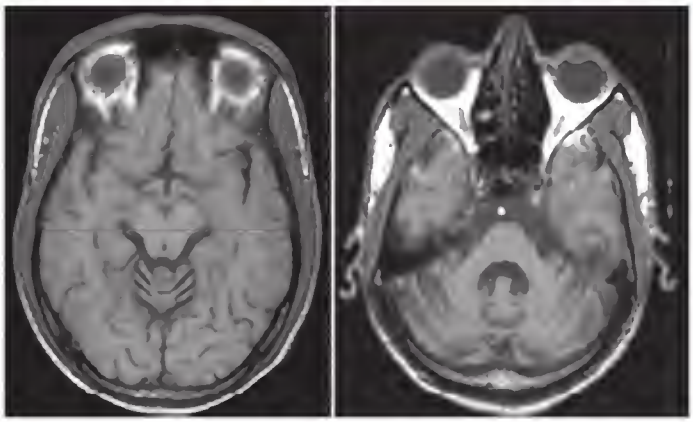


Figure 1: T1 weighted MRI scans of a patient with SCA2 showing severe cerebellar (vermian and hemispheric) and brainstem atrophy.

or polyneuropathy signs. Accordingly, MJD has been classified into three clinical types:

(a) In type I MJD (amyotrophic lateral sclerosis-parkinsonism-dystonia type) the symptoms appear early, at 10 to 30 years. Dystonia of face, neck, trunk and limbs is prominent, along with increased tone and weakness of limbs, pyramidal signs, dysarthria, dysphagia, and abnormalities of eye movements (horizontal and vertical nystagmus, paresis of upward gaze, hypometric and hypermetric saccades).

(b) Type II MJD (ataxic type) is the commonest form of MJD, have an intermediate age of onset (20 to 50 years) and progression and present with prominent cerebellar ataxia and pyramidal signs without any significant extrapyramidal signs.

(c) Type III MJD (ataxic-amyotrophic or neuropathic type) has a later age of onset (40 to 75 years) and slowest progression. There is pancerebellar involvement with ataxia, dysarthria and incoordination of limbs along with prominent peripheral neuropathy. The latter includes distal sensory loss, amyotrophy, fasciculations and weakness.

SCA5

In SCA5 there is mutation of the β-III Spectrin; SPTBN2 gene on chromosome 11q13. The disease is a relatively 'pure' cerebellar syndrome with disease onset in the 4th decade and the course is slowly progressive. Apart from ataxia, incoordination and dysarthria, abnormalities of eye movements are common.

SCA6

SCA6 is a relatively 'pure' cerebellar ataxia with family history of AD transmission in approximately three-fourths of the patients; the rest are sporadic. There is CAG repeat expansion in the gene

for α_{1A} voltage-dependent calcium channel subunit (CACNL1A4, also known as CACNA1A gene) at chromosome 19p13.

SCA7

The characteristic finding in SCA7 is retinal degeneration. There is expanded CAG repeat at chromosome 3p14.1 to p21.1. The mutant protein is Ataxin-7. The age of onset of symptoms is variable, the average being around 20 years. Marked anticipation may be present especially with paternal inheritance. The initial symptoms may be ataxia, dysarthria or visual. The early visual abnormalities are blue-yellow colour blindness, which proceed to frank visual loss and macular degeneration. Other features are variable and may include pyramidal signs, ophthalmoparesis, and hearing loss.

SCA12

SCA12 has been reported from India and Germany. There is expanded CAG repeat in 5' untranslated region of gene protein phosphatase 2 regulatory subunit B, β (PPP2R2B) on chromosome 5q31-q33. The mean age of onset of symptoms is in the 4th decade (vary from 8 to 55 years), and characterised by tremor of arm, or gait ataxia and dysarthria.

Dentato-Rubro-Pallido-Luysian Atrophy (DRPLA)

DRPLA is a CAG repeat disorder most often reported from Japan. There is expansion of the CAG triplet of the DRPLA gene mapped to chromosome 12p13.31. The DRPLA gene product is *atrophin*. The age of onset is variable (1st to 6th decade) depending on the size of expansion, with paternal transmission resulting in stronger anticipation. The clinical picture consists of progressive ataxia, myoclonus, seizures, choreoathetosis, dystonia, and dementia. The patients with larger CAG expansion have younger onset with myoclonus, epilepsy and dementia, while those with smaller CAG expansion have older onset and symptoms of ataxia, chorea and dementia.

Episodic Ataxias (EA)

These are genetically determined ion channel disorders, also known as 'channelopathies' and are characterised by intermittent ataxias. These are rare disorders and to date at least five types of EA have been described (EA-1 to EA-5). Of these EA-1 and EA-2 are the most important (**Table 3**).

EA-1

It is an episodic ataxia/myokymia syndrome caused by a missense point mutation in the potassium voltage-gated channel gene KCNA-1 on chromosome 12p13. The onset of symptoms is in childhood to second decade. The patients have brief episodes of ataxia and myokymia around the eyes and hands lasting for few minutes. There may be choreoathetotic movements during the attack. The attacks may be precipitated by sudden change of posture, emotion, vestibular stimulation, and exercise. There is no ataxia between attacks. Acetazolamide or anticonvulsants may reduce the frequency of attacks.

EA-2

There is stop codon nonsense mutation of the α1A voltage-dependent calcium channel subunit gene CACNA1A on chromosome 19p13, similar to SCA6. The onset of symptoms is in early childhood or in adolescence, and is characterised by episodes of ataxia, nystagmus and truncal instability lasting for 30 minutes to 6 hours. Other associated symptoms may include vertigo, nausea, vomiting, headache and generalised weakness. The attacks may be provoked by stress, exercise or fatigue. Interictal cerebellar signs may be present and some patients may later develop progressive ataxia. As in EA-1, acetazolamide may be helpful in preventing attacks.

Episodic ataxias should be differentiated from metabolic disorders, described earlier, which can also cause intermittent ataxia.

AUTOSOMAL RECESSIVE ATAXIAS

Autosomal recessive cerebellar ataxias (ARCA) are a group of neurological disorders, usually manifesting before 20 years of age, characterised by degeneration or abnormal development of cerebellum and spinal cord. Based on clinicogenetic criteria ARCA can be classified into four main categories (**Table 4**): (i) congenital ataxias (developmental disorders), (ii) degenerative

Table 4: Autosomal Recessive Spinocerebellar Ataxias (ARSCA) with Known Genetic Defect or Identified Loci

Congenital and developmental
- Joubert syndrome
- Gillespie's syndrome

Degenerative ataxias
- Friedreich's ataxia
- Early onset cerebellar ataxia with retained tendon reflexes (EOCARR)
- Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSCAS)
- Marinesco-Sjögren syndrome
- Infantile-onset spinocerebellar ataxia (IOSCA)
- Mitochondrial recessive ataxic syndrome (MIRAS)
- Spinocerebellar ataxia with axonal neuropathy (SCAN)
- Coenzyme Q_{10} deficiency with cerebellar ataxia
- Posterior column ataxia with retinitis pigmentosa

DNA repair defects
- Ataxia Telangiectasia (AT)
- Ataxia Telangiectasia-like disorder (ATL)
- Ataxia with oculomotor apraxia (types 1 and 2) (AOA1 and AOA2)
- Spinocerebellar ataxia with axonal neuropathy (SCAN1)
- Xeroderma pigmentosum

Metabolic ataxias
- Progressive ataxias
  - Ataxia with isolated Vitamin E deficiency (AVED)
  - Abetalipoproteinaemia
  - Cerebrotendinous xanthomatosis (CTX)
  - Refsum's disease
- Disorders associated with intermittent ataxias
  - Hyperammonaemic syndromes (urea cycle disorders)
  - Aminoacidurias
    - Maple syrup urine disease
    - Hartnup's disease
    - Isovaleric aciduria
  - Disorders of pyruvate and lactate metabolism
    - Pyruvate dehydrogenase deficiency
    - Pyruvate carboxylase deficiency
    - Multiple biotin dependent carboxylase deficiency
- Metabolic disorders in which ataxia occurs as a minor feature
  - Hexosaminidase deficiency
  - Metachromatic leucodystrophy
  - Adrenoleucodystrophy
  - Neuronal ceroid lipofuscinosis
  - Sialidosis
  - Wilson's disease

ataxias, (iii) ataxias with a DNA repair defect, and (iv) ataxias associated with metabolic disorders.

Friedreich's Ataxia

Friedreich's ataxia (FA) is the most common inherited degenerative ataxia (~50%), and constitutes approximately 75% of those with onset <25 years. It was first described by Nikolaus Friedreich in 1863. The estimated prevalence is one person in 30,000 to one in 50,000 in most populations; however, no data is available from India. It is inherited as an AR disorder, and consanguineous marriages increase the frequency of the disease. The classic form of FA (about 98% of patients) maps to 9q13 to 9q21, and the mutant gene *frataxin* contains expanded GAA triplet repeats (200 to 900 repeats, whereas the normal is 7 to 22). More than 95 % of patients are homozygous for the expanded GAA repeats, whereas a small percentage of patients are compound heterozygotes who have one copy of the GAA expansion and a point mutation of the *frataxin* gene. *Frataxin* is a mitochondrial protein required for iron homeostasis and prevents free radical toxicity in the tissues. Mutant *frataxin* gene results in loss of iron transporter with resultant accumulation of oxidised intramitochondrial iron, free radical injury and finally irreversible cell injury. In patients with FA *frataxin* mRNA is extremely low or undetectable. There is neuronal degeneration of the posterior columns, spinocerebellar tracts (especially cervical segments), corticospinal tracts, dorsal root ganglia, Clark's column and peripheral nerves.

The mean age at onset of symptoms is 15.5±8 years (usually <20 years) but ranges from 2 to 51 years. The late onset type (after 20 years) is referred to as LOFA (late onset FA). The common presenting symptoms are ataxia of gait, frequent falls and titubation. However, scoliosis and cardiomyopathy may be present before neurological symptoms. Speech and co-ordination of upper limbs may be normal in the first few years. At an advanced stage there is incoordination in both upper and lower limbs, stance and gait ataxia, truncal titubation, dysarthria, wasting of distal muscles of lower limbs and later upper limbs, hyporeflexia in upper limbs and areflexia in lower limbs, Babinski's sign, normal tone, weakness (greater distally than proximally), and decreased vibration sensation at the ankles. Musculoskeletal abnormalities are common and include kyphoscoliosis and pes cavus. Cardiac involvement occurs in 90% of patients and manifested by hyper-trophic cardiomyopathy, murmurs and conduction defects. Approximately 20% of patients have diabetes mellitus. Nerve conduction studies show presence of axonal sensory neuropathy. Neuroimaging shows presence of cervical cord atrophy without cerebellar atrophy. Patients are usually wheelchair bound by a mean age of 25 years, and the median age of death is 35 years. Women have a significantly better prognosis than men. Genetic testing confirms a clinical diagnosis of FA.

Ataxia Telangiectasia

Ataxia Telangiectasia (AT), also known as Louis-Bar syndrome, is an AR progressive ataxic disorder with onset in early childhood. It is caused by mutations in the single ATM (ataxia telangiectasia mutated) gene located on chromosome 11 (11q22 to 23). The protein product of this ATM gene is a kinase, which is a key regulator of multiple signalling cascades, forms a part of the synaptonemal complex and plays a role in meiotic and mitotic recombination, probably by sensing the double-strand breaks in DNA.

The neurological manifestations of AT include cerebellar ataxia, dysarthria, extrapyramidal manifestations. Ataxia is first manifested when the child learns to walk. As the disease progresses mild polyneuropathy, hyporeflexia, distal muscle wasting can be present. Cognition is usually normal, though later mild cognitive decline can be present. Extraneurological manifestations include oculocutaneous telangiectasias, recurrent sinopulmonary infections, endocrine alterations (absence of secondary sexual characters and type 1 diabetes mellitus), and thymic hypoplasia causing variable immunodeficiency state involving humoral and cellular immune systems. The characteristic telangiectatic lesions appear at the age of 3-5 years and consist of transversely oriented subpapillary venous plexuses most prominent over the outer parts of the bulbar conjunctiva (**Figure 2**). Other cutaneous changes include premature greying of hair, vitiligo, loss of subcutaneous fat, and café-au-lait spots. There is an increased incidence of malignancies, such as lymphomas, acute leukaemias, breast cancer, etc. Laboratory investigations show cerebellar atrophy on neuroimaging, absence or decrease of immunoglobulins such as IgA and IgE, elevated levels of alpha fetoprotein, chromosomal instability especially those of chromosome 7 and 14, abnormal sensitivity to ionizing radiation, and characterisation of mutations in the ATM gene. There is no specific treatment except prevention and control of infections and treatment of malignancies and avoidance of diagnostic tests involving radiation.

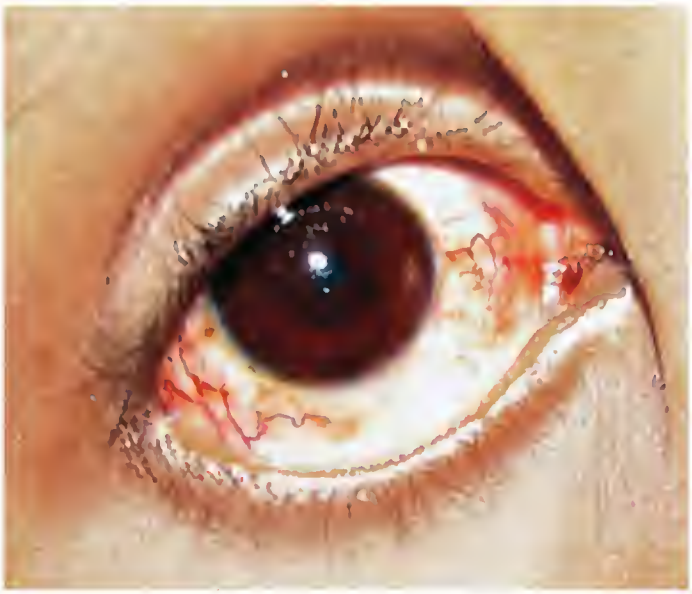


Figure 2: Transversely oriented subpapillary venous plexuses most prominent over the outer parts of the bulbar conjunctiva, in a patient with ataxia telangiectasia.

Other Ataxias

There are other ataxic syndromes associated with DNA repair defects and where either the abnormal gene or locus is known. These are xeroderma pigmentosum (ataxia, choreoathetosis, spasticity, deafness, progressive mental deterioration, skin photosensitivity), Cockayne syndrome (psychomotor retardation, skin photosensitivity, cataract, retinitis pigmentosa, blindness, sensorineural deafness, and ataxia), ataxia telangiectasia-like disorder (ATLD), Nijmegen breakage syndrome (NBS), ataxia with oculomotor apraxia (types 1 and 2), and SCA with axonal neuropathy.

Ataxias Associated with Metabolic Disorders

Progressive or intermittent ataxia is an important feature in several metabolic disorders described below. There are several other rare AR metabolic disorders in which ataxia occurs as a minor feature. The progressive metabolic ataxia of importance are briefly discussed below.

Ataxia with isolated vitamin E deficiency (AVED)

Vitamin E or its major active form-α-tocopherol, is a major liposoluble antioxidant molecule in the body. Vitamin E deficiency results in reduced protection against oxidative stress caused by free radical toxicity, leading to neurological dysfunction manifested by ataxia and neuropathy. In ataxia with isolated AVED, the only abnormality is very low vitamin E level. This is a genetically determined disorder (AR) resulting from mutation in the α-tocopherol transfer protein (α-TTP) gene on chromosome 8q13. The mutated α-TTP gene causes an inability to incorporate a-tocopherol into lipoproteins for transport to various tissues. The onset of symptoms range from 2 to 52 years. The main clinical manifestations of AVED are progressive sensory and cerebellar ataxia. Other findings include dysarthria, areflexia and loss of vibration and position sensations in the lower limbs, bilateral Babinski's sign, scoliosis and pes cavus. Cardiomyopathy is the most common systemic finding but is probably less common than in FA. Moreover, patients with AVED have more head titubation, less neuropathy and a slower course of disease than patients with FA. Electrophysiological studies show axonal sensory neuropathy and MRI may show mild cerebellar atrophy. Laboratory tests reveal low level of vitamin E and diagnosis is confirmed by genetic analysis. In AVED, therapeutic doses of vitamin E should be initiated at the earliest. The treatment can result in cessation of progression of neurological symptoms and signs and amelioration of established neurological abnormalities.

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX) is an AR lipid storage disorder with predominant accumulation of cholestanol and cholesterol in almost every tissue of the body. Extraneurological manifestations begin in childhood and include bilateral cataracts, chronic diarrhoea, and tendon xanthomas found in achilles tendon and over the extensor tendons of fingers, toes, on the tibial tuberosities and in the triceps. Neurological manifestations, which generally start around 20 years of age, may include progressive mental retardation, presenile dementia, behavioural changes, convulsions, pyramidal or extrapyramidal signs, cerebellar signs specifically ataxia and dysarthria, sensorimotor peripheral neuropathy, and bulbar palsy with dysphagia. Diagnostic tests include measuring cholestanol in serum, elevated cholesterol/cholestanol in the tissues. Neuroimaging studies show cerebral, cerebellar and cervical cord atrophy, cerebral and cerebellar white matter hypodensities. Management includes early diagnosis and treatment with chenodeoxycholic acid to lower the cholesterol levels.

Refsum's disease

Refsum's disease or heredopathia atactica polyneuritiformis, an AR disorder, has characteristic clinical and biochemical features. In most patients, there is mutation of the gene for the peroxisomal enzyme phytanoyl CoA hydroxylase, *PHYH*, on chromosome 10 resulting in disturbed peroxisomal function and phytanic acid storage. There is accumulation of phytanic acid in serum and tissues. In addition there is impaired calcium homeostasis and mitochondrial dysfunction. The onset of symptoms is between 10 and 20 years, characterised by retinitis pigmentosa resulting in night blindness, restricted peripheral vision and often blindness. Anosmia and sensorineural deafness are also initial symptoms. At a later stage patient develops ataxia that results from neuropathy, cerebellar and motor involvements. Neuropathy, which first manifests in lower limbs, initially involves propioception and later other modalities. There is diminution and later loss of knee and ankle reflexes. Thickening of nerves and wasting and weakness may be present in severe disease. In stressful conditions, such as rapid weight loss or illness, there can be mobilisation of phytanic acid from fat stores which can lead to acute worsening of symptoms. Extraneurological manifestations include ichthyosis, cardiac involvement, nephropathy and skeletal abnormalities (such as pes cavus, shortening of terminal phalanges of thumb, symmetrical short fourth metatarsals and over-riding of toes). The course of the disease is progressive, often with exacerbations and remissions of symptoms. Laboratory investigations show elevated levels of serum phytanic acid, demyelinating type of neuropathy on electrophysiological tests, elevated CSF protein and elevated levels of creatine kinase in some patients. Management strategies include dietary restriction of food containing high content of phytanic acid such as, fish and milk products. In acutely ill states, where there is sudden increase of serum phytanic acid, plasmapheresis has been reported to be beneficial.

Abetalipoproteinaemia

This is a rare AR disorder initially described by Bassen and Kornzweig in 1950. There is mutation in the gene for the large subunit of microsomal triglyceride transfer protein located on chromosome 4q22 to 24. This gene functions in the assembly of apolipoprotein-B containing very low-density lipoproteins and chylomicrons. This leads to intestinal malabsorption of lipids and all fat soluble vitamins. Vitamin E deficiency may be a pathogenic factor in producing the neurological manifestations. The initial symptoms start in infancy or early childhood with inability to thrive and chronic diarrhoea resulting from malabsorption of fat. The neurological symptoms occur later (6 to 12 years of age), characterised by weakness of limbs and ataxia. The ataxia is initially a result of sensory neuropathy, and later cerebellar component is added. Loss of night vision and hyporeflexia may be early manifestations, and at a later stage there is progressive diminution of vision resulting from retinal degeneration (retinitis pigmentosa). Muscle contractures are common, and in some cases Babinski's sign and mental retardation have been reported to be present. The laboratory findings include acanthocytes in peripheral blood smear (>50% of erythrocytes in a fresh smear), low erythrocyte sedimentation rate, marked reduction of serum low-density lipoprotein, cholesterol (<70 mg/dL) and very low density lipoprotein, and low levels of vitamin E. Pathologic studies reveal foamy vacuolated epithelial cells in intestinal mucosa. Treatment with large doses of vitamin E can prevent progression of neurological dysfunction. Concomitant administration of vitamin A is recommended.

Familial hypolipoproteinaemia

Familial hypolipoproteinaemia is an AD disorder characterised by hypocholesterolaemia, acanthocytes in peripheral blood smear, retinitis pigmentosa, and pallidal atrophy (HARP syndrome). Most patients are asymptomatic. Treatment includes vitamin E supplementation and restriction of dietary fat.

ATAXIA IN MITOCHONDRIAL DISORDERS

Mitochondrial disorders result from mutations in the mitochondrial genome or mutations of the nuclear genes that code for a component of the mitochondrion. Accordingly they are transmitted exclusively by maternal inheritance (maternal genome) or by Mendelian inheritance (nuclear genome). The disorders are sometimes referred to as mitochondrial encephalomyopathies due to frequent involvement of brain and muscle tissues. The syndromes often have elevated lactate or lactate-to-pyruvate ratio in the blood and CSF due to respiratory chain abnormalities. In disorders with muscle involvement 'ragged-red' muscle fibres can be seen on Gomori trichrome stains in sections of frozen muscle. The common syndromes which can have ataxia as one of the prominent manifestations are Kearns-Sayre syndrome (KSS), myoclonic epilepsy with ragged red fibres (MERRF), mitochondrial encephalomyopathy, lactic acidosis, with stroke-like episodes (MELAS), subacute necrotising encephalomyelopathy (Leigh's disease), and the syndrome of neuropathy, ataxia, retinitis pigmentosa (NARP).

NON-HEREDITARY ATAXIAS

Idiopathic Late Onset Degenerative Cerebellar Ataxia

Idiopathic cerebellar ataxia of adult onset is characterised by progressive cerebellar ataxia without evidence of a focal or non-focal symptomatic cause of the disorder, absence of any neurodegenerative disorders in the relatives and no history of consanguinity of parents. Some of these disorders remain as pure cerebellar disorders, do not fit the criteria of multiple system atrophy (see below) and investigations rule out any secondary causes (as discussed below).

Multiple System Atrophy

Multiple system atrophy (MSA) is a sporadic disorder characterised by varying degrees of cerebellar ataxia, parkinsonism, signs of corticospinal involvement and autonomic failure. The onset of symptoms is usually in the around 50 years and the median survival is 6 to 9 years. According to the predominant clinical manifestations, MSA is subgrouped into three broad phenotypes: (i) striatonigral degeneration (SND), (ii) OPCA, and (iii) progressive autonomic failure (PAF). However, at a later stage of the disease, there may be overlap of symptoms.

Symptomatic Ataxias

This group includes progressive symmetrical cerebellar ataxia with evidence of non-focal symptomatic origin (**Table 5**) and focal cerebellar ataxias with focal or multifocal cerebellar lesions (**Table 6**).

Symptomatic symmetrical (non-focal)

Ataxias due to drugs and toxins: Acute and reversible ataxias include those caused by acute alcohol intoxication, and exposure to several drugs and toxins described below. Chronic exposure over years may lead to irreversible cerebellar damage. Cerebellar degeneration resulting from chronic

Table 5: Symptomatic Ataxias: Symmetrical

Acute syndrome (hours to days)
- Infections (para-or post-infectious):
  - Acute viral cerebellitis (chickenpox, coxsackie, enteroviral, etc.)
  - Slow viral infections
  - Falciparum malaria
  - Enteric fever
  - Post vaccinial
- Toxic
  - Acute alcoholic intoxication
  - Overdosage of drugs such as phenytoin, lithium, barbiturates, etc.
- Hyperthermia (e.g. hyperpyrexia, neuroleptic malignant syndrome, heat stroke, etc.)
- Hypoxia

Subacute syndrome (days to weeks)
- Toxic
  - Alcohol
  - Drugs (e.g. phenytoin, lithium, chemotherapeutic) agents
  - Heavy metals, solvents, organochlorine compounds, etc.
- Nutritional/alcohol as a result of deficiencies of vitamins B1, B12, E.
- Metabolic/endocrinal
  - Hypoglycaemia
  - Hepatic encephalopathy
  - Hyponatraemia
- Paraneoplastic

Chronic syndrome (months to years)
- Drugs such as anticonvulsants (especially phenytoin) and lithium
- Paraneoplastic
- Anti-gliadin antibody syndrome
- Hypothyroidism
- Associated with antibodies to glutamic acid decarboxylase (GAD)
- Ataxia due to acquired vitamin E deficiency

Table 6: Symptomatic Ataxias: Focal, Unilateral or Asymmetric Bilateral

Acute syndrome (hours to days)
- Vascular
  - Infarction
  - Haemorrhage
- Infections
  - Cerebellar abscess

Subacute syndrome (days to weeks)
- Neoplastic
  - Cerebellar gliomas
  - Metastatic
- Demyelination
- Infections
  - Granulomas, e.g. tuberculomas, neurocysticercosis
- Multifocal leucoencephalopathy

Chronic syndrome (months to years)
- Stable gliosis secondary to causes mentioned in (A) and (B) above
- Congenital lesions such as Arnold-Chiari or Dandy-Walker malformations

alcoholism is probably the commonest form of chronic cerebellar ataxia.

Several drugs and toxins predominantly affects the cerebellum, and include phenytoin, barbiturates, carbamazepine, lithium, cytosine arabinoside, and 5-fluorouracil, exposure to methylmercury and bismuth, toluene, carbon tetrachloride, thallium, gasoline sniffing, glue sniffing, spray painting, organochlorine compounds, etc. Phenytoin, unlike other anti-epileptic drugs, can cause permanent cerebellar damage.

Hypoxia, ischaemia, hyperthermia and trauma: Purkinje cells of the cerebellum are highly vulnerable to deleterious effects of hypoxia, ischaemia and hyperthermia. In survivors of hypoxic insults there may be cerebellar signs along with prominent extrapyramidal manifestations. Often the cerebellar signs may be overshadowed by generalised cerebral dysfunction associated with the hypoxic states. Hyperthermia associated with heat strokes, neuroleptic malignant syndrome and even transient hyperpyrexia due to infections can lead to cerebellar damage.

Nutritional, metabolic and endocrine causes: Deficiencies of vitamin B1, B12 and E may result in cerebellar ataxias. Wernicke's encephalopathy caused by thiamine deficiency affects oculomotor and cognitive systems as well as cerebellum. The most common cause of thiamine deficiency is alcohol abuse. Gaze paresis, nystagmus, papillary dysfunction, dysautonomia, confusion and varying degree of altered sensorium, severe stance and gait ataxia characterise the syndrome. There may be seizures, hypotension and hypothermia. Vitamin B12 deficiency causes the classic syndrome of subacute combined degeneration of cord, but may rarely present with cerebellar ataxia. Vitamin E deficiency can lead to a progressive spinocerebellar syndrome with peripheral neuropathy and retinal degeneration.

Among the endocrine causes, hypothyroidism is the most important disorder associated with chronic cerebellar ataxia. Ataxia may be the only sign. All cases of sporadic ataxia should be screened for hypothyroidism. Replacement of thyroid hormone results in a striking therapeutic effect even after several years of cerebellar dysfunction.

Paraneoplastic syndromes: Paraneoplastic cerebellar degeneration (PCD) occurs as a result of remote effects of systemic cancer, and is probably an immune mediated disorder. Features include dizziness, nausea, blurry or double vision, sometimes associated with oscillopsia, instability of gait, variable degree of ataxia of upper and lower limbs, dysarthria and dysphagia. A flu-like illness may precede these symptoms. Tumours most frequently associated with PCD are cancer of lung, ovary, breast and Hodgkin's lymphoma, small-cell lung cancer being the most frequent. Treatment of PCD is usually unsatisfactory. Rarely patients may respond to plasma exchange, intravenous immunoglobulins or steroids if given early.

Infections of cerebellum: Disorders of cerebellum could be related to neuroinfections either directly, which usually cause focal signs described below, or by immune-mediated mechanisms.

In immune-mediated injuries, there is diffuse cerebellar involvement. The majority of the acute ataxias in childhood, related to infections are associated with chickenpox. Other infections associated with acute or subacute 'meningo-cerebellitis' include infections due to enterovirus (Coxsackie), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and measles. A similar syndrome can occur after vaccinations, and can be associated with enteric fever, and falciparum malaria. In enteric fever, ataxia usually appears in the second week of illness, may have other neurological manifestations, and is usually self-limited. Acute ataxic syndrome associated with falciparum malaria may be rarely a presenting manifestation or more commonly an ataxic syndrome occur 3 to 4 weeks after the illness. There is progression up to 2 weeks usually followed by a complete recovery.

Subacute or chronic cerebellar ataxia related to infections has been reported with slow viral infections or prion diseases, such as chronic progressive rubella panencephalopathy of children, Creutzfeld Jakob disease (CJD), and the new variant CJD, i.e. bovine spongiform encephalopathy (BSE). Meningovascular syphilis and tabes dorsalis can cause chronic ataxia due to degeneration of the posterior column and spinocerebellar pathways in the spinal cord.

Focal cerebellar ataxias

A large number of disorders (**Table 6**) can cause focal unilateral ataxia or asymmetric bilateral ataxia due to involvement of only one cerebellar hemisphere or asymmetrically of both hemispheres with or without the vermis (**Figures 3A to C**). According to the nature of lesion, the onset of ataxia may be acute or subacute, and the deficit may be maximum at the onset or progress.

CEREBELLAR ATAXIAS DUE TO CONGENITAL ANOMALIES AND MALFORMATIONS

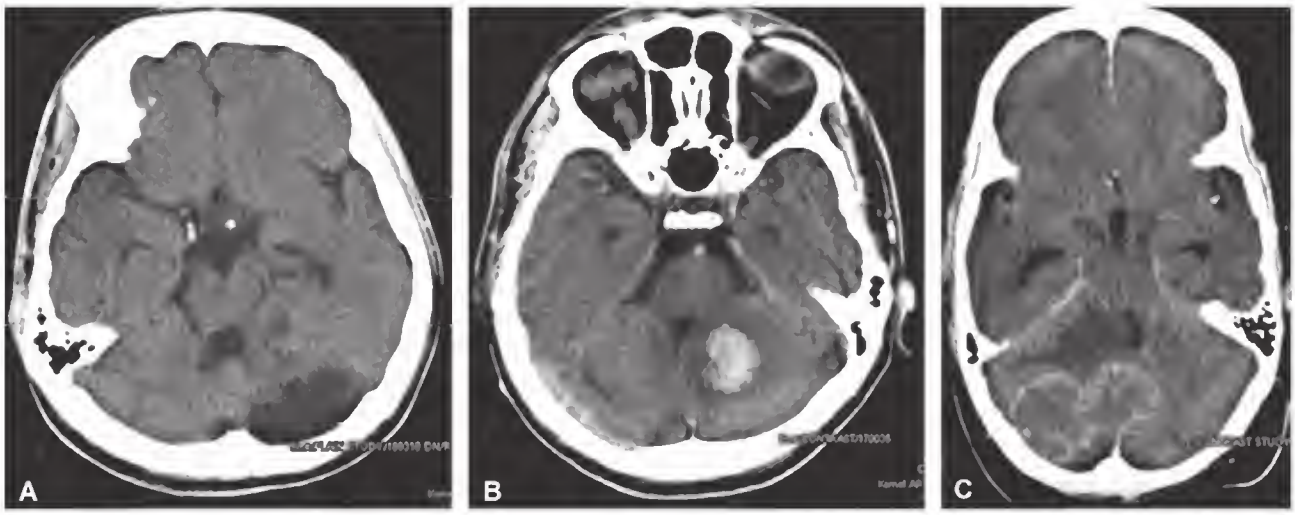
There are well-recognised intrauterine insults (radiation, certain drugs, viral infections, ischaemia) and many chromosomal and genetic disorders which affect the cerebellar growth and development, resulting in syndromes of nonprogressive cerebellar hypoplasias, often improving with age.

The important soft tissue abnormalities include syndromes resulting from agenesis or dysgenesis of vermis and that of midline malformation. The important syndromes with midline malformation include Dandy-Walker malformation and Arnold-Chiari malformations, which are mostly sporadic. These may be associated with bony (craniovertebral) malformations (basilar invagination/impression and atlantoaxial dislocation) and vascular malformations (arteriovenous malformations and aneurysms) of the posterior cranial fossa.

The bony and soft tissue abnormalities of the posterior cranial fossa, foramen magnum and upper cervical cord are often referred to as craniovertebral junction anomalies. Patients may present with adult onset sporadic ataxia.

Arnold-Chiari Malformations

In *Type I*, there is protrusion of cerebellar tonsils through the foramen magnum into the upper cervical spinal canal. It is sometimes associated with basilar impression where there is upward displacement of the foramen magnum an occipital bony floor, resulting in a small posterior fossa. Syringomyelia of upper cervical cord, or sometimes syringobulbia can be associated with *Type I* Arnold-Chiari malformation (**Figure 4**). The symptoms include a progressive cerebellar ataxia, headache due to increased intra-cranial pressure, progressive spastic quad-riparesis, downbeating nystagmus, and signs of cervical syringomyelia



Figures 3A to C: CT scan of patients with unilateral cerebellar ataxia resulting from (A) infarction, (B) haemorrhage, and (C) granulomas (tuberculoma).

(dissociated sensory loss), and lower cranial nerve palsies. In *Type II* Arnold-Chiari malformation there is downward displacement of medulla oblongata, inferior vermis and tonsils that impinge on the foramen magnum causing hydrocephalus. Associated lumbar meningomyelocele is common. In *Type III* Arnold-Chiari malformation, there is midline bony defect with displacement of cerebellar and brainstem tissue into an infratentorial meningoencephalocele. *Type IV* Arnold-Chiari malformation is uncommon and is characterised by cerebellar hypoplasia.

Dandy-Walker Malformations

In this syndrome there is failure of development of the midline portion of the cerebellum and partial or complete agenesis of the vermis. These result in a large posterior fossa cyst as a result of the dilatation of the posterior half of the fourth ventricle. The cyst causes significant obstructive hydrocephalus.

MANAGEMENT

There is no specific drug that has been scientifically documented to improve cerebellar functions. For episodic ataxias 1 and 2, carbonic anhydrase inhibitors such as sulthiame and acetazolamide (Diamox), and anti-epileptic drugs, such as, carbamazepine and phenytoin have been used to prevent attacks. In ataxias with predominant extrapyramidal manifestations, such as SCA3/MJD, dopaminomimetic drugs have been used. Other drugs reported to provide some symptomatic benefit in ataxias, include propranolol, amantadine, buspirone, 5-hydroxytryptophan, topiramate, zolpidem, and coenzyme Q_{10}. Uncontrolled open label studies using a combination of coenzyme Q_{10} and vitamin E have shown improvement of cardiac function and possible stabilisation of neurological symptoms in FA, and low-dose idebenone (a synthetic analogue of coenzyme Q_{10}) probably reduces cardiac hypertrophy without improvement of neurological functions. Metabolic ataxias and other symptomatic ataxias should be managed according to the primary cause.

The mainstay of treatment for progressive cerebellar ataxia is balance training and regular balance exercises to increase the performance of the remaining functioning cerebellar neurons. In FA, management of kyphoscoliosis, exercises to improve respiratory muscle strength and early detection and therapy of cardiac abnormalities are important.



Figure 4: T1 weighted MRI showing Arnold-Chiari malformation Type I with syringomyelia. There is caudal displacement of cerebellar tonsils into the cervical canal.

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20.22 Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

BK Bajaj

INTRODUCTION

Motor neurons are the neurons through which the brain exerts control over skeletal muscles of the body. They are classified into upper and lower motor neurons. The upper motor neurons (UMN) are the motor neurons which have their cell bodies in the cerebral cortex and which form the corticobulbar and corticospinal tracts. These neurons exert direct or indirect control over the lower motor neurons. Lower motor neurons (LMN) are the motor neurons which directly innervate skeletal muscles and which have their cell bodies in the brainstem or spinal cord. The term 'motor neuron disease' (MND) was first coined by Lord Russell Brain in 1969 to refer to the specific disorder of both the upper and the lower motor neurons. The term 'amyotrophic lateral sclerosis' (ALS) has been in vogue for the same presentation since the first descriptions of the disorder by Jean Martin Charcot in the 19th century. It is important to differentiate the terms MND and ALS from the 'motor neuron disorders or diseases' which is used for a heterogeneous group of diseases or disorders of neurons of varied aetiology having in common the involvement of upper and/or lower motor neuron systems (**Table 1**).

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder of undetermined aetiology characterised by progressive motor paralysis due to degeneration of primarily the motor neuron (UMN and LMN) population in the motor cortex, brainstem and spinal cord. The term 'amyotrophy' refers to atrophy of muscle fibres consequent to denervation of muscles due to anterior horn cell degeneration and 'lateral sclerosis' refers to sclerosis or hardening of anterior and lateral corticospinal tracts which are replaced by progressive gliosis. The celebrated neurologist of the 19th century, Jean Martin Charcot is credited with the first detailed descriptions of the disorder 'la sclérose latérale amyotrophique' which affects both the lower motor neurons and upper motor neurons. ALS is also known as Lou Gehrig's disease after the name of the famous baseball player of the United States, Lou Gehrig, who was diagnosed with the disease at the peak of his career in the 1930's. When there is presence of both the upper and the lower motor neuron features at presentation, this is referred to as classic or Spinal or Charcot's ALS. Modern clinical practice recognises the existence of several variants or syndromes related to the spectrum of presentation of ALS including primary lateral sclerosis (PLS), progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), flail arm syndrome (Vulpian-Bernhardt syndrome), flail leg syndrome (Pseudopolyneuritic form) and ALS with multisystem involvement (**Table 2**). The underlying common molecular and cellular pathology of all these syndromes, along with characteristic ubiquitin-immunoreactive (Ub-IR) and TAR DNA binding protein-43 (TDP-43) reactive intraneuronal inclusions, are considered the unifying characteristics of these disorders. Other motor neuron diseases like spinal muscular atrophy, bulbospinal atrophy have molecular pathology distinct from ALS and, while being motor neuron disorders, are not included as ALS or MND.

This is pertinent to note that the terms 'motor neuron disorders' or 'motor neuron diseases' include inflammatory and immune disorders, sporadic and familial disorders and disorders of undetermined cause. ALS or MND is one of the motor neuron diseases or disorders.

Table 1: Classification of Motor Neuron Disorders

- **Upper motor neuron disorders**
  - Neurodegenerative disorders
    - Primary lateral sclerosis
  - Toxins
    - Neurolathyrism
    - Konzo
  - Infection related/Immune mediated
    - HTLV-1 associated myelopathy
    - HTLV-2 associated myelopathy
  - Inherited disorders
    - Hereditary spastic paraparesis
    - Adrenomyeloneuropathy
- **Lower motor neuron disorders**
  - Neurodegenerative disorders
    - Progressive muscular atrophy
    - Benign focal amyotrophy/brachial monomelic amyotrophy/hirayama disease
  - Infections/immune mediated
    - Poliomyelitis
    - Post-polio syndrome
    - Subacute motor neuronopathy in lymphoproliferative disorders
  - Inherited disorders
    - Spinal muscular atrophy
    - X-linked bulbospinal neuronopathy (Kennedy)
    - Heredity bulbar palsy with deafness (Brown-Vialetto-van Laere)
    - Hereditary bulbar palsy without deafness (Fazio-Londe)
    - Hexosaminidase deficiency
  - Physical agents/toxins
    - Postirradiation lower motor neuron disease
- **Upper and lower motor neuron disorders**
  - Amyotrophic lateral sclerosis
    - Sporadic ALS
    - Familial ALS

Table 2: Spectrum of Motor Neuron Disease/ALS

Sporadic and familial ALS
Primary lateral sclerosis
Progressive bulbar palsy
Progressive muscular atrophy*
Juvenile ALS
Western Pacific ALS†
Madras variant MND†

**Nat included in El Escarial Criteria for ALS.*
†These have features in additian ta UMN & LMN invalvement and as yet not strictly considered ta be presentatian af ALS.

EPIDEMIOLOGY

The incidence and prevalence of ALS are fairly uniformly distributed throughout the world. The classic or spinal ALS has an annual incidence of around 1 to 2.7 per 100,000 population per year and a prevalence of around 2.7 to 7.4 per 100,000 population. In hospital based studies from different regions of India, there are reports that motor neuron disease constitutes around 0.11% of all neurological cases seen in outpatient departments of a tertiary care centre. There is male predominance in sporadic spinal ALS with male to female ratio of 1.2 to 1.5:1. Hospital based studies from India have reported higher male to female ratio of 2:1 to 7:1. These studies included atypical forms of motor neuron disease as well. The male preponderance has been variously attributed to putative protective effects of female hormones, increased likelihood of exposure to possible risk factors in males and under ascertainment of female patients. There are reports of female predominance in bulbar onset variety of ALS. While there are no such reports from India, internationally there is some recent data suggesting that the gender ratios for ALS might be approaching equality. There is notable clustering of cases of ALS in certain regions like Chamorro people of Guam and Kii peninsula of Japan. ALS has a peak age of onset in the sixth and seventh decades with reports of onset as early as in the second decade. Most of the available data suggests earlier onset of ALS in Indian population by one to two decades. The mean age of onset of 46.5 years is reported from NIMHANS, Bengaluru, India. Worldwide, the reported mean duration of disease from symptom onset to death is around 3 years. Around 20% and 10% of patients with ALS (PALS) survive for 5 and 10 years, respectively. Indian studies report longer survival of patients with one study reporting an unusually long median survival of 9.5 years. The younger age of onset is possibly the reason for the longer survival in the Indian population. The younger population with greater neuronal reserve have longer survival.

Sporadic ALS constitutes 90% to 95% of cases and the rest are familial ALS with predominantly autosomal dominant pattern of inheritance. While there are no comprehensive Indian epidemiological studies available, familial ALS is probably rarer in India than in the west. There are reported differences in the pattern of presentation of MND in India, with Madras variant of MND (MMND) being commoner in Southern states of Tamil Nadu, Karnataka, and Andhra Pradesh. MMND was first described by Meenakshisundaram from Madras (now renamed Chennai). This variant of MND has been reported subsequently from Thailand, China and in an Italian of South Indian origin. MMND has younger age of onset with mean age of 15.8 ± 7.9 years and has a few peculiar presenting features. Because of the presence of additional neurological features, MMND is usually not clubbed with ALS. Future research may reveal the exact place of the various presentations in the taxonomy of the motor neuron disease.

AETIOPATHOGENESIS

The aetiology of ALS remains undetermined. The most favoured hypothesis is that it is the result of complex genetic-environmental interactions as the causal factor for motor neuron degeneration. There is insufficient evidence to implicate any of the earlier proposed hypotheses of motor neuron degeneration secondary to viral infections, exogenous toxins, immune activation, and hormonal dysfunctions. The molecular pathway causing motor neuron degeneration is likely a complex interplay of multiple cellular mechanisms including excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, neurofilament aggregation, protein aggregation, and deficits of neurotrophic factors and signalling pathways on a possible background of genetic predisposition. Various proposed ALS susceptibility genes include APOE, SMN, peripherin, vascular endothelial growth factor, and paraoxonase.

ALS Parkinsonism dementia complex (Western Pacific ALS) is a disorder of ALS with a combination of Parkinsonism and Dementia of Alzheimer type. It was described from the Chamorro population of the Western Pacific Island of Guam and subsequently from New Guinea and the Kii peninsula of Japan. Accumulated epidemiological evidence suggests an environmental factor, a toxin in native cycad seed.

In familial ALS (FALS), mutation in Cu-Zn Superoxide mutase (SOD-1) has been reported in 20% of cases. Mutation in ALSIN gene has been recognised in recessively inherited juvenile ALS of North African origin. FALS types 1 to 10 are reported. Of these FALS type - 2 and 5 are autosomal recessive, the rest have autosomal dominant inheritance except that the mutation SOD-1 (Asp90-Ala) leads to autosomal recessive FALS-1 and missense mutation of SOD-1 gene results in autosomal dominant inheritance. X-linked dominant mutation and other rare mutations have also been documented in some families. ALS-frontotemporal dementia has an autosomal dominant pattern of inheritance.

Histopathology

Degeneration and loss of motor neurons with astrocytic gliosis and presence of intraneuronal inclusions, such as Bunina bodies (small eosinophilic, hyaline intra-cytoplasmic inclusions staining positive for cystatin, and transferrin) ubiquitinated inclusions (UBIs) or ubiquitin – immunoreactive inclusions (Ub-IR), and hyaline conglomerate inclusions are observed in patients with ALS. There is relative sparing of motor nucleus of Onufrowicz and oculomotor nuclei. Bunin bodies are present in 70% to 100% of ALS cases and UBIs/Ub-IR inclusions are seen in 95% of patients.

CLINICAL PRESENTATION

About two thirds of patients may have typical or spinal form of ALS and present with focal muscle weakness of distal or proximal upper or lower limbs. There is spread of weakness to contiguous muscles in the same region before another region is involved. Initially there may be involvement of muscles in the apparent distribution of a peripheral nerve, the pseudoneuritic pattern, or one limb may be affected first, the monomelic presentation. Some patients present with weakness in both the distal lower limbs as is seen in a length dependent neuropathy and is called pseudopolyneuritic presentation. Approximately 25% of patients present with bulbar symptoms like dysarthria, dysphonia, and dysphagia. Weakness that is restricted to one side of body, Mills' hemiplegic variant, may sometimes be the presenting pattern of involvement. In one to two per cent of patients, weakness starts in the respiratory group of muscles and they either present with dyspnoea on exertion or the disease is suspected when there is failure to wean a patient off ventilator support for another incidental unrelated condition or situation. Up to 10% of patients

present with bilateral upper limb weakness and wasting, flail arm or flail person in barrel syndrome. Patients may present with bulbar or pseudobulbar presentation (**Table 3**). Head drop may be the initial presentation of the disease in a small minority of patients. Peculiarly, fasciculations are usually not the initial presenting symptom of ALS. However, these are present in almost all patients at presentation. Absence of fasciculation should lead to consideration of other possible diagnoses. Patients with ALS may complain of cramps in unusual muscles such as thighs, abdomen, back or even tongue. In addition to motor symptoms, patients with ALS often have non-motor associated symptoms including sleep disturbance, subtle cognitive dysfunction and mood changes.

Table 3: Salient Features of Pseudobulbar Palsy (Involuntary emotional expression disorder)

Corticobulbar tracts involvement
Spastic dysarthria, dysphonia, dysphagia (usually milder than in bulbar palsy)
Emotional lability (inappropriate or forced crying or laughter)
Brisk jaw jerk
Hyperactive gag reflex

DIAGNOSIS

The diagnosis of ALS can be made by clinical history, examination and electrophysiological assessment. The condition must be differentiated from other 'ALS mimickers' which may present like ALS or one of its variants. It is prudent to do laboratory investigations to rule out other conditions and the extent of such investigation should be guided by clinical history and examination findings. All patients over 50 years of age and those who are smokers should have a chest X-ray to look for neoplastic lesions. Thyroid function tests should be done in patients to exclude hyperthyroidism or thyrotoxicosis which can present with multi-segmental fasciculations with brisk reflexes and weakness. Parathormone dysfunction and hypovitaminosis B12 should be excluded, as dictated by the clinical presentation. Appropriate neuroimaging, like MRI of spine or brain, may be required when there is suspicion of other conditions like cervical spondylotic myelopathy or myeloradiculopathy, craniovertebral junction anomalies, multiple sclerosis, paraneoplastic disorder, and various other suspected cerebral and spinal lesions according to the appropriate clinical setting. Flail arm syndrome may be a presentation of HIV infection. Muscle biopsy is not required for the diagnosis. It may be fruitful to exclude suspected inclusion body myositis in appropriate cases. World Federation of Neurology established diagnostic criteria for ALS at El Escorial, Spain in 1990. These were further modified in 2000 at Airlie House, Virginia, USA. These criteria are known as El Escorial Airlie House criteria for ALS. These criteria, while essential for research on ALS, should only serve as a guide for diagnosis of ALS in day-to-day practice. ALS is divided into definite, probable, laboratory supported definite, and possible ALS based on history and examination findings of 4 regions including bulbar, cervical, thoracic, and lumbosacral. The diagnosis of ALS requires clinical, electrophysiological, or pathological evidence of lower motor neuron degeneration, and clinical evidence of upper motor neuron degeneration with evidence of progressive spread of symptoms and signs within a region or other regions.

Neuroimaging Studies

Role of MRI is in excluding the ALS 'mimickers'. There are reports of signal changes in corticospinal tracts on MRI of PALS. 'Garland sign' and 'Wine-glass sign' have been reported in Indian literature. 'Garland sign' is garland like appearance of T2 hyperintensity in corticospinal tract and corpus callosum as visualised on coronal section images of MRI Brain. 'Wine-glass appearance' is white matter hyperintensity involving corticospinal tracts from internal capsule to brainstem on T2 images in coronal section MRI Brain.

Electrophysiology

Neuroelectrophysiology, including nerve conduction study and electromyography, are invaluable adjuncts for diagnosis of ALS. These are particularly useful in evaluation or documentation of lower motor neuron disease. Nerve conduction study is normal in PALS except for low amplitude of compound muscle action potential (CMAP) which is due to wasting of muscles being recorded. Distal latency and nerve conduction velocity are normal in all patients except when there is associated incidental or consequential neuropathy due to other cause or pressure palsy of a predisposed nerve. Sensory nerve conduction study is also normal in patients. EMG examination reveals increased insertional activity, fibrillations, and positive sharp waves suggestive of active denervation. Chronic denervation and reinnervation is suggested by motor unit potentials of increased amplitude and duration with polyphasia. Fasciculations with abnormal and complex morphology are seen in patients. On electromyography, one may observe 'split hand' phenomenon wherein there are severe changes in the lateral hand or thenar eminence and the medial part or hypothenar eminence is relatively spared. Electrodiagnosis should be carried out in at least 3 of the 4 regions of neuraxis, i.e bulbar, cervical, thoracic, and lumbosacral.

Motor unit number estimation (MUNE) may be helpful in quantitative assessment of progressive motor axon loss and is a useful endpoint for clinical trials. Transcranial magnetic stimulation to measure central motor conduction can help document upper motor neuron involvement (involvement of corticospinal tracts), but is not routinely required.

MANAGEMENT

While there is no cure available for ALS, there have been considerable advances in the management of PALS. The goal of therapy at present remains improvement in the quality of life of patients. To achieve this goal multidisciplinary care comprising of a neurologist, physician, rehabilitation specialist, and paramedics is required. The patient with ALS should be appropriately disclosed the diagnosis and options available should be discussed. Repeated meetings may be required to make the patient and his relatives fully comprehend the problems and possible choices. Issues relating to end of life care, nutritional, and respiratory management should be discussed with patient and relatives at the earliest possible.

Disease modifying agents/specific therapy

Riluzole is the first specific drug approved for use in ALS. It results in modest effect on survival of PALS. Cochrane meta-analysis of controlled riluzole trials have shown that the drug results in 9% increment in probability of survival for one year. It probably prolongs the survival by 2 to 3 months, when taken for 18

months in clinically probable or definite ALS, with symptoms for less than 5 years, FVC more than 60% and age less than 75 years. The uncommon side effects of the drug include fatigue, gastrointestinal upset, deranged liver function tests, and dizziness. Liver function tests should be regularly monitored during therapy. The recommended dosage of Riluzole is 50 mg once a day for two weeks, followed by 50 mg twice daily.

There are more than 100 neuroprotective agents, besides riluzole, which have been studied in animal models and humans. Subcutaneous recombinant human insulin-like growth factor, glial cell line derived neurotrophic factor, ciliary neurotrophic factor, oral xaliproden, minocycline, ceftriaxone, Coenzyme Q-10, Vitamin E, celecoxib, L-deprenyl, N-acetylcysteine, calcium channel blockers, and various other agents have been tried and found not to be significantly effective. There is a currently ongoing trial on the role of memantine in PALS.

Gene therapy approach to deliver neurotrophic factors directly to neurons, using genetically engineered adeno-associated viruses expressing neurotrophic factors, have been used in SOD-1 mouse models. No such studies have taken place for humans. Autologous stem cell transplantation is still in experimental state and cannot be applied as a practice as yet.

Supportive care

While there is no specific curative therapy available for ALS, this must not mean denial of the available advanced supportive measures to improve quality of life of patients and a dignified living. Nutritional support, respiratory support, prevention of aspiration, management of speech, treatment of spasticity, pain, cramps, constipation, insomnia, and depression with appropriate pharmacotherapy and non-pharmacological measures must be given to all the patients.

Nutrition management

Oral intake of PALS progressively declines and, dysphagia and aspiration are dangerous imminent realities. History of choking, weight loss and total daily intake should be checked in all the patients. Initially, changes in the form and texture of food items and use of high calorie supplement are adequate for proper nutrition. Eventually enteral feeding, percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG), and in some cases Percutaneous Jejunostomy has to be done in order to maintain proper nutrition. PEG is the standard procedure for PALS. It is advisable to consider this before FVC drops to less than 50%. PRG is better and safer in those with FVC less than 50%. It is important to note that aspiration is a continued risk for patients on PEG. When aspiration becomes problematic, percutaneous jejunostomy should be done.

Management of speech and communication

Problems in communication are an important hindrance in patients' daily living and often a source of great frustration for both the patient and family members. Speech therapist referral should be done early in the course to maintain independent communication as long as possible. Various communication devices including alphabet boards, picture boards, and voice synthesizers can be used for improved communication.

Respiratory management

All PALS eventually develop respiratory failure and require ventilator support. Dyspnoea on exertion or talking, orthopnoea, excessive day time somnolence, headaches and confusion may all indicate respiratory failure. Clinical signs including tachypnoea, prominent use of accessory muscles of respiration, paradoxical breathing and weak cough are evident in these patients. Forced vital capacity (FVC), sniff nasal inspiratory pressure (SNIP) and overnight pulse oxymetry are helpful in deciding about their management. FVC of less than 50%, SNIP value less than 32% is highly predictive of respiratory failure. Such patients are usually provided with non invasive ventilation. Bilevel positive airway pressure (BIPAP) ventilation improves symptoms and prolongs the survival. BIPAP does not prolong the life indefinitely; decision about invasive ventilation has to be made at some point of time.

Other symptomatic treatments

Treatment of symptoms like spasticity (with Baclofen/ Tizanidine), cramps (with vitamin B-complex, calcium channel blockers, levetiracetam), sialorrhoea (anticholinergics, tricyclic anti-depressants), depression (selective serotonin reuptake inhibitors/tricyclic anti-depressants) and fatigue with appropriate pharmacotherapy and physiotherapy should be offered to all the patients.

PROGRESSIVE MUSCULAR ATROPHY

This motor neuron disorder is not included in the El Escorial Criteria for ALS. However, for practical purposes, it is appropriate to consider the LMN syndrome, PMA at one end of the spectrum of ALS and the UMN syndrome, PLS at the other (**Tables 4 and 5**). The disorder comprises 8% of all adult onset motor neuron diseases. Most authors agree that one cannot conclude that PMA presentation will not progress to ALS subsequently until after 4 years after onset. Laboratory testing reveals raised creatine kinase (CK) levels to less than 10 times the normal. Exclusion of other diagnostic possibilities such as chronic inflammatory demyelinating polyradiculopathy, multifocal motor neuropathy with conduction block (MMNCB) and a myopathy should be done before concluding PMA. Treatment of PMA is similar to that of ALS.

Table 4: Salient Features of Progressive Muscular Atrophy

Age of onset earlier than ALS by a decade
LMN involvement during entire course
Diagnosis not made until 3 to 4 years (lest UMN signs appear)
Focal asymmetric weakness in distal extremities with gradual spread
Bulbar and respiratory involvement eventually develops in later stages
Better 5 year survival than ALS (2/3rd survive beyond 5 years)

Table 5: Reasons for Considering PMA as a Variant of ALS Representing One End of Spectrum (PMA is not recognised as a variant of ALS as per El Escorial Criteria)

Motor conduction studies may reveal corticospinal tract involvement (2/3rd of patients in one series)
PMA presentation in some cases of FALS described
Pyramidal tract pathology seen in sporadic PMA
Subset of PMA presentation progress rapidly, like ALS

PRIMARY LATERAL SCLEROSIS

PLS accounts for 2% to 4% of all ALS cases and is conventionally distinguished from ALS by the absence of LMN involvement.

The salient features of the condition are mentioned in **Table 6**. Other features like fasciculations, cramps, bladder dysfunction, cognitive deficits, and abnormal voluntary eye movements have all been observed, rarely, in this group of patients. Median disease duration is 19 years and survival of 6 years to 40 years has been reported in two separate series. Pathological changes include a striking loss of Betz cells in layer 5 of frontal and prefrontal cortex with laminar gliosis of layers 3 and 5 and degeneration of corticospinal tracts. The disease is diagnosed by exclusion of other conditions like Hereditary Spastic Paraparesis, HTLV-1 Associated Myelopathy, Hex-A deficiency, multiple sclerosis and high cervical region compressive myelopathy.

Table 6: Salient Features of Primary Lateral Sclerosis

Diagnosis of exclusion
Onset: a decade earlier than ALS (Early 50s')
UMN involvement during entire course
Diagnosis not confirmed until 4 years after onset
Slowly evolving spastic paraparesis later involving upper limbs
Median disease duration:19 years
Reports of development of LMN signs in some as late as 27 years after onset. Diagnosis needs to be revised to ALS in such cases

MADRAS VARIANT MND

This variant of MND has been reported from Southern India. Majority of reported cases are sporadic and a few familial cases have been documented by a study from NIMHANS, Bengaluru. The pattern of inheritance in Familial MMND appears to be mostly autosomal recessive with a case of autosomal dominant pattern reported in Indian literature.

Salient features of MMND are given in (**Table 7**). The Madras Motor Neuron Disease can be classified as sporadic MMND, sporadic MMND variant, Familial MMND and Familial MMND variant. Clinical and audiological evidence of sensorineural impairment is an important criterion for diagnosing MMND. The MMND variant has evidence of optic atrophy, in addition to the features common for MMND. A few cases with mild cerebellar signs, principally mild gait ataxia, are seen. Features in MMND are like ALS except very young onset, facial palsy and deafness. These are the reasons that the entity is not clubbed with ALS.

Table 7: Salient Features of Madras Variant MND

Younger age of onset (1st and 2nd decade)
Wasting and weakness of predominantly distal muscles of limbs
Bulbar dysfunction (predominantly IX to XII cranial nerve nuclei) and facial muscle involvement
Pyramidal dysfunction
Sensorineural hearing impairment
Optic atrophy in small group of patients (when present, called Madras MND variant)

JUVENILE ALS

This is another young onset motor neuron disorder presenting in less than 25 years of age with UMN and LMN symptoms and signs. This is different from MMND as patients often develop additional neurological features like choreic movements, cerebellar ataxia, and mental retardation in the absence of deafness. The patients do not have bulbar manifestations till late in the course of disease.

POSTPOLIO SYNDROME

The patients who suffer poliomyelitis, after a prolonged period of relative stability, may develop new disabilities affecting activities of daily living. Patients develop progressive muscular atrophy, weakness, pain, and fatigue. This is called postpolio syndrome.

The prevalence of postpolio syndrome has been variously reported as 20% to 85% of people who were earlier afflicted with acute poliomyelitis. The wide variation is possibly due to different diagnostic criteria used.

Diagnosis of postpolio syndrome is of exclusion. The triad of fatigue, weakness, and pain are the most common manifestation. Cold intolerance, dysphagia, muscle twitching and cramps, respiratory distress, and voice changes are the other symptoms. The diagnosis is supported by electromyography which demonstrates longstanding neurogenic changes. Macro EMG can help in precise quantification of motor units and their size.

Symptomatic treatment of fatigue, underlying depression, and use of analgesics for pain are important aspect of management. Surgery for correction of joint deformities, arthosis, and limb length inequality can help. Orthopaedic braces and assistive devices, as per individual patient needs, should be provided. Lifestyle management including weight management, avoidance of over exertion and group therapy may improve the symptoms.

Intravenous immunoglobulins have been tried with some success in individual patients, and small open-label studies. Lamotrigine has been reported as promising for pain, fatigue, and improvement of quality of life.

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20.23 Demyelinating Diseases of Nervous System

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Demyelinating diseases comprise of diseases of central and peripheral nervous system in which disruption of myelin is a dominant feature. Diseases affecting central nervous system (CNS) myelin can be classified on the basis of whether a primary biochemical abnormality of myelin exists (dysmyelinating) or whether some other process damages the myelin or oligodendroglial cells (demyelinating). Demyelinating diseases include autoimmune, infectious, toxic, metabolic, and vascular processes; dysmyelinating diseases in which a primary abnormality of the formation of myelin exists include several hereditary disorders (**Table 1**). The present chapter concentrates on inflammatory demyelinating diseases of central and peripheral nervous system that are presumably immune-mediated.

Table 1: Diseases of Myelin

Central nervous system
- Autoimmune
  - Acute disseminated encephalomyelitis (ADEM)
  - Acute haemorrhagic leucoencephalopathy (AHLE)
  - Multiple sclerosis (MS)
- Infectious
  - Progressive multifocal leucoencephalopathy (PML)
- Toxic/metabolic
  - Carbon monoxide
  - Vitamin B12 deficiency
  - Mercury intoxication
  - Alcohol/tobacco amblyopia
  - Central pontine myelinolysis
  - Marchiafava-Bignami syndrome
  - Hypoxia
  - Radiation

Vascular
- Binswanger's disease

Hereditary disorders of myelin metabolism (dysmyelinating)
- Adrenoleucodystrophy
- Metachromatic leucodystrophy
- Krabbe's disease
- Alexander's disease
- Canavan-van Bogaert-Bertrand disease
- Pelizaeus-Merzbacher disease
- Phenylketonuria (PKU)

Peripheral nervous system
- Acute inflammatory demyelinating neuropathy (AIDP)
- Chronic inflammatory demyelinating neuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

ADEM is a demyelinating syndrome most commonly affecting young adults and children and occurs in association with vaccination (post-vaccination) or systemic infection (para-infectious encephalomyelitis) (**Tables 2 and 3**). Unlike multiple sclerosis (MS), ADEM is almost always monophasic. Salient differences between ADEM and MS as given in **Table 4**.

Table 2: Acute Disseminated Encephalomyelitis (ADEM) and Related Disorders

- ADEM
  - Uniphasic, para/post-infectious or post-vaccination inflammatory demyelinating disorder of CNS
- Acute haemorrhagic leucoencephalitis (AHLE)
  - Hyperacute form of ADEM, usually occurring after non-specific upper respiratory infections, more tissue destructive
- Site restricted forms of monophasic acute inflammatory demyelinating disorders
  - Transverse myelitis
  - Optic neuritis
  - Cerebellitis
  - Brainstem encephalitis
- Chronic or recurrent forms of parainfectious or post-vaccination encephalomyelitis
- Multiphasic form of ADEM
- Combined central and peripheral nervous system inflammatory demyelinating disorders
  - Post-vaccination : Rabies, Influenza
  - Post-infectious : Measles

Table 3: Triggering Events of ADEM

Infections

Viral

Measles	Rubella
Mumps	Epstein-Barr virus
Influenza A or B	Cytomegalovirus
Hepatitis A or B	Coxsackie
Herpes simplex	Dengue
Human herpes virus E	Human immunodeficiency virus (HIV)
Varicella	

Bacterial

Mycoplasma pneumoniae	*Streptococcus pyogenes*
Chlamydia	*Salmonella typhi*
Legionella	*Leptospira*
Lyme's disease	*Mycobacterium tuberculosis*
Campylobacter	*Brucella*

Vaccines

Rabies	Japanese B encephalitis
Diphtheria, tetanus, pertussis	Polio
Smallpox	Hepatitis B
Measles	Influenza
Mumps	Meningococcal A and C
Rubella	

Drugs

Gold	Sulphonamides
Arsenical compounds	Streptomycin/ PAS

Clinical Manifestations

The hallmark clinical feature is the development of a focal or multifocal neurological disorder following exposure to virus or receipt of vaccine. The onset of the CNS disorder is usually rapid, with peak dysfunction within several days. Initial features include encephalopathy ranging from lethargy to coma,

seizures, and focal and multifocal signs reflecting cerebral (hemiparesis), brainstem (cranial nerve palsies), and spinal cord (paraparesis) involvement. Other reported findings include movement disorders and ataxia.

Table 4: Differences between ADEM and Multiple Sclerosis

Characteristics	ADEM	Multiple Sclerosis
Onset	Abrupt	Subacute
Age group	More common in children	Young adults
Sex distribution	Possible male preponderance	1.7:1 to 2:1 (F/M)
Triggering event	Preceding infection/ vaccination in 70%	Uncommon
Temporal profile	Monophasic; rarely relapsing	Relapsing
Clinical features		
Altered sensorium	More common	Rare
Seizures	More common	Rare
Neurologic deficits	Multifocal	Usually single deficit
Optic neuritis	Bilateral	Unilateral
Transverse myelitis	Complete myelopathy	Incomplete
Headache	More common	Rare
Meningismus	More common	Rare
Cerebrospinal fluid (CSF)		
Cell count	Mild to moderate pleocytosis	Normal or mild pleocytosis (never >75 cells/ µL)
Proteins	Modestly elevated (50 to 150 mg/dL)	Normal or slightly elevated (never >100 mg dL)
Oligoclonal bands	Uncommon, transient	Common and persistent
Magnetic resonance imaging (MRI)		
Distribution of lesions	Bilateral confluent, extensive lesions	Scattered asymmetric lesions
White matter lesions	Confluent, ill-defined, periventricular, and subcortical white matter lesions	Well-defined, periventricular preponderance, juxtacortical
Grey matter lesions	Thalamic and basal ganglia involvement common (**Figure 1**)	Uncommon
Corpus callosum lesions	Rare	Common (Dawson fingers) (**Figure 2**)
Oedema and mass effect	May be present	Usually absent
Follow up MRI	No new lesion or lesion resolution	New lesions - dissemination in time and space
Mortality	10% to 25%	Rare

Pathologic Features and Pathogenesis

ADEM is characterised by perivascular inflammation, oedema, and demyelination within the CNS. The pathology of encephalomyelitis following infections and vaccines is indistinguishable from each other. ADEM results from an aberrant immune attack on the brain and/or spinal cord, triggered by temporally related infections or vaccinations.

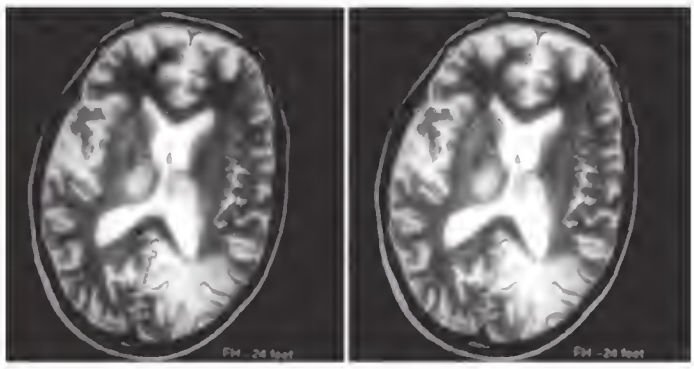


Figure 1: MRI brain T2W image in a 28 years man showing postinfectious ADEM showing hyperintense bilateral lesions in thalami and in the left parieto-occipital area.

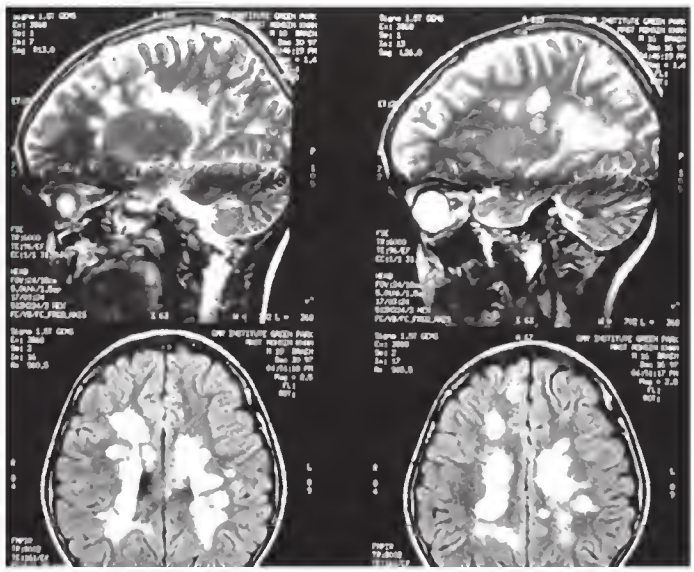


Figure 2: Multiple white matter lesions perpendicular to the lateral ventricles and in and around corpus callosum suggestive of multiple sclerosis. Patient had relapsing-remitting MS and visual evoked potentials (VEP) were markedly prolonged.

Treatment

An initial regime of high-dose intravenous methylprednisolone (3 to 5 g over a period of five days), is followed by a prolonged oral prednisolone tapered over 3 to 6 weeks. If a patient does not respond adequately to corticosteroids, therapy should be escalated, preferentially with intravenous immunoglobulin (Ig) (0.4 g/kg/d over 5 days). Alternatively, or if this approach fails, plasmapheresis can be considered. In very severe cases, immunosuppression with cyclophosphamide or mitoxantrone should be attempted.

MULTIPLE SCLEROSIS (MS)

MS is the most common inflammatory-demyelinating disease of the CNS and the most frequent cause of non-traumatic neurologic disability in young and middle-aged adults.

Epidemiology

MS affects ~350,000 individuals in the United States (US) and 2.5 million individuals worldwide. It is approximately threefold more common in women than men. The age of onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the lifespan. Approximately 10% of cases begin before 18 years of age, and with onset as early as 1 to 2 years of age or as late as the eighth decade have

been described. Whites are especially vulnerable, particularly those of Northern Europe, Northern US, and Canada. By contrast, prevalence is low in Japan (6 per 100,000), in other parts of Asia, in Equatorial Africa, and in the Middle East. MS was considered to be uncommon in Indian subcontinent, but the widespread availability of magnetic resonance imaging (MRI) has led to an increased recognition of MS in India. Optico-spinal form is seen more commonly in India.

MS risk also correlates with high socioeconomic status, which may reflect improved sanitation and delayed initial exposures to infectious agents.

Genetic Considerations

Though not clearly inherited in a simple Mendelian pattern, MS tends to cluster within families (**Table 5**). Susceptibility to MS is polygenic.

Table 5: Risk of Developing MS

Risk of developing MS	
1 in 3	If an identical twin has MS
1 in 15	If a fraternal twin has MS
1 in 25	If a sibling has MS
1 in 50	If a parent or half-sibling has MS
1 in 100	If a first cousin has MS
1 in 1000	If a spouse has MS
1 in 1000	If no one in the family has MS

Clinical Manifestations

The onset of MS may be abrupt or insidious. Symptoms of MS are extremely varied and depend on the location and severity of lesions within the CNS (**Tables 6 and 7**). Examination generally reveals evidence of neurologic dysfunction, often in asymptomatic locations.

Table 6: Initial Symptoms of MS

Symptom	Per Cent	Symptom	Per Cent
Sensory loss	37	Lhermitte	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paraesthesias	24	Visual loss	2
Diplopia	15	Facial palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal attacks	4	Epilepsy	1
Bladder	4	Falling	1

Table 7: Common Clinical Features of MS

Clinical Features Suggestive of MS	Clinical Features not Suggestive of MS
Onset between ages 15 and 50	Onset before age 10 or after 60
Relapses and remissions	Steady progression
Optic neuritis	Early dementia
Lhermitte's sign	Rigidity, sustained dystonia
Internuclear ophthalmoplegia Fatigue	Cortical deficits such as aphasia, apraxia, alexia, neglect
Worsening with elevated body temperature	Deficit developing within minutes

Pathogenesis

The lesions of MS (plaques) vary in size from 1 or 2 mm to several centimetres. Acute MS lesions are characterised by perivenular cuffing with inflammatory mononuclear cells, predominantly T cells and macrophages, with disruption of the blood-brain barrier. In many lesions, myelin-specific autoantibodies are present, presumably promoting demyelination directly with prominent astrocytic proliferation (gliosis) as the lesions evolve. Surviving oligodendrocytes may partially remyelinate the surviving naked axons, producing so-called shadow plaques.

The signs and symptoms of MS are the manifestations of CNS demyelination. Although relative sparing of axons is typical of MS, partial or total axonal destruction can also occur, especially within highly inflammatory lesions. Evidence also suggests that axonal loss is a major contributor to irreversible neurologic disability in MS.

Disease Course

Four clinical types of MS have been described:

1. *Relapsing/remitting MS (RRMS)* – accounts for 85% of cases at onset and is characterised by discrete attacks with often complete recovery over ensuing weeks to months.
2. *Secondary progressive MS (SPMS)* – always begins as RRMS. At some point, however, the clinical course changes so that the patient experiences a steady deterioration in function un associated with acute attacks. For a patient with RRMS, the risk of developing SPMS is ~2.5% each year.
3. *Primary progressive MS (PPMS)* – accounts for ~15% of cases. These patients experience a steady functional decline from onset.
4. *Progressive/relapsing MS (PRMS)* – accounts for ~5% cases. These patients experience a steady deterioration from disease onset, along with occasional attacks super-imposed.

Diagnostic Criteria

The current diagnostic criteria for MS has been proposed by McDonald and colleagues in 2005 (**Tables 8 and 9**).

Table 8: Revised McDonald *et al* Diagnostic Criteria for MS

Clinical (Attacks)	Objective Lesions	Additional Requirements to Make Diagnosis
2 or more	2 or more	None
2 or more	1	Dissemination in space by MRI ***or*** 2 or more MRI lesions consistent with MS plus positive CSF ***or*** await further clinical attack implicating other site
1	2 or more	Dissemination in time by MRI ***or*** second clinical attack
1	1	Dissemination in space by MRI ***or*** 2 or more MRI lesions consistent with MS plus positive CSF ***or*** await further clinical attack implicating other site ***AND*** dissemination in time by MRI ***or*** second clinical attack
0 (progression from onset)	1 or more	Disease progression for 1 year (retrospective or prospective) ***AND*** 2 out 3 of the following: Positive brain MRI (9 T2 lesions ***or*** 4 or more T2 lesions with positive VEP), Positive spinal cord MRI (2 or more focal T2 lesions), Positive CSF

Table 9: Paraclinical Evidence in MS Diagnosis

What is positive MRI

Three out of four of the following:

(i) One Gadolinium-enhancing lesion or cord lesion ***or*** 9 T2 hyperintense brain and/or cord lesions if no Gd-enhancing lesion

(ii) 1 or more brain infratentorial or cord lesions

(iii) 1 or more juxtacortical lesions

(iv) 3 or more periventricular lesions

MRI evidence of dissemination in time

A Gd-enhancing lesion demonstrated in a scan done at least 3 months after onset of initial clinical event at a site different from initial event, ***or***

A new T2 lesion detected in a scan done at any time compared to a reference scan done at least 30 days after initial clinical event

Positive CSF

Oligoclonal IgG bands in CSF (and not serum) ***or*** elevated IgG index

Positive VEP

Delayed but well preserved waveform

Table 10: Currently Approved Disease-Modifying Drugs for MS

DMD	Use in MS
IFN-β IFN-β-1a, 30 μg IM once weekly (Avonex) IFN-β-1a, 22 or 44 μg SC three times weekly (Rebif) IFN-β-1b, 250 μg SC every other day (Betaseron)	Considered first-line treatment for RRMS
Glatiramer acetate, 20 mg SC once daily (Copaxone)	Considered first-line treatment for RRMS
Natalizumab 300 mg IV once monthly (Tysabri)	Generally recommended only for patients who have had suboptimal response to, or are unable to tolerate, other MS therapies, or those with rapidly evolving severe RRMS. Requires careful monitoring due to increased risk of PML
Mitoxantrone, 12 mg/m^2 IV every three months, lifetime maximum dose 140 mg/m^2	Second-line treatment for worsening RRMS. Also used for treatment of PRMS or SPMS. Requires careful monitoring due to serious safety concerns (leukaemia and cardiomyopathy)

Treatment

Therapy for MS can be divided into several categories: (1) treatment of acute attacks, (2) treatment with disease-modifying agents that reduce the biological activity of MS, and (3) symptomatic therapy. Treatments that promote remyelination or neural repair do not currently exist but would be highly desirable.

Acute attacks or initial episodes

Glucocorticoids are used to manage either first attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Intravenous methylprednisolone 500 to 1000 mg/dL for 3 to 5 days, is given, either without a taper or followed by a course of oral prednisone beginning at a dose of 60 to 80 mg/d and gradually tapered over two weeks.

Plasma exchange (seven exchanges: 40-60 mL/kg per exchange, every other day for 14 days) may benefit patients with fulminant attacks of demyelination (not only MS) that are unresponsive to glucocorticoids.

Relapsing forms of MS (RRMS, SPMS with exacerbations)

Table 10 shows the currently approved disease-modifying therapies for MS. **Table 11** outlines the treatment paradigm used currently.

A key aspect of treatment in MS is to begin therapy with disease-modifying drugs (DMDs) as early as possible to minimise further axonal damage and irreversible disability.

Novel therapies in development for MS

Emerging parenteral therapies include the anti-CD52 monoclonal antibody alemtuzumab, MBP8298, anti-CD20 monoclonal antibodies, and the anti-CD25 monoclonal antibody daclizumab. Several promising oral agents are also in phase III development [BG-12, Cladribine, Fingolimod (FTY720), Laquinimod, Teriflunomide].

Symptomatic treatment

There have been no recent major breakthroughs in the symptomatic therapies for MS except in the management of spasticity. Recently, intrathecal delivery of baclofen has dramatically altered the way such patients are managed. Intrathecal baclofen pump device allows a constant flow of baclofen into the spinal fluid at lumbar region, which brings about a dramatic relief from spasticity in lower extremities.

PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY (PML)

PML is a CNS disease characterised by multiple foci of demyelination that progressively increase in size and number. It is now recognised as a form of opportunistic viral infection of oligodendrocytes by JC virus (papova virus group) resulting from impaired cell mediated immune response. It is usually seen in association with acquired immunodeficiency syndrome (AIDS), malignancies, particularly leukaemia and lymphomas, granulomatous diseases like tuberculosis and sarcoidosis and therapeutic immunosuppression (e.g. collagen vascular disorders, organ transplantation).

In the pre-AIDS era, the most common age of onset was the sixth to seventh decade but it is now reported even in children as young as seven years who are HIV positive.

The clinical presentation of PML is of a focal neurological deficit, which typically evolves over hours or days. The onset can be abrupt in which case it can be confused with stroke. The most common site of affliction is the cerebrum (80% to 90%). Cerebellum and brainstem (10% to 20%) and spinal cord is rarely involved.

Diagnosis is based on a high index of suspicion, on clinical grounds in subjects with neurological deficit developing in the background of depressed immunity. Polymerase chain reaction (PCR) technique is now available for the diagnosis. MRI brain is paramount for the diagnosis (**Figure 3**).

Table 11: Multiple Sclerosis Treatment Strategies

Disease Course/Stage	Treatment Options	Evidence
Monosymptomatic (e.g. optic neuritis) – acute attack	IV methylprednisolone, 1000 mg for 5 days, without oral taper, or with oral prednisone tapered over two weeks	Class I evidence
Relapsing-remitting, no disease activity for several years, and/or no activity on MRI	IV corticosteroids if acute attack occurs	Class I evidence
Relapsing-remitting, current disease activity, and/or activity on MRI	IV corticosteroids for acute attacks, plus for prevention (1) IFN-β-1a (Avonex), or (2) IFN-β-1a (Rebif), or (3) IFN-β-1b (Betaseron), or (4) glatiramer acetate	Class I evidence
Relapsing-remitting, disease activity while on interferon or glatiramer acetate, or intolerance to either agent	Switch to natalizumab	Class I evidence
Relapsing-remitting, accumulating disability while on interferon or glatiramer acetate	Switch to natalizumab or mitoxantrone	Class I evidence for mitoxantrone, no studies for natalizumab in this population
Rapidly progressing disability	Switch or add mitoxantrone	
Secondary progressive multiple sclerosis (SPMS)	Mitoxantrone	Class I and II evidence
Primary progressive multiple sclerosis (PPMS)	No established therapy. Trials of mitoxantrone and rituximab are currently underway	

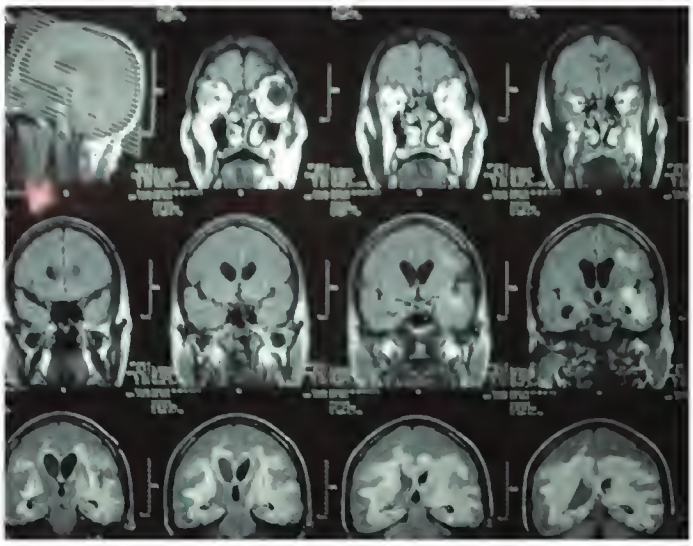


Figure 3: MRI brain showing bilateral extensive white matter lesions in an elderly individual suggestive of PML. Tissue histopathology confirmed the diagnosis.

Usually this disease has a relentless progressive course and most of the patients usually die within 3 to 6 months. No specific therapy. is available though there are some reports of improvement with cytosine arabinoside and cidofovir. HIV associated PML has been reported to show good response to highly active anti-retroviral therapy (HAART) therapy.

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (AIDP)

AIDP is considered to be an immunological disorder with an acute, often fulminant evolution characterised by a syndrome of rapidly progressive flaccid paralysis, areflexia and albuminocytological dissociation in the CSF. It is popularly referred to as Gullain-Barre syndrome (GBS) after the French army neurologists, Georges Guillain and Jean Alexandre Barre, who described this entity in 1916.

Epidemiology

AIDP is a non seasonal illness that affects persons of all ages. With the decline of acute anterior poliomyelitis, AIDP is the most common acute paralytic disease in Western countries. The mean annual incidence is 1.8 per 100,000 population. Incidence rates increase with age from 0.8 in those younger than 18 years to 3.2 for those 60 years and older.

Antecedent Events

Approximately two thirds of patients report a preceding event, most frequently an upper respiratory or gastrointestinal infection, surgery, or immunisation 1 to 4 weeks before the onset of neurological symptoms. Specific infections implicated include cytomegalovirus, Epstein-Barr virus, varicella zoster virus, hepatitis A and B, HIV, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*. The most common bacterial organism linked to GBS and particularly its axonal forms is *Campylobacter jejuni*. Vaccinations implicated include New Jersey influenza vaccine, tetanus and diphtheria toxoids, rabies and oral polio; and drugs include streptokinase, suramin, gangliosides, and heroin. Several cases have occurred in immunocompromised hosts with Hodgkin's lymphoma or in pharmacologically immunosuppressed patients after solid organ or bone marrow transplantation.

Clinical Features

Patients commonly present with acute onset sensory symptoms in the form of paraesthesias followed by rapidly ascending (rarely descending) weakness. In some patients there may be severe pain in the limbs and back. Involvement of limbs is usually symmetrical and respiratory involvement can occur in a period of three to four weeks. Cranial nerves may be affected, most commonly the facial (50%), bulbar (30%), and ocular (10%). The deep tendon reflexes may be diminished or absent. Sensory loss is uncommon but occasional patients may develop glove and stocking

distribution of sensory loss. Papilloedema may be present in 1% of cases. Sphincter disturbances may occur in 15% cases especially early in the course. Autonomic dysfunction has been reported in 65%, and includes persistent tachycardia (50%), systolic hypertension, sinus bradycardia and severe postural hypotension.

A tentative classification of GBS subtypes has been proposed (**Table 12**).

Table 12: Classification of GBS Subtypes

Acute inflammatory demyelinaring polyradiculoneuropathy (AIDP)
Acute motor axonal neuropathy (AMAN)
Acute motor sensory axonal neuropathy (AMSAN)
Millar-Fisher syndrome
Acute pandysautonomia
Sensory GBS

Course

Approximately 30% reach maximum deficit in seven days, others progress up to four weeks. Neurological disability can be graded according to Hughes' grading scale (**Table 13**). Respiratory involvement occurs in 50% patients with 20% to 30% requiring assisted ventilation. Common causes of death include respiratory failure, pulmonary embolism, infection and autonomic disturbances. Relapses occur in 2% of patients.

Table 13: Neurological Disability Grading in GBS

Grade 0	:	Healthy
Grade 1	:	Minor signs or symptoms of neuropathy but capable of manual work
Grade 2	:	Able to walk without support of a stick but incapable of manual work
Grade 3	:	Able to walk with a stick, appliance, or support
Grade 4	:	Confined to bed or chair bound
Grade 5	:	Requiring assisted ventilation
Grade 6	:	Dead

Investigations

The CSF findings consist of an elevated protein level (100 to 1000 mg/dL) without accompanying pleocytosis. It is often normal when symptoms have been present for ≤48 h; by the end of the first week the level of protein is usually elevated. A transient increase in white cell count (10 to 100/μL) occurs occasionally; however, a sustained CSF pleocytosis suggests an alternative diagnosis (viral myelitis) or a concurrent diagnosis such as HIV infection.

Electrophysiological studies (nerve conduction) may reveal prolonged distal motor and F-wave latencies, absent or impersistent F waves, conduction block, reduction in distal compound muscle action potential (CMAP) amplitudes with or without temporal dispersion, and slowing of motor conduction velocities. In cases with primary axonal pathology, reduced amplitude of CMAP is seen.

Lumbosacral spinal MRI may demonstrate gadolinium enhancement of lumbar roots.

Diagnostic Criteria

Diagnostic criteria for GBS is given in **Table 14**.

Table 14: Asbury and Cornblath Diagnostic Criteria for GBS

Features required for diagnosis
Progressive weakness in both arms and both legs
Areflexia
Features supportive of diagnosis
Progression of symptoms over days to four weeks
Relative symmetry of symptoms
Mild sensory symptoms or signs
Cranial nerve involvement especially bilateral weakness of facial muscles. Recovery beginning 2 to 4 weeks after progression ceases
Autonomic dysfunction
Absence of fever at the onset
Laboratory features supportive of diagnosis
Elevated concentration of proteins in the CSF with <10 cells/μL
Typical electrodiagnostic features

Treatment

Treatment should be initiated as soon as possible after diagnosis, as immunotherapy is no longer effective two weeks after the first motor symptoms. Either high-dose intravenous immunoglobulin (IVIg) or plasmapheresis can be initiated, as they are equally effective. A combination of the two therapies is not significantly better than either alone. Careful observation of cardiorespiratory function, prevention of complication due to prolonged immobilisation and analgesia are other aspects to be taken care of.

Glucocorticoids have not been found to be effective in GBS. Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be managed conservatively without IVIg or plasma exchange (PE).

Specific Treatment

Intravenous immunoglobulin (IVIg)

IVIg is indicated in subjects who are unable to walk unassisted. The dose recommended is 0.4 gm/kg/day for 5 days intravenously (total of 2.0 g/kg body weight). Ideally IgA deficiency should be ruled out before the administration of IVIg.

Plasmapheresis/plasma exchange

Plasmapheresis means separation of whole blood into plasma and cellular components and PE means same process with replacement by fluids. Several factors like antimyelin antibodies, cytokines, complement components, and other inflammatory mediators, which are potentially pathogenic factors, are removed by PE from the circulation.

A course of plasmapheresis usually consists of 40 to 50 mL/kg PE four times over a week. Meta-analysis of randomised clinical trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27% to 14% with PE), and increases the likelihood of full recovery at one year (from 55% to 68%).

Liquorpheresis

Liquorpheresis (CSF filtration) is a new technique developed to purify CSF from pathological factors (probably responsible for manifestation of GBS).

IVIg is preferred mode of treatment over PE because of easy administration and less of haemodynamic fluctuations (**Table 15**).

Table 15: Complications and Side Effects of PE and IVIg

Plasma exchange	Intravenous Immunoglobulin
Haemodynamic and cardiovascular Hypotension Acute respiratory distress syndrome Acute cardiac insufficiency Myocardial infarction Arrhythmias	Headache including precipitation of migraine Back pain Fever Tachycardia Aseptic meningitis
Complications due to vascular access Septicaemia Thrombosis	Rash (erythema multiforme, purpuric erythema, maculopapular, petechial)
Associated with replacement fluids/anticoagulants Allergic reactions Hepatitis, HIV (FFP) Citrate toxicity Bleeding	Alopaecia Eczema Reversible neutropaenia Haemolysis Immune complex arthritis, Thromboembolism Transmission of Hepatitis C
Depletion of plasma components Loss of clotting factors, globulins Loss of protein bound drugs	Deep venous thrombosis Congestive cardiac failure Acute hypotension
Technical complications Clotting in the tubing Air embolism Haemolysis	Oligaemic renal failure Cerebral vasospasm Anaphylaxis
Death (0 to 0.3%)	

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

CIDP is a common, albeit underdiagnosed and potentially treatable disease with an estimated prevalence of about 1 to 2 per 100,000 in adults. It causes progressive or relapsing weakness and numbness of the limbs.

Patients with AIDP reach their maximum deficit in less than four weeks whereas in CIDP progression lasts more than eight weeks. It is always necessary to exclude alternative diagnoses, such as hereditary, metabolic, vasculitic, paraneoplastic, and paraproteinaemic neuropathies.

Clinical Features

CIDP has a peak incidence in fifth and sixth decades with a male preponderance. About 65% have a relapsing course and 35% a progressive or monophasic course. There is a significant earlier onset in patients with relapsing disease. About 35% have a history of preceding infection or some other possible antecedent event. Weakness is present in both proximal and distal muscles, while paraesthesia and sensory loss are usually distal. Weakness of lower cranial nerves and intercostal muscles may occur. Hyporeflexia or areflexia develop in almost all. Papilloedema is present in 7%, and thickened nerves in 11%.

Pathology and Pathogenesis

CIDP is a multifocal demyelinating disease of peripheral nervous system, with myelin destruction mediated by macrophages that attack myelin without disturbing the integrity of Schwann cells.

Laboratory Studies

The CSF protein is elevated at some stage of the illness in almost every case of CIDP. Mononuclear cells, usually <10/μL are present, but in CIDP associated with HIV disease, a moderate pleocytosis is usual. The electrophysiological findings include multifocal nerve involvement with slowing of conduction velocity, temporal dispersion of compound action potentials, and conduction block.

Treatment

Corticosteroids, PE and IVIg are the modalities of choice. Corticosteroids (prednisone) regimen consists of an initial high daily dose of 1 to 1.5 mg/kg for one month, which is gradually tapered to an alternate day regimen of the same dose over a period of six months. If improvement commences, dose levels are lowered steadily, if weakness increases, the dose must be increased.

PE is used in some centres as the initial therapy. It produces striking benefit in patients with relapsing disease, often needing only a small number of exchanges for a brief period of time. Patients with progressive type of CIDP may require at least four weeks of alternate day pheresis for improvement to start. If no improvement occurs after 12 weeks, PE is stopped and corticosteroids are instituted. PE is not the initial treatment in older individuals because of risks of volume depletion and hypotension.

IVIg (400 mg/kg body weight for 5 days) is similar in efficacy with PE. The limiting factor is its cost and that the beneficial effect is short-lived.

Immunosuppressive therapy with azathioprine, cyclophosphamide, cyclosporine A, or lymphoid radiation, autologous stem cell transplantation is advocated for patients unresponsive to the above treatment strategies.

DISTAL ACQUIRED DEMYELINATING SYMMETRIC NEUROPATHY

Features of the disorder include an increased prevalence in men and in persons over the age of 50 years, a predominantly distal sensory loss, a mild distal weakness (as opposed to the more generalised motor deficits in classic CIDP), and an unsteady gait. IgM paraproteinaemia is present in nearly two-thirds of patients with this condition. IgM-associated cases seem to respond poorly to immunosuppressive therapy.

MULTIFOCAL MOTOR NEUROPATHY (MMN)

MMN is characterised by asymmetric weakness without sensory loss, often starting in distal arm muscles (**Figure 4**). A partial motor conduction block at multiple sites is a characteristic electrophysiologic feature. CSF protein and cell counts are usually normal. Although corticosteroids and plasmapheresis are ineffective treatments, MMN improves with IVIg or cyclophosphamide.



Figure 4: Asymmetric progressive weakness and wasting of five years duration in 40 years male in the left thenar eminence. Nerve conduction studies revealed pure motor involvement with conduction block suggestive of MMN. The patient's disease process halted following IVIg therapy.

MULTIFOCAL ACQUIRED DEMYELINATING SENSORY AND MOTOR NEUROPATHY

Multifocal acquired demyelinating sensory and motor neuropathy (Lewis-Sumner syndrome) has similarities to both CIDP (i.e. motor and sensory deficits, an elevated CSF protein content, and abnormal results on motor and sensory nerve conduction studies) and multifocal motor neuropathy (i.e. asymmetrical presentation of symptoms, and conduction block). A reasonably good response to treatment with IVIg or cyclophosphamide is seen.

RECOMMENDED READINGS

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2. Lublin FD, Miller AE. Multiple sclerosis and inflammatory demyelinating diseases of the central nervous system. In: Bradley WG, Daroff RB, Fenichel GM and Jankovic J, editors, *Neurology in Clinical Practice;* 5th Ed. Philadelphia: Butterworth-Heinemann; 2008: pp 1583-613.

20.24 Nutritional and Toxic Disorders of the Nervous System

UK Misra

Nutritional deficiency is a global problem and is common in the developing countries contributed by poverty, dietary deficiency, and coexisting infections. Protein energy malnutrition and vitamin B complex deficiency are important in the context of neurological involvement. Nutritional deficiencies are often multiple and may affect different organs such as skin, mucous membrane, hair, and the nervous system. All the parts of the nervous system such as cerebrum, cerebellum, spinal cord, peripheral nerves, and muscles may be affected independently or in various combinations. The important nutritional disorders of the nervous system are presented in **Table 1**.

Table 1: Important Nutritional Deficiencies Affecting the Nervous System

Vitamin B complex deficiency syndrome (B1, B6, B12, folic acid deficiency)
Vitamin D deficiency—osteomalacic myopathy
Vitamin E deficiency
Protein-energy malnutrition
Iodine deficiency disorders

VITAMIN B COMPLEX DEFICIENCY SYNDROME

Vitamin B12 Deficiency

The neurological manifestations of vitamin B12 deficiency are caused by defective production of intrinsic factor as a result of autoimmune gastritis produced by anti-parietal cell antibodies or as a result of gastrectomy, malabsorption syndrome, surgical resection, and blind loop syndromes. Drugs like colchicine produce vitamin B12 deficiency. Vegetarians with inadequate milk are also at risk of vitamin B12 deficiency. Nearly 20% of AIDS patients have low vitamin B12. Nitrous oxide exposure can result in a clinical syndrome similar to vitamin B12 deficiency. The daily requirement of vitamin B12 is 1 to 2µg and is present in meat, fish, eggs, milk, and fortified cereals.

Pathology

The pathological changes of vitamin B12 deficiency have been described as subacute combined degeneration of spinal cord characterised by swelling of myelin sheath followed by demyelination and astrocytic gliosis. The changes begin in lower cervical and upper thoracic spinal cord and spread up and down. The lateral columns are also affected. Papillomacular bundles of optic nerve reveal degeneration. Demyelination is also seen in cerebral white matter. Axonal degeneration without significant demyelination is seen in peripheral nerve.

Clinical features

The neurological manifestations of vitamin B12 deficiency evolve generally in subacute or chronic manner. The initial symptoms are paraesthesia, weakness, and ataxic gait due to sensory ataxia. A quarter of patients may have Lhermitt's sign. Motor deficits which appear later are limited to the legs and manifest with weakness, spasticity, hyperreflexia, extensor plantar response and gait ataxia.

In vitamin B12 deficiency, myelopathy is more common (80%) than neuropathy (20%). Neurobehavioural changes such as irritability, mental slowing, depression, confusion, delusion, hallucination, personality change, and dementia may occur. Visual impairment, loss of taste, and dyspepsia may also occur. Optic atrophy, brainstem, and cerebellar signs have been rarely reported. Anaemia is usually mild to moderate and may even be absent.

Laboratory tests

Haematological investigations reveal mild to moderate anaemia, macrocytosis, hypersegmented neutrophils, and megaloblastic bone marrow. Antibodies to intrinsic factor have replaced Schilling test because of non availability and radiation exposure. Estimation of serum B12 level provides confirmatory evidence of vitamin B12 deficiency in appropriate clinical setting. If serum B12 is normal in a strongly suspected patient with B12 deficiency syndrome, serum homocysteine and methyl malonic acid should be done which are raised. Electroencephalography (EEG) may be normal or reveal non-specific slowing. Visual evoked potential reveals prolongation of P100 latency even with normal visual functions. Tibial somatosensory evoked potentials are abnormal more frequently than motor, which may be slow or unrecordable. Peripheral nerve conductions are abnormal in minority of cases. Magnetic resonance imaging (MRI) reveals hyperintense signal changes on T2 sequence in subcortical white matter. Spinal MRI shows T2 hyperintensity in the posterior region of the cervico-thoracic spinal cord and spinal cord atrophy in advanced cases (**Figure 1**).

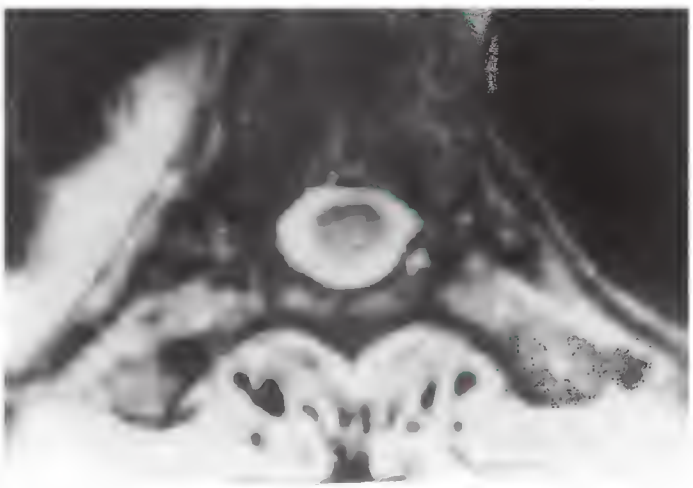


Figure 1: Spinal MRI axial section of a patient with vitamin B12 deficiency showing posterior hyperintensity.

Treatment

The patient with vitamin B12 deficiency should be treated with vitamin B12 1000 µg IM daily for 5 to 10 days followed by weekly dose for 1 month and then monthly for the rest of life. Symptomatic improvement occurs in first 6 months, though it may not be complete for 1 year or more. Recovery depends on early diagnosis and prompt treatment. The underlying cause of vitamin B12 deficiency should be addressed.

Folate Deficiency

Folate deficiency usually results in megaloblastic anaemia and neurological involvement is rare. The daily requirement of folate is 1 mg and is present virtually in all foods. The neurological syndrome in folate deficiency is similar to vitamin B12 deficiency and may occur due to inadequate intake, alcoholism, addiction, increased demand, such as haemolytic anaemia, pregnancy, malabsorption and drugs, such as 5-fluorouracil, cytosine arabinoside, phenytoin, pentamidine, nitrous oxide, etc. The patients with folic acid deficiency are more likely to be malnourished than vitamin B12. The neurological abnormalities include subacute combined degeneration, peripheral neuropathy and dementia though have been reported with folate deficiency, but are controversial. The usual therapeutic dose of folic acid is 1 mg but up to 5 mg may be required in patients with malabsorption. Duration of therapy depends on the underlying cause of deficiency.

Nicotinic Acid Deficiency (Pellagra)

Nicotinic acid can be synthesised in the body from tryptophan. Nicotinic acid is available in meat and starchy cereals. Daily requirement of niacin is 5 to 20 mg. Dietary deficiency of niacin causes pellagra (rough skin) which has been reported from Deccan plateau of India and Udaipur where consumption of maize, millet or jowar is high. High consumption of maize or millet results in imbalance of dietary amino acids, or a complex deficiency state of niacin or tryptophan. Pellagra is characterised by classical triad of diarrhoea, dermatitis, and dementia. The main gastrointestinal manifestations include, stomatitis, diarrhoea, and abdominal discomfort. The neuropsychiatric manifestations are fatigue, irritability, depression, apathy, confusion, dementia, hallucination, and eventually organic psychosis. In acute nicotinic acid deficiency, impaired consciousness, extrapyramidal signs, grasp, and sucking reflex may be present. Polyneuropathy may occur due to deficiency of other vitamins. The skin lesions are hyperkeratotic, hyperpigmented, and desquamated. Dermatitis is symmetrical and present in sun-exposed areas due to photosensitivity.

Diagnosis of pellagra is based on clinical picture, therapeutic response to niacin, and low urinary excretion of nicotinic acid metabolite and tryptophan. Plasma tryptophan and RBC nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate levels are also reduced. For treatment of endemic pellagra, niacin 10 mg orally daily is required but 40 to 200 mg daily or 25 mg 2 to 3 times daily parenterally may be needed in severe deficiency.

Thiamine Deficiency

Thiamine has specific role in nervous system independent of its function in general metabolism. Daily requirement of thiamine is 0.3 to 1.6 mg and it is widely present in vegetables and cereals. Cooking above 100°C, results in loss of thiamine. Thiamine requirement increases with high carbohydrate diet, pregnancy, lactation, and thyrotoxicosis. Excessive loss of thiamine occurs in diarrhoea, dialysis, and diuretic phase of renal failure. Defective absorption of thiamine occurs in malabsorption syndrome, alcoholism, and folate deficiency. In thiamine deficiency, nervous and cardiovascular systems are affected and result in three distinct syndromes; beriberi, Wernicke's encephalopathy and Korsakoff's syndrome.

Beriberi

Beriberi occurs due to consumption of milled rice or food containing thiaminase, such as raw fish, shrimps and raw animal tissue. Thiamine deficiency occurs in alcoholics, food faddists and patients who are starving, on dialysis or on diuretics. Neuropathy in beriberi progresses over several weeks and manifests with paraesthesia, cramps, tenderness, and leg weakness. Cardiac syndromes such as palpitation, tachycardia, dyspnoea, fatigue, and pedal oedema may also be present. On examination there is evidence of symmetric distal sensory, motor, and reflex dysfunction. Nerve conduction study and histopathology are consistent with axonal neuropathy.

Thiamine 50 to 100 mg intramuscularly daily is prescribed for 3 weeks followed by daily oral dose of 2.5 mg. Recovery occurs gradually over weeks to months. Infantile beriberi occurs in infants who subsist on mother's milk who consume polished rice as staple diet. The infant manifests with cardiac symptoms and heart failure which can be fatal. Central nervous system involvement includes drowsiness, ophthalmoplegia and convulsions. Infantile beriberi is a medical emergency and requires thiamine 5 to 25 mg parenterally.

Wernicke's encephalopathy

Wernicke's encephalopathy comprises of acute syndrome of amnesic confusional state, ophthalmoplegia and gait ataxia due to haemorrhage around aqueduct, third and fourth ventricle. Wernicke's encephalopathy is most commonly associated with chronic alcoholism, hyperemesis gravidarum, malignancy, diabetes, prolonged parenteral nutrition, starvation and anorexia nervosa. The incidence of Wernicke's encephalopathy has been estimated to be 0.8% to 2.8% and 20% of these patients are undiagnosed during their lifetime.

MRI reveals atrophy of mamillary bodies with T2 hyperintense signal changes in medial thalamus and mamillary bodies. Wernicke's encephalopathy is treated by thiamine 50 to 100 mg intravenously daily in acute stage followed by oral administration. Ocular signs respond within hours but horizontal nystagmus may persist indefinitely. Apathy and lethargy improve over days or weeks followed by gait ataxia which improves slowly. Many patients are left with persistent amnesia.

Korsakoff's psychosis

Korsakoff's psychosis refers to an amnesic confusional state where memory is impaired out of proportion to cognitive functions. Most patients are disoriented to time and place in the early stage with prominent confabulatory state. Like Wernicke's encephalopathy, Korsakoff's syndrome is best known with chronic alcoholism and has been attributed to thiamine deficiency resulting in changes in diencephalon and temporal lobe. The histopathological changes are similar to Wernicke's encephalopathy. In addition, there is involvement of medial nucleus of thalamus which is responsible for amnesia.

Pyridoxine (Vitamin B6) Deficiency

Pyridoxine is widely and uniformly available in meat, liver, vegetables and whole grain cereals. Daily requirement of pyridoxine is 0.3 to 2.1 mg which increases during pregnancy, dialysis, and high protein intake. A number of drugs, such as isoniazid, cycloserine, and penicillamine result in vitamin B6 deficiency by inhibiting the function of coenzymes. Several genetic defects also cause abnormality in pyridoxine metabolism resulting in convulsion, brain damage and death. Isolated pyridoxine deficiency in adults is rare as it is amply present in food. The clinical picture of pyridoxine deficiency comprises of following syndromes; sporadic infantile seizure, hereditary pyridoxine seizure, and peripheral neuropathy.

Sporadic infantile seizure

Sporadic case of infantile seizures due to vitamin B6 deficiency occurs in developing countries as a result of breast feeding by malnourished mothers. The infants have a normal birth history and development until irritability, exaggerated auditory startle and recurrent convulsions develop. Seizures respond dramatically to pyridoxine administration and the child has normal development.

Hereditary pyridoxine seizures

Several genetic disorders cause abnormality of vitamin B6 metabolism. In one group, infants develop brain damage and die if not treated with pyridoxine. In contrast to dietary deficiency, infant develops seizures within days of birth and requires a larger dose of pyridoxine supplementation to control seizures. In any patient with undiagnosed seizures with poor response to anticonvulsants, pyridoxine therapy should be considered.

Peripheral neuropathy

Patients receiving hydralazine, isoniazid and penicillamine without vitamin B6 supplementation may develop neuropathy. Peripheral neuropathy occurs in 50% patients who are slow acetylators of isoniazid. Tingling, numbness, and burning sensation in the feet are initial symptoms. Distal weakness, absent ankle reflex, and impaired sensations are noted. Hypervitaminosis of pyridoxine is also reported to result in predominantly sensory neuropathy.

VITAMIN E DEFICIENCY

Daily requirement of vitamin E is 3 to 10 mg and it acts as antioxidants. Neurological complications of vitamin E deficiency occur almost exclusively in patients with fat malabsorption and rarely due to congenital defect in intestinal vitamin E transport and in abetalipoproteinaemia. Pathological studies reveal degeneration of large myelinated fibres of peripheral nerve, posterior column and sensory roots. Accumulations of lipoproteins are seen in neurons of spinal cord, cerebellum, and endothelial cells. Vitamin E deficiency following malabsorption manifests after 15 to 20 years though may occur at earlier age of 2 to 3 years because of poor reserve. The clinical presentation includes ataxia and weakness, decreased proprioception and gaze paresis, resembling spinocerebellar ataxia; 50% patients have nystagmus and external ophthalmoplegia. Diagnosis is confirmed by low serum vitamin E levels. Nerve conduction studies are consistent with mild axonal neuropathy, somato-sensory and visual evoked potentials are abnormal and serum CK is mildly raised. Oral supplementation of vitamin E in a dose of 50 to 100 mg daily is most effective, if started early in course of the disease. If there is no improvement, higher dose or parenteral administration may be tried.

VITAMIN D DEFICIENCY

The patients with vitamin D deficiency may present with osteomalacic myopathy which has been described in females with poor nutrition, multiple pregnancies, continued lactation, especially in Muslims with *Purdah*. Osteomalacic myopathy can be found even in unmarried young females. In a study on 628 patients with osteomalacia from New Delhi, 84% patients had dietary vitamin D deficiency, 98% were females, 79% unmarried. Pelvic muscle weakness often follows bone pain. Shoulder girdle muscle weakness is rare. Bone tenderness, lumbar lordosis, waddling gait, Gower's sign, and brisk tendon jerks are characteristics of osteomalacic myopathy. Carpopedal spasm occurs in 50% and paraesthesia in 25% of patients. The diagnosis of osteomalacia is based on radiological (looser's zone, codfish vertebrae, triradiate pelvis, pseudo-fracture in adults and cupping of lower end of radius and ulna in children) and biochemical findings (high alkaline phosphatase, low serum calcium, phosphorus and mildly elevated serum CK). Electromyography may show myopathic features. Muscle histology is normal or shows non-specific fibre atrophy which is attributed to disuse or malnutrition rather than myopathy.

Treatment of osteomalacic myopathy is calciferol 2,000 to 4,000 IU for 6 to 12 weeks followed by daily supplementation of 200 to 400 IU. In dietary deficiency calcium supplementation 500 to 1,000 mg daily is also recommended. The laboratory parameters return to normal after a short period of vitamin D supplementation, pain disappears quickly and muscle weakness improves slowly over a period of several months.

PROTEIN ENERGY MALNUTRITION (PEM)

PEM is common in the developing countries, insufficient consumption of protein and calories results in loss of body mass and fat, though in a particular patient either may predominate. Two polar forms of PEM are found—marasmus and kwashiorkor.

Marasmus manifests with stunted growth, loss of adipose tissue, wasting, absence of oedema and pronounced weight loss (<60% of normal expected weight for the age). Kwashiorkor manifests with growth failure, oedema, hypoalbuminaemia, fatty liver, and preservation of subcutaneous fat. Kwashiorkor is attributed to selective protein malnutrition. It is associated with relative preservation of body weight between 60% and 80% expected for the age. PEM occurs in both adults and children and differentiation between the two polar terms has little clinical significance.

Acute Effects

PEM results in signs and symptoms related to both central and peripheral nervous system and muscles. Neuropsychological symptoms include apathy, irritability, attention deficit, slow learning, language deficit, and poor social skills. Rarely features of myelopathy have been reported in juvenile PEM. Soft neurological signs in rural malnourished children have correlated with degree of malnutrition. Peripheral nerve involvement is more pronounced in PEM, especially during vulnerable period, but effect is negligible if PEM occurs later. Generalised weakness, hyperreflexia, occasional sensory abnormalities, and autonomic dysfunction have been reported in PEM.

Delayed Effects

The intellectual consequences of PEM have been difficult to define because of concurrent social deprivation. The neurological and cognitive sequel of PEM depends on age, severity and duration, malnutrition on one hand and neurological reserve and plasticity on the other. Impairment of reasoning and organisation of knowledge, memory and perception have been reported in children 8 years after being rescued from Kwashiorkor. These changes further improved after dietary supplementation. Changes in motor nerve conduction velocity and motor unit potential are reversible but sensory nerve action potential may recover partially. Cognitive evoked potentials were normal in children who suffered malnutrition in infancy, but the amplitude of P3 was significantly higher compared to controls and this was regarded as a compensatory phenomena following earlier PEM. The laboratory tests reveal evidence of malnutrition, such as anaemia and hypoalbuminaemia. EEG and nerve conduction studies reveal non-specific changes.

IODINE DEFICIENCY DISORDERS

Nutritional iodine deficiency affects large population in developing countries of Asia, Africa and Latin America. In India iodine deficiency is endemic in sub-Himalayan regions. About two million people live in iodine deficient areas and one-third of them have goitres. Neurons are especially susceptible to iodine deficiency. Thyroid dysfunctions in pre-natal and post-natal period often results in irreversible brain damage. Endemic Iodine deficiency, results in two polar forms of cretins, viz. neurologic cretin and myxoedematous cretin.

Neurologic cretins have profound mental retardation, deaf mutism, lesser degree of hearing loss, rigidity and bradykinesia, less frequently strabismus, kyphoscoliosis and frontal lobe release signs. Signs of hypothyroidism may or may not be present. Myxoedematous cretinism is associated with profound intellectual impairment, growth retardation, delay in bone age, and features of hypothyroidism. Early diagnosis of iodine deficiency and hypothyroidism in the neonate may be difficult because of paucity of physical signs. Early diagnosis is critical, because delay in treatment may result in irreversible brain damage. Hence, a high index of suspicion is required especially in iodine deficiency areas.

CHEMICALS AFFECTING THE NERVOUS SYSTEM

The ever increasing list of chemical toxins is linked to industrialisation of society. Some of the important industrial neurotoxins, their use, important source of intoxication, salient clinical features and specific therapies are mentioned in **Table 2**. The toxicity of some of the chemicals which are especially relevant in the Indian context is briefly discussed.

Arsenic

Acute arsenic poisoning occurs due to high dose of inorganic arsenic compounds. The neurological symptoms include headache, vomiting, confusion, visual symptoms, convulsions, and features of raised intra-cranial tension. Skin changes occur 1 to 6 weeks after exposure and include hyperkeratosis and raindrop pigmentation and Mee's lines in the nails. Chronic arsenic poisoning occurs through contamination of food and water and results in non-specific symptoms, such as malaise,

Table 2: Some Important Industrial Chemicals and their Neurotoxicity

Chemicals	Use or Source of Exposure	Clinical Picture	Treatment
Acrylamide	Printing, paper making	Sensory motor neuropathy	—
Arsenic	Rats poison, pesticide, paint, glass, enamel	Encephalopathy, neuropathy	DMSA
Carbon disulphide	Rayon, cellophane and rubber industry	Acute: headache, irritability, delirium	
		Chronic: polyneuropathy, Parkinsonism	—
Carbon tetrachloride	Solvent, fire extinguisher	Acute: stupor, coma convulsions Chronic: headache, vertigo, visual phenomena, optic atrophy, Parkinsonism, peripheral neuropathy	—
DDT	Pesticide	Tremor, seizures, irritability, ataxia	
Ethylene glycol	Antifreeze	Stupor, coma, convulsion	Ethanol
Hydrogen sulphide	Rayon and tanneries	Delirium, seizures, coma	
Lead	Storage battery, polishing, soldering, silver refining	Encephalopathy, neuropathy	BAL, Ca-EDTA penicillamine,
Manganese	Mining, smelting, dry batteries	Hallucination, confusion, psychosis, Parkinsonism, dystonia, spastic paraplegia	Ca-EDTA
Methyl bromide	Fumigant, insecticide, refrigerant	Acute psychosis, convulsions	BAL
Methyl alcohol	Solvent, antifreeze	Visual symptoms, blindness, polyneuropathy	Ethanol
Methyl-N-butyl ketone	Solvent, plastic industry	Polyneuropathy	—
Methyl mercury	Industrial effluent	Neuropsychiatric, cerebellar, choreoathetosis, Parkinsonism, visual and hearing loss	BAL, penicillamine
Organophosphate: Tri-o-cresyl phosphate, Mepafax	In petrol to control pre-ignition	Peripheral neuropathy	—
Thallium	Extraction from ore, pesticide, firework, optical lens industry	Acute: confusion, delirium, coma, neuropathy, autonomic dysfunction, hair loss, memory loss, ataxia, tremor, foot drop	Prussian blue, potassium chloride

nausea, vomiting and diarrhoea. Arsenic neuropathy is the commonest peripheral neuropathy caused by metal. Acute or subacute form of arsenic neuropathy which is a symmetrical sensorimotor neuropathy resembling Guillain-Barre syndrome. Nerve conduction studies reveal slowing of sensory conduction and sensory nerve action potentials may not be recordable in majority of patients. Urine and nail clippings are useful for monitoring recent exposure (above 25 µg/L). Arsenic neuropathy results in distal axonopathy. Large myelinated fibres are especially involved in axonal degeneration. Evidence of segmental demyelination has been reported in some cases.

The antidotes for arsenic poisoning are dimercaprol (British anti-lewisite, BAL) and dimercaptosuccinic acid. Chelation may not significantly alter the course of neuropathy which improves slowly and spontaneously once further exposure is prevented.

Thallium

Thallium is used as insecticide, rodenticide and intentional poison. It is absorbed from dermal, gastrointestinal and through inhalation. Its clinical picture is similar to arsenic poisoning but for alopecia which manifests after 2 weeks of poisoning (**Figure 2**). The diagnosis of thallium poisoning is confirmed by blood thallium levels. Prussian blue prevents absorption from intestine and is given orally 250 mg/kg in divided doses. Induced emesis and gastric lavage are indicated within 4 to 6 hours of poisoning. Activated charcoal is used to interrupt enterohepatic circulation. Forced diuresis and potassium chloride enhance renal excretion. Role of haemodialysis, laxative and vitamin B complex therapy has been highlighted in the management of thallium poisoning.



Figure 2: Total alopaecia in a patient with thallium poisoning.

Fluoride

In India, fluorosis is endemic in Andhra Pradesh, Punjab, Haryana, Tamil Nadu, Karnataka, Gujarat, Uttar Pradesh, Maharashtra and Kerala. Neurological complications occur in about 10% of patients of fluorosis and include compression of the spinal cord or nerve roots or both. Rarely entrapment of peripheral nerves also occurs. There is no specific medical treatment for the neurological complications of fluorosis. In selected cases of myeloradiculopathy, surgical decompression has been tried with limited success.

Lead

The clinical features of lead poisoning in children are dominated by encephalopathy and in adults by neuropathy and rarely there may be illness like motor neuron disease. Symptomatic lead poisoning is characterised by abdominal pain, irritability, lethargy, anorexia, ataxia, slurred speech, convulsions, and coma. Visual loss may occur due to post-papilloedematous optic atrophy. In adults, the clinical picture comprises of lead colic, headache, joint pain, fatigue, anaemia, and peripheral neuropathy. Wrist drop and foot drop are common manifestations of lead neuropathy. Chelation therapy is recommended in all children with blood lead exceeding 55 µg/dL and 25 to 55 µg/dL if associated with encephalopathy or urinary excretion exceeds 200 µg/dL 8 hours after a single dose of Ca EDTA. In adults chelation is recommended if blood lead exceeds 80 µg/dL.

Manganese

The initial stage of intoxication is marked by a prolonged confusional hallucinatory state. Extrapyramidal symptoms include mask-like facies, drooling, monotonous dysarthric speech, stiffness, rigidity, and tremors. Corticospinal and cerebellar signs may follow. Rarely axial rigidity and dystonia have been reported. Sham-mirth or pathological laughter is considered a common feature. Spinal cord involvement in manganese poisoning was reported for the first time from India; the clinical picture is similar to that of amyotrophic lateral sclerosis. The neuropathological changes include neuronal loss and gliosis mainly affecting the pallidum, striatum, frontoparietal and cerebellar cortex, and hypothalamus. Calcium disodium edetate has been tried in the treatment of manganese poisoning with variable results. In the dystonic form of manganese poisoning, levodopa has been more useful than other anti-parkinsonian drugs.

Pesticides

A large number of pesticides are used in India, of which organochlorine (DDT, hexachlorocyclohexane, endosulphan), organophosphate (malathion, fenthion DDVP) and carbamate (Carbaryl, Baygon, Aldicarb) are most commonly used.

The syndrome of delayed organophosphate neurotoxicity follows poisoning with compounds, such as tri-ortho-cresyl phosphate, mepafox and liptophos. Ten to 20 days after the poisoning following a well-defined cholinergic phase, predominantly motor neuropathy develops. Mild sensory loss and spasticity may also be present. Pathologically, axonal degeneration and myelin loss are present distally in the largest fibres, which show dying back phenomenon. Delayed neurotoxicity is attributed to inhibition of neurotoxic esterase in the CNS.

Ethyl Alcohol

Ethyl alcohol is the commonest external toxin which affects the nervous system. Acute alcohol intoxication manifests with slurred speech, ataxia, diplopia, nystagmus, and uninhibited behaviour. These symptoms appear in a beginner at blood alcohol level below 100 mg/dL but in a chronic alcoholic these may appear at 200 mg/dL or above. At blood alcohol level of 300 mg/dL, coma may set in. Severe intoxication may result from rapid drinking which may be fatal due to a direct inhibitory effect on the brain. There is no specific therapy for acute alcoholic coma; prevention of aspiration and maintenance of oxygenation of the brain are of primary importance.

Sudden withdrawal of alcohol from a physically dependent patient can be dangerous. Many alcoholics are tremulous and irritable on waking up in the morning but they improve on drinking. If deprivation is prolonged, the symptoms may aggravate and hallucinations may appear; which are commonly auditory. Delirium tremens is a more serious condition. Besides tremor and hallucination, there may be confusion, sleepiness, restlessness, and autonomic over-activity. The patient is flushed, sweating with tachycardia, fever, dilated pupils, and tremulousness. The patient is apathetic but mutters or screams unintelligibly. Most attacks of delirium tremens subside in 1 to 2 days but mortality is 15%. Treatment includes control of infection, maintenance of fluid and electrolytes (over-enthusiastic fast correction may lead to central pontine myelinolysis) and parenteral vitamin B complex. Of the many sedatives recommended, benzodiazepines are most useful. Alcohol withdrawal can lead to seizure which may vary from a single fit to status epilepticus which is managed by lorazepam or diazepam. Regular anti-epileptic is not required.

Chronic alcoholism is often associated with nutritional deficiencies especially of vitamin B complex group. This is because of poor intake due to gastritis and high energy content of alcohol. The common nutritional syndromes include peripheral neuropathy, amblyopia, Wernicke's encephalopathy, and Korsakoff's psychosis.

Alcoholic cerebellar degeneration has a distinctive clinical picture. There is subacute or gradual onset of gait ataxia with relatively slight in co-ordination of arms. There are no ocular signs or mental changes. Nystagmus, dysarthria, and tremors are rare. Pathologically, there is atrophy restricted to the anterior lobe of the cerebellum. It has been thought to be due to nutritional deficiency. This condition remains unchanged or is slowly progressive. Remissions do not occur.

RECOMMENDED READINGS

1. Misra UK, Kalita J, Yadav RK, *et al.* Thallium poisoning: emphasis on early diagnosis and response to haemodialysis. *Postgrad Med J.* 2003; 79: 103-5.
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20.25 Metabolic Disorders of Nervous System

Vrajesh Udani

The age of molecular genetics has seen an explosion of gene mapping and identification of mutations responsible for the disease. Finally, abnormal gene products like receptors, neurotransmitters, cytoskeletal and signalling proteins responsible for the diseased state are being identified and should help in understanding the pathophysiology, paving way for rational therapy.

GENETICS

Most of these conditions are genetically transmitted and there is usually a risk of recurrence. Autosomal recessive (AR) inheritance is by far the most common and consanguinity is a significant risk factor. The risk of an affected offspring is about 25% in each pregnancy while the risk of a carrier is 50 per cent. Anticipation is (successive generations are affected earlier and more severely) another characteristic of these disorders. Fifty per cent of the offsprings are at risk. In the less common X-linked recessive inheritance (XLR), the mother is an asymptomatic or minimally symptomatic carrier with 50% of the male offsprings having a full-blown disease and 50% of the females being carriers. Mitochondrial inheritance (MI) is recognised since the last 2-3 decades. Here mitochondrial DNA transmits the disease. This is maternally inherited as mitochondria come from the ovum. There is a great deal of phenotypic heterogeneity because of heteroplasmy (variable numbers of wild and mutant mitochondria in different tissues).

CLASSIFICATION

There are several different classifications with both advantages and limitations. We will highlight the most commonly used.

Grey versus White Matter Disease

This is an old classification used for mainly chronic progressive storage disorders (**Table 1**). It was before the imaging era and may have limited relevance today.

Table 1: Examples of Disease Predominantly Affecting Grey or White Matter

Degenerative disorders of grey matter	Degenerative disorders of white matter
Neuronal ceroid lipofuscinosis	Globoid cell leucodystrophy
Menke's disease	Metachromatic leucodystrophy
Alper's disease	Maple syrup urine disease
	Alexander's disease
	Canavan's disease
	Adrenoleucodystrophy

Subcellular Organelle Affected

Here the classification is according to the predominant subcellular organelle affected, e.g. Lysosomal or peroxisomal disorders (**Table 2**). Usually a metabolic block results in an accumulation of products or depletion of necessary metabolites leading to disturbances in neuronal function or survival.

Table 2: Examples of Lysosomal and Peroxisomal Disorders

Lysosomal Disorders	Peroxisomal Disorders
GM1/GM2 Gangliosidosis Mucopolysaccharidosis	Zellweger's spectrum disorder (multiple enzyme defects)
Metachromatic leucodystrophy Gaucher's disease Niemann-Pick's disease	Adrenoleucodystrophy (defect of single peroxisomal enzyme)

Intermediary Metabolism Defects

Here the metabolic block does not lead to storage disease. However, there is intoxication with unwanted metabolites as in aminoacid disorders and organic acidaemias or failure of energy production as in mitochondrial disorders and fatty acid oxidation defects.

Disorders of Mineral Metabolism

Wilson's (excess copper) and Menke's (copper deficiency) diseases are classic examples.

Acute versus Chronic Diseases

Typically, the acute encephalopathies are seen in infants and toddlers and are usually due to diseases causing metabolic intoxication like organic acidaemias or energy failure, e.g. mitochondrial disorders. Chronic encephalopathies come at any age and are typically slowly progressive or static. They are seen in the lysosomal, peroxisomal, mitochondrial disorders and disorders of metal metabolism (**Table 3**).

Table 3: Examples of Diseases Presenting Acutely

Disease	Presentation
Ornithine transcarbamylase deficiency (urea cycle disorder)	Hyperammonaemia
Maple syrup urine disease (aminoaciopathy)	Neonatal encephalopathy
Proprionic acidaemia (organic acidaemia)	Encephalopathy-ketotic hyperglycinaemia

DIAGNOSTIC INVESTIGATIONS

One should reach a working clinical diagnosis before ordering tests. Non-directed investigations in every case are certainly not cost effective in our country.

Biochemical Tests

Screening tests are listed in **Table 4**. They are useful in screening for the aminoacidopathies, organic acidaemias, fatty acid beta-oxidation defects and mitochondrial disorders. In developed nations and now increasingly in India as well, these have been replaced by tandem mass spectroscopy (TMS) which can screen

blood and urine samples for >100 disorders. In India, further refinements like quantitative aminoacids in plasma and organic acids in urine are available by HPLC, GCMS and Gas chromatography (Table 4).

Table 4: Screening Tests for Inborn Error of Metabolism (IEM)

Blood	Urine
Complete blood count, peripheral smear examination	pH
Glucose	Ketones
Ketones	Gas Chromatography
Calcium	Mass Spectroscopy (GCMS)
Electrolytes	organic acid analysis
Blood gas	
Anion gap	
Ammonia	
Aminotransferases	
Lactate, pyruvate	
Uric acid	
Caeruloplasmin	
Phenylalanine	
Tandem Mass Spectrometry (TMS)	

Role of TMS

Tandem Mass Spectrometry (TMS, also called MS/MS) is very specific and accurate in identification of compounds in blood. It can measure very small amounts of material with excellent precision. Mass spectrometers can be thought of as very sensitive weighing scales or instruments that weigh molecules. TMS can analyse a filter paper dried blood spot specimen for 45+ metabolic disorders including organic acid, amino acid and fatty acid oxidation disorders in a single two minute analyses.

Radiology

MRI should be the primary imaging modality in patients with suspected inborn error of metabolism (IEM). It is in most cases sensitive as well as on various occasions specific for neurometabolic disorders. White matter changes (leucodystrophies) are easily identified while grey matter diseases (poliodystrophies) can be diagnosed by demonstrating progressive cortical atrophy on sequential imaging. Myelination is best noted by MRI.

Certain disorders like Leigh's disease may have variable neuroimaging findings like cerebellar atrophy; cavitatory lesions in the basal ganglia and brainstem as well as diffuse leucoencephalopathy; Occasionally malformations of cortical development (MCDs) can be seen as well.

Contrast enhanced MRI may be helpful in differentiating among leucodystrophies, e.g. post-contrast rim enhancement in Alexander's disease. MR spectroscopy (MRS) identifies the biochemical state of the central nervous system. Metabolites measured by MRS include n-acetyl aspartate (NAA), creatine, choline, lactate, glutamate , myoinositol and likewise. Canavan's disease has a larger than normal NAA peak, while mitochondrial disorders have abnormally high lactate peak. Diffusion tensor imaging and tractography is helping in diagnosis of hypomyelinating disorders like Pelizaeus-Merzbacher disease (PMD).

Advancement in MRI has made it mandatory for every patient with cryptogenic neurological disability or suspicion of metabolic disorder to undergo cranial MRI and if needed MRS/diffusion tensor imaging.

Neurophysiology

EEG is rarely specific for a particular disorder. However, epileptic abnormalities suggest grey matter disease. Nerve conduction velocity (NCV) studies demonstrate, evidence of demyelinating peripheral neuropathy in certain leucodystrophies (metachromatic leucodystrophy, Krabbe's disease) or the mitochondrial disorders like Leigh's disease. Electroretinogram (ERG) is abnormal in neuronal ceroid lipofuscinosis and peroxisomal disorders while brainstem auditory-evoked responses (BAER) confirm deafness in some of the mucopolysaccharidosis (MPS), peroxisomal diseases and Refsum's disease. Giant visual-evoked potential (VEP)/somatosensory-evoked potential (SSEP) scalp potentials suggest the possibility of progressive myoclonic epilepsy syndromes [Lafora Body disease, neuronal ceroid lipofurcinosis (NCL), myoclonic epilepsy with ragged red fibres (MERRF), etc.]

Histology

Biopsies of affected organs have nowadays been replaced by more specific enzymatic and molecular tests. Ultrastructural skin and conjunctival biopsies are still useful in neuronal ceroid lipofuscinosis and Lafora Body disease; ragged red fibres in mitochondrial disorders as well as glycogen and lipid storage disorders are identified on muscle biopsy. Brain biopsy would now seem unethical.

Molecular Diagnosis

Molecular techniques are now available to diagnose many of the mitochondrial syndromes like mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, myoclonic epilepsy with ragged red fibres (MERRF), spinocerebellar atrophies (SCAs), including Friedreich's Ataxia, Huntington's disease and the leucodystrophies (Canavan's disease, Pelizaeus-Merzbacher disease). This helps to make a very specific diagnosis not only in the patient but also in presymptomatic children, carriers and in the unborn foetus. After sequencing of the entire human genome this diagnostic technique may ultimately replace all others.

The next section deals with specific neurometabolic diseases with emphasis on those commonly seen in the Indian subcontinent.

NEONATAL-ONSET DISEASES

Neonates usually have acute encephalopathies because most illnesses presenting at this time have a complete deficiency of the enzyme. Manifestations occur only after birth. All toxic metabolites are cleared by the placenta in utero.

Disorders Presenting as an Acute Encephalopathy

The neonate becomes lethargic and hypotonic, feeds poorly, vomits, and finally develops seizures. Diagnosis needs a high index of suspicion as many diseases of the neonate like hypoglycaemia, bilirubin encephalopathy, meningitis/encephalitis and even hypoxic-ischaemic encephalopathy develop similar symptoms albeit with some differences. Consanguinity and history of prior neonatal deaths must alert the physician to the possibility of metabolic diseases.

Examination reveals stupor, poor cry, hypotonia, poor neonatal reflexes, tremor, occasionally ophthalmoplegia and sometimes evidence of other system involvement like respiratory distress and jaundice. In patients with partial deficiencies, presentation is in later life with intermittent ataxia, encephalopathy, vomiting and acidosis during illnesses or high protein loading.

Urea cycle disorders

The prevalence is estimated at 1 in 30,000 live-births. Common conditions include the X-linked ornithine transcarbamylase (OTC) deficiency, carbamyl phosphate synthetase deficiency and citrullinaemia.

All the symptoms of acute encephalopathy are seen. Seizures are prominent later and are often intractable. Cerebral oedema causes vomiting and a full fontanel. Tachypnoea leads to respiratory alkalosis. In organic acidaemias, on the other hand tachypnoea is due to metabolic acidosis – an important differentiating point between the two.

Diagnosis rests on a marked elevation of ammonia with respiratory alkalosis. Orotic aciduria is seen in OTC deficiency and high citrulline is noted in citrullinaemia. Specific enzyme estimations can be carried out in leucocytes or hepatic cells.

Treatment includes urgent peritoneal or haemodialysis followed by protein restriction and use of sodium benzoate or phenylacetic acid. Arginine should be supplemented. If left untreated or improperly managed, death or severe disability is inevitable.

Disorders of branched chain aminoacids

Maple syrup urine disease (MSUD) and the organic acidaemias (isovaleric acidaemia, propionic acidaemia and methylmalonic acidaemia) are caused by different enzyme deficiencies in the catabolism of branched chain amino acids - leucine, isoleucine and valine (**Figure 1**).

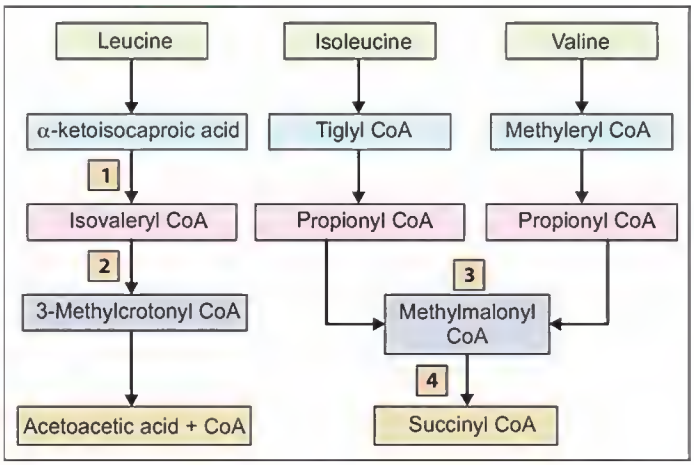


Figure 1: Branched chain aminoacid metabolism. *(1) Branched chain A - ketoacid dehydrogenase (MSUD); (2) Isovaleryl - CoA dehydrogenase (isovaleric acidaemia); (3) Propionyl - CoA carboxylase (propionic acidaemia); (4) Methylmalonyl - CoA mutase (methylmalonic acidaemia).*

Maple syrup urine disease (MSUD)

MSUD is due to a complete deficiency of ketoacid dehydrogenase and has a frequency of 1 in 200,000. An acute encephalopathy with a maple syrup smell in the urine is characteristic. Cerebral oedema can be lethal. Diagnosis is suggested by a deep blue colour in the $FeCl_3$ and a yellow precipitate in the 2,4 DNPH test.

Isovaleric acidaemia

This is a rare disorder caused by a deficiency in the enzyme isovaleryl CoA (**Figure 1**). The clinical picture is similar with a strong smell of sweaty feet. Mortality is high. Protein restriction, leucine free foods, carnitine and glycine supplements may help to a degree.

Diseases Presenting with Early Prominent Seizures

Nonketotic hyperglycinaemia

An acute encephalopathy with hiccups and persistent myoclonia is seen. These are distal and fragmentary. The seizures are initially intractable but diminish over time. The infant is left severely handicapped.

Pyridoxine-dependent seizures

Defective binding of glutamate decarboxylase with its co-factor pyridoxal-5-phosphate leads to a deficiency of g-aminobutyric acid (GABA), a major inhibitory neurotransmitter. Intrauterine convulsions are on record and clonic seizures are persistent from the initial days. The babies are jittery, irritable and have feeding difficulties. Characteristically crying continues during the seizures. IV pyridoxine 40 to 300 mg abolishes the seizures and normalises the electroencephalogram (EEG). This has to be continued life-long.

Disorders Presenting with Severe Hypotonia

Peroxisomal disorders

Zellweger's syndrome and neonatal adrenoleucodystrophy are AR prototype disorders of the first type. The incidence is estimated at 1 in 50,000.

Zellweger's syndrome presents with dysmorphic facies, severe hypotonia, hepatomegaly, increased hepatic enzymes, hearing loss, retinal pigmentary degeneration, severe retardation and seizures. There are feeding difficulties and the babies are poorly responsive. There is arthrogryposis (contractures of the fingers, knee and ankle) and areflexia. Brain malformations, renal cysts and sometimes biliary cirrhosis are noted. Life span is only a few months to a year. Neonatal adrenoleucodystrophy is a milder variant with subclinical adrenal insufficiency and failure to thrive.

The diagnosis is made by elevations of very long chain fatty acid (VLCFA), pipecolic, phytanic and bile acids in leucocytes.

Galactosaemia

This disorder is caused by a deficiency of galactose-1-phosphate uridyl transferase or its epimerase. It is now localised to 9pl3 and the frequency is 1 in 6,200. It presents with hyperbilirubinaemia vomiting and diarrhoea and if untreated children either die of sepsis or develop retardation and cataracts.

Disorders of Early Infancy (Onset usually before 6 months) with Seizures as a Prominent Symptom

Biotinidase deficiency

Refractory seizures start between 1.5 and 3 months. Hair becomes sparse, easily pluckable and alopecia results (**Figure 2**). Skin rash with seborrhoea is characteristic. Candidial infections occur due to immune dysfunction. Hypotonia, psychomotor regression, visual and hearing deficits occur later. Acidosis with alterations in sensorium are life threatening. If untreated most die within a year of onset.



Figure 2: Infant with biotinidase deficiency showing sparse hair.

Diagnosis rests on the characteristic clinical picture, high plasma lactate, ammonia and acidosis. A prompt cessation of seizures within 48 hours with biotin therapy confirms the diagnosis. Biotinidase assay done on a blood spot is now part of neonatal screening of metabolic disorders in even in India. The children remain completely normal with early treatment. Mutations in the BTD gene, located on 3p25 is responsible for partial or complete biotinidase deficiency.

Menke's disease

This X-linked disorder is due to a primary defect in the intestinal transport of copper leading to a deficiency of copper containing enzymes. In early infancy and sometimes from in the first month, males present as psychomotor regression/delay and myoclonic jerks. The infants are poorly reactive and develop sparse, hypopigmented wiry hair, which breaks easily. Hypothermia is characteristic. Microcrania is usual. Subdural haematomas may develop due to rapid brain shrinkage and paradoxically infants present as macrocrania. Tortuous intra-cranial vessels and temporal lobe changes are seen on MRI. A low ceruloplasmin and copper and a high lactate/ammonia is characteristic. Early treatment with Copper Histidine may improve an otherwise downward course.

Alper's disease

This is a heterogeneous group of conditions with spongy degeneration of the cerebral grey matter. Mutations within polymerase gamma gene (POLG) are associated with the disease. The liver is variably involved and many die of chronic hepatitis and cirrhosis. Developmental delay, refractory myoclonic or generalised seizures (**Figure 3**), status epilepticus and acute regression are manifestations. Raised liver enzymes, low albumin and abnormal liver histology of hepatitis or cirrhosis are characteristic.

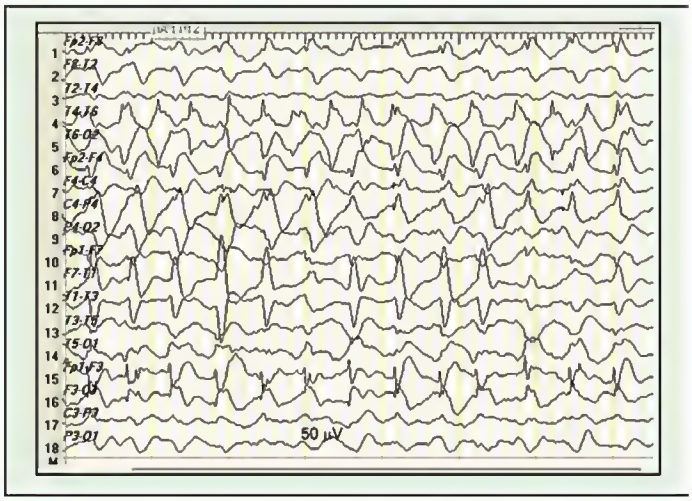


Figure 3: Typical EEG findings in a patient with POLG mutation proven Alper's disease.

Disorders Presenting as Psychomotor Retardation/Regression

Krabbe's disease

The gene of this AR leucodystrophy maps to chromosome 14. Beta-galactocerebrosidase is deficient and leads to storage of sphingosine in globoid cells in the brain and in the Schwann cells of the peripheral nerve.

Onset is below 3 months sometimes as early as in the neonatal period. Hyperacusis - increased startle response and later opisthotonus and spasticity are prominent. There are reduced or absent reflexes due to the associated demyelinating neuropathy. Infantile spasms and severe hypotonia are atypical presentations.

Early cord stem cell transplant or bone marrow transplant may be useful in less symptomatic children.

Tay-Sachs disease

This AR condition is due to a deficiency of hexosaminidase A and the gene has been localised to chromosome 15. Sandhoff disease is due to a deficiency of both Hexosaminidase A and B and is due to a mutation on chromosome 5q13. These two diseases are common in India (**Table 5**). Onset is below 3 months with delay or regression. Early hyperacusis is universal. Hypotonia, later spastic tetraparesis and a macular cherry red spot are very suggestive. Macrocephaly and seizures are other manifestations. Sandhoff's' disease has additional hepato-splenomegaly.

Pelizaeus-Merzbacher disease

This X-linked leucodystrophy is caused by deletions in the gene for proteo-lipid protein, which is a constituent of normal myelin. It is localised to Xq21-22. Rotatory nystagmus and roving eye movements are initially seen. Hypotonia, developmental delay and later cerebellar signs and spasticity supervene. Mental functions are less affected. Progression occurs later and many succumb by 5 to 7 years though prolonged survival is common.

Phenylketonuria

This AR aminoacidopathy is seen with a frequency of 1 in 10,000 and was one of the first disorders screened in normal newborns. It seems uncommon in Western India though it occurs with high frequency from South India. There is a deficiency of phenylalanine hydroxylase resulting in hyperphenylalaninaemia. In untreated

infants, developmental delay and later regression becomes apparent in early infancy. Diagnosis is suggested by a green colour in the $FeCl_3$ test. Treatment with a phenylalanine-restricted diet as soon as possible prevents mental retardation if levels are maintained between 5 and 10 mg/dL for life.

Table 5: Frequency of Common Metabolic Disorders in India (1,042 children)

Leucodystrophies	N = 118
Metachromatic leucodystrophy	47%
Megalencephalic leucoencephalopathy	29%
Krabbe's disease with subcortical cysts	14%
Other lysosomal storage diseases	N = 496
Mucopolysaccharidosis	64%
Tay Sachs/Sandhoff's disease	14%
Niemann-Pick type A	10%
GM1 gangliosidosis	6%
Gaucher's disease	4%
Aminoacid disorders	N = 206
Phenylketonuria	45%
Homocystinuria	22%
Maple syrup urine disease	21%
Organic acidaemias	N = 41
Glutaric aciduria Type 1	29%
Propionic acidaemia	19%
Methylmalonic acidaemia	19%
Mitochondrial disorders	N = 57
Leigh's disease	30%
KSS/MERRF/MELAS	11%
Others	
Wilson's disease	N = 81
Urea cycle defects	N = 21
Biotinidase deficiency	N = 21

Courtesy: Data mainly from KEM Hospital, Mumbai, PD Hinduja Hospital, Mumbai, AIIMS, New Delhi, NIMHANS, Bangalore, Bombay Hospital, Mumbai and others.

Disorders Presenting with Visceromegaly

Niemann-Pick disease types A, B, C

Types A, B are due to a deficiency of sphingomyelinase and type C is a cholesterol metabolism disorder (discussed separately). For Type A the gene has been mapped to chromosome 11. Onset is between 3 and 6 months with feeding problems, failure to thrive and predominantly hepatomegaly. A cherry red spot is seen in 50% of patients. Emaciation, opisthotonus, spasticity and blindness are end-points. Vacuolated lymphocytes and histiocytes in the blood or bone marrow, so called foam cells, are suggestive. Sphingomyelinase reduction/absence is diagnostic and readily available.

Gaucher's disease

This AR disease has a deficiency of beta-glucocerebrosidase and the gene coding the enzyme is at 1q21 to 31. Type I usually occurs in adult life, but childhood presentations are known. Clinical phenotype includes visceromegaly, bone disease and pulmonary manifestations. Type 3 occurs in later life as a spinocerebellar syndrome and dementia. Type 2 occurs in early infancy.

Onset is around 3 to 5 months of life with characteristic neck retraction, bulbar palsy, ophthalmoplegia and developmental regression. Massive splenomegaly and pancytopaenia are seen. PAS-positive cells ('Gaucher' cells) in the bone marrow and enzyme estimation clinch the diagnosis.

Though enzyme replacement is effective against Type 1, it is extremely costly and probably has little effect on neurological manifestations. Splenectomy and bone marrow transplant have also been tried in Type I.

Disorders with Macrocephaly

Canavan's disease

This AR leucodystrophy is due to a deficiency in aspartoacylase which leads to accumulation of N-aspartic acid in the white matter. It has been mapped to chromosome 17. Onset is with macrocephaly and delayed development before six months of age. The disease progresses rapidly with spasticity, seizures, cortical blindness.

Megalencephalic leucoencephalopathy with subcortical cysts (MLC)

The first reports were from the Netherlands. In the same year, Singhal from India described 30 patients, majority from the Agrawal community. AR inheritance is likely.

Macrocrania is noticed at birth or early infancy and is often misdiagnosed as hydrocephalus. After a rapid increase in the first couple of years, it stabilises. Initial development is normal or only mildly delayed. Motor problems in the form of mild clumsiness become obvious in a few patients in the preschool years. Cognitive functions appear normal in most. Later spastic ataxia occurs and may progress. Learning problems are frequent. Minor head injuries precipitate seizures followed often by a sudden deterioration in motor functions. Prognosis is variable with some children remaining stable and others becoming nonambulant. In some MRI changes may actually regress.

Alexander's disease

This sporadic disorder of the white matter is due to astrocytic dysfunction and is due to mutations in the glial fibrillary acidic protein (GFAP) gene. Rosenthal fibres are the pathological hallmark of the disease. The infantile form affects predominantly males who have psychomotor arrest/regression, macrocephaly and later spasticity and seizures. MRI shows evidence of predominantly frontal white matter demyelination with contrast enhancement. Outcome is poor with death by 2 to 3 years in most.

Disorders Characterised by Hypotonia and Weakness

Infantile pompe disease

This AR glycogen storage disorder type IIa is caused by deficiency of lysosomal acid maltase (now called alpha-glucosidase). The defective gene is localised to 17q. Macroglossia, hypotonic weakness, areflexia and cardiomyopathy are characteristic. The latter may be fatal.

Congenital disorders of glycosylation (previously called carbohydrate deficient glycoprotein syndrome)

This recently described disorder is characterised by a deficiency of carbohydrates in sialoproteins. The deficient enzyme in the common Type I is phosphomannomutase and the gene is linked to chromosome 16.

Disorders with Late Infantile Onset

These disorders have their onset between 6 months and the first 2 to 3 years of life. In these children vis-a-vis young infants, it is simpler to make a diagnosis of a progressive disease, as obviously acquired skills are lost.

Disorders with the Hurler Phenotype

Many diseases presenting primarily with retardation or regression also have non-neurological manifestations. **Table 6** lists the many conditions that conform to the so-called Hurler phenotype. Hypothyroidism should always be excluded.

Table 6: Conditions Conforming to Hurler Phenotype

Hurler Phenotype	'Hurler Phenotype' Diseases
Coarse facial features	Mucopolysaccharidosis
Abdominal hernia	Mannosidosis
Corneal opacity	Fucosidosis
Deafness	Sialidosis
Dysostosis multiplex	GM1
Mental retardation	Gangliosidosis
Stiff joints	Mucolipidosis
Visceromegaly	Multiple sulphatase deficiency

Mucopolysaccharidosis (MPS)

Currently, there are seven types described. These are the most common metabolic disease in India with a 23% incidence in one large series. Hurler (Type 1) is the commonest MPS in North and South India while Hunter (Type 2), Sanfillipo (Type 3) and Morquio (Type 4) predominate in West India. Deficiency of either a lysosomal glucosidase or sulphatase leads to storage of glycosaminoglycans in the brain, reticuloendothelial system and the connective tissue leading to the varied manifestations. **Table 7** lists the important features of the different MPS.

Table 7: Main Characteristics of the MPS

Type	Systemic Manifestations	Neurological Features	Urine Excretion	Mode of Inheritance
Hurler (IH)	Marked severe dwarfism	Severe	DS+HS	AR
Schie (IS)	Very mild	Mild	DS+HS	AR
Hunter (II)	Marked severe dwarfism	Mild-Moderate	HS	XLR
Sanfillipo (III)	Mild/Absent	Severe and Progressive	HS	AR
Morquio (IV)	Marked osseous	Absent	KS	AR
Maroteaux-Lamy (VI)	Marked osseous Severe dwarfism	Absent	DS	AR
Sly (VII)	Mild to severe	Absent to Severe	DS+HS	AR

DS = Dermatan sulphate; HS = Heparan sulphate; KS = Keratan sulphate, Different enzyme deficiencies in different subtype.

Enzyme replacement by a bone marrow transplant is encouraging and is being tried in all the MPS with maximum success in those with little or no neurological manifestations.

Disorders Presenting as Gait Difficulty

Metachromatic leucodystrophy

This AR disorder is the commonest single metabolic disorder reported from India. There is a total or partial deficiency of arylsulphatase A and this is mapped to chromosome 22. There are three forms—late infantile, juvenile and adult. Severity differences are accounted by different mutations causing the disease. Onset is with gait difficulty at a mean of 17 months. Initially ataxia or spasticity is seen with depression of tendon reflexes. Blindness and mental regression occur later. Sometimes a floppy infant presentation may be mistaken for an acquired peripheral neuropathy. Cherry red spots are seen in a few. Raised CSF protein, reduced nerve conduction velocities consistent with demyelination and diffuse white matter changes on MRI (sparing the subcortical 'U' fibres) are characteristic. Enzyme diagnosis is readily available. Bone marrow transplant in early disease sometimes helps to stabilise it.

The juvenile variety comes in school age with progressive spastic ataxia without neuropathy while the adult disorder presents as an organic psychosis.

Neuroaxonal dystrophy

This AR as yet unclassified disorder may be a disorder of retrograde axonal transport. Onset is around 14 to 18 months. Arrest in motor and later regression of motor milestones occurs. Severe hypotonia and areflexia suggest a neuromuscular disorder. Later spasticity, dementia and blindness due to optic atrophy are seen.

Ataxia telangiectasia

This AR condition is also a neurocutaneous disorder.

A slow saccadic eye movement disorder results in sudden head thrusting movements—oculomotor apraxia. Choreoathetosis and dystonia are prominent in some. Ocular telangiectasia occurs after age two. Immune deficiency and lymphoreticular malignancies are common. Ataxia progresses and patients become nonambulant by 10 to 15 years. Diagnosis rests on a high alpha-foetoprotein, low IgA and IgE. MRI shows cerebellar atrophy and chromosomal analysis reveals spontaneous and radiation induced breakages. Truncating mutations in the ATM gene located on 11q22 to 23 account for the disorder.

Avoidance of X-rays and chemotherapies and prompt treatment of infections prolongs life.

Disorders Presenting with Movement Disorder

Glutaric aciduria type 1

This AR organic acidaemia is due to a deficiency of glutaryl CoA-dehydrogenase. Initial macrocephaly and mild developmental delay are seen. An acute 'encephalitis' presentation with seizures and altered sensorium is followed by sudden regression, severe dystonia and hypotonia.

Lesch-Nyhan syndrome

This X-linked disorder is due to deficiency of hypoxanthine guanine phosphoribosyl transferase and has been mapped to Xq26-27. The excess hypoxanthine results in hyperuricaemia. Initial developmental delay and hypotonia is followed by dystonia and choreoathetosis. Later spasticity and self mutilation becomes prominent. Moderate retardation with behavioural problems is common. Death occurs as renal failure secondary to uric acid nephropathy supervenes. Gouty arthritis also develops. Allopurinol prevents the joint problems but is ineffective for the neurological manifestations.

Disorders with Intermittent Neurological Worsening

Partial enzyme defects in the urea cycle disorders, organic acidaemias and certain aminoacidurias maple symptoms urine disease, Hartnup disease come with intermittent neurologic dysfunction as either ataxia or altered sensorium. Most have been discussed previously.

Fatty acid oxidation defects

This group of disorders are due to multiple enzyme deficiencies like the medium, short and long chain acyl CoA-dehydrogenases. There is a carnitine deficiency resulting in impaired lipid transport and beta oxidation.

Leigh's syndrome

This is a common mitochondrial disorder in India. It is seen from infancy to adult life with a characteristic spongiform changes secondary to hypervascularity due to capillary proliferation in the brainstem, cerebellum, and basal ganglia. In the majority of cases, dysfunction of the respiratory chain (particularly complexes I, II, IV, or V), of coenzyme Q, or of the pyruvate dehydrogenase complex are responsible for the disease. Hypotonia, ophthalmoplegias, respiratory irregularities, and bulbar symptoms point to the predominant brainstem pathology. Choreoathetosis, dystonia, seizures, episodic stupor, optic neuropathy, and peripheral neuropathy are other manifestations. High plasma and CSF lactate and pyruvate is very suggestive but not universal.

Treatment with low carbohydrate diet, high dose vitamins (B1, riboflavin, C, K), carnitine, and coenzyme Q is occasionally helpful. Acetazolamide may help in a few cases.

CHILDHOOD AND ADOLESCENT ONSET DISORDERS PRESENTING AS SEIZURES/DEMENTIA

Progressive myoclonic epilepsy (PME) is a symptom complex with a triad of epilepsy, myoclonus, and dementia. Visual disturbances and cerebellar ataxia are other manifestations. In South India of 30 cases analysed, Lafora Body disease (21 cases) was the most common; the others include NCL, Unverricht Lundborg disease and MERRF.

Neuronal ceroid lipofuscinosis

This AR disorder is associated with neuronal storage of lipopigments. Infantile, late infantile, juvenile, and adult onset varieties are described.

Lafora body disease

This AR disease has now been associated with mutations in the EPM2A and EPM2B genes. Periodic acid-Schiff (PAS) positive polyglucosan storage Lafora bodies are seen in several tissues including the brain, liver, and sweat glands. Mean onset age is around 13 years. Generalised tonic clonic seizures, fragmentary distal intention and action myoclonus and dementia occur finally in all patients. Cerebellar signs and visual failure occur in some. Skin and liver biopsies are diagnostic. Deterioration is rapid with death within 5 to 6 years of onset.

Unverricht lundborg disease

This is a milder disorder with relatively preserved intelligence and incapacitating intention myoclonus. A triplet repeat expansion in the cystatin B gene is localised to chromosome 21. Prognosis has been improved by the use of myoclonus-reducing drugs like piracetam, N-acetyl cysteine, 5-hydroxytryptophan and anti-epileptics like zonisamide, levetiracetam, valproate, clonazepam, and primidone.

Myoclonic epilepsy with ragged red fibres (MERRF)

This maternally inherited mitochondrial disorder has a point mutation in the mitochondrial gene for transfer RNA, the most common being A8344G. There is a combined deficiency of complexes I, IV and III of the respiratory chain. Intention and action myoclonias are the main manifestations with seizures. Cerebellar ataxia, impaired position sense, deafness, mild dementia, optic atrophy, and myopathy are also seen. CSF and plasma lactate are often raised. Muscle biopsy showing ragged red fibres is diagnostic.

Disorders Presenting as Stroke

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)

This mitochondrial disorder has mutations in the mitochondrial genome. The onset is between 3 and 35 years (though usually in teenage years) with an abrupt onset of hemiparesis, hemianopia or aphasia, encephalopathy and seizures preceded by migraine-like headaches and vomiting. Epilepsia partialis continua, progressive deafness, short stature, progressive ophthalmoplegia, GI complaints, intellectual and behavioural regression, retinal and cardiac dysfunction are other manifestations. Plasma and CSF lactate is increased. Muscle biopsies show the diagnostic ragged red fibres. Mutation analysis identifies more than 80% of cases and is most commonly A3243G in the mitochondrial genome.

Homocystinuria

This AR disorder is due to a deficiency of cystathione beta synthase localised to chromosome 21. There is an accumulation of homocysteine and methionine and a depletion of cysteine. Onset is in infancy with non-specific developmental delay. The characteristic ectopia lentis and thromboembolic manifestations occur later. High plasma and urine homocysteine levels confirm the diagnosis. Pyridoxine is useful in a third. Other treatments include a low methionine, high cysteine diet with folate and B12 supplementation. Aspirin is used as an antiplatelet agent.

Presenting as Movement Disorder

Wilson's disease

This AR disorder of copper metabolism is associated with mutations in the ATP7B gene. There is an absence of a copper transport protein leading to reduced biliary excretion and accumulation in the liver and tissues like the CNS and cornea.

This is a very common metabolic disorder reported from India (**Table 5**). Onset of hepatic disease is between 3 and 5 years of age though neurologic manifestations come after eight years. It is earlier in the Indian population as the daily intake of copper is high. Acute hepatitis, fulminant hepatic failure, recurrent jaundice, chronic hepatitis and cirrhosis are all manifestations. Neurologic manifestations include a dystonic form with drooling and dysarthria, an akinetic rigid syndrome, a pseudosclerotic form with intention tremor and a choreic form. Resistant rickets, renal tubular dysfunction, acute/recurrent haemolysis, acute psychosis and cataracts are other

manifestations. Presence of the Kayser-Fleischer ring at the corneal limbus, low caeruloplasmin and high urinary copper are suggestive. Treatment with chelating agents like penicillamine, trimethyl tetramine may in many cases cause worsening in neurological presentation of Wilson's disease. Although ammonium tetrahydromolybdate, a new chelating agent is effective and better tolerated it is not yet available for commercial use. Use of zinc acetate has been useful in stabilising neurological manifestations of Wilson's disease. The dosage varies between 50 and 150 mg per day in divided doses depending on the age of the patient. Urinary copper and zinc should be done at least annually for monitoring. Recently free copper estimation in the serum helps in monitoring the copper status during treatment.

Huntington's disease

This autosomal dominant CAG triplet repeat disorder is localised to chromosome 4. The abnormal protein is identified and is named Huntingtin. There is anticipation and the transmitting parent is usually the father. Only 5% to 19% of Huntington's present before 20 years of age. Among them, onset is between 3 and 9 years with a progressive dementia, akinetic-rigid syndrome, dysarthria, and chorea. Occasionally it can present as a progressive myoclonus epilepsy (PME). Slow saccades are characteristic. MRI shows caudate atrophy; positron emission tomography (PET) identifies presymptomatic individuals. Genetic testing (number of CAG repeats) confirm the disease in patients and presymptomatic relatives.

Neurodegeneration with brain iron accumulation (previously called Hallervorden-Spatz disease)

This AR disorder has axonal spheroids similar to neuroaxonal dystrophy (see above). There is destruction of the globus pallidi and substantia nigra with deposition of iron and calcium. Initially they present in late infancy as clumsy ataxic gait. Slowly progressive dystonia and rigidity presents later between 5 and 10 years and the oromotor muscles are maximally involved leading to significant feeding and hence nutritional problems. Mental deterioration and bilateral pyramidal signs come later. Night blindness is due to retinitis pigmentosa and is often early. Calcification in the pallidum and the characteristic 'eye of the tiger' appearance in the pallidum on MRI are diagnostic. Outcome is uniformly poor. Recently trials of treatment with deferiprone, an iron chelator are underway.

Presenting with Dementia and Visual Failure

Juvenile neuronal ceroid-lipofuscinosis (NCL) (see above) and X-linked adrenoleucodystrophy are the two common disorders.

Adrenoleucodystrophy

In this peroxisomal disorder there is impaired ability to oxidise VLCFA due to a deficiency of lignoceroyl CoA ligase. It has been mapped to Xq28. Other types are the adult onset adreno-myeloneuropathy and only adrenal insufficiency without CNS involvement. Onset is between 4 to 8 years with behaviour changes, aggression and scholastic deterioration. Cortical blindness and auditory inattention follow. There may be a skin hyperpigmentation due to the adrenal insufficiency. MRI shows demyelination in the posterior white matter, which enhances with contrast. Low cortisol and a high adrenocorticotrophic hormone (ACTH) are characteristic though not universal. High VLCFA is diagnostic. Prenatal and carrier diagnosis is possible. Lorenzo's oil (erucic and oleic acid) helps normalise the high VLCFA but has little effect on the neurologic deterioration. Mustard oil may be used to replace edible oil in the diet. Carefully selected candidates for HSCT (haematopoietic stem cell transplant) have a good prognosis especially in the pre-symptomatic period of the disease (male relatives of affected boys).

Presenting with Gait Disturbances

The juvenile onset leucodystrophies and the spinocerebellar degenerations are the two major groups of diseases. The former has been touched upon earlier.

Friedreich's ataxia

This disease has been covered extensively in the chapter on cerebellar disorders.

Abetalipoproteinaemia

This AR disorder is confused with Friedreich's ataxia. It is due to reduced apolipoprotein B leading to defective fat absorption and secondary deficiency of fat soluble vitamins. Initially there are features of malabsorption with failure to thrive and bulky stools. Later the vitamin E deficiency leads to ataxia, proprioceptive sensory loss, areflexia and ocular movement abnormalities. There is retinitis pigmentosa with night blindness. Acanthocytes on smear are characteristic. Cholesterol, triglycerides, vitamin A and E levels are reduced. Absent or reduced apolipoprotein B is diagnostic. Vitamin A and E supplementation along with a long chain fatty acid restricted diet halts progression.

Refsum's disease

This AR disorder is due to phytanic oxidase deficiency leading to accumulation of phytanic acid. It presents like an intermittent or progressive peripheral neuropathy, ataxia, retinitis pigmentosa, anosmia and progressive hearing loss. Ichthyosis is common and sometimes a cardiomyopathy is seen. Diagnosis is confirmed with a high phytanic acid. Phytol-free diet reverses the changes. Plasma exchange is used initially in reducing the phytanate load especially during crises.

Kearns-Sayre syndrome

This mitochondrial disorder is associated with mitochondrial DNA deletions. Initially episodes of stupor are seen. A prominent progressive ataxia, external ophthalmoplegia, ptosis and retinitis pigmentosa are characteristic. High CSF protein and sometimes symptomatic heart block are characteristic. High dose vitamins and coenzyme Q are tried but are rarely effective.

Niemann-Pick type C

This AR disorder is due to defective intra-cellular cholesterol esterification and is mapped to 18pll. The less severe, more common form presents at 4 to 5 years with scholastic failure and gait difficulty. Bone marrow shows storage cells e.g. the sea blue histiocyte.

Cerebrotendinous xanthomatosis

This rare disorder is caused by a deficiency of a liver mitochondrial enzyme 27 hydroxylase leading to increased cholestanol and bile alcohols. It is mapped to chromosome 2. There is a slow dementia, juvenile onset cataracts and tendinous xanthomas. A progressive spastic ataxia with a neuropathy occurs in teenage years and early atherosclerosis may lead to vascular events.

DIFFERENTIAL DIAGNOSIS

Developmental disabilities: Includes autism and disintegrative disorders.

Infections: Includes subacute sclerosing panencephalitis (SSPE)

Epileptic encephalopathies: Includes infantile spasms, Lennox-Gastaut syndromes, etc.

Immune mediated encephalitis: Includes NMDA receptor antibody, and voltagegated potassium channel antibody related encephalitis, etc.

PREVENTION

Prevention of these disorders are obviously far more rewarding than treatment strategies in neurometabolic disorders.

Neonatal Screening

TMS done routinely for all neonates may be useful in screening for more than 100 inborn errors of metabolism. Many countries have made it mandatory through government funded programmes. For it to be cost effective large numbers need to be screened. Also treatable disorders are given priority. In our setting screening all high risk newborns, e.g. h/o previous neonatal death, consanguinity, etc. may be a fruitful exercise.

GENETIC COUNSELLING AND PRENATAL DIAGNOSIS

Prenatal diagnosis of a disorder needs: a definitive diagnosis in the previous sibling; and genetic metabolic tests which have a high sensitivity and specificity in the diagnosis of that particular disorder in the Indian population. Chorionic villus sampling (CVS) at ~ 10 to 12 weeks is the preferred option while amniotic fluid sampling is done after 16 weeks if the patient presents later.

RECOMMENDED READING

1. Scriver CR, Beaudet AL, Sly WS, *et al*; editors. *The Metabolic and Molecular Basis of Inherited Disease*; 7th Ed. New York: McGraw-Hill; 1995.

20.26 Intra-Cranial Space Occupying Lesions

P Sarat Chandra, PN Tandon

INTRODUCTION

The term space-occupying lesions clinically include neoplastic and non-neoplastic lesions like developmental and parasitic cysts, inflammatory granulomas, chronic abscesses etc, which by their growth produce symptoms and signs (either focal neurological deficits or features of raised intra-cranial pressure). In the following chapter, only the neoplastic lesions will be discussed.

EPIDEMIOLOGY

The incidence of brain tumours is estimated to be about 5–20 per 100,000 population. These affect all ages but with two distinct peaks, one in childhood (3 to 12 years) and another in adults (55 to 65 years). They constitute the second most common malignancy (after leukaemia) in children. Secondaries from systemic, specially breast, lung kidneys, thyroid, are common amongst the elderly, constituting nearly 25% of all systemic cancers. The incidence of primary central nervous system (CNS) lymphoma is on a rise with increasing HIV infection. **Table 1** shows a simplified classification of intra-cranial tumours.

AETIOLOGY AND PATHOGENESIS

Aetiology of neoplastic lesions of the brain is ill understood. Most CNS neoplasms are thought to arise from individual cell mutations. However, a few factors have been shown to be of significance.

- A prior history of irradiation to the head for reasons other than treatment of the diagnosed tumour increases chance of primary brain tumour.
- A few inherited diseases, such as neurofibromatosis, tuberous sclerosis, multiple endocrine neoplasia (type 1), retinoblastoma, and haemangioblastomas as part of Von Hippel Landau syndrome increase the chances to develop CNS tumours.
- Primary CNS lymphoma is a relatively frequent occurrence in HIV patients.
- Metastatic tumours reach the brain via haematogenous dissemination through the arterial system.
  - Lung cancer is the commonest solid tumour metastasising to brain, followed by breast, melanoma and colon cancer,
  - Prostate, uterine, and ovarian cancers are rare sources of brain metastasis.

Recent molecular studies have indicated the role of oncogenes, a variety of growth factors and chromosomal aberrations in the pathogenesis of some of the tumours.

Tissue culture, *in vitro* and *in vivo* labelling studies for cell kinetics, invasive index, chromosomal analysis in tumour tissue, evaluation of specific tumour markers have provided new insights regarding the pathogenesis of some of these tumours. Nevertheless, it must be acknowledged that we are still a long way from understanding the biology of most of the tumours.

Still, molecular diagnosis has become a standard for accurate characterisation of many brain tumours. The neurofibromatosis 2 tumour suppressor gene on chromosome 22q is inactivated in 40% of sporadic meningiomas. A homologous gene, DAL-1 (differentially expressed in adenocarcinoma of the lung), located on chromosome18p11.3 is lost in 60% of sporadic meningiomas. In malignant astrocytomas, there are losses of alleles at loci on chromosomes 1, 9, 10, 13, 17, 19, and 22 along with losses of p53 tumour suppressor genes and deletion of p15, and p16.

Pathophysiology

Tumours of the brain produce neurologic manifestations through a number of mechanisms.

1. By damaging specific neural pathways traversing the brain. Tumours can invade, infiltrate, and supplant normal parenchymal tissue, disrupting normal function.
2. The growth of intra-cranial tumours with accompanying oedema leads to raised intra-cranial pressure.
3. Tumours proximal and/or close to the third, lateral and fourth ventricles may obstruct the flow of cerebrospinal fluid, leading to hydrocephalus.
4. In addition, tumours generate new blood vessels (i.e., angiogenesis), disrupting the normal blood-brain barrier and promoting oedema.

The cumulative effects of tumour invasion, oedema, and hydrocephalus elevates the intra-cranial pressure (ICP) and impairs cerebral perfusion. Intra-cranial compartmental rise in ICP may provoke shifting or herniation of tissue under the *falx cerebri*, through the *tentorium cerebelli*, or through the foramen magnum.

Slow-growing tumours, particularly tumours expanding in the so-called silent areas of the brain, such as the frontal lobe, may be associated with a more insidious course. These tumours tend to be larger at detection.

Some tumours may predominantly present with epilepsy without any features of neurological deficits and raised intra-cranial pressure (ganglioglioma, dysembryonic neuro-epithelial tumours, cavernous malformations).

Most primary brain tumours do not metastasise. Rarely, when neural element tumours metastasise, intraparenchymal metastasis occurs much earlier than distant haematogenous dissemination via the arterial system.

Metastatic brain tumours from non-CNS primary tumours may be the first sign of malignancy, or they may herald a relapse. Nonetheless, the signs and symptoms of brain metastases simulate those of primary brain tumours.

Table 1: Classification of Intra-Cranial Tumours Neoplastic Lesions (modified from WHO Classification, 2000)

Neuroepithelial (Neuroectodermal)	Tumours arising from the structures of the brain, e.g. glial, neurons, etc.
Astrocytoma	
Oligodendroglioma	
Ependymoma	
Mixed Gliomas	
Choroid Plexus tumours	
Uncertain origin	
Neuronal and mixed Neuronal/Glial	
Pineal Parenchymal	
Embryonal	
Tumours of nerve sheath	Tumours arising from the covering of the nerves
Schwannoma	
Neurofibroma	
Malignant (peripheral) nerve sheath tumour	
Tumours of the meninges	Tumours arising from the covering of the brain
Meningioma	
Mesenchymal (not meningothelial)	
Benign	
Malignant	
Haemangiopericytoma	
Primary melanocytic lesions	
Lymphoma	Tumours arising from lymphocytes, usually of B cell lineage
Germ cell tumours	Tumours arising from germcells of CNS (similar to dysgerminoma of testis)
	germinoma
Cysts and tumour-like lesions	
Rathke cleft cyst	
Epidermoid cyst	
Dermoid cyst	
Colloid cyst	
Tumours of the sellar region	
Pituitary adenoma	
Craniopharyngioma	
Local extension of regional tumours	
Metastatic	
Unclassified	

CLINICAL FEATURES

Brain tumours as a rule, present with an insidious onset and progressive course. Infrequently, a tumour may manifest like a stroke, generally secondary to haemorrhage in the tumour. Rarely, there may be spontaneous remissions and exacerbations. The clinical features depend upon the age of patient, location of the tumour, its nature and rate of growth, and its effect on the cerebrospinal fluid (CSF) pathways. Brain tumours cause symptoms and signs by raising the ICP, interfering with the function of the region of brain involved. This may be either irritative or paralytic. As neuronal function is organised in a hierarchical manner, damage to one region may result in the manifestation of release symptoms and signs from a lower region. Clinical features may arise due to disturbance of function of neighbouring structures on account of oedema and vascular disturbances, or by displacement and distortion of remote structures due to foraminal herniations.

Raised Intra-Cranial Pressure

The bulk of neoplasm, oedema provoked by it and the extent of disturbance of CSF dynamics, singly or jointly, raise the ICP.

Headache

It is by far the most common symptom.

- Headache is the worst symptom in nearly 50% of patients.
- Most headaches in patients with brain tumours are non-specific and resemble tension-type headaches.
- A change in any patient's headache pattern should be cause for concern.
- New onset of headache in middle-aged or older patients should be investigated.
- The location of headache may indicate the side of the brain affected, but it does not indicate the precise site of tumour.
- Pituitary tumours confined to the sella cause midline vertex headaches.
- Typically headache is intermittent initially and becomes progressively more severe and persistent. It is only in very severe cases that it assumes the characteristic 'brain tumour' headache: often worse on waking up in the morning, interferes with sleep, throbbing in character, becomes worse on straining or exertion, usually diffuse, and relieved on vomiting.
- Tumours situated anteriorly tend to produce frontal and retro-orbital pain in the territory of trigeminal nerve. Tumours situated posteriorly or in the posterior fossa produce occipital pain in the distribution of the second cervical nerve.
- Suboccipital and nuchal pain, with or without associated neck stiffness, is of grave omen, being a manifestation of foraminal herniation.
- Vomiting is a frequent symptoms of raised ICP, but it may or may not be associated with nausea and often occurs at the peak of headache. It may be the initial or only symptom of a brain tumour in children, especially those with midline tumours in the posterior fossa, i.e. medulloblastoma or ependymoma.

Papilloedema

It is the swelling of the optic disc and, is clinically an unequivocal sign of raised intra-cranial pressure. It appears late in children in whom the skull can expand. It is also delayed in cases of slow growing tumours like meningiomas and neurofibromas. It appears early in rapidly growing tumours like gliobastomas and midline cerebellar tumours like medullo-blastomas. It may not manifest any symptom, in early stages but could progress rapidly to produce blindness with or without episodes of transitory visual obscurations. Its early detection is of paramount importance, to prevent irreversible visual loss. Hence the golden clinical rule of examining the fundus of each and every patient presenting with a neurological illness.

Optic atrophy

Persistent papilloedema leads to secondary optic atrophy even after the raised pressure is relieved by removal of the tumour. The visual loss may be irreversible.

Abducens palsy

Unilateral or bilateral abducens nerve palsy resulting in diplopia and paralytic squint is one of the most common false-localising signs of raised ICP and occurs due to stretching of both the nerves over the petrous bones ('pulled like the reigns of the horse') due to the descent of the brainstem, due to raised ICP.

Disturbance of higher mental functions like concentration, memory judgment and behaviour may result from raised ICP. With increasing ICP sensorial disturbances result, such as apathy, drowsiness, stupor and coma.

A tumour can produce focal symptoms and signs directly by destroying the neural tissue, by compressing it , by displacing or distorting it, or indirectly by involving a functionally eloquent area in secondary changes like oedema and vascular changes. These may result in irritative (epileptic) or paralytic manifestations.

Epilepsy

Seizures, focal or generalised, may be the earliest expression of a brain tumour.

- A 'Jacksonian pattern' (originally described by Hughlings Jackson), though uncommon yet strongly diagnostic of a focal structural lesion of the cortex. Here a focal seizure begins in one extremity and then progresses until it becomes generalised.
- Depending on the rate of growth of the tumour, seizures may be present for months to years before a brain tumour is diagnosed.
- Any middle-aged or elderly patient presenting with a first seizure should have CNS tumour high in the differential diagnosis.
- Patients with a brain tumour may present with acute neurologic changes mimicking those associated with stroke.

Mental status changes

Especially memory loss and decreased alertness, may be subtle clues of a frontal lobe tumour. Complaints may be as mundane as sleeping longer, appearing preoccupied while awake, and apathy.

Focal Neurological Deficits

- Tumours arising close to the motor and/or sensory strip present with progressive hemiparesis and sensory disturbances. Likewise tumours arising from language areas present with expressive aphasia (from left frontal opercular 'Broca's area') or with difficulty of comprehension (from left posterior temporal 'Wernicke's area').
- Temporal lobe neoplasms may lead to depersonalisation, emotional changes, and behavioural disturbances.
- Loss of smell strongly suggests a olfactory groove meningioma or basifrontal glioma (Foster Kennedy syndrome: optic atrophy with loss of smell).
- An acoustic neuroma may present as intermittent (then progressive) hearing loss, disequilibrium, and tinnitus.
- Symptoms of paediatric posterior fossa tumours include increased irritability, unsteadiness, ataxia, headache, vomiting, and progressive obtundation.
- Supratentorial tumours in children are more commonly associated with seizures, hemiparesis, visual field cuts, speech difficulties, and intellectual disturbance.
- Pituitary adenomas may be divided into two broad categories: nonfunctional and hypersecretory. Nonfunctional pituitary adenomas remain asymptomatic until they are large enough to encroach upon the optic chiasm and disturb normal vision. Most hypersecretory pituitary adenomas secrete prolactin, with affected women noting an amenorrhoea-galactorrhoea syndrome. Men with prolactin pituitary adenomas more commonly complain of headache, visual problems, and impotence.

Deformity of the skull, seen as generalised enlargement due to hydrocephalus or localised bulge in association with an arachnoid cyst in children, may occasionally be a presenting feature. Hyperostosis of the skull overlying a meningioma can at times produce a visible swelling. Lytic lesion of the skull with extra-cranial extension of the tumour is occasionally seen in cases of meningioma and rarely gliomas. Extension of a tumour along the optic nerve or through the superior orbital fissure may produce proptosis.

INVESTIGATIONS

Before ordering any investigation, it is essential to ascertain the site of the tumour on the basis of a careful neurological examination. This helps to plan appropriate investigations.

X-ray skull, even though hardly used nowadays can often provide useful information regarding the presence of a tumour and its site and nature, particularly in areas which have inaccessibility to a computerised axial scans (CT) or Magnetic Resonance Imaging (MRI) scans. Evidence of raised ICP should arouse suspicion of a tumour, e.g. bony changes, hyperostosis associated with meningiomas, ballooning of sella in cases of pituitary tumours, enlargement of internal acoustic meatus caused by acoustic neuromas or of optic foramen by an optic nerve glioma are a direct evidence of a specific tumour.

Plain X-ray may reveal calcification, which may be a tell-tale evidence of tumour.

Displacement of physiological calcification in midline structures like the pineal could suggest the side of a tumour.

With the availability of more sensitive and specific investigations like CT and MRI scans, the routine use of skull X-rays has become redundant, for all practical purposes. CT scan with contrast enhancement and MR imaging not only reveal the tumour, but also its precise site, size and often the nature, the extent of associated oedema, cystic degeneration, and the status of CSF pathways. MRI is preferred when a neoplasm is suspected to be near a dense bone, e.g. acoustic neuroma, tumours in the region of the foramen magnum, microadenomas of the pituitary. Similarly, small tumours in the brainstem or spinomedullary junction are better delineated in an MR study. Use of MR spectroscopy may help to determine the nature of the tumour.

Functional MR (fMRI) imaging would provide a precise relationship of the tumour to important functional regions of the brain like speech area or sensorimotor strip which help in better planning of surgery.

More recent MR imaging techniques have vastly enhanced the accuracy for diagnosis of tumours, cystic lesions and the associated brain involvement, e.g. Fluid attenuation inversion recovery sequence (FLAIR) shows the effect of fluid on the lesions. Diffuse tensor imaging (DTI) enables visualising white matter fibres in the brain and can map (tractography) subtle changes in white matter and provide its relationship to the tumour.

Cerebral angiography which was once a sheet anchor of diagnosis is now used to assess the anatomical relationship to the major vessels or to assess the vascularity of a tumour in case pre-operative embolisation is planned. MR angiography can provide a lot of this information.

A detailed neuro-ophthalmic examination and estimation of serum levels of appropriate hormones is essential for all patients with pituitary adenomas or craniopharyngiomas.

Neuro-otological investigations, including brainstem-evoked potentials (BAER), help to determine the damage in cases of acoustic neuromas. Pneumoencephalography and ventriculography are now only of historical interest.

MANAGEMENT

Early diagnosis is a prerequisite for good results. Once an important function like vision, hearing or speech is impaired or lost, even successful removal of the tumour would not resolve these functions. In our country where inflammatory lesions constitute a significant, percentage of all intra-cranial space occupying lesions, it is necessary to be alert, to this possibility since many of these; especially tuberculomas can be satisfactorily treated medically. Whenever in doubt, it is necessary to establish a histological diagnosis. Surgery, with or without radiotherapy, is the treatment of choice for a majority of neoplastic lesions. Wherever possible, total removal or maximal possible cytoreduction (especially in case of gliomas) is desirable.

Most tumours are associated with raised ICP due to brain oedema or hydrocephalus. Pre-operative use of diuretics and corticosteroids help to relieve oedema. In the event of severe rise of ICP due to hydrocephalus, especially associated with midline tumours in patient in poor general condition, external ventricular drainage or ventriculo-peritoneal shunt can be life-saving and reduce the risks of surgery. Microsurgical techniques with ultrasonic suction have markedly improved the results of surgery. The role of radiation, chemotherapy and immunotherapy is decided on individual basis. Surgery on very vascular meningiomas can be made safer by pre-operative vascular embolisation using interventional neuroradiological techniques. The residual tumour following incomplete surgical removal can now be treated with radio-surgery.

Many brain tumours may be safely operated with morbidity and mortality being same as surgery for any other part of the brain. Advances in imaging, neuroanaesthesia, operating techniques (operating microscopes, ultrasonic aspirators, brain mapping techniques, neuronavigation and stereotaxy) has now allowed surgery of tumours located in most difficult areas (mortality of 1% to 2%). However, malignant astrocytomas and glioblastoma multiforme (GBM) still carry a grim outlook. Surgery is the first consideration for supratentorial tumours (gliomas, meningiomas, ependymomas), posterior fossa tumours (medulloblastomas, ependymomas), para/intra-ventricular tumours (ependymomas, choroid plexes papillomas, pineal regions tumours) and pituitary region tumours (pituitary adenomas, craniopharyngiomas). However, the approach depends on the size and location of the tumours, e.g. pituitary tumours may be removed both through a trans-sphenoidal and a trans-cranial route.

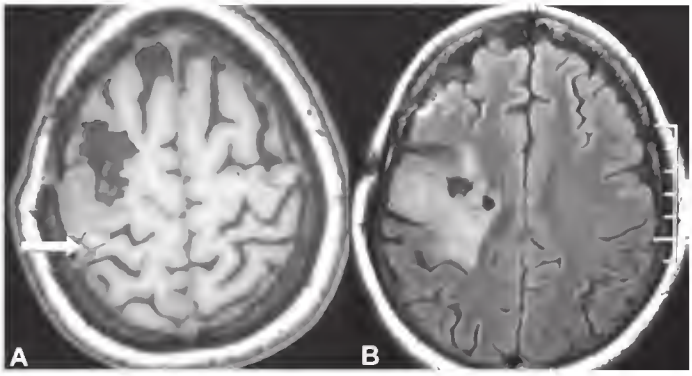
For benign tumours removed completely, e.g. meningiomas and low grade gliomas there is no need for adjuvant treatment. However, tumours like GBM require full adjuvant treatment like radiotherapy and chemotherapy.

Contrary to earlier beliefs, even tumours in the neighbourhood of eloquent areas of the brain and those already causing neurological deficit like dysphasia or motor paralysis can be successfully treated with improved and not worsened deficit. Thus, maximal tumour removal, i.e. cytoreduction, remains the most important part of the therapeutic strategy. However, deep seated tumours and those involving optic pathways, basal ganglia and brainstem continue to pose a therapeutic challenge. Stereotactic biopsy followed by radiotherapy remains the mainstay of their management.

COMMON TUMOURS

Gliomas

Gliomas are the most common intra-cranial neoplasms, constituting 35% to 50% of all brain tumours. They may arise in any part of the brain, the supratentorial ones being the most frequent. They are a heterogeneous variety of tumours with varying grades of malignancy, the juvenile cystic astrocytoma being the most benign and glioblastoma the most malignant. The majority of cerebral gliomas are located in the frontal, temporal and parietal lobes. These spread by contiguity, often crossing the midline, but rarely metastasise outside the cranial cavity. Astrocytomas (**Figures 1A and B**), mixed gliomas and oligodendrogliomas are slow-growing tumours but may suddenly begin to grow rapidly and exhibit all the characteristics of a GBM.



Figures 1A and B: (A) Shows a low grade glioma (grade II) which is hypointense on T1 weighted MRI and not enhancing on contrast. The functional MRI study showed the leg activity much behind the tumour (arrow) which gave useful information to the neurosurgeon to allow complete resection. The patient was doing well at 4 years of follow-up and did not require radiotherapy, (B) shows the FLAIR (fluid attenuation inversion recovery sequence) which shows an accurate extent of tumour.

Glioblastoma is a very rapid growing tumour with an average life expectancy of 3 to 4 months without treatment and less than a year in spite of all therapy. CT scan with contrast enhancement and MR scan with gadolinium enhancement delineate these tumours well showing areas of necrosis, with severe oedema.

One of the greatest challenges of glioma therapy is the virtual inevitability of their recurrence. A variety of radiotherapy schedules, a number of chemotherapeutic protocols and experimental trials of immunotherapy, gene therapy and even stem cell therapy are being evaluated currently.

Medulloblastoma

It is a tumour of childhood, constituting 20% to 25% of all paediatric brain tumours. It commonly affects the cerebellar vermis, and is a highly cellular tumour. It usually presents with a short history of headache, vomiting and truncal ataxia. CT scan reveals a well-circumscribed enhancing tumour in the vermis, involving the fourth ventricle and producing hydrocephalus. Treatment consists of surgery followed by chemotherapy; 40% to 70% of patients survive for 5 years and 25% to 40% for 10 years.

Cerebellar Astrocytoma

It is a distinct clinical entity mostly occurring in children. It is often possible to completely excise these tumours, resulting in virtual cure. Recurrence may, however, occur after many years following subtotal removal. Radiotherapy and chemotherapy are not indicated.

Ependymomas

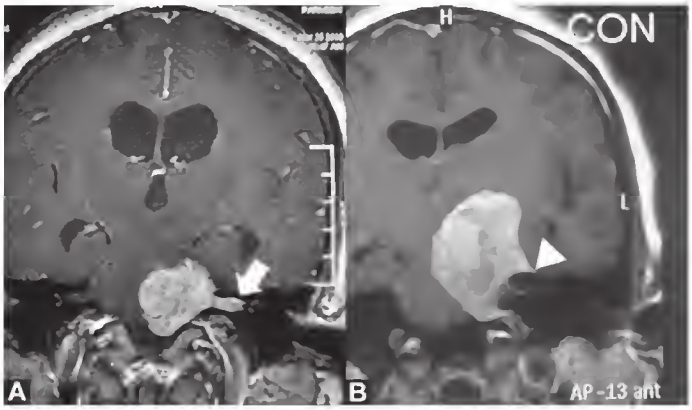
They arise from, ependymal cells lining the primitive central canal and hence occur in close proximity to the ventricular system. These constitute 5 per cent of all gliomas and two-thirds are situated infratentorially, the fourth ventricle being the commonest location. They have a tendency to disseminate along the CSF pathways to the spinal cord. Treatment consists of maximal tumour removal followed by radiotherapy.

Oligodendroglioma

Oligodendroglioma constitute approximately 5% to 7% of all primary brain tumours. Majority of these tumours are supratentorial predominantly affecting the frontal lobes. These tumours grow relatively slowly. A quarter to one-third of them show calcification on plain X-ray of the skull. The treatment consists of radical surgical excision as possible followed by radiotherapy.

Acoustic Schwannoma

It is also called acoustic neuroma or neurinoma, arises from the vestibular nerve. They constitute approximately 8% of all intra-cranial tumours. They commonly occur between the fourth and sixth decade of life, with a slight female preponderance. A majority of these tumours are sporadic and unilateral, but 5% to 10% may be bilateral as a manifestation of von Reckling hausen's neurofibromatosis. The tumour arises in the internal auditory meatus and extends into the cerebellopontine angle. The signs and symptoms are initially those referable to the eighth nerve, i.e. tinnitus, hearing impairment and vestibular dysfunction. As the tumour enlarges, it involves the facial, trigeminal and much later glossopharyngeal and vagus nerve. Large tumours also manifest signs and symptoms of cerebellar and brainstem involvement. Raised ICP is a late feature seen only with large tumours. It is possible to diagnose these tumours when they are small and still restricted to the acoustic meatus by brainstem auditory-evoked potential (BAER), CT and MR scan with gadolinium enhancement (**Figures 2A and B**). The aim of surgery is to achieve total excision with preservation of the facial and as far as possible the eighth nerve using microsurgical techniques; this is possible only in case of small tumours. One of the most gratifying advances in brain tumour surgery is in acoustic neurinomas. Utilising micro-surgical techniques it is now possible to save the facial nerve in 80% to 90% of tumours less than 3 cm in diameter and 60% to 70% of even larger tumours. Hearing preservation is also being increasingly achieved. With the advances in neuroimaging it is now possible to diagnose small tumours (<3 cm), which can be successfully treated with stereotactic radio-surgery using gamma-knife or Linnac. With advances in micro-surgery and skull base surgery it is now possible to completely excise even large tumour with a mortality of <5%, preservation of facial nerve in 60% to 70% and even the eighth nerve function in some.



Figures 2A and B: MRI (with gadolinium contrast) shows an acoustic tumour (A) Note that this tumour is well demarcated from the surrounding brainstem enhancing homogenously and well with contrast with an extension into the internal acoustic meatus (arrow). This is to be differentiated from a meningioma, (B) which too enhances well with contrast but has a wide attachment to the meninges 'dural tail' (arrow head) and has no extension into the internal acoustic meatus.

Meningiomas

These are the most common benign tumours of the brain, constituting about 10% to 15% of all intra-cranial neoplasms. They are generally located in the neighbourhood of major dural venous sinuses. They mostly occur in the middle decades of life, more often in females. This may not be possible (due to the very large size of tumour or its close relationship to vital structures, such as the optic nerve, the brainstem, a major venous sinus or the Circle of Willis. Small tumours (<3 cms in size) on residual tumour after subtotal resection can be successfully treated with stereotactic radio-surgery. These tumours are generally very vascular. The clinical picture depends upon the site and size of the tumour. Focal epilepsy and slowly progressive neurological deficits often precede symptoms and signs of raised ICP. A tumour may remain asymptomatic till it attains a large size. Occasionally these may be multiple and rarely malignant. Plain X-ray skull may reveal hyperostosis, lytic lesions, enhanced vascular markings and tumour calcification. CT scan reveals a well circumscribed hyperdense or isodense tumour with significant contrast enhancement. MR angiography may be utilised to determine the vascular anatomy in relation to the tumour. Cerebral angiography may be useful for selected

patients. Total surgical excision is the ideal treatment. This may not always be possible in which case the residual tumour may be treated with radiotherapy.

Pituitary Tumours

These constitute 8% to 12% of all intra-cranial neoplasms. The most common pituitary tumour is an adenoma arising from the anterior pituitary.

The functional tumours often produce clinical symptoms of endocrinopathies while they are still small (microadenomas) and restricted within the sella. Only when a tumour grows outside the sella can it compress the optic chiasm and nerves; the optic chiasm is situated 8 to 13 mm above the diaphragma sellae. A variety of visual field defects have been observed, the most common being bitemporal hemianopia, either incomplete or complete. As the tumour progresses it may result in primary optic atrophy and blindness. If the tumour invades the cavernous sinus it may produce oculomotor nerve palsies. A very large tumour may press on the hypothalamus, further aggravating the endocrinal dysfunction and producing behavioural and sensory disturbances. Management of these tumours requires careful evaluation of endocrinal and visual status. Medical therapy using bromocriptine or other dopamine agonists is the first-line of treatment for prolactinomas. Trans-sphenoidal surgery is indicated if the tumour is unresponsive to dopamine agonists, or the patient cannot tolerate these, as also for patients with rapid progression of visual loss. Octreotide, a cyclic octapeptide analogue of somatostatin, has been extensively used for the treatment of acromegaly or as an adjuvant to surgery if the growth hormone levels remain high post-operatively. For most other tumours trans-sphenoidal surgery is the treatment of choice, unless the tumour is very large or has atypical extension (temporal or retroclival) when transcranial surgery is preferable.

Radiotherapy is reserved for patients with incomplete tumour removal. Instead of conventional radiotherapy stereotactic radiosurgery is being used to treat residual tumours, selected tumours in place of surgery, or recurrent tumours). Hormone replacement is required post-operatively for patients with hypopituitarism.

Craniopharyngiomas

They are the commonest intra-cranial tumours of childhood. They constitute 3% to 5% of ICSOL at all ages and 12% to 15% of tumours in childhood. They can occur in adults as well. These tumours are located mainly in the suprasellar region, though they can occur anywhere along the infundibulum. They are predominantly cystic in nature with a high incidence of calcification. Clinically they manifest with features of raised ICP, endocrinological deficits and visual symptoms. Short stature, obesity and hypogonadism with delayed sexual development characterise the patients in the paediatric age group. In adults gonadal failure leads to loss of libido and secondary amenorrhoea. Visual impairment, papilloedema, primary or secondary optic atrophy and visual field defects are observed. Plain X-ray skull, by revealing characteristic changes in the sella and tumour calcification, is diagnostic in 70% to 80% of paediatric patients. CT or MR scan confirm the diagnosis. Complete endocrinal evaluation is necessary. Large tumours need surgical excision. Alternative treatment modalities like stereotactic aspiration of predominantly cystic tumours, followed by instillation of radioactive agents, or radio-surgery for small, solid tumours have provided gratifying results in selected cases. Hormone replacement, both pre and post-operatively, is necessary.

Pineal Region Tumours

Tumours in the pineal region constitute a distinct clinico-pathological entity. They account for only 1% of all intra-cranial neoplasm and often present with a characteristic clinical syndrome - 'the pretectal' or 'Parinaud's syndrome.' By pressure on the tectum, they produce vertical gaze palsy (restriction of upward gaze), binocular impairment of papillary light reflex and convergence retraction nystagmus. Some of these manifest endocrinal syndromes like precocious puberty, diabetes insipidus, hypogonadism or panhypopituitarism. Raised ICP due to hydrocephalus is present in a majority of these patients. Owing to their strategic location they present a challenge for surgical excision. Stereotactic biopsy and radiotherapy provide alternative strategy.

RECENT ADVANCES

Recent advances in neuroimaging, improved anaesthetic and intensive care management, use of new technologies, such as micro-surgery, image guided or frameless stereotactic surgery, interactive image-guided surgery using pre-operative CT/MR, use of endoscopes have dramatically improved the management of brain tumours, even those strategically located. Tumours located in eloquent areas (e.g. motor/sensory or language areas) now undergo accurate localisation of these areas using modalities like functional MRI, intra-operative brain mapping and be operated under awake conditions. Intra-operative MRI is another recent tool that allows the surgeon to visualise residual tumour in the operating room itself by performing an MRI on table and is useful particularly for performing total resection in low grade gliomas. The overall post-operative mortality has come down to negligible levels. The post-operative morbidity has been minimised.

Gene therapy for gliomas is showing a promising future. Herpes simplex virus-thymidine kinase gene therapy reached the most advanced (phase 3) of all gene therapy methods in clinical trials for glioblastoma multiforme. There was reduction in the size of the tumour with prolongation of life, but the tumours still grew and the patients died. The development of this therapy was discontinued because of lack of significant efficacy. Several modifications of viral-vector mediated gene therapy are still in clinical trials. Unfortunately a cure for gliomas is not in sight. While there is a place for technological advances, there is even greater need for research on biology of these tumours.

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20.27 Head Injury

AK Singh

DEFINITION

There is no agreed definition of head injury for epidemiological purposes. Anatomically, head refers to the scalp, skull, meninges, blood vessels and brain, i.e. all the structures above lower jaw. Trauma to any of these structures, technically, should be called head injuries, but traditionally, maxillofacial trauma is considered separately from head trauma. The term 'craniocerebral trauma' is the closest to clinical usage.

EPIDEMIOLOGY

Deaths from Trauma

Injuries are a leading cause of deaths. In 1998, about 5.8 million people died of injuries worldwide and they constituted 16% of global disease burden. India with 1% of world vehicles accounts for 6% of global road accidents. India also has a disproportionately high death rate from road accidents – at 29 per 100,000 people it is double to that of developed nations. India records 35 incidents per 1,000 vehicles, amongst the highest in the world. Head trauma is present in majority (76% according to a Mumbai study of 2004) of polytrauma victims with severe Traumatic Brain Injury (TBI) present in 47%.

Causation

Road traffic accidents are the leading causes (60%), followed by falls (20% to 25%) and violence (10%). According to Delhi police records, in road accidents, 41% of victims are pedestrians, 27% two wheeler drivers/riders and 14% pedal cyclists. Alcohol intake is reported in 15% to 20% at the time of injury.

Cost

The estimated cost of road accidents in India is 3% of gross domestic product (GDP). Costs are direct and indirect. Direct cost is the monetary value of real goods and services that were provided for health care and indirect costs are the monetary loss incurred by society because of interruption of productivity by the injured person. The family which provides the support in the recovery phase also suffers significant monetary loss besides the emotional trauma and the physical effort required for providing such care.

PATHOMECHANICS

A traumatic impact on head is a physical event that disrupts tissues, which either injures the tissue directly or starts a biochemical cascade leading to brain injury. Traditionally, we divide brain injury into primary (e.g. skull fractures, mass lesions and tissue tears) and secondary brain injuries [raised ICP and its effect and hypoxia-ischaemia, but in injuries such as diffuse axonal injuries the cascade of molecular events is common and in secondary white matter changes; only our current imaging methods are unable to show them. Some basic physical terms that are needed and used for understanding the pathomechanics are described as follows.

Mechanical Concepts

Impact, impulse and force

Impact is a type of impulsive loading. The two can accelerate a stationary head or decelerate a moving head. Mostly an impact on the head will lead to skull deformation or fracture and associated brain injuries. The magnitude of force applied to the head in an impact is a function of the mass and velocity of the striking object.

Mass

Other things (stiffness and impact velocity) being equal to the ratio of the mass of the object striking, or struck by, the head to the mass of the head itself determines the head acceleration produced by the impact.

Impact velocity

The mass and the impact velocity of the head determine the energy that must be managed to prevent head injury in an impact. There is no physical difference between the forces involved in a stationary head being hit or a moving head striking a fixed object, the other parameters being the same.

Stiffness

Stiffness is different from hardness. The less a spring deflects under a load, the stiffer it is said to be. On the other hand, a pane of glass is very hard on the surface, but will bend easily when loaded. It has low stiffness.

Moving head

Mechanism and extent of head injury depend on whether the head is free to move when stuck. If head is not free to move the entire crushing force is spent in site of impact leading to greater crush injury.

Acceleration of head

If the line of action (the vector) of the impacting force passes through the centre of gravity of the head, the head will accelerate without rotation. But if the vector passes eccentrically, the head will rotate in addition to being accelerated.

Stress

Stress is force per unit area. Mechanical stress is produced in skull and brain by an impact and the consequent head acceleration.

Strain

It is the response of the material being stressed. It is measured in terms of the proportional change in length in the direction of the tensile or compressive stress.

Shearing force

Shearing stress is force per unit area with the area measured in plane of the force. Shearing strain is proportional displacement measured in terms of the material's thickness.

Injuries to Head on Impact

Skull fractures

They can be grouped into three types: penetration fractures at impact site; comminuted fractures at site of impact; and linear fractures remote from impact site (Melvin and Evans, 1971). If the surface area of impacting object is less than one square inch, depressed fractures result with fracture starting at the external table and the diploe failing under the compressive load of the impact. If the loading of skull exceeds the minimum failure level of the diploe (approximately 1500 psi), a penetrating fracture results. Remote linear fractures usually result when the blunt trauma occurs to head. Base of skull fractures are such fractures. These are probably due to local outbending of the skull, remote from the site of impact. Once initiated, the fracture progresses bilaterally towards and away from the site of impact. For this to happen, however, the skull had to withstand local bending at impact site otherwise a depressed fracture will result.

Focal brain Injuries at the site of impact

Local skull deformation at the site of impact often causes direct damage to underlying brain. This occurs almost always with depressed fractures but even the minor indentation of skull in the first few milliseconds of the impact can compress the underlying brain even though the skull may return to its original position with no external evidence of bony deformation. These injuries are called coup injuries.

Remote focal brain injury

Contrecoup is an injury to brain on the far side of the impact site on the head. Possibly these are the results of rapid and localised pressure changes near the brain surface due to cavitation effects due to movement of brain relative to cranial cavity; brain and skull have different physical characteristics of deformation. In case of occipital impacts, however, it is possible that the remote injuries to basal frontal and temporal regions are the result of movement of brain against the irregular bony anatomy of those areas.

Multifocal and diffuse injuries

Holbourn in 1943 hypothesised that the brain is effectively incompressible. Thus pure linear acceleration could not deform brain, but angular acceleration, however, will setup shear strains within brain, thus causing injuries. These are diffuse axonal injuries and injuries to neurovascular structures. Holbourn's hypothesis has been validated by many researchers.

PATHOLOGY

Traumatic brain injuries are classified as primary, due to mechanical deformation of tissues, or secondary, due to various complications of primary mechanical injuries like brain damage.

Primary Traumatic Brain Injuries

- Diffuse/multifocal
  - Diffuse axonal injury (DAI)
  - Diffuse vascular injury (DVI)
- Focal
- Vascular injury resulting in
  - Intra-cerebral haemorrhage
  - Subdural haemorrhage
  - Extradural (epidural) haemorrhage
  - Subarachnoid haemorrhage
- Axonal injury
- Contusion: A complex dynamic evolving time dependent neural tissue injury involving vascular, glial, neuronal injury along with secondary oedema and ischaemia
- Laceration

Secondary Brain Damage/Injuries

- Diffuse
  - Diffuse hypoxic-ischaemic damage
  - Diffuse brain swelling
- Focal
  - Focal hypoxic-ischaemic injury
  - Focal brain swelling

PATHOPHYSIOLOGY OF TRAUMATIC BRAIN INJURIES

Brain is contained within the skull, a rigid and inelastic container. Only small increase in volume within the intra-cranial compartment can be tolerated before pressure within rises dramatically. This concept was defined by the Monro-Kellie doctrine, which states that the total intra-cranial volume is fixed because of the inelastic nature of the skull. In an adult, the intra-cranial volume is approximately 1,500 ml, of which the brain accounts for 85% to 90%; intravascular cerebral blood volume accounts for 10%; and cerebrospinal fluid (CSF) accounts for the remainder (<3%). When a significant head injury occurs, cerebral oedema often develops, which increases the relative volume of the brain. As the intra-cranial volume is fixed, the pressure within this compartment rises unless some compensatory action occurs, such as a decrease in the volume of one of the other intra-cranial components. This is intimately related to the concept of intra-cranial compliance, which is defined as the change in pressure due to changes in volume.

Simply stated, the brain has very limited compliance and cannot tolerate significant increases in volume that can result from diffuse cerebral oedema or from significant mass lesions, such as a haematoma. The rationale for each treatment of head injury is based on the concept of the Monro-Kellie doctrine and how a particular intervention affects the intra-cranial compliance. When the volume of any of the components of the total intra-cranial volume is decreased, the ICP is reduced.

A second crucial concept in TBI pathophysiology is the concept of cerebral perfusion pressure (CPP). The CPP is defined as the difference between the mean arterial pressure (MAP) and the ICP. In practical terms, CPP is the net pressure of blood delivery to the brain. In the noninjured brain in individuals without longstanding hypertension, cerebral blood flow (CBF) is constant in the range of MAPs of 50 to 150 mm Hg. This is due to autoregulation by the arterioles, which will constrict or dilate within a specific range of blood pressure to maintain a constant amount of blood flow to the brain. When the MAP is less than 50 mm Hg or greater than 150 mm Hg, the arterioles are unable to autoregulate and blood flow becomes entirely dependent on the blood pressure, a situation is defined as 'pressure-passive flow'. The CBF is no longer constant but is dependent on and proportional to the CPP. Thus, when the MAP falls below 50 mm Hg, the brain is at risk of ischaemia due to insufficient blood flow, while a MAP greater than 160 mm Hg causes excess CBF that may result in increased ICP. While autoregulation works well in the noninjured brain, it is impaired in the injured brain. As a

result, pressure-passive flow occurs within and around injured areas and, perhaps, globally in the injured brain. While passive damage is instantaneous, secondary brain insults occur from hours to several days after TBI and significantly alter the prognosis.

BIOCHEMICAL CHANGES

Transient mechanical microporation, cell rupture, activation of voltage and ligand gated NMDA channels and ischaemia result in entry of Ca^{++} and Na^{+} inside cells and egress of potassium ions from cells and altered state of consciousness. Even in concussive states without significant parenchymal damage, the concentration of extracellular K^{+} is increased by 50 fold. There is a direct relationship between extracellular potassium and mortality. Excess potassium in extracellular fluid (ECF) is sequestered by the glial cells, leading to swelling of the astrocytic footplates, cytotoxic oedema, increased ICP and secondary ischaemia. Disturbance of calcium homeostasis through inward movement of Ca^{++} results in metabolic cascades with dire consequences. Elevated levels of calcium in cytosol results in multimeric transformation of proteins in mitochondrial outer membrane and formation of mitochondrial permeability transition pore (MPTP). The MPTP allows abnormal concentrations of calcium in the mitochondrial matrix, disturbance of electron transport, formation of reactive oxygen species and activation of lipases, proteases and endonucleases, hence enhanced cell necrosis. Release of apoptogenic protein from mitochondria, along with intrinsic pathways, signal activation of apoptotic processes result in programmed cell death. Abnormal concentrations of Ca^{++} into the axons activate calpain-mediated cytoskeletal damage and axonal transport. The long-term effect of cytoskeletal damage is axotomy and Wallerian degeneration.

CLINICAL EXAMINATION AND GRADING

Severe closed head injuries are nowadays routinely investigated by an early CT scan, which visualises most pathological lesions of immediate surgical importance. In neuro ICUs, it is also a routine to monitor ICP and other neurophysiological parameters to better calibrate medical and surgical management. So is there any role, nowadays, for clinical neurology in traumatic brain injuries? The initial clinical assessment is still very crucial for triage and as a baseline for assessing progress for often the development of clinical symptomatology is more helpful in deciding what line of treatment to follow. Prognosis depends, to a large extent, on initial examination findings. Further, neuroradiological findings must be interpreted in light of clinical findings. Thus, neurological examination of head injury patients remains indispensable. However, modern strategies of severe head injury management have enforced a very basic change in the nature of this examination; early endotracheal intubation is established as an independent prognosticator for recovery from TBI. Therefore, the first neurological examination is now usually performed at the accident site or in the emergency room by someone with no special training in neurology, i.e. the paramedic, the intensivist or the emergency physician who must be, therefore, competent in performing an appropriate neurological examination before intubation and respiratory paralysis are started. This means that such people must be skilled in making a few basic neurological observations and recording them faithfully. These observations are done in two stages. The primary survey records, amongst other things, the consciousness level and the pupillary response (**Table 1**). If intubation is needed, a quick assessment of limb movements must be done.

Table 1: The Primary Survey—the ABCDE

	Survey	Check	Note and Record
A	Airway	Patent Noisy	Obstruction
B	Breathing	Effective	Rate and depth Chest movements Air entry Cyanosis
C	Circulation	Adequate	Pulse rate and volume Skin colour Capillary return Haemorrhage Blood pressure
D	Disability (= neurological status)	Normal	Conscious level: AVPU or preferably Glasgow coma scale (GCS) pupillary light reactions
E	Exposure (= undress)	Other injuries	Limb movements on command or on painful stimuli

In secondary survey, after resuscitation, the findings of the initial survey are checked and an assessment is made of limb movements, vision and cutaneous sensations (**Table 2**).

Table 2: The Secondary Survey—Conscious Level

History	From patient and observers
Reassessment of vital signs	As in primary survey
External signs of injury	Inspection and palpation of scalp, face, eyes and neck
Conscious level	GCS is repeated; this entails evaluation of speech and record of airway
Vision	Pupils: evaluation of size, symmetry and light reactions. Acuities and fields: assessed bedside
Limb weakness: lateralised or localised?	Detected from observation of spontaneous movement, movement on commands and on pain

GLASGOW COMA SCALE

Glasgow coma scale (**Table 3**), published by Graham and Teasdale, 1976, is the most prominent of the scores used for performing a quick assessment of neurological status, for assessing the progress and for prognosticating.

Table 3: Glasgow Coma Scale

Category	Response	Score
Eye opening	Spontaneous	4
	To sound	3
	To pain	2
	None	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor response	Obeys commands	6
	Localises pain	5
	Flexion: withdrawal	4
	Flexion: abnormal	3
	Extension	2
	None	1
Maximum score	—	14
Number of levels	—	13

Paediatric Scoring Systems

Infants or children cannot perform some of the functions tested in GCS. It is not easy to assess the conscious level in a child. A slightly modified scale is thus used for assessing infants and children (Table 4).

Table 4: Paediatric Coma Scale

Category	Response	Score
Eye opening	Spontaneous	4
	To sound	3
	To pain	2
	None	1
Best verbal response	Oriented	5
	Words	4
	Vocal sounds	3
	Cries	2
	None	1
Best motor response	Obeying	5
	Localising	4
	Flexing	3
	Extending	2
	None	1
Maximum score	—	9 to 14 depending on age of infant/child

The Pupils

Pupillary size, shape and reactivity should be recorded and then periodically reassessed to monitor the progression of disease. It is necessary to use a strong focused beam and to shield the opposite eye when performing this examination. Differential pupillary size and reactivity is often the first sign of impending brain herniation.

Eye Movements

In routine neurological examination of an unconscious patient, spontaneous eye movements should be looked for. If none is present, one should look for the Doll's eye reflex—the oculocephalic reflex—by turning the head laterally and vertically, but only after excluding cervical spinal injury. Eye movements along with the respiratory rate and rhythm are the best guides to state brainstem functions. The brainstem score made by Jennett *et al* has not found wide usage. Bonn *et al* from Liege have devised a brainstem reflex score, which when combined with GCS, in the form of Glasgow-Liege Scale (GLS), provides a more complete picture of status of an unconscious patient (Table 5).

Table 5: Liege Reflex Scale (Bonn *et al* 1982)

Brainstem Reflex	Method of Eliciting	Score
Fronto-orbicular	Light tap on glabella	5
Vertical oculocephalic	Rapidly moving head up and down	4
Pupillary light	Shining bright light in eye	3
Horizontal oculocephalic	Rapidly turning head sideways	2
Oculocardiac	Pressure on eye globe	1
No response	—	0

Fundus Examination

In acute phase, it is difficult to conduct the examination, which must be done without atrophine instillation since pupillary examination is far more informative. Retinal haemorrhages may indicate a phase of sudden rise in ICP. Massive intraocular haemorrhage may endanger vision. Papilloedema is usually not present initially but the baseline examination is useful in assessing, if it develops later on.

Limb Movements and Reflexes

The GCS examines motor functions but only the best response. It is necessary to note if either side or a limb has decreased response, the extent of its temporal course and presence of changes in tone; decreased tone indicating lower motor neuron (LMN) lesions, i.e. peripheral lesions, and increased tone suggesting upper motor neuron (UMN) lesions. Plantar reflex must be noted and monitored.

Cardiorespiratory Parameters

Raised ICP leads to slowing of pulse rate, rise in systolic BP (begins with rising pulse pressure) and irregularity and slowing of respiration (Cushing's triad). In children, a losing of pulse often happens before a fall in conscious level. Tachycardia and hypotension point to an extra-cranial source of blood loss.

Extra-cranial and external findings

Scalp and face should be carefully examined, carefully recording wounds, abrasions and swellings on a diagram. Photographs are very useful for medicolegal purposes. Impact site can be very useful, if a CT is not available and an emergency craniotomy is needed. Impact sites also have medicolegal and litigation implications. Orbital swelling may indicate anterior fossa fractures. Bruising behind ear (Battle's sign) may indicate a fracture of petrous bone, often a sign of temporal extradural haematoma.

RADIOLOGICAL ASSESSMENT

The CT scan, since its inception, has remained the investigation of choice for first and subsequent examinations for deciding the course of management (Figure 1). In an emergency room, a CT examination must include the cervical spine as well since in road traffic accidents, the cervical spine is injured in a significant number of victims. The MRI can show injuries not seen on CT and is useful in subacute and chronic phases especially for prognostication, grading of DAI and for assessing vascular injuries. In acute phase, its major role is in assessing cervical spinal cord trauma in an unconscious and intubated patient. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging are useful for cerebral protection strategies and for research into changed metabolism of injured brain. Plain X-rays of skull are nowadays used, either in centres unequipped with a CT scan or in patients with minor head injuries for identifying those with a fracture so that those can be electively scanned within the next 24 hours. At least two views at right angle to each other must be taken for a plain X-ray examination.

MANAGEMENT

Emergency

- Initial resuscitation and management: Hypotension (SBP <90 mm Hg) or hypoxia (apnoea, cyanosis, or O_2 saturation <90% or PaO_2 <60 mm Hg) must be monitored and avoided/corrected as soon as possible
- Maintain SBP >90 mm Hg
- Admit all head injury patients for observation at least for 24 hours

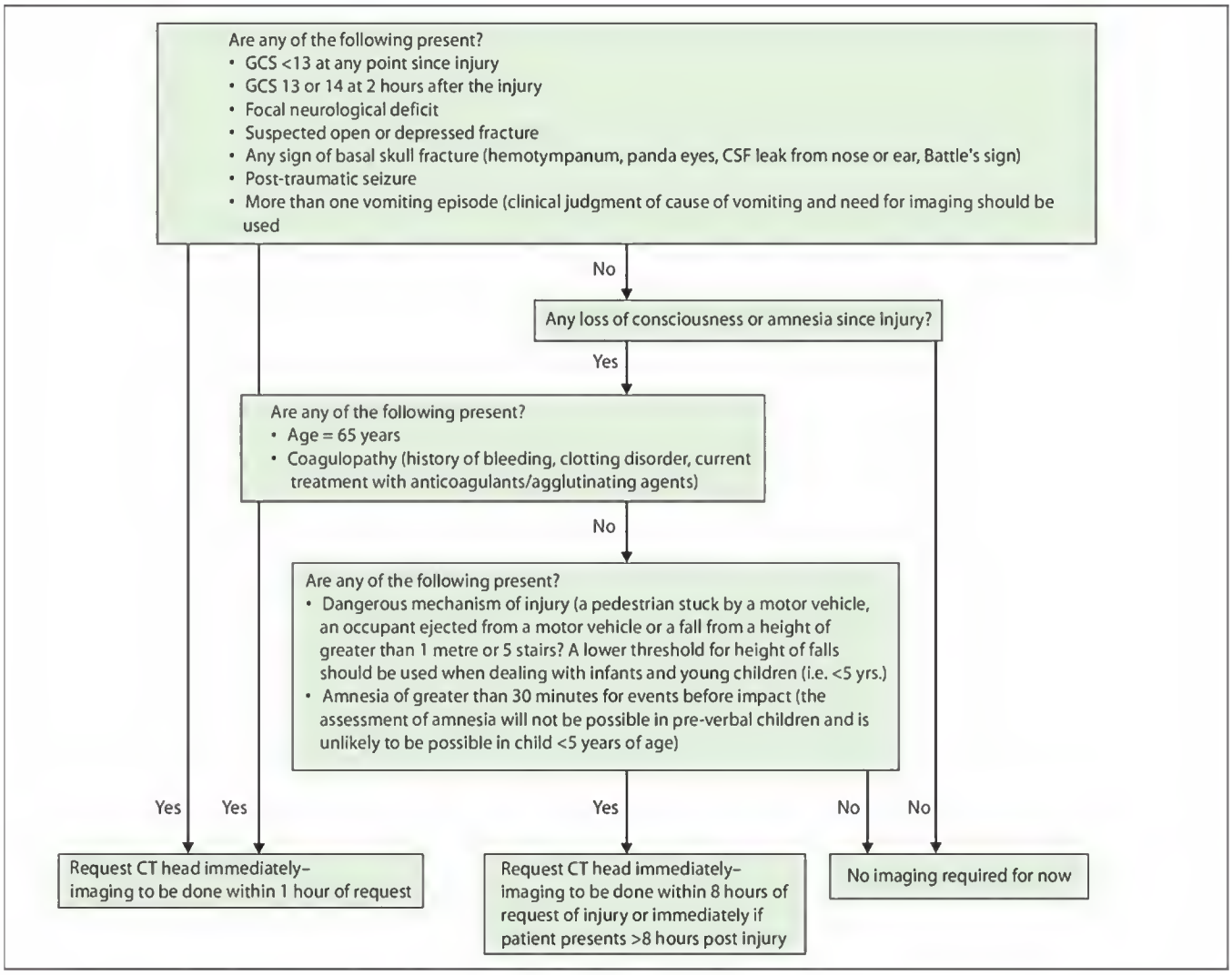


Figure 1: NICE guidelines for CT after head injury (2003).

- Nursing
  - Elevate head end 30° to 45°
  - Neuro check every 1 hour
  - Nil per orally (NPO) till alert; begin with clear fluids and advance as tolerated
  - Isotonic IV fluids: NS + 20 mEq KCl/L run at maintenance dose of approximately 100 mL/hour for adults; for children–2,000 mL/m^2/day
  - Mild analgesic
  - Antiemetics infrequently to avoid oversedation; avoid phenothiazines; use trimethobenzamide
- Patients with GCS <13 or with CT abnormalities
  Admit in ICU, preferably neuro ICU for further observation and management of ICP
- Use of paralytics and sedatives
  - Sedation and neuromuscular blockade can be useful for transporting head injury patients, but they interfere with neurological examination.
  - Paralytics should be used if sedation is inadequate, routine use of these can lead to higher pneumonia and longer ICU stay. Therefore, these should be used when absolutely essential for controlling ICP or shifting patients.
- Intubation and hyperventilation
  - Secure the airway with intubation, if needed – GCS <8; hypoxic despite supplemental O_2; maxillofacial injuries; need for pharmacological paralysis for evaluation or management.
  - If skull base fracture is suspected, avoid nasotracheal intubation and nasogastric tube placement.
  - Hyperventilation should be used in conjunction with ICP monitoring. Only if there is evidence of tentorial herniation or progressive neurological deterioration should one consider hyperventilation and that too for brief periods only. Aim at pCO_2 = 30 to 35 mm Hg. Below pCO_2 of 30 mm Hg HPV reduces CBF without reduction in ICP.
- Mannitol in emergency room
  - Mannitol to be given as a bolus approximately 0.25 to 1 gm/kg over <20 minutes. Peak effect occurs in approximately 20 minutes.
  - It is to be administered in the following cases:
    a. Evidence of raised ICP.
    b. Evidence of mass effect (focal deficit like hemiparesis).
    c. Sudden deterioration (including pupillary dilatation) prior to CT.

d. After CT, if a lesion associated with raised ICP is identified.
e. After CT, if patient is going for operation—to 'buy' time.
f. To assess 'salvageability' – in patients with no brainstem functions, look for return of brainstem reflexes.

- Anti-epileptic medication:
  As of now there is no evidence to recommend routine prophylactic use of phenytoin or carbamazepine for preventing late onset seizures. However, AEDs should be used prophylactically in patients at high risk for developing early onset seizures after TBI.

Conditions with increased risk of post-traumatic seizures

- Acute subdural, epidural or intra-cerebral haematoma
- Open-depressed fracture with parenchymal injury
- Seizure within first 24 hours after injury
- GCS less than 10
- Penetrating brain injury
- History of significant alcohol abuse
- Cortical contusion on CT

SURGICAL

Timing of decompression and adequacy of decompression are the two most important factors in prognosis. Great surgical skills are not required for these very simple and basic neurosurgical procedures nor are very advanced equipment needed for performing these procedures.

Exploratory Burr Holes

In a trauma patient, the triad of altered consciousness, asymmetrical pupils and contralateral hemiparesis is due to midbrain compression due to an uncal herniation, which is mostly due to an extra-axial intra-cerebral haematoma. The prognosis of patients with transtentorial herniation is poor. Outcome is improved by the speed with which decompression is done. Burr holes are primarily diagnostic tools since adequate decompression can often not be done through them alone but they do permit a modest decompression while a definitive craniotomy is done. With widespread availability of CT scan exploratory burr holes are rarely used nowadays. Burr holes when indicated should be placed, preferably, in the operation room but if the patient is rapidly deteriorating they can be put in emergency room/intensive care unit. A few lives may be saved thus, even in centres within house CT and 24 x 7 operating rooms.

Decompression

The site and exact techniques vary according to the site of haematoma and the location, i.e. whether it is sub or epidural or intra-cerebral. For acute subdural haematomas, the prognosis is grave and very time-dependent. If the haematoma is significant, it must be removed by a large, often a hemispheric one, craniotomy. In this, as in malignant traumatic oedema, the bone flap is best stored in the subcutaneous plane of the patient. The bone flap should be replaced as soon as the patient is stable. In epidural haematomas which are causing clinical symptoms, the craniotomy is placed on the haematoma site. In intra-cerebral haematomas a smaller suitably placed craniotomy is adequate since damage to overlying brain must be kept to a minimum. In temporal lesions which have already caused transtentorial herniation, best results are obtained by infratemporal lobectomy and section of free edge of tentorium to release the uncus and equalise CSF pressures within supra- and infra-tentorial compartments.

Depressed Fractures

Pond fractures

These are found in infants and in very small children where the bones are still elastic and thus skull vault often bends inwards under an impact. Small indentations, especially those away from eloquent areas, require no elevation and the bone often gets remodelled as the child grows. But large depressions, especially those on the motor area, are best elevated using a small burr hole and a blunt Penfield dissector for elevating the depressed bone.

Large or comminuted fractures

These should be surgically debrided and converted into simple fractures as early as possible.

Penetrating Wounds

Missile

Gunshots are self sterilising due to the high heat. However, the gunshots also drive in many dirty particles, hair and dirt from outside. These wounds should be removed and the wound closed after debridement.

No missile penetrating wounds

They require debridement at the earliest.

CSF Otorrhoea

Mostly settles down with conservative treatment which includes prophylactic antibiotics and dehydrants.

CSF Rhinorrhoea

Majority of post-traumatic CSF rhinorrhoea settle down with conservative management within a week. Sometimes, if the defect is large or if there is significant basal contusion surgical repair with removal of contused brain may be required. Late CSF leaks are mostly sealed using the trans-nasal endoscopic route.

PREVENTION

Primary Event

Prevention is always better than cure and a lot less costly too. Public awareness and education are the cornerstone, since the victims are part of society and will influence laws that govern. One such public awareness programme is the 'Think First Prevention Programme'. Some of the important aspects are:

Road traffic safety

Obey traffic rules

Alcohol control

- Avoid driving after consuming alcohol
- Take a taxi

Better Roads and Speed Control

Pot-holed roads with poor lighting and unmanned crossings cause problems. Roundabouts seem to be better at reducing speed than cross roads.

Vehicle Design

- Non-shattered windscreens, airbags and seat belts must be provided for all commuters.

- Airbags should be for all occupants, not only front seat passengers.
- Children should be harnessed and on the rear seat. Seat belts, properly designed, save many lives.
- All occupants, including the ones on rear seats should fasten the belts in a moving vehicle.

Driver Behaviour

In India, it is still possible to obtain a driver licence without any training! Road rage is becoming common. Traffic rules are observed only when the constable is present.

Helmets

For motorcycle, scooter and bicycle drivers and riders have prevented more serious head injuries than any other single measure. Helmets, properly designed and constructed, act as second skull absorbing most of the shock of an impact thus deflecting the force from harming brain.

Secondary Insult

The entire management from the moment of impact is geared towards preventing or minimising secondary injuries that are set in motion from the moment of primary injury.

RECOMMENDED READINGS

1. Ganong WF. Circulation through special regions. In: Ganong WF, editor. *Review of Medical Physiology;* 21st Ed. New York: McGraw Hill; 2003.
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20.28 Myelopathies

S Venkataraman

Diseases of the central nervous system (CNS) can be confined to the spinal cord, sometimes resulting in extensive and varied clinical syndromes of quadriplegia, paraplegia with sensory deficits and bladder involvement because the spinal cord contains the entire motor/sensory output of the trunk and limbs in a small cross sectional area. Disorders of the spinal cord can be caused by hereditary, traumatic, vascular, inflammatory, neoplastic, demyelinating disorders and nutritional deficiency. Myelopathy, is a generic term to denote the involvement of the spinal cord, due to compressive or non-compressive causes. Many spinal cord diseases (compressive/non-compressive) may be treated efficiently if identified at an early stage. Neuroimaging techniques like CT/MRI have greatly improved the diagnostic accuracy in spinal cord disorders and have shifted the emphasis more in favour of compressive lesions. Though the conditions causing myelopathy (compressive/non-compressive) are dealt with in this chapter, certain diseases like motor neuron disease, fluorosis and myelopathy due to cervical/lumbar spondylosis have been dealt with in detail elsewhere.

A review of spinal anatomy and vascular supply of the spinal cord will ensure a better understanding of disorders causing myelopathy.

ANATOMY

The spinal cord is 42 to 45 cm long and occupies the vertebral column, extending from the foramen magnum above to the conus medullaris at its lower end at the level of the L1-L2 intervertebral space. The filum terminale, the remnant of the neuroectodermal bud, accompanies the arachnoidal sac to its termination at the second sacral segment. The spinal cord has two enlargements the cervical and lumbar from which originate the nerves of brachial and lumbar plexuses, respectively (**Figure 1**). Spinal cord is covered immediately by the pia mater which is continuous with the pia of the brain and is bathed in cerebrospinal fluid (CSF), with the arachnoid mater and the dura mater forming the outer meningeal sheaths. The dura mater is firmly attached to the edge of the foramen magnum at its upper end, but below, there is an epidural space containing veins and fatty tissue. The nerve roots and spinal nerves in the spinal canal up to the intervertebral foramina are covered by meningeal sheaths and are also bathed in CSF. The cord is kept in place in the spinal canal by two rows of transverse denticulate ligaments.

The spinal cord gives out paired nerve roots, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal. Ventral or anterior roots are motor and dorsal or posterior roots are sensory. These two roots coalesce to form the mixed spinal nerve, and there are a total of 31 pairs. The first cervical segment lacks a dorsal root in human beings. The dorsal root has a dorsal root ganglion. The nerve roots exit from the vertebral column through the intervertebral foramina. As the growth of the cord lags behind that of the vertebral column, in the embryonic stage, the

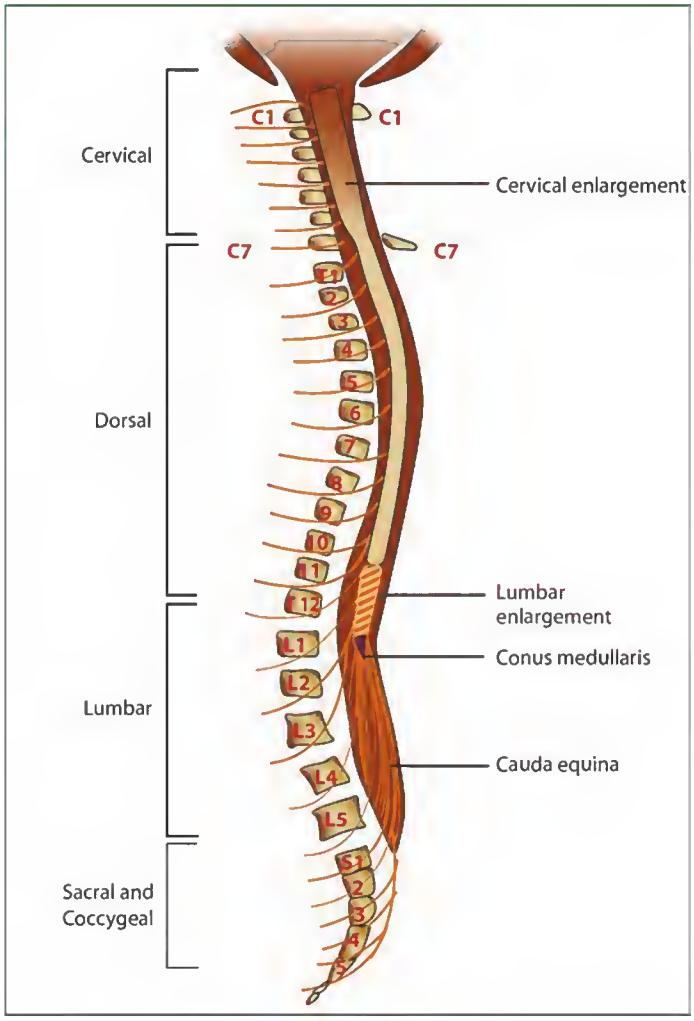


Figure 1: Spinal nerves.

downward direction of the spinal nerves is progressively greater as we approach the lower end of the cord, though at the cervical end, the 8th cervical spinal nerve exits between the C7 and T1 vertebrae. In the lumbosacral region, the nerve roots descend below the cord forming the cauda equina.

A cross section of the spinal cord shows an internal mass of grey matter shaped like a butterfly, with the anterior portion which is mainly motor and the posterior portion which is sensory.

The white matter is made up of columns and ascending and descending tracts. The dorsal columns (gracile and cuneate fasciculi), lying between the posterior horns of the spinal grey matter contain primary afferent fibres from cutaneous and articular mechanoreceptors. The dorsal columns and dorsal spinocerebellar tracts are ipsilateral with respect to their peripheral input while the ventral spinocerebellar and spinothalamic tracts are crossed. The spinoreticular pathways

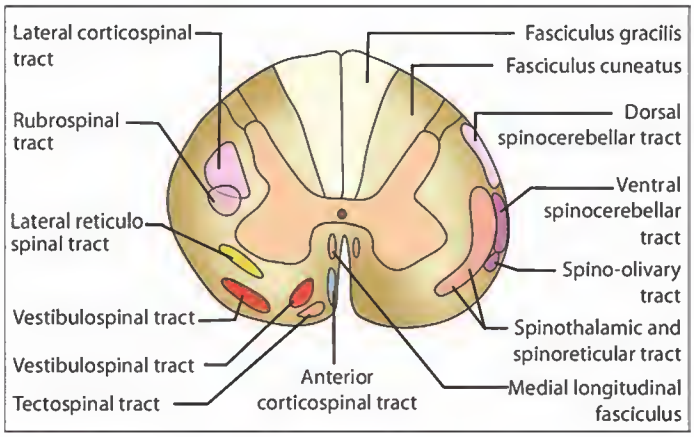


Figure 2: Cross-section of spinal cord.

are both crossed and uncrossed. The long descending tracts are found in the lateral and anterior funiculi (**Figure 2**). Of these the corticospinal tract from the sensorimotor cortex and the rubrospinal tract from the red nucleus are crossed, while the reticulospinal fibres from the reticular system are both crossed and uncrossed. The long descending tracts are found in the lateral and anterior funiculi. The vestibulospinal fibres from the vestibular nucleus of the medulla are uncrossed.

Arterial Supply

Arterial supply is divided into extraspinal system (extramedullary) and intraspinal system (intramedullary).

Extraspinal system

The extraspinal system is formed by the anterior and posterior spinal arteries. There is a single anterior spinal artery which supplies the anterior two thirds of the cord and paired posterior spinal arteries supplying posterior one-third of the cord on either side (dorsal columns and the dorsal horns).

These are in turn supplemented by radicular arteries arising from, vertebral, ascending and deep cervical arteries and the aorta. The most important radicular artery is the 'artery of Adamkiewicz' which supplies the cord below T9-T10 level. Another area of importance is the mid-thoracic region (T4) which is poorly vascularised and is considered as the vascular 'watershed area'.

Intraspinal system

The branches from anterior and posterior spinal arteries form a perimedullary circuit around the cord. Branches from this plexus supply the deeper parts of the cord.

Dermatome

A dermatome is a well defined segmental portion of the skin to which the sensory component of each spinal nerve is distributed (**Figure 3**). The cutaneous distribution usually coincides with the segmental distribution of underlying muscle innervation (myotome). Thus, a single nerve root lesion may be traced by detecting the dematomal distribution of the sensory deficit and the 'segment-pointer muscle' that is involved.

CLINICAL LOCALISATION OF SPINAL CORD DISEASES

The presence of a transversely defined level below which motor, sensory and autonomic functions are altered is the hallmark of spinal cord disease. At the level of the lesion weakness of the affected muscles supplied by the segment and loss/diminished tendon reflexes are elicitable. The level of sensory loss or impairment indicates the damage to the spinothalamic tracts one or two segments above perceived level of a unilateral spinal cord lesion and at the level of a bilateral lesion. Below the level of lesion there is upper motor neuron type of weakness—spasticity, brisk or exaggerated deep tendon reflexes and extensor plantar response—due to involvement of descending cortico-spinal tracts. Autonomic dysfunction below the level of lesion manifests as abnormality in sweating, bladder, bowel and sexual dysfunction.

The uppermost level of lesion in a spinal cord disorder can be assessed by observing 'segmental sign' which corresponds to the disturbed motor/sensory innervation of the affected segment – a band of hyperalgesia or hyperpathia at the upper end of sensory disturbance, atrophy/fasciculations in the muscles innervated by the affected segments and diminished/absent deep tendon reflexes involving the muscles supplied by the affected segment.

The main features of transverse level spinal cord lesion at various levels may be summarised as under:

Cervical cord lesions may produce quadriplegia and weakness of diaphragm. Weakness in upper limbs is of lower motor neuron type and upper motor neuron type in lower limbs. Quadriplegia occurs with C4/5 lesion; weakness of biceps with C5/6 and weakness of triceps and extensors of wrist and fingers with C7 lesions may be prominent.

Dorsal cord lesions may be localised with sensory level/back pain at – T4 for nipple level and T10 for umbilical level. With T9/T10 level lower abdominal muscles may be weak and on abdominal wall contraction umbilicus may move up (Beevor's sign).

Lumbar cord lesions between L2-L4 segments results in weakness of adduction/flexion of thigh and extension of knee with loss of knee jerk, whereas lesions between L5 and S1 cause weakness of foot and ankle movements, flexion of knee and extension of thigh with loss of ankle jerk.

Sacral cord/conus medullaris: Lower sacral and coccygeal segments are contained in the tapering Conus end of the spinal cord. Conus medullaris involvement results in bilateral saddle anaesthesia (S3-S5), bladder and bowel dysfunction and impotence. Bulbo-cavernosus and anal reflexes (S4/5) are absent, whereas muscle strength is by and large preserved.

Cauda equina lesions are characterised by low back and radicular pain, asymmetric weakness in legs, asymmetry in deep tendon reflexes with relative sparing of bladder and bowel function.

PATTERNS IN SPINAL CORD DISEASE

Spinal cord contains ascending and descending pathways which may be crossed or uncrossed. The posterior columns, spino-cerebellar and pyramidal tracts are uncrossed (ipsilateral to the side they supply) in spinal cord whereas afferent fibres mediating pain and temperature ascend contralateral to the side they supply.

Based on the anatomic configuration of the tracts, characteristic clinical syndromes are identifiable.

Foramen Magnum Syndrome

At this level decussating pyramidal fibres for the leg cross caudal to the fibres for the arms and results in weakness of legs—crural paresis. Compressive lesions cause weakness of ipsilateral shoulder and arm followed by weakness of ipsilateral/contralateral leg and lastly contralateral arm. There may be pain in suboccipital region radiating to neck and shoulders.

Central Cervical Cord Syndrome

The damage occurs to the grey matter and crossing spinothalamic tracts near the central canal. In the cervical cord it produces weakness of arm out of proportion to leg weakness with dissociated sensory loss—loss of pain and temperature in cape distribution in contrast to preservation of touch, joint and vibration sense. Usual causes are trauma, tumours, anterior spinal artery ischaemia and syringomyelia.

Anterior Spinal Artery Syndrome

Occlusion of anterior spinal artery results in extensive destruction of anterior two thirds of the cord bilaterally sparing posterior columns. Motor, sensory and autonomic functions are lost below the level of lesion with the exception of retained

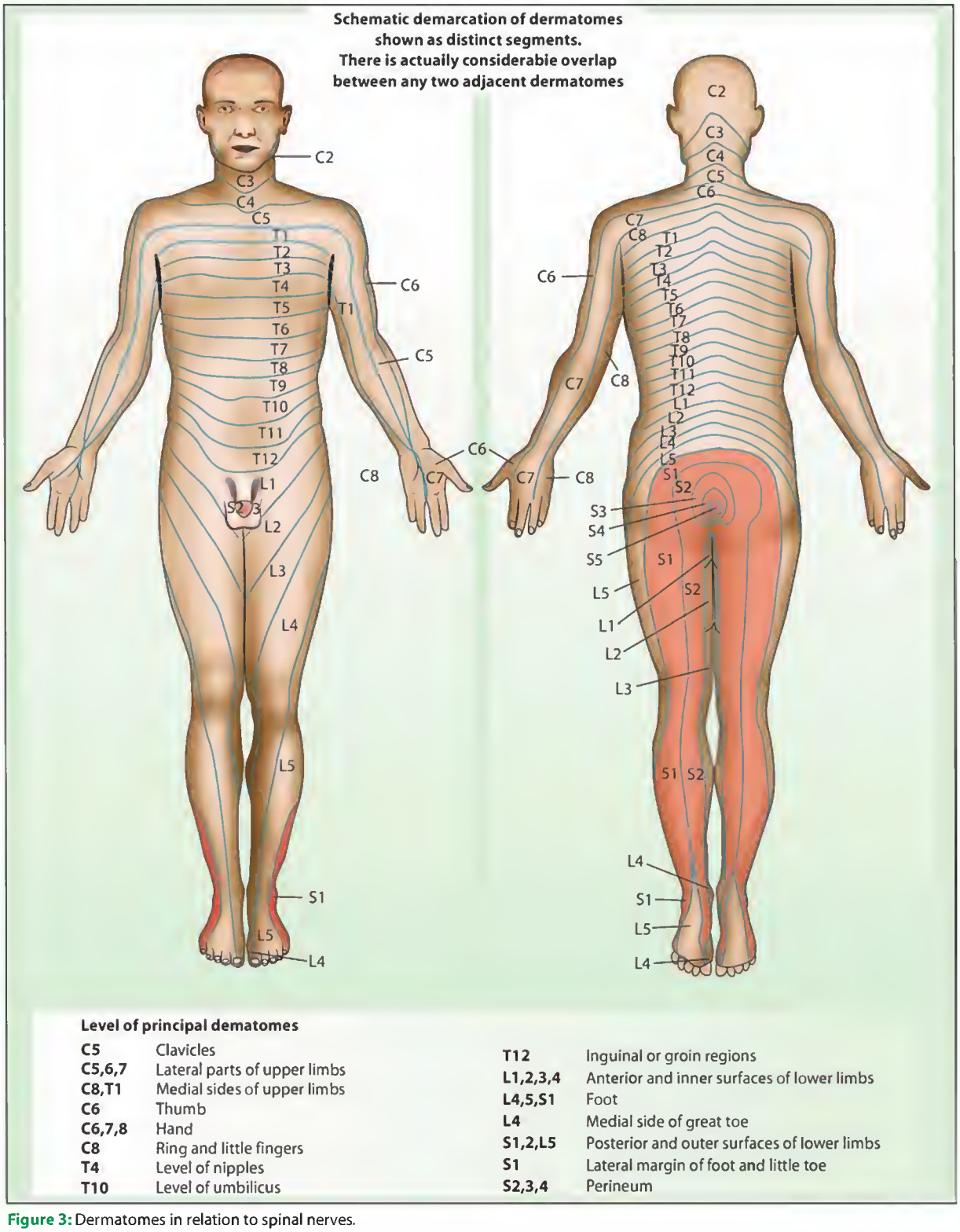


Figure 3: Dermatomes in relation to spinal nerves.

vibration and position sensations. Usual aetiology is embolic occlusion of anterior spinal artery.

Posterior Spinal Artery Syndrome

This is rare as posterior spinal arteries are paired. Clinically there is segmental paraesthesiae of burning nature. The cortico-spinal tracts are usually spared and the condition is usually reversible. Sensory and tendon reflexes levels are good indicators of levels of lesion. Other conditions where posterior columns are preferentially involved are vit B12 deficiency and tabes dorsalis.

Brown-Sequard Syndrome

This is a 'hemi cord' syndrome with ipsilateral paresis, cortico-spinal signs and impairment of vibration, joint and position sense and contralateral impairment of pain and temperature sensation usually with preserved touch sensation. There may be unilateral 'segmental sign,' such as radicular pain, muscle atrophy and loss of deep tendon reflexes. This is seen mainly from penetrating injuries to the cord though partial lesions are more common than classical pattern.

After identifying the spinal cord disease one should attempt to localise: (a) rostro-caudal level of the lesion - cervical, thoracic, lumbar or sacral; (b) extent of the lesion in all axes; and (c) whether compressive or non-compressive and if compressive whether extradural, intradural but extramedullary or intramedullary.

The principal structure outside the dura is the vertebral column, which surrounds the cord as a protective fortress. Most extradural diseases originate in or involve the bone or cartilage of the vertebral column and compress the dura and cord. Malignant tumours, infections, spondylitis, disc herniations, fractures (traumatic or spontaneous) and dislocations can compress the dura and compromise the cord. Most extradural diseases are classified as 'surgical' and 'urgent', since the longer the cord is compressed it is unlikely that the damage will be reversible after decompression. Occasionally epidural abscesses, tumours or haematomas compress the cord without involving the bone.

The majority of intradural extramedullary lesions are benign tumours either meningiomas or neurofibromas, that produce gradually evolving symptoms.

In sharp contrast most intramedullary diseases are medical and the differential diagnosis is much broader. Viral infections, transverse myelitis, infarction, haemorrhage, cysts, tumours and degenerative diseases lead the list.

NEUROGENIC BLADDER

Bladder Innervation

The normal anatomy and physiology of micturition and bladder innervation form a complex subject. The bladder is a hollow bag made of a syncytium of smooth muscle with stretch receptors. There is no true internal urethral sphincter, but the smooth muscle arrangement around the bladder neck produces a sphincteric action. The external urethral sphincter is made of striated muscle.

The parasympathetic fibres are derived from S2 to S4 segments and traverse the pelvic nerves. They fuse with the sympathetic fibres to form the vesical plexus. The sympathetic fibres emerge from the sympathetic trunk at L1-L4 and form the hypogastric plexus. The somatic efferent fibres to the external urethral sphincter are derived from S1, S2 segments and little below and form the pudendal nerve. The afferent fibres from the bladder proceed centrally along the routes taken by the efferent. The stretch receptors are stimulated by a rise in intravesical tension achieved in normal bladder function by filling with urine to a capacity of about 400 mL. This causes a parasympathetically induced contraction of the detrusors and simultaneous opening of the internal sphincter. The role of the sympathetic innervation in the function of micturition is not clear. It has been suggested that it plays a part in maintaining 'bladder tone' in conjunction with the parasympathetic innervation. Animal experiment in the cat suggests that sympathetic innervation has an inhibitory effect on bladder tone and raises the threshold for micturition. During ejaculation, backflow of seminal fluid into the bladder is prevented by mediation of the sympathetic fibres to the ductus deferens.

The regulation of bladder tone is essentially a spinal reflex function. However, like other spinal reflexes it comes under the control of higher centres. The two mutually exclusive activities of the bladder, i.e. the storage and voiding are controlled by neural processes that exist in pons and suprapontine influences act to switch it from one state to another. The pontine micturition centre (PMC) has a lateral part which controls storage (continence) and a medial part which is the site of activation for micturition. There are no direct afferent inputs from the bladder to PMC, but connections between periaqueductal grey are thought to provide information as to the state of fullness of the bladder.

In the neurological process that determine the switch from storage to voiding , in man, the extent of bladder fullness is the critical factor, as the urgency may not necessarily reflect the bladder volume. It is likely that frontal input is involved in the inhibition of micturition until it is socially appropriate. Thus, to effect both storage and voiding, higher control as well as connection between pons and the sacral spinal cord must be intact, as also the peripheral innervation that arise from the most caudal segments of the sacral cord.

Disturbances of Bladder Function

Lesions involving the sacral reflex arc cause retention of urine. In tabes dorsalis, the afferent fibres are involved, producing a painless distended bladder with overflow incontinence. Lesions of the *cauda equina* interrupt the afferent and efferent fibres causing incontinence of urine with loss of control over anal/urethral sphinctors. Involvement of the afferent fibres alone causes a painful distension of the bladder.

Lesion Above the Sacral Centre

Incomplete lesions of the spinal cord affect the inhibitory fibres for sympathetic outflow. This produces difficulty in holding urine and micturition is precipitate. Incomplete lesions can also interfere with the descending fibres concerned with voluntary initiation of micturition, causing retention of urine or hesitancy of micturition. With complete transection of the cord, there is initial retention of urine during the phase of spinal shock. Subsequently, reflex evacuation of the bladder occurs by means of the sacral reflex arc. This may be facilitated by stimulation of the sacral cutaneous areas.

Central Lesion

Diseases involving the superior frontal and anterior cingulated gyri cause loss of control of micturition. When the lesion is more

anterior, the patient is not worried or embarrassed by the incontinence due to a disinhibition state.

Investigation of Bladder Function

Normal micturition can be studied by a constant recording of intravesical and intraurethral pressure, and with perineal floor electromyography (EMG) with fluoroscopic monitoring. These urodynamic studies facilitate the diagnosis of neurogenic bladder dysfunction.

Treatment of Bladder Disturbance

When retention of urine occurs, bladder drainage by means of an indwelling catheter under strict aseptic conditions is necessary. Intermittent catheterisation may be resorted to, to prevent infection. Prophylactic antibiotics may be necessary. Parasympathomimetic drugs like carbachol and bethanecol cause contraction of the detrusor and are useful in flaccid paralysis of the bladder. In spastic paralysis, propantheline, which acts as a muscarinic antagonist causing relaxation of the detrusor may be tried.

SPINAL CORD DISEASES—DEPTH LOCALISATION

Extradural Pathology

Extradural lesions usually involve the bone first; so bone pain usually precedes neurological symptoms. Localised bone tenderness in response to fist percussion and radiologically demonstrable abnormalities of the vertebral column are often present at the level of the lesion. As the bony process expands, nerve roots that lie just out side the dura are distorted or compressed, root pain and paraesthesias result. Movement, straining or a cough or a sneeze often increases bone pain and root pains.

With further expansions or bone displacement the cord is compressed, causing relatively symmetric loss of pyramidal tract and posterior column function below the level of the lesion.

Intradural Pathology

With the intradural extramedullary lesions bone pain and tenderness are absent but root pain and cord compression otherwise mimic extradural disease; signs of cord compression are usually asymmetric.

Intramedullary Pathology

Osseous pain, tenderness and radiographic abnormalities are absent, and root pain is seldom prominent. Motor and sensory sign may be asymmetric, sensory loss can be dissociated (touch can be preserved in regions of loss of pain) and since centrally placed lesions may not affect outer fibres in the long tracts, sensation in the distal legs and perineum may be spared. Intramedullary disease is often painless or can have radicular type of pain. Bladder symptoms are more common and occur early.

Myelopathy is a generic term for specific disorders of the spinal cord caused by a heterogeneous group of conditions in which there is acute, subacute or chronic involvement of the spinal cord with or without the involvement of the nerve roots (myeloradiculopahy) or peripheral nerves (myeloneuropathy).

Clinically myelopathy is characterised by a definite sensory level below which there is a loss or diminution of sensation, a reflex level at the level of lesion indicated by the absence of corresponding deep tendon reflex and exaggerated deep tendon reflexes caudal to this level and a motor level with evidence of lower motor neuron dysfunction like wasting and fasciculations at the level of lesion and caudally features of upper motor neuron findings. Symmetric dysfunction involving the bladder and bowel confirm the lesion to be myelopathy.

Radiculopathy is characterised by segmental myotomal weakness; dermatomal sensory loss and corresponding reflex loss. A very sensitive clinical finding in root lesions is a depressed deep tendon reflex of the muscle that receives much of its innervation from the affected root. Radiculopathy is characterised by root pain, which is deep burning, and diffuse in ventral root affliction (myalgic) and a rapid electric-shock like sensation (neurologic) in dorsal root lesions. In myelo-radiculopathy features of both myelopathy and radiculopathy coexist.

INVESTIGATIONS IN DISEASES OF SPINAL CORD

Investigations in spinal cord disorders consist of examination of CSF, electrophysiological studies and neuroimaging. Plain radiographs of appropriate areas of spine has become less important with the advent of neuroimaging techniques. Conventional myelography was earlier the deciding line between compressive and non-compressive causes of myelopathy but has been superceded by CT scan, CT myelography and MRI. In many cases where conventional myelography is normal, CT scan or CT myelography may demonstrate structural lesion responsible for compression of the cord.

MRI has the advantage of being non-invasive mode of neuroimaging for diagnosis of structural lesions of spinal cord. Both sagittal and axial views can be obtained to confirm/exclude compression of the cord. Intramedullary lesions of spinal cord like tumours, AV malformations and syringomyelia can be visualised even before obstruction of subarachnoid space is evident. Thus, with the availability of MRI, there is a shift in favour of compressive lesions of myelopathy and the concept of compressive myelopathy has been extended to include CT scan, CT myelography and MRI findings for exclusion of compressive lesions-extradural,extra/intramedullary.

Electrophysiological studies like somato-sensory evoked potentials (SSEP) may help in confirming the cord involvement whereas nerve conduction (motor/sensory) studies/EMG may be of help to diagnose radiculopathy/neuropathy.

Role of CSF is mainly in the inflammatory/infective/demyelinating lesions of the spinal cord. It should be done only after ruling out compressive pathology by an appropriate imaging modality.

COMPRESSIVE MYELOPATHY

Spinal Cord Trauma

Fifty per cent of spinal cord injuries occur due to road traffic accidents. In direct injury to the cord with high velocity missile or a sharp instrument, often the vertebral column is also involved in the injury. In the presence of predisposing conditions like cervical or lumbar spondylosis, spinal canal stenosis, rheumatoid arthritis, the cord is prone to damage with even moderate force. Analysis of the mechanism of injury is of prime importance. The force of the violence may result in flexion, hyperextension, rotation or vertebral compression. The resultant cord injury may

be contusion, stretch, laceration or crush injury. Often the vertebral column is also involved in the injury.

Prognostication in spinal cord injuries depends on several factors. The higher the level of cord injury, the greater is the sensory, motor and autonomic involvement. Injury may be at a single level or involve multiple levels. The transection may be complete or a partial section, again determining the resultant disability. Whether the onset of the symptomatology is gradual or sudden is also of significance for prognostication.

Pathology

The spinal cord is soft and oedematous during acute phase and there may be haemorrhage. The destruction of white and grey matter is of varying extent. During the phase of repair, the oedema subsides, macrophage set to work and post-traumatic myelomalacia with thinning of the cord occurs. As a final step, cavitation and gliosis occur. Sometimes, the expansion of the cord (traumatic syringomyelia) may occur several months after partial recovery from spinal injury with reappearance of neurological symptoms and signs. Other late sequelae are cord atrophy and progressive myelopathy. Subarachnoid adhesions can form, resulting in cord tethering or multiple arachnoid cysts.

Clinical Features

Spinal cord trauma can cause a variety of syndromes depending on the extent of cord involvement. This syndromic classification of lesions is not confined to spinal cord injuries alone, but can be applied to various other types of spinal cord lesions as well.

Complete Transection

Transection of the cord is an acute event most often due to spinal injury, with accompanying fracture of vertebrae adjoining it. Below the level of the lesion, there is flaccid paralysis, as all function is lost due to spinal shock. Within one to six weeks minimum reflex activity appears. The bulbocavernosus reflex is the first reflex to recover, and when this is brisk in the presence of severe cord injury, it may indicate poor recovery. The tendon reflexes become exaggerated and plantar responses become bilaterally extensor. Reflex emptying of the bladder takes over. Muscle tone return with spasticity setting in. Other syndromes like Brown-Sequard syndrome, central cervical cord syndrome, anterior or posterior spinal artery syndrome as mentioned earlier can occur. Depending on the level of cord involvement, any of the cord syndrome described earlier may be encountered.

Treatment

Basic physiological parameters must be recorded on the spot and multiple injuries including head injury assessed. It must be kept in mind that due to autonomic failure, a sudden drop in the blood pressure may occur or paralytic ileus may set in. The patient requires to be carried onto the stretcher, in the horizontal position with the back well supported to avoid damage to the cord. Radiograph of spine, antero-posterior, lateral and oblique views, help in immediate assessment of the extent of injury, presence of vertebral fracture or dislocation with possible pressure on the spinal cord, or involvement of the nerve roots. CT scan, with close transverse images can be reformatted in the other planes to provide further information if required. But MRI, where available, is the imaging modality of choice in spinal cord disorders and trauma and may be resorted to subsequently where indicated. Of particular value is the sagittal view to pick up the lesion and also any soft tissue injury around the vertebrae, as bone does not yield an MR signal.

A complete general medical check up, and neurological assessment must be carried out initially in order to plan the treatment regimen. Treatment must be comprehensive and include management of pain, muscle spasms, prevention of bedsores, and bladder care in the presence of incontinence. Intermittent catheterisation of the bladder may be preferable and urinary infection must be prevented or checked early. In conservative management methylprednisolone is given during the acute phase. Neurosurgical opinion is sought and early decompression may be indicated in some cases of spinal injury.

Various splints may be used to immobilise, realign and stabilise the vertebral column and traction may be indicated. The halo ring and Gardner Wells tongs are useful devices here. The rehabilitation programme must include regular physiotherapy, prevention of contractures, occupational therapy, patient counselling, and family counselling to encourage maximum family participation in long term patient care. Lioresal may help to reduce spasticity. Gait training use of walking calipers, or use of hands to independently push the wheel-chair require to be taught to the patient, depending on the extent of disability. The recent concepts on regeneration of nervous tissue, comprehensive medicare, greater public awareness, availability of employment under the handicapped quota and even a possible participation in the para Olympics has encouraged a more positive attitude in the paraplegic.

INFECTIVE CAUSES OF THE CORD COMPRESSION

Tuberculosis

(See chapter on Neurotuberculosis in this section)

Spinal Arachnoiditis

Spinal arachnoiditis is an inflammatory process of the arachnoid mater, often chronic with adhesions to the dura and pia mater. The outstanding pathological feature of the condition is thickening and loss of translucency of the arachnoid membrane. In subacute arachnoiditis plenty of inflammatory cells per present.

In India, tuberculosis is the main cause of arachnoiditis. And usually involves the thoracic region. Tuberculous arachnoiditis may follow as a sequel to tuberculous meningitis or may be a direct spread from caries spine. Trauma and chemical inflammation following spinal anaesthesia, myelography and intrathecal medication, radiation and pyogenic infection are other aetiological factors. In 20% to 50% of cases, the primary cause remain unknown. Any level of the cord may be affected.

The clinical presentations may be radicular pain. Spastic paraplegia with progressive deterioration occurs sometimes with poor response to anti tuberculous treatment. The

differential of spinal arachnoiditis includes other causes of cord compression.

Myelography is important and shows a patchy hold up dye for several segments above and below the area of cord mainly involved. The prognosis is poor in thoracic arachnoiditis, but lumbar arachnoiditis (reported more often in developed countries recently) responds moderately well to surgery. The prognosis is best in a localised lesion. MRI spine with contrast has replaced the need for myelography.

Spinal Cysticercosis

(See chapter on Tapeworm and Roundworm Infections in section Infectious Diseases)

Spinal Epidural Abscess

The causative organism is usually *Staphylococcus aureus*, followed by streptococci, Gram-negative bacilli and anaerobes.

The disease is characterised by fever, backache, followed by radicular pain, within a few days. Headache and back stiffness, may be present. After a few days, progressive paraparesis, sphincteric involvement and sensory loss occur. This is a surgical emergency and if intervention is delayed, ischaemia of the cord occurs and the process becomes irreversible. The antibiotic of choice must be given. Spinal cord abscess is a rare condition with signs and symptoms indistinguishable from spinal epidural abscess. Occasionally, it may occur as a complication of spinal dysraphism.

Fungal and Parasitic Infection

A wide variety of fungi, namely actinomyces, blastomyces, coccidiodes and *Aspergillus* may cause cord involvement from an osteomyelitic focus or through haematogenous spread. *Echinococcus* and *Schistosoma* may also cause spinal cord pathology.

TUMOURS OF THE SPINAL CORD

Tumours of the spinal cord may be extradural, intradural, intradural-extramedullary or intramedullary. Neurofibromas, meningiomas, metastatic tumours, sarcomas, chordomas, and teratomas are extramedullary tumours which usually manifest clinical signs by pressure on the nerve roots with lancinating pain in the dermatome of the affected roots which increases on coughing. This may be followed by segmental distribution of muscle weakness and wasting. Intramedullary tumours of the spinal cord have the same cellular origin as tumours arising in the brain, namely ependymomas, astrocytomas, oligodendrogliomas and some non-gliomatous tumours. These tumours cause cord compression and also invade the white matter. Investigations of importance are CSF cytology and contrast myelography, but ideally CT scanning or MRI. All tumours causing compression require laminectomy, decompression and excision. If malignant, they will require radiotherapy. Epidural spinal cord compression by metastases is more common than compression by primary spinal tumours, 70% of the metastasis being to the thoracic spine. Bony lesions occur in the majority of patients with spinal metastasis. Ependymomas, unlike astrocytomas do not invade normal tissue and can be removed surgically with minimum morbidity. Differences between extra and intramedullary tumours are summarised in **Table 1**.

Table 1: Difference between Extramedullary Tumours and Intramedullary Tumours

Extramedullary Tumours	Intramedullary Tumours
Extramedullary tumours arise outside the spinal cord (extradural or intradural) and the symptom complex may be due to pressure of the tumour on nerve root, compression of the spinal cord or occlusion of spinal blood vessels	Intramedullary tumours arise within the substance of the spinal cord and interfere directly with structural pattern by invading and destroying nerve roots tracts and grey matter
The tumour usually occupies a few segments and produces focal signs	The tumour occupies multiple segments and may even stretch throughout the length of the cord
Root pain may be the presenting symptom. With cord compression, spastic paraplegia, sensory deficit level and poor bladder control occur. Total transection of the cord results in flaccid paralysis. Sacral involvement occurs rarely, and is based on lamination of the fibres	Following features are seen: a. Central pain with conus medullary tumours b. Root pains with cauda equina tumours c. Symptoms depend on location of the tumour. If high cervical or cervical they mimic syringomyelia
The commonest tumours are neurofibromas, and meningiomas	The commonest tumours are ependymomas and gliomas in the cervical region. Dermoids and teratomas occur only in children
CSF protein is markedly raised in extradural lesions and raised in intradural extramedullary lesions	CSF protein may be normal in cervical cord lesions or raised especially in ependymomas. In conus medullaris lesions, CSF protein is markedly raised
Visible, palpable or radiographic evidence of vertebral destruction points to an extradural extramedullary tumour, e.g. cold abscess or gibbus	Bony changes in adults in intramedullary presentations are unusual. MRI scan is more definitive
Radiological diagnosis Plain X-ray Erosion of the pedicle early sign of intradural extramedullary tumour (e.g. Neurofibroma) Reduction of intervertebral space is characteristic of Pott's disease. Preservation of intervertebral space suggests a diagnosis of secondaries	Bony changes may be is an completely absent
Myelogram The classic signs are 'meniscus sign', in intradural tumours and 'brush border sign' in extradural tumours. The block may be complete of incomplete	'Expansion sign' of the cord is diagnostic of syringomyelia
CT Scan The above radiological findings are seen with greater anatomical clarity	Usually no bony changes are seen unless there is associated syringomyelia
MRI Spinal cord definition is excellent. Craniovertebral junction anomalies are well brought out	Spinal cord definition is excellent. Expansion sign caused by Syringomyelia is cleared defined

NON-COMPRESSIVE MYELOPATHY

Non-compressive myelopathies (NCM) are a group of spinal cord diseases where compression has been ruled out by available neuroimaging techniques. They constitute about 46% to 62% of all myelopathies. Cord involvement may or may not be associated with affection of brain (encephalomyelitis), radicles (myeloradiculopathy) or nerves (myeloneuropathy). Cord structure may be thoroughly destroyed or the damage may only be limited to white matter (leucomyelitis) or anterior horn cells (poliomyelitis, motor neuron disease). The onset of NCM may be acute, subacute or insidious. The course of illness can be monophasic with complete remission or progression with or without remissions and relapses.

In Western countries non-compressive lesions of spinal cord may be due to demyelinating diseases or hereditary spastic paraplegia whereas infections and nutritional factors may be responsible in developing countries. Demyelinating diseases including multiple sclerosis are being increasingly recognised as a cause of non-compressive myelopathy. After detailed investigation in 4.4 % to 26.6% of cases of paraplegia in different series no cause could be attributed and these cases have been labelled as 'Myelopathy of unknown origin' or 'Obscure myelopathies'.

Disease of the spinal cord without evidence of compression on myelography, CT myelography or MRI can be classified according to aetiology. They can be (a) acute (viral, immuno-allergic, toxic, demyelinating disease), (b) subacute (neurolathyrism, tropical spastic paraparesis), and (c) chronic (infectious and radiation myelopathy). Viruses like that of poliomyelitis have predilection for anterior horn cells and are dealt elsewhere in this book. Some of the important conditions causing non-compressive myelopathy in India are highlighted (**Table 2**).

Inflammatory Disorders of the Spinal Cord

Acute transverse myelitis

Acute transverse myelitis is development of isolated spinal cord dysfunction over hours or days without any evidence of compressive lesion. One third of the patients have preceding febrile illness. Nearly 50% develop maximal deficit in one week. MRI of the spine will reveal abnormal signal changes involving long segments with or without contrast enhancement. Treatment includes short course of steroids along with other supportive and rehabilitation therapy. Nearly 20% of the patients have a favourable response.

CSF shows increased protein and mononuclear cells which may number from a few to several hundreds.

Non-compressive myelopathy due to infections

Most viruses, except HTLV-1 and AIDS, invade the spinal cord and affect grey matter nuclei predominantly sparing white matter long tracts (e.g. anterior horn cell damage due to the poliomyelitis virus and posterior horn cell due to Herpes Zoster). This is an important observation and helps in distinguishing viral myelitis from other causes of myelopathy. In cases of inflammation of the spinal cord where white matter tracts bear the brunt of involvement, aetiologies other than viral myelitides such as parainfectious myelitis, post vaccination myelitides, multiple sclerosis and paraneoplastic myelopathy are to be considered.

Table 2: Causes of Non-Compressive Myelopathy

Infections	
Viral	Poliomyelitis
	Rabies
	Herpes Zoster/Varicella
	Mumps
	Viral hepatitis
	EV 70 disease
	AIDS related myelopathies
Bacterial/ Spirochaetal	Bacterial meningitis
	Typhoid
	Tuberculosis
	Syphilis
Parasitic	Schistosomiasis
	Malaria (falciparum)
Immuno-allergic (Post-and parainfectious)	
	Influenza and other viral infections
	Post exanthematous (measles, varicella)
	Post vaccinal (smallpox, rabies, poliomyelitis)
Demyelinating diseases	
	Multiple sclerosis
	Neuromyelitis optica
	Eales' disease
	Acute disseminated encephalomyelitis (ADE)
Heredofamilial/Degenerative disease	
	Motor neuron disease
	Heredofamilial spastic paraplegia
	Spinocerebellar ataxia
Toxic myelopathy	
	Neurolathyrism
	Intrathecal Injections
	Chemotherapeutic agents
	Penicillin
	Spinal anaesthetics
	Contrast media
	TOCP
	Arsenic
	SMON
Vascular disorders	
	Arteriosclerosis
	Dissecting aneurysm of aorta
	Surgery on abdominal aorta
	Angiography
	Systemic lupus erythematosus
	Polyarteritis nodosa
	Vascular malformations (angiomas, AV malformations)
Physical agents	
	Irradiation myelopathy
	Electrical injury to spinal cord
Metabolic/Nuritional	
	Pernicious anaemia / Vit B12 neuropathy
	Pellagra
	Myelopathy of chronic liver disease
	Hypocupric myelopathy
Tropical spastic paraplegia	
	HTLV – 1 associated myelopathy
Paraneoplastic myelopathy	

Acute anterior poliomyelitis

The clinical syndrome of acute anterior poliomyelitis is a febrile illness associated with flaccid motor weakness or paralysis and signs of meningeal inflammation. However, the enteroviruses, echoviruses, and coxsackie viruses also cause the clinical syndrome of anterior poliomyelitis. In areas where polio vaccination programme has all but eradicated polio, these enteroviruses are responsible for the majority of cases of paralytic poliomyelitis syndrome. However, these non-polio enteroviral poliomyelitis cases do not occur as epidemics. Polio like syndrome also has been reported secondary to mumps virus, infectious mononucleosis and rabies virus.

Post-infectious and post-vaccination myelitis

Post-infectious or parainfections myelitis, post-vaccination myelitis, multiple sclerosis and acute necrotising myelitis are the most common cases of acute transverse myelitis and ascending myelitis. The aetiology of these disorders is unknown. These disorders share a similar pathology and are thought to share similar inflammatory pathogenesis. This group of disorders involve white matter tracts predominantly or both white and grey matter (transverse myelopathy) in contrast to viral myelitis which shows a predilection for grey matter. The exanthematous fevers that are antecedent to myelitis include viral diseases like rubeola (measles), rubella (German measles), mumps, influenza, *Mycoplasma pneumoniae*, infectious mononucleosis and varicella. The incriminated vaccines include those against tetanus, poliomyelitis, rabies and smallpox. However, in many cases myelopathy occurs without an apparent infection or vaccination.

The pathogenesis is immunological and an autoimmune response to a CNS antigen such as myelin basic protein may be responsible. Alternatively circulating immune complexes may induce a vascular injury. The time interval between exposure to the infection or vaccination and the development of the neurological disorder varies but is commonly 7 to 10 days. Pathological changes are found in the blood vessels and the perivascular regions. Hyperaemia, perivascular cellular exudate and oedema and haemorrhage are found in arterioles, venules and capillaries. Even though clinical examination reveals signs of only myelopathy both the brain and spinal cord usually are involved on pathological examination. The clinical features are highly variable. Systemic symptoms including fever, malaise, nausea, vomiting and muscle pain suggesting an infectious aetiology appear first. Paraesthesias in lower extremities, back pain or radicular pain heralds the illness and myelopathy may develop without any of the above features.

Thoracic spinal cord is the most frequent site of involvement. Myelopathy may be accompanied by a polyradiculopathy. Symptoms and signs of cord involvement usually evolve acutely with the majority of patients developing maximal neurological deficit within several days. The specific signs are weakness, sensory loss and sphincter dysfunction. Routine laboratory studies are usually normal or non-specific. The CSF may be normal but typically shows a moderate lymphocytic pleocytosis. Other signs of CNS inflammation may include a slightly elevated protein usually less than 120mg/dL and elevated IgG and the presence of oligoclonal bands. CSF glucose concentration is normal. MRI of brain may reveal areas of demyelination. Spinal MRI with gadolinium enhancement is diagnostic. Therapy is non-specific. Cortiosteroids or ACTH is routinely used. Prednisolone 1 mg/kg/day for a two-week period and tapered over a further one week is preferred.

Myelopathy Due to Demyelinating Diseases

Multiple sclerosis (MS)

(See chapter on Demyelinating Diseases of Nervous System in this section)

Devic's disease

Neuromyelitis optica or Devic's disease is characterised by involvement of the spinal cord and the optic nerves simultaneously and is common at the extremes of age. Pathologically, there is a greater degree of axonal degeneration than in MS and the spinal cord shows a frank necrotic picture. Clinical presentation reflects the sites of pathology and unilateral or bilateral visual impairment is followed within days or weeks by a transverse or ascending myelitis. Because of necrotising nature of the remission of lesions is less likely.

Eales' disease

Neurological involvement in association with classical changes of Eales' disease in eyes (retinal periphlebitis) has been described from India initially by Singhal and Dastur in 1976. Neurological insult is very severe in the very first episode of Eales' disease and severe motor weakness, sensory loss and sphincteric involvement ensue.

Acute Disseminated Encephalomyelitis (ADEM)

Although the incidence of MS is low in India, the incidence of postinfectious or postvaccinial allergic demyelination, i.e. acute disseminated encephalomyelitis (ADEM) is not very low. It is the common experience in India that ADEM is seen following upper respiratory infections, exanthematous fevers and following vaccinations. An approximate incidence of ADEM is 1 per 1,000 cases with measles, 1 per 100,000 cases with varicella and 1 in 1,000 to 1 in 4,000 following vaccination against rabies. ADEM is a monophasic illness with either a solitary site such as cord or brainstem or may have wide spread lesions in both brain and spinal cord.

Toxic Myelopathy

Consumption of khesari dal can lead to neurolathyrism and similarly consumption of edible oil TOCP (Triorthocresyl phosphate) can lead to myelopathy.

Neurolathyrism

(See chapter on Lathyrism in Poisoning and Toxicology Section)

Myelopathy Due to Physical Agents

Radiation myelopathy

The criteria for diagnosis are: the spinal cord must have been included in the area irradiated, the main neurological lesion must be within the area exposed to irradiation and cord compression due to metastasis should have been convincingly excluded. Four major syndromes have been recognised.

Early and transient form: This consists of mild subjective symptoms of paraesthesias and electric-shock like sensations on neck flexion (Lhermitte's sign) and starts at about a latent period of three months after irradiation and disappears in about

three months. The differential diagnosis for the cause of Lhermitte's sign includes spinal metastasis and unrelated disorders such as cervical spondylosis, subacute combined degeneration, post traumatic syndrome, multiple sclerosis and cisplatin chemotherapy. The pathogenesis is thought to be reversible damage to myelin in the ascending sensory tracts of the spinal cord, which allows axons to be abnormally sensitive to mechanical deformation.

Lower motor neuron disease: There is a selective damage to anterior horn cells in the upper or lower limbs. A painless amyotrophy and weakness, usually of the lower extremities, develops subacutely 3 to 8 months following high dose radiation therapy to the spinal cord. Sensory abnormalities are not found and the sphincters remain intact. The course is subacutely progressive but ultimately self-limited.

Acute transverse myelopathy: The third form of radiation myelopathy is that of an acutely developing paraplegia or quadriplegia presumably secondary to infarction of the spinal cord. It may be secondary to radiation induced vascular pathology.

Chronic radiation myelopathy: This is the only form for which pathological correlation has been established. Most typically the neurological symptoms begin five months to many years following therapy. A spinal dose of 3,750 Rads in 3 to 4 weeks should not be exceeded. Symptoms reveal involvement of various fibre systems of the cord resulting in weakness, sensory impairment, and bowel and bladder incontinence ending in a total transverse lesion of the cord. Progressive damage to vascular endothelium may be the primary event leading to spinal cord ischaemia. Corticosteroids may have a role in the management.

Myelopathy due to electrical injuries

The cervical cord is frequently the site of injury because the electrical current often passing from hand to hand or lightning injury sustained during rainy weather. The latter type of injury has been recorded in armed forces personnel travelling in armoured vehicles with helmets in rainy weather. Spinal cord damage may be either acute or delayed. Acute injuries may be secondary to heating of tissue or to tissue ischaemia. Both grey matter and white matter tracts may be damaged, so that sensory, motor and sphincter disturbances may occur. Occasionally, a delayed progressive spinal cord syndrome develops. This syndrome may be difficult to differentiate clinically from spinal muscular atrophy or amyotrophic lateral sclerosis.

Vascular and Autoimmune Causes of Myelopathy

Many systemic diseases predispose to spinal cord infarction. Invasive procedures may be complicated by spinal cord infarction. Causes of spinal cord infarction include aortic dissection, atherosclerosis, collagen vascular disease and other inflammatory/infectious diseases, diabetes, trauma, Caisson's disease, spondylosis and various surgical and other invasive procedures. Fibrocartilagenous embolisation is a very rare but interesting cause of spinal cord infarction. Spinal cord infarction is of two types: arterial and venous.

Arterial infarction

Among the arterial infarctions anterior spinal artery infarction is by far more common than posterior spinal artery infarction. Anterior spinal artery infarction is common in thoracic cord and those affected abruptly develop a transverse level and below the level of the lesion, acute paralysis, dissociated sensory loss and loss of sphincteric function. There will be history of radicular pain in a girdle distribution for two to three days. Usually the motor paralysis below the level of infarction is initially flaccid and areflexic owing to spinal shock. A sensory level to pain and temperature with preservation of posterior column function is typically found. Thoracic cord is most commonly involved because this is the watershed area for blood flow in the rostro-caudal axis. Aortic dissection causes an infarction of spinal cord with a sensory level for pain and temperature near the T4 level. Posterior spinal artery infarction is rare and damage extends into the posterior horns of the spinal cord, resulting in global anaesthesia at the affected level and below the level of infarction there is loss of vibration and position sensations.

Venous infarction

Venous infarction of spinal cord may be either haemorrhagic or non haemorrhagic. Severe sepsis, carcinomatosis and vascular malformations cause venous infarctions. Haemorrhagic venous infarction presents with sudden onset of back, leg or abdominal pain evolving over 1 to 2 days to flaccid weakness and loss of sensation below the level of the haemorrhagic infarction and loss of sphincteric function. Dissociated sensory loss is not a feature of venous infarction. Non haemorrhagic venous infarction presents subacutely with painless progressive lower extremity weakness, sphincteric disturbances and sensory loss below the level of the lesion.

Autoimmune diseases

The spinal cord may be the target of a variety of systemic autoimmune diseases like Sjogren's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, polyarteris nodosa, Wegner's granulomatosis, and Behcet's disease. Twenty per cent of patients with primary Sjogren's syndrome develop CNS involvement. In these cases episodic multifocal involvement of the brain and spinal cord may occur mimicking multiple sclerosis. Acute or subacute transverse myelopathy, chronic progressive myelopathy, neurogenic bladder and other spinal cord syndromes have all been described. An immune vasculopathy is the favoured pathogenetic mechanism in these cases. Myelopathy is a well documented complication of SLE and it is due to vascular disease.

Caisson's disease

In individuals who are subjected to high underwater pressure (like deep sea divers) nitrogen bubbles form and get trapped in spinal vessesls. Most often the upper thoracic cord is involved. There are ischaemic changes mainly in the white mater of upper thoracic cord. Posterior columns are more affected than lateral and anterior columns. There may be complete transverse myelopathy as soon as the individual is resurfaced, but the condition may improve, leaving an asymmetrical and incomplete but permanent residual deficit. Immediate treatment consists of recompression in a hyperbaric chamber and gradual decompression. Treatment of residual deficit is symptomatic with antispasticity drugs.

Metabolic and Nutritional Myelopathy

The common causes of myelopathy due to metabolic and nutritional factors include diabetes mellitus, cyanocobalamin deficiency, pellagra and chronic liver disease.

Subacute combined degeneration of cord

This treatable disease was first described in detail at the turn of the century and results from vitamin B12 deficiency and is often associated with megaloblastic anaemia. Degenerative and demyelinating changes occur in the white matter of the posterior and lateral columns of the spinal cord and also in white matter of brain. Peripheral nerves may show signs of demyelination and axonal degeneration. Symptoms secondary to sensory peripheral neuropathy and/or damage to ascending white matter tracts are first noted and are usually progressive and ascend the extremities. Many patients first note pins and needles tingling or numbness in the feet followed by hands. Vibration and position sensations are disturbed and Romberg's sign usually becomes positive. The motor symptoms generally are weakness and stiffness in the lower extremities. Gait may be spastic or ataxic or combined type. Deep tendon reflexes may be absent in ankles if peripheral neuropathy predominates. Babiniski sign eventually develops. Sphincter disturbances are atypical. When the brain is involved, a variety of neuropsychiatric findings may occur along with visual and other cerebral manifestations. Diagnosis depends on serum B12 level and two stage Schilling test. Treatment consists of parenteral B12 administration.

Copper deficiency/hypocupric myelopathy

Recently copper deficiency has been recognised as a cause of myelopathy in patients who have undergone gastric surgery, with sensory ataxia, spastic gait and demyelination in the CNS, optic neuritis and peripheral neuropathy. The clinical picture is like that of vitamin B12 deficiency myeloneuropathy with normal levels of vitamin B12 and low serum copper levels. Associated myelodysplasia may be present and resolves with copper supplementation. Though progress of deficit can be contained with copper intake, recovery is not complete.

HTLV-1 Associated Myelopathy

A slowly progressive myelopathy characterised by symmetric upper motor neuron paraparesis, sphincter disturbances and mild sensory signs is encountered in tropics (Tropical spastic paraparesis/TSP) and Japan (HTLV-I associated myelopathy/HAM). The retrovirus human T-lymphotrophic virus type-1 has been implicated as the causative agent. TSP and HAM are likely to be the same disease because HTLV-I antibodies are demonstrated in serum and CSF in both the conditions. However, a positive serology without neurologic disease has been reported in up to 26% of some populations studied and the presence of HTLV-I antibody does not necessarily indicate a causal relationship. The usual clinical presentation is progressive lower extremity weakness, often associated with lumbar or thoracic pain. Paraesthesias are common but prominent sensory disturbances are unusual. Bladder dysfunction is common. The signs and symptoms are usually bilateral. Weakness usually involves the legs more prominently than the arms, but spasticity is typically found in all extremities. The serum and CSF HTLV-I antibody titres do not correlate with disease severity. The therapy of HAM is unsatisfactory. Corticosteroid therapy and plasmapheresis may be temporarily effective in some patients.

Paraneoplastic Myelopathy (Non-Metastatic Manifestation of Malignancies)

Paraneoplastic myelopathy refers to spinal cord disease in patients with malignancy where the myelopathy is not due to compression from the tumour, effects of treatment, metabolic or electrolyte imbalance or identifiable disease unrelated to malignancy. The pathogenesis is unknown and paraneoplastic myelopathy occurs as a non-metastatic manifestation of carcinomas. It differs from transverse myelitis in that disturbance is not limited to a single spinal cord level. Pathologically there is an ischaemic myelopathy characterised by symmetric necrosis involving both grey and white matter with a predilection for the thoracic spinal cord. The clinical picture is a rapidly ascending sensory motor myelopathy. The course is typically short with death occurring within a few months. In chronic paraneoplastic myelopathy the symptoms are those of motor neuron disease. Wasting and fasciculations are evident in the affected musculature. The diagnosis of paraneoplastic myelopathy is difficult. It is seen in a variety of carcinomas and lymphomas. There is no specific laboratory test for paraneoplastic myelopathy and it has to be differentiated from intramedullary metastasis, radiation myelopathy and other diseases.

Acute and Subacute Myelopathy of Unknown Aetiology

Transverse myelitis is a syndrome of diverse aetiology. Some pathological processes that may give rise to transverse myelitis include post infectious and post vaccination myelitis, multiple sclerosis and acute necrotising myelitis, viral myelitides, spinal cord infarction, radiation myelopathy, vascular malformations and paraneoplastic syndrome. Despite exhaustive attempts to diagnose the aetiology and pathogenesis of acute or subacute non-compressive myelopathy, there are many cases in which no specific diagnosis can be made at the time of clinical presentation. Such entities are termed as non-compressive myelopathy which is defined as a clinical syndrome of bilateral intramedullary dysfunction, which may be ascending or static and often involves several spinal segmental levels. The diagnosis of non-compressive myelopathy is a clinical after the exclusion of known causes such as cord compression secondary to neoplasm or abscess. This myelopathy of obscure nature occurs in 25% to 40% of patients with paraplegia.

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20.29 Peripheral Neuropathy

AK Meena

INTRODUCTION

A common complex neurological disorder seen frequently. There has been an exponential increase in knowledge about its pathophysiology, new avenues of diagnosis and management which has improved its understanding and management significantly.

GENERAL CONSIDERATIONS

The peripheral nervous system (PNS) includes all neural structures lying outside the pial membrane of the spinal cord and brainstem with the exception of the optic nerves and olfactory bulbs, which are but special extensions of the brain. The nerves within the spinal canal and attached to ventral and dorsal surfaces of the cord are called ventral and dorsal roots and those attached to ventrolateral surface of the brainstem are the cranial nerve or roots. Both the roots form the spinal nerves which divide into dorsal and ventral rami. Dorsal ramus supplies the back and the ventral rami supply the limbs and the ventral body wall. The ventral rami in cervical and lumbosacral regions form the plexus.

The thick protective and supporting sheaths of perineurium and epineurium have a vascular supply through longitudinal arrays of richly anastomosing nutrient arterial branches. The perineurium comprises the connective tissue sheaths that surround and separate each bundle of nerve fibres (fascicles) of varying size, each fascicle containing several hundred axons. The sheath that binds and surrounds all the fascicles of the nerve is the epineurium. The fine connective tissue covering of individual nerve fibres is the endoneurium. Longitudinally oriented and widely anastomotic endoneurial vessels also nourish the nerve fibres and are susceptible to the disease.

PATHOLOGIC REACTIONS OF PERIPHERAL NERVE

Several distinct histopathologic changes are recognised in the peripheral nerve, although they are not disease-specific and may be present in varying combinations in any given case. The classic ones are *segmental demyelination*, *Wallerian degeneration*, and *axonal degeneration* (**Figure 1**).

Myelin sheath is the most susceptible element of the nerve fibre, for it may break down as part of a primary process involving the Schwann cells or of the myelin itself, or it may be damaged secondarily as a consequence of disease affecting its axon. Focal degeneration of the myelin sheath with sparing of the axon is

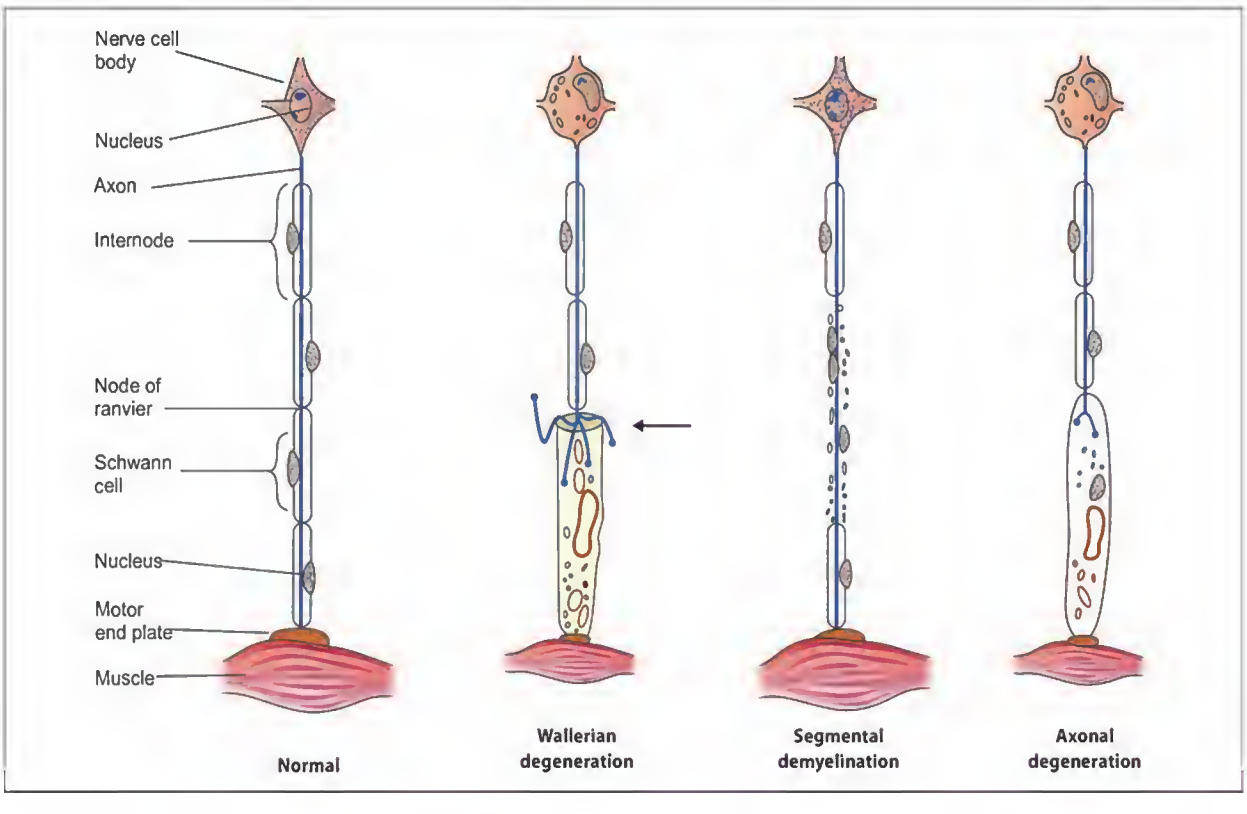


Figure 1: Diagram of basic pathologic process affecting peripheral nerves. Arrow in the figure shows the degeneration of myelin and with chromatolysis. *Courtesy: Dr Arthur Asbury.*

called *segmental demyelination*. The characteristic change of segmental demyelination is the disappearance of the sheath over segments of variable length, bounded on each end by a preserved segment of myelin. Certain diseases affect the neuron primarily rather than the axon and cause either a motor or sensory *neuropathy*. In the former case, the anterior horn cell is affected by a disease process (motor neuron disease or motor neuronopathy) and in the latter; the sensory ganglion cell (ganglionopathy) is destroyed. A type of wallerian distal degeneration of the respective nerve fibres follows. Common to many lesions of peripheral nerves is *Wallerian degeneration* a reaction of both the myelin and axon distal to the site of disruption of the axon along with chromatolysis. (Dying forward phenomenon). *Axonal degeneration* is a process where the axon degenerates as part of the dying back phenomenon due to neuronal disease in more generalised metabolic polyneuropathies.

Clinical Features

The clinical features and examination have been detailed in Chapter 2 of this section. Here these are tabulated in **Table 1** and some of them have been described in following paragraphs.

Table 1: Symptoms Associated with Peripheral Neuropathy

	Positive Symptoms	Negative Symptoms
Somatic nerves	—	—
Sensory	Pain, tingling	Numbness, lack of feeling
Motor	Cramps, fasciculations	Weakness, atrophy
Autonomic	Hyperhydrosis, diarrhoea	Orthostatic hypotension, impotence, anhydrosis, constipation

Orthopaedic Signs

Limb inspection can reveal structural and trophic changes in the feet, lower legs, and hands. High arches (*Pes cavus*) and hammertoe deformities suggest long-standing neuropathies. Fallen arches can also be observed in severe neuropathies. Toes and foot injuries unnoticed by the patient suggest a marked degree of sensory loss.

Autonomic Signs

Autonomic nervous system is involved in many peripheral neuropathies, but symptoms and signs of dysautonomia are uncommonly voiced by the patient and must be asked for. Orthostatic dizziness and changes in blood pressure (a drop of >30 mm Hg systolic pressure and >15 mm Hg diastolic pressure recorded 60 to 90 seconds after standing following 5 minutes of supine rest) support autonomic involvement.

Investigations of Peripheral Neuropathy

Electrodiagnostic studies

Electrodiagnostic studies (EDX) are essential in early evaluation and differential diagnosis of peripheral neuropathies. They are composed of nerve conduction studies (NCS) and needle electromyography (EMG). The procedure should be tailored to the diagnosis. Depending on patients symptoms EDX may be needed: to localise a problem to peripheral rather than central nervous system; differentiate peripheral nerve disease from diseases of neuromuscular transmission and muscle; to localise the pathology to individual nerves, roots, plexus, or motor neurons; to characterise dysfunction as axonal, demyelinating or both. In addition, it tells us whether the neuropathy is generalised or multifocal; information often impossible to discern by the clinical examination. It may indicate severity and chronicity of neuropathy by documenting the degree of axonal loss and motor unit reinnervation (**Table 2**).

Table 2: Simplified Electrodiagnostic Features of Primary Demyelinating and Axonal Pathology

Parameter	Demyelinating Pathology	Axonal Pathology
Distal motor action potential amplitude	Mild to moderate reduction	Normal to moderate reduction
Distal latency	Moderate-gross prolongation	Normal-mild prolongation
Conduction velocity	Moderate-gross slowing	Normal-mild slowing
Conduction block	Present	Absent
Temporal dispersion	Abnormal	Normal
F- latency	Moderate-gross prolongation	Normal-mild prolongation
Needle EMG	Mild-moderate denervation (fibrillation potentials)	Mild-severe denervation

Physiologic tests are available to evaluate qualitatively and quantitatively the autonomic dysfunction by simple as well as sophisticated tests in specialised centres. Quantitative sensory testing is the use of precisely measured and repeatable sensory stimuli to determine the absolute threshold of sensation within specific somato-sensory modalities, which is simple and reproducible.

Nerve biopsy

Nerve biopsy is of little help in diagnosing, early detection and monitoring the progression of peripheral neuropathy. It is useful only in small number of cases. The indications for nerve biopsy are necrotising vasculitis, amyloid neuropathy and Hansen's disease. It may be diagnostic in metachromatic leucodystrophy, Dejerine-Sottas disease, neoplastic infiltrations, and sarcoid neuropathy. Combined muscle and nerve biopsy may be useful in sarcoid and vasculitic neuropathy. Skin biopsy is now gaining importance especially in amyloidosis, vasculitis and to diagnose painful small fibre neuropathy.

Laboratory tests

Minimum essential laboratory tests in the evaluation of peripheral neuropathy include complete blood count, ESR, biochemistry profile, thyroid function tests, vitamin B12 and serum anti-nuclear antibody levels. Other specialised tests should be tailored according to the pattern of neuropathy and clinical suspicion. GTT and serum protein immunoelectrophoresis should also be included especially in chronic neuropathies in adults (**Table 3**).

Approach to the Patient with Peripheral Neuropathy

The classification of peripheral neuropathies and approach are based on several factors like pattern of involvement, disease onset, pathology and aetiology (**Figure 2**). Structural approach to full localisation and characterisation of neuropathy that focuses the differential diagnosis and leads to a rational lists of laboratory tests involves several steps (**Table 4**).

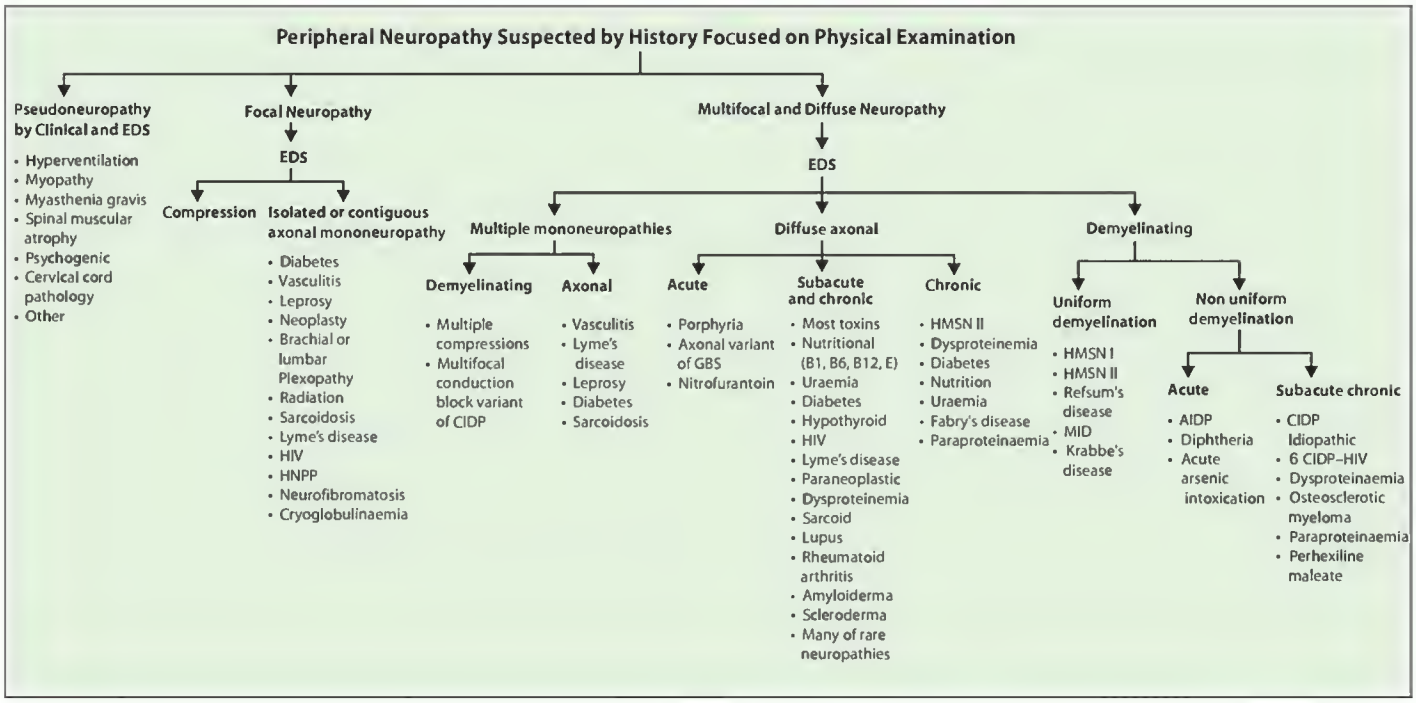


Figure 2: Diagnostic algorithm for PNS disease, with specific diseases.

Table 3: Laboratory Studies in the Evaluation of Patients with Suspected Neuropathy

Routine Tests	Special Tests
Complete blood count with eosinophil count	Rheumatoid factor
Renal function studies	Complement levels (C3, C4, CH50)
Serum glucose and glycosylated haemoglobin (lumbosacral plexus neuropathy)	Serum C-ANCA, and P-ANCA
Liver function studies	Cryoglobulins
Urinalysis	Anti-dsDNA and Sm antibodies
Erythrocyte sedimentation rate	Anti-SSA and SSB antibodies
Anti-nuclear antibody	Anti-Scl 70 and centromere antibody
Serum B12	Lyme titre
	Hepatitis B virus titre
	Hepatitis C virus titre
	HIV
	Cytomegalovirus titre
	Epstein-Barr virus titre
	Serum and urine immunofixation electrophoresis, ACE levels
	GTT

Table 4: Diagnostic Evaluation Steps Leading to Full Neuropathy Characterisation

First step	
Within the peripheral system	Exclude cortical, spinal, psychogenic loci
Second step	
What part of the peripheral nervous system?	Root, plexus, single nerve, multiple nerves Peripheral neuropathy
Third step	
What is the time course?	Acute, subacute, chronic, progressive, relapsing-remitting, event-linked
Fourth step	
What nerve fibres are involved?	Sensory, motor, autonomic, combinations
Fifth step	
What is the primary pathology?	Demyelination, axonal, mixed
Sixth step	
What are the other pertinent features?	Family, medical, social histories

There are several patterns of peripheral neuropathy (**Table 5**). The prototypic and most common pattern is symmetric and length-dependent, involving sensory loss and pain and, less frequently, distal weakness. As progressively shorter nerves are affected, symptoms and signs unroll up the leg as a stocking. Nerve length at knee level is approximately equal to the length innervating the hand, and with further progression, symptoms and signs unroll up the arm as a long glove (Glove and stocking type neuropathy). Most length-dependent polyneuropathies are chronic and involve axonal pathology. Causes of polyneuropathy are many and reflect metabolic abnormalities. Diabetes mellitus is the most common underlying cause of this type, followed by hereditary neuropathies and idiopathic or cryptogenic neuropathies represent up to 25% of polyneuropathies.

Pattern including both proximal and distal limb segments, is usually demyelination at multifocal sites along roots and nerves, e.g. acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Table 5: Patterns of Peripheral Neuropathy and Examples of Disorders and Causes

Sensory-motor symmetric (length-dependent pattern)	Diabetes, nutritional, medications, toxins, metabolic disorders, hereditary
Sensory-motor symmetric (proximal and distal pattern)	Acute inflammatory demyelinating polyradiculopathy, chronic inflammatory demyelinating polyradiculopathy
Sensory-motor asymmetric (plexus pattern)	Diabetes amyotrophic, idiopathic plexopathy, vasculitic mononeuritis multiplex
Sensory-motor asymmetric (nerve pattern)	Leprosy, systemic lupus, rheumatoid arthritis, leukaemia, polyarteritis nodosa, sarcoidosis, cryoglobulinaemia, Wegener's granulomatosis
Sensory symmetric or asymmetric	Paraneoplastic neuronopathy, Sjogren's syndrome, idiopathic ganglionitis, vitamin B6 toxicity, leprosy
Motor symmetric or asymmetric	Amyotrophic lateral sclerosis, multifocal motor conduction block neuropathy, lower motor neuron syndrome, poliomyelitis, West-Nile syndrome, lead neuropathy
Autonomic symmetric or asymmetric	With other neuropathies (diabetes, acute inflammatory demyelinating polyradiculopathy), isolated involvement (amyloidosis)

Asymmetric patterns are less common and include different lesion sites and pathological processes. Unilateral and focal symptoms and signs in a limb must be distinguished from radiculopathy, plexopathy, or mononeuropathy or mononeuritis multiplex. In some situations like diabetes mellitus, length-dependent neuropathies coexist with radiculopathies, plexopathies, and mononeuropathies. Atrophic weakness without sensory loss that does not follow a radicular, plexopathy, or mononeuropathy pattern suggests motor neuron disease (amyotrophic lateral sclerosis-ALS).

Onset and time course of neuropathy is important in determining the cause of the neuropathy (**Table 6**). Fibre type (pure sensory, motor or autonomic) involvement also helps in aetiological diagnosis of peripheral neuropathy (**Table 7**). Determining the primary pathological process demyelination and axonal loss is important for the diagnosis, treatment and prognosis. Electrodiagnostic tests can differentiate between the two. Nerve biopsy is of limited value in this aspect as it only evaluates a small segment, is not reproducible and is least sensitive for demyelinating pathologies.

Table 6: Peripheral Neuropathy Time Courses and Examples of Associated Neuropathies

Acute apoplectic	Vasculitic mononeuritis multiplex, idiopathic plexopathy
Days to weeks	Acute inflammatory demyelinating polyradiculopathy, porphyria, acute toxic exposure, proximal diabetic neuropathy, paraneoplastic sensory neuronopathy, diphtheritic polyneuropathy, critical illness neuropathy
Chronic, Years insidious	Diabetic polyneuropathy, chronic inflammatory demyelinating poly-radiculopathy, idiopathic hereditary

Table 7: Neuropathies based on Fibre Type Involvement

Motor Neuropathies	Sensory Neuropathies	Autonomic Neuropathies
GBS, porphyria, motor variant of CIDP, MMNCB, lead neuropathy, TOCP, amiodarone, perhexiline	Megadose pyridoxine, vitamin B12 deficiency, paraneoplastic sensory neuronopathy, nutritional neuropathies, Sjogren's syndrome	Diabetes mellitus, amyloidosis, hereditary sensory and autonomic neuropathy, acute pandysautonomia, paraneoplastic sensory and autonomic ganglionopathy

Treatment of Peripheral Neuropathy

Treatment should focus on disease modification if possible (discussed in relevant type of neuropathies) and reduction in neuropathic pain. Anti-epileptic agents, tricyclic antidepressants, and opiates are the mainstay of therapy for neuropathy. All these medications have side effects of drowsiness and reduced mental concentration, which are frequently dose limiting (**Table 8**).

Table 8: Selected Drugs for the Treatment of Neuropathic Pain

Category	Examples	Comments
Analgesics		
Opioids	Morphine, 30 mg/75 kg four times a day Oxycodon 10 to 40 mg	Analgesic tolerance is not inevitable; side effects include constipation
Adjuvant Analgesics		
Tricyclic antidepressants	Nortriptyline, start with 25 mg/day and titrate to 150 mg/day Amytriptyline, start with 10 to 25 mg/day and titrate to 75 to 125 mg/day	Side effects include sedation and mental clouding, cardiac arrhythmias, bladder disturbances, orthostatic hypotension
Traditional anti-convulsants	Carbamazepine, 400 mg three times a day	Side effects include ataxia, aplastic anaemia/agranulocytosis
	Valproate, 750 mg three times a day Phenytoin 100 to 300 mg/day	Side effects include ataxia
Novel anti-convulsants	Gabapentin, 600 mg three times a day	Requires titration; side effects include ataxia
	Lamotrigine, 25 to 100 mg three times a day Topiramate 100 to 400 mg Oxcarbazepine 300 to 600 mg/day Pregabalin 150 to 300 mg/day	Requires titration; side effects include ataxia and rash

ACUTE POLYNEUROPATHIES

A number of polyneuropathies present acutely of which Guillain-Barre syndrome (GBS) because of its frequency and severity is most demanding of the physician's attention.

Landry-Guillain-Barre-Strohl Syndrome

GBS is a prototype of acute onset polyneuropathy. It is usually a monophasic immune-mediated disorder. The term GBS is often considered to be synonymous of AIDP, but with the increasing

recognition over the past few decades of variants, the number of disease that fall under the rubric GBS has grown to include axonal variants and more restricted variants, such as Miller-Fisher syndrome (MFS).

Epidemiology

The reported incidence rates for GBS are 1 to 2 per 100,000 population. The lifetime likelihood of any individual acquiring GBS is 1:1000. The subtypes of GBS have different incidence rates in different parts of the world. In Europe and North America AIDP is dominant contributing to 90% of the cases. In contrast in China and Japan AIDP forms less than 40%, with acute motor axonal neuropathy (AMAN) being the commonest subtype. The picture is intermediate when we look at other population. In Indian series the incidence of AIDP and AMAN are virtually equal, although AMAN is commoner in younger patients. There seems to be a slight preponderance of AIDP in studies by Gupta *et al* and by Meena *et al* (unpublished data from NIMS, Hyderabad). Available Indian literature indicates a peak incidence between June-July and September-October. In the western countries GBS is common in the 5th decade, but in India it occurs more commonly in younger age. GBS is equally common in men and women and can occur at any age. There is a male preponderance among the hospitalised population.

Clinical Features

An otherwise unremarkable infection, such as an upper respiratory infection, often predates the onset of GBS by up to 14 days. Many antecedent infections have been identified, including *Campylobacter jejuni*, cytomegalovirus (CMV), *Mycoplasma pneumonia*, Epstein-Barr virus, influenza virus, JEV. Surgery, immunisation, and parturition have also been associated with GBS. GBS usually begins abruptly with distal, relatively symmetrical onset of paraesthesias and quickly followed by progressive limb weakness. Progression is rapid, with 50% of patients reaching clinical nadir by 2 weeks and more than 90% by 4 weeks. Current diagnostic criteria include <4 weeks of progression to clinical nadir. Approximately 80% to 90% of patients with GBS become non-ambulatory during the illness. Pain is prominent in 50% of patients. Neurological examination is characterised by distal and often proximal, relatively symmetrical, weakness. Though GBS is essentially a motor neuropathy, sensory dysfunction is seen in few patients. It is seen more in demyelinating form of GBS. Sensory examination is often normal in the early phase of the disease. GBS patients often develop cranial nerve weakness, usually in the form of facial or pharyngeal weakness. Diaphragmatic weakness due to phrenic nerve involvement is also common. Approximately one-third of hospitalised patients with GBS require mechanical ventilation because of respiratory muscle or oropharyngeal weakness. Autonomic disturbance usually manifests as tachycardia but more serious autonomic nervous system dysfunction may occur, including life-threatening arrhythmias, hypotension, hypertension, and gastrointestinal dysmotility. The incidence is between 27% and 55% and is much more common in AIDP.

Pathogenesis

Major advances have been made in understanding the mechanisms of some of the subtypes. The histological appearance of the AIDP subtype resembles experimental autoimmune neuritis, which is predominantly caused by T cells directed against peptides from the myelin proteins P0, P2, and PMP22. There is evidence for the involvement of antibodies and complement. Strong evidence now exists that axonal subtypes of GBS, AMAN, and acute motor and sensory axonal neuropathy (AMSAN), are caused by antibodies to gangliosides on the axolemma that target macrophages to invade the axon at the node of Ranvier. About a quarter of patients with GBS have had a recent *Campylobacter jejuni* infection, and axonal forms of the disease are especially common in these people. The lipo-oligosaccharide from the *C. jejuni* bacterial wall injection into rabbits induces a neuropathy that resembles AMAN. Antibodies to GM1, GM1b, GD1a, and GalNac-GD1a are in particular implicated in AMAN and, with the exception of GalNacGD1a, in acute motor and sensory axonal neuropathy.

Diagnosis

The diagnosis is based on both clinical and laboratory criteria. Supportive ancillary testing for GBS includes cerebrospinal fluid (CSF) analysis and electrodiagnostic testing, both of which may be normal in the early phase of GBS. The limitations of ancillary testing in the early phase combined with the importance of prompt treatment of GBS mandates that the clinician at times make the diagnosis based solely on history and examination. Albumino-cytological dissociation, an elevated CSF protein concentration (with normal cell count) is only found on initial CSF analysis in 50% of patients; elevated CSF protein concentration occurs in more than 90% of patients at clinical nadir. CSF pleocytosis is not seen in GBS and raises the question of infectious (HIV, CMV, Lyme, sarcoid), carcinomatous, or lymphomatous polyradiculoneuropathy. Although anti-ganglioside antibodies have been implicated in the pathogenesis of GBS assaying antiganglioside values in a patient with GBS other than MFS at the present time has no diagnostic value in routine practice.

Electrodiagnostic Studies

Electrodiagnostic studies are performed to support the clinical impression. Electrodiagnostic studies of patients with GBS often demonstrates feature of demyelination, such as temporal dispersion and conduction block, significantly slow conduction velocities, and prolonged distal and F-wave latencies. Electro-diagnostic studying features of acquired demyelination (e.g. conduction block, temporal dispersion, non-uniform slowing of conduction velocities) are particularly helpful because these findings are characteristic of immune-mediated demyelinating neuropathies. Another electrodiagnostic study hallmark of GBS is the 'sural sparing' pattern; i.e. the finding of a normal sural sensory nerve response in the setting of abnormal upper extremity sensory nerve results. Low compound motor nerve action potential amplitudes on distal stimulation are a feature in motor axonal variant of GBS. Low CMAPs of 0% to 20% of the lower limit of normal carry a poor prognosis.

Variants of GBS

Commonly recognised variants of GBS include those with axonal forms, variants based on particular fibre type involvement (sensory or autonomic), and MFS. Variants with regional or a markedly asymmetric distribution also occur. There are also differences in abruptness of onset and time to reach nadir, which can complicate diagnosis and decisions about treatment. For example, some patients have progression more

than 4 weeks but clinical features similar to GBS. This disease is referred to as subacute inflammatory demyelinating polyradiculoneuropathy (SIDP). AMSAN and AMAN are the two variants characterised by immune attack directed at axons rather than Schwann cells and myelin. Other regional variants of GBS also occur that affect other specific areas of the body (**Table 9**).

Table 9: Variants of Guillain-Barre Syndrome

Regional	Functional
Miller-Fisher syndrome (ophthalmoplegia, ataxia, areflexia)	Ataxia without dysarthria Pure sensory
Cervicobrachial-pharyngeal, often with ptosis	Pure motor
Oculopharyngeal	Pandysautonomia
Paraparesis	AMAN
Bilateral facial or abducens weakness with distal paraesthesias	AMSAN
Ophthalmoplegia with GQ1b autoantibodies	

AMAN occurs in large epidemics during summer in northern China and more sporadically elsewhere. It mostly affects children and young people, usually from rural areas. Onset of motor weakness is abrupt. In addition to acute motor paralysis, many patients have transient neck and back stiffness early in the course with resolution within a day. There are no sensory symptoms or signs. Sensory nerve conduction studies are normal and motor nerve studies are remarkable for low or absent CMAP amplitudes with normal conduction velocities.

AMSAN shares many pathological features with AMAN but differs clinically from it in patient's age of onset (usually adults rather than children), geographic distribution (can occur anywhere), time of onset (not only summer time), involvement of sensory nerves, course (protracted), and outcome (usually severe residual disability). The course is protracted and outcome is poor, with only 20% ambulating at 1 year.

MFS is more recognisable and distinct regional variant of GBS. Like GBS, onset of MFS often follows an infection, e.g. *C. jejuni*. MFS patients classically present with external ophthalmoparesis, areflexia, and ataxia, although MFS patients often present with fewer components of the classical clinical triad or with additional clinical features (facial weakness, oropharyngeal weakness, internal ophthalmoparesis, and central nervous system involvement). Bicker-staffs brainstem encephalitis (BBE) is a related syndrome in which alteration of consciousness or corticospinal tract signs are seen in addition to ophthalmoparesis and ataxia. Many patients with MFS or BBE also have 'overlapping GBS' with flaccid quadriparesis. Anti-GQ1b antibodies are present in 95% of patients with acute MFS and in approximately two-third of patients with BBE. The recognition of the various clinical presentations and the high sensitivity and specificity of anti-GQ1b antibody testing suggest rubric name of 'anti-GQ1b antibody syndrome'.

MFS is generally a benign, self-limiting condition. Almost all treated and untreated patients return to normal activities within 6 months of disease onset, usually with resolution of ophthalmoplegia within 1 to 2 months and ataxia within 3 to 4 months.

Differential diagnosis include ascending transverse myelitis, toxins, (arsenic, thallium, heavy metal poisoning), acute vasculitis, HIV neuropathy, acute intermittent porphyria, diphtheria, Botulism, poliomyelitis, hypokalaemic paralysis and *myasthenia gravis*.

MANAGEMENT

Patients with GBS who are symptomatic but are able to walk unaided for more than 5 metres and who are stable can be managed conservatively at peripheral centres. However, they should be observed for progression of the disease, especially if they are still within the first week of the onset of the disease. Blood pressure and heart rate fluctuations, clinical signs of respiratory failure should be carefully and meticulously monitored and should be mechanically ventilated during respiratory failure. If any of these signs are detected they should be immediately shifted to higher centres for further management. In the acute phase in bed-bound adult patients require both supportive therapy and immunotherapy can be used taking into consideration the cost factors and the clinical status (staging, complications and other co-morbid conditions) of individual patients. Dysautonomia should be effectively managed depending on the haemodynamic status of the patient.

Hyponatraemia is the common electrolyte abnormality in GBS and is due to SIADH (in majority of the cases) and natriuresis. The treatment is different for both. Both require replenishment of sodium but SIADH need fluid restriction and in case of natriuresis requires intravascular volume expansion. The best way to differentiate these two conditions is by measuring central venous pressure.

Deep Vein Thrombosis Prophylaxis

All patients should be given subcutaneous fractionated or unfractionated heparin and support stockings until they are able to walk independently to prevent deep vein thrombosis. If a prolonged bedridden period is anticipated and a tracheostomy already has been performed, institute oral anticoagulant treatment with warfarin.

Pain and sensory symptoms are reported in majority of patients with GBS and should be treated effectively with opioid analogues. Sedation and bowel hypomotility may become a problem. Other drugs like gabapentin, carbamazepine acetaminophen, NSAIDs and tricyclic anti-depressants also can be tried.

Nutrition

Nasogastric or gastric tube feeding should be instituted early and slowly. High energy (40 to 45 non-protein kcal) and high protein diet (2 to 2.5g/Kg) have been recommended so as to reduce muscle wasting and assist respiratory weaning. Continuous enteral feeding seems to be better tolerated than bolus feeding in these patients.

Surveillance for infections with weekly or more frequent sputum and urine cultures and blood count may be useful but the use of these tests should be guided by clinical circumstances.

Immunotherapy

Plasma exchange (50 mL/kg weight) and intravenous immunoglobulins (0.4 gm/kg/day for 5 days) both are effective

immunotherapies for adult and paediatric patients with GBS if given during the first few weeks of the disease. Potential limitations and complications with plasma exchanges include venous access, line sepsis, hypotension, and rarely air embolus and haemolysis. Intravenous immunoglobulins is relatively safer, easy to administer, with least side effect profile including fever, malaise, headache, aseptic meningitis, reversible renal failure and very rarely hyperviscosity syndrome. The main limitation is the cost.

PORPHYRIA

A severe, rapidly advancing more or less symmetrical relapsing and mainly motor polyneuropathy often associated with abdominal pain, psychosis, and convulsions may be a manifestation of acute intermittent porphyria. See details in Section 18, Chapter 6.

SUBACUTE AND CHRONIC NEUROPATHIES

In this category are neuropathies that evolve over several weeks and months (subacute) to years (chronic, e.g. vasculitic neuropathy, metabolic, nutritional, toxins and paraneoplastic polyneuropathies. Inherited polyneuropathies have a prolonged disease course in several years to decades. Despite considerable increases in the number of identifiable causes of peripheral neuropathy, idiopathic polyneuropathy still accounts for a significant proportion of cases.

DIABETIC NEUROPATHY

Diabetes is the most common cause of neuropathy. The true incidence or prevalence of diabetic neuropathy is not known, due to a lack of agreement on the definition of diabetic neuropathy. There are several reasons for this, including variability in clinical manifestations, a lack of consensus regarding clinical criteria to diagnose early neuropathy, and a lack of minimum electrodiagnostic criteria to diagnose subclinical neuropathy. Thus, the reported prevalence of diabetic neuropathy varies from 5% to 100%. Overall, the incidence of neuropathy in diabetes increases with the duration of diabetes and the degree of hyperglycaemia. See details in Section 9, Chapter 17. A summary is given in **Table 10**.

Table 10: Classification of Diabetic Neuropathy

Generalised Neuropathies	Focal or Multifocal Neuropathies
Distal symmetric polyneuropathy	Compressive focal neuropathies
Large fibre sensory	Carpal-Tunnel syndrome, ulnar neuropathy, peroneal neuropathy
Small fibre painful sensory	Noncompressive focal and multifocal neuropathies
Subclinical neuropathy	Diabetic amyotrophy
Acute painful diabetic neuropathy	Mononeuritis multiplex
Autonomic neuropathy	Cranial neuropathies
	Femoral, sciatic, ulnar, peroneal neuropathy
	Truncal neuropathies

MALIGNANCY RELATED NEUROPATHIES

Peripheral neuropathy can arise in a wide range of situations in context of malignancy. Chemotherapy accounts for the larger group of neuropathies associated with cancer and have largely been documented over the last decades. Oncologists are generally well aware of the toxicity of the main agents. Sequelae of radiotherapy, including plexopathies, lower motor neuron syndrome, cranial nerve dysfunction and exceptional peripheral nerve tumours, have now been well described.

Cancer Neuropathies

Neuropathies may directly result from cancer infiltration either from a solid tumour or from lymphoma. It may also be an indirect consequence of a dysimmune mechanism for instance in paraneoplastic neuropathies or as vasculitic neuropathy. Histopathologically proven vasculitic axonal neuropathies with cancer are seen in 15% of the cases. The complication is more frequent in patients with solid tumours (47.6%) and lymphoid malignancies (35.3%) than in patients with myelodysplastic syndromes (14.3%).

Paraneoplastic Neuropathies

These are associated with autoantibodies called oncogenes which cross react with peripheral nerves. Several types of neuropathies have been reported as paraneoplastic. However, subacute sensory neuronopathy still remains the most typical from in this setting, occurring mostly in small cell lung cancer (70% to 80% of cases) and sometimes in breast or ovarian cancer. See details in Section 21, Chapter 15.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

CIDP is a commonly under-recognised acquired neuropathy. Humoral and cellular mechanisms contribute to the autoimmune attack against peripheral nerve myelin. CIDP is distinguished from the subacute and GBS forms based on tempo: progressive weakness of 2 months or more. Sensory loss and decreased reflexes are frequently noted. The disease may progress in a relapsing, or progressive form (steady or step-wise progressive course). The relapsing form peaks in the third decade of life, and the progressive form is more typical in older individuals.

Diagnosis

The classic CIDP phenotype is characterised by symmetric proximal and distal weakness, large fibre sensory loss, increased CSF protein content, demyelinating changes on nerve conduction studies or nerve biopsy, and response to immunomodulating therapy. However, all large series have identified variants of this presentation.

A multifocal variant may present with asymmetric limb weakness. Approximately 50% of patients present with multifocal acquired demyelinating sensory and motor polyneuropathy (MADSAM), later progressing to a more diffuse neuropathy similar to the classical phenotype.

A distal phenotype with distal sensory loss and evidence for demyelination on nerve conduction studies or nerve biopsy may occur in the absence of weakness or with weakness of intrinsic foot/hand muscles, or ankle/wrist flexors or extensors. This phenotype is more common in elderly, and it could be misdiagnosed as lumbosacral radiculopathy or axonal polyneuropathy.

Multifocal motor neuropathy is another phenotype of CIDP. Cranial nerve involvement may also occur in CIDP. Increased CSF

protein occurs in more than 80% of patients, reflecting proximal nerve root involvement. Routine blood tests, including the ESR, are generally normal. Sometime patients with CIDP can be seropositive for P0 protein.

Electrophysiology

Electrodiagonistic studies play a critical role in characterising acquired demyelinating findings, such as slow nerve conduction velocities, prolonged distal motor latencies, prolonged F-wave latencies, conduction block, and abnormal temporal dispersion. Because CIDP is a multifocal disease, the ability to identify demyelination on nerve conduction increases by sampling a larger number of nerves. Some authors have suggested that nerve conductions of 8 motor nerves increased the yield of diagnosing CIDP, compared with unilateral or lower limb studies.

Treatment

Corticosteroids, plasma-exchange and IVIG are the modalities of choice. Steroids regimen consists of 1 to 1.5 mg/kg body weight for 4 to 6 weeks and which is gradually tapered to alternate day regimen of the same dose over a period of 6 months. Azathioprine 2 to 3 mg/kg body weight is commonly used as a steroid sparing drug in the maintenance phase. Plasma exchange produces dramatic responses in relapsing remitting type of CIDP. Often 3 to 4 exchanges on alternate day for a period of 4 weeks is required to obtain a clinical response. IVIG is becoming the treatment of choice due to least side effects and ease of administration even at peripheral centres and clinics. It is usually preferred in elderly patients. The dose is 2 g/kg body weight over 5 days and repeated after several weeks to months to maintain the clinical response. The main limiting factor is the cost. Cyclophosphamide, cyclosporine, lymphoid irradiation are advocated in patients who are refractory to the above treatment.

Multifocal Motor Neuropathy with Conduction Block (MMNCB)

MMNCB is an immune-mediated neuropathy predominates in men. They usually begin as acute or subacute motor mononeuropathy (foot and wrist drop) without sensory deficits. It may be associated with atrophy and fasciculations and mimic ALS. The characteristic feature on electrodiagnosis is multifocal conduction block and normal sensory conduction study. IVIG infusions are the drug of choice and cyclophosphamide can be used.

PARAPROTEINAEMIC NEUROPATHIES

Monoclonal Gammopathy of Undetermined Significance (MGUS)

In patients with neuropathy, particularly demyelinating neuropathies, the paraprotein associated with MGUS is frequently IgM. IgG and IgA are less represented than in the normal population. The paraproteins are usually kappa light chains. Approximately half of the patients with IgM MGUS have anti-MAG antibodies. They are typically older males, in the 6th and 9th decades of life. The characteristic clinical picture goes by the acronym distal-acquired demyelinating sensory neuropathy; as the name suggests, it is an insidiously progressive, distal, predominantly sensory neuropathy, with mild distal weakness. Large fibre sensation is affected more than small fibre sensation, resulting in sensory ataxia. Although the majority of patients with DADS have an M-protein (DADS-M), some do not (DADS). DADS-M is probably a distinct clinical entity from DADS. Whereas most patients show an insidious course with more sensory dysfunction, some may have significant weakness and more aggressive course).

Patients with DADS-M show slowed motor conduction velocities with excessively prolonged distal latencies on electrophysiologic studies, more so than DADS. Sensory responses are often attenuated or absent. Unlike IgM MGUS-related neuropathy there is no clinical homogeneity in the presentation of IgG or IgA MGUS.

Multiple Myeloma

Peripheral neuropathy associated with multiple myeloma can be due to perineurial or perivascular IgG kappa deposition, or due to treatment-related toxicity. Very rarely, IgM paraprotein is seen with multiple myeloma. Patients typically develop mild, symmetric sensory-greater-than-motor symptoms in the distal extremities; with concurrent amyloid deposition, the symptoms are more painful. Electrophysiology shows axonal damage, but histopathology can show demyelination as well, although more recent studies are lacking.

POEMS

The paraprotein found in this syndrome is usually IgG or IgA lambda. The acronym POEMS was coined in 1980 to point out the salient features of this condition (polyneuropathy, organomegaly, endocrinopathy, myeloma, hyperpigmented skin). It can have myriad presentations, and goes by several other names, including Crow-Fukase syndrome and Takatsuki syndrome. Clinically, the patients are younger (late 40s), and have severe sensory and motor weakness. Electrophysiology shows a demyelinating neuropathy with superimposed or secondary axonal loss, and nerve biopsy can show endoneurial deposits and uncompacted myelin lamellae.

WALDENSTROM'S MACROGLOBULINAEMIA

The disorder is rarely associated with peripheral neuropathy, seen only in 5% to 10% of cases. Neuropathy is associated with IgM kappa with or without anti-MAG antibodies. It is clinically indistinguishable from IgM MGUS-related neuropathy with anti-MAG antibodies, or DADS-M. Electophysiologic studies show demyelination; pathological studies show widening of lamellae as in IgM MGUS.

AMYLOIDOSIS

Peripheral neuropathy symptoms are often present for a long time prior to the diagnosis of amyloidosis, a multisystem disorder characterised by IgG or IgA lambda paraproteinaemia and deposition of immunoglobulin light chains in end organs. Either vascular insufficiency or a direct toxic effect of amyloid is the presumptive cause of the neuropathy. The patients experience prominently painful, progressive, symmetric, sensory and motor dysfunction, frequently with autonomic involvement as well. Electrophysiologic studies show an axonal, sensory-greater than motor neuropathy. The overall prognosis is poor, with a median survival of two and half years.

DRUGS AND TOXIN-INDUCED PERIPHERAL NEUROPATHY

Medication and toxin-induced neuropathies constitute a minority of cases, estimated at 2% to 4%, but are crucial to identify because

of potential reversibility, especially if uncovered prior to significant nerve damage. Arsenic, organophosphorous exposure, lead, thallium, gold, mercury and platinum are some of the common causes of toxin-induced polyneuropathy.

Numerous medications (**Table 11**) and toxins have been associated with neuropathy and have been convincingly linked with neuropathy. However, objective proof is lacking for many. Criteria have been applied to establish causation as opposed to simple association: (1) strong dose response relationship; (2) consistent manifestations; (3) close proximity of symptoms to exposure; (4) stabilisation or improvement after drug cessation; (5) reproduction in animal models or characteristic neuropathology; and (6) exclusion of other causes. However, these principles may not be applicable because: (1) some triggers for a neuropathy may be idiosyncratic; (2) low-level chronic exposure is difficult to link to a delayed onset of a disorder; (3) improvement may be minimal or delayed if significant axonal damage has occurred; (4) experimental animals may show different toxic effects from humans; and (5) worsening may continue after stopping the drug (coasting).

Table 11: Drugs Causing Neuropathy

Amiodarone	Nitrofurantoin
Chloramphenicol	Perhexiline
Chloroquine	Phenytoin
Colchicine	cis-Platinum
Dapsone	Pyridozine
Dideoxycytidine (zalcitabine), dideoxyinosine	Simvastatin
Disulfiram	Suramin
Gold	Taxol (docetaxel, paclitaxel)
Isoniazid	Thalidomide
Metronidazole	Vinca alkaloids

The majority of medication and toxin-induced neuropathies affect peripheral nerve axons and cause a distal, symmetric, sensory-predominant axonal neuropathy in a 'dying-back' pattern. However, some stem from direct injury to dorsal root ganglion neurons, peripheral myelin, or Schwann cells that can produce other patterns, including demyelinating features, asymmetry, and even frank conduction block in some examples. Onset is generally over weeks to several months. Sensory neurons and axons are usually more vulnerable than motor fibres. Some toxins produce predominant damage to small-diameter fibers and others to large diameter fibres. Skin lesions like hyperkeratosis, 'Meeslines' are features suggestive of arsenic exposure. Alopecia is seen in thallium exposure. There are a variety of neurotoxic mechanisms, including direct toxicity or toxic metabolites, secondary vitamin deficiency, interference with DNA and metabolic function, mitochondrial injury, apoptosis, and immune triggers.

NUTRITIONAL AND ALCOHOLIC NEUROPATHIES

See in nutritional and toxic disorders.

INHERITED NEUROPATHIES

Amongst the inherited neuropathies hereditary motor sensory neuropathy otherwise called as Charcot-Marie-Tooth disease type 1 and 2 are the commonest forms of chronic neuropathies although more than 50 genetic types have been described (**Tables 12A and 12B**).

Table 12A: Inherited Neuropathies

Type	Clinical Features	EDX Findings	Gene Abbreviation
CMT 1A	Distal symmetric weakness and atrophy; sensory loss and areflexia; skeletal abnormalities	mNCVs <38 m/s; no	*PMP22*
CMT 1B			*PO*
CMT 1C			*LITAF*
CMT 1D			*EGR2*
CMT 2A	Similar to CMT 1, but usually without hypertrophic nerves	mNCVs >38 m/s	*KIF1B*
CMT 2B1			*LMNA*
CMT 2B2			*RAB7*
CMT 2C			Unknown
CMT 2D			*GARS*
CMT 2E			*NEFL*
CMT 2F			Unknown
CMT 2G			*PO*
CMT 3A	Onset in infancy or childhood; prominent proximal and distal weakness; hypertrophic nerves; areflexia	mNCVs <10 m/s	*PMP22*
CMT 3B			*PO*
CMT 3C			*EGR2*
CMT 4A	Autosomal-recessive; early-onset severe neuropathy with hypertrophic nerves; demyelinating pathology	mNCVs <38 m/s	*GDAP1*
CMT 4B1			*MTMR2*
CMT 4B2			*MTMR13*
CMT 4C			*KIAA1985*
CMT 4D			*NDRG1*
CMT 4E			*EGR2*
CMT 4F			*PRX*
HNPP	Recurrent compressive Neuropathies; tomaculous pathology	Mild diffuse slowing of mNCVs; partial conduction block at sites of entrapment	*PMP22*
CMTX	X-linked inheritance; similar presentation as CMT 1; females usually less affected than males	Intermediate slowing of mNCVs; mNCVs >25 m/s	*CX32*
HSAN 1	Neuropathic ulcers; nociceptive loss	Absent or reduced SNAPs	*SPTLC1*
HSAN 2	Painless deformities; nociceptive loss	Similar to HSAN 1	Unknown
HSAN 3	Familial dysautonomic; neonatal onset	Reduced SNAPs	*IKBKAP*
HSAN 4	Congenital insensitivity to pain; fever	Normal	*NTRK1*
HSAN 5	Congenital insensitivity to pain; fever	Normal	*NTRK1*
HMN I	Undefined	mNCVs normal; denervation in clinically weak muscles	Undefined
HMN II	Distal weakness		Undefined
HMN III	Undefined		Undefined
HMN IV	Undefined		Undefined
HMN V	Upper limb involvement		Undefined
HMN VI	Respiratory failure		*IGHMBP2*
HMN VII	Vocal cord paralysis		Undefined
Familial Amyloid Polyneuropathies			
Type 1	Adult onset (Portugese)	Axonal	Transthyretin
Type 2	Adult onset (Indiana)	Axonal	Transthyretin
Type 3	Adults	Axonal	Apolipoprotein A1
Type 4	Adults, lax skin, blood hound face, corticospinal and posterior column deficit	Axonal	Gelsolin

Table 12B: Disorders of Lipid Metabolism and Other Disorders Causing Neuropathy
Metachromatic leucodystrophy
Krabbe's disease
Fabry's disease
Adrenomyeloneuropathy
Refsum disease
Tangier disease
Giant axonal neuropathy
Porphyria
Mitochondrial neuropathies
Severe PNS, CNS demyelination

Diagnosis of a hereditary neuropathy can be challenging and should be included in the differential diagnosis of chronic peripheral neuropathies. The first task is establishing whether there is a family history. This is straight forward when there are reports of similarly affected individuals in multiple generations, but more difficult when there is no known family history. This frequently arises due to the wide range of phenotypic variability in inherited neuropathies; family members may be asymptomatic or only mildly affected and have never sought medical evaluation. Patients may come from small families with a paucity of first- or second-degree relatives. The evaluating neurologist should take a thorough family history, perform a neurological examination, and ideally obtain electro-diagnostic testing. Slow progression of symmetric distal weakness and sensory loss dating to childhood or adolescence supports the possibility of an inherited neuropathy. Questions about motor development, athletic performance, and distal orthopaedic injuries are helpful. Steady progression is consistent with inherited neuropathies; a fluctuating course suggests an acquired condition.

Physical findings suggestive of an inherited neuropathy include Pescavus, hammertoes, and, to a lesser degree, scoliosis. Motor deficits are usually in combination with sensory loss in a symmetric and distal distribution. Muscle atrophy and weakness preferentially affects the anterior compartment of the leg resulting in toe and ankle dorsiflexion weakness. Sensory deficits can be asymptomatic. Patients rarely complain of 'positive' Neuropathic symptoms such as burning, tingling or pain. Electrodiagnostic testing helps guide the decision on which genetic tests to order. Genetic testing should be pursued only for only for patients who understand the implication of testing. A caveat is that none of these genetic testing is 100% sensitive or specific and a negative test does not exclude a hereditary neuropathy.

Treatment

Despite advances in diagnosis, there is no cure for these neuropathies. Treatment consists of patient education and supportive services. The mainstay of treatment is physical and occupational therapy, supports and bracing as well as aids to mobility. Promising therapies may involve the use of neurotrophic factors.

VASCULITIC NEUROPATHY

Causes of vasculitis are many. Peripheral neuropathy is a recognised complication of vasculitis. For the practicing clinician, certain clinical and laboratory features should raise suspicion for a vasculitic neuropathy. Classically, patients have painful sensory loss and weakness in the distribution of multiple peripheral nerves, so-called 'mononeuritis multiplex'. However, perhaps more commonly there is a confluence of multiple mononeuropathies that evolves in a summated fashion to produce a generalised, asymmetric, polyneuropathy or a lumbosacral plexus neuropathy. In some cases, the clinical pattern resembles a nondescript distal, symmetric, pure sensory or sensorimotor polyneuropathy. The course may be explosive at onset, but more often the neuropathy develops in a stuttering or stepwise pattern over weeks to months. Occasional patients have a very chronic, insidious course with symptoms that have been present for years before the time of diagnosis. The course may be indolent and static in some patients with non-systemic vasculitic neuropathy (NSVN).

Virtually all patients with neuropathy caused by systemic vasculitics also have constitutional symptoms, including fever, weight loss, and organ-specific involvement, such as rash, renal, bowel, or pulmonary involvement. Serologic abnormalities frequently indicate a systemic inflammatory process. Others have established diagnosis of a connective tissue or other inflammatory disorder.

Electrodiagnostic studies are especially helpful by demonstrating widespread, subclinical involvement in patients. Skin biopsy establishes the diagnosis of vasculitic neuropathy. In most cases, a nerve biopsy is mandatory to confirm the diagnosis in patients with suspected NSVN. A combined muscle and nerve biopsy may increase the diagnostic yield and is recommended. Characteristic pathological findings include: (1) T-cells and macrophages invading small epineural arteries (often <100 im in size); and (2) destruction or structural damage of the vessel wall with fibrinoid necrosis.

Non-Systemic Vasculitic Neuropathy

The features of NSVN are similar to those of systemic vasculitis; most patients have pain, weakness, and sensory loss in peripheral nerve territories, with slow progression over months to years that conforms to: (1) classic mononeuritis multiplex (13 to 45%); (2) confluent multiple mononeuropathies leading to an asymmetric, sensorimotor, axonal polyneuropathy, plexopathy, or polyradiculoneuropathy involving the arms and legs or legs alone (30 to 85%); or (3) distal symmetric polyneuropathy (2 to 25%). The course of NSVN is more indolent compared with systemic vasculitic neuropathy, and symptoms may be present for several years before the diagnosis is established .Probably less than 10% of patients with NSVN develop systemic features with long-term follow-up.

Treatment

Vasculitic neuropathy is treated with steroids. Other immuno-suppressive drugs that are used are azathioprine and pulse cyclophosphamide in severe cases.

HANSEN'S DISEASE

See in Dermatology Section.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) NEUROPATHY

Several types of neuropathy occur in patients with HIV infection (**Table 13**) and in large urban centres HIV-related neuropathies are seen frequently. Now with the introduction of HAART therapy the opportunistic infections are decreasing on one hand but on the other HIV neuropathy and HIV dementia are on the rise.

Table 13: Peripheral Neuropathies in HIV Patients
Distal Painful Neuropathy
Neuropathy due to nutritional deficiency
Neuropathy due to antiretroviral drugs
Guillian-Barre syndrome
Chronic Inflammatory demyelinating polyradiculoneuropathy
Multiple mononeuropathies
Acute lumbosacral polyradiculopathy

Distal painful neuropathy is very common in the late stages of HIV infection. The main symptom is continuous burning discomfort, mostly in the feet, where some degree of sensory loss also is apparent. Motor involvement usually is minor, although the patients often are debilitated by concurrent infections or weight loss. In some patients with this type of neuropathy there is an identifiable cause, such as vitamin B12 deficiency or treatment with a retroviral drug known to be neurotoxic, e.g. dideoxycytidine, but in most, the cause is uncertain. HIV has been cultured from sural nerve homogenates, and HIV nucleic acid can be found in dorsal root ganglia. Active cytomegalovirus (CMV) infection was found in 9 of 12 patients with distal painful neuropathy in one report, but the role (if any) of CMV in the pathogenesis of distal painful neuropathy is unclear.

Acute and chronic inflammatory demyelinating polyneuropathies typically occur in otherwise asymptomatic patients with HIV infection, sometimes at the time of seroconversion. The clinical picture is similar to that in non-HIV patients, except that a lymphocytic pleocytosis (20 to 50 cells/mm^3) is frequent in the CSF. HIV testing is increasingly considered part of the investigation of any patient with an inflammatory demyelinating neuropathy, and is mandatory if there is a CSF pleocytosis. As in non-HIV patients, both the acute and chronic forms appear to respond well to plasma exchange or IVIG infusions.

MONONEUROPATHIES AND COMMON COMPRESSION AND ENTRAPMENT NEUROPATHIES

The diagnosis of mononeuropathy is based on the motor, reflex and sensory changes confined to the territory of single nerve. Focal neuropathies may result from compression, entrapment, ischaemia, direct trauma, such as lacerations and missile wounds, involvement in fractures or dislocations, brachial mononeuritis, Hansen's disease, diabetes or idiopathic. The terms compression and entrapment are often used more or less interchangeably, sacrificing some accuracy (**Table 14**). Compression neuropathy refers to nerve damage due to pressure applied to a nerve, whether external or internal. The term *entrapment neuropathy* is appropriate when the pressure is exerted by some anatomic or pathoanatomic structure, such are the transverse carpal ligament in carpal tunnel syndrome (CTS). Thus, all entrapment neuropathies are compression neuropathies, but not all compression neuropathies are due to entrapment. Almost any nerve in the body can be compressed

Table 14: Entrapment Neuropathies	
Nerve	**Site of Entrapment**
Suprascapular	Spinoglenoid notch
Lower trunk of medial cord of brachial plexus	Cervical rib or band at thoracic outlet
Median	
Wrist	Carpal tunnel
Elbow	Between heads of pronator teres (pronator syndrome)
Ulnar	
Wrist	Guyan's canal (ulnar tunnel)
Elbow	Bicipital groove, cubital tunnel
Posterior interosseous nerve	Radial tunnel—at point of entrance into supinator muscle (arcade of Frohse)
Lateral femoral cutaneous (meralgia paraesthetica)	Inguinal ligament
Obturator	Obturator canal
Posterior tibial	Tarsal tunnel; medial malleolus – flexor retinaculum
Interdigital plantar	Plantar fascia: heads of 3rd and 4th metatarsals

or entrapped, and by definition involvement is limited to the distribution of a single peripheral nerve. Entrapment neuropathies are all chronic conditions; compression neuropathies due to externally applied pressure can develop acutely over several hours (post-operative ulnar neuropathy, tourniquet paralysis, Saturday night radial nerve palsy), subacutely over days to weeks (peroneal neuropathy at the fibular head due to prolonged bed rest or a short leg cast), or chronically over months to years (ulnar neuropathy in the retroepicondylar (RTC) groove). In some instances, a nerve is injured by relatively low force applied repetitively over a long period (ulnar neuropathy in the RTC groove, ulnar neuropathy at the wrist due to bicycling, peroneal at the fibular head due to habitual leg crossing). The diagnosis of mononeuropathy is based on electrodiagnosis and magnetic resonance imaging in entrapment neuropathies. The treatment of entrapment is surgical decompression.

IDIOPATHIC BRACHIAL NEURITIS (NEURALGIC AMYOTROPHY, PARSONAGE-TURNER'S SYNDROME)

This illness begins abruptly in an otherwise healthy individual, may complicate an infection, vaccination, antibiotics, childbirth, or any surgical procedure. Begins as an ache or deep burning in and around the shoulder neck or in axilla followed several days by motor weakness sensory and reflex loss. Pain subsides with onset of weakness. At times it may be bilateral. Electrodiagnostic studies is helpful in localising the lesion to restricted or diffuse involvement. Therapy is purely symptomatic but steroids may be beneficial. Recovery of paralysis and sensory deficit is usually complete by 6 to 12 weeks.

RECOMMENDED READING

1. Ropper AH, Samuels MA. *Adam's and Victor's Principle's of Neurology*. 9th edition.

20.30 Disorders of Autonomic Nervous System

Garima Shukla

One of the most important parts of the nervous system, the autonomic nervous system (ANS) innervates all organs of the body. The visceral and homeostatic functions of the human body, especially the control of arterial blood pressure and body temperature, are vital for survival, but involuntary.

ANATOMIC ASPECTS

Anatomically, most of the ANS is located in close proximity to the visceral organs it supplies. It is divided into the 'craniosacral parasympathetic' and the 'thoracolumbar sympathetic' parts which act in a complimentary fashion to balance various visceral functions.

Parasympathetic System

The cranial part of the parasympathetic ANS commences from visceral nuclei of the brainstem, the Edinger-Westphal nucleus, superior and inferior olivary nuclei, dorsal motor nucleus of the vagus and reticular nuclei. Pre-ganglionic fibres extend from these to the peripheral ganglia located close to the effector organs, viz. pupillary sphincter, ciliary muscle, submandibular and sublingual salivary glands, parotid gland, thoracic and abdominal viscera. Post-ganglionic fibres from these ganglia extend to and supply these effector organs.

The sacral part (pre-ganglionic fibres) originates in the lateral horns of the S2-S4 spinal cord segments, relaying in ganglia located in the walls of pelvic viscera, from where short post-ganglionic fibres arise and supply these organs.

Sympathetic System

Pre-ganglionic fibres of the sympathetic ANS originate in the intermediolateral cell column of the spinal grey matter from C8 or T1 to L2 spinal cord segments; they are small myelinated fibres forming the 'white communicating rami'. These relay in pre- and para-vertebral ganglion chains, from which the short un-myelinated post-ganglionic fibres arise and pass through the 'grey communicating rami' to T5-L2 spinal nerves and form plexuses which supply the heart and all other important viscera of the thorax and abdomen.

AUTONOMIC DISORDERS

Primary Disorders of the ANS

Primary autonomic failure should be diagnosed only after exclusion of common secondary causes enlisted in the next section, since the autonomic symptoms might often be the first manifestations of the underlying aetiology. Presentation may be acute/subacute or it may be chronic. Both these subtypes are entirely different entities.

Acute/subacute pandysautonomia

Acute pandysautonomia (APD) is an autonomic neuropathy characterised by severe widespread sympathetic and parasympathetic failure without somatosensory involvement. Its aetiology has not been established. However, there is a hypothesis regarding it being part of the spectrum of the Guillain-Barre syndrome in view of the following observations:

1. Nearly 50% patients with APD have a presumed viral infection that precedes the onset of symptoms,
2. High protein in cerebrospinal fluid (CSF) may be found in these patients, and
3. Response to intravenous immunoglobulins has been demonstrated in some patients.

There are recent reports of ganglionic acetylcholine receptor (AChR) autoantibodies as anti-neuronal antibodies that could be causative in autonomic neuropathy. Clinical presentation is with various autonomic symptoms like orthostatic dizziness, sweating, urinary and bowel disturbances. The course is generally self-limiting and patients may become symptom free over a period of weeks to months.

This syndrome may purely involve the ANS or may have associated involvement of other neurological systems. It might also completely spare a part of the ANS (pure cholinergic or pure adrenergic pandysautonomia).

Chronic autonomic failure syndromes

Pure autonomic failure: Chronic pure autonomic failure is a chronic degenerative condition, with a possible overlap with the spectrum of multiple system atrophy (MSA). Since the hallmark in MSA is degenerative involvement of more than one neurological system, this rare condition of pure autonomic failure is recognised as a separate entity.

Multiple system atrophy (MSA): MSA is a chronic degenerative disorder, often presenting predominantly either with Parkinsonian (MSA-P) or with cerebellar (MSA-C) features. Autonomic dysfunction is often present early in the course, in fact, may help clinch the diagnosis if it is the presenting feature with marked orthostatic hypotension and dizziness, urinary frequency, hesitancy, urge incontinence and bowel incontinence or more commonly, constipation.

Autonomic failure with Parkinson's disease (PD): Symptoms of autonomic dysfunction may not appear early in the course of PD often. Patients with PD generally respond well to levodopa/carbidopa combination for a number of years. Yet, clinical distinction between MSA-P and PD can sometimes pose a diagnostic challenge. Cardiac I^{123}MIBG (methyliodobenzyl-guanidine) SPECT imaging can serve as a valuable tool for this purpose. In MSA, the autonomic involvement is pre-ganglionic. Hence, cardiac sympathetic innervation tested with this imaging study is normal, while in PD, where there is post-ganglionic sympathetic dysfunction, significant loss of cardiac sympathetic innervation can be found.

Ross syndrome: Ross syndrome is a rare disorder of thermoregulation usually presenting in adulthood with chronic history of heat intolerance or progressive loss of sweating,

initially with patchy involvement, later becoming confluent. It is characterised by the clinical triad of anhidrosis, Holmes-Adie's pupil and generalised hyporeflexia. Cholinergic sudomotor damage has been observed in all patients reported in literature. Nolano *et al* found an involvement of pilomotor and vasomotor fibres and, although to a lesser extent, of somatic unmyelinated and myelinated nerve fibres in the 12 patients they reported and studied for detailed sudomotor function and skin biopsies.

Secondary Disorders of the ANS

A vast variety of neurological and general medical conditions can be associated with secondary involvement of the ANS. Some of these are listed here in **Table 1**. However, a comprehensive review of all conditions is beyond the purview of this chapter.

Table 1: Common Causes of Secondary Autonomic Neuropathy

Hereditary Conditions
- Riley-Day syndrome
- Hereditary sensory autonomic neuropathy

Metabolic Disorders
- Diabetes mellitus
- Chronic renal failure
- Chronic liver disease
- Alcoholism
- Adverse effects of drugs (antihypertensives, anticholinergics, anti-parkinsonian agents, etc.)
- Wilson's disease

Inflammatory
- Guillain-Barré syndrome
- Transverse myelitis

Infections
- Bacterial: Tetanus
- Parasitic: Chagas' disease
- Viral: Human immunodeficiency virus

Neoplasia
- Brain tumours, especially of third ventricle

CLINICAL FEATURES

Symptoms of Autonomic Dysfunction

Cardiovascular manifestations

Orthostatic hypotension: Orthostatic hypotension has been formally defined by expert consensus as a fall in systolic blood pressure (SBP) of at least 20 mm Hg and/or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 minutes of standing. Symptoms typically arise from hypoperfusion of various organs in the erect posture. The common symptoms are presented in **Table 2**.

Table 2: Common Symptoms of Autonomic Neuropathy

Dizziness, syncope, blurring/greying	Due to cerebral of vision, cognitive deficits hypo-perfusion
'Coat hanger ache' (in paracervical regions)	Due to and suboccipital hypoperfusion of muscles
Low backache	
'Subclavian steal' like syndrome	
Oliguria	Due to renal hypoperfusion
Non-specific symptoms like generalised weakness and fatigue	

Hypertension: Severe hypertension can be typically observed in patients with cervical spinal cord trauma, patients with tetanus and the Guillain-Barre syndrome. Patients may manifest only with occipital headache, but sometimes, with more varied and severe manifestations like palpitations with bradycardia, profuse sweating and flushing over the face and coldness of extremities.

Postural orthostatic tachycardia syndrome (POTS): POTS is currently defined as the presence of symptoms of orthostatic intolerance associated with a heart rate (HR) increase of 30 bpm (or rate that exceeds 120 bpm) that occurs within the first 10 minutes of standing or upright tilt, not associated with other chronic debilitating conditions, such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone. Symptoms resemble those of orthostatic hypotension; however, occurrence of palpitations in the erect posture is often the main feature. Symptoms, if severe, can restrict even routine day-to-day activities.

Facial and peripheral vascular changes: Facial and neck region flushing with coldness of extremities can be observed in patients with autonomic dysfunction, more characteristically in patients with spinal cord trauma and primary autonomic failure.

Sudomotor disturbances: Generalised or focal anhydrosis or hyperhydrosis may be observed in a variety of conditions including the Ross syndrome, hereditary sensory autonomic neuropathies, diabetic neuropathy, etc. Similarly, hypothermia or hyperthermia, both can be seen, the latter typically occurring as a consequence of anhidrosis.

Gastrointestinal disturbances

Reduced salivation can cause dry mouth in various autonomic disorders. This can further lead to dysphagia on eating dry food. Gastroparesis causing distension of the abdomen is seen commonly in diabetics with autonomic neuropathy. Diarrhoea and constipation might occur frequently. Fecal incontinence may particularly be observed in patients with MSA.

Bladder disturbances

Day-time oliguria and nocturnal polyuria can occur due to hypoperfusion of the kidneys in erect posture in day-time, with redistribution of blood supply during sleep in supine position at night. Apart from this, sphincter disturbances can result in hesitancy, urgency and incontinence as well.

Sexual disturbances

Erectile dysfunction resulting from parasympathetic disturbances, is often among the first clinical manifestations of various disorders of the ANS, e.g. diabetic neuropathy, MSA, etc. Retrograde ejaculation and priapism are the other features seen.

Eye manifestations

Horner's syndrome with ptosis and miosis; Holmes-Adie's myotonic pupillary dilatation as well as reduced lacrimation can be frequently found among patients suffering from various autonomic disorders.

Bedside Examination

On general physical examination, dry skin, abnormal sweating, abnormal 'triple response' can be found. Change in blood pressure (BP) and heart rate (HR) in supine *versus* standing

position give important information about orthostatic hypotension and/or tachycardia.

Pupillary abnormalities and the Horner's syndrome, as well as reduced lacrimation confirmed by the Schirmer's test can be easy bedside clues to autonomic dysfunction.

Some other cardiovascular tests which can be performed bedside are the mental arithmetic test, isometric hand grip test and the cold pressor tests (looking for normal *versus* abnormal rise in HR and BP with these manoeuvres).

Detailed systemic and neurological examination give extremely important information about the aetiology of the autonomic disorder, e.g. parkinsonian features in MSA and PD, hyporeflexia pointing towards possibility of peripheral neuropathies or the Ross syndrome, etc.

LABORATORY EVALUATION OF AUTONOMIC FUNCTION

The reader can find a detailed description of the various laboratory tests of autonomic function elsewhere. Most of these may not be available for routine testing at majority of the centres; nevertheless, comprehensive evaluation of a patient with suspected autonomic dysfunction necessitates performing at least some of the simpler, more easily available tests.

Tests of Sudomotor Function

1. Quantitative sudomotor axon reflex testing (QSART): It is a sensitive measure of postganglionic sympathetic axon integrity, in which at the test site, a multi-compartment sweat cell is applied to the skin, acetylcholine (ACh) is iontophoresed in one compartment and the sweat response is recorded in a second compartment.
2. Thermoregulatory sweat testing (TST): The adequate stimulus is a rise of core temperature usually generated by raising ambient temperature so as to raise blood and mean skin temperature. The efferent sympathetic response is mediated by pre-ganglionic centres right from the hypothalamus, up to the white rami; post-ganglionic paths include the sympathetic chain and post-ganglionic sudomotor nerves to sweat glands.
3. Sympathetic skin response (SSR): A very sensitive and simple test which can be easily conducted in any electromyography laboratory with electrical current or physiological phenomena like a deep breath or cough can act as a stimulus. Its major drawbacks are its variability and rapid habituation with high false negative values.

Tests of Cardiovagal Function

1. HR response to deep breathing (or other stimuli like isometric hand grip) can be measured systematically in the laboratory apart from its utility as a simple bedside tool as well.
2. Valsalva ratio: For measurement, the subject, while rested and recumbent, is asked to maintain a column of mercury at 40 mm Hg (not exceeding 50 mm Hg) for 15 seconds via a bugle with an air leak (to ensure an open glottis). The responses should be repeated until two responses of similar beat-to-beat BP and HR responses are obtained.
3. Tilt table testing for orthostatic hypotension. Changes in BP and HR are measured after positioning the patient in a 60 to 75° tilt on the tilt-table, immediately and 3 minutes after change in position.

   Beat to beat measurement of arterial BP can be carried out with the use of special tonometry devices, both for simple measurement of postural changes in BP, and for the calculation of the Valsalva ratio.

MANAGEMENT

Management of the autonomic disorders is often symptomatic. Identifying and targeting the primary aetiology of the dysfunction should be the primary aim of treatment.

Most treatment strategies are directed towards management of symptomatic postural hypotension. The approaches utilised are mostly non-pharmacological, suggesting the patients to avoid the following:

- Sudden head-up postural change (especially, on waking),
- Prolonged recumbency,
- Straining during micturition and defaecation,
- High environmental temperature (including hot baths),
- 'Severe' exertion,
- Large meals (especially, with refined carbohydrate),
- Alcohol, and
- Drugs with vasodepressor properties; along with suggestions regarding
  - small frequent meals,
  - high salt intake,
  - judicious exercise (including swimming), and
  - body positions and manoeuvres.

In severe cases, oral fludrocortisone (50 to 100 µg at night) can be used as an initial drug of choice, however, non-responders can require treatment with ephedrine 15 mg three times daily that may be increased to 30 or 45 mg three times daily, octreotide 25 or 50 mg, ideally 30 minutes before food ingestion to avoid postprandial hypotension or desmopressin 5 to 40 mg intranasally or 100 to 400 mg orally at night to reduce nocturnal polyuria which can worsen day-time postural hypotension.

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20.31 Myasthenia Gravis

Sumit Singh, Atma Ram Bansal

Myasthenia gravis is an autoimmune disorder where antibodies against the nicotinic acetylcholine receptors (AChRs) on the post-synaptic membrane of the neuro-muscular junction (NMJ) inhibit neuro-muscular transmission. It is characterised by fatiguable skeletal muscle weakness, and diurnal variation of symptoms. Once considered a fatal illness, *M. gravis* can now be managed safely and effectively due to significant advances in management. Thomas Willis (1672) was the first to describe myasthenia and Osserman (1958) classified *M. gravis* according to severity of clinical symptoms. *M. gravis* is the commonest NMJ disorder, with a prevalence of 14.2 cases per million in the US and 20 to 70 cases per million in the UK.

AETIOPATHOGENESIS AND PATHOLOGY

The NMJ has three components: Pre-synaptic motor nerve terminal where acetylcholine (ACh) is synthesised, packaged into vesicles and released, the synaptic cleft, and the post-synaptic membrane which contains acetylcholine receptors (AChRs) and anticholinesterase enzyme. There is a constant turnover and renewal of AchRs at the NMJ. AchR antibodies are found in nearly 80% to 90% of patients with generalised *M. gravis* and 50% to 60% of patients with ocular *M. gravis*. These antibodies block the AchRs, destroy the muscle end-plate by activating the lytic compliment pathway which causes simplification and distortion of normally folded post-synaptic membrane, and cross link with AChRs and accelerate endocytosis and degradation of AChRs. Extra-ocular muscles are more vulnerable for *M. gravis* because their NMJ has less prominent synaptic folds; fewer post-synaptic AchRs and smaller motor units. The role of thymus gland in *M. gravis* has been proposed since a long time. Thymic hyperplasia occurs in 60% to 70% of *M. gravis* patients, more so in females. Thymomas are frequently associated with autoimmunity and their cells express numerous AChRs like epitopes. The aetiological causes of *M. gravis* are shown in **Table 1**.

Table 1: Aetiological Classification of Myasthenia

Type of Myasthenia	Aetiology
Acquired autoimmune	Autoimmunity
Transient neonatal *M. gravis*	Transplacental transfer of maternal anti-acetylcholine receptors (AChRs) antibodies
Drug-induced *M. gravis*	D-penicillamine, curare, aminophylline, quinine, procainamide and calcium channel blockers
Congenital myasthenic syndromes	Genetic abnormality in acetylcholine receptors

CLINICAL FEATURES

M. Gravis has a bimodal peak of age at onset. The first peak is in adolescence and the second in fifth or sixth decade. Females are more commonly affected at a younger age. Incidence is roughly equal for male and female sex during puberty and between 40 to 50 years of age. *M. gravis* presents with a history of fluctuating proximal muscle weakness which worsens with activity, typically worsening towards evening and improving in the morning and after rest. About 60% to 70% of patients present with diplopia due to extra-ocular muscles involvement, often asymmetrical, mimicking 3rd, 4th, or 6th cranial nerve palsy or internuclear ophthalmoplegia (INO). Pupillary functions are never affected, but weakness of orbicularis oculi may impair eyelid closure as well. The weakness of muscles of eye opening as well as closing is seen in very few diseases of which *M. gravis* is the commonest. Involvement of muscles of mastication causes drooping of the jaw while chewing hard foods. Facial muscle involvement causes lack of facial expression and a 'snarl' on attempted smiling. Bulbar muscle weakness presents with dysphagia and dysphonia and may result in aspiration pneumonia. Speech may have nasal intonation but improves with rest. Cognitive, sensory or autonomic symptoms are absent. The most commonly affected muscles in decreasing order of frequency are: Levator palpebrae superioris, extra-ocular muscles, proximal limb muscles (upper limbs > lower limbs), facial muscles and neck extensors. Intercurrent infections, emotional upset, febrile illness, exposure to heat, menstruation, vaccination, certain drugs, (**Table 2**), pregnancy, hyperthyroidism, and hypokalaemia may precipitate *M. gravis*. In a previously undiagnosed case, delayed recovery after general anaesthesia or a difficult weaning off the ventilator can indicate *M. gravis*. Thyroid disorders may be seen in nearly 13% of the cases.

Table 2: Drugs to be Avoided in *Myasthenia gravis*

Analgesics	Narcotics
Anaesthetics, local	Cocaine, procaine, lidocaine, bupivacaine, prilocaine
Antacids or laxatives containing magnesium	Maalox, mylanta
Antiarrhythmics	Quinidine, lidocaine, procainamide
Antibiotics	Aminoglycosides, quinolones, telithromycin, erythromycin, clindamycin, ampicillin, imipenem, vancomycin, metronidazole
Anticonvulsants	Phenytoin
Antihypertensives	Beta-blockers, calcium channel blockers
Antimanics	Lithium salts
Antipsychotics	Chlorpromazine
Antirheumatic	Chloroquine
Arthritis agents	Penicillamine-induced *M. gravis*
All neuro-muscular blocking agents	Succinyl choline, pancuronium, vecuronium, rocuronium, atracurium, pipecuronium etc.
Anti-malarials	Chloroquine, hydroxychloroquine

On examination, ptosis and squint with a normal pupillary response are characteristic of *M. gravis*. The presence of fatiguable ptosis or double vision is almost pathognomonic of *M. gravis*. Muscle bulk is normal and muscle wasting is rarely seen. Deep tendon reflexes are usually preserved and sensory examination is normal. There is no muscle weakness if the patient is examined after a period of rest; therefore the involved muscles need to be exercised to manifest the weakness.

DIAGNOSIS (FIGURE 1)

Pharmacological Tests

Edrophonium test (tensilon test) or neostigmine test

Edrophonium is a very short-acting ACh esterase inhibitor. In patients with suspected myasthenia, incremental test dosage of 2 mg and then 8 mg is given intravenously and improvement in muscle power is observed, under cardiac monitoring for arrythmias. The test is more useful in patients with ocular myasthenia. Neostigmine methylsulphate is given in doses of 1.5 mg intramuscular or subcutaneously. Improvement in weakness occurs in 15 to 20 minutes and reaches its peak in 30 minutes. It is advisable to give atrophine injection 0.6 mg prior to neostigmine. False positive test can be seen in Lambert-Eaton myasthenic syndrome, amyotrophic lateral sclerosis, neuropathies, and brainstem lesions.

Ice pack test

This test is useful when ptosis is present. Application of ice pack to the eyelids for 2 to 5 minutes improves ptosis in nearly 80% of cases. The test is much simpler and safer than tensilon test.

Electrophysiological tests

Repetitive nerve stimulation test (RNST): RNST is based on the principle of demonstrating electrophysiological evidence of fatiguability in the muscles. The nerves are stimulated at a frequency of 2 to 5Hz and a 10% decrement in the compound muscle action potential (CMAP) indicates fatiguability, suggesting myasthenia. The decrement is enhanced following exercise.

Serological tests

Anti-AchR antibodies: The detection of IgG antibodies against the alpha 1 subunit of nicotinic AchRs in serum is the gold standard test for confirming *M. gravis*. 80 to 85% of generalised *M. gravis* and 50 to 60% of ocular *M. gravis* have high titres of these antibodies. Anti AchR negative (seronegative *M. gravis*) should be tested for anti muscle specific tyrosine-kinase (MUSK) antibodies which are found in approximately 40% of seronegative patients. Patients with MUSK antibodies are usually females, usually have bulbar myasthenia and carry a poor prognosis.

Radiological evaluation

Computed tomography/magnetic resonance imaging of chest should be done in all patients to screen for thymic hyperplasia or thymoma. Patients should also be screened for tuberculosis as they might require long-term immunosuppressants.

Differential Diagnosis

The presentation of a fatiguable proximal muscle weakness with diurnal variation of symptoms and diplopia with evidence of weakness of muscles of eye closure and eye opening with normal pupils virtually establishes the diagnosis of *M. gravis*.

Thyrotoxicosis can present with diplopia and exophthalmos which is not seen in *M. gravis*. Polymyositis presents with muscle pain and high creatine phosphokinase levels and proximal muscle weakness. The extraocular muscles (EOM) are spared and there is no diurnal variation. Psychogenic weakness should be suspected if there is fatiguability, with fluctuating weakness. Motor neuron disease patients have diffuse fasciculations and usually spared eye movements. Gullaine-Barre syndrome patients can have a proximal muscle weakness but the EOM are spared and the reflexes are absent.

APPROACH TO A PATIENT WITH SUSPECTED MYASTHENIA GRAVIS

Treatment

Management of *M. gravis* has been revolutionised in the last decade. Treatment plan depends upon the rate of progression, distribution, severity and pattern of weakness. The treatment of *M. gravis* can be considered to involve 3 steps.

SYMPTOMATIC TREATMENT

Acetylcholine-Esterase Inhibitors (AchEI)

These drugs provide symptomatic relief in *M. gravis* patients by inhibiting the Ach esterase enzyme in the synaptic cleft, thereby increasing the availability of Ach in the synaptic cleft. Neostigmine is administered 15 mg every 3 to 4 hours. Parentral dose is 0.5 to 2.5 mg intravenous, intramuscular or sub-

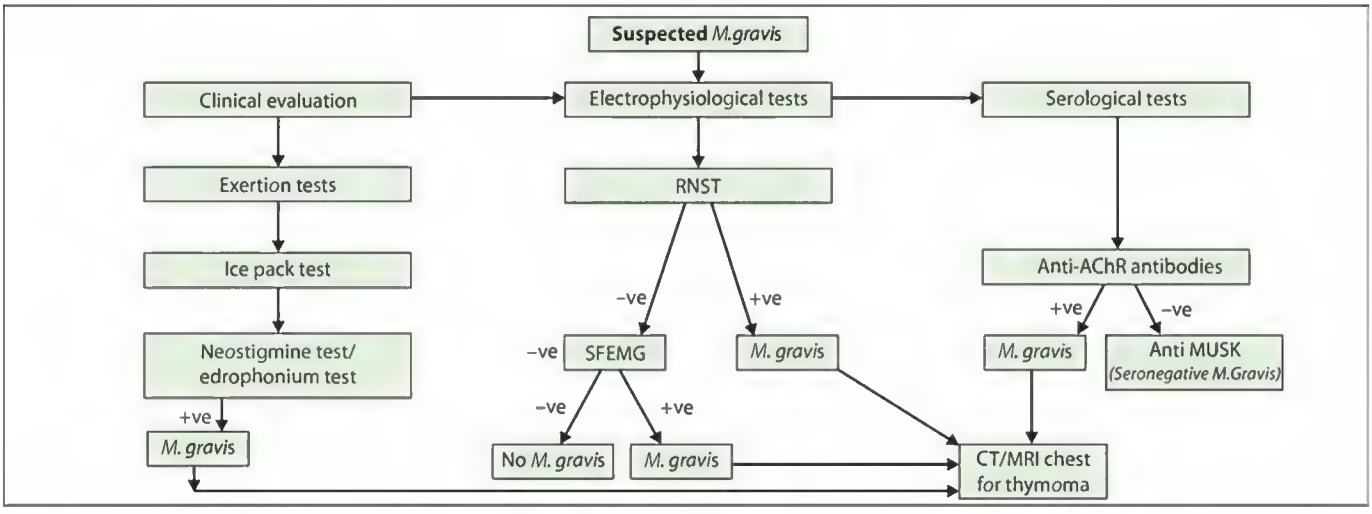


Figure 1: Algorithm for diagnosis of *Myasthenia gravis*.

RNST = Repetitive nerve stimulation test; AChR = Acetylcholine receptor; SFEMG = Single fibre electromyography; MUSK = Muscle specific tyrosine kinase; CT = Computed tomography; MRS = Magnetic resonance imaging; +ve = Positive; –ve = Negative.

cutaneous. Total dose should not exceed 375 mg per day orally or 10 mg per day parenterally. Pyridostigmine is the most common agent used, as it has a longer duration of action. The starting dose is 15 to 30 mg every 4 to 8 hours with a maximum dose of 1,500 mg per day. Sustained release preparations of pyridostigmine can be used to tide over nocturnal/early morning symptoms. Side-effects of these drugs are similar and include salivation, diarrhoea, palpitations and abdominal colic, which if severe can be controlled by giving probanthine and glycopyrrolate. Over dosage of AchEI can cause cholinergic crisis.

Immunomodulating Therapies

Immunomodulation suppresses the immune system to induce a clinical remission and is achieved by the administration of corticosteroids or non-steroidal immunosuppressants.

Corticosteroids

Prednisolone in doses of 1 mg/kg per day has been shown to reduce AChR antibodies levels, which correlates with clinical improvement. The starting dose is low (10 to 20 mg per day), preferably after admission, to avoid early worsening noted in patients on high dose regimen. The improvement usually begins in 2 to 3 weeks and maximum benefit is realised after 2 to 3 months or more. Once remission is attained and the patient remains asymptomatic for 2 to 3 months, a very slow tapering can be tried. Adverse effects of steroids include weight gain, osteoporosis, and increased infections secondary to immunosuppression. Corticosteroids are also needed in patients who experience a relapse after thymectomy. Some patients with ocular myasthenia respond poorly to Ach esterase inhibitor drugs and improve only with steroids.

Nonsteroidal Immunosuppressants

These agents include azathioprine, cyclophosphamide, cyclosporine, methotrexate,and mycophenolate mofetil. Azathioprine is the most commonly prescribed drug and is gradually titrated by 50 mg per week increments to daily doses of 2 to 3 mg/kg per day. It takes 3 to 6 months to start working and might be delayed for as long as 12 months. Complete blood counts, platelet count and liver function tests should be done periodically in all patients who are on azathioprine. Sometimes steroids and azathioprine are started together, and after 2 to 3 months the steroids are tapered off gradually to minimise the side-effects due to them, while azathioprine takes over the immunosuppression.

Cyclosporine (3 to 6 mg/kg per day), cyclophosphamide (2 to 5 mg/kg per day), and methotrexate (7.5 to 15 mg per week) can be tried in patients with severe disease, who do not respond or have unacceptable side-effects to other drugs. Tacrolimus and rituximab are other immunosuppressants which may be used in special circumstances.

Emergency Treatment

Plasma exchange

Plasma exchange is used in myasthenic crisis, in patients with severe disease, or to stabilise patients before thymectomy. Plasma exchange produces temporary improvement by removing Ach R antibodies, complement and immune complexes from the blood. 30 to 50 mL/kg plasma is removed on alternate days for 4 to 6 cycles. The improvement is temporary and lasts for 4 to 10 weeks. The immunosuppressive treatment continues after plasma exchange as well.

Immunoglobulins (IVIG)

IVIG can be used for the same indications as plasma exchange in *M. gravis*. The possible mechanisms are competition with autoantibodies and formation of anti-idiotypic antibodies. The standard dose is 2 gm/kg over 5 days. The advantage of IVIG is low risk of side-effects compared to plasmapheresis. The drug is very costly and the results are similar to plasma exchange.

Surgical Treatment

Thymectomy can be performed using open approach or by videoscopic or robotic means with similar results. The benefit of thymectomy is not immediate and may take 1 to 3 years and in some patients 'benefit' of a remission may take as long as 7 to 10 years. Thymectomy is indicated in patients with anti AchR positive generalised myasthenia with disease onset prior to the age of 60 years. In young children or in patients with non-thymomatous ocular *M. gravis* thymectomy should be avoided. The presence of thymoma is an absolute indication for thymectomy.

MYASTHENIC CRISIS

Myasthenic crisis is defined as sudden worsening of respiratory function in *M. gravis* requiring ventilatory support. Myasthenic crisis needs to be differentiated from cholinergic crisis which results from excessive dosage of AchEI. Miosis and the SLUDGE syndrome (salivation, lacrimation, urinary incontinence, diarrhoea, gastrointestinal upset, hypermotility and emesis) may help in differentiating the two conditions. Injection of tensilon worsens cholinergic crisis but improves the myasthenic crisis. Patients with myasthenic crisis must be treated aggressively. The AchEI medications should be stopped to give drug holiday, and the airway should be secured. Infections should be controlled actively and IVIG or plasma exchange should be used to achieve rapid control of symptoms.

LEMS

It is a rare pre-synaptic disorder of neuro-muscular transmission due to antibodies formed against the voltage-gated calcium channels (VGCCs) on the pre-synaptic motor nerve terminal inhibiting the release of the Ach. Malignancy, particularly small cell carcinoma of the lung, is present or subsequently discovered in 50 to 70% of patients with LEMS. The symptoms include ptosis, diplopia and dysarthria autonomic symptoms like dry mouth. proximal muscle weakness, depressed tendon reflexes and augmentation of power after few seconds of activity. Nerve canduction velocity test shows low amplitude compound muscle action potential, which will show post exercise potentiation. Removal of the causative tumour, immunosuppression, and 3, 4-aminopyridine may be used for treatment.

Transient neonatal M. gravis is seen in 21% of infants born to women with acquired *M. gravis*. Children have poor sucking and generalised hypotonia. Complete recovery is expected in less than 2 months in 90% of patients and in the remaining 10% by 4 months. The disease occurs due to transplacental transmission of the maternal AChR antibodies.

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20.32 Diseases of Muscles

SV Khadilkar

INTRODUCTION

Diseases of muscle constitute about 10 per cent of all neurological problems and hence are important for the clinicians. Muscles can be affected by a variety of causes, genetic and acquired. Over the past few years, the fields of genetics and immunocytochemistry have expanded exponentially and this had led to a wealth of understanding of the inherited myopathies. The pathophysiological mechanisms of the disease processes are being elucidated at the molecular level and considering the rapidity of such developments, corrective therapy for these disorders appears to be a possibility. As compared to the inherited myopathies, the acquired disorders have a better outlook particularly if they are inflammatory in origin.

CLINICAL FEATURES

Weakness

The main clinical feature of myopathies is weakness of muscles. Most muscle diseases produce symmetrical weakness of the large muscles of the girdles and trunk. Hip girdle is the most commonly affected and results in difficulty in getting up from squatting position or from low chair and inability to climb stairs. The weakness of the hip abductor muscles result in the characteristic waddling gait. Upper girdle weakness prevents the patient from performing chores like hanging clothes on a clothes line or taking down items from high shelves. A patient having trunk weakness has difficulty in turning in bed and getting up from recumbent position. Neck muscle weakness manifests with inability to control neck while in a vehicle as it rapidly accelerates and decelerates. This results in neck pain and stiffness. Amongst the cranial musculature, facial weakness, ptosis and external ocular movement weakness are seen from time to time. The restriction of the ocular movements is gradually progressive and symmetrical, hence diplopia is not common. This is in contrast with the myoneural junction disorders and nerve diseases, where the asymmetry almost always leads to diplopia. Myopathic patient has to use his/her head and neck movements to compensate the inadequacy of eye movements. Facial weakness presents with inability to close eyes fully and difficulty in drinking with a straw. At the onset of the weakness, myopathies involve the distal musculature only exceptionally, but distal muscles may be affected in many myopathies in the later stages of the processes. Such patients develop difficulty in opening lids of jars, turning keys in key holes and tend to trip easily on uneven ground with repeated falls.

Hypertrophy

Hypertrophy of muscles is seen in some myopathic patients. Calves, glutei and deltoids are the muscles where the hypertrophy is evident. The hypertrophy is most pronounced in conditions like Duchenne muscular dystrophy and Becker muscular dystrophy (**Figure 1**). To a lesser extent, it is seen in other forms of muscular dystrophies. It can also be seen in patients having infestations of muscles by Cysticercus cellulosae and *Trichinella spiralis*. In these conditions, if the patient is asked to stand on tiptoes, the calves can be seen to knot up in multiple small swellings, unlike the uniform contraction seen in dystrophies. It is important to remember that mild muscular hypertrophy can be seen in conditions of neurogenic origin like the spinal muscular atrophies and radiculopathies.



Figure 1: Severe calf hypertrophy in a patient with Becker muscular dystrophy.

Myotonia

Myotonia, delayed relaxation after sustained contraction, can be elicited by percussion and sustained grip. Myotonic disorders form a distinct subgroup of myopathies. Fasciculations and other abnormal movements of the lower motor neuron unit are very uncommon in myopathies, and the examination of the sensory system is essentially normal. The deep tendon reflexes remain normal for a long time in these illnesses and tend to get diminished, as the patient looses strength significantly and is immobilised.

An important clinical point needs emphasis at this stage. Inherited myopathies like dystrophies tend to have a pattern of muscular weakness. In contrast to this selectively seen in inherited

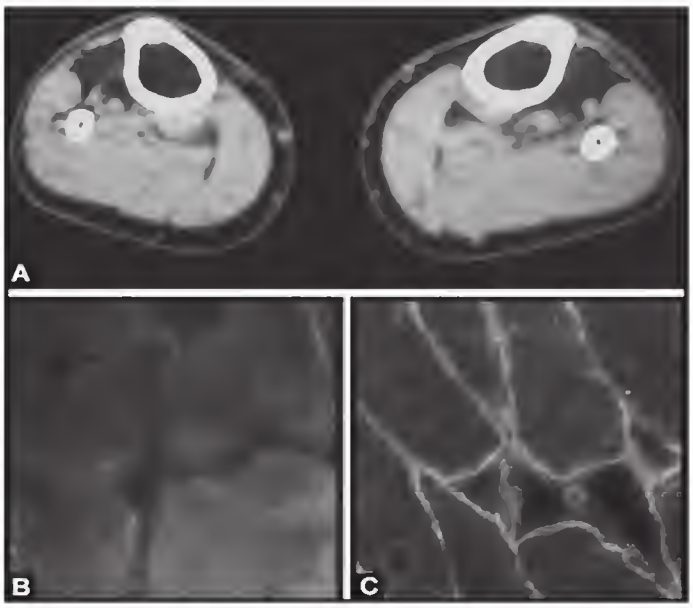
myopathies, the metabolic and inflammatory myopathies have a more uniform or nonselective distribution of weakness.

DIFFERENTIAL DISORDERS

Any condition affecting the lower motor neuron can present with weakness as the chief symptom and needs to be differentiated from primary muscle disease. The initial step is to differentiate between pure motor disorders from sensorimotor disorders. Sensorimotor disorders arise from either the nerves or the roots. Neuropathies are essentially distal and often symmetrical. Radiculopathies produce pain and asymmetrical loss of sensorimotor function over limited areas of one or two roots as is classically seen in the disc disease. Pure motor disease arises from muscles, as described earlier, they are proximal and symmetrical. Anterior horn cell disorders are almost always asymmetrical, proximal and distal in their distribution and have fasciculations as seen in motor neuron disease and spinal muscular atrophies. Additionally, they may have upper motor neuron signs. The last group of conditions that need to be considered in the differential diagnosis is the myoneural junction diseases like myasthenia gravis. These conditions preferentially involve certain groups of muscles namely the external ocular muscles and swallowing. The symptoms fluctuate and at a given time when the patient has rested, there may not be any clinical signs. Hence it is important to examine the patient when he or she is at the worst. Besides fatigability and weakness, in these diseases, there is no other lower motor neuron sign.

INVESTIGATIONS

Serum creatine kinase (CK) is usually elevated in myopathies to a level higher than that seen with neurogenic conditions. Electrophysiology is a very useful tool to differentiate myopathies from neurogenic conditions. In myopathies, small polyphasic potentials with early recruitment is seen. Inflammatory myopathies tend to show increase in spontaneous activity. CT or MRI can be used to study the pattern of muscular weakness (**Figures 2A to C**). Muscle biopsy is taken from a modestly affected muscle and stained with haematoxylin and eosin. Changes in the fibre size, position of nuclei, inflammation, degeneration, regeneration and changes in connective tissue and blood vessels are noted. When facilities are available, special immunological stains are performed on fresh frozen muscle for analysis of the cytoskeletal proteins. Lastly, DNA diagnosis is performed to confirm the diagnosis.



Figures 2A to C: (A) Selective atrophy of the tibialis anterior and gastrocnemius muscles. Immunocytochemistry shows (B) absence of dystrophin and (C) normal staining.

CLASSIFICATION

Myopathies can be basically classified in two main categories, inherited myopathies and acquired myopathies. These two large categories have been subdivided as shown in **Table 1**.

Table 1: Classification of Myopathies

Inherited myopathies

Dystrophies

X-linked
- Duchenne muscular dystrophy
- Becker
- Emery-Dreifuss
- Scapuloperoneal

Autosomal dominant
- Facioscapulohumoral dystrophy
- Oculopharyngeal dystrophy
- Limb girdle dystrophy (1A -1E)
- Emery-Driefuss dystrophy

Autosomal recessive
- Limb girdle dystrophy (2A-2M)
- Congenital muscular dystrophy

Myotonias
- Myotonia dystrophica DM1
- Myotonia dystrophica DM2 (PROMM)
- Paramyotonia
- Chondrodysplastic myotonia

Congenital myopathies
- Central core disease
- Centronuclear myopathy
- Nemaline myopathy
- Myotubular myopathy
- Minicore myopathy
- Fingerprint body myopathy
- Sacrotubular myopathy

Distal myopathies
- AR: Miyoshi, Nonanka
- AD: Welander, Udd, Markesbery-Griggs, Scapuloperoneal, Desminopathy, Gower-Laing myopathy

Metabolic myopathies
- Glycogen storage disease: Acid maltase deficiency, Myophosphorylase deficiency
- Lipid storage disease: Carnitine Palmitoyl acyl transferase deficiency, defects of Beta oxidation

Mitochondrial cytopathies
- Progressive external ophthalmoplegia
- Kearns-Sayre syndrome
- MELAS, MERRF
- Pure myopathy syndrome

Channelopathies
- Sodium: Paramyotonia congenita, Hyperkalemic periodic paralysis
- Calcium: hypokalaemic periodic paralysis, Malignant hyperthermia
- Potassium: Anderson's disease
- Chloride: myotonia congenita (Thomson's disease), generalised myotonia (Becker's disease)

Acquired myopathies

Infective: viral, bacterial, parasitic, fungal infections, e.g. trichinosis, toxoplasmosis

Inflammatory myopathies: polymyositis, dermatomyositis, inclusion body myositis, eosinophilic polymyositis, granulomatous myositis, idiopathic orbital myositis

Endocrine myopathies: thyroid, parathyroid, pituitary, adrenal disorders, diabetes mellitus, Vitamin D related disease

Drugs and toxins: statins, corticosteroids, anasthetic drugs, amphophilic compounds like chloroquine, HCQ, amiodarone, zidovudine, penicillamine, drugs of abuse like alcohol, LSD, heroin, amphetamine

INHERITED MYOPATHIES

Muscular Dystrophies

Dystrophy is an inherited, progressive, primary disease of the muscle with evidence of degeneration and regeneration of the muscle fibres. Most dystrophies are inexorably progressive, but the rate of progression is variable. Dystrophies have been classified according to their mode of inheritance into X-linked, autosomal and mitochondrial inheritance.

Duchenne's muscular dystrophy (DMD)

It is the most common dystrophy with an incidence of 1:3500 live male births and is seen all over the world. This condition is transmitted as X-linked recessive and hence females are carriers and males are symptomatic. It affects boys at the age of 3 to 4 years. The initial symptoms are of repeated falls and weakness while climbing stairs and getting up from ground. Gower's manoeuvre is seen as children get up from ground, using their hands to straighten up (**Figure 3**). Patients get progressive weakness of the girdle muscles. In the early stages, calf hypertrophy is striking. Weakness is rapidly progressive, the child becomes wheelchair bound by the age of 8 to 10 years, and the lifespan rarely exceeds 20 years. A proportion of patients have mental sub normality and cardiac abnormalities. These are usually accompaniments, but in an occasional patient, assume larger proportions. The genetic abnormality is present on the short arm of the X chromosome at site xp 21; hence, the disease is also called Xp21 myopathy. The gene is one of the largest genes known and has 79 exons and many hot spot regions susceptible for deletions, followed by point mutations and duplications. The gene product is a protein called dystrophin which is a part of subsarcolemmal cytostructural proteins. The deficiency of dystrophin leads to weakness of the sarcolemma, the muscle membrane gives way on traction leading to the cell degeneration. Regeneration possibly is a corrective phenomenon.

In patients with DMD, the serum CK is very high, usually in thousands, and the EMG shows myopathic findings. The muscle biopsy shows features of degeneration and regeneration with increase in the connective tissue. Inflammatory cells are seen eating away the necrotic muscle fibres. Presently, it is possible to perform dystrophin immunocytochemistry on the fresh frozen muscle to achieve an accurate diagnosis. It is also possible to study the gene which has an application in the genetic counselling. Mother and sisters of the patient should be studied for the presence of genetic abnormalities and, if positive, they have a risk of bearing affected children. It is possible to study the DNA from chorionic villous biopsy from an 'at risk' pregnancy and carry out abortion only if the DNA shows gene defect. Knowledge of these aspects has certainly resulted in benefits in antenatal counselling.

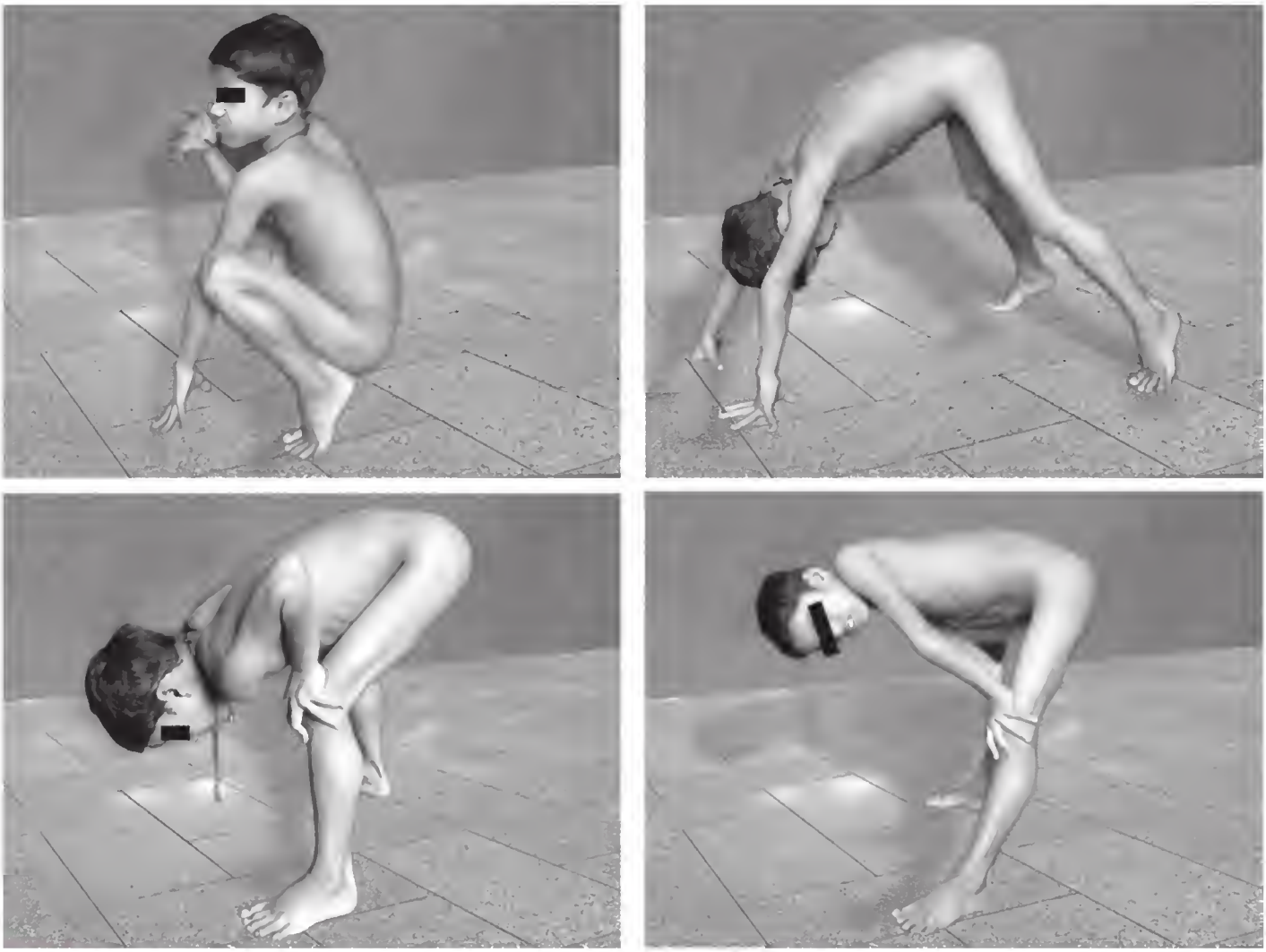


Figure 3: Gower's Sign

Presently, in addition to physiotherapy, some physicians use corticosteroids in the doses of 0.75 to 3.0 mg per kg wt. in various regimens like daily dose, ten day on and 10 day off or 20 day off pattern. This therapy reduces the CK values. Inflammatory response as seen on muscle biopsy also reduces. The muscle strength also tends to improve in a limited manner for the period of 6 to 12 months, leading to reduced falls and improvement in the quality of life. However, substantial lasting clinical improvement is rare and hence the therapy cannot be justified universally. In the author's personal view, a dose of 0.75 mg per kg per day on a ten day on and 10 day off period is perhaps the best in avoiding the changes in the hypothalamopituitary axis. Contracting a disease like tuberculosis is also a genuine concern in our country. Attempts at gene therapy and stem cell therapy are gaining ground and, in recent future, may have practical applications.

Becker muscular dystrophy

It is similar to Duchenne's dystrophy. The genetic defect lies at the same site of the dystrophin gene, but is such that some amount of dystrophin can be synthesised and utilised by muscles. Hence, the clinical disorder is mild and affected individuals can live up to 40 years. The aspects of genetics are identical to the DMD. The mutations in Becker muscular dystrophy tend to be in the central hot spot of the gene and tend to be 'in frame' in nature so that some dystrophin can be functionally relevant.

Facioscapulohumeral dystrophy (FSHD)

It is an autosomal dominant condition with a gradual but step ladder evolution and a characteristic pattern of weakness affecting facial, scapular, anterior tibial muscles and later, the proximal limb musculature. Disease onset is in first or second decade. Sleeping with open eyes, inability to close eyes tightly, to whistle, and abnormal smile suggest facial weakness. Swallowing and chewing is usually unaffected. Scapular winging (**Figure 4**) is very striking. Biceps, triceps, forearm and wrist extensors are predominantly affected and deltoids, forearm and wrist flexors are spared. Beevor's sign is positive in majority of patients with FSHD. In the lower limbs hip flexors, knee extensors and anterior tibial muscles are affected asymmetrically. Association with retinal damage and exudates, sensory neural deafness are noted in some cases (Coat's disease). Cardiac involvement is uncommon but in few cases labile hypertension is seen.



Figure 4: Scapular Winging: FSHD

CK is elevated several fold, EMG study is myopathic and muscle biopsy shows dystrophic changes along with angulated fibres. DNA study confirms the diagnosis. The genetic abnormality is an abnormal deletion of tandem 4q telomere gene leading to over expression of proximal transcriptor gene at FSH locus. Anticipation is also noted in FSHD.

Limb girdle muscular dystrophies (LGMDs)

Limb girdle muscular dystrophies (LGMDs) are heterogenous and are autosomal in transmission. Five types of dominant and ten types of recessive genetic abnormalities have been described by now and the list is increasing. As a group, they have early severe

Table 2: Limb Girdle Muscular Dystrophies

AD	Age of Onset	Gene/Gene Product	Clinical Features
LGMD 1A	3-4 decade	Myotilin	Arm more than leg, proximal muscle involvement. May affect distal limb, facial, pharyngeal muscles, vocal cord
LGMD 1B	1-2 decade	Lamin A/C	Proximal muscle weakness. Early contractures, cardiac abnormalities like conduction defects, cardiomyopathy, arrhythmias
LGMD 1C	Early childhood	Caveolin-3	Leg more than arm proximal muscle involvement. May affect distal limb muscles, asymptomatic CK elevation. Exertional myalgia
LGMD2A	1-2 decade	Calpain-3 (CANP-3)	Proximal muscle involvement. Hip followed by shoulder and posterior thigh muscles and anterior abdominal muscles affected early. Achilles' tendon contracture', later elbow, wrist, finger contractures
LGMD2B	2-3 decade	Dysferlin	Majority have distal and proximal myopathy, early calf muscle weakness and atrophy
LGMD 2C-F	Early childhood	Sarcoglycans (alpha, beta, gamma, delta)	Severe and mild forms, severe forms resemble Duchenne's or Becker's dystrophy with early onset proximal muscle involvement, calf hypertrophy and loss of ambulation
LGMD2G	Childhood	Telethonin	Leg more than arm proximal muscle weakness with significant weakness of quadriceps and anterior tibial muscles
LGMD2H	1-2 decade	TRIM-32	Very slowly progressive proximal muscle weakness
LGMD2I	1-3 decade	Fukutin related peptide	Variable, resemble congenital muscular dystrophy to BMD phenotype. Cardiomyopathy in some cases.
LGMD2J	1-3 decade	Titin	Proximal muscle weakness, later distal involvement

forms resembling the Duchenne's muscular dystrophy and slow forms going in to adulthood. They result in progressive muscular weakness of limb girdles and some have cardiac myopathies as well. A large body of literature has accumulated to date as to the protein products and the pathophysiology of LGMDs. Most genetic defects seem to result in alterations of various proteins responsible for maintaining the integrity of the sarcolemma, thus weakening it and resulting in cell damage. Some others alter the membrane repair processes and the enzymatic intra-cellular reactions. This knowledge is vital for the future evolution of the therapeutic strategies. Following table gives the salient features of the subtypes of autosomal dominant and recessive LGMDs.

Oculopharyngeal muscular dystrophy (OPMD)

It is an AD disorder which begins in 5th to 6th decade of life. OPMD is caused by mutation in the gene that encodes for poly (A) binding protein-2, involved in m-RNA polyadenylation. Patients present with slowly progressive ptosis and restricted eye movements, but contrast to myasthenia gravis these patients don't complain of diplopia as the involvement is symmetrical and slow. Patients find difficulty in swallowing due to pharyngeal weakness, later nasal regurgitation occurs. Occasionally some patients develop proximal limb muscle involvement late in course of illness. Death occurs due emaciation, respiratory infections. Main differential diagnosis is myasthenia gravis. Muscle biopsy shows dystrophic changes with rimmed vacuoles. Hallmark of illnesses is the presence of 8 to 10 mm intranuclear filamentous inclusions.

Emery-Dreifuss muscular dystrophy (EDMD)

There are two forms of EDMD; one is X-linked and another is AD. Disease onset is in 1st to 3rd decade of life. There is progressive weakness and wasting of shoulder, anterior tibial and arm muscles. Early contractures of tendon of Achilles, wrist, elbow and spine are prominent and form a clinical distinguishing feature. Cardiac abnormalities like cardiomyopathy, atrial arrhythmias, conduction blocks are reported and may lead to sudden death. Female carriers can develop cardiac complication at late ages. DNA study confirms the diagnosis. X-linked disease is due to mutation in emerin, a nuclear membrane protein; AD is due to lamin A/C protein, caused by mutation of LMNA gene. Emerin and lamin A/C both are structural proteins, maintaining structural integrity of membrane. Muscle biopsy shows dystrophic features and EMG is myopathic. In these patients, ECG and echocardiography needs to be evaluated at intervals to access cardiac function. Management is supportive. Physiotherapy, prevention of contracture and dealing with cardiac complication are of importance.

Congenital muscular dystrophies (CMD) (Table 3)

Congenital muscular dystrophies (CMD) are disorders of basal membrane proteins like merosin, Golgi organ protein that are involved in glycosylation of sarcoglycan and dystroglycans and extracellular matrix proteins like collagen. A common feature to all is AR inheritance and early age of presentation. Children have diffuse weakness, feeding difficulty, early contractures, delayed milestones and reduced life span. CNS malformations and MRI change in white matter are common, particularly in merosin deficient myopathies. EMG is myopathic and muscle enzymes are elevated.

MYOTONIC DISORDERS

Patients suffering from myotonia have abnormalities of the sarcolemma. On receiving a nerve signal, the muscle membrane undergoes a series of depolarisation and the result is failure of relaxation. This is clinically seen as the inability to relax hand grip. Two distinct types have been identified, dystrophia myotonica type 1 (DM 1) and dystrophia myotonica type 2 (DM 2 or PROMM).

Table 3: Congenital Muscular Dystrophies (CMD)

Type	Locus or Gene	Clinical Features	CNS Abnormalities
Classic CMD			
CMD 1A (occidental type) (merosin negative)	Merosin (laminin α2)	Hypotonia, diffuse weakness, delayed milestones, contractures	Cognitive function relatively spared, seizure in 12-15 %. White matter lucencies on MRI. May
CMD 1B (merosin positive integrin deficiency)	Integrin α7	Hypotonia, diffuse weakness, delayed milestones, contractures	or may not be present
CMD 1C (merosin positive FRRP deficiency)	FKRP 1	Slowly progressive, ambulation preserved till late	
Disorders of glycosylation			
Fukutin	Fukutin	Hypotonia, diffuse weakness, delayed milestones, contractures	Seizures and mental retardation very common. MRI shows hypomyelination, hydrocephalus, lucency especially in frontal white matter
Muscle eye brain disease	POMGnt1	Hypotonia, diffuse weakness, delayed milestones, contractures	Above all plus retinitis, cataract, glaucoma, optic atrophy
Walker Warburg Syndrome	POMT1, POMT2, fukutin, FKRP	Hypotonia, diffuse weakness, delayed milestones, contractures. Severest of all CMDs. Death in 2 to 4 years	Refractory seizure, profound mental retardation, MRI hypomyelination, cortical dysplasia, pontine and cerebellar hypoplasia, many other CNS malformation
Disorder of collagen			
Ulrich CMD	Collagen type 6	Neonatal weakness, joint laxity, contractures	Mental retardation
Other CMDs			
CMD with rigid spine	SEPN1 (selenoprotein n1)	Hypotonia, delayed milestones, contractures,	Rigid spine, scoliosis
LARGE CMD	LARGE	Diffuse weakness, contractures	Profound mental retardation, MRI: significant white mater changes

Dystrophia Myotonica Type 1 (DM1)

It is the most common myotonic disorder. It is a multisystem disease due to genetic defect, on chromosome 19. This is a triplet repeat disease, where the number of CTG repeats expands beyond a point, leading to a gain of function problem. The gene product is a protein kinase which is present in all the cells, hence, the manifestations are seen in many systems. The disease is inherited as autosomal dominant and tends to express more severely in successive generations, the phenomenon of anticipation. Maternal and paternal transmissions may differ in severity. The muscular weakness is pronounced in a characteristic fashion affecting the sternocleidomastoids, temporalis, masseter and facial muscles giving typical facial appearance (hatchet faced) (**Figure 5**). This is also one of the few myopathies resulting in weakness of distal and ocular musculature. Patients have grip myotonia and muscular



Figure 5: Myotonic Dystrophy: Swan Neck, temporal hallowing and facial weakness.

weakness, premature baldness, early cataracts, day time sleepiness and testicular atrophy, loss of libido and other endocrine dysfunction including increase risk of diabetes. There is abnormal sensitivity to anaesthetic drugs. Cardiac complications like cardiomyopathy, congestive cardiac failure and arrhythmia can occur, hampering quality of life.

Physical demonstration of myotonia is better in cool environment. Classical method is to percuss thenar or forearm muscles, or to ask the patient to grip hard for 15 seconds and watch for delayed relaxation. EMG, along with myopathic changes, shows characteristic myotonic discharges (a sound similar to revving of a motorcycle). In muscle biopsy, ring fibres are seen along with dystrophic changes. Myotonia can be reduced by using membrane stabilisers like phenytoin sodium or carbamazepine. Quinine, Tocainide, procainamide and mexiletine are also known to reduce myotonia. Cataracts need surgery. Cardiac manifestations need periodic observation and appropriate therapy.

Congenital myotonic dystrophy is severe form of DM 1, occurring in children of affected mothers. Clinical features are hypotonia, inverted V like tented upper lip, feeding difficulty, failure to thrive, recurrent respiratory infections and severe mental retardation.

Dystrophica Myotonica Type 2 (DM2) or PROMM

It is a proximal variant of DM1, where main feature is proximal limb weakness. Other features are same like DM1, but cardiac and endocrine abnormalities are less manifest and prognosis is better. Mutation in the ZNF9 on chromosome 3q21 is the genetic defect, which result from CCTG expansion in intron 1.

Myotonia Congenita

It is another group of myotonic disorders which presents in the second or third decade of life with hypertrophy of all muscles (Herculean appearance) and grip myotonia. In myotonic patients, exercise helps the patient and the myotonia becomes less obvious as the muscle is repeatedly used. These patients are usually not significantly weak. The response to membrane stabilisers is better in these patients.

Paramyotonia Congenita

It is a rare disease. In these patients, the myotonia worsens with exercise and with exposure to cold temperatures. With repeated use of a muscle, a profound weakness may ensue, lasting for hours. Upper body and facial muscles are more affected. A useful test is to place a towel soaked in ice cold water over the patient's eyelid for two minutes. The patient is asked to look upward for a few seconds and then look down. Eyelid myotonia is seen as baring of the sclera above the iris. On greater cooling, paramyotonia disappears and the eyelid becomes paralysed. These patients often harbour a mutation in the sodium channel gene changing the characteristics of the channel function.

CONGENITAL MYOPATHIES

As a group, the congenital myopathies have some clinical features in common. They present at birth, often as floppy child and unlike most other myopathies, the weakness either remains static or actually improves as the age advances. Progressive deterioration is exceptional in the congenital myopathies. Affected patients are usually very thin, 'skin and bones' but are surprisingly strong for the lack of muscle bulk, associated with skeletal abnormalities, contracture and cardiac complication in some case and recurrent respiratory infection. The main abnormalities are seen only on muscle biopsies and are a result of faulty maturation of the muscle cells. Depending upon the muscle biopsy findings, they are sub classified. Nemaline myopathy, Rod body myopathy, Zebra body myopathy, trilaminar myopathy and central core disease are some of the congenital myopathies. As the natural history is of improvement, the outlook is better than other myopathies and active physiotherapy is advisable. Only a minority of patients from this group tend to deteriorate with time.

DISTAL MYOPATHIES (TABLE 4)

Distal myopathies are those muscle disorders in which there is predominantly distal muscle involvement in the early part of the illness (**Figure 6**). This is in contrast to the common pattern

Table 4: Distal Myopathies

Pattern of weakness	Disease	Age of Onset	Mode of Inheritance	Genetics	Additional Features
Predominantly hand involvement	Welander distal myopathy	4th to 6th decade	AD	Unknown (linked to chromosome 2p13	Slowly progressive
Posterior tibial involvement	Miyoshi myopathy	Childhood to adolescence	AD	Dysferlin	Later involvement of proximal and multiple muscle group
Anterior tibial involvement with distal upper limb weakness	Udd	3rd to 4th decade	AR	Titin	No cardiac involvement
	Markesbery-Griggs	3rd to 4th decade	AD	ZASP gene	Cardiomyopathy common
	Nonaka	<30 year	AR	GNE-gene	Spares heart and quadriceps
	Gower-Laing	<30 year		MYHC 1(MYHC7)	Early foot drop
	Scapuloperoneal	4th to 6th decade	AD/X-linked	FHL-1	Early foot drop
	Desminopathy	3rd to 4th decade	AD	Desmin	Fatal cardiac arrhythmias



Figure 6: Wasting of calf muscles: Miyoshi myopathy.

of proximal weakness seen in most myopathies. In distal myopathies, a close differential diagnosis of neuropathic or anterior horn cell disorders needs consideration and apart from clinical features, muscle enzyme elevation and electrophysiology helps in the differential diagnosis. Following table gives the different forms of distal myopathies with their important features.

MUSCLE CHANNELOPATHIES

These disorders are characterised by episodic muscle weakness, nondystrophic myotonia and occasionally permanent weakness, caused by altered muscle membrane excitability. These are due to mutation in the gene that code for sodium, potassium, calcium or chloride channels.

Periodic Paralysis

Periodic paralysis are a group of disorders wherein the patients get repeated episodes of weakness of the limb muscles. These episodes last for few hours to few days and are often precipitated by exercise, heavy meals or fasting. The basic abnormality is in the handling of potassium by the muscle cells. In an attack, the potassium can be normal, low or high and the values do not necessarily correlate with the degree of weakness.

Hypokalaemic Periodic Paralysis

In hypokalaemic periodic paralysis, attacks occur in the morning, triggered by ingestion of a carbohydrate load or strenuous exercise the previous day. Severe generalised weakness with aching and hyporeflexia is seen. Sensations, level of consciousness and respiratory function are preserved. The weakness also spares the bulbar and facial muscles. Attacks are infrequent and last for several hours. Recurrent attacks lead to persistent weakness in some patients. Thyrotoxicosis and other causes of hypokalaemia like renal, adrenal and gastrointestinal disorders have to be ruled out. This disorder is a calcium channelopathy.

It is important to avoid the precipitating factors and to prevent the attack. During the attack, the serum potassium levels should be checked. It is also useful to do an electrocardiogram. Once the paralytic attack has started, administration of potassium is standard therapy, and it hastens the recovery of the periodic paralysis. It is given mainly to prevent cardiac arrhythmias that potentially can be life-threatening. Potassium is usually administered intravenously, even though there is no proven advantage of using this route of administration. Very rapid intravenous correction of potassium may be counterproductive. Oral supplements may be needed for long time. A low sodium and carbohydrate diet, exposure to cold and acetazolamide may help prevention of further attack.

Hyperkalaemic Periodic Paralysis

In hyperkalaemic periodic paralysis, attacks last from minutes up to an hour and are milder but more frequent. Onset of this sodium channelopathy is earlier in childhood and attacks are precipitated by rest after exercise, stress and potassium load. A useful feature is the presence of myotonia in between attacks. Acetazolamide 125 to 250 mg thrice daily can be used

prophylactically. In acute severe hyperkalaemia intravenous calcium gluconate, glucose-insulin drip and thiazide diuretics may need to be used.

STORAGE DISORDERS

If the glucose or the lipid metabolism of the muscle is defective due to an enzymatic deficiency, the patients get exercise intolerance. They may be totally asymptomatic at rest but when asked to exercise, they develop muscles pain and weakness. Rest improves them. In the cases of lipid metabolism defects, clinically patients sometimes have a 'second wind phenomenon', wherein after the initial weakness, they can go on exercising again for a certain time before finally getting disabled. A detailed study of the muscle biopsy, in particular, staining for glycogen and lipids can show abnormal accumulation of these metabolites, and electron microscopy can further clarify the nature of the deposits. Advanced enzymatic studies are necessary to get down to the exact enzymatic defect. Currently, no therapeutic options are available for most of these conditions, but the future holds promise of enzyme replacement and gene therapy. Avoiding excessive physical exertion is very important.

MITOCHONDRIAL DISORDERS

This comparatively newly recognised group of disorders is getting to be seen regularly in muscle clinics. The mitochondrial energy production is affected due to enzyme defects in the mitochondrial respiratory chain. As the mitochondria are derived only from the ovum, these disorders are maternally transmitted. They present with a variety of peripheral and central manifestation. Chronic external ophthalmoplegia, limb weakness, stroke like episodes and myoclonic epilepsy are commonly seen. The combination of central and peripheral deficits should alert the physician about the diagnosis. In addition, skeleton is also affected and short statue is regularly seen in conditions like Kearns Sayre syndrome. The laboratory diagnosis involves sophisticated methods. Serum lactate and pyruvate levels may be elevated in approximately two thirds of patients. Cardiac conduction defects may be seen. The diagnosis can be further substantiated on a muscle biopsy by demonstration of ragged red fibres on Gomori trichrome stain and the demonstration of abnormal mitochondria on the electron microscopy. Care need to be exercised in the interpretation of the muscle biopsy as mitochondrial function deteriorates in normal individuals with age. Exact detection of the enzyme defect needs a specialised laboratory set-up. It is presently possible to sequence the whole of the mitochondrial genome in few centres in India. A proportion of patients having mitochondrial disorders are benefited by supplementing cofactors like riboflavin, thiamine, biotin and coenzyme Q, but the long term outcome is variable and unpredictable.

ACQUIRED MYOPATHIES

Infective Myopathies

The muscle may be attacked by infectious agents. Viruses like influenza, coxsackie and many other viruses can produce acute myositis. This leads to swelling and pain in the muscles with weakness. The condition is acute and often self limiting. At times it can be severe and lead to myoglobulinuria and renal failure. Staphylococci are capable of producing multiple abscesses in the muscle. These patients need urgent antibiotics. Large pockets of pus may need to be drained. Such a situation is more common in immunocompromised individuals but can be seen otherwise as well. Parasites like cysticercus cellulosae and Trichinella spiralis can infest the muscles in large numbers and may lead to pain and hypertrophy of the affected muscles. On asking the patient to contract the large muscles, small lumps can be seen and the biopsy of lump can give the definitive diagnosis. Albendazole in the dose of 15 to 25 mg per kg body weight is given for a period of 1 to 3 weeks for cysticercosis and as well as trichinosis.

Inflammatory Myopathies

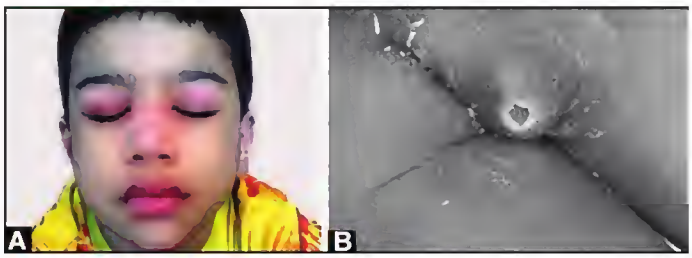
Inflammatory myopathies represent a group of disorders characterised by proximal muscle weakness and inflammation of skeletal muscles. Various classifications of inflammatory myopathies exist in literature. Six major categories of myositis can be identified: (1) dermatomyositis, (2) polymyositis, (3) overlap syndromes, (4) cancer-associated myositis, (5) inclusion body myositis, and (6) other forms including rare focal and diffuse variants. Three most common disorder are polymyositis, dermatomyositis and inclusion body myositis.

Polymyositis

Polymyositis patients may present insidiously with a variety of non-specific symptoms including fatigue, malaise, weight loss, myalgias, or arthralgias that may mimic other disorders and result in delay in diagnosis. The muscle involvement is predominantly proximal and affects the pelvic girdle more than the shoulder girdle. The distal musculature is affected to a much lesser extent. Dysphagia is commonly associated with these conditions, as is neck muscle weakness. Facial and ocular muscles are not affected. The evolution of weakness is acute or sub acute. The muscle weakness tends to be non-selective in nature, which is a clinical distinction from the inherited processes like dystrophies.

Dermatomyositis

Dermatomyositis patients have, in addition to proximal muscle weakness, cutaneous involvement in the form a rash affecting the skin over knuckles, eyelids and the anterior part of the chest occurs (**Figure 7A**). The Gottron's papules are considered to be pathognomonic of dermatomyositis and such rashes are rarely seen in other immunological conditions. Skin calcinosis is a vexing and often disabling complication seen in late stages of dermatomyositis, when the activity of myositis is settling down (**Figure 7B**).



Figures 7A and B: (A) Heliotrope rash of dermatomyositis. (B) Gluteal Calcinosis.

Inclusion body myositis

It is a distinct sub group of inflammatory myopathies. Patients are generally older males and the condition develops slowly over months to years. In these patients, the pattern of weakness is different and tends to be much asymmetrical and distal as well as proximal in its distribution. Wrist drop and finger drops

are common. Such cases may be confused with the neurogenic processes like spinal muscular atrophy and other system diseases.

In inflammatory myopathies, in addition to the muscles, other organ systems are affected. Pulmonary involvement in the form of interstitial lung disease is not uncommon, as is dysphagia relate to the GI involvement. Cardiomyopathy and arthralgias are less often encountered. Inflammatory myopathy especially dermatomyositis may be associated with malignancy. The exact nature of the relationship between malignancy and myositis has created continued controversy. However, most authorities agree that there is an increased incidence of malignancy in myositis patients.

The serum CK levels are very high, usually in thousands and the EMG examination shows a myopathic pattern with the additional finding of spontaneous fibrillations. Muscle biopsy done early in the disease course shows evidence of random necrosis of muscle fibres with evidence of muscle regeneration. The blood vessels may be inflamed and interstitial inflammatory cellular response is seen. At times, myositis may be presenting non metastatic manifestation of internal malignancy and hence, a search for malignancy is indicated particularly if the patient is elderly.

Both poly and dermatomyositis respond to corticosteroid therapy steroids are given in the doses of 1 to 2 mg per kg body weight till there is reduction in the serum CK and clinical improvement begins. Later other immunosuppressants like azathioprine or methotrexate can be added and the doses of steroids reduced. In the rare event of acute severe deterioration, intravenous immunoglobulin and plasmapheresis may be used for rapid 'rescue'. The overall outlook of these patients is satisfactory, but long-term immunosuppression may be needed, and steroid dependency may be seen. Rarely malignancy surfaces later and changes the prognosis. Age of onset, severity of illness, associated co-morbidities and delayed treatment are some prognostic factors, influencing ultimate outcome. It is particularly important to recognise and to treat this group of reversible myopathies.

ENDOCRINE AND METABOLIC MYOPATHIES

Thyroid and parathyroid disorders are the common endocrine entities resulting in myopathy. Usually, the myopathies are a small part of the whole endocrine abnormality and hence easy to diagnose, but at times it can be the presenting feature. Other endocrinopathies can also potentially cause muscle weakness. Osteomalacia, osteoporosis, renal insufficiency and many metabolic conditions can lead to mild myopathy. The osteomalacic myopathy results in painful waddle and reflexes may become brisk. This condition is common in multiparous women wearing burkha and other settings of vitamin D deficiency.

DRUG-INDUCED AND TOXIC MYOPATHIES

A wide variety of drugs are capable of damaging muscles. Corticosteroids, statins and anti-epileptic agents are probably the most common ones. Steroids produce myopathy by down regulating the anabolism of the muscle. Toxins also produce muscular weakness as a part of the various system mani-festations. The weakness is reversible to a large extent after the offending agent is withdrawn, but the time lag can be of many months.

CONCLUSION

Muscular weakness can result from wide variety of hereditary and acquired conditions. The inherited myopathies tend to have selective involvement and slow evolution, while the acquired ones produce more generalised weakness and can be rapid. Good history taking, including the family history and the drug intake, coupled with careful examination and investigations like serum CK, EMG and muscle biopsy help in achieving accurate diagnosis. Inflammatory myopathies are most rewarding to treatment and many other acquired ones also respond well. The therapeutic options for the inherited myopathies are limited at the moment, but the genetic advances are opening up the possibilities of more successful therapy in near future.

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Section 21

Oncology

Section Editor: S.K. Bichile

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21.1 Basic Considerations of Oncology

SH Advani

Paradigm shift in diagnostic technology and therapeutic modalities have resulted in revolution in the treatment of cancers and have improved the life of cancer patients (**Table 1**). Studies using molecular biology techniques have underlined the role of viruses in certain malignancies. The development of monoclonal antibody technology has resulted in more precise classification of lymphoproliferative malignancies. Advances in supportive care have minimised the adverse effects of intensive cancer therapy. Bone marrow transplantation has become a major treatment modality. Oncologists are now able to tailor therapy according to clinical risk factor, tumour histology, stage and gene profile analysis. Due to enhanced understanding of the molecular pathways, new targeted therapy is becoming a reality. Soon, we shall see personalised and customised therapy in many cancers.

Table 1: Treatment Results with Modern Chemotherapy

Cancers in which drugs have achieved normal life span for some patients	
Acute lymphoblastic leukaemia (childhood)	Choriocarcinoma
Testicular tumours	Rhabdomyosarcoma
Histiocytic lymphomas	Retinoblastoma
Burkitt's lymphoma	Osteogenic sarcoma
Hodgkin's disease	Gastrointestinal stromal tumour
Ewing's sarcoma	
Cancers in which responders have demonstrated improvement in survival	
Adult acute leukaemia	Ovarian cancer
Multiple myeloma	Breast cancer
Lymphocytic lymphoma	Neuroblastoma
Chronic myeloid leukaemia (CML)	Renal cell carcinoma
Cancers responsive to chemotherapy with no survival advantage	
Head and neck cancers	Malignant melanoma
Gastrointestinal cancers	Malignant carcinoid tumour
Central nervous system cancers	Soft tissue sarcoma
Bladder carcinoma	Oesophageal cancer
Lung cancer	
Endocrine gland tumours	
Cancers only marginally responsive or unresponsive to chemotherapy	
Hypernephroma	Hepatocellular cancer
Pancreatic cancer	Thyroid cancer

MECHANISM OF CARCINOGENESIS

The cancer cell evolves through a series of steps from normal, initiated and pre-neoplastic to pre-malignant and finally to highly malignant neoplasm. The three major steps in this process are initiation, promotion, and tumour progression (**Figure 1**). A single brief exposure to a carcinogen induces changes in the tissue, termed initiation. The nature of the structural alterations in initiated cells is diverse. Chemicals and ultraviolet irradiation directly alter DNA structure. Cancer arising after viral infections may occur through recombination of the viral and host genomes. Promotion is ability of a compound to induce an area of proliferation in initiated tissue and stimulate tumour formation. Dietary fat has been implicated as a tumour promoter in the development of colon cancer. Finally, tumour progression usually refers to the later stages of tumour cell evolution that are irreversible and alter the reactivity and potentialities of neoplastic clones. Proliferating foci in a promoting environment may undergo additional changes and become progressively more malignant. Once the tumour develops, individual traits such as hormone responsiveness, growth rate, histologic type, and invasiveness function as independent variables capable of progression.

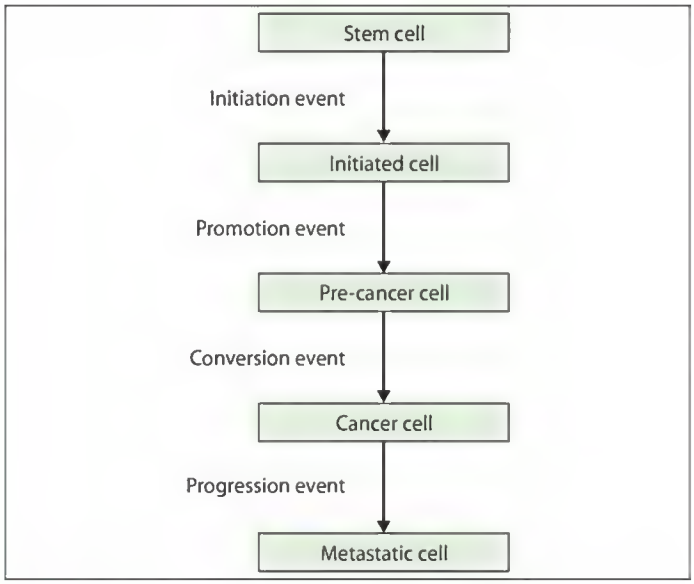


Figure 1: Mechanism of carcinogenesis.

The spread of tumour from a primary lesion to a distant site is a major cause of morbidity and mortality. Metastasis is an active process consisting of three stages: attachment of cells to extracellular matrix, local degradation of extracellular matrix, and locomotion through the locally degraded matrix. This active locomotion of tumour through host tissue barriers is presumed to be affected by both tissue-secreted chemotactic factors as well as motility factors secreted by the tumour cells. Once the tumour cell has migrated to a metastatic site, additional metastatic foci may occur by repetition of these steps.

MOLECULAR BIOLOGY

Human genome project has given insight into biology of human cancer. Many molecular structures serve as markers for diagnosis of cancers. Markers that reflect clonality such as

cytogenetic abnormalities can be useful for the diagnosis of cancer. A number of tests are available for marker detection including fluorescence *in situ* hybridisation (FISH), southern blot hybridisation, polymerase chain reaction, immunohistochemistry, and cDNA microarrays. These techniques can detect numeric changes in chromosomes, translocations, deletions, amplifications, alterations in DNA nucleotide sequence, demonstration of viral DNA sequence in tumour cells, and detection of tumour antigens.

Among cancers in which molecular biology has had greatest impact is chronic myeloid leukaemia (CML). The marker of this disease is the Philadelphia chromosome t(9;22) which is detected by all available molecular diagnostic methods. Now targeted therapies like imatinib mesylate targeting the bcr/abl gene is being used to treat CML. The diagnostic marker in neuroblastoma is amplification of N-myc, a proto-oncogene. In breast cancer, the erbB2 oncogene has helped to select patients for Herceptin therapy. In retinoblastoma, the detection of an inherited defect in the retinoblastoma gene-I (RB-I), a tumour suppressor gene, has been used to assess the risk in individuals with a family history of retinoblastoma.

PRINCIPLES OF THERAPY

The life cycle of both normal and neoplastic cell starts with mitosis or cell division. This is followed by differentiation with distinct phases known in sequence as G1 (first gap phase), S phase (DNA synthesis phase), G2 phase (second gap phase), and mitosis (M phase) (**Figure 2**). Tumours also contain non-cycling but living cells (G0 phase). The growth fraction is the ratio of the proliferating cells to the total cells.

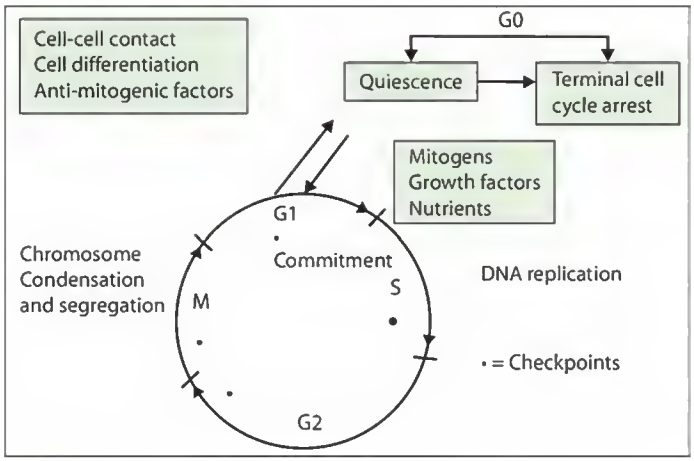


Figure 2: Cell cycle.

G0 = Non-cycling but living cells; G1 = First gap phase; G2 = Second gap phase; M = Mitosis phase; S = DNA synthesis phase.

Cancer cells divide more slowly than their normal counterparts. However, they spend a longer time in cell division, leading to some selectivity in the therapeutic action. It has been postulated that differences in the kinetics of cell proliferation is the basis of differential sensitivity between normal and cancer cells. Alternative explanations for chemotherapeutic efficacy include an ineffective repair mechanism in cancer cells, as well as chemotherapy-induced reduction of growth factor release required for proliferation of tumour cells.

The treatment of cancer has two aspects; specific and supportive treatment. Specific therapy consists of surgical removal, irradiation and chemotherapy, most patients require a combination in these three modalities, and advances in supportive care have contributed remarkably to improvement in the quality of life during therapy for these patients.

The use of blood product transfusions, indwelling central catheters to maintain ready venous access, enteral and parenteral nutrition, and colony-stimulating factors have greatly reduced the morbidity and mortality in patients undergoing chemotherapy. Right atrial catheter insertion is now mandatory to provide proper supportive care. Partial correction of thrombocytopaenia to maintain a platelet count of greater than 10,000/mm^3 reduces the risk of haemorrhage. In tumour lysis syndrome the use of allopurinol along with forced diuresis can be life-saving. Good nutritional support including parenteral nutrition when required improves the outcome. Use of 5-HT3 receptor blockers (granisetron) has transformed the quality of life of patients undergoing highly emetic therapies.

Infection prevention is now considered more important than interventional therapy. The best tested and most effective initial empirical antibiotic regimen for treating patients with febrile neutropaenia is a combination of aminoglycoside or an aminoglycoside with cephalosporin. Availability of growth factors (G-CSF) has reduced the duration of febrile neutropaenia. Antifungal drugs and antiviral drugs have improved the morbidity and mortality of patients.

Biologic Response Modifiers

Manipulation of the host immune response to cancer is the major goal of biological therapy. Antitumour immune responses are difficult to demonstrate in patients of cancer; however, cancer immunotherapy seeks to evolve effective immune responses to human tumours. These agents act as biologic response modifiers, and function by altering the host response to cancer, however some cause direct toxicity. They demonstrate peak activity within a narrow concentration range, higher or lower concentrations may cause a suboptimal effect. Optimal clinical dose is that which produces maximum desired effect and may not be the highest dose tolerated without unacceptable toxicity.

Antibodies in Cancer Therapeutics

Unconjugated antibodies have been used since the earliest trials of monoclonal antibodies in humans, but limitations of its use are absence of suitable tumour cell surface targets, antigenicity of the immune monoclonal antibodies in humans, modulation of the target structure from the tumour cell surface and poor recruitment of immune effector mechanisms.

IDEC-C2B8 is an anti-CD20 antibody with humanised framework and Fc regions. The antibody fixes human complement and elicits antibody-dependent cellular cytotoxicity. When used in patients with B-cell lymphomas, it produces good tumour regression rate with minimal toxicities and low rate (approx 10%) of anti-antibody development. Anti-CD20 antibody (rituximab) is being routinely used in B-cell lymphomas.

Trastuzumab is (C-cerb2) antibody used for Her-2 amplified breast cancer with promising results. Alemtuzumab is being used for chronic lymphocytic leukaemia (CLL). Cetuximab is EGFR antibody (epidermal growth factor receptor) which has shown promising result in metastatic colorectal cancer along with chemotherapy (irinotecan). Bevacizumab, vascular endothelial growth factor receptor (VEGFR) along with

chemotherapy has shown improved response rate in colorectal cancer against chemotherapy alone.

Anti-Idiotype Therapy

Antibody approaches defined only a single tumour-specific antigen which is the idiotype of clonally distributed antibody on the surface of certain B-cell lymphomas. Because it represents a unique protein structure in the combining site of antibody, the idiotype can serve as an antigen for antibody production. An immunological response to the idiotype could lead to tumour protection.

Common side effects seen are chills and fever, transient shortness of breath, headache, nausea, emesis, diarrhoea, myalgias, transient leucopaenia or thrombocytopaenia, and transient elevations of hepatic enzymes.

Radioimmunotherapy

In theory, the radio-labelled antibody homes to its antigenic target and delivers a cytotoxic assault on only the tumour cell to which it attaches, thus limiting collateral damage to surrounding normal tissues. Ibritumomab, tiuxetan, and tositumomab is being used for non-Hodgkin's lymphoma. Limitation of radioimmunotherapy is that conjugation of antibody to radionuclide is not always stable, leading to inappropriate destination of radioactivity. Besides, antibodies tend to be taken up in a non-specific fashion by the reticulo-endothelial system and antibodies, large molecules can be excluded from the space occupied by the target tumour.

Immunotoxins and Fusion Toxins

These reagents are chemicals and targeting is provided by antibodies or by lymphokines, growth factors, and so on that specifically bind receptors on the surfaces of target tumour cells. Attached to the targeting moiety is the cytolytic moiety which is usually derived from plants or bacteria. These toxins work by inhibiting protein synthesis and kill either resting or dividing cells and require fewer than 10 molecules in the cytosol to be effective. Toxins being investigated include ricin A, pokeweed antiviral protein, pseudomonas exotoxin A, and diphtheria toxin.

Bispecific antibodies

These are antibody constructions that recognise a tumour-associated antigen with one arm and recognise and activate an immune effector cell structure with the other arm. Approximation of a tumour cell with an activated immune effector could result in tumour cell elimination. These bispecific antibodies can be obtained either by chemical hetero-conjugation or by fusion of two hybridomas of desired specificity to yield a tetradoma. The desired product can be isolated either by chromatographic or other separation techniques. In pre-clinical models, anti-idiotype X anti-CD3 bispecific antibodies have demonstrated the ability to inhibit tumour cell growth.

Cytokines

Interferons

Interferons are potent cytokines that possess antiviral immunomodulatory and antiproliferative actions. These proteins are synthesised by cells in response to various inducers and in turn cause biochemical changes leading to an antiviral state in cells of the same species. Most animal viruses are sensitive to the antiviral actions of interferons, but many DNA viruses are relatively insensitive. Interferon biological activity is measured in terms of antiviral effects in cell culture and expressed as international units (IU). Two major classes are seen, Type I which consists of α and β; and Type II which consists of γ. Type I interferons are produced by different cell types whereas the Type II are produced by T-lymphocytes.

Absorption, distribution and elimination

Oral administration does not result in detectable serum levels or increases in 2-5 (A) synthetase activity in peripheral blood mononuclear cells. Plasma levels are dose-related, peaking at 4 to 8 hours and returning to baseline by 18 to 36 hours. After intramuscular (IM) or subcutaneous (SC) injection of interferon (IFN)-α, absorption is more than 80%. Levels of 2-5(A) synthetase in peripheral blood mononuclear cells show increases beginning at 6 hours and last for 4 days after a single injection (marker of biologic activity). The antiviral state peaks at 24 hours and slowly decreases to baseline by 6 days after injection. IFN-β following IM or SC injections result in negligible plasma levels but increases in 2-5 (A) synthetase levels may occur. After systemic administration low levels are detected in respiratory secretions, cerebrospinal fluid, eye, and brain. After intravenous dosing, clearance of interferon from plasma occurs in a complex multiexponential manner. Plasma elimination half-life of IFN-α is 2 hours, recombinant IFN-β is 1 hour and IFN-γ is 0.5 hour. After IM or SC injection of IFN-α, the plasma levels increase over a 5 to 9 hours period and then slowly decline. Elimination from the blood relates to the distribution to the tissue's cellular uptake and catabolism primarily in the kidney and liver. Negligible amounts are excreted in the urine.

Side effects

Acute influenza-like syndrome is common; it is characterised by fever, chills, headache, myalgia, arthralgia, nausea, vomiting, and diarrhoea. Fever resolves in 12 hours and can be controlled by antipyretics. Dose-limiting toxicities include bone marrow suppression with granulocytopaenia and thrombocytopaenia, neurotoxicity manifested by somnolence, confusion, behavioural disturbances, seizures, debilitating neurasthenia with fatigue and weight loss, thyroid dysfunction, cardiotoxicity, elevated hepatic enzymes, hypertriglyceridaemias, hepato-toxicity, alopaecia, proteinuria, azotaemia, interstitial nephritis, and impaired fertility. Clinical unresponsiveness can occur secondary to development of serum neutralising antibodies to exogenous interferons.

Interferons may reduce the metabolism of various drugs like theophylline by the hepatic P450 system and increase bone marrow toxicity of myelotoxic drugs, like zidovudine.

Therapeutic Uses

Chronic phase of chronic myeloid leukaemia

Interferon-α can control blood counts and induce complete haematological response in 70% of patients and complete cytogenetic response in 15% patients. Recommended schedule is 5×10^6 units/m^2/day or thrice a week. With the advent of imatinib mesylate, interferon is not the treatment of choice.

Hairy cell leukaemia

Splenectomy has been the first treatment approach in this disease. However, interferon-α has been an effective non-surgical treatment. Seventy five per cent of treated patients achieved a complete or partial remission. First relapse was seen after a period

of 12 to 24 months post therapy. These patients responded to repeat course of IFN-α. Mechanism of action is probably antiproliferative or immunomodulatory in nature.

Interleukin-2

This was first recognised as a growth factor for T-lymphocytes because of its ability to stimulate the production of T-helper and cytotoxic cells. It is currently available as a recombinant protein. Interleukin-2 (IL-2) treatment led to increased cytotoxicity in T-lymphocytes and natural killer cells.

Pharmacokinetics

Half-life of IL-2 is very short (α-13 minutes, β-83 minutes), thus it is used as a continuous infusion or multiple intermittent doses. Liposome encapsulated IL-2 and conjugation of IL-2 with polyethylene glycol has been used to extend the half-life of IL-2 and to enhance its delivery to immune cells in tumours. The most significant antitumour responses have been seen with continuous intravenous infusion for 5 days every other week for 2 cycles or intravenous bolus dosing every 8 hours daily for 5 days every other week.

Toxicity

Toxicities are likely to be related to the activation and expression of lytic lymphocytes in the organs and within vessels resulting in the release of cytokines like tumour necrosis factor and interferons. Common side effects are fever with chills, capillary leak syndrome with hypotension, weight gain, respiratory distress requiring intubation, oliguria, renal dysfunction, and death (1%). Minor side effects are nausea, vomiting, diarrhoea, anaemia, thrombocytopaenia, liver dysfunction, cardiac arrhythmias, and occasionally mental status changes. It is mainly used in metastatic melanoma and renal cell carcinoma.

Erythropoietin (EPO)

Anaemia is common in cancer patients. It may occur solely as a result of the anaemia of chronic disease (ACD) or it may be caused or exacerbated by myelosuppressive therapy and radiation therapy. Clinically, ACD is typically mild to moderate in severity (haemoglobin of 8 to 10 gm/dL). The pathophysiology of ACD has three features: mild decrease in RBC survival; a decreased reutilisation of bone marrow iron stores; and inadequate erythropoietin (EPO) response to the degree of anaemia.

Anaemia in cancer patients develops slowly. Patients develop symptoms when haemoglobin levels are less than 8 gm/dL. Blood transfusion has been the mainstay of therapy, but recombinant genetically produced EPO is a potential option in addition to transfusion.

Indications of EPO in cancer

Myelodysplastic syndrome (MDS) results from a stem cell defect with dyserythropoiesis and not true EPO deficiency. However, the inadequate endogenous EPO response relative to the degree of anaemia suggests that at least some MDS patients may benefit from recombinant human EPO.

Recommended dose is 150 units/kg thrice a week with a step-wise escalation to 300 units/kg thrice a week if no response is seen in first 4 weeks. The desired erythroid response is expected within 4 weeks and usually occurs in 8 weeks. The hormone is administered parenterally by intravenous or subcutaneous routes. The basis for thrice weekly administration of EPO is because absorption of subcutaneous recombinant human EPO occurs more slowly with relatively low serum EPO levels being maintained for 48 hours.

EPO does not affect haematopoietic stem cells but acts on more mature erythroid progenitor [Burst-forming unit-erythroid (BFU-E)] cells. It appears that the hormone does not alter the natural history of MDS in terms of possible disease progression or leukaemic transformation.

CELLULAR APPROACHES

Graft versus Leukaemia (GvL) Effect

The molecular and cellular mechanisms that underline the GvL effect are not well understood. The relationship between GvL effect and graft *versus* host disease (GvHD) is blurred. Major histocompatibility complex differences have long been associated with GvHD. The role of minor histocompatibility antigen expression in GvHD and GvL effect is becoming apparent. T-lymphocytes play an important role in these reactions of which CD4+ T-lymphocyte is particularly important in GvL effect. Natural killer (NK) cells may also be involved in the GvL effect.

Haematopoietic Transplantation as Adoptive Immunotherapy

Allogenic bone marrow transplant was initially considered as a means to deliver supralethal doses of chemotherapy and total body radiation for the treatment of haematological malignancies. The marrow transplantation was considered as a supportive care modality to restore haematopoiesis. The high-dose therapy, however, in many cases does not eradicate the malignancy and that the marrow transplant itself confers an important graft *versus* malignancy effect that is critical to prevent relapse.

Donor Leucocyte Infusion

In patients relapsing after bone marrow transplantation, the leukaemia typically recurs in host-derived cells, but residual normal haematopoiesis and immunity remain largely donor-derived. Infused donor lymphocytes are, therefore, not subject to rejection; but acute GvHD is a major problem. After infusion of donor lymphocytes, there is initially little change in peripheral blood counts, but after a median of 4 months, responding patients may suddenly become hypoplastic. The hypoplasia is followed by recovery from donor-derived haematopoietic cells and return to complete chimerism.

Immunisation Strategies

Passive administration of anti-idiotype antibodies has been used to induce active immune responses against the idiotype. In a pilot clinical trial, autologous dendritic cells pulsed *ex vivo* with tumour-specific idiotype protein were infused intravenously. This procedure was followed by injection of idiotype antigen 2 weeks later. The cycle of pulsed dendritic cells and antigen was repeated two times at monthly intervals and again at approximately 6 months. Each of the patients in the study developed measurable tumour-specific cellular immune responses.

Cytokine-Driven Cellular Vaccines

Creation of local high concentrations of cytokines in proximity to tumour cells can lead to immunoinflammatory responses that are capable of tumour elimination, induction of specific resistance to tumour challenge, and in certain cases to

eradication of established tumour. Local destruction of cytokine gene transfected tumour cells can lead to systemic immunity against transfected tumour cells.

EVOLVING THERAPIES IN CANCER

Uncontrolled proliferation is the hallmark of malignant cell behaviour. Many of the growth factors that are frequently upregulated in tumour trigger tyrosine-kinase signalling pathways. Presently, research is directed at these dysfunctional signalling pathways and oncogene targets.

Unregulated Cell Division

Malignant cells escape from the normal control mechanisms that regulate the rate and frequency at which they divide. It has been found that tumour cells appear to have unregulated cyclin-dependent kinases (CDKs), which trigger cell cycle progression and cell division. Another target is to develop drugs that regulate the cell cycle in an effort to block uncontrolled cell multiplication and force the malignant cell into apoptosis or cell death.

Cell Survival and Immortality

Normally, repeat genetic sequences called telomeres, which are found at the ends of chromosomes, shorten following each cell division. In this way, the length of the telomere indicates its age to the cell. The cell is pre-programmed, so that after a certain number of divisions, it will undergo apoptosis. Tumour cells however contain an abundance of telomerase, which causes the telomeres to be readjoined to the ends of the chromosome. Telomerase immortalises malignant cells by preserving the integrity of telomeres. An approach to cancer therapy for the future is to identify telomerase inhibitors that prevent malignant cells from evading apoptosis.

Dissemination and Metastasis

Tumour cells emit substances known as matrix metalloproteases (MMPs), which allow metastatic cells to permeate blood vessels and invade distant tissues. MMP inhibitors will potentially curtail the metastatic spread of tumours.

Sustained Angiogenesis

Tumours are dependent on the formation of new blood vessels to support growth and metastasis. Many tumours produce large amounts of VEGF, which signals normal blood vessels to grow. Angiogenesis inhibition is an extremely promising approach.

Signal Transduction Inhibitor

The nucleus of a cell controls gene expression, macromolecule production and cellular proliferation via signals delivered from the cell membrane. These signalling pathways involve transmembrane receptors that can be stimulated by circulating growth factors. The intracellular domain of many of these receptors contains protein kinases. Once activated, these kinases initiate a phosphorylation cascade that is thought to result in increased tumour cell growth. Several targets within these signalling pathways are of interest for therapeutic intervention.

Imatinib mesylate, oral bcr/abl tyrosine kinase inhibitor has brought a paradigm shift in the treatment of malignancy. It has shown complete haematologic, cytogenetic and molecular remission, even in blast phase of CML. Imanitib can also inhibit C-Kit related tyrosine kinase and help in controlling gastrointestinal stromal tumor. Gefitinib, another EGFR receptor inhibitor has also shown good disease control in lung cancer. Sorafenib and sunatinib, oral tyrosine kinase inhibitors, have shown promising results in renal cell cancer. Thalidomide, with its immunomodulatory and anti-angiogenic effects, has shown good response in multiple myeloma. These are the results of translational research from the laboratory to the bedside. Resistance has been observed to these newer oral targeted molecules too. Trials with combination of these drugs are in progress, the results appear promising and eventually cure will be possible.

Tumour microenvironment consisting of stromal cells and extracellular matrix appears to play an important role in carcinogenic process. Thalidomide, an inhibitor of tumor-stromal interaction has become an important therapeutic agent in multiple myeloma.

21.2 Principles of Cancer Biology and Pathology

Anita M Borges

Cancer is a chronic condition with a genetic basis. Some normal cells grow faster to cancer cells. Cancer is better defined as a clonal disorder of dysregulated growth and differentiation leading to a persistent accumulation of phenotypically altered cells and tissues, which if left unchecked, will result in death or severe morbidity. This explains many of the observed characteristics of cancer (**Table 1**).

Table 1: Commonly Observed Characteristics of Cancer Cells and Tissues

Enhanced response to growth promoters
Relative resistance to growth inhibitors
Genetic instability
Neoangiogenesis
Loss of contact inhibition of growth
Invasion of natural boundaries
Abnormal locomotive properties
Immune evasion
Ability to grow at other sites (metastasis)
Immortalisation
Tendency to manifest a stem cell phenotype (loss of differentiation)

THE MOLECULAR BASIS OF CANCER

Cancer is a clonal acquired genetic disease. All cells in a tumour are the progeny of one transformed cell. This cell differs from its normal counterpart in the expression of key genes involved in growth regulation, apoptosis, DNA repair, cell adhesion and angiogenesis. These genetic events leading to cancer confer the cell and its progeny properties of the malignant phenotype (**Table 1**). Much is known about the molecular mechanisms of carcinogenesis, but there is no single molecular definition of cancer.

MULTISTEP CARCINOGENESIS

Important steps in carcinogenesis, initiation, promotion, and malignant progression (**Figure 1**) may take years. Molecular genetic events underlying the multistep model of carcinogenesis are best characterised in the adenoma-carcinoma model of colonic cancer (**Figure 2**). Genetic instability is a hallmark of cancer with a tumour continuously undergoing clonal evolution (**Figure 1**). Cancer starts as a single clone. As genetic events occur randomly within tumour cells, the tumour becomes genetically heterogenous. Genetic instability as discussed later is critical to the evolution of cancer. Genetic instability is also a cause of treatment failure. Genes involved in cancer are of two types: Gatekeeper genes (e.g. TP52) are those genes which directly regulate tumour growth and caretaker genes (e.g. BRCA1, BRCA2).

Molecular pathogenesis of colorectal cancer illustrates the intricacies in tumour development. The adenomatous polyposis coli (APC) gene is the major gatekeeper of the colon. Patients with inherited mutations of this gene develop thousands of

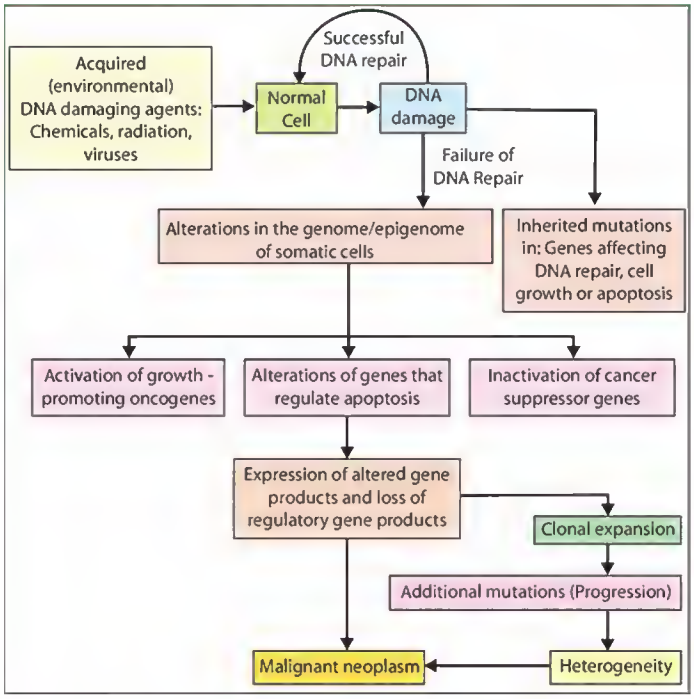


Figure 1: The molecular basis of cancer.

colonic adenomas. APC mutations are sufficient to initiate growth of small benign tumours but are insufficient for tumour progression. Other genetic pathways participate in progression including:

1. Transforming growth factor-beta (TGF-β) is a small polypeptide hormone that negatively controls colon cell growth.
2. H-ras is involved in signal transduction.
3. p53 gene is an important component of response to DNA damage that inhibits growth of cells with DNA damage by blocking the cell cycle. It also stimulates programmed cell death (apoptosis). Mutations in the p53 gene allow cells with damaged DNA to divide and propagate mutation. These cells are also resistant to apoptosis. Cells with mutations accumulate and tumour progresses.

The mismatch repair system, a system that repairs subtle mistakes made during copying of the genome, is a caretaker system. Inherited alterations of these genes lead to hereditary non-polyposis colorectal cancer (HNPCC). Mismatch repair genes in humans include hMSH2, hMSH1, hPMS2, GTBP. Sporadic colorectal cancers generally do not have defects in mismatch repair but have a different form of caretaker defect, named CIN, for chromosome instability. CIN tumours develop losses or gains of whole chromosomes at a rate that is 10 to 100 times higher than that of normal cells. The chromosomes involved include those containing gatekeepers. Alterations of chromosomes containing gatekeepers impede the ability of cells to control

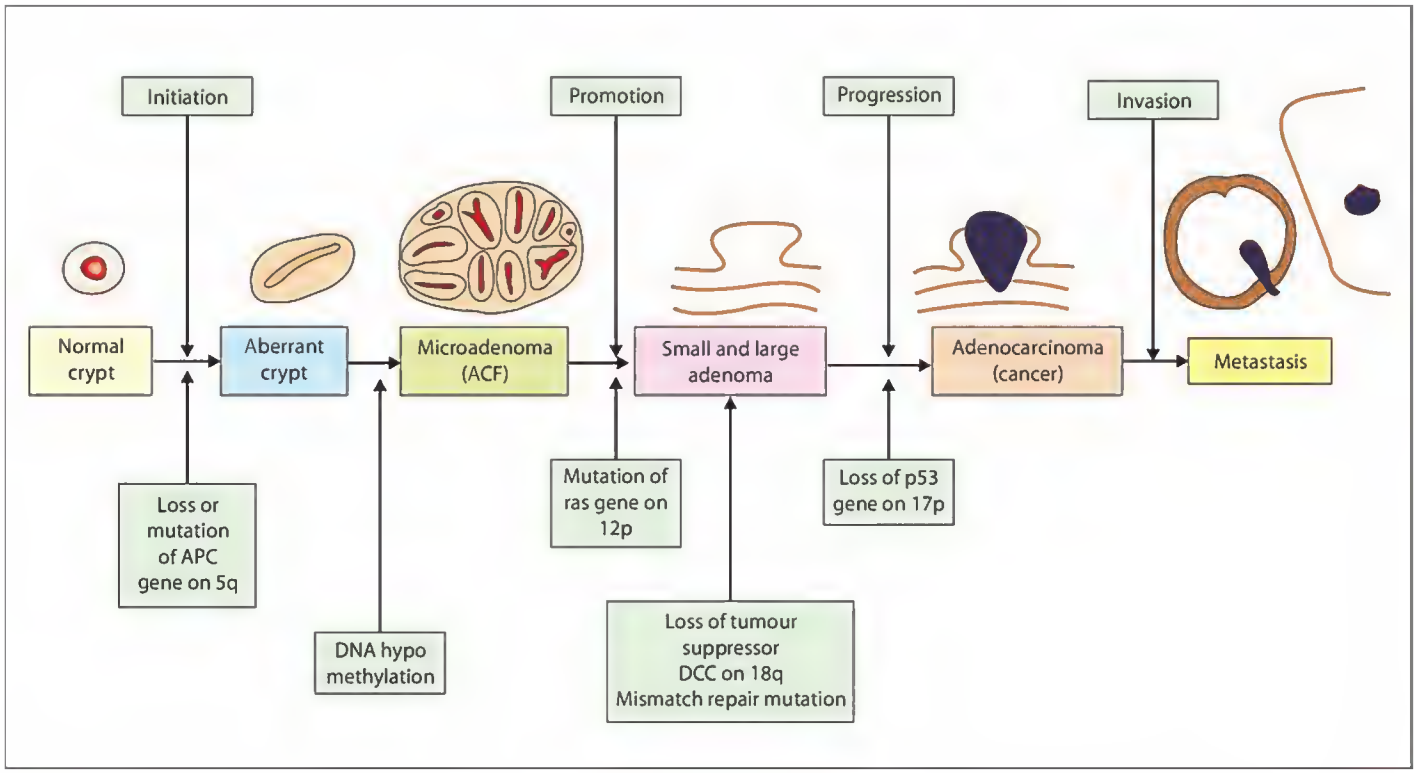


Figure 2: Adenoma carcinoma sequence.

cell growth properly. CIN develops very early during the tumourigenic process in the colon.

ONCOGENES AND TUMOUR SUPPRESSOR GENES

Oncogenes

Transforming retroviruses are oncogenic RNA viruses. Surprisingly they have a homology with highly conserved vertebrate genes. These segments are vertebrate genes, known as proto-oncogenes, that had been pirated by the virus. Most proto-oncogenes are involved in normal growth and differentiation coding for growth factors, growth factor receptors, G proteins, and cytoplasmic kinases involved in signal transduction, and nuclear proteases. Their deregulation leads to transformation and proliferation. Involvement of c-Myc in Burkitt's lymphoma, H-ras in oral cancer and thyroid cancer, K-ras in pancreatic cancer, and RET in medullary thyroid carcinoma. Oncogene activation occurs by gene amplification e.g. HER-2neu in breast cancer and N-myc in neuroblastoma are examples of oncogene involvement in cancer.

Tumour Suppressor Genes

In contrast to oncogenes, tumour suppressor genes check proliferation. Loss of function of these genes deregulates the cell cycle and contributes to tumour formation. Knudson had predicted the existence of a tumour suppressor gene from his epidemiologic studies on hereditary, and sporadic forms of retinoblastoma. Knudson hypothesised that children with hereditary retinoblastoma (early, multiple and bilateral tumours) carried a germline mutation of a key gene on one allele, and that a second genetic event occurred after birth that affected the function of the unaffected allele in the retinal cells. The retinoblastoma gene was the first tumour suppressor gene to be described. Documentation of Rb mutations in familial retinoblastoma proved Knudson's hypothesis. The Rb gene product pRB binds to the E2F family of transcription factors. Unbound E2F pushes the cell into S phase. The retinoblastoma gene function is disrupted in a variety of cancers including osteosarcoma, breast cancer, small cell carcinoma of the lung, and oesophageal cancer. Other tumour suppressor genes are p53, APC, WT1, and VHL.

CANCER CYTOGENETICS

Numerical and/or structural changes in chromosomes are common. Aneuploidy (chromosome number less than a multiple of the haploid number) is one of the most common cytogenetic findings in solid tumours. Some tumours, especially haematopoietic malignancy and solid tumours in children, exhibit tumour specific chromosomal abnormalities. These are of three main types:

Balanced Translocations

Philadelphia chromosome seen in chronic myeloid leukaemia and some cases of adult acute lymphoblastic leukaemia, is a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11) (**Figure 3**). The resulting fusion between parts of BCR and ABL genes has transforming properties. The t(8;14)(q24;q32) in Burkitt's lymphoma juxtaposes the oncogene c-Myc on chromosome 8 to the enhancer region of the Ig heavy chain gene. Other translocations include t(11;22) (q24; q11.2-12) in Ewing's sarcoma and the t(X;18) (p11.2;q11.2) in synovial sarcoma.

Deletions

Deletions are responsible for abrogation of tumour suppressor genes in familial retinoblastoma and Wilms tumour.

Gene Amplification

Gene amplification leading to overexpression of N-myc is seen in neuroblastoma. The gene is situated on 2p. Karyotypically, multiple repeats of the gene sequence result in one of two appearances; double minutes where fragments of the repetitive

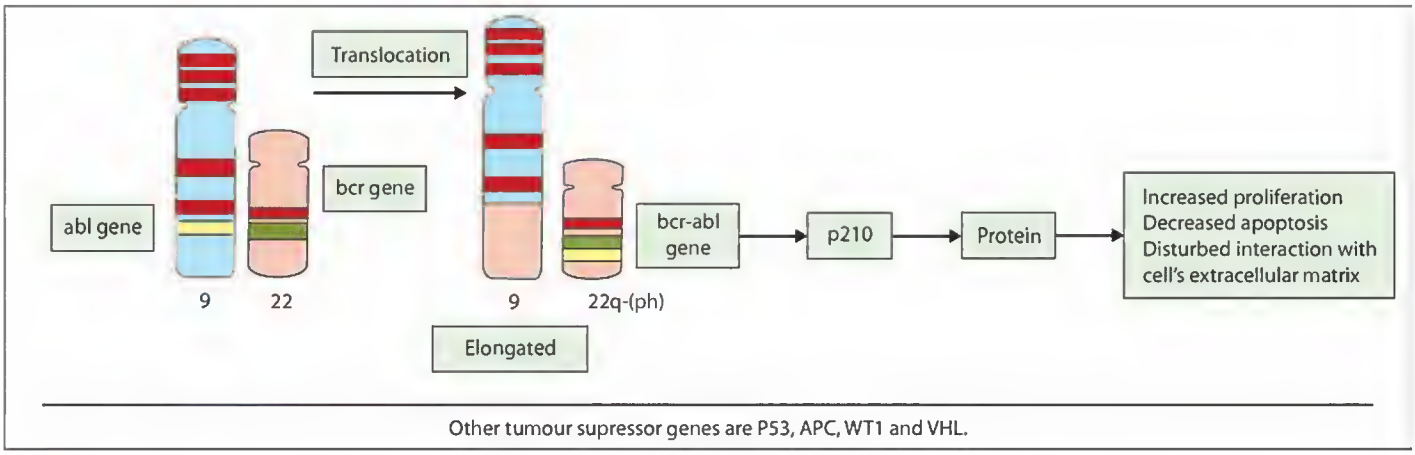


Figure 3: Philadelphia chromosome in CML – t(9,22).

DNA appear as tiny extra chromosomes or as homogeneously staining region (HSR) in G-banded preparations (**Figure 4**).

INHERITED CANCER SYNDROMES AND GERMLINE MUTATIONS

Germline Tumour Suppressor Inactivation

Familial retinoblastoma, familial APC, Wilms tumour, and Li-Fraumeni syndrome result from inactivation of tumour suppressor genes.

Germline Oncogene Activation

Multiple endocrine neoplasia (MEN), hereditary papillary renal cell carcinoma (MET), and familial melanoma (CDK4) result from germline oncogene activation.

DNA Repair Defects

Failure to repair DNA defects lead to increase in mutation rates and cancer risk. Xeroderma pigmentosum, ataxia telangiectasia (hypersensitivity to radiation), Bloom syndrome, Fanconi's anaemia, familial breast and ovarian cancer syndrome and hereditary non-polyposis colorectal cancer are examples of DNA repair defects predisposing cancer.

Non-Syndromic Hereditary Cancer

Clinicians regularly come across families in which multiple members have had cancers at various sites, without fitting into one of the distinct cancer family syndromes. Studies on such families will throw further light on the problem of heredity and cancer.

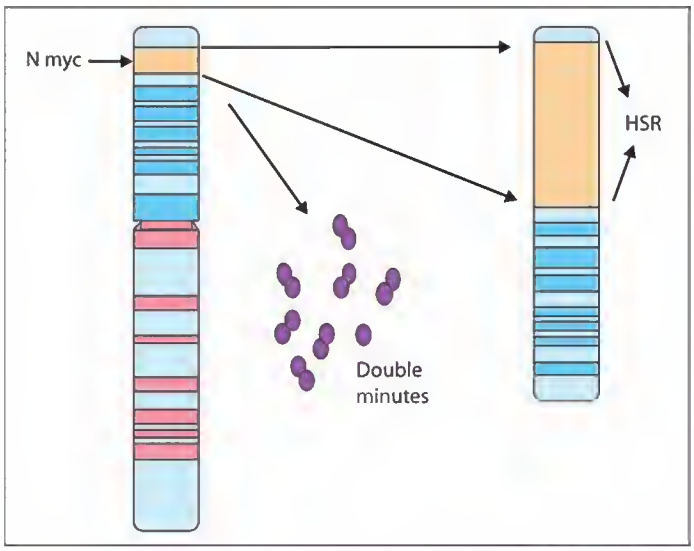


Figure 4: Amplification of the N-myc gene on chromosome 2p in human neuroblastoma.

MECHANISMS OF INVASION AND METASTASIS

Metastasis, the establishment of tumour cells at distant sites in the body, is the hallmark of cancer. Metastasis is known to occur from very small tumours and the incidence increases with tumour size and stage. Metastasis is a multistep active process. The tumour cells must acquire the ability to invade stroma, stimulate neoangiogenesis, transgress stroma, invade vessel walls, extravasate into the extravascular environment and grow in a new microenvironment to establish metastasis. The entire set of abilities is needed for metastasis and each of these is independently acquired because of the genetic instability referred to above. Metastatic cascade is inefficient. Very small proportion of the cells breaking away from the tumour establish metastasis.

TUMOUR INVASION INTO THE EXTRACELLULAR SPACE

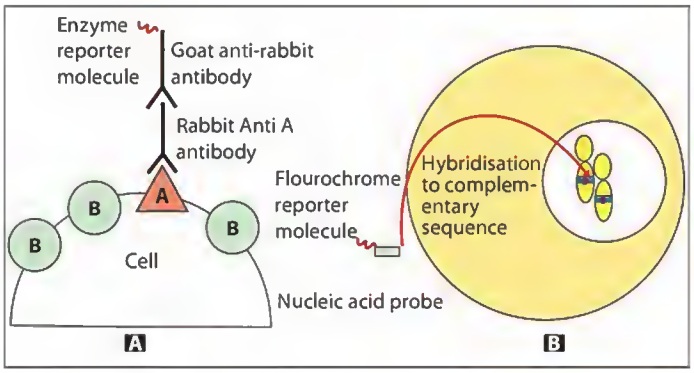
Invasive tumours show downregulation of cell-cell adhesion and alterations of normal cell-stromal interactions. Cancer cells also secrete a variety of proteolytic enzymes that degrade extracellular matrices and display greater motility. Tumour cells are able to detach themselves from their normal positions, break through basement membranes, and move through the extracellular space (ECS).

NEOANGIOGENESIS

A growing tumour needs vessels to prevent its centre from becoming hypoxic. Hypoxia stimulates new vessel formation by secretion of angiogenic factors, e.g. vascular endothelial growth factor (VEGF). Tumours that are unable to stimulate angiogenesis are unable to grow beyond 2 mm in diameter and have a very low metastatic potential. New vessels formed in the tumour bed are usually poorly formed and are particularly vulnerable to invasion by tumour cells that are present in the ECS.

APPLIED BIOLOGY OF CANCER

For more than a century the microscope has been the mainstay in the diagnosis and classification of malignant tumours. However, ancillary techniques (**Figures 5A and B**) such as immunohistochemistry (IHC) and fluorescent in-situ hybridisation (FISH) have improved diagnosis and classification. They have also identified potential targets for therapeutic intervention viz. receptors, amplified genes and aberrantly expressed proteins involved in deranged signalling pathways.



Figures 5A and B: Diagrammatic representation of (A) immunohistochemistry (B) FISH.

WHAT CLINICIANS WANT FROM PATHOLOGISTS

Clinicians expect from pathologists diagnosis of precancer and early cancer (screening); diagnosis and classification of established cancer; tumour grading wherever appropriate; staging; information on completeness of therapy (margins of resection and minimal residual disease); prediction of tumour response to treatment (identification of targets, chemoresponsiveness, radiotherapeutic responsiveness); monitoring the course of the disease and identification of early relapse; and prognostication.

PRACTICAL APPLICATIONS OF CYTOGENETICS AND MOLECULAR GENETICS

Specific cytogenetic markers in haematology viz. the Philadelphia chromosome in CML are used in routine diagnosis. The monitoring of the clearance of bcr-abl transcripts from the bone marrow of CML patients is today the gold standard in evaluating response to treatment and early relapse. Several solid tumours also show diagnostic cytogenetic markers. The t(11;22) translocation which represents the EWS-FLI1 fusion gene is manifested in the majority of Ewing's sarcomas. In atypical cases, techniques such as FISH or RT-PCR are used to arrive at an accurate diagnosis which is necessary for a good therapeutic response. Cytogenetics has helped to classify common soft tissue sarcomas – rhabdomyosarcomas in children and liposarcomas in adults.

Targeted therapy is the current buzzword in cancer therapeutics. Targeted therapy often needs documentation of target molecules by IHC and DNA studies. In patients with breast cancer demonstration of oestrogen and progesterone, receptor is needed for anti-oestrogenic therapy, and c-erbB2 for trastuzumab. Similarly, documentation of CD20 is needed for rituximab and c-Kit for imatinib therapy in gastrointestinal stromal tumours. Several other monoclonal antibodies against a variety of targets are now in use in clinical oncology and several others are in the pipeline. With each new target, a method of demonstrating it in the tissues becomes necessary, expanding the role that pathology plays in clinical therapeutics.

Prediction of susceptibility to cancer is now possible in families with known cancer syndromes by screening family members. This is regularly advised in patients with hereditary colon cancer especially those with familial adenomatous polyposis coli where prophylactic colectomy saves lives. Screening for RET mutations allows prophylactic thyroidectomy in patients with the MEN 2 syndrome. This prevents medullary carcinoma, a cancer that is difficult to eradicate once it is overt. Screening for HNPCC and BRCA mutations for familial colon, and breast and ovarian cancer respectively is also possible. However, psychological trauma can result when knowledge of susceptibility comes without the availability of definitive prevention strategies. Judicious patient counselling is, therefore, required before these tests are ordered.

GENE EXPRESSION PROFILING

One of the conundrums in everyday clinical practice is why patients with similar tumours have such different outcomes. The answers may lie in the molecular heterogeneity of tumours with similar appearances, the differential host response to the tumour, or differential host metabolism of common drugs. Gene expression profiling or DNA microarray technology, as it is often known, is currently being used to answer these questions (**Figure 6**). The hope is that differences in gene expression between tumours will not only explain why they behave differently, but may identify tumours that can be treated less or more aggressively or differently in different individuals. Pharmacogenetics, a specific treatment for a specific patient, which was once a distant dream, is now a very achievable goal.

SERUM TUMOUR MARKERS

Many tumours secrete substances into the blood stream that are useful in diagnosing the presence of the tumour and monitoring relapse. β-Human chorionic gonadotropin (β-hCG)was the first and still remains the most often estimated of these so called tumour markers. These markers are by no means specific to tumours. All of them are expressed by normal cells in foetal life or during repair and regeneration. They are, therefore, not useful for screening or the primary diagnosis of cancer. However, they are routinely used for monitoring the progress of tumour control.

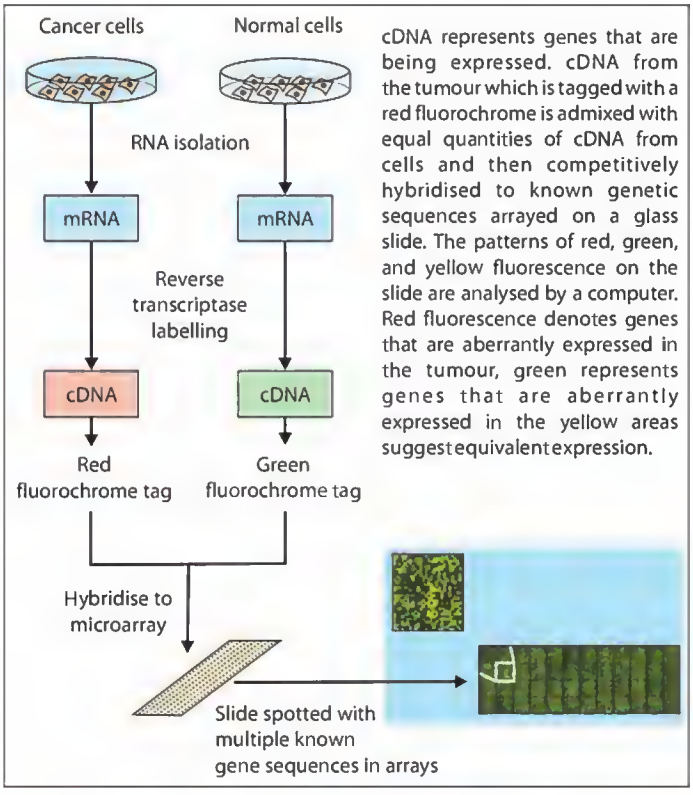


Figure 6: Gene expression profiling – DNA microarray.

21.3 Cancer Screening and Prevention

Atul Sharma, MP Ram Prabhu

INTRODUCTION

Cancer has not been considered a major health issue in developing countries where an overwhelming number of infectious diseases and rampant sanitary problems were higher priorities but according to a 2005 report by the World Health Organization (WHO) unfortunately, cancer is now becoming more of a global burden than it was ever before. An increase in the incidence of cancer in developing nations means that the international implications of the disease now require greater attention. This increase can be attributed to increased life expectancy in highly populated countries like China and India, a rise in the number of smokers in developing nations and an increase in lung cancer incidence.

As per the American Cancer Society, the worldwide estimate of cancer incidence is 12 million (2007) out of which 6.7 millions are in economically developing country of Asia. Lung cancer is the most common cancer world wide. WHO has estimated that by 2020, 15 million new cases will be diagnosed each year globally. In India, according to National Cancer Registry Programme estimates, 700,000 to 900,000 new cancer cases occur in India every year. With the cancer incidence further rising, it poses a huge public health and economic challenge.

The increase in cancer trends in the developing nations could be controlled and the economic burden of fighting this disease could be lessened by effective measures of cancer screening and prevention.

CANCER SCREENING

Cancer screening is a method wherein physical examination and investigative methods are used in an asymptomatic population in order to detect cancer at an earlier stage and rendering it more amenable to treatment and cure. Thereby, it reduces overall mortality of that cancer in that particular population. Screening is a form of secondary prevention because it does not prevent the occurrence of cancer; rather it helps cancer to be detected at an earlier stage.

Screening of cancer began in 1941 when George Papanicolaou published his work on cervical cancer screening using Pap smear. In 1960s, breast cancer screening with mammography came into practice when it was shown to reduce breast cancer mortality in a study by Health Insurance Plan of New York.

For a cancer to be eligible for screening, certain criteria should be met. First of all, the particular cancer must be an important public health problem in terms of morbidity and mortality. It should have a detectable pre-clinical phase which is sufficiently long when screening tests can be employed. An effective treatment should be available and the treatment should be more effective in the pre-symptomatic phase. The screening test should be accurate, acceptable to the population, easy to administer, cost-effective, and safe. An appropriate screening strategy in terms of age and interval of screening should be available.

Accuracy of screening test implies that it should be able to distinguish between diseased and non-diseased people. It is measured by sensitivity and specificity. Sensitivity refers to ability of the test to identify diseased subjects among a screened population and is given by the number of people who test positive divided by those who actually have the disease. Specificity refers to ability of the test to correctly identify the subjects without that particular disease. It is given by the number of people with a negative test divided by actual number of people who do not have the disease.

None of the screening test available currently is 100% sensitive and specific. Sensitivity and specificity are inversely related. A highly sensitive test can also give false positive results wherein the subject who actually is disease-free may be labelled positive by the test. This leads to futile diagnostic procedures and mental stress for subject. Similarly, highly specific tests can have false negativity wherein subjects who actually have the disease are labelled negative and an opportunity to treat and perhaps cure the disease is lost.

Screening in Specific Cancers

Colorectal cancer (CRC)

Colorectal cancer (CRC) is the third most common in incidence and mortality in United States although it is not among 10 leading cancers in most of Indian cancer registries. Colorectal cancer screening has shown to not only reduce the mortality by 3% but also incidence by 2%. Cancer screening tools currently available for CRC are faecal occult blood testing (FOBT), double contrast barium enema, colonoscopy, and flexible sigmoidoscopy. FOBT has been proven to be effective in 3 randomised controlled trials and a Cochrane review which showed 16% reduction in CRC mortality. Virtual colonoscopy wherein contrast enhanced CT scan is used to visualise whole colorectum is also currently being tested. American cancer Society Guidelines (based on US Multisociety Task Force on CRC) for an average risk individual include annual FOBT testing, flexible sigmoidoscopy once every 5 years, colonoscopy once every 10 years and double contrast barium enema once every 5 to 10 years beginning at the age of 50 years. For high-risk individuals, screening should start at an early age and tests should be done more frequently.

Cervical cancer

Pap smear is the standard test to screen cervical cancer. United States Preventive Task Force recommends screening to start within 3 years of earliest sexual activity, not later than 21 years of age. Pap smears are to be performed annually till 3 consecutive tests are normal where after it is performed once in 3 years till 65 to 70 years of age. Sensitivity of 50% to 75% and a specificity of 69% to 94% have been reported. Human

papillomavirus (HPV) DNA testing has been recently used to screen for cervical cancer, and has been approved by United States Federal Drug Authority (USFDA) for primary screening in cervical cancer along with Pap smear. In a large study of 130,000 patients in India, a single HPV test that is performed 15 to 20 years after the median age of first sexual intercourse detected many easily treatable, persistent infections and pre-cancers while limiting over-treatment and lowering the rate of death from cervical cancer within 5 to 10 years when compared to routine Pap smear or visual inspection of cervix with acetic acid (VIA).

Cervical cancer is the most common cancer among women in India. In the developing countries including India, cervical cancer screening programmes are in rudimentary stage and are hampered by many issues like lack of education and awareness and by social issues. Pap smear testing requires expertise to interpret results, infrastructure, and a long follow-up of patients. VIA by trained nurse-midwives is an easy, simple screening method which does not require any expertise or infrastructure. This has been tested in large studies in Zimbabwe and recently in India and was found to have a sensitivity of 76.7% and specificity of 64.1% .

Breast cancer

Breast cancer is the most common cancer in western countries among females and second leading cause of cancer related mortality in females. In India, breast cancer is most common cancer in urban areas like Delhi and Mumbai. Breast cancer screening helps to detect the disease at an early stage as a result of which mortality comes down as does the requirement of extensive surgery and chemotherapy. Breast self examination (BSE), clinical breast examination (CBE), and mammography have all been used in breast cancer screening. Randomised studies have shown reduction in relative risk of death due to breast cancer using mammography.

In United States, there was a 2.1% reduction in breast cancer mortality due to screening in 1990s. For normal females, the screening recommendations are to do mammogram annually starting from the age of 40 years. However, for high-risk individuals (positive family history or chest wall irradiation) it should be started at an early age. MRI of breast is recommended for patients with BRCA1 and BRCA 2 mutations. Recently, the US Preventive Services Task Force has come up with recommendations against routine screening mammography in women aged 40 to 49 years and recommends biennial screening mammography for women between the age of 50 and 74 years.

Prostate cancer

Prostate cancer although not the commonest cancer in India, is the most common cancer in the developed countries. Serum Prostate Specific Antigen (PSA) and digital rectal examination are the two methods used in prostate cancer screening. Screening with PSA has resulted in significantly increased numbers of cancers and also at an earlier stage. However, the benefit from prostate cancer screening remains controversial since many patients diagnosed with prostate cancer may not die of cancer and treatment may not benefit.

Screening has not been found to be beneficial in ovarian and endometrial cancer. In lung cancer, screening the role of annual chest CT scans is still under investigation.

CANCER PREVENTION

Cancer screening aims to detect pre-cancerous and early cancer while primary preventions of cancer aims at reducing the incidence of cancer. Tobacco consumption in any form, alcohol consumption, viral oncogenesis, industrial exposure to carcinogens, and hereditary cancer syndromes are some important risk factors for cancer. Risk factors in many cancers are now known.

Tobacco consumption accounts to 50% of the cancers in India including head and neck cancer, lung cancer, oesophageal, gastric, breast, and bladder cancers. Lung cancer incidence has fallen in United States following reduction in incidence of smoking. Given the high mortality rate of lung cancer (5-year survival rate of 15% only), prevention by smoking control appears to be the best possible option to reduce lung cancer mortality. Nicotine replacement therapy, anti-depressants like bupropion and other drugs like clonidine have been used to promote quitting. Preventive measures have been carried out by the Indian Government in the form of ban on smoking at public places.

Chemoprevention is defined as the use of natural or synthetic compounds to block, prevent, or reverse the development of invasive cancer. Retinoids and beta-carotene have been tried in head and neck cancers for the prevention of second primaries but have not shown consistent benefit. In fact, beta-carotene was found to be detrimental in some lung cancer trials. Vitamin E and selenium did not reduce incidence of prostate cancer in a large study.

Vaccination against hepatitis B has caused significant reduction in incidence of hepatocellular carcinoma in children in Taiwan. Two HPV vaccines, namely, Gardasil (quadrivalent) and Cervarix (bivalent) have shown efficacy in preventing cervical pre-cancerous lesions in females. Both vaccines are approved in various western countries and Gardasil has been approved by the Indian Academy of Paediatrics in India.

Improvement in socio-economic status has resulted in reduction of incidence of cervical cancer. On the other hand, obesity is an important risk factor for the development of gastroesophageal junction cancer, colorectal cancer, endometrial, and breast cancer. Dietary and lifestyle modifications like consumption of high fibre diet, fruits and vegetables and physical exercise can lead to drop in the incidence of such cancers.

Helicobacter pylori, a normal commensal organism of gastric mucosa has been implicated in gastric adenocarcinoma. Eradication of *H. pylori* has been recommended in certain high-risk groups, like patients with atrophic gastritis, first degree relatives of gastric cancer patients and in patients after resection of low-risk gastric adenocarcinomas. But problems of emergence of resistance to antibiotics and re-infection hamper such an approach. Dietary carcinogens like nitrosoamines are also implicated in gastric cancer. Reduction in use of canned foods and preservative added foods has resulted in the decline of gastric cancer.

Chronic asbestos exposure is a risk factor for the lung cancer. Similarly, exposure to other industrial carcinogens like coal tar, aromatic dyes, cadmium, and radiation exposure are implicated to be carcinogenic.

Familial cancer syndromes like BRCA-1 and BRCA-2 mutations, Hereditary non-polyposis colon cancer (HNPCC) syndrome, familial adenomatous polyposis (FAP) colon cancer syndrome confer high risk to individuals in that family. Prophylactic bilateral mastectomy reduces breast cancer risk by 90% in BRCA-1 gene mutation carriers. Similarly, bilateral oopherectomy reduces the risk of breast cancer by 50% in addition to reducing the risk of ovarian cancer. Both are options against screening in genetic breast-ovarian cancer syndromes. Prophylactic proctocolectomy is done in FAP and genetic counselling should be offered to such individuals and surveillance measures should be continued.

CONCLUSIONS

Creating awareness of cancer among public, advocating and implementing smoking control measures, protection from industrial carcinogens and vaccination against preventable cancers can help reduce the burden of cancer. Screening in cancers of breast, cervix, and colorectal has great potential in reducing the incidence of advanced disease and thereby, mortality. Although benefit from cancer screening is straightforward, realising the fullest benefit is often not possible due to difficulties in large scale implementation and adherence to screening recommendations even in the developed nations. However, dedicated effort to attain such goals will definitely benefit population at risk.

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21.4 Principles of Drug Treatment of Cancer

Lalit Kumar, Prabhat Singh Malik

INTRODUCTION

The systemic treatment of cancer has its roots in the initial work of Paul Ehrlich, who coined the term chemotherapy. Chemotherapy, which includes newly developed targeted treatments, has been the main mode of drug treatment of cancer for the past five decades. Initial studies in 1960 to 70's led to the development of concept of combination chemotherapy and provided effective treatment for childhood acute lymphoblastic leukaemia, advanced Hodgkin's lymphoma and diffuse large B-cell lymphomas and testicular germ cell tumours. These lessons have been subsequently applied to other cancer types as well. Major limitations to the clinical efficacy of chemotherapy have been toxicity to the normal tissues of the body and the development of drug resistance. In the past decade, better understanding of molecular biology and pathways/targets have led to the target specific therapy. This has resulted in a paradigm shift in the management of many cancers.

Tumour Growth and Response to Cytotoxic Chemotherapy

The key principles of chemotherapy were initially defined by Skipper *et al* using the murine leukaemia model. Cytotoxic effects of anticancer drugs are predicted to follow logarithmic cell kill kinetics. Thus, if an individual drug leads to a 3 log kill of cancer cells and reduces the tumour burden from 10^{10} to 10^{7} cells, the same dose used at a tumour burden of 10^{5} cells reduces the tumour mass to 10^{2}. On the other hand, human solid cancers support a Gompertzian model of tumour growth and regression. According to the Gompertzian model, the growth fraction peaks when the tumour is approximately 37% of its maximum size. In general, when patients with advanced solid tumours are treated, the tumour mass is larger, its growth fraction is low, and the fraction of cells killed is, therefore, small.

CELL CYCLE AND THERAPEUTIC TARGETS

The cell cycle of cancer cells is qualitatively similar to that of normal cells. Each cell begins its growth during a post-mitotic period, a phase called G_1(Gap1), during which enzymes necessary for DNA production, other proteins, and RNA are produced. G_1 is followed by a period of DNA synthesis (S), in which essentially all DNA synthesis for a given cycle takes place. When DNA synthesis is complete, the cell enters a pre-mitotic period -G_2 (Gap2), during which further protein and RNA synthesis occurs. This gap is followed immediately by mitosis (M), at the end of which actual physical division takes place, two daughter cells are formed, and each cell again enters G_1. G_1 phase is in equilibrium with a resting state called G_0. Cells in G_0 are relatively inactive with respect to macromolecular synthesis and are consequently insensitive to many chemotherapeutic agents, particularly those affecting macromolecular synthesis.

INDICATIONS FOR CHEMOTHERAPY

Chemotherapy as Primary Therapy

For a number of cancers, chemotherapy is the main treatment and is considered curative even in advanced stage. These include: childhood malignancies, e.g. acute lymphoblastic leukaemia (ALL), Burkitt's lymphoma, Wilms' tumour, and embryonal rhabdomyosarcoma; in adults: choriocarcinoma , Hodgkin's and non-Hodgkin's lymphoma (NHL), acute lymphoblastic and myelogenous leukaemia, germ cell cancer, ovarian and localised small-cell lung cancers, are examples of cancers treated primarily with chemotherapy.

Neoadjuvant Chemotherapy

For many chemosensitive tumours in advanced stage, 3 to 4 cycles of chemotherapy may be administered prior to local treatment (e.g. surgery/radiation therapy), this is called *neoadjuvant or induction chemotherapy*. This results in reduction in the size of primary tumour facilitating local treatment, e.g. better chance of complete resection with local treatment, e.g. surgery (e.g. locally advanced breast cancer, epithelial ovarian cancer, etc.) or radiation (e.g. cancer of head and neck, cervix, anal canal, urinary bladder) while reducing the potential spread of micro-metastatic spread. Osteogenic sarcoma, rhabdomyosarcoma, Ewing's sarcoma, and Wilms' tumour, etc. are common paediatric tumours treated with this approach in advanced stages. Clinical benefit is usually optimised when chemotherapy is administered in combination with radiation therapy (concurrently), e.g. locally advanced cervical cancer, head and neck cancer, cervix, anal canal cancer, etc.

Adjuvant Chemotherapy

It is administered after local treatment, e.g. after surgery for breast and ovarian cancers and has been demonstrated to improve outcome. This is called *adjuvant chemotherapy* and helps to prevent local and systemic relapse by eradicating micro metastasis. Advanced colon cancer, non-small cell lung cancer, head and neck cancer, cervical cancer, Wilms' tumour, and osteogenic sarcoma are other cancers where such an approach is beneficial.

Route of Administration

Most chemotherapeutic drugs are administered intravenously (IV) either as slow IV push through a running drip or as IV infusion over a longer period. Oral formulations of few chemotherapeutic drugs (e.g. alkylating agents, antimetabolites) are also available. In certain situations, chemotherapeutic drugs can be instilled locally. The common examples are: (a) intrathecal use of methotrexate and/or cytarabine for (CNS) prophylaxis/ treatment of CNS leukaemia, (b) intra-arterial use for chemo-embolisation in hepatocellular carcinoma and limb perfusion for malignant melanoma.

Consolidation Chemotherapy

It refers to the phase of treatment after achieving remission with induction chemotherapy. The goal is to eradicate residual disease. This term is mainly used in the context of haemato-logical malignancies, e.g. acute lymphoblastic and myeloblastic leukaemias.

Maintenance Chemotherapy

ALL or acute promyelocytic leukaemia (APML), subtype of AML prolonged low-dose therapy is required (usually 1.5 to 2 years) to maintain remission and prevent relapses. This is termed as *maintenance therapy*.

Palliative Chemotherapy

In advanced cancers when cure is not possible, the aim of therapy is to improve symptoms, and improve quality of life. The use of chemotherapy with such intention is termed as *palliative chemotherapy*. A careful decision should be taken in such situations and main consideration should be to minimise toxicities (including cost and hospitalisation) with adequate efficacy and convenience of the patient.

Salvage Chemotherapy

Chemotherapy used for the treatment of relapse after initial response is termed as *salvage chemotherapy*. This is with chemo-sensitive tumours at advanced stage, e.g. Hodgkin's lymphoma, aggressive NHL, leukaemias, and certain paediatric cancers.

High-Dose Chemotherapy

High-dose chemotherapy regimens are based on the observation that in chemo-responsive cancers, the dose-response curve for many anti-cancer agents is rather steep, and an increased dose of chemotherapeutic drug(s) can produce markedly increased therapeutic effects. Although, it is associated with potentially life-threatening complications that require intensive support, usually in the form of haematopoietic stem cell support from the patient (*autologous*) or from human leucocyte antigen (HLA) matched sibling or unrelated donor. High-dose regimens have definite curative potential in defined clinical settings like chemosensitive relapsed Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, and childhood neuroblastoma (stage III-IV). Its role is currently under investigation in conditions like high-risk testicular germ cell tumours, Ewing's sarcoma, etc.

CLASSIFICATION OF CYTOTOXIC CHEMOTHERAPY DRUGS

Conventionally, most chemotherapeutic agents can be grouped according to whether their activity is greater when the cell is in a specific phase of the cycle. Agents that are most active against cells in a specific phase of the cell cycle are called *'cell cycle phase specific drugs'* (**Table 1**). The implication of the phase specificity is that a short exposure by the drug even in high doses would not kill a large proportion of the tumour cells because all the cells would be in different phase of cell cycle. Rather, a prolonged exposure either by repeated administration or by increasing the duration of infusion would achieve a better cell kill as most of the cells will pass through that specific phase of the cell cycle.

1. *Cell cycle phase non-specific drugs:* This group includes agents that are effective while cells are active in cycle but are not dependent on the cell being in a particular phase. Main examples are most of the alkylating agents and the antitumour antibiotics.
2. *Cell cycle non-specific drugs:* A third group of drugs appears to be effective whether cancer cells are in cycle or are resting. Drugs in this category include: mechlorethamine (nitrogen mustard) and the nitrosoureas.

Table 1: Cell Cycle Phase Specific Drugs

Phase of Greatest Activity	Class of the Drug	Drug
Gap 1 (G_1)	Enzyme	Asparaginase
	Corticosteroid	Prednisone
G1/S junction	Purine analogue	Cladarabine
DNA synthesis (S)	Pyrimidine analogue	Cytarabine, fluorouracil, gemcitabine
	Folic acid analogue	Methotrexate
	Purine analogue	Thioguanine, fludarabine
	Topoisomerase-I inhibitor	Topotecan
	Substituted urea	Hydroxyurea
Gap 2 (G2)	Antibiotic	Bleomycin
	Topoisomerase-II inhibitor	Etoposide
	Microtubule polymerisation and stabilisation	Paclitaxel
Mitosis (M)	Mitotic inhibitor	Vinblastine, vincristine, vindesine, vinorelbine

Table 2 presents classification of cytotoxic chemotherapeutic drugs according to their chemical structures and clinical activities.

MECHANISM OF ACTION OF CHEMOTHERAPEUTIC AGENTS

Alkylating Agents

These are cell cycle specific but not phase specific and act by means of cross-linking of DNA strands. These agents may have serious long-term toxicities on bone marrow stem cells and gonads.

Topoisomerase Inhibitors

The DNA topoisomerases are enzymes that alter DNA topology by causing and resealing DNA strand breaks. Topoisomerase-I relaxes supercoiled DNA for a variety of crucial cellular processes. Topoisomerase-II catalyses the double stranded breaking and resealing of DNA, thereby allowing the passage of one double helical segment of DNA through another. So these enzymes are essential for cellular events like transcription, replication, and mitosis. These enzymes are targets of this group of cytotoxic agents. Topoisomerase-I is inhibited by campothecin derivatives, like topotecan and irinotecan while topoisomerase-II is inhibited by anthracyclines and epipodophyllotoxins (etoposide and teniposide).

Antitumour Antibiotics

These drugs have been derived from micro-organisms. They are usually cell cycle non-specific agents and act through intercalation, by inserting itself through DNA basepairs, and thereby preventing DNA replication.

Mitotic Spindle Inhibitors

These agents are especially active in M and G2M phase of cell cycle. They act by inhibiting microtubule assembly by binding to tubulin (Vinca alkaloids) or by stabilising microtubules and preventing their disassembly and producing non-functional microtubules (Taxanes). Some of them are natural products (vincristine, vinblastine, paclitaxel) while others are semi-synthetic products (vinorelbine, docetaxel).

Anti-Metabolites

These agents are cell cycle S-phase specific and kill tumour cells by acting as a false substrate in biochemical pathways. Based on their chemical structures, these are sub-classified as pyrimidine analogues, purine analogues, antifolate, and others.

TOXICITY OF CHEMOTHERAPEUTIC DRUGS

No chemotherapeutic agent is free of toxicities or side effect. Depending on their biological properties, the tissue/organ specific toxicities manifest. Common side effects of chemotherapeutic agents are nausea, vomiting, myelo-suppression, alopaecia, mucositis, etc. These can be group specific or particular drug specific. Common adverse effects of these agents are shown in **Table 2**.

RESISTANCE TO CHEMOTHERAPEUTIC AGENTS

Resistance to antineoplastic chemotherapy is a combined characteristic of a specific drug, a specific tumour, and a specific

Table 2: Classification of Cytotoxic Chemotherapeutic Agents

Group	Drug	Uses	Adverse Effects
Alkylating Agents			
Classical	Cyclophosphamide	Lymphomas, acute leukaemia, breast cancer, childhood tumours, e.g. rhabdomyosarcoma, PNET	Myelosuppression, nausea/vomiting, alopaecia haemorrhagic cystitis
	Ifosfamide	Lymphomas, sarcomas, germ cell tumours, etc.	Haemorrhagic cystitis, neurotoxicity, nausea, alopaecia, mild myelosuppression
	Busulfan	As a part of conditioning regimen for stem cell transplantation (CML-not used routinely now)	Cumulative myelosuppression, sterility, pulmonary fibrosis
	Chlorambucil	CLL, Indolent B cell NHL	Myelosuppression, mild gastrointestinal upset
	Melphalan	Multiple myeloma, as part of high-dose therapy for stem cell transplantation	Myelosuppression, mucositis (in high doses), nausea/vomiting, alopaecia
	Thiotepa	Cancers of breast, ovary and intracavitary for malignant effusions	Myelosuppression, chemical cystitis (during intravesical administration)
Nitrosoureas	Carmustine (BCNU)	Astrocytoma, as part of high-dose therapy for stem cell transplantation, especially for lymphomas	Delayed myelosuppression,nausea/vomiting, hypotension (with rapid administration), mucositis, interstitial lung disease
	Lomustine (CCNU)	Astrocytoma	Delayed myelosuppression,nausea/vomiting, mucositis, interstitial lung disease, secondary leukaemia
Platinum compounds	Cisplatin (CDDP)	A wide variety of tumours	Nausea/vomiting, nephrotoxicity, peripheral neuropathy, ototoxicity, hypomagnesaemia
	Carboplatin	Nearly same as cisplatin	Thrombocytopaenia, nausea, hypersensitivity
	Oxaliplatin	Colorectal cancer, gastic, pancreatic, and biliary cancers	Peripheral neuropathy, acute dysaesthesias, allergic reactions
	Satraplatin	Prostate cancer	Myelosuppression
Antitumour antibiotics	Actinomycin D	Sarcomas, gestational trophoblastic neoplasms, Wilms' tumour, germ cell tumours	Myelosuppression, nausea/vomiting, alopaecia, hyperpigmentation, radiation recall
	Bleomycin	Lymphomas, germ cell tumour, malignant effusion	Pulmonary fibrosis, hypersensitivity, fever, hyperpigmentation of skin
	Mitomycin C	Breast cancer and stomach cancer	Haemolytic uraemic syndrome, myelosuppression, nausea, alopaecia
Topoisomerase Inhibitors			
Epipodophyllotoxins	Etoposide (VP-16)	Testicular cancer, Lung cancer, lymphomas, ALL, AML	Myelosuppression, nausea, hypotension (with rapid infusion), mucositis
	Teniposide	ALL, lymphomas	Myelosuppression, nausea, mucositis
Camptothecin derivatives	Irinotecan	Colorectal cancer, small cell lung cancer	Diarrhoea, myelosuppression
	Topotecan	Ovarian cancer, small cell lung cancer	Myelosuppression, nausea
Anthracyclins	Daunorubicin	Acute leukaemias (AML,ALL)	Cardiotoxicity, myelosuppression, nausea, vomiting
	Doxorubicin	ALL, NHL, HL, breast cancer, ovarian cancer, stomach cancer	Cardiotoxicity, myelosuppression, nausea/vomiting, radiation recall
	Epirubicin	Breast cancer, gastric cancer	Cardiotoxicity, myelosuppression, nausea, vomiting
	Idarubicin	AML	Cardiotoxicity, myelosuppression, nausea/vomiting
Mitotic Spindle Agents			
Taxanes	Paclitaxel	Ovarian cancer, breast cancer, lung cancer	Peripheral neuropathy, myelosuppression, hypersensitivity
	Docetaxel	Cancers of breast and lung	Myelosuppression, fluid retention, alopaecia, mucositis
	Ixabepilone	Metastsatic breast cancer	Myelosuppression, alopaecia, peripheral neuropathy
Vinca alkaloids	Vincristine	ALL, NHL, HL, sarcomas	Peripheral neuropathy, paralytic ileus, constipation, jaw pain
	Vinblastine	HL, germ cell tumour	Myelosuppression, abdominal cramps, jaw pain
	Vinorelbine	Cancers of breast, lung, ovary	Myelosuppression, nausea, allergic-type pulmonary reactions
	Vindesine	Leukaemias	Myelosuppression, peripheral neuropathy

Contd...

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Group	Drug	Uses	Adverse Effects
Antimetabolites			
Pyrimidine analogues	Cytarabine	AML, ALL, NHL	Myelosuppression, nausea, mucositis, cerebellar toxicity (in high dose), fever
	5-Flourouracil (5-FU)	Cancers of breast, colon, oesophagus, stomach, head and neck	Myelosuppression, mucositis, diarrhoea, reversible cerebellar toxicity
	Capecitabine	Cancers of breast,colon, gall bladder	Diarrhoea, hand foot syndrome
	Uracil/Tegafur	Same as 5-FU	Diarrhoea, hand foot syndrome
	Gemcitabine	Cancers of pancreas, lung, ovary, urinary bladder, breast	Myelosuppression, nausea, flu-like syndrome
Purine analogues	6- Mercaptopurine	ALL (maintenance)	Myelosuppression, mild nausea, reversible cholestasis
	6- Thioguanine	ALL and AML	Myelosuppression, mucositis, diarrhoea
	Cladarabine	Hairy cell leukaemia, Indolent B cell NHLs	Myelosuppression,immunosuppression with decreased CD4 cells
	Fludarabine	CLL, Indolent B cell NHLs	Myelosuppression (may be prolonged), prolonged immunosuppression
	Pentostatin	Hairy cell leukaemia	Myelosuppression, immunosuppression, altered taste
Miscellaneous Agents			
Others	Methotrexate	Gestational trophoblastic neoplasia (GTN), ALL, lymphomas (NHL), Osteosarcomas	Renal dysfunction, myelosuppression, mucositis
	Pemetrexed	Mesothelioma, non-squamous lung cancer	Myelosuppression, hand foot syndrome, mucositis
	L- Asparaginase	ALL	Hypersensitivity reactions, hepatic dysfunction, coagulopathy, hyperglycaemia, encephalopathy
	Procarbazine	CNS lymphoma, astrocytoma	Prolonged myelosuppression, flu-like syndrome
	Dacarbazine	HL, sarcomas	Myelosuppression, flu-like syndrome, phlebitis, mucositis
	Temozolamide	Glioblastoma	Myelosuppression, nausea
Immuno-modulators	Thalidomide	Multiple myeloma	Constipation, somnolence, peripheral neuropathy, venous thrombosis
	Lenalidomide	Multiple myeloma, myelodysplasia	Myelosuppression, venous thrombosis, diarrhoea
Proteasome inhibitors	Bortezomib	Multiple myeloma, refractory NHL (Mantle cell)	Peripheral neuropathy, thrombocytopaenia, fatigue, diarrhoea

PNET = Peripherol neuroectodermol tumour; CLL = Chronic lymphocytic leukoemio; NHL = Non-Hodgkin's lymphomo; ALL = Acute lymphoblostic leukoemio; AML = Acute myeloblostic leukoemio; HL = Hodgkin's lymphomo

host, whereby the drug is ineffective in controlling the tumour without excessive toxicity. Resistance to chemotherapeutic drugs has been postulated to arise either from cells not being in the appropriate phase of the cell cycle to allow drug lethality, or from decreased uptake, increased efflux, metabolism of the drug, or alteration of the target, e.g. by mutation or over expression. Indeed, p170 (p170 P-glycoprotein; *mdr* gene product) was recognised from experiments with cells growing in tissue culture as mediating the efflux of chemotherapeutic agents in resistant cells. Certain neoplasm, particularly haematopoietic tumours, have an adverse prognosis if they express high levels of p170, and modulation of this protein's function has been attempted by a variety of strategies.

COMBINATION CHEMOTHERAPY

Combination chemotherapy using conventional cytotoxic agents is aimed to provide maximal cell kill and to prevent and/or slow the development of drug resistance. It provides a broader range of interaction between drugs and tumour cells with different genetic abnormalities in a heterogeneous tumour population. Certain principles have been useful in guiding the selection of drugs in the most effective drug combinations, and they provide a paradigm for the development of new drug programmes.

1. Only drugs known to be partially effective against the same tumour when used alone should be selected for use in combination.
2. When several drugs of a class are available and are equally effective, a drug should be selected that has toxicity that does not overlap with the toxicity of other drugs to be used in the combination.
3. Drugs should be used at their optimal dose and schedule, and drug combinations should be given at consistent intervals. Because long intervals between cycles negatively affect dose intensity, the treatment-free interval between cycles should be the shortest possible time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow.
4. There should be a clear understanding of the biochemical, molecular, and pharmacokinetic mechanisms of interaction between individual drugs in a given combination, to allow for maximal effect.

Precautions During Administration of Chemotherapy

Most of the chemotherapeutic drugs are available as parenteral therapy for intravenous administration. Different solvents might be required (normal saline for cisplatin while D5W for its analogues like carboplatin and oxaliplatin). The clinician, pharmacist, and the nurse should be aware of this and a readily available chart must be kept at the work-place. As a rule of thumb, not to mix two chemotherapeutic agents in a single solvent pouch so as to avoid incompatibility. The duration of administration as per the protocol, provided in the literature should be adhered to unless a new approach is explored in an

experimental protocol. Drugs to be administered through different routes (e.g. methotrexate for intrathecal route and vincristine for IV route) must be kept in separate trays. It is uncommon but anecdotal cases have been reported where vincristine (highly vesicant drug) has been administered by intrathecal route with fatal outcome.

Extravasation

This is defined as the leakage or infiltration of drug into the subcutaneous tissues. Vesicant drugs that extravasate are capable of causing tissue necrosis or sloughing. Irritant drugs cause inflammation or pain at the site of extravasations. Common signs and symptoms of extravasation are pain or burning at the intravenous site, redness, swelling, and inability to obtain a blood return, and change in the quality of the infusion. Any of these complaints or observations should be considered symptom of extravasation(s) until proved otherwise. Common drugs with vesicant and irritant properties are tabulated in **Table 3**.

Following guidelines are helpful in the management of extravasation.

1. Stop administration of the chemotherapeutic agent.
2. Leave the needle/catheter in place and immobilise the extremity.
3. Attempt to aspirate any residual drug in the tubing, needle, or suspected extravasation site.
4. Administer the appropriate antidote (**Table 3**). This may include instillation of a drug antidote or application of heat or cold to the site.
5. Provide the patient and/or caregiver with instructions, including the need to elevate the site for 48 hours and the continuation of antidote measures as appropriate.

Table 3: Common Vesicant and Irritant Drugs and Potential Antidotes

Chemotherapeutic Agent	Pharmacologic Antidote	Non-pharmacologic Antidote
Doxorubicin, daunorubicin epirubicin, darubicin, mitoxantrone	None	Topical cooling
Vincristine, vinblastine vinorelbine	Hyaluronidase 150 units/1 mL SC	Warm compresses
Etoposide (VP-16)	None	Warm compresses
Paclitaxel	None	Topical cooling
Cisplatin, oxaloplatin	Sodium thiosulphate	None
	Case reports of use of anti-inflammatory drugs and high dose dexa-methasone	Case reports of topical cooling but may make neuropathy worse

6. Discuss the need for further intervention with the physician, and photograph, if indicated.
7. Document extravasation occurrence according to institutional guidelines.
8. Continued monitoring of extravasation site at 24 hours, 1 week, 2 weeks, and additionally as guideline recommends.

Secondary complications, such as infection and pain may occur. Follow-up photographs at these periods, if possible, are helpful in monitoring extent of injury and progress in healing.

Hormonal Therapy

The family of steroid hormone receptor-related molecules has emerged as prominent targets for small molecules useful in the treatment of cancers. When bound to their ligands, these receptors can alter gene transcription and, in certain tissues, induce apoptosis. Certain cancers are very sensitive to hormonal treatment. Common examples are steroids for lymphomas, leukaemia (ALL, CLL), myeloma, anti-androgen agents for prostate cancer, and anti-estrogens for breast cancer.

Glucocorticoids

Glucocorticoids are generally given in 'pulsed' high doses in leukaemia and lymphomas, where they induce apoptosis in tumour cells. Commonly used steroids are prednisolone, methylprednisolone, and dexamethasone. While using such high doses of steroids, one need to remember common complications of steroids like Cushing's syndrome, inadvertent adrenal suppression, hyperglycaemia, and infections particularly fungal and pneumocystis pneumonia and herpes reactivation.

Anti-Oestrogens

Tamoxifen is a partial estrogen receptor antagonist; it has a ten fold greater anti-tumour activity in patients with breast cancer, whose tumours express oestrogen receptors than in those who have low or no level of expression. Tamoxifen is commonly used for patients with breast cancer expressing estrogen receptors, as adjuvant therapy in both pre- and post-menopausal women for at least 5 years after surgery. Side effects include a somewhat increased risk of oestrogen-related cardiovascular complications, such as thrombo-embolic phenomenon, and a small but increased risk (1.5 times compared to population) of endometrial carcinoma, which appears after chronic use (usually more than 5 years).

Aromatase

It refers to a family of enzymes that catalyse the formation of estrogen in various tissues, including the ovary and peripheral adipose tissue and some tumour cells. Aromatase inhibitors are of two types, the irreversible steroid analogs, such as exemestane and the reversible inhibitors such as anastrozole or letrozole. Anastrozole is superior to tamoxifen in the adjuvant treatment of breast cancer in post-menopausal patients with estrogen receptor-positive tumours. Letrozole treatment affords benefit following tamoxifen treatment. Adverse effects of aromatase inhibitors may include an increased risk of osteoporosis.

Progestins

Medroxyprogesterone and megesterol acetate have some activity in breast and endometrial cancers. They act by disrupting hypothalamic pituitary-gonadal axis, and thus, alter expression of oestrogen receptors or have androgenic effect. Main adverse effects are fluid retention, hepatic dysfunctions, and increased risk of thromboembolic events.

Anti-Androgens

Prostate cancer is classically treated by anti-androgens. Bilateral orchiectomy is the standard treatment in metastatic prostate cancer. If orchiectomy is not accepted by the patient, testicular androgen suppression can also be effected by lutenising hormone–releasing hormone (LHRH) agonists such as leuprolide and goserelin. These agents cause tonic stimulation of the LHRH receptor, with the loss of its normal pulsatile activation resulting in decreased output of lutenising hormone by the anterior pituitary. Therefore, as primary hormonal manipulation in prostate cancer, one can choose orchiectomy or leuprolide, but not both. The addition of androgen receptor blockers, including flutamide or bicalutamide is of additional benefit; the combined use of orchiectomy or leuprolide plus flutamide is referred to as *total androgen blockade*.

Others

Adrenocortical carcinomas can cause Cushing's syndrome as well as syndromes of androgen or oestrogen excess. Mitotane can counteract these by decreasing synthesis of steroid hormones. Islet cell neoplasms can cause debilitating diarrhoea, treated with the somatostatin analogue octreotide. Prolactin-secreting tumours can be effectively managed by the dopaminergic agonist bromocriptine.

MOLECULAR TARGETED THERAPY

A number of molecular targets have been identified during the past decade. These targets often play a key role in the signal transduction pathway that regulates tumour cell growth, proliferation, migration, angiogenesis and apoptosis. Molecular targeted therapy is a broad term comprising of several classes of agents including tyrosine kinase inhibitors and monoclonal antibodies (MAbs) (**Table 4**).

Tyrosine Kinase Inhibitors

Tyrosine kinase (TK) plays a key role in the transduction of the signals within cellular cascades that are responsible for the regulation of gene transcription within the nucleus. Tyrosine

Table 4: Molecular Targeted Therapy

Drug	Indication	Mechanism of Action	Adverse Effects	Dose
Bcr-Abl tyrosine kinase inhibitors (TKI)				
Imatinib	CML, c-Kit +unresectable or metastatic GIST	Inhibition of Bcr-Abl, c-Kit receptor and PDGF TK, thereby inhibiting cell proliferation and induction of apoptosis	Oedema (fluid retention) nausea, rash and musculoskeletal pain	CML CP-400 mg/day; CML AP/BC - 600-800 mg/ day; GIST 400-600 mg/day
Dasatinib	CML CP/AP/BC, Both as first line and second line	Multi-targeted TKI affecting BCR-ABL, the SRC family, c-KIT, EPHA2 and PDGFR tyrosine kinases	Myelosuppression, oedema/fluid retention, nausea, fatigue, rarely QTc prolongation	70 mg twice daily
EGFR Inhibitors				
Gefitinib	Locally advanced or metastatic NSCLC	Inhibits intracellular phosphorylation of the EGFR tyrosine kinase	Acneform rash, GI upset (diarrhoea, nausea, vomiting and anorexia) and rarely, interstitial lung disease	250 mg daily
Erlotinib	Locally advanced or metastatic non-small cell lung cancer, metastatic carcinoma pancreas	Inhibits intracellular phosphorylation of the EGFR TK	Gastrointestinal upset (diarrhoea, nausea, vomiting and anorexia), mucositis, acneform rash, fatigue and rarely deep vein thrombosis	150 mg daily for NSCLC 100 mg daily for pancreatic cancer
Cetuximab	Metastatic colorectal cancer and squamous cell carcinoma of head and neck	Binds to extracellular domain of the EGFR	Acneform rash, dry skin, fissuring, malaise, and rarely, interstitial lung disease	Loading dose: 400 mg/ m^2/IV followed by 250 mg/m^2 once every week
HER 2 Inhibitors				
Trastuzumab	Breast cancer over expressing HER2/neu protein (both adjuvant and metastatic setting)	Binds to extracellular domain of the HER2/neu protein	Infusion-related reactions (fever, chills), and cardiomyopathy	Loading dose of 4 mg/kg IV followed by 2 mg/kg once every week
VEGF Inhibitors				
Sunitinib	Metastatic renal cell carcinoma	Inhibits multiple tyrosine kinases including VEGFR 1, 2 and 3; SCF (-KIT); PDGFR and FMS	Hypertension, rash, hand foot syndrome and yellow skin discolouration	50 mg daily for 4 weeks in a 6-week cycle
Bevacizumab	Metastatic colorectal cancer	Recombinant humanised Mab that binds and neutralizes VEGF	Hypertension, proteinuria, impaired wound healing and thromboembolic events	5-10 mg/kg IV every 2 weeks
Raf tyrosine kinase inhibition				
Sorafenib	Advanced renal cell carcinoma	Multi-targeted TKs	Rash, hand foot syndrome, hypertension, fatigue and rarely, thromboembolism	400 mg twice daily

Contd...

Contd...

Drug	Indication	Mechanism of Action	Adverse Effects	Dose
Other Monoclonal Antibodies				
Alemtuzumab	Chronic lymphocytic leukaemia	Anti-CD52 antibody	Hypotension, rash, fever, chills, pancytopaenia and rarely pulmonary fibrosis	Initial dose 3 mg IV, to be increased to 30 mg daily once tolerated. Maintenance dose: 30 mg three times a week
Rituximab	CD20 + NHL	Anti-CD20 antibody	Cytokine release syndrome (Hypotension, fever, chills, bronchospasm, urticaria and angioedema), myelosuppression	375 mg/m^2 IV 3 to 4 weekly
Ofatumumab	Chronic lympocytic leukaemia, follicular NHL	Anti-CD20 antibody	Infusion reactions, progressive multifocal encephalopathy, reactivation of hepatitis B	12 doses administered as follows: 300 mg dose (dose 1), followed 1 week later by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses
Gemtuzumab ozogamicin	Relapsed/refractory acute myeloid leukaemia	Anti-CD33 antibody conjugated with a cytotoxic antitumour antibiotic, calicheamicin	Infusion related reactions VOD cerebral haemorrhage, epistaxis, and rarely, ARDS	9mg/m^2 on day 1 and 15 every 4 weeks

PDGF = Platelet-derived growth factors; CML = Chronic myelogenous leukaemia; GIST = Gastrointestinal stromal tumour; SRC = steroid receptor co-activator; EPHA = Ephrin type A2; ARDS = Acute respiratory distress syndrome; TK = Tyrosine kinase; EGFR = Epidermal growth factor receptor; GI = Gastrointestinal; NSCLC = Non-small cell lung cancer; IV = Intravenous; SCF = Stem cell factor; FMS = McDonough Feline sarcoma virus; NHL = Non-Hodgkin's lymphoma; VOD = Veno-occlusive disease

kinases (TKs) are further classified into receptor or non-receptor tyrosine kinases. Examples of receptor tyrosine kinase include epidermal growth factors (EGFR) (ERB/HER) family members, vascular endothelial growth factor receptors, and platelet derived growth factor receptors. Example of the non receptor tyrosine kinase includes BCR-ABL, c-Kit, and c-Src.

Monoclonal Antibodies

Monoclonal antibodies (MAbs) are targeting agents that recognise the cell surface proteins/receptors as antigens, particularly on the surface of the tumour cells. There are three main classes of MAbs: conjugated, unconjugated, and radioimmunoconjugate. Commonly used targeted therapy, their uses, mechanisms of action, adverse effects, and doses are summarised in **Table 4**.

Unconjugated MAbs directly affect the signalling pathways by inhibiting ligand-receptor interactions. These may also indirectly stimulate host defense mechanism, such as antibody dependent cellular cytotoxicities (ADCC). Examples of unconjugated MAbs include rituximab, trastuzumab, cetuximab, alemtuzumab, and bevacizumab.

Conjugated MAbs are MAbs combined with protein toxins or cytotoxic agents. Examples of conjugated MAbs include gemtuzumab ozagamicin and deninleukin difitox. Radioimmunoconjugates are MAbs in combination with radioisotopes intended to deliver a sterilising dose of radiation to the tumour and include ibritumomab tiuxetan and tositumomab.

MAbs are manufactured from multiple sources of B-lymphocyte (i.e. murine, human, and primate). Murine MAbs are derived entirely from mice. Chimeric MAbs are composed of murine variable regions of the antibody with a constant region derived from human, making 65% to 90% of the agent of human origin. Humanised MAbs consist of variable and constant region derived from humans with complementary determining regions from mice, making approximately 95% of the agent of human origin. Human MAbs are derived entirely from humans.

The United States Adopted Names (USAN) council has developed guidelines for the nomenclature of the MAbs for standardisation purposes. In general, the product source identifiers precede the suffix *–mab*. **Table 5** lists the product source identifiers.

Table 5: Product Source Identifiers

Source	Identifiers
Human	- u -
Mouse	- o -
Rat	- n -
Humanised	- zu -
Pimate	- i -
Chimeric	- xi -

CONCLUSIONS

Development of targeted therapy (molecules) have already made significant impact in the management of certain diseases, e.g. imatinib mesylate, a TKI, is now the first-line of drug in the management of all phases chronic myeloid leukaemia. Similarly, development of immunomodulators, e.g. thalidomide and lenalidomide and immunomodulators have revolutionised the management of multiple myeloma. The EGFR inhibitors for non-small cell lung cancer, sunutinib for renal cell cancer are other examples which have made significant impact in the management of these cancers. Among monoclonal antibodies, rituximab and trastuzumab have been incorporated along with chemotherapy in the first-line management of B-cell NHL and

Her-2-neu positive breast cancer, respectively. Many more agents are currently under phase-I and II trials are likely to enter in phase-III studies in the coming years. Optimising regimens/schedule with or without concurrent chemotherapy with aim to reduce the toxicities, and the development of resistance are likely to be areas of research in future studies.

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21.5 Principles of Radiotherapy

GK Rath

INTRODUCTION

Radiotherapy is defined as the treatment of diseases (mostly malignant) with ionising radiation. It is relatively a new subject as compared to other medical specialties. However, there is no other medical field which had more speedy evolution than radiation oncology.

RADIATION PHYSICS

Radiation therapy produces its effect by depositing the energy in the tissues. The source of radiation can be either radioactive isotopes or high energy X-rays or electrons. The other forms of radiation energy which are relatively less common in use are neutrons, protons, and heavy ions. Radioactive isotopes occur naturally and can be generated artificially. Becquerel recognised radioactivity in 1896 and is honoured by having the unit of activity named after him. The activity of a radioisotope decays over time. Its energy spectrum, decay spectrum, and half-life characterise the isotope. A particular isotope may decay via the production of alpha particles or beta particles, through electron capture, internal conversion, or a combination of these reactions. The commonly used radioactive isotopes are enlisted in **Table 1**, along with their physical characteristics.

The basis of radiation therapy is the interaction of ionising particles (X-rays, γ rays, or electrons) with tissues at the molecular level. This interaction depends on the energy created by the production of secondary charged particles, usually electrons, which can break chemical bonds and inflict cellular injury. The interaction of a photon beam with matter results in the attenuation of the beam. Five major types of interactions typically occur, namely, coherent scattering, photoelectric effect, Compton scattering, pair production, and photo-disintegration. The particular type of interaction is related to photon energy. In radiation therapy, the photoelectric effect, Compton effect, and pair production are of interest, with the Compton effect being the predominant interaction.

Table 1: Radioactive Isotopes with their Characteristics

Isotope	Half-life	Energy (MeV)
Ra-226	1600 years	0.047 to 2.45 (0.83 avg)
Co-60	5.26 years	1.17,1.33
Cs-137	30 years	0.662
Ir-192	74.2 days	1.36 to 1.06 (0.38 avg)
I-125	60.2 days	0.028 avg

Photoelectric effect involves the interaction of the photon with the tightly bound inner electrons and is proportional to the cube power of the absorbing matter's atomic number. This interaction is responsible for the different radiographic densities seen on diagnostic radiographs.

Compton effect involves interaction with outer electrons that are bound more loosely. This effect is related to electron density and, therefore, results in much more uniform tissue absorption than lower energy photons. In radiation therapy, Compton effect predominates; therefore, the contrast observed on therapy port films is inferior to diagnostic radiographs.

Pair production involves interaction of the photon with the atomic nuclear electromagnetic field. This interaction becomes significant at high energies (>10 MeV) and is proportional to the atomic number of the absorbing matter.

UNITS OF RADIATION

The dose of radiation absorbed correlates directly with the energy of the beam. Therefore, an accurate measurement of absorbed dose is critical in radiation treatment. The deposition of energy in tissues results in damage to DNA and diminishes or eradicates the cell's ability to replicate indefinitely. The basic unit of radiation absorbed dose is the amount of energy (Joules) absorbed per unit mass (kg). This unit, known as the gray (Gy), has replaced the unit of rad used in the past (100 rads = 1 Gy; 1 rad = 1 cGy).

In order to measure dose in a patient, one must first measure the ionisation produced in air by a beam of radiation. This quantity is known as exposure. One can then correct for the presence of soft tissue in the air and calculate the absorbed dose in grays. The dose absorbed by tissues due to these interactions can be measured and plotted to form a percentage depth dose curve. As energy increases, the penetrative ability of the beam increases and the skin dose decreases.

RADIATION BIOLOGY

The exact mechanism of cell death due to radiation is still an area of active investigation. Double-stranded breaks of nuclear DNA is the most important cellular effect of radiation. This breakage leads to irreversible loss of the reproductive integrity of the cell and eventual cell death.

Radiation damage can be directly ionising; however, in clinical therapy, damage is most commonly indirectly ionising via free-radicals produced from the radiolysis of cellular water.

Radiation can also affect the processes of the cell cycle necessary for cell growth, cell senescence, and apoptosis (programmed cell death). Many of these processes are only now beginning to be understood and manipulated to make radiation therapy more effective.

The therapeutic mechanism for radiation is based on the intrinsic ability of cells to repair damage and the ability of the radiation oncologist to take advantage of any geometric separation between the malignant and non-malignant tissues.

A logarithmic curve of survival versus dose characterises cell survival after exposure. The curve forms an initial shoulder followed by a logarithmic decline in survival, which varies with the dose. Sublethal damage, which must be overcome with each

fraction of radiation therapy, is thought to cause the initial shoulder. Repeated small doses of radiation are less damaging to a sensitive cell than a single fraction of equivalent total dose. Manipulation of the cellular environment can alter the shape of the survival curve.

In addition to the intrinsic cellular radiosensitivity, cell survival is found to be related to oxygen concentration, position of the cell in the mitotic phase, and dose rate. These features are responsible for the 4 *R*'s of radiobiology, viz. repair, redistribution, repopulating, and reoxygenation.

CLINICAL USE OF RADIATION

Radiation therapy is administered to those cancers where there is a selective ability for the radiation to destroy cancer cells while allowing the adjacent normal cells to repair themselves from injury. Cancer cells vary in their sensitivity to destruction by radiation. This sensitivity depends on the origin of the cancer. For example, skin cancer is generally more sensitive, meaning more easily destroyed, than a cancer originating in the brain.

In addition, cancer cells in the same tumour may vary in their sensitivity to radiation depending on their location in the mass. Generally, the outer areas of the tumour are more sensitive. This is related to the amount of oxygen reaching the cancer. The peripheral regions are better oxygenated and are destroyed more easily than tumour cells at the centre. Some cancers, such as melanoma, are usually resistant to radiation therapy and little or no benefit is achieved by using it.

The goal of radiation can be first, curative or radical in which radiation therapy is given with the intent of eradicating the tumour; second, palliative, that is, to alleviate or reduce symptoms of pain; and third, adjuvant where radiation is delivered after the primary treatment like surgery to reduce the risk of tumour recurrence.

There are basically two types of radiation treatment; external beam radiation therapy (EBRT) and brachytherapy. A patient may receive one or the other, or a combination of both EBRT or teletherapy which signifies treatment of patient when the source of radiation lies outside the body. The various equipments of EBRT are linear accelerator (**Figure 1**), telecobalt unit, etc. The treatment with EBRT spares the skin (skin sparing effect). Linear accelerator is preferred for the treatment of deep seated tumours like thoracic tumours, pelvic tumours, etc. Telecobalt unit is the backbone of any radiotherapy department in developing countries like India because it is cost-effective and requires low maintenance cost. Modern sophisticated equipments like stereotactic radiotherapy (X-knife) and stereotactic radiosurgery (gamma knife) are expensive machines but very useful in selective patients.



Figure 1: Linear accelerator.

EBRT treatment with conventional fractionation is done once a day with 1.8 to 2.0 Gy, 5 times a week and lasts for about 5 to 7 weeks. Majority of the tumours require EBRT doses in the range of 50 to 70 Gy (**Table 2**). It is a painless and non-invasive procedure. Inoperable patients can be treated with reasonably good results. Radiotherapy can be given on emergency basis in certain situations like severe bleeding from cervical cancer, spinal cord compression, etc. The irradiated organs are preserved in contrast to the surgical treatment. The treatment can be carried out on an outpatient department basis. Disadvantages of radiotherapy include prolonged treatment and associated toxicity in some patients.

Table 2: Radiation Dose Schedules for Different Tumours

Tumour	Radiotherapy Doses (Gray [Gy])
Head and neck	60 to 70
Cervix	80 to 90
Breast	50 to 60
Seminoma	25 to 35
Lymphomas	25 to 45
Brain	50 to 60
Lung	50 to 60
Wilm's tumour	10 to 20
Soft tissue sarcoma	60 to 70
Oesophagus	60 to 65
Ewing's sarcoma	45 to 55
Anal canal	50 to 55

Brachytherapy is the treatment with radioactive material implanted into the tumour bearing area. The various radioactive materials used are Iridium-192, Cesium-137, Iodine-125 and Palladium-103, etc. Currently, the brachytherapy treatment is performed with the help of remote afterloading units (**Figure 2**) where there is no risk of radiation exposure to the staff. Brachytherapy has the advantage of delivering high dose of radiation in shorter time simultaneously sparing the surrounding normal structures. The usual treatment with low dose rate brachytherapy takes about 3 days and requires one or such fractions. On the other hand, high dose rate brachytherapy treatment is delivered in minutes but multiple fractions (average 3 to 7 fractions) are required. The tumours where brachytherapy is preferred are cancers of cervix, endometrium, oesophagus, head and neck and chest wall tumours.

EFFECTS OF RADIATION ON NORMAL TISSUES

Radiation effects on normal tissues are divided into acute and chronic effects. Acute effects occur during the course of therapy and during the follow-up period (approximately 2 to 3 weeks after the completion of a course of irradiation). Chronic effects can manifest after 6 months to 1 year of the treatment. Every tissue or organ tolerates a certain dose of radiation beyond which it shows significant deleterious



Figure 2: Remote afterloading brachytherapy unit.

effects. **Table 3** shows the radiation tolerance of different organs in the human body.

The mucous membranes of the oral cavity and the oropharynx respond early to fractionated radiation. Erythema is often evident after 1 week of treatment at conventional doses. This condition progresses over the next few weeks through various stages of mucositis, ranging from small patches to confluent or even ulcerated areas. Healing begins while the patient is still undergoing treatment but may continue for several weeks after the radiation is completed.

Table 3: Normal Tissue Tolerance of Various Organs to Fractionated Conventional Radiotherapy

Organ	Radiation Tolerance (Gy)
Kidney	23
Femoral head	52
Spinal cord	45
Brainstem	50
Eye lens	10
Lung	30
Parotid	32
Heart	40
Liver	30

Loss of taste is a common acute effect of radiation treatment in the head and neck area. Taste loss begins early and progresses rapidly during the 3rd to 5th week of treatment. Patients may report diminished acuity, odd sensation, or complete absence of taste. Xerostomia is often present and exacerbates this loss of taste. This condition is often accompanied by loss of appetite and weight loss. Recovery of taste is a slow and, frequently, an incomplete process.

The major salivary glands (i.e. parotid and submandibular glands) are responsible for nearly 80% of salivary production. The parotid glands primarily consist of serous acini, while the submandibular glands produce mucinous and serous secretions. The minor salivary glands, which are distributed throughout the oral mucosa, produce mostly mucinous secretions. The loss of salivary function is usually complete after modest doses of radiation to the parotid glands. The basal flow rates correlate with the response to radiation therapy. With 40 to 60 Gy, fewer than 20% of patients have a measurable salivary flow. For patients receiving fewer than 30 Gy, some function may return after 6 to 12 months. However, at dose levels exceeding 50 Gy, xerostomia usually is irreversible. Dry mouth is probably the most common problem for patients who receive therapeutic doses of radiation. Numerous approaches have been tried to address this problem. Pilocarpine 5 mg three times a day has been shown to stimulate residual salivary function. Some patients use artificial saliva substitutes, but most patients find them inadequate.

Skin effects, which were at one time dose-limiting, are rarely a problem. While erythema is common after several weeks of radiation, severe skin reactions, such as those observed in the orthovoltage era, are uncommon. Even with megavoltage treatment, skin tanning, and dry desquamation can occur. The addition of certain chemotherapeutic drugs can enhance skin and other effects.

The late effects of radiation can be a source of ongoing morbidity from a course of radiation therapy. Just as with the acute effects, the chronic effects are related to site, dose, volume, and time. Other therapies, such as surgery and chemotherapy, can increase the probability and severity of radiation-related morbidity.

RECENT ADVANCES IN RADIOTHERAPY

There have been significant advances in radiotherapy in the recent years. Delivery of radiotherapy has become very precise and has moved from conventional planning approach to more and more conformal approaches. The main advantages of these are that we are able to give more and more dose to the tumour, at the same time limiting the dose to the normal structures. Intensity modulated radiotherapy is a type of conformal radiotherapy where we can modulate the intensity of the radiation within the beam leading to a better dose distribution inside the tumour. Image guidance for delivering radiation has come into a routine practice now which is called image guided radiotherapy. This technique helps to rectify errors of positioning of the patient or due to organ motion. There have also been tremendous advances in the stereotactic approach in the delivery of radiation. In stereotactic radiotherapy we deliver fractionated radiation to a target to ablate the tumour. In stereotactic radiosurgery which is done by gamma-knife or a linear accelerator, single sitting of ablative dose is given in a sterotactic set up. Stereotactic body radiotherapy (SBRT) is a new approach in treating very small lesions anywhere in the body. SBRT is highly promising and has the potential to replace surgery for early stage lung cancers.

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21.6 Head and Neck Cancers

VP Gangadharan

INTRODUCTION

Head and neck cancers, a heterogeneous group of neoplasms involving mucosal surfaces of the lips, tongue, oral cavity, pharynx, nasopharynx, hypopharynx, larynx, and paranasal sinuses, are typically squamous cell carcinomas and have distinct clinical presentations and prognosis and management. Patients who present with early stage disease (stage I and II) are treated with radiation therapy (RT) or surgery. Stage III or stage IV disease requires a multidisciplinary approach with chemotherapy, radiation, and surgery.

EPIDEMIOLOGY AND AETIOLOGY

Head and neck cancers are among the 10 most frequent cancers in the world. These constitute 12% of male and 7% of female cancers in the developing world and 7% of male and 2% of female cancers in the developed world. The age-standardised rates of head and neck cancers in 1990, in males exceeds 30 per 100,000 in regions of France, Hong Kong, India, Central and Eastern Europe, Spain, Italy, Brazil and among US Blacks. High rates (more than 10 per 100,000) in females are found in India, Hong Kong, and Philippines. Head and neck cancers are amongst the top five cancers in almost all parts of India.

Smoking, particularly *bidi* smoking, alcohol drinking, and chewing betel quid with tobacco are main aetiologic factors for head and neck cancers in India. Epstein-Barr virus infection is associated with nasopharyngeal carcinoma which occurs endemically in some countries of the Mediterranean and Far East. Incidence of second primary cancers in upper aerodigestive tracts of patients with head and neck cancers is about 5% at the time of diagnosis and 20% subsequently. The multiple synchronous and metachronous neoplasms suggest that the entire respiratory mucosa is predisposed to carcinogens, so is at risk of development of pre-malignant or malignant lesions (so called field defect).

MOLECULAR PATHOLOGY

Mutations in tumour suppressor genes (commonly p53 gene) and alterations involving chromosomes 3, 9, 13, and 17 have been identified in both pre-malignant and malignant head and neck cancers. Amplification of oncogenes is less common.

CLINICAL PRESENTATION AND STAGING

The manifestations vary according to the stage and primary site of the tumour. Oral cavity cancers present as non-healing ulcers or painful lesions. White (leucoplakia) or red (erythroplakia) plaques may represent dysplasia, hyperplasia or carcinoma *in situ* and must be differentiated from candidiasis (can be wiped off) or lichen planus (white lines related to denture irritation). Tumours at the base of tongue or oropharynx cause alteration in speech and tongue mobility. Cancers of nasopharynx, oropharynx, or hypopharynx rarely show early symptoms. Hoarseness of voice may be an early symptom of laryngeal cancer. High-risk patients (>40 years of age, history of tobacco or alcohol abuse) with non-specific manifestations in head and neck need thorough otolaryngologic examination, particularly if symptoms persist longer than 2 to 4 weeks.

Advanced head and neck cancers cause pain, bleeding, otalgia, serous otitis, sinusitis, nasal obstruction, cranial neuropathies, dysphagia, odynophagia, trismus, decreased tongue, mobility, fistulas, skin involvement and massive unilateral and bilateral cervical lymphadenopathy.

Physical examination includes inspection of all visible mucosal surfaces and palpation of the floor of mouth, tongue, and neck. All visible lesions should be biopsied and the patient should have complete otolaryngological examination.

Staging work-up documents the extent of disease and excludes coincident second primary cancers or pre-malignant lesions in upper aerodigestive tract. It includes endoscopic examination of nasopharynx, larynx, hypopharynx, cervical oesophagus and proximal trachea with multiple biopsies of high-risk areas (nasopharynx, pharyngeal tongue, tonsillar fossa, and pyriform sinus) particularly in patients without obvious primary tumour. A chest radiograph and a computed tomography (CT) or magnetic resonance imaging (MRI) from the base of the skull to the thoracic inlet can be performed. Patients with cervical lymphadenopathy and no detectable primary should undergo excision biopsy of suspected lymph nodes if fine needle aspiration cytology fails to reveal the tumour.

TNM staging system of the American Joint Committee on Cancer is used to classify head and neck cancers. This classification varies according to the specific anatomic subsites. Head and neck cancers have a high tendency to spread to adjacent sites and to the cervical lymph nodes. Distant metastases are found in less than 10% of patients at initial diagnosis.

TREATMENT

The choice of treatment depends not only on stage but also on the specific site of the disease. It is important to maintain adequate nutrition, to treat opportunistic infections and to have adequate dental care and hygiene during the treatment.

Localised Disease

Less than one-third of the patients present with early lesions without detectable lymph node involvement or distant metastases. Such cases are treated with curative intent by surgery or RT. Generally, RT is preferred for laryngeal cancers to preserve voice, and surgery is preferred for oral cavity lesions to avoid long term-complications of RT, such as xerostomia and dental decay. Overall, 5-year survival rate is 60% to 90%.

Most head and neck cancers (except cancers of vocal cord, paranasal sinuses, lip, and salivary gland) have high incidence of occult cervical node metastases; therefore require treatment to ipsilateral neck either with RT or cervical lymph node

dissection (radical, modified radical or selective), even if nodes are not clinically involved.

Radical RT dosage is 70 Gy in 35 fractions over 7 weeks. Brachytherapy can be used as a definitive treatment for early stage tumours or combined with external beam RT in more advanced lesions in selected tumours (tongue, floor of mouth, tonsil, and nasopharynx) with excellent results.

Loco-Regionally Advanced Disease

Combined modality treatment including surgery, RT, and chemotherapy can produce 5-year survival in 30% to 40% patients with large primary tumours or lymph node metastases. Sequencing of treatment may vary. Chemotherapy may be administered before (neoadjuvant or induction), during (concurrent) or after (adjuvant) RT or surgery.

Induction chemotherapy

Induction chemotherapy followed by definitive RT in chemotherapy-responders is indicated for patients with cancer of the larynx and hypopharynx who wish to preserve their larynx. This strategy allows for tumour reduction and organ preservation in almost half of survivors. Compared to surgery plus RT, this modality results in decreased frequency of subsequent distant metastases. However, survival is not improved.

Intravenous cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil (5-FU) (1,000 mg /m^2 per day) as continuous intravenous infusion for 5 consecutive days (days 1 to 5), repeated every 3 weeks, is the most common regimen. The overall response rate is 85% with a 40% complete remission rate; two-thirds of clinical complete remissions are found to be in pathologic complete remissions in resected specimens. Taxanes (paclitaxel or docetaxel) can be added to PF-based induction therapy to improve survival, minimise toxicity, and increase the rate of organ preservation. Response varies by site, with the larynx and nasopharynx being most responsive and oral cavity the least responsive.

Adjuvant chemotherapy

Adjuvant chemotherapy, given after the patient is rendered disease-free, may benefit selected subset of patients with high risk of local recurrence (positive resection margins, more than 1 positive lymph nodes, extracapsular spread of tumour).

Concurrent chemoradiotherapy

The rationale for simultaneous chemoradiation is based on experimental evidence of synergism between chemotherapy and RT to kill tumour cells. Compared with sequential chemotherapy and RT, concomitant chemotherapy plus RT is associated with increased toxicity, and is considered for patients with good performance status. Meta-analysis of randomised trials in head and neck cancers has shown survival benefit of 8% at 5 years for patients receiving concomitant chemotherapy with 5-FU and RT.

Targeted therapy

Most research in this area is focused on epidermal growth factor receptor (EGFR) inhibitors. Cetuximab (anti-EGFR antibody) in combination with radiation has been approved in treatment of patients with locally advanced head and neck cancers.

Recurrent or Metastatic Disease

These patients are generally treated with palliative chemotherapy; response rates average 30% to 50% with duration of response only 3 months. Patients generally die within 6 months. Drugs like methotrexate, 5-FU, cisplatin, paclitaxel, and docetaxel are used either as single or in combination.

Various treatment options for head and neck cancers are summarised in **Figure 1**.

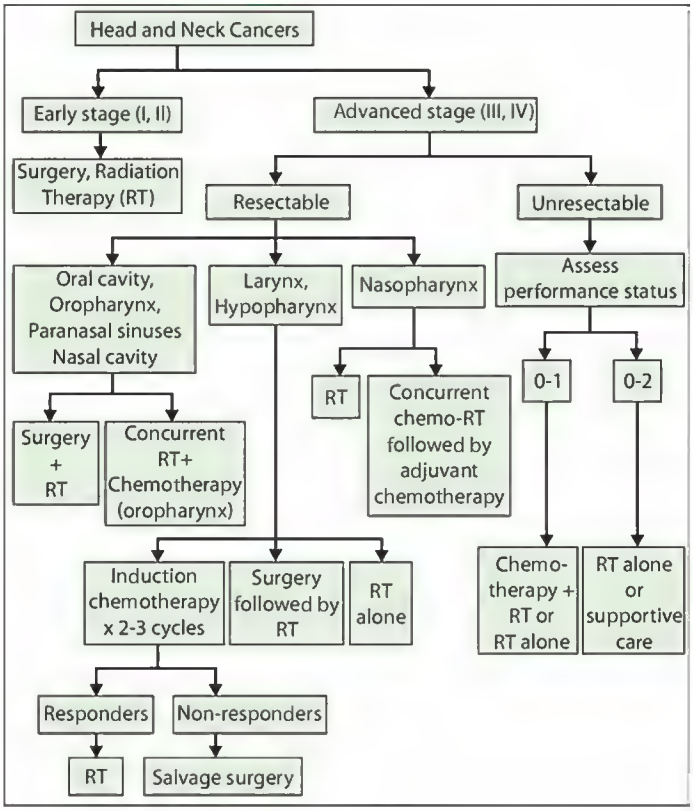


Figure 1: Treatment of squamous cell carcinoma of head and neck.

Adverse Effects of Treatment

Radical surgery results in cosmetic and functional deformity and speech impediment. Acute sequelae of RT include mucositis and dysphagia; chronic sequelae include xerostomia, loss of taste, cataract, mandible necrosis, neck fibrosis, and second malignancies. Chemotherapy complications vary with the regimen but usually include myelosuppression, stomatitis, diarrhoea, nausea, vomiting, and nephrotoxicity (with cisplatin). Post-treatment rehabilitation should be emphasised.

SALIVARY GLAND TUMOURS

The parotid tumours account for 80% of salivary gland neoplasms in adults and about 75% of these are benign. In contrast, nearly half of the tumours arising in submandibular or minor salivary glands are malignant including mucoepidermoid, adenoid cystic or adenocarcinoma. Benign tumours are usually treated with surgery while invasive tumours need both surgery and RT. Malignant tumours may recur regionally; distant metastases may occur as late as 10 to 20 years post-treatment. For metastatic disease, chemotherapy (doxorubicin alone or in combination with cisplatin) is given with palliative intent.

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21.7 Breast Cancer

Vinay H Deshmane

INTRODUCTION

The last decade has seen rapid advances in our understanding of breast cancer, facilitated by numerous clinical trials, and an ever expanding knowledge of the molecular changes associated with malignancy. More importantly, these advances have been translated into clinical practice. Tumours can now be classified on the basis of their molecular signatures, which are being used to determine prognosis and treatment. There is an increasing array of drugs available for treatment and newer surgical techniques to enable breast preservation. This increased range of options has resulted in an individualised approach to the treatment of breast cancer.

EPIDEMIOLOGY AND AETIOLOGY

Breast cancer is common in the West where women have a lifetime risk of 1:8. In India, the lifetime risk is lower although the incidence is rising. In 2008, the Indian Cancer Society population based registry recorded 100,000 new cases, and 52,000 deaths due to breast cancer. The lifetime risk in the city of Mumbai has increased from 1:27 a few years ago, to 1:22. The urban-rural divide persists with cervical cancer being the commonest female cancer in rural areas. However, in the cities of Mumbai, Delhi, Chennai, and Bangalore breast cancer has overtaken cervical cancer to become the commonest cancer in women. The cause of this change remains unknown, and has loosely been attributed to a 'Western lifestyle'. However it may be attributed to increasing awareness, access to mammography and an economically increasing middle-class, with access to medical care.

Various factors incriminated to increase the risk of breast cancer are presented in **Table 1**. The other factors are age, sex, lifestyle (Western lifestyle), high fat diet, and increase in body mass index.

Table 1: Risk Factors for Breast Cancer Development

Factors	Relative Risk
BRCA mutation	3.0 to 7.0
Breast density	1.8 to 6.0
ADH on prior biopsy	3.7
Bone density	2.7 to 3.5
Age at first birth	1.9 to 3.5
Mother or sister with breast cancer	2.6
Age at menopause	2.0
Prior benign biopsy	1.7
Postmenopausal BMI	1.7
Age at menarche	1.4
Alcohol	1.4
HRT	1.2 to 1.4
OCP	1.2 to 1.4

BRCA = Breast cancer gene; ADH = Atypical ductal hyperplasia; BMI = Body mass index; HRT = Harmane replacement therapy; OCP = Oral cantraceptive pills.

A past history of a benign breast biopsy may also be associated with an increased risk of breast cancer. In the biopsy, changes in cell morphology and presence of proliferation are pointers to the risk.

PATHOLOGY

The majority of breast cancers start from the ductal epithelium, which extends from the nipple to the terminal duct unit situated in the breast lobule. The major histological subtypes are ductal and lobular carcinoma. The classification is shown in **Table 2**.

All invasive carcinomas with the exception of medullary carcinoma are graded (**Table 2**) using the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) based on morphological features (tubule formation, nuclear pleomorphism, and mitotic count). The grade of the tumour is determined by, assigning a value of 1 (favourable) to 3 (unfavourable) for each feature, and adding together the scores for all the three categories.

Table 2: Histopathologic Types and Grades

WHO classification of breast cancer	
Non-invasive carcinoma	
Ductal carcinoma *in situ*	
Lobular carcinoma *in situ*	
Invasive carcinoma	
Invasive ductal carcinoma	
Invasive lobular carcinoma	
Mucinous carcinoma	
Medullary carcinoma	
Papillary carcinoma	
Tubular carcinoma	
Adenoid cystic carcinoma	
Secretory (juvenile) carcinoma	
Apocrine carcinoma	
Carcinoma with metaplasia (metaplastic carcinoma)	
Inflammatory carcinoma	
Other (specify)	
Paget's disease of the nipple	
The Nottingham combine histopathologic grade (G)	
GX	Grade cannot be assessed
G1	Low combined histologic grade (favourable)
G2	Intermediate combined histologic grade (moderately favourable)
G3	High combined histologic grade (unfavourable)

More recently a classification based on molecular signatures has been proposed (**Table 3**). Gene expression profiling studies have identified four major subtypes, viz. luminal A, luminal B, HER2, and basal-like. These subtypes reflect clinical features, response to therapy and treatment outcome. Luminal A and B express hormone receptors, account for 70% of the breast cancers and have a good prognosis, although luminal B are usually higher grade and may express human epidermal growth factor receptor

2 (HER2). They respond to hormone treatment (A better than B) and have a variable response to chemotherapy (B better than A). HER2 cancers (15%) have a high HER2 receptor expression and are generally ER/PR negative. They tend to respond to trastuzumab and anthracycline based chemotherapy and are associated with a poor prognosis. Basal-like breast cancers are associated with the worst prognosis. These demonstrate a high expression of basal epithelial genes, basal cytokeratins, and low expression of estrogen receptor, progesterone receptor, and HER2. These constitute 15% of the breast tumours, are often referred to as 'triple negative' tumours, have a poor prognosis and do not respond to either hormonal treatment or trastuzumab. The basal-like phenotype is commonly seen with BRCA-1 associated breast cancers. Platinum-based chemotherapy is being increasingly used to treat this subset of cancers.

Table 3: Molecular Classification of Breast Cancer

Based on gene expression profiles	
Luminal A	
Luminal B	
HER2	
Basal - like	
Based on immunohistochemical markers (ER, PR and HER2)	
Luminal (A and B)	ER/PR +ve; HER2 –ve
HER2	ER/PR –ve; HER2 +ve
Basal-like	ER –ve, PR –ve, HER2 –ve (Also called triple negative)

ER = Oestrogen receptor; PR = Progesterone receptor; HER2 = Human epidermal growth factor receptor 2.

Although classifying breast tumours based on gene expression is of interest, a more practical classification is based on the presence of immunohistochemical markers, viz. oestrogen receptor, progesterone receptor, and HER2. These are used as surrogate markers to reflect the molecular subtypes on gene expression. Luminal (A and B) are ER/PR positive and HER2 negative, HER2 cancers are ER or PR negative and HER2 positive, while basal-like are ER, PR and HER2 negative.

NATURAL HISTORY OF BREAST CANCER

Breast cancers may grow at different rates. However on an average, these are considered to be slow growing. It is estimated that by the time a breast cancer lesion assumes the size of 1 cm it has been in the body for a period of 7 to 10 years. It spreads by direct extension to surrounding tissue, via lymphatics and by the blood stream. The ipsilateral axillary lymph nodes are the commonest site of involvement. Other sites of involvement include the internal mammary lymph nodes especially in medial quadrant tumours and the supraclavicular nodes. Distant organs commonly involved are the lungs, liver, brain, and bones.

CLINICAL FEATURES

The commonest presentation is that of a lump in the breast, frequently situated in the upper outer quadrant of the breast. It may be associated with skin changes, which are subtle to begin with and become more pronounced as the lesion grows. In late disease, the classical appearance of 'peau de orange' is noted. Other symptoms include a vague lumpy area, breast pain, nipple discharge, nipple retraction, nipple eczema, swelling of the breast and a lump in the axilla. On occasion, patients may present with symptoms suggestive of disseminated disease, such as weight loss, bone pains, ascites or headache and vomiting.

DIAGNOSIS

The diagnosis of breast cancer rests on a detailed history and examination. Confirmation is by pathological evaluation. This may be easily achieved by fine needle aspiration cytology (FNAC). FNAC provides a cytological diagnosis but is unable to differentiate between non-invasive and invasive cancer. A core needle biopsy or an open biopsy (incisional/excisional) provides adequate tissue for a definitive histopathological diagnosis.

Imaging modalities, viz. mammography, ultrasonography and magnetic resonance imaging (MRI) provide complementary information. Mammography is a soft tissue X-ray of the breast in two directions (mediolateral and craniocaudal). It can detect microcalcifications, which may be the earliest sign of breast cancer and is the modality of choice for breast cancer screening. However, it is known to miss 10% to 15% of all breast cancers. Ultrasonography is used as an adjunct to mammography. It is especially useful in dense breasts and in young women, where mammography is of limited use. However, it is less sensitive than mammography and not recommended as a screening modality.

Magnetic resonance imaging is the most sensitive technique to detect breast cancer. It is useful in ruling out local recurrence after breast conserving treatment (BCT) and in evaluation of indeterminate masses. It is the preferred modality for screening high-risk women and is used to rule out multicentric disease in patients considered for BCT.

Triple Diagnosis

To minimise mistakes, the concept of 'triple diagnosis' is used in the diagnosis of breast cancer. Based on a review of clinical findings, fine needle aspiration and imaging studies confirmed that the diagnosis of cancer is only made if all three modalities are definitely indicative of the presence of breast cancer. If there is a lack of complete agreement between all the three components, then histological proof (core biopsy/incisional biopsy/excisional biopsy) should be obtained before a definitive diagnosis of breast cancer can be made.

Staging

Following diagnosis, the stage of the disease is determined by investigations, such as serum alkaline phosphatase, liver enzymes, an ultrasound evaluation of the liver, and a chest X-ray. A CT scan of thorax and abdomen and an isotope bone scan are indicated in selected patients. A PET scan may also be performed in individualised cases, however, its routine use is not recommended at the moment. Current recommendations suggest clinical staging with mammography and liver function tests, based on which patients are classified into low risk and high risk for occult metastases and locally advanced breast cancer. Further investigations are advised on an individualised basis.

The Manchester system and the TNM system (Tumour, Node and Metastases) staging system [American Joint Committee on Cancer (AJCC) classification] are used to stage the disease (**Table 4**).

MANAGEMENT

Management of breast cancer is based on the stage of the disease. The overall scheme is determined on whether the disease is early

and localised to the breast and axillary lymph nodes (loco-regional disease/operable cancer), extensive local disease (locally advanced breast cancer [LABC]) or associated with visceral/bony metastases. Treatment is multi-disciplinary and based on a combination of local treatment (surgery and radiotherapy) and systemic treatment (chemo-, hormone, and targeted therapy).

Table 4: Staging of Breast Cancer (Manchester and TNM Classification)

	T		N		M
Manchester Stage	**Tumour Grade**	**Clinical Extent (cm)**	**Node Grade**	**Clinical Extent**	**Distant Metastases**
TIS	Tis	No palpable tumour	N0	No nodal metastases	M0 = no known distant metast-ases
I	T1	<2	N0	No nodal metastases	
II	T2	2 to 5	N1	Mobile axillary lymph nodes	
III a	T3	>5	N2	Fixed axillary lymph nodes/ Internal mammary involvement	
III b	T4	Any size with skin/ chest wall invasion	N3	*N3a:* Infra-clavicular *N3b:* Internal mammary and axillary *N3c:* Supra-clavicular lymph node involvement	
IV					M1 = distant metast-ases

TNM stage grouping			
Stage	**T**	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
II A	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
II B	T2	N1	
	T3	N0	
III A	T0	N2	
	T1	N2	
	T2	N2	
	T3	N1	
	T3	N2	
III B	T4	N0	
	T4	N1	
	T4	N2	
III C	Any T	N3	
IV	Any T	Any N	M1

EARLY BREAST CANCER/ OPERABLE BREAST CANCER

The aim of treatment is to cure, control the disease in the breast and axilla, and conserve form and function.

In early disease, surgery with or without adjuvant radiation therapy is adequate for local control of the disease. If the primary tumour size is small there is a choice of surgical procedures, viz. BCT or modified radical mastectomy (MRM). The extent of surgery whether BCT or MRM is based on a detailed discussion of the advantages and disadvantages with the patient. Both approaches result in comparable results in terms of local and systemic control resulting in equal long-term survival. Data from breast conservation trials have confirmed BCT to be safe in selected patients.

Surgery

Modified radical mastectomy consists of removal of the entire breast with lymph nodes in the axilla. The extent of lymph node dissection may vary from complete clearance to less extensive procedures. More recently, the concept of sentinel lymph node biopsy has been introduced. However, this should only be undertaken in specialised centres.

Breast conservative treatment (BCT) consists of a wide excision of the breast lump with negative margins and an axillary dissection (in continuity or through a separate incision). Every patient undergoing BCT is advised adjuvant radiation therapy to the breast, which is usually administered for a period of 6 weeks. Shorter durations of radiation therapy, as well as intraoperative radiation therapy are being evaluated and should be considered experimental at the moment.

Oncoplastic surgery refers to the integration of plastic surgery techniques with excisional surgery. It encompasses minor techniques to maintain aesthetic breast shape and size following lump excisions, to reconstructions following mastectomy.

Radiation Therapy

This is administered in daily fractions to the breast ± regional lymph node basin. The usual dose is 50 Gy in the form of external radiation (with or without a boost to the local tumour bed). Indications for post-operative radiotherapy include all patients undergoing BCT and certain patients undergoing MRM, viz. large primary lesions greater than 5 cm, multiple involved axillary lymph nodes and those with poor prognostic features in the primary lesion, viz. lymphovascular invasion, high-grade lesions.

Systemic Treatment

Systemic therapy is decided on the risk of developing recurrent disease. The risk is calculated on the basis of age, menopausal status, tumour characteristics (size, grade, lymphatic invasion/ vascular invasion, margins of excision), lymph node status (number of positive nodes, extra-nodal spread), hormone receptor status of the primary lesion (oestrogen, ER and progesterone, PgR receptor status) as well as the epidermal growth factor receptor Cerb B2 (Her2 neu) status. Computerised programmes (*Source*: www.adjuvant.com) which can estimate the risk of failure are available to guide clinical decision making.

All patients who have a primary tumour which is greater than 1 cm in size and a tumour grade greater than 1 are advised some form of systemic treatment. Systemic therapy may be in the form of chemotherapy, hormone therapy, targeted therapy or a combination of these. 'Oncotype Dx' and 'Mammaprint' are molecular profiling tests which classify patients into high risk,

intermediate risk, and low risk of recurrence categories with the aim of individualising treatment decisions.

Chemotherapy

Chemotherapy is administered at 3 weekly intervals. It is usually multi-drug and multi-cycle. The common adjuvant regimen used is FEC (5-fluorouracil, epirubicin, and cyclophosphamide). Taxol is increasingly used for aggressive disease. Chemotherapy usually consists of 6 cycles; however, there are alternative regimens that utilise 4 and 8 cycles. Other dose dense and dose intensive regimens are also available.

Hormone Therapy

Hormone therapy is considered in hormone receptor positive tumours. Pre-menopausal women are advised tamoxifen 20 mg per day and post-menopausal women either tamoxifen (20 mg) or one of the aromatase inhibitors, e.g. anastrozole 1 mg per day, letrozole 2.5 mg per day, exemestane 25 mg per day. Hormone therapy is advised for a period of 5 years.

Surgical or medical oophorectomy using [luteinising hormone-releasing hormone (LHRH) agents] provides another avenue of treatment in premenopausal women who are hormone receptor positive. An oophorectomy may be combined with tamoxifen or an aromatase inhibitor to provide 'complete receptor blockade'.

Targeted Therapy

Targeted therapy in the form of monoclonal antibody to the epidermal growth factor receptor (EGFR, trastuzumab) may also be added as adjuvant treatment in patients who overexpress the Cerb B2/HER2 neu receptor. The treatment is recommended for a period of 1 to 2 years at 3 weekly intervals.

During chemotherapy and targeted therapy, it is essential to monitor patients carefully, as there is significant toxicity associated with these agents.

LOCALLY ADVANCED BREAST CANCER

The aim of treatment is to control micrometastatic disease and to downstage the size of the primary lesion to increase cure rates and to decrease the extent of local surgical procedures. This is achieved by systemic treatment. Both chemotherapy and primary hormone treatment are associated with excellent response rates. Following downstaging of the disease, surgery is undertaken to optimise local control. This is followed by further systemic treatment (chemo-/hormonal/targeted therapy) and radiotherapy.

An important development has been the feasibility of breast conservative surgery in patients who respond well to systemic therapy. Numerous studies have demonstrated that it is safe to offer breast conservation to patients whose tumours have adequately decreased in size following primary systemic therapy. However, the option should be carefully discussed with the patient, and if there is any doubt, it is probably better to proceed with a mastectomy.

METASTATIC BREAST CANCER

In the presence of metastasis (visceral or bone involvement) the primary modality of treatment is systemic (chemotherapy or hormonal therapy) as the aim is to control disseminated disease. The accepted practice is to start with systemic chemotherapy. However, recent data indicate that hormonal treatment may be effective in carefully selected post-menopausal women who are strongly hormone receptor positive. Once the metastatic disease is adequately controlled, attention is directed towards control of the disease in the breast. Treatment options include mastectomy or breast conservation in selected cases, viz. small primary lesion presenting with metastases. If the mastectomy is associated with a loss of skin cover, it may be accompanied by reconstructive measures. Radiation therapy is administered to patients with extensive local disease and all patients who undergo breast conservation.

Palliative radiation therapy to sites of bony metastases is useful in controlling the disease. Bisphosphonates, viz. zoledronic acid infusions are also administered at regular intervals for control of skeletal symptoms and to prevent fractures. Surgery may be indicated for stabilisation of pathological fractures or vertebral collapse.

PROGNOSIS

The prognosis of breast cancer does not depend on its chronological age but on its metastatic potential. A range of factors including tumour size grade, receptor status, proliferation markers and oncogene product measurements are assessed. Microarrays are used to prognosticate breast tumours into high, intermediate and low risk, based on their genetic profiles. The best clinical indicators of prognosis are lymph nodal status and tumour size.

Survival ranges from 80% to 90% at 10 years for stage I disease, 60% to 70% for stage II, 40% to 55% for stage III, and 10% to 20% for stage IV disease.

HIGH-RISK STATES AND BREAST CANCER PREVENTION

Women who are carriers of BRCA 1 and 2 mutations, or who have a family history consistent with genetically transmitted breast cancer are considered to be at a higher risk than the general population. Presence of lobular carcinoma *in situ* or atypical hyperplasia in a breast biopsy is also considered as an indicator of a high-risk state.

Assessment of such patients involves a detailed evaluation of the level of risk using certain "risk models" (e.g. Gail, Brcapro, etc.). Based on the level of risk, the patient is counselled. Management options include increased surveillance, medical interventions (viz. anti-oestrogen therapy) or surgical interventions such as a prophylactic oophorectomy or bilateral prophylactic mastectomy.

BREAST CANCER SCREENING AND METHODS FOR EARLY DIAGNOSIS

The main methods for the early diagnosis of breast cancer include screening mammography of the breasts, clinical breast examination, and breast self-examination (BSE).

Current recommendations of the American Cancer Society for early diagnosis include BSE once a month starting at the age of 20, clinical breast examinations about once every 3 years for women in their 20s and 30s and yearly for those over 40 years and yearly mammograms after the age of 40. Magnetic

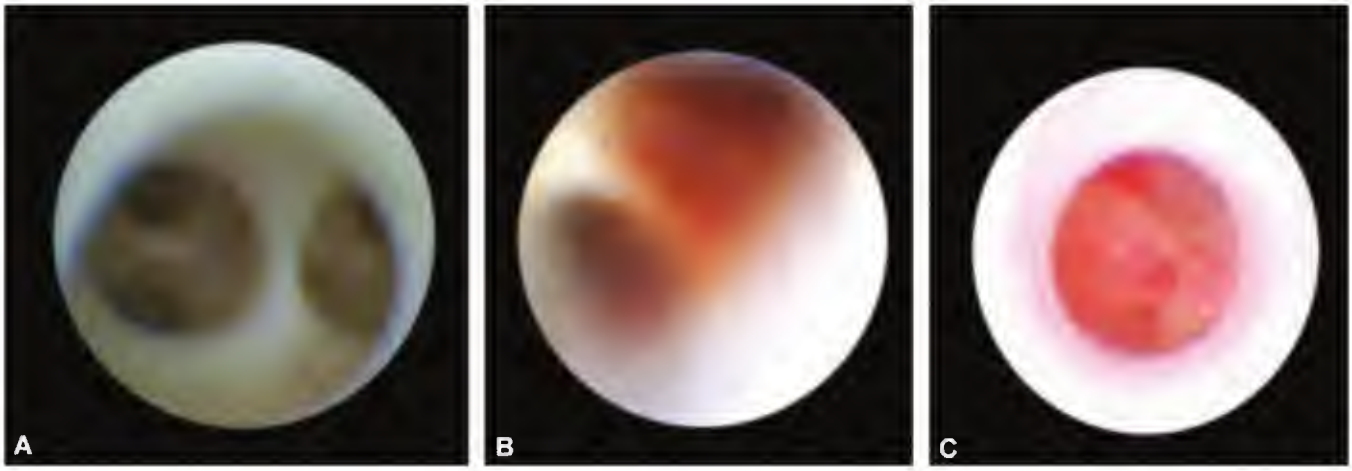


Figure 1: Appearance of ducts on mammary ductoscopy. (A) Normal ductal bifurcation; (B) Intra ductal bleeding; (C) Intraductal growth.

resonance imaging screening is recommended for women with a 20% to 25% or greater life-time risk of breast cancer.

NEWER DEVELOPMENTS: MAMMARY DUCTOSCOPY

Mammary ductoscopy (**Figure 1**) is a new technique in which a microendoscope just a mm in diameter is inserted into breast ducts to visualise early epithelial abnormalities. Ductal washings can be collected and tissue biopsy obtained (much like a bronchoscope). The role of this technique is being evaluated and early data indicate that it is likely to be most useful in assessing patients with nipple discharge. Appearances on ductoscopy of normal ducts, intraductal bleeding and early intraductal growths are shown in **Figure 1**. Lesions identified on ductoscopy can be excised for definitive histological diagnosis, providing an exciting avenue for the early diagnosis of breast cancer.

RECOMMENDED READINGS

1. Harris JR, Lippman ME, Morrow M, *et al*. In: Harris JR, Lippman ME, Morrow M, editors. *Diseases of the Breast;* 4th Ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
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21.8 Tracheobronchial and Lung Cancers

Kirti M Patel

LUNG CANCER

The term lung cancer is used for tumours arising from the respiratory epithelium (bronchi, bronchioles and alveoli). It is one of the commonest malignant neoplasms all over the world. (**Table 1**). It accounts for more cancer deaths every year than breast, colon and prostate cancer combined. As per records in different registries in India, there is an increase in incidence of lung cancer owing to the widespread use of cigarettes (**Table 2**).

Table 1: Incidence of Common Cancers – World, Developed and Developing Countries

Rank	World	Developed Countries	Developing Countries
Males			
1	Lung	Lung	Lung
2	Stomach	Prostate	Stomach
3	Prostate	Colon/rectum	Liver
4	Colon/rectum	Stomach	Oesophagus
5	Liver	Bladder	Colon/rectum
Females			
1	Breast	Breast	Breast
2	Uterine cervix	Colon/rectum	Uterine cervix
3	Colon/rectum	Lung	Stomach
4	Lung	Stomach	Lung
5	Stomach	Corpus uteri	Colon/rectum

cadmium, polonium, hydrazine and vinyl chloride. Thus, smoking prevention and cessation is better to save many lives than advances in diagnosis or treatment.

Occupational, exposure to asbestos, radon, hydrocarbons, chromium, nickel, and arsenic also increase risk of cancer. The risk in smokers who are exposed to asbestos is increased 90 folds. Other risk factors include recurrent lung inflammation, lung scar, and family history of lung cancer.

Lung cancer occurs principally between the ages of 45 and 65 years. Initially, partial obstruction by tumour, may lead to obstructive emphysema of the lobe or segmental atelectasis. Later,complete obstruction may cause collapse of the lobe predisposing to secondary infection or abscess distal to carcinoma. Pleura may be involved directly or by lymphatic spread. Invasion of chest wall, intercostal nerves or the brachial plexus causes severe pain. The tumour may spread into the mediastinum and invade or compress the pericardium, oesophagus, superior vena cava, trachea, phrenic, or left recurrent laryngeal nerves. Lymphatic spread to supraclavicular and mediastinal lymph nodes is also frequently observed. Metastases commonly occur in liver, bone, brain, adrenals, and skin. A small primary tumour with widespread metastatic deposits is characteristic of small cell type lung cancer (**Figure 1**).

Table 2: Incidence of Lung Cancer at Gujarat Cancer and Research Institute, Ahmedabad

Year	Lung Cancer						Total Cancers		
	Male	Small cell cancer	Non-small cancer	Female	Small cell cancer	Non-small cancer	Male	Female	Total
2001	767	114	653	106	6	100	6607	4745	11352
2002	680	83	597	99	8	91	6498	4376	10874
2003	734	82	652	93	3	90	7043	4808	11851
2004	632	97	535	78	5	73	6225	4075	10300
2005	568	63	505	67	5	62	6091	4330	10421
2006	416	75	341	54	7	47	5269	3757	9026
2007	526	69	457	78	6	72	6493	4582	11075
2008	543	79	464	72	7	65	6970	4972	11942

AETIOLOGY

Lung cancer appears to develop from stem cells that can differentiate along multiple lines (**Table 3**). Smoking is a major cause as 85% to 95% of patients have a history of smoking. The risk is 30 times greater in smokers than non-smokers. Passive smoking also increases the risk by two folds as does smoking cigars or pipes. The risk is related to cumulative dose and duration of smoking (**Table 4**). Following the cessation of smoking the risk steadily declines but never approaches that of non-smokers. Smoking increases the risk of all histologic types of lung cancer. Cigarette smoke contains various carcinogens such as (1) Polycyclic aromatic hydrocarbons, (2) Heterocyclic compounds, (3) N-nitrosamines, (4) Phenolic compounds, (5) Metals and inorganic compounds like nickel,

Table 3: Aetiological Factors in Lung Cancer

Cigarette smoking	Occupational
Particulate phase	Asbestos
Benzpyrene	Radioactivity (uranium mines, radon)
Benzofluoranthenes	Metal works (nickel, chromium, iron oxide)
Dibenzanthracene	Arsenicals (sheep-dip workers)
Nicotine	
Catechol	
Nickel and cadmium	
Vapour phase	
Nitrogen oxides	
Formaldehyde	
Hydrazine	
Urethane	

Table 4: Cigarette Smoking and the Lifetime Risk of Lung Cancer

Smoking (Pack-years)	Risk of lung cancer (%)
20	1
60	5
90	8
100	13
120	20
>135	33

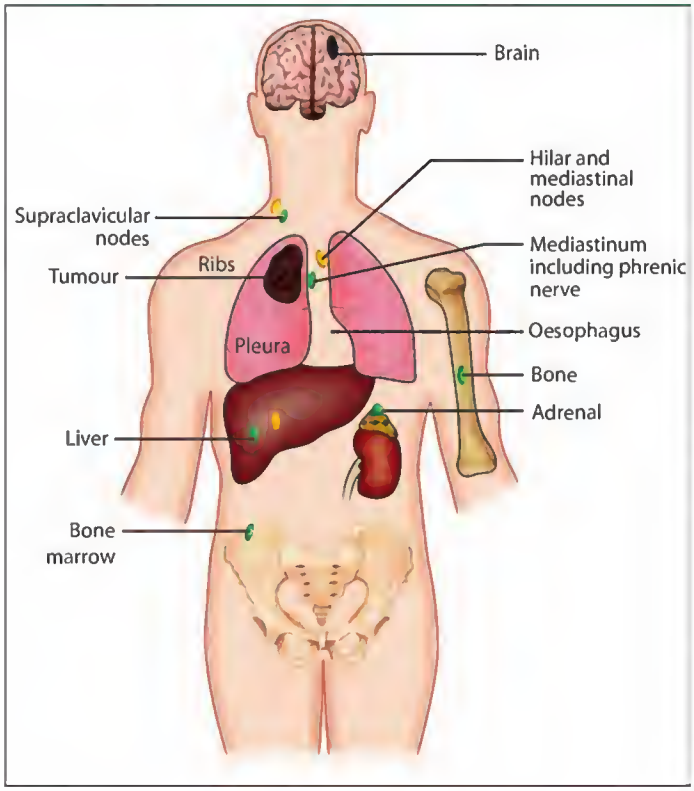


Figure 1: Sites of metastases of lung cancer.

CLASSIFICATION AND PATHOLOGY

The WHO classification of lung tumours is based on progress in the understanding of the biology of these tumours. For therapeutic purpose, it is mainly divided into: Non-small cell lung cancer (NSCLC) which includes squamous (Epidermoid), adenocarcinoma, large cell (large cell anaplastic) (**Table 5**) and small cell lung cancer (SCLC). NSCLC accounts for 80% of total lung cancers. Undifferentiated carcinomas, carcinoids, bronchial gland tumours are rare lung tumours.

Squamous Cell Carcinoma

Represents 30% to 35% of lung cancers. Frequently occurs in smokers and older males. More often central (80%) and relatively slow growing.

Adenocarcinoma

Represents about 40% of the lung cancer cases and often arises in the periphery of the lung parenchyma. It may grow in acinar, papillary, bronchoalveolar or solid growth patterns and produce mucin. It is most common cell type occurring in non-smokers, especially women includes subtypes such as bronchoalveolar adenocarcinoma (BAC).

Bronchoalveolar Carcinoma

It includes only non-invasive tumours where the neoplastic cells spread out along pre-existing alveolar structures (lepidic spread). It may manifest as a solitary peripheral nodule, multifocal disease, or a pneumonic form, with rapid spread from one lobe to another.

Table 5: The Classification of Lung Cancers

Preinvasive lesions
- Squamous dysplasia/carcinoma *in situ*
- Atypical adenomatous hyperplasia

Invasive malignant lesions
- Squamous cell carcinoma (SCC)
- Adenocarcinoma
  - Bronchoalveolar variant
- Large cell carcinoma
- Small cell carcinoma
- Adenosquamous carcinoma
- Carcinoid tumours
- Carcinoma of the salivary gland
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
- Unclassified

It manifests in mucinous and non-mucinous variants. Mucinous BAC is multifocal and fatal. Non-mucinous BAC arises from type II pneumocytes and epidermal growth factor receptor (EGFR) mutations give rise to bronchoalveolar differentiation. It is most common in non-smoking middle-aged Asian women. EGFR mutations confer sensitivity to EGFR tyrosine kinase inhibitors (TKI).

Large Cell Carcinoma

It is poorly differentiated and represents about 5% to 15% of lung cancers. It may occur in any part of the lung. Tumours are usually large when diagnosed with possibility of brain and mediastinal involvement. It is less responsive to chemotherapy and carries a poor prognosis.

Small Cell Carcinoma

Represents 15% to 20% of all lung cancers with strong association with smoking. More often central or hilar (95%) than peripheral (5%). It is more aggressive than NSCLC, grows rapidly with widespread disease at the time of diagnosis. These tumours are made up of small, round cells with large nuclei that stains blue with haematoxylin and eosin, (H and E).

CLINICAL FEATURES

Lung cancer may present in a number of different ways (**Table 6**). When tumour arises in a large bronchus symptoms occur early, but peripheral bronchus tumours can attain a very large size without producing symptoms. Signs and symptoms are caused by local tumour growth, invasion or obstruction of adjacent structures, growth in the lymphnodes or distant metastasis or as a result of non-metastatic paraneoplastic syndromes. Few asymptomatic patients are identified, usually during routine chest radiograph.

Cough, usually dry and brassy, is the commonest early symptom. Later, it may become productive. A change in the character of the 'regular' cough of smoker should always alert the clinician to the possibility of bronchial carcinoma. Repeated episodes of scanty haemoptysis or blood streaking of sputum is a common symptom, especially in tumours arising in large bronchi. Occasionally, central tumours invade large vessels, causing massive haemoptysis, which may be fatal. Breathlessness may reflect occlusion of large

bronchus, resulting in collapse of a lobe or lung or the development of a large pleural effusion. Stridor may occur when spread of tumour to the subcarinal and paratracheal glands cause compression of the main bronchi or lower end of the trachea or rarely, when the trachea is the site of primary tumour.

Pleural pain usually reflects malignant invasion of the pleura. Involvement of the intercostal nerves or brachial plexus may cause pain in chest or upper limb along the corresponding nerve root distribution. Bronchial carcinoma in the apex of the lung (superior sulcus tumour or Pancoast's syndrome) may cause Horner's syndrome (ipsilateral partial ptosis, exophthalmos, miosis and hypohidrosis) due to involvement of the sympathetic chain at or above the stellate ganglion and pain in the shoulder and inner aspect of the arm caused by involvement of the lower part of brachial plexus. Mediastinal spread may result in dysphagia. Symptoms due to metastasis include focal neurological deficits, seizures, personality change, jaundice, bone pain, or skin nodules. Lassitude, anorexia, and weight loss usually indicate the presence of metastatic spread. Paraneoplastic syndromes may precede pulmonary symptoms (**Table 7**).

Table 6: Symptoms and Signs of Lung Cancer

- **Primary Disease**
  - Central or endobronchial tumour growth
    - Cough
    - Sputum production
    - Haemoptysis
    - Dyspnoea
    - Wheeze (classically unilateral)
    - Stridor
    - Pneumonitis, with fever and productive cough (secondary to obstruction)
  - Peripheral tumour growth
    - Pain, from pleural or chest wall involvement
    - Cough
    - Dyspnoea
    - Pneumonitis
- **Regional involvement (either direct or metastatic spread)**
  - Hoarseness (recurrent laryngeal nerve paralysis)
  - Tracheal obstruction
  - Dysphagia (oesophageal compression)
  - Dyspnoea (pleural effusion, tracheal or bronchial obstruction, pericardial effusion, phrenic nerve palsy, lymphatic infiltration, and superior vena cava obstruction)
  - Horner's syndrome (sympathetic nerve palsy)
- **Metastatic involvement (common sites)**
  - Bone involvement
    - Pain, exacerbated by movement or weight bearing; often worse at night
    - Fracture
  - Liver metastases
    - Right hypochondrial pain
    - Icterus
    - Altered mentation
  - Brain metastases
    - Altered mental status
    - Seizures
    - Motor and sensory deficits

PHYSICAL SIGNS

Physical examination may reveal clubbing of fingers and hypertrophic pulmonary osteoarthropathy, characterised by periostitis of the long bones, most commonly the distal tibia, fibula, radius, and ulna. This causes pain and tenderness in the affected joints and often pitting oedema over the anterior aspect of the shin. Radiographs of the bone show sub-periosteal new bone formation. Supraclavicular lymph nodes may be enlarged.

Signs in the chest are variable. Examination is usually normal unless there is significant bronchial obstruction or the tumour has spread to the pleura or mediastinum. Some show physical signs of collapse, segmental or lobar, due to obstruction of a bronchus. A monophonic or unilateral rhonchi (wheeze) suggests the presence of a fixed bronchial obstruction and presence of a stridor indicates obstruction at or above the level of the main carina. A hoarse voice indicates left recurrent laryngeal nerve palsy, nerve paralysis causes unilateral diaphragmatic palsy and hence dullness to percussion and absent breath sounds at the lung base. Initially superior vena cava syndrome presents as bilateral engorgement of the jugular veins and later as oedema affecting the face, neck and arms.

Table 7: Paraneoplastic Syndromes in Carcinoma of Lung

- **Endocrine**
  - Hypercalcaemia
  - Syndrome of inappropriate ADH secretion (SIADH)
  - Cushing's syndrome
  - Carcinoid syndrome
  - Gynaecomastia
  - Hyperthyroidism
- **Neurological**
  - Encephalopathy
  - Subacute cerebellar degeneration
  - Peripheral neuropathy
  - Autonomic neuropathy
  - Lambert Eaton syndrome
  - Polymyositis
  - Optic neuritis
- **Skeletal**
  - Clubbing
  - Hypertrophic pulmonary osteoarthropathy
- **Haematological**
  - Anaemia
  - Pure red cell aplasia
  - Thrombocytopaenia
  - Thrombocytosis
  - Disseminated intravascular coagulation (DIC)
- **Cutaneous**
  - Hyperkeratosis
  - Dermatomyositis
  - Acanthosis nigricans
  - Hyperpigmentation

INVESTIGATIONS

The diagnosis of lung cancer requires detecting the tumour, establishing its cell type and defining the stage of the malignancy.

RADIOLOGICAL EXAMINATION

Chest Radiograph

The presence of lung cancer is usually suggested by abnormalities, viz. unilateral hilar enlargement, peripheral pulmonary opacity, collapse, pleural effusion, broadening of mediastinum, enlarged cardiac shadow, elevation of hemidiaphragm, and rib destruction (**Figure 2**).



Figure 2: Left-sided apical bronchogenic carcinoma.

CT Scan

In addition to confirming abnormalities seen on a plain chest radiograph, this can detect lesions that cannot be resolved on a chest radiograph and has played an important role in a staging mediastinal lesion. Magnetic resonance imaging (MRI) of chest is generally superior to chest computed tomography (CT) in determining the presence of chest wall or vertebral body invasion and superior sulcus tumours. Bone scan, brain CT, abdominal CT, spinal MRI studies are done to detect abnormalities in bones, brain, liver and adrenal glands and changes in vertebrae and involvement of spinal cord.

Positron emission tomography scan

It is more sensitive than CT scan in identifying mediastinal nodal disease and can identify asymptomatic distant metastatic disease in up to 20% of the patients. The high negative predictive value allows non-invasive staging of mediastinal nodes in early stage disease. However, Positron emission tomography (PET)/CT is more sensitive and accurately stages patients with early stage disease and avoids inappropriate surgery. Some low grade malignant tumours, such as bronchoalveolar carcinoma and carcinoid are frequently false negative on PET scan.

Obtaining Pathologic Proof

The diagnosis of lung cancer must be proved by histology or sputum cytology. Repeated sputum cytology is positive in only 60% to 80% of centrally located neoplasms and 15% to 20% of the peripheral ones. It has been replaced by the flexible fibreoptic bronchoscopy for centrally located tumours. CT-guided biopsy is useful for peripheral located tumours (**Figure 3**).

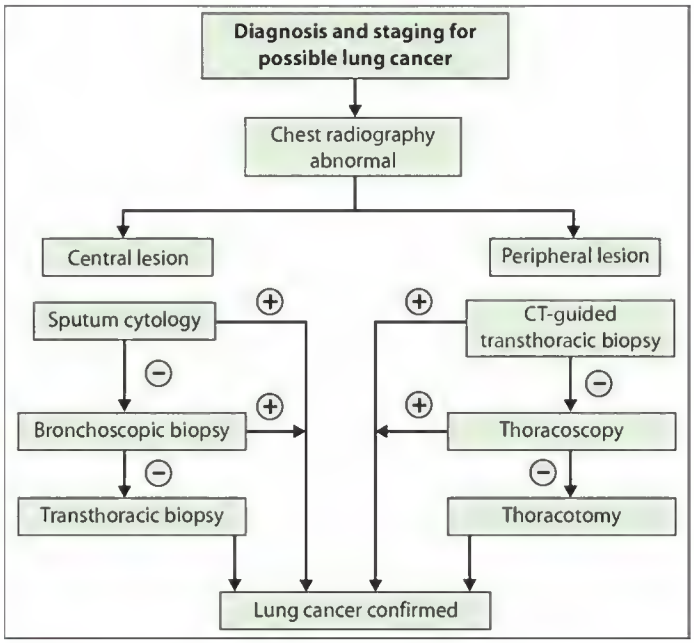


Figure 3: Diagnostic approach for possible lung cancer.

Staging TNM

TNM system is used for NSCLC (**Tables 8 and 9**). Small cell lung cancer (SCLC) is defined as either limited or extensive disease (**Table 10**). Staging evaluation of lung cancer includes history and physical examination, haemogram, biochemistry including electrolytes, liver functions and lactate dehydrogenase, imaging studies of the chest, abdomen, brain and bone scan. Bone marrow aspiration and biopsy is needed in some cases.

Table 8: TNM Staging System for NSCLC

T - Primary Tumour	
T0	No evidence of primary tumour
Tx	Positive cytology but tumour not demonstrable
Tis	Carcinoma *in situ*
T1	Tumour less than 3 cm diameter, no proximal invasion
T2	More than 3 cm but not more than 7 cm, main bronchus ≥ 2 cm from carina, invades visceral pleura, partial atelectasis
T3	Tumour more than 7 cm or of any size with extension into chest wall, diaphragm, mediastinal pleura or within 2 cm of carina, total atelectasis or separate nodules in same lobe
T4	Tumour of any size with invasion of mediastinal organs or vertebral body, carina, trachea, separate nodule in different ipsilateral lobe
N - Regional lymph nodes	
N0	Nodes negative
N1	Ipsilateral hilar, peribronchial nodes
N2	Ipsilateral mediastinal and subcarinal nodes
N3	Contralateral mediastinal or hilar nodes, scalene or supraclavicular nodes
M - Distant metastasis	
M0	No metastasis
M1	Metastasis present Malignant effusion, nodule in contralateral lobe, pleural nodules Distant metastasis

DIFFERENTIAL DIAGNOSIS

Solitary pulmonary nodule on chest radiograph needs to be differentiated from pneumonia, cysts and tuberculosis. Solitary

cavitary lesion on chest radiograph needs to be differentiated from tuberculosis or lung abscess. Differential diagnosis of lung cancer includes metastatic cancer from other organs, lymphoma, or infection.

Table 9: Staging of NSCLC

Stage	TNM Subset
IA	T1a or T1b, N0, M0.
IB	T2a, N0, M0
IIA	T1a or T1b, N1, M0
	T2a, N1, M0
	T2b, N0, M0
IIB	T2b, N1, M0
	T3, N0, M0
IIIA	T1a or T1b, N2, M0
	T2a or T2b, N2, M0
	T3, N1 or N2, M0
	T4, N0 or N1, M0
IIIB	Any T, N3, M0
	T4, N2, M0
IV	Any T any N with M1a or M1b

Table 10: Two Stage Classification for SCLC

Limited Disease (30%)
- Primary tumour confined to one hemithorax
- Can be encompassed in single tolerable radiation field
- Ipsilateral hilar lymph nodes
- Ipsilateral and contralateral supraclavicular lymph nodes
- Ipsilateral and contralateral mediastinal lymph nodes

Extensive Disease (70%)
- Extends beyond ipsilateral hemithorax
- Pleural or pericardial effusion
- Metastasis in the contralateral lung
- Distant metastasis (brain, bone, liver, etc.)

TREATMENT

Treatment varies according to the type of disease, stage and host factors such as age, performance status and the presence of concomitant diseases. Current modalities used in various combinations are surgical resection, radiation therapy and chemotherapy. Radiotherapy and in some cases chemotherapy can relieve distressing symptoms (**Figure 4**).

Surgical Treatment

Anatomic surgical resection (lobectomy, bilobectomy, sleeve lobectomy, or pneumonectomy) with or without regional lymph node resection is considered current standard of care in stage I and II NSCLC who are medically fit to undergo surgery. Cure can only be achieved by surgical resection. Surgical treatment offer 5-year survival rates of >75% in stage I disease and 50% in stage II disease. Post-operative adjuvant therapy is useful to improve the treatment results of these patients. Palliative resections are seldom advisable.

Treatment	Stage							
	IA	IB	IIA	IIB	IIIA	IIIB	IV	Recurrence
Surgery	■	■	■	■				
Radiation Therapy	■	■	■	■	■	■	■	■
Chemoradiation						■		
Palliative chemotherapy						■	■	■
Post op radiation						■		

Figure 4: Treatment in NSCL (Shaded area denotes modality of treatment).

Radiotherapy

Unfortunately in the majority (85%) of cases, surgery is not possible and such patients can be offered only palliative therapy. Definitive radiotherapy is frequently recommended for stage I and II patients for whom surgery is contraindicated. It is also widely used for patients with stage III lesions if the disease is limited to one hemithorax and the ipsilateral supraclavicular lymph nodes. Overall response with radiotherapy is achieved in 35% of the cases. Palliative radiotherapy usually succeeds when given for the relief of haemoptysis, superior vena cava obstruction, bone pain due to osseous metastasis and various symptoms due to metastasis to the brain.

Chemotherapy

The goals of chemotherapy are prolongation of survival and amelioration of symptoms. Agents in NSCLC include cisplatin, carboplatin, paclitaxel, docetaxel, vinorelbine, gemcitabine, irinotecan, pemetrexed, gefitinib, and erlotinib. Ifosfamide, vinblastine, mitomycin C and etoposide are also active but to a lesser degree. Combinations are better than single agents (**Table 11**). Chemotherapy consisting of platinum compounds

Table 11: Chemotherapy for NSCLC

Regimen	Dose	Cycle duration
Carboplatin-Paclitaxel		
Carboplatin	AUC 5 IV, d1	q21d
Paclitaxel	175-225 mg/m² IV, d1	
Carboplatin-Docetaxel		
Carboplatin	AUC 5 IV, d1	q21d
Docetaxel	75 mg/m² IV, d1	
Gemcitabine-Carboplatin		
Gemcitabine	1,000 mg/m² IV, d1, 8	q21d
Carboplatin	AUC 5 IV, d1 only	
Vinorelbine-Cisplatin		
Vinorelbine	30 mg/m² IV, d1, 8	q21d
Cisplatin	80 mg/m² IV, d1 only	
Pemetrexed-Cisplatin		
Pemetrexed	500 mg/m² IV, d1	q 21d
Cisplatin	75 mg/m² IV, d1	
Combination with Targeted Agents		
Bevacizumab-Chemotherapy		
Carboplatin	AUC 6	q 21d
Paclitaxel	200 mg/m² IV, d1	for 6 cycles
Bevacizumab	15 mg/kg IV, d1	q 21d till progression
Cetuximab-Chemotherapy		
Cisplatin	80 mg/m² IV, d1	q 21d
Vinorelbine	25 mg/m² IV, d1	for 6 cycles
Cetuximab	400 mg/m² IV, d1	
	250 mg/m² weekly	till progression
EGFR Tyrosine Kinase Inhibitors		
Gefitinib	250 mg/d oral	till progression
Erlotinib	150 mg/d oral	till progression

AUC = Area under the curve.

plus third generation agents is the current standard of care for patients with advanced NSCLC. The choice of chemotherapy depends upon the performance status, histology, toxicity, convenience of administration, and cost. In a patient beyond 4 courses of platinum containing regimens produces no survival benefit but increases the incidence of side effects. Older patients (>70 years) may be best treated with monotherapy with agents like vinorelbine, gemcitabine, etc.

The drugs with activity against SCLC include cisplatin, carboplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, irinotecan, and topotecan. Commonly used combination chemotherapy are summarised in **Table 12**. In limited stage SCLC, concurrent chemotherapy (CCT), and local radiation therapy (thoracic RT) is the standard treatment. In patients with complete response to CCT + RT prophylactic cranial irradiation is recommended to decrease the risk of brain metastasis and to improve survival. In SCLC because of high incidence of second malignancies and local regional and distant recurrence, patients need to have frequent check ups after completion of treatment. In patients with extensive stage disease, combination chemotherapy is superior to single agent. Radiation therapy can be used for palliation of localised symptoms. Results of treatment for lung cancer are summarised in **Table 13**.

Table 12: Chemotherapeutic Regimens in SCL

Regimen	Dose	Duration
EP		
Etoposide Cisplatin	120 mg/m² IV, d1-3 60 mg m/m² IV, d1	Repeated every 4 weeks, for 4 cycles
Etoposide Carboplatin	100 mg/m² IV, d1-3 AUC 6 IV, d 1	Repeated every 4 weeks, for 4 cycles
Etoposide Cisplatin	100 mg/m² IV, d1-3 25 mg/m² IV, d1-3	Repeated every 3 weeks, for 4 cycles
Etoposide Cisplatin	80 mg/m² IV, d1- 3 80 mg/m² IV, d1	Repeated every 3 weeks, for 4 cycles
CI		
Cisplatin Irinotecan	60 mg/m² IV on d1 60 mg/m² IV on d 1,8, 15	Every 4 weeks, for 4 cycles
Carboplatin Irinotecan	AUC-5 IV on d1 50 mg/m² IV on d 1,8,15	Every 4 weeks, for 4 cycles
Relapsed Disease		
CAV		
Cyclophosphamide	1,000 mg/m² IV, d1	Repeated every 3 weeks, for 4 to 6 cycles
Doxorubicin Vincristine	45 mg/m² IV, d1 1 mg/m² IV, d1	
Single Agents		
Paclitaxel	175 mg/m² IV, d1	Every 3 weeks
Docetaxel	75 mg/m² IV, d1	Every 3 weeks
Gemcitabine	1000 mg/m² IV d 1, 8, 15	Every 3 weeks
Topotecan	1.5 mg/m² IV, d 1-5	Every 3 weeks

Targeted Therapy

Increased understanding of molecular abnormalities in lung cancer, has led to development of targeted therapies. Overexpression of the EGFR is one such abnormality, which is

Table 13: Results of Treatment for Lung Cancer

	Treatment	Outcome (5-year survival)
NSCLC		
Stage I	Surgery + chemotherapy	60% to 70%
Stage II	Surgery + chemotherapy	40% to 50%
Stage IIIA	Neoadjuvant chemotherapy	15% to 30%
Stage IIIB or Unresectable disease	Concurrent chemoradiation	10% to 20%
Stage IV	Chemotherapy (3-4 cycles)	<5%
SCLC		
Limited	Concurrent chemoradiation	15% to 25%
Extensive	Chemotherapy	<5%

common in NSCLC. Stimulation of the EGFR pathway leads to increased growth potential, increased ability to metastasise, and increased angiogenesis (new blood vessel formation) in the cancer cells. Cancers overexpressing EGFR have been shown to have increased resistance to therapy, increased metastatic potential, and poorer prognosis.

Gefitinib

It is a EGFR tyrosine kinase inhibitor (TKI) that blocks activation of EGFR pathway. Gefitinib when used as first-line in Asian patients with adenocarcinoma who had never smoked or were former light smokers (none in last 15 years) showed a higher response rate in comparison to carboplatin-paclitaxel (43% *vs* 32%), with similar median survival. Patients who were positive for the EGFR gene mutation had significantly longer progression-free survival.

Erlotinib

A second EGFR-TKI, demonstrated improved response rates and overall survival (6.7 *vs* 4.6 months), compared to placebo in the second- and third-line setting. However, no benefit was seen when erlotinib was combined with chemotherapy. Response rates and survival were better in females, Asians, nonsmokers, particularly those with adenocarcinoma, especially bronchoalveolar cancer.

Cetuximab

It is a monoclonal antibody that binds to the EGFR receptor. It was studied in the first-line setting, in combination with cisplatin-vinorelbine, in patients with NSCLC that expressed EGFR by immunohistochemistry. In responding patients, cetuximab was continued till progression. Patients receiving cetuximab had an increased response rate (36% *vs* 29%), and improved median survival.

Bevacizumab

It is an anti-angiogenesis agent used with standard first-line carboplatin-paclitaxel. It improved median overall survival, and response rate (35% *vs* 15%) compared to chemotherapy alone. It is contraindicated in squamous cell histology, brain metastases, and clinically significant haemoptysis.

NEW IN LUNG CANCER

For Diagnosis

- Development of ras mutations in bronchial epithelium can be detected in the sputum samples as early as one month to four years prior to the clinical diagnosis of lung cancer.

- Detection of p53 protein in sputum samples of patient with bronchial dysplasia and antibodies to p53 in lung cancer.

Prognostic and Predictive Biomarkers

Epidermal growth factor receptor (EGFR) mutation is predictive of treatment benefit from EGFR-TKI therapy. High ERCC1 levels are prognostic of better survival but predictive of poor response to platin-based chemotherapy. K-ras mutation is a poor prognostic factor and predictive of resistance to platinum/vinorelbine chemotherapy or EGFR-TKI therapy. High RRM1 levels are prognostic of better survival but predictive of poor response to gemcitabine-based chemotherapy. Diminished expression of fas, ErbB-1, cyclin A, proliferating cell nuclear antigen (PCNA) are associated with long-term survival.

Therapeutics

1. Gene therapy – replacing defective gene/ protein or decreasing expression of the over expressed ones-studies focused on p53, c-erb B-2 and ras
2. Anti-sense therapy
3. Monoclonal antibody therapy
4. Agents to enhance apoptosis
5. Vaccines targeting MAGE-3, Tol-9 receptor, TGF, and MUC-1
6. Immunotherapy
7. Multiple tyrosine kinase inhibitors, such as sunitinib and sorafenib.

PROGNOSIS

The overall prognosis in bronchial carcinoma is very poor, with around 80% of the patients dying within a year of diagnosis and less than 5% of the patients surviving 5 years after diagnosis (**Table 13**). The best prognosis is with well differentiated squamous cell tumours, which have not metastasised and are amendable to surgical treatment. Efforts directed towards early detection and treatment have failed to reduce lung cancer mortality substantially. Thus, primary prevention through prevention and cessation of smoking remains the single most important measure for combating this frustrating disease.

TRACHEOBRONCHIAL TUMOURS

Tracheal tumours are uncommon, making up less than 1% of all respiratory malignancies. Tumours in the tracheobronchial tree can be classified as primary malignant tumours, secondary malignant tumours, or benign tumours (**Table 14**). The majority of primary malignant tumours originate from the surface epithelium or the salivary gland.

Squamous cell

It is the commonest primary tracheobronchial malignancy. It can be exophytic or infiltrative and involves the posterior wall of the lower two-thirds of the trachea with mediastinal or pulmonary metastasis at diagnosis.

Adenocarcinoma

It is extremely uncommon in the trachea. Both are managed as described in lung cancer.

Table 14: Classification of Tracheobronchial Tumours

Primary malignant tumours
- Surface epithelium
  - Squamous cell carcinoma (SCC) (most common), adenocarcinoma, neuroendocrine tumours (carcinoid tumour, large cell neuroendocrine tumours, small cell carcinoma)
- Salivary glands
  - ACC (second most common), MEC
- Mesenchyme
  - Sarcoma, malignant lymphoma

Secondary malignant tumours
- Direct invasion
  - Thyroid cancer, laryngeal cancer, lung cancer, oesophageal cancer
- Haematogenous metastasis
  - Melanoma, breast cancer, renal cell carcinoma, colon cancer

Benign tumours
- Surface epithelium
  - Squamous cell papilloma, papillomatosis,
- Salivary glands
  - Pleomorphic adenoma, mucous gland adenoma, oncocytoma
- Mesenchyme
  - Hamartoma, leiomyoma, lipoma, fibroma,

Neurogenic tumour

Salivary gland tumours

Arise from the bronchial seromucous glands. The malignant tumours are more common than benign. These are more common in the trachea than in the bronchi due to the preferential location of the commonest glandular tumour, adenoid cystic carcinoma (ACC).

Carcinoid tumours

Pulmonary and bronchial carcinoid tumours account for 1% to 2% of all pulmonary neoplasms. Carcinoid tumours of the tracheobronchial tree are frequently typical and usually involve the main, lobar, or segmental bronchi. They are vascular but have lower uptake on FDG-PET.

Benign tumours

Benign tumours of the tracheobronchial tree are rare, accounting for less than 10% of all airway neoplasms, and usually arise from the mesenchymal tissue. The commonest are hamartomas and squamous cell papillomas. They are well demarcated, round, and less than 2 cm in diameter. They originate in the submucosa, and the overlying epithelium is usually intact and smooth. The affected patients are asymptomatic until 50% to 75% of the luminal diameter is occluded.

Clinical Presentation

Tracheal or the main bronchus tumours cause progressive airway obstruction and present with cough, shortness of breath, or wheeze. Sometimes, tumour growth or mucosal erosion may cause haemoptysis. The diagnosis is usually delayed. Benign tracheal tumours and ACC have a mean symptom duration of 24 months as compared to 12 months for mucoepidermoid carcinoma.

Evaluation

Chest radiographs may demonstrate collapse of a lobe or an entire lung or hyperinflation of the lung distal to a bronchial tumour due to a ball valve effect. Computed tomography (CT) of the chest may demonstrate a tracheal or bronchial mass and invasion of the great vessels but underestimates the extent of submucosal invasion. Patients with malignant tumours are evaluated for metastatic disease that typically includes examinations of the lung, brain, bone, adrenal glands and liver. Endoscopic examination of the airway with rigid bronchoscope provides a diagnosis, and may be used for dilatation of a stricture or for removal of a tumour to relieve symptoms.

Treatment of Tracheobronchial Tumours

Resectable tumours

Local treatment options consist of brochoscopic resection, segmental airway resection, and radiotherapy. Of these techniques, only segmental tracheal or bronchial resection permits complete removal of the tumour.

Bronchoscopic resection

It is a less invasive, restores airway lumen, but does not provide for complete resection or confirmation of resection margins. The primary role is therefore palliative.

Surgical resection

The tumour size, length, and depth influences resectability. The location of tracheal tumours in the mediastinum restricts radical resection. The average length of most resected tracheal tumours measures less than 3 cm, except ACCs which often involve a longer tracheal segment. Due to close margins in mediastinum, adjuvant radiotherapy is now standard therapy. Operative procedures performed for tracheal tumours are laryngotracheal, tracheal, and carinal resection whereas for bronchial tumours, they are main bronchial resections with parenchymal sparing and sleeve lobectomy.

Unresectable tumours

Main criteria are tumour length, regional disease, and distant metastasis. The goals of treatment are to restore a patent airway and to slow progression of disease. Regional radiation or bronchoscopic destruction provide effective local palliation therapy. Local destruction of tumour may be accomplished by the laser, cryosurgery, brachytherapy, photodynamic therapy, or argon beam coagulation. Malignant strictures can be stented.

Prognosis

Benign bronchial tumours have an excellent long-term prognosis and do not recur if completely resected. The malignant bronchial gland tumours have a limited disease-free survival after resection due to distant metastasis and regional disease. Other malignant tracheal tumours are mostly unresectable with poor long-term survival.

See cancer lung in Section 23, Chapter 19.

21.9 Tumours of the Gastrointestinal Tract (Stomach and Oesophagus)

KM Mohandas

INTRODUCTION

Gastrointestinal tract (GIT) is one of the commonest sites for development of cancer. In India, the GIT cancers constitute 15% to 25% of all cancers. Gastrointestinal tract (GIT) cancers are primarily a disease of the elderly population. In the clinics, majority of Indian patients are diagnosed at a younger age because less than 5% of Indian population is above 65 years of age. As the Indian population grows older with increasing life expectancy, the burden of GIT cancers will increase many folds in India. Almost all GIT cancers arise as a result of prolonged exposure to aetiological causes like tobacco, poor diet and infections, like *Helicobacter*, hepatitis and papilloma virus, which are preventable. The stage based on Tumour Nodes and Metastasis (TNM) is the most important prognostic factor for GIT cancers. Surgery is the primary curative treatment for GIT cancers. Patients with the cancer limited to the wall of the GIT have excellent long-term survival following en bloc surgery. Majority of the GIT cancers in India are well advanced at the time of diagnosis. Most patients are suited for palliation only which is possible by surgery, endoscopy, radiotherapy, and chemotherapy. There has been some progress in chemotherapy with and without radiotherapy in improving the outcomes of patients with GIT cancers. A collective effort by Indian physicians can prevent exposure to carcinogens and help in early diagnosis of GIT cancers, and thereby, contribute in the control of GIT cancers in India. Some pointers are listed in **Table 1**. It is important to remember some condition involving stomach and oesophagus which may be mistaken and malignancy may be missed (**Table 2**).

Table 1: Common Precursors of Gastric Cancers (Stomach)

Benign Disease	Malignant Disease
Achalasia or corrosive strictures	Squamous carcinoma of oesophagus
GERD with Barrett's metaplasia	Adenocarcinoma of the oesophagus
Chronic gastritis due to *H. pylori*	Gastric adenocarcinoma and MALT lymphoma

GERD = Gastro-oesophageal reflux disease; MALT = Mucosa-associated lymphoid tissue.

Table 2: Commonly Mistaken Diagnoses for GIT Cancers (Oesophagus and Gastric)

Primary Cancer	Common Mistaken Diagnosis
Oesophageal cancer	Peptic stricture, achalasia, web, impacted foreign body
Gastric cancer	Gastritis, peptic ulcer, pyloric stenosis, thick folds

OESOPHAGEAL CANCER

There are many types of benign and malignant tumours of the oesophagus. Leiomyoma is the commonest benign tumour and has an excellent prognosis following resection. Majority of primary oesophageal cancers are carcinomas. The commonest is squamous carcinoma, followed by adenocarcinoma. Other cancers are very rare and include lymphoma, leiomyosarcoma, and metastatic cancer.

Squamous Carcinoma of Oesophagus

It is one of the common GI cancers. It is the fourth leading cancer in Indians. The incidence rates are higher in China, Puerto Rico, Singapore, South Africa, Switzerland, France, and the Caspian Littoral area of Iran. Squamous carcinoma is aetiologically associated with tobacco chewing and smoking, alcohol abuse, human papilloma virus infection, corrosive strictures, sclerotherapy, Plummer-Vinson syndrome, irradiation of the mediastinum, achalasia, and previous squamous carcinoma of the head and neck region. Tylosis and squamous cell papilloma is precursor lesion for squamous carcinoma. Adenocarcinoma is more common in Western populations and occurs mainly in the distal oesophagus. As the incidence of squamous carcinoma is declining, the incidence of adenocarcinoma is rising. Adenocarcinomas of the oesophagus are difficult to differentiate from the adenocarcinoma of the proximal stomach when in an advanced stage. Adenocarcinoma of the oesophagus develops in Barrett's oesophagus. Barrett's oesophagus develops following long-standing gastro-oesophageal reflux disease (GERD). Other less common cancers of the oesophagus include variants of squamous carcinoma such as spindle cell carcinoma, adeno-squamous carcinoma, oat cell carcinoma, carcinoid tumour, sarcoma, and primary malignant melanoma. Several other cancers are known to metastasise to the oesophagus. The cancer can arise anywhere in the oesophagus and develop as a stricture, protruding mass, or an ulcerated plaque.

Symptoms and Signs

The incidence of oesophageal cancer peaks after 70 years of age. Oesophageal cancer presents with progressive dysphagia over several weeks and months often with progressive weight loss and weakness. Dysphagia begins with difficulty in swallowing solids, then progresses to semisolids, liquids, and finally saliva. Chest pain and back pain is ominous sign, suggestive of local spread of the cancer (**Table 3**). Hoarseness due to compression of the recurrent laryngeal nerve and Horner's syndrome due to compression of sympathetic nerves may occur. Compression of nerves elsewhere may cause spinal pain, hiccups, or paralysis of the diaphragm. Malignant effusions and pulmonary metastasis produces dyspnoea. Progressive tumour growth produces odynophagia, vomiting, haematemesis, melaena and iron-deficiency anaemia, aspiration, cough, lung abscess, and pneumonia. Superior vena cava syndrome, malignant ascites, oesophago-respiratory fistula, and bone pain suggests very advanced disease. Oesophagus is drained all along its length by a rich lymphatic plexus resulting

in early metastasis into internal jugular, cervical, supraclavicular, mediastinal, and coeliac lymph nodes. Blood-borne metastasises to bone, lung, liver and other distant sites (e.g. brain, adrenal glands, kidneys, and peritoneum) are not uncommon.

Table 3: Warning Signs of Digestive Cancer

Gut specific
Difficulty in swallowing solid foods or medicines
Fullness after meals and/or early satiety
Vomiting of undigested foods
New abdominal pain
Jaundice
Bleeding per rectum
Non-specific
Nausea, anorexia, weight loss
Depression, insomnia
Venous thrombosis

Investigations

Fibreoptic endoscopy is the investigation of choice as it enables biopsy and cytological sampling necessary to confirm diagnosis. The combined yield of biopsy and brush cytology is over 95%. Endoscopy is also useful for placing feeding tubes and palliating dysphagia by dilation and stenting. Barium swallow can demonstrate the location and the degree of stenosis, length of stenotic tumour, deviation of luminal axis, and the presence of regurgitation or tracheo-oesophageal fistula. Over 98% of upper oesophageal cancers are squamous carcinoma. Ten to twenty-five per cent of lower oesophageal cancer and 80% of gastro-oesophageal junction cancers are adenocarcinomas. A multi-detector computed tomography (MDCT) of the chest and upper abdomen is the essential for staging oesophageal cancer. Multi-detector computed tomography (MDCT) detects infiltration of the tumour to mediastinal structures, enlarged lymph nodes, metastasis to distant organs, and malignant effusions. It is useful for precise planning of the radiation fields. MRI does not offer additional advantage over CT. An endoscopic ultrasound (EUS) is needed in all patients being considered for surgery for detailed loco-regional staging of the cancer and adjacent lymph nodes.

Prognosis and Treatment

The prognosis of advanced oesophageal cancer is poor and less than 10% of patients diagnosed after the onset of dysphagia survive over 5 years. For early oesophageal cancer, a 5-year survival may be as high as 80%. The site and type of cancer, stage, co-morbidity, and the patient's preferences influence the optimal treatment modality. Most localised oesophageal cancer is treated with curative intent using surgical resection or radiotherapy. Adenocarcinoma occurring in the distal oesophagus is most often treated with distal oesophagectomy and radiation is used as the primary treatment of upper oesophageal cancers. Recent studies support the use of pre-operative chemoradiotherapy and peri-operative chemotherapy which is also useful for locally advanced cancers. For patients having more advanced cancer with metastasis, recurrent cancer or severe co-morbid illness palliative treatments such as oesophageal dilation, prosthesis (stent) placement, internal radiotherapy, and laser photocoagulation are used. Chemotherapy has limited role in the palliation of advanced oesophageal cancer.

Objectives of pre-treatment assessment include (i) confirmation of diagnosis by histology, (ii) determine the extent of the disease, (iii) exclusion of extra-mural extension of the tumour, (iv) exclusion of distant metastasis, (v) to establish the resectability of tumour, and (vi) to assess operative risk of the patient.

Surgical therapy of oesophageal cancer is associated with 5% to 15% mortality rates and a 10% to 20% of 5-year survival. Surgery must be undertaken in high volume centres to reduce mortality. Complication rates, operative mortality rates, and 5-year survival are mainly dependent on the patient selection. En bloc resection of tumour with lymph nodes is more risky in elderly patients, those with cardiac ejection fraction less than 40%, and forced expiratory volume in one second of less than 1.5L. The 2-year survival is poor in patients with cancer extending beyond the oesophageal wall or metastasis to lymph nodes. Nevertheless, surgery is still one of the most effective forms of therapy and permits over 80% of patients eat a soft or solid diet.

The choice of surgery is determined by the location, size and stage of the tumour, the experience of the surgeon, and the intent of treatment. In curative resection, the entire tumour with clear proximal and distal margins of normal oesophagus and all the involved lymph nodes are removed en bloc. The defect of the oesophagus is repaired by creation of a gastric tube and oesophagogastric anastomosis, or with small-bowel or colonic interposition. Complications of surgery include septicaemia, pneumonia, anastomotic leaks and strictures, bilious gastro-oesophageal reflux, and dumping syndrome.

External beam radiotherapy (EBRT) is an effective primary therapy for patients who are at high risk for surgery or have advanced disease. External beam radiotherapy (EBRT) is contraindicated in patients with tracheo-oesophageal fistula. Rarely patients with aortic involvement by tumour may experience massive haemorrhage following EBRT. Occasionally, oedema caused by EBRT may worsen oesophageal obstruction, dysphagia, and odynophagia. Temporary oesophageal dilation or placement of a feeding tube may be required to provide enteral nutrition. Radiotherapy may also produce nausea, vomiting, anorexia, fatigue, oesophagitis, odynophagia, stricture, radiation pneumonitis, radiation pericarditis, myocarditis, and transverse myelitis. Chemotherapy is combined with EBRT to enhance the tumour response.

Chemotherapy is primarily used along with surgery or radiotherapy to improve response rates and survival rates. Several drugs have moderate anti-neoplastic activity against squamous and adenocarcinoma. These include 5-fluorouracil (5-FU), capecitabine, gemcitabine, mitomycin, cisplatin, oxaliplatin, carboplatin, bleomycin, methotrexate, and paclitaxel. Shrinkage rates of tumour vary from 10% to 70% depending on the morphology, size and stage of primary tumours and the combination of drugs used. Cisplatin is the most commonly used drug in combination with 5-FU, methotrexate, and less commonly bleomycin. Multi-modality therapy (surgery, radiotherapy, and chemotherapy in the same treatment plan) is used to control both local disease and distant metastases. Chemotherapy given peri-operatively with or without external radiation therapy is superior to surgery or radiation therapy alone in patients with loco-regional cancer. Chemotherapy or radiotherapy given alone after surgery has little benefits.

Pre-operative radiotherapy alone or in combination with chemotherapy is effective in reducing tumour bulk, increasing resectability, and improving survival of complete responders. There is little evidence to support the use of post-operative radiotherapy in prolonging survival compared with surgery alone. Combined modality radiotherapy with 5-FU and cisplatin might result in prolonged disease-free and overall survival in patients with unresected oesophageal cancer. Benefit occurs in patients with adenomatous or squamous cell cancer and is superior to that achieved with radiotherapy alone. Patients with locally advanced adenocarcinoma of the lower end of the oesophagus benefit from peri-operative chemotherapy and post-operative chemoradiotherapy.

Oesophageal dilation is a palliative therapy for maintaining the swallowing at any time during the course of illness. The dilation is very safe, and the balloon dilators passed under direct endoscopic vision or over a guide wire enhance the safety. The effect of dilation is temporary, and needs to be repeated every 6 to 8 weeks. Oesophageal stents are placed across the malignant strictures to restore the oesophageal lumen for longer periods and to close tracheo-oesophageal fistulas. Currently available, expandable metallic and plastic stents have increased the ease and safety of stent insertion. Endoscopic laser therapy with Nd: YAG is used to vaporise the tumour and establish the lumen. Laser treatment however is palliative, needs to be repeated and expensive. The complication rate for laser therapy is similar to that of stent placement. Photodynamic therapy is another treatment designed to destroy tumour cells without damaging surrounding normal tissues. Photo-activation of the dye absorbed by the cancer cells causes self-destruction from cytotoxic oxygen singlet within the tumour cells. Laser therapy and photodynamic therapy (PDT) are expensive for routine use in India.

Prevention and Screening

Barrett's oesophagus, the precursor of adenocarcinoma, rarely regresses with medical therapy and anti-reflux surgery. Endoscopic surveillance of malignant transformation is often recommended at 3- to 12-month intervals depending on the degree of metaplasia, but its cost-effectiveness is controversial. PDT and endoscopic mucosal resection (EMR) are useful means to ablate Barrett's oesophagus with dysplasia. Newer endoscopic techniques like narrow band imaging, confocal microscopy, and fluorescence endoscopy are under investigation for screening. Routine uses of anti-oxidants and vitamin supplements do not reduce mortality.

STOMACH CANCER

Ninety-five per cent of stomach tumours are adenocarcinomas. Less common cancers are lymphomas (which may be localised primarily in the stomach) and leiomyosarcomas. The incidence of stomach cancer is very high in Japan, Chile, and Iceland. In the USA, gastric cancer is most common in Northerners, the poor, and the African-American populations. In India, the incidence of stomach cancer has decreased to about 2 to 8 per 100,000, making it the seventh most common cause of death from cancer. The incidence of stomach cancer peaks after 70 years of age, and hence, is associated with several co-morbid illnesses.

Aetiology and Pathogenesis

Gastric adenocarcinoma is hypothesised to arise through a series of events starting with chronic gastritis, atrophy and hypochlorhydria, metaplasia, dysplasia, and carcinoma in situ. Benign peptic ulcers of the stomach do not turn malignant, and in very few patients where it had occurred probably had undetected cancer at the outset. *Helicobacter pylori* is responsible for gastric adenocarcinoma and mucosa-associated lymphoid tissue tumours of the stomach. Gastric polyps are likely to be malignant if the polyps is more than 2 cm in diameter, has villous histopathology or when multiple polyps are present at a time. The incidence of stomach cancer is lower in patients with duodenal ulcer.

Pathology

Gastric adenocarcinomas are classified on the depth of infiltration of the tumour. Adenocarcinoma limited to the mucosa and submucosa is termed early gastric cancer irrespective of their nodal metastatic status. The Japanese Society for Gastroenterological Endoscopy has proposed a classification for early gastric cancer that is widely used. Identification is based on gross morphology: type I—protruded; type II—superficial (elevated, flat, or depressed); type III—excavated. Early gastric cancer is most often detected by mass screening programmes and is amenable for EMR. Patients with early gastric cancer have excellent long-term prognosis. When the tumour infiltrates the muscularis propria, the gastric cancers are labelled as advanced. Advanced cancers are grossly classified as protruding, ulcerated, infiltrating, and combined types. Protruding tumours have the best prognosis. Tumour size does not predict the risk of co-existing metastasis. The smallest tumour can metastasise to distant sites at the time of diagnosis. Extensive tumour infiltration of the stomach wall with fibrous reaction results in 'leather bottle' stomach (linitis plastica). Most gastric cancers occur in the antrum and pyloric region; the incidence of proximal tumours is increasing.

Symptoms and Signs

Satiety (fullness or distension) after a meal occurs if the cancer obstructs the pyloric region. Pain is suggestive of ulceration or deep infiltration. Proximal stomach cancers cause dysphagia from obstruction to the oesophagogastric junction. Infiltrative cancer may be confused with oesophageal cancer or achalasia. Linitis plastica is suggested by early satiety, a never-changing shape of the stomach on barium studies and thickened gastric wall on MDCT. Loss of weight and weakness results from dietary restriction. Massive haematemesis or melaena is uncommon except in gastrointestinal stromal tumours and lymphomas, but anaemia may develop due to occult blood loss. Sometimes, the first symptom or sign is from a metastasis with the primary tumour in the stomach remaining silent. More advanced cancer causes severe weight loss, palpable mass, or enlarged neck nodes develop. Ultimately, tumour spread leads to enlarged liver, pelvic deposits, abdominal distension from ascites, jaundice, skin nodules, and even pathological fractures.

Diagnosis and Staging

Differential diagnosis commonly involves several benign disorders such as peptic ulcer, chronic gastritis, and rarely infections like tuberculosis. Endoscopy allows direct inspection and multiple biopsies sampling suspicious mucosa and needle aspiration of submucous tumours and when combined with brush cytology has a yield of over 98%. Cytology on gastric washings increases the yield. Rarely, special techniques (e.g. lift and cut technique or EMR) may be required. Conventional barium

Table 4: Treatment Summary of GIT Cancers

Cancer Site	Stage at Diagnosis by Imaging (Preferably a MDCT)		
	Localised	**Loco-regional**	**Metastatic**
Oesophagus radiation	Surgery Chemoradiation	Chemoradiation Followed by surgery or surgery alone	Intra-luminal Stenting Laser ablation
Stomach	EMR Radical surgery	Radical surgery and chemotherapy	Chemotherapy Bypass Stenting

EMR = Endoscopic mucosal resection.

X-rays are unreliable. A double-contrast barium examination is preferred over conventional barium examinations.

Staging of gastric cancer is necessary for treatment planning and includes MDCT, EUS to exclude pancreatic infiltration and peritoneal infiltration and a laparoscopy before performing surgery. The role of PET scan is under evaluation.

Treatment

The treatment options are depicted in **Table 4**. Surgery is the primary treatment of gastric cancer. Complete excision of the tumours with combined excision of the tumour with all the draining lymph nodes is needed for achieving cure. Presence of residual microscopic tumour as shown by involved surgical margins and many lymph nodes suggests incurable disease. The controversy on the role of extended lymph node dissection compared to standard resection is unresolved. Role of palliative surgery for debulking tumours or creating bypass-like gastrojejunostomy should be individualised based on the tumour site, extent, stage and patient's co-morbidity. Several endoscopic techniques such as placement of stents combined with chemotherapy have helped to avoid palliative surgery.

The role of chemotherapy and radiotherapy has been increasing in the overall management of gastric cancer. There has been progress in surgical adjuvant therapy of stomach cancer. Neoadjuvant peri-operative chemotherapy given along with surgery is useful in increasing cure rates for stomach cancer. Similarly, post-operative adjuvant chemoradiotherapy given after complete surgical resection improves survival rates. Palliative chemotherapy has achieved some success in improving survival and quality of life of patients with incurable gastric cancer. Combined chemotherapy and radiotherapy is used to cure gastric lymphoma without surgery. Targeted chemotherapy using imatinib is used for non-resectable gastric malignancy.

21.10 Colorectal Cancer

K Govind Babu

Colorectal region is that part of the large bowel extending from the ileocaecal valve to the anus. Colorectal cancer is a significant contributor to the morbidity and mortality in the developed countries. With rapid urbanisation and change in dietary habits, it is seen more frequently in the developing countries as well.

In the United States of America, it is the fourth most common cancer. In India, the age standardised incidence is 4.6 to 6 per 100,000.

AETIOPATHOGENESIS

The aetiology of colorectal cancer is complex involving several factors including the environment and genetics. This interplay brings about the metamorphosis of the normal mucosa through premalignant adenomas to overt malignancy over several years. Family history confers an increased risk. Involvement of first degree relatives increases the risk two-fold. Epidemiological studies suggest a dominant inheritance for cancer. Genetic polymorphisms are seen for glutathione S-transferases, methylenetetrahydrofolate reductase and N-acetyltransferases. The variation of these in different populations may explain the geographic variation in colorectal cancer.

Colorectal cancers develop by a series of steps influenced by inherited factors and the environment, from an early adenoma to a metastatic disease, associated with activation of oncogenes and inactivation of tumour suppressor genes, Kinzler and Vogelstein at Johns Hopkins have put forth a model to explain these events, referred to as the 'Vogelgram' of colorectal cancer.

Genetic Factors

There exists an inherited predisposition to colorectal cancers. The well studied are hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). HNPCC is associated with dysfunction in many deoxyribonucleic acid (DNA) repair genes, such as MSH2, MLH1, PMS1 and PMS2. Most cases of colorectal cancers do not have an inherited component and are termed as 'sporadic'. These result from a series of genetic events as shown in **Figure 1**.

The familial adenomatous polyposis (FAP) syndrome has inactivation of the APC gene in over 80% of sporadic cases. It is estimated that it takes at least seven somatic mutations and a few decades for these sporadic cases to evolve. The other rare syndromes accounting for about 1% of adult and paediatric colorectal cancers are the haemartomatous polyposis syndromes, of these are the Peutz-Jeghers syndrome, Cowden's syndrome.

Environmental Factors

Many environmental factors have been implicated in colorectal cancers.

Diet

It is important as global epidemiologic studies have shown that these are more prevalent in the more developed nations. It has also been seen that the first generation migrants from less developed nations acquire the increased risk who have diet low in fibre content.

Two major components having a bearing are: (i) the total fibre and fat soluble fibre contents. It is hypothesised to dilute faecal carcinogens, decrease the colon transit time and generate a favourable luminal environment, and (ii) the other factor is the association of animal fat and colorectal cancer has also been reported in several studies. It has also been found that saturated fatty acids increase the risk, intake of red meat is also associated with increased risk as also ingestion of fried, barbequed, and processed meats. Alcohol and cigarette consumption also increase the risk.

Vegetables and fruits have been shown to have a protective effect. This is thought to be due to antioxidants and plant phenols.

Physical inactivity

It is associated with more of colonic than rectal cancer. Some data exists to show beneficial effects of coffee and tea.

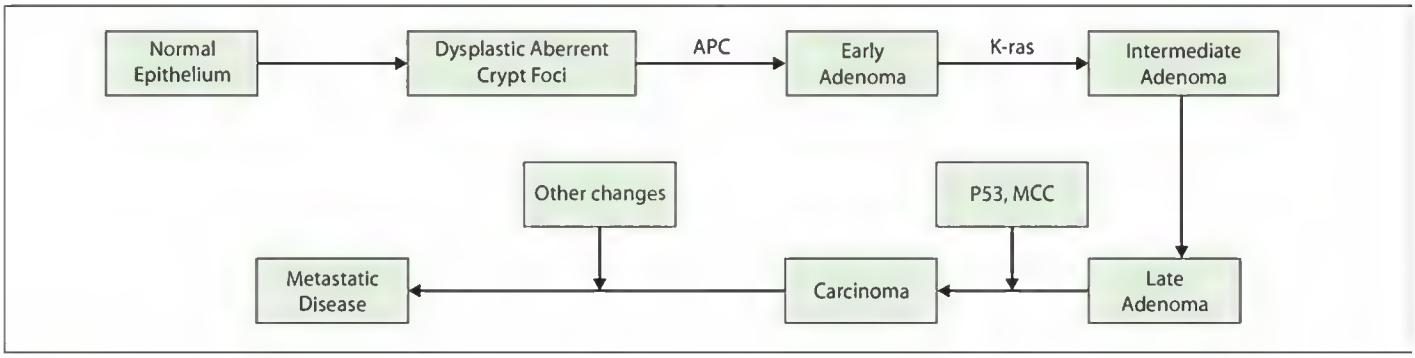


Figure 1: Molecular model of colorectal carcinogens.

APC = Adenomatous polyposis coli gene on 5q chromosome; K-ras = Mutated in 50% of colorectal cancers; DCC = Deleted in colorectal cancer, is a tumour suppressor gene; P53 = Tumour suppressor gene on 17p chromosome; MCC = Mutated in colon cancer, gene on 5q.

PATHOLOGY

Most primary tumours of the large bowel are adenocarcinomas, other cancers in this region are lymphomas, stromal tumours. The anatomic and histopathology of the tumours have a prognostic significance. The annular circumferential lesions have a shorter survival than those that involve only a portion of bowel wall. Those with a polypoidal lesion survive twice as long as those with infiltrating lesion. Tumours of the ascending colon seem to fare better than those with involvement of descending colon. The histological features that have a prognostic significance include tumour grade, vascular lymphatic and perineural infiltration and the presence or absence of inflammatory infiltrates. Poorly differentiated signet ring and mucinous tumours fare far worse than well-differentiated tumours.

CLINICAL FEATURES

Symptoms can help in anatomic localisation of the tumours. Those in the ascending colon present with abdominal pain, bleeding, weight loss rather than with obstruction that is more common in the descending colon along with altered bowel habits.

Physical examination may reveal anaemia, emaciation, and palpable mass in the abdomen. Rectal examination may show bright red blood in left colonic tumours or altered blood in right colonic tumours. If at presentation it has metastasis then findings will depend on the sites of metastasis—jaundice if the liver is involved, pleural effusion if lung and pleura are involved, pathological fractures in case of bony involvement is seen, etc.

The patient evaluation should include a detailed history, family history, and physical examination. Laboratory evaluation should cover haematology, liver function and renal function tests. The carcinoembryonic antigen (CEA) increases in about half the patients and is useful in monitoring the patient's response to therapy.

DIAGNOSIS

Colonoscopy and biopsy are the most common procedures to establish a pathologic diagnosis. A pan-body computed tomography (CT) can be done if metastasis is suspected. Stool occult blood testing, that was popular in the past remains an unreliable test. The advances in molecular biology have opened avenues to do DNA analysis on stool and study genetic alterations including analysis of genes like ras and its mutations. This could, in the future, be a very effective screening tool for detecting colorectal cancers.

Once the diagnosis is made, staging the disease is imperative for appropriate treatment.

It was in 1932 that the Dukes pathologic staging was introduced. It was essentially based on the depth of involvement of the bowel wall, lymph node involvement, and distant metastases. This system has undergone several modifications and is used for its ease. But the present day staging system is the TNM of the International Union Against Cancer (UICC) based on this system we have stage 0, I, II, III, and IV.

The staging of colorectal cancer is important for giving proper therapy and prognostication. In addition to staging, histological features also have a prognostic importance. A 5-year survival for a well-differentiated and moderately differentiated type is 57% and 54%, respectively while poorly differentiated one has a low survival rate of 35%.

MANAGEMENT

The management of colorectal cancers is a multi-modality approach that is tailored to the stage of the disease and involves surgery, radiation, chemotherapy, and biotherapy.

Colonoscopy is the first procedure that picks up the lesion. Small polypoidal lesions can be removed during this procedure and sometimes may be curative, larger lesions have to be biopsied to have a histological diagnosis.

Surgery

Surgery plays an important role in the management of colorectal cancers for invasive cancers of stage I, II, and III. The type and extent of surgery is decided by the size and anatomic location of the tumour. The resection of the colon is based on the understanding of the blood supply of the different parts. The surgical management also depends on the complication of the tumour such as obstruction perforation. Laparoscopic surgery is fast replacing conventional surgery as experience is improving and in the long run may be more cost-effective.

Radiation

Radiotherapy is not indicated for colon cancers in stage T1 and T2. No radiation is required in rectal cancers with good surgical clearance. Local recurrences are a problem in advanced rectal cancers and here radiation is employed to reduce them.

Pre-operative chemoradiotherapy protocols have led to sphincter preservation in distal rectal cancers and this is an important advancement in maintaining quality of life of these patients.

Systemic Therapy

This include chemotherapy and also the use of biological agents, one of the oldest drugs which continues to be an important agent is the fluoropyrimidine, 5-fluorouracil (5-FU).

Several advances have occurred leading to fine tuning of systemic therapy. Some of these are: role of adjuvant therapy for locally advanced disease, effective scheduling of 5-FU dose and administration, the incorporation of newer drugs, identification of tumour characteristics to predict response.

Adjuvant Chemotherapy

Patients of high risk stage II (T4 N0 M0) and stage III are candidates for adjuvant chemotherapy although high-risk stage II is controversial, it needs to be individualised, however is useful in those presenting with obstruction or perforation.

The drugs used are 5-FU and folinic acid for 6 months. The earlier regime of 5-FU and levamisole for 1 year is no more used today.

The more recent regimen incorporate oxaliplatin into them and are popularly referred to as FOLFOX regimes with several modifications, the most widely used is the FOLFOX regime. Irinotecan is another drug used sometimes in place of oxaliplatin. Trials have been done incorporating both oxaliplatin and irinotecan with 5-FU but have not shown any advantage except adding to toxicity.

The arrival of oral fluoropyrimidines—capecitabine and legofer are good alternatives to injectable 5-FU.

Investigational approaches include portal vein infusion with 5-FU, intraperitoneal chemotherapy with 5-FU, edrecolomab—a monoclonal antibody, vaccines, and active specific immunotherapy.

Follow-up after curative treatment includes physical examination and CEA levels every 3 months, yearly CT of chest, abdomen and pelvis for 3 years and a colonoscopy every 2 to 3 years. A rising CEA with a normal CT could warrant a positron-emission tomography.

Chemotherapy for Advanced Disease

Unresectable metastatic colorectal cancers are not curable. The goals here are symptom control and improving quality of life, and to lengthen progression-free and overall survival.

Patients with good performance status, good organ reserves, no significant co-morbidities and/or well motivated are the ones who would derive substantial advantages with aggressive treatment protocols while the other group should get less intensive protocols or supportive care only. Chemo-immunotherapy has made tremendous progress in the treatment of metastatic colorectal cancers. The median overall survival has increased from 4 months with best supportive care to nearly 24 months now. This could increase further with newer molecules being added to the armamentarium every day.

The backbone of most protocols still remains 5-FU and folinic acid. The activity of 5-FU has been effectively modified by using it as a protracted infusion, the response rates increasing by nearly 10% over bolus 5-FU agents that have got incorporated into the regimes include interferon, ralitrexed, irinotecan, oxaliplatin and monoclonal antibodies such as bevacizumab and cetuximab.

CONCLUSIONS

The understanding of the molecular pathology of colorectal cancers parallel with the development of chemotherapy and biological agents have brought about a vast change in the management of colorectal cancers. Cures in the adjuvant setting and meaningful prolongation of survival in metastatic colorectal cancer is now a reality.

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21.11 Genitourinary Cancers

Sudeep Gupta

INTRODUCTION

Genitourinary malignancies constitute some of the most common cancers worldwide and in India. From an oncologist's point of view, these can vary from being the most gratifying (germ cell tumours of testis and ovary) to the most frustrating tumours to treat. Some of these tumours can be detected early with the help of screening (cervical cancer) or awareness programmes (penile cancer). The decisions regarding management require active patient participation and understanding since there can be difficulties in social adjustment and loss of sexual and reproductive functions. The aim of this chapter is to briefly introduce the subject to students and highlight the significance of clinical features and basic investigations to identify these malignancies in an unselected patient population followed by a brief discussion of the salient therapeutic options. The ovarian, uterine, and cervical cancers are discussed in detail in the next chapter on 'gynaecological malignancies.'

RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is the third most common and the most lethal of all genitourinary malignancies. It accounts for 5% of all malignancies in India. The peak incidence of RCC is in the 7th decade.

Aetiology

The exact cause remains unclear. Smoking, obesity, analgesic abuse, cadmium, and end stage renal diseases are recognised risk factors for RCC. Endogenous genetic risk factors include hereditary familial forms of kidney cancer, such as the von Hippel-Lindau (VHL) disease, familial hereditary papillary renal cell carcinoma (HPRCC), hereditary leiomyoma RCC (HLRCC), the Birt-Hogg-Dube Syndrome (BHD), and tuberous sclerosis (TS). The von Hippel-Lindau tumour suppressor gene is mutated in more than 50% of sporadic cases of clear cell RCC.

Pathology

Renal cell carcinoma originates from the renal tubular epithelium. RCC has a number of distinct subtypes, each with a unique genetic basis and tumour biology. RCC is now classified into conventional clear cell constituting about 70% of renal cancers, papillary, chromophobe, oncocytic, and collecting duct carcinoma. Tumour spread occurs by direct extension into the peri-renal tissue or renal veins or by haematogenous metastasis and lymphatic dissemination. About 25% to 30% of patients have evidence of metastatic disease at presentation.

Clinical Features

Currently, more than 50% of patients with RCC are detected incidentally due to increased use of non-invasive imaging to evaluate a variety of non-specific symptoms. Incidentally detected RCC is generally smaller and of lower stage than symptomatic RCC. The classic triad of flank pain, gross haematuria, and palpable abdominal mass is now rare (6% to 10%), but when present, signifies an advanced stage of the disease. Patients with metastatic disease may present with symptoms, such as bone pains, chronic cough, etc. Paraneoplastic syndromes are seen in about 20% to 30% of patients with symptomatic RCC, such as hypertension due to increased renin secretion. According to the 2002 revision of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Centre (UICC), TNM system is the currently accepted staging system for RCC.

Investigations and Work-Up

Contrast enhanced computed tomography (CECT) of chest, abdomen, and pelvis is the most important investigation for the assessment of a renal mass. A solid mass with significant heterogenous post contrast enhancement (due to characteristic high vascularity), which is less than that of the normal renal parenchyma is virtually diagnostic of RCC. Fine needle aspiration cytology/biopsy is rarely indicated when a renal abscess or infected cyst is suspected and when RCC must be differentiated from metastatic malignant disease or renal lymphoma.

Management

Surgery is the mainstay of treatment of localised RCC. Radical nephrectomy is the gold standard for patients with localised RCC and has a cure rate of 70% to 90%. The principles of radical nephrectomy include early ligation of renal vessels, removal of kidney and ipsilateral adrenal gland surrounded by the Gerota's fascia and regional lymphadenectomy from the crus of the diaphragm to the bifurcation of aorta or inferior vena cava. Presently, there is no role for adjuvant treatment after radical or partial nephrectomy.

Approximately one-third of patients with RCC present with metastatic disease and another 40% to 50% will develop metastasis some time during their natural history. The majority of these patients will die of disease within 12 to 24 months, if left untreated. RCC is somewhat unique amongst genitourinary cancers in being completely resistant to conventional chemotherapy drugs. Until recently the only available treatments for metastatic RCC were immunotherapeutic agents interferon alpha and interleukin-2. The response rates were less than 10% and there was considerable toxicity from these agents. Recently, a better understanding of the molecular perturbations in RCC has led to the development of a number of targeted agents with robust therapeutic effects in this disease.

The following drugs are currently in use for metastatic RCC:

1. Sunitinib

This is a small molecule drug that inhibits the tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptor; platelet derived growth factor, cKIT and FLT-3. It is

recommended as a first-line therapy in metastatic conventional clear cell RCC.

2. Bevacizumab

A monoclonal antibody against VEGF and is used in combination with interferon.

3. Everolimus and temsirolimus

These are inhibitors of the mammalian target of rapamycin (m-TOR) and recommended in poor risk patients and those who progress after other drugs.

4. Sorafenib

This is a small molecule oral multikinase inhibitor. It is recommended as second-line therapy.

Prognosis

The estimated 5-year survival rates for RCC range from 80% to 90% in low-risk non-metastatic patients to 10% in patients with metastatic RCC.

URINARY BLADDER CANCER

Bladder cancer is the commonest urological malignancy in India and the second most common genitourinary malignant disease in the world. Males are commonly affected (M:F= 2.4:1) and this malignancy occurs mostly in the elderly with median age at presentation of about 60 to 70 years.

Aetiology and Risk Factors

Cigarette smoking is the single most important environmental aetiological factor. Other risk factors include chemical exposure to aromatic amines, aniline dyes in industries, analgesic abuse, and schistosoma infestation in certain regions of the world.

Pathology

Carcinoma of bladder is a heterogeneous disease which presents as superficial, muscle invasive, or metastatic disease. Morphologically, the majority (70%) are exophytic papillary tumours confined to mucosa (Ta) or invade submucosa (T1). About 50% to 70% of superficial tumours recur and 5% to 20% of them progress to invasive disease. Histopathologically, the majority of bladder cancers are transitional cell carcinomas (90% to 95%). Low-grade tumours have high local recurrence rate but usually do not invade muscularis. High-grade superficial tumours have high propensity to transform to invasive tumours. All invasive tumours are high grade.

Clinical Features

Patients usually present with painless haematuria (80% to 90%) or with unexplained urinary frequency or irritative voiding symptoms. Lower urinary irritative and obstructive symptoms may be the sole presenting symptoms in the absence of haematuria. The currently accepted staging classification of primary bladder cancer is as follows:

Ta : Non-invasive papillary carcinoma
T1 : Invasion of lamina propria
T2 : Invasion of muscularis propria
T3 : Invasion of perivesical tissues
T4 : Invasion of adjacent organs or pelvic/abdominal wall

Investigations

Cystoscopic examination of the bladder and pathological evaluation of the resected lesion form the cornerstone of diagnosis. Transurethral resection of the bladder tumour (TURBT) is the most important test for judging the depth of tumour penetration. Inclusion of muscle in biopsy is essential. An important component of the work-up is examination under anaesthesia after TURBT to evaluate the presence of residual induration and mass. CECT of chest, abdomen and pelvis and urine cytology are the other investigations that are done at initial evaluation and follow-up.

Management

Treatment of non-muscle invasive disease

TURBT is the standard of care for superficial bladder cancers. The goal of TURBT in Ta/T1 bladder tumours is to make correct diagnosis and remove all visible lesions. These tumours are classified as low or high risk based on tumour grade, size, number, and invasion of lamina propria. Based on their risk stratification patients receive either intravesical chemotherapy or Bacillus-Calmette Guerin. They are followed up with serial cystoscopies after treatment to monitor for recurrence.

Treatment of muscle-invasive disease

Radical cystectomy is the preferred treatment for invasive bladder cancers in patients whose medical condition allows a major surgical procedure. Pelvic lymphadenectomy is routinely performed as a part of radical cystectomy for bladder cancers. Such patients may also benefit from neoadjuvant chemotherapy using either the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or gemcitabine-cisplatin combinations. Bladder conservation can be done in selected patients with multi-modality treatment involving neoadjuvant chemotherapy followed by concurrent chemoradiation.

Chemotherapy for metastatic bladder cancer

The common sites of metastatic spread include lymph nodes, lung, liver, and bones. Chemotherapy is the standard therapy for patients with metastatic bladder cancer in good performance status. The gemcitabine-cisplatin combination is often used.

TESTICULAR CANCER

Testicular cancer constitutes about 1% of all malignancies in males in India. Germ cell tumours (GCT) comprise of 95% of malignant tumours arising from testis. These tumours predominantly affect young males. Testicular tumours in elderly males are usually lymphoma or seminoma.

Aetiology and Risk Factors

Numerous studies have established cryptorchidism as a major risk factor for the development of testicular cancer with the relative risk being 2.5 to 17 folds. Importantly this risk also extends to the contralateral normally descended testis indicating that the propensity for cancers is due to the abnormal gonadal development rather than malposition. The putative protective effect of orchiopexy is controversial and never well established. Patients with Klinefelter syndrome are also at increased risk for mediastinal GCT.

Pathology

Testicular GCT is considered by many to represent the malignant counterpart of normal embryonic components. It is classified into two major subgroups: seminoma and non-seminoma. Seminomas comprise about 40% of all germ-cell neoplasms and

are considered to have spermatocyte as the normal counterpart. Non-seminomatous GCT include embryonal carcinoma, endodermal sinus or yolk-sac tumour, choriocarcinoma, teratomas (mature, immature and with malignant transformation), and mixed tumours with more than one component. The most common genetic abnormality in GCT is an isochromosome of the short arm of chromosome 12. These tumours spread by lymphatics to retroperitoneal lymph nodes and haematogenously to lung, liver, and other sites. Pure seminomas are associated with raised lactate dehydrogenase (LDH), β–beta-hCG (less than 5 times) but never α-fetoprotein(AFP). Non-seminomatous GCT are often associated with raised β-hCG, LDH, and AFP which constitute valuable tumour markers that are useful in the diagnosis and follow-up. The most marked increase in β-hCG is seen in choriocarcinomas and the most marked increase in AFP is seen in endodermal sinus tumours.

Clinical Features

A testicular tumour usually presents as a painless scrotal swelling, heaviness, tenderness, and loss of testicular sensation. Involvement of retroperitoneal lymph nodes may produce back pain or abdominal swelling. Widely disseminated parenchymal disease in lungs, liver, bone, and brain is uncommon but, if present, may produce systemic symptoms. The currently accepted staging for testicular cancer is the TNM system that incorporates tumour markers in addition to the usual information on tumour, nodes, and metastases.

Stage I : Tumour confined to the testis/spermatic cord or scrotum with or without elevated markers

Stage II : Involvement of regional (retroperitoneal) lymph nodes

Stage III : Presence of distant metastasis to either non-regional lymph nodes/lung or other sites

In addition to the staging, metastatic GCT are classified into low, intermediate and high risk categories based on the histology (seminoma *versus* non-seminoma), location of the primary (gonadal *versus* extra-gonadal), location of the metastases (pulmonary *versus* non-pulmonary), and tumour marker levels. This International Prognostic Risk Stratification is important since treatment strategy is based on the risk category and it is accurately prognostic.

Investigations

The diagnosis of testicular cancer is based on clinical suspicion. High resolution bilateral trans-scrotal ultrasound can reliably differentiate a solid testicular mass from hydrocoele and paratesticular masses and is a useful initial diagnostic evaluation. In suspected case of testicular cancer, biopsy should not be performed. Serum tumour markers (AFP, β-hCG, LDH) and CECT scan of chest, abdomen and pelvis are required for staging and risk stratification.

Management

High inguinal orchiectomy is the initial procedure that is both diagnostic and therapeutic. Routine retroperitoneal lymphadenectomy in clinically and radiologically negative patients is controversial and not universally practiced. Tumour markers should be repeated after surgery. Subsequent treatment is planned according to histology, tumour marker levels, and metastasis.

Seminoma

Localised disease is curable with orchiectomy and either low-dose adjuvant radiotherapy to para-aortic nodes or single-dose carboplatin (dosed to an area under curve of 7) in more than 95% of patients. In view of the low toxicity of single cycle of carboplatin, this has become the standard of care in many institutions. Patients with non-bulky stage II disease are treated with radiation to retroperitoneal and ipsilateral pelvic lymph nodes, which results in risk of relapse less than 5%. An acceptable alternative is combination chemotherapy with the BEP (bleomycin, etoposide and cisplatin) or EP (etoposide and cisplatin) regimens. Patients with bulky stage II or stage III disease are treated with chemotherapy that results in cure rate of more than 90%. Post-chemotherapy retroperitoneal lymphadenectomy can prevent subsequent relapse in selected patients.

Non-seminomatous germ cell tumour

In patients with stage I and non-bulky stage II non-seminomatous GCT, 2 to 3 cycles of BEP or 4 cycles of EP result in cure rate of more than 95%. Some centres advocate prophylactic retroperitoneal lymph node dissection (RPLND) in patients with stage I disease to obviate the need for chemotherapy. In patients with bulky stage II and good risk stage III disease, the treatment of choice is BEP chemotherapy given up to 2 cycles beyond marker normalisation, which is usually a total of 3 cycles. Any residual masses post-chemotherapy should be surgically removed since these can harbour mature teratoma. Cure rates of more than 80% can be expected in this group of patients. In patients with intermediate and high risk metastatic non-seminomatous GCT, 4 cycles of the BEP regimen is considered a standard treatment, but this will be inadequate in up to half of these patients. These patients require second-line chemotherapy with more complex and toxic regimens. Surgical consolidation of residual post-chemotherapy masses is a critical component of a successful therapeutic strategy in these patients.

Prognosis

Testicular tumours are one of the most curable cancers even in the presence of metastatic disease. Localised tumours have long-term survival of more than 95%. Good risk metastatic tumours have 80% to 90% survival compared to 50% in high risk metastatic tumours.

PROSTATE CANCER

Prostate cancer is the most common non-cutaneous cancer among males in the West. The age adjusted incidence rate in urban Indian population is about 6 to 8 per 100,000 compared to 60 to 120 in the Western populations. This disparity is fuelled, at least partly, by the widespread adoption of prostrate specific antigen (PSA) screening in the latter regions. The natural history of clinically localised disease is variable, with lower-grade tumours having a more indolent course, while some high-grade lesions progress rapidly to metastatic disease. The indications for screening are controversial as it may result in treatment of those tumours that may never manifest in individual's life time. The United States Preventive Services Task Force specifically recommends against routine PSA screening in the population.

Aetiology and Risk Factors

Androgens are a major driving force for normal prostate development and are also implicated in its carcinogenesis. There is a high incidence of clinically occult cancers in autopsy series of older men dying of unrelated causes indicating that most cancers are not responsible for morbidity and mortality. Apart from increasing age, other risk factors for prostate cancer include high body mass index, Western lifestyle, and African-American ancestry.

Pathology

A large number of cancers arise from prostatic acinus and are adenocarcinomas. They are now universally graded according to the Gleason system that essentially scores the dominant and the next most common pattern along a scale of 1 (well differentiated) to 5 (poorly differentiated). The final score is obtained by adding the two scores, e.g. 4 + 3 = 7.

Clinical Features

Many patients are diagnosed because of incidental digital rectal examination and PSA estimation. Some patients present with haematuria, obstructive or irritative urinary complaints. Metastatic symptoms include weight loss and loss of appetite, bone pain or features of cord compression. Prostate cancer has a marked propensity to metastasise to bones, especially those in the axial skeleton. The classical bone metastasis from prostate cancer are osteoblastic. Other sites of metastasis include lymph nodes, lung, liver and brain. The most commonly used staging systems in clinical use are the TNM and the American Urological Association staging. It is useful to think of prostate cancer as organ (prostate) confined, locally advanced (involvement of seminal vesicle or regional nodes), and metastatic.

Investigations

The appropriate tests include trans-rectal ultrasound (TRUS), serum PSA, conventional MRI or MRI with endorectal coil, CECT of abdomen and pelvis, radionuclide bone scanning, and chest radiograph. TRUS-guided biopsies of involved and uninvolved peripheral regions are essential for establishing the diagnosis.

Management

The appropriate options for the management of localised low-stage cancers include watchful waiting, radical prostatectomy and external beam or interstitial radiation therapy. The first option is generally chosen for unfit patients. There is no conclusive evidence of the superiority of surgery over radiation, but the pattern of morbidity is different. Patients with high-risk cancers are candidates for adjuvant androgen deprivation therapy usually in the form of an luteinising hormone releasing hormone (LHRH) agonist like goserelin. In patients with locally advanced cancers, neoadjuvant hormonal therapy using androgen deprivation followed by local radiation is a common treatment approach. The hormonal manipulation is continued for up to 3 years in this group of patients. In patients with metastatic cancer, the initial treatment of choice is androgen deprivation therapy, either by bilateral orchidectomy or use of LHRH agonists. The initial addition of anti-androgen drugs like bicalutamide or flutamide to androgen deprivation ('total androgen blockade') has not been proven to be more efficacious compared to androgen deprivation alone. The anti-androgen drugs and ketoconazole are an option after disease progression on androgen deprivation. In patients with androgen independent tumours, the therapeutic options include withdrawal of anti-androgen drugs and chemotherapeutic agents like docetaxel, estramustine and mitoxantrone. Bisphosphonates like zoledronic acid have been shown to reduce the skeletal morbidity and symptoms in patients with bone metastasis. Recently, newer drugs like abiraterone (an androgen biosynthesis inhibitor) and cabazitaxel (a chemotherapeutic agent) have been approved for advanced prostatic cancer.

CARCINOMA OF PENIS

It is an uncommon malignancy in Western countries, but in India and other developing countries it is not so uncommon. In some parts of Asia, Africa and South America, its incidence is as high as 10% of all cancers as compared to 3% in developed countries. In recent times, there has been some decrease in its incidence, which may be attributed to better personnel hygiene and health awareness.

Aetiology

Penile cancer has been very strongly associated with poor local hygiene and phimosis. In various studies phimosis was associated with penile cancer in more than 50% of cancers. The accumulation of smegma under the prepuce leading to irritation and secondary bacterial infection has been proposed to be the mechanism of cancer development. Neonatal circumcision as practised by Jewish community has been found to virtually eliminate the risk of cancer of penis. Penile cancer has been strongly associated with phimosis as it is found in more than half of the patients in most large series. Circumcision in childhood or after puberty does not have benefit comparable to neonatal circumcision.

Infection with human papillomavirus (HPV) particularly HPV 16, exposure to multiple sexual partners, as well as use of tobacco products has been found to be associated with penile cancer. Thus, avoidance of tobacco products, neonatal circumcision, and maintaining penile hygiene represent important preventive strategies against penile cancer.

Pathology

The most common histology of penile cancer is squamous cell carcinoma, which constitutes more than 95% of all penile cancers, while others may include melanoma, basal cell carcinoma, lymphoma, and sarcomas. The squamous cell carcinomas are graded using Broders' classification. Low-grade tumours (grade I and II), which are typically confined to prepuce and glans penis, constitute nearly 80% of penile cancers. On the other hand, most lesions involving shaft of the penis are high-grade (grade III). Thus, grade and stage are often correlated. Lymph node metastasis depends upon the vascular invasion in the surgical specimen. The exuberant variant of squamous cell carcinoma known as verrucous carcinoma has a very low potential for lymph node metastasis and therefore has a good prognosis.

Penile cancers are associated with various pre-malignant stages which allow clinicians the opportunity for early diagnosis and cure. The various pre-malignant lesions are leucoplakia, balanitis xerotica obliterans, Buschke löwenstein tumour.

Clinical Features

Local signs and symptoms of erythema or induration to a frankly ulcerated, fungating, foul-smelling mass is the common presenting feature, while pain is not usually prominent. The prepuce and glans are most commonly involved and it is usually associated with a tight phimosis. In late stages of cancer, the shaft of penis get involved leading to its destruction. Urethral involvement is late and it usually results in urethral erosion leading to multiple urethral fistulas. In India and other developing countries, it has been found that the 50% of patient's delay taking medical advice by up to 1 year.

Diagnosis and Staging

The work-up includes thorough genital and inguinal nodes examination to evaluate the local and regional extent of disease. The most important prognostic marker in penile cancer is local lymph node involvement. The most common metastatic sites are bone, lung, and liver. The TNM classification is used to stage the primary tumour and the extent of nodal metastasis.

In early stage, local disease, no radiologic imaging is required while in obese patients, a CECT pelvis may be done to evaluate the inguinal nodes status and in few aggressive cancers, a contrast-enhanced MRI may be required.

Management

Surgical therapy

The management of penile cancer is mainly surgical and in selected cases, radiotherapy is done. The treatment of the primary lesion includes a 2 cm proximal margin of resection to avoid local recurrence and is the standard of care. Leaving the patient with inadequate penile length for hygienic upright micturition and sexual intercourse should be avoided. The partial or total penectomy is done depending upon the primary cancer stage.

In advanced stages (T4), various operative procedures include emasculation hemipelvectomy, or even hemicorpectomy.

Radiotherapy

It is effective in a select group of patients. It is attractive from a cosmesis point of view but has significant disadvantages in the form of tumour recurrence rate. Radiation therapy permits preservation of the penis, thereby obviating the psychosocial and physical morbidity caused by partial or total penectomy. External-beam and brachytherapy techniques have been used for treatment of the primary cancer. Circumcision is usually recommended before the radiation therapy to prevent post radiation secondary phimosis and it also helps in better evaluation of tumour extent. Although radiation has been shown to control early (T1 and T2) lesions with a 65% to 80% success rate, treatment of more advanced T-stage penile cancers is fraught with local recurrences (20% to 40%) and significant risk of tumour progression to nodal and systemic disease with loss of the window of curability.

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21.12 Gynaecological Malignancies

PP Bapsy, Ankit Jain

Gynaecological malignancies constitute 15% of all cancers in women and remain a major problem throughout the world. In India, cancer of the cervix uteri is the most common cancer in women.

CARCINOMA CERVIX

Cervical cancer is the second most common malignancy in women worldwide, and remains a leading cause of cancer deaths in women from developing countries. It had bimodal age peaks, the first being in the third decade and the second in the sixth decade with median age at 51.4 years. It is one of the cancers which showed a marked change in epidemiological trend that was attributed to mass screening with Papanicolaou tests (Pap smears). Due to inadequacy of screening and social attitudes cancer cervix in developing countries is diagnosed at an advanced stage.

Aetiology

Early epidemiological data demonstrated a direct causal relationship between cervical cancer and sexual activity. Major risk factors observed includes; sexual intercourse at a young age, multiple sexual partners, promiscuous male partners, and history of sexually transmitted diseases.

However, the search for a potential sexually transmitted carcinogen had been unsuccessful until breakthroughs in molecular biology enabled scientists to detect a viral genome in cervical cells. Strong evidence now implicates human papilloma viruses (HPV) as a prime suspect. Approximately 95% of the cervical cancers are associated with HPV. The high-risk HPV includes types 16, 18, 31 and 33. The disease is aggressive in HPV-positive individuals. Three main factors have been postulated to influence the progression of low-grade squamous intra-epithelial neoplasia (SIL) to high-grade SIL. These include the type and duration of viral infection and high-risk HPV type.

Natural History

The squamo-columnar junction of the cervix is the most common site for continuous metaplastic changes and most cancers arise from this zone. The mean age of women with cervical intra-epithelial neoplasia (CIN) is 15.6 years younger than women with invasive cancer; suggesting a slow progression of CIN to carcinoma *in situ* (with an intact basement membrane) and invasive cancer (invasion beyond the basement membrane). It may later penetrate the cervical stroma and invade lympho-vascular channels.

Cervical cancer usually follows a relatively orderly pattern of metastatic progression. Spread may occur by direct invasion into cervical stroma, corpus vagina and parametrium, lymphatic permeation and metastasis which in turn is taken into consideration for staging. Although cervical cancer can spread to all pelvic nodes, the obturator nodes are most frequently involved. Haematogenous spread occurs most commonly to lung, liver and bone, less common sites are bowel, adrenal glands, spleen and brain.

Pathology

The various pathological types of cervical cancer are listed in **Table 1**.

Table 1: Histological Types of Carcinoma Cervix

Squamous cell cancer
Anaplastic small cell cancer
Neuro-endocrine differentiation
Adenocarcinoma
Others-mixed Müllerian
Adenosarcoma
Leiomyosarcomas
Lymphoma
Melanoma
Metastatic-breast, colon

Clinical Features

Abnormal vaginal bleeding (post-coital, inter-menstrual, post-menstrual or post-menopausal) is the commonest symptom. In sexually inactive women, the disease is asymptomatic until late stage. Malodorous discharge may arise due to invasion of bladder or bowel which occurs very late in the course of the disease. Examination usually reveals exophytic, endophytic, ulcerative, or polypoid lesions. It should include palpation of groin nodes, liver, and supraclavicular areas to exclude metastasis.

Diagnosis

Early diagnosis can be extremely difficult due to asymptomatic nature of early disease, origin of some tumours in the endo-cervical canal, and false-negative Pap smears.

Colposcopy

Colposcopy is the examination of epithelium of the cervix, genital tract, and ano-genital area using magnified illumination after application of specific solution (3% to 5% acetic acid, Lugol's iodine) to detect abnormal appearances consistent with neoplasia or to affirm normality. The characteristic appearances arise from magnification and illumination of underlying capillaries and abnormal Pap smear.

Biopsy

Obvious tumour growth should undergo punch biopsy for histological confirmation. A cervix that appears unusually firm or expanded should be subjected to a biopsy and endocervical curettage (ECC).

Once the diagnosis is established, imaging studies are performed for staging purposes. A routine chest radiograph

should be obtained to help rule out pulmonary metastasis. Computed tomography (CT) of the abdomen and pelvis is performed to look for metastasis in the liver, lymph nodes, or other organs and to help rule out hydronephrosis/hydroureter. Trans-vaginal ultrasound (TVS) is recommended wherever CT is not performed. Cytoscopy is usually reserved to confirm the abnormal findings in the CT/TVS. Magnetic resonance imaging (MRI) delineates better than CT, hence it is likely to be a more useful imaging study to decide on operability.

Screening

Screening for cervical cancer is one of the most prevalent and successful public health measures for the prevention of cancer. False-negative rate for Pap smear is 10% to 18% and a negative Pap smear should not be relied on in symptomatic patients. Sensitivity ranges from 50% to 98%. A simple flow-chart of the management of abnormal Pap smear is shown in **Figure 1**.

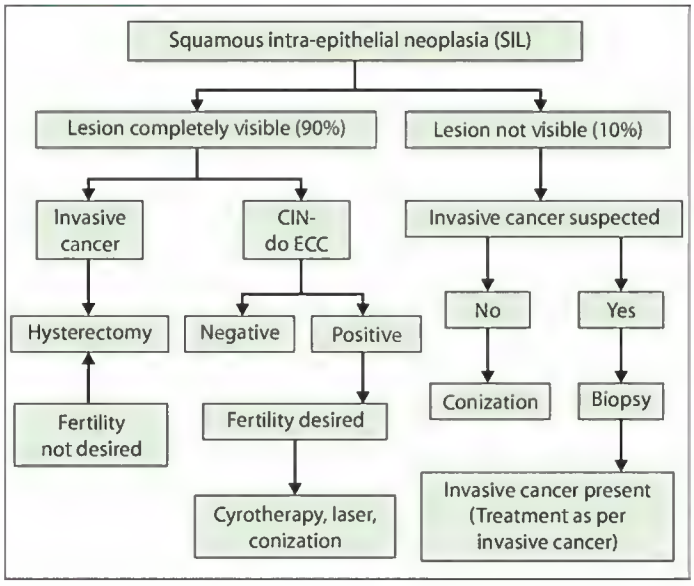


Figure 1: Management of abnormal Pap smear.

CIN = Cervical intra-epithelial neoplasia; ECC = Endocervical curettage.

American Cancer Society screening suggests Pap test and pelvic exam yearly for all women who have reached 18 years of age. After three normal tests, Pap tests can be carried out less often at the discretion of the physician. The recent WHO guideline recommends at least one Pap smear in the lifetime of women in developing countries. Indian Council of Medical Research recommends at least one Pap smear before the age of 40 years.

Staging

The International Federation of Gynecology and Obstetrics (FIGO) or TNM staging system is followed all over the world. The comparison of the staging systems with 5-year survival is shown in **Table 2**.

Prognostic Factors

The FIGO stage of the cervical cancer is the most important prognostic factor (**Table 2**). Other prognostic factors include patient's age, performance status, and biological markers like aneuploidy and S phase fraction.

Table 2: FIGO Staging of Cervical Cancer with 5 years Overall Survival (OS)

TNM	Cervix Uteri	FIGO	5 Years Survival
Tis	*In situ*	0	100%
T1	Confirmed to uterus		I
T1a	Diagnosed only by microscopy	IA	>95%
T1b	Clinically visible or microscopic lesion, ≤ 4cm	IB	IB 80 to 90%
T2	Beyond uterus but not pelvic wall or lower third vagina		II
T2a	No parametrium	IIA	80%
T2B	Parametrium	IIB	65 to 75%
T3	Lower third vagina/pelvic wall hydronephrosis		III
T3A	Lower third vagina	IIIA	40 to 50%
T3b	Pelvic wall / hydronephrosis	IIIB	30 to 40%
T4	Mucosa of bladder /rectum; beyond true pelvis	IVA	10 to 15%
M1	Distant metastasis	IVB	0%

Treatment

Stage IA: The treatment of choice for stage 1A disease is surgery—total hysterectomy; radical hysterectomy and conization are accepted procedures. Intra-cavitary radiation is an option for selected patients.

Stage IB or IIA: For patients with stage IB or IIA disease, treatment options are either combined external beam radiation (presently) concurrent chemo-radiation with cisplatin given at 40mg/m^2 per week during the course of radiation therapy with brachytherapy or radical hysterectomy with bilateral pelvic lymphadenectomy. Most retrospective studies have shown equivalent survival rates for both procedures, although such studies usually are flawed due to patient selection bias and other compounding factors. However, a recent randomised study showed identical overall and disease free survival rates.

Stage IIB/III/IV A: Concurrent chemo-radiation is the treatment of choice.

Stage IV B: Usually treated with irradiation to palliate central disease or distant metastasis. Chemotherapy with cisplatin, 5-FU, ifosfamide, paclitaxel, irinotecan, gemcitabine may be tried, but responses are ill-sustained and survival benefit is minimal.

Recurrence

Recurrence following surgery is treated with radiotherapy. It is often used individually to control bleeding, pelvic pain, or urinary or partial large bowel obstructions from pelvic disease. Palliation with chemotherapy is an alternative if initial modality of treatment is radiation.

UTERINE CANCER

Endometrial cancer is the fourth most common cancer in women, following breast, lung, and colorectal cancer, in that order. However, in developing countries, it is much less common than carcinoma of the cervix. The median age of persons with this malignancy is early in the 7th decade of life, although most patients are aged 50 to 59 years. Approximately

5% cases of endometrial carcinoma can be in women younger than 40 years of age.

Aetiology

Multiple epidemiological risk factors have been identified which include obesity (10-fold increase), nulliparity (2-fold) and late menopause (aged >52 years), all secondary to the unopposed oestrogen action. In recent times, tamoxifen, one of the most widely used anticancer drug has been suggested to cause an increased incidence of carcinoma body uterus. Other factors include smoking, sedentary lifestyle, and some genetic syndromes.

Natural History

Endometrial cancer may originate in a diffuse multi-focal pattern. Early tumour growth is characterised by an exophytic and spreading pattern. Later tumour growth is characterised by myometrial invasion and growth towards the cervix. Four routes of spread occur beyond the uterus. Direct/local spread accounts for the majority of local extension beyond the uterus. Lymphatic spread to pelvic, para aortic, and, rarely, inguinal lymph nodes.

Haematological spread is responsible for metastases to the lungs, liver, bone, and brain (rare). Peritoneal/trans-tubal spread results in intraperitoneal implants, particularly with uterine papillary serous carcinoma (UPSC), similar to the pattern observed in ovarian cancer.

Pathology

Sixty per cent of endometrial carcinomas are adenocarcinomas. Other histological subtypes include adenosquamous, clear cell and papillary serous carcinomas. Sarcomas make up about 4% of the uterine corpus malignancies, including carcinosarcomas or mixed homologous Müllerian tumours (48% to 50%), leiomysarcomas (38% to 40%) and endometrial sarcomas containing histological components foreign to the uterus, such as rhabdomysarcomas, osteosarcomas, and chondrosarcomas.

Clinical Features

The most common symptom in up to 90% of women is post-menopausal bleeding. Most women recognise the need for prompt evaluation, although only 10% to 20% of the women with post-menopausal vaginal bleeding have a gynaecological malignancy. Because of this prompt evaluation, 70% to 75% of the women are diagnosed with surgical stage I disease. Because bleeding usually occurs from the endometrium, pelvic examination findings may be entirely normal, with no gross evidence of disease on the cervix and with a normal-sized uterus.

Screening

Currently, no screening tests for cancer of the uterus are recommended for asymptomatic women.

Diagnosis

Besides routine haematological tests, there is no specific marker for the carcinoma body uterus. The histological confirmation is obtained by endometrial sampling.

Imaging

Trans-vaginal ultrasound (TVS) is the commonest investigation employed. Chest radiographs are useful in the work-up to exclude distant metastases. Computed tomography and/or MRI are typically not necessary in the work-up of endometrial cancer or uterine sarcomas because the first-line therapy for the vast majority of these patients includes exploratory surgery. Local extension and metastatic disease, requiring comprehensive staging, can be predicted using clinical evidence, including obvious cervical disease and high tumour grade on the endometrial biopsy specimen.

Staging

The commonly used FIGO staging is represented in **Table 3**.

Table 3: FIGO Staging System for Uterine Cancer

Stage IA:	Tumour limited to endometrium
Stage IB:	Invasion to less than one half the myometrium
Stage IC:	Invasion to more than one half myometrium
Stage IIA:	Endo-cervical glandular involvement only
Stage IIB:	Cervical stromal invasion
Stage IIIA:	Tumour invades serosa and/or adnexa and/or positive peritoneal cytology
Stage IIIB:	Vaginal metastasis
Stage IIIC:	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IVA:	Tumour invasion of bladder and/or bowel mucosa
Stage IVB:	Distant metastases including intra-abdominal and/or inguinal lymph nodes
According to the degree of histological differentiation they are graded into:	
Class G1:	Non-squamous or non-morular solid pattern of 5% or less
Class G1:	Non-squamous or non-morular solid pattern of 6% to 50%
Class G1:	Non-squamous or non-morular solid pattern of more than 50%

Treatment

Surgery is the treatment of choice and whenever feasible the patients should undergo either simple or modified radical hysterectomy. Radiation therapy, chemotherapy and hormonal therapy play a minor role in the treatment of uterine cancers. Of these only radiotherapy has some place in primary therapy for early endometrial cancer and uterine sarcomas. It is (total dose to tumour of up to 80 Gy) the treatment of choice for those patients who are poor surgical candidates. It is used in adjuvant setting in cases of node-positive disease and positive surgical margins. It can also be used with palliative intent in stage IVA.

Role of hormone therapy is limited and medroxyprogesterone acetate. Megestrol therapy is efficacious for those low-grade tumours that are oestrogen and/progesterone receptor-positive in adjuvant and palliative settings.

If advanced disease is not amenable to localised/whole abdominal radiotherapy or hormonal therapy, chemotherapy is initiated. Doxorubicin, cisplatin, and taxanes are the most effective agents used. Combination of the two agents increases the progression-free interval, with a complete remission in about 10% to 15% of the cases and a partial response in 25%.

Survival

Overall 5-year survival rates for all grades and histological subtypes are 87%, 72%, 51%, and 9% for surgical stage I, II, III, and IV disease, respectively.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic neoplasia (GTN) can be benign or malignant. Histologically, it is classified into a hydatidiform mole, an invasive mole (chorioadenoma destruens), choriocarcinoma, and a placental site trophoblastic tumour (PSTT). Three per cent of patients with hydatidiform mole develop choriocarcinoma. The incidence is 1500 times more after molar pregnancy than normal term delivery. Choriocarcinoma is twice as common in antecedent hydatidiform mole (29% to 83%) followed by ectopic pregnancy (11% to 42%) and live-births (5% to 34%).

Pathology

Histologically, hydatidiform moles look like placental tissue, but oedema of the villi demonstrates varying sizes. During the proliferation of the trophoblast there is no/or scarce development of foetal blood vessels. Therefore, tumour relies on vessels of the tissue it invades. The syncytio-trophoblast is largely responsible for secretion of β-human chorionic gonadotrophin (β-hCG). Choriocarcinoma are aneuploid and can be heterozygous, depending on the type of pregnancy from which the choriocarcinoma arose. If a hydatidiform mole preceded the choriocarcinoma, the chromosomes are of paternal origin. Maternal and paternal chromosomes are present if a term pregnancy preceded the choriocarcinoma.

Clinical Features

Majority of the patients present within a year of an apparently normal pregnancy or non-molar abortion. Vaginal bleeding or blood-stained discharge may be associated with or without abdominal pain and mass. Extra-uterine masses and ovarian involvement are common. One-third of the patients may present with features due to distant pulmonary or brain metastasis. Occasionally thyrotoxicosis is present with very high levels of hCG because of cross-reaction between alpha subunit of hCG and TSH. Common sites for metastasis are lungs (80%), vagina (30%), pelvis (20%) and brain (10%). Bowel metastasis (<5%) may present with haemorrhage, intra-peritoneally or within the lumen of the bowel.

Investigations

Besides routine haematology and biochemical parameters, β-hCG is mandatory in all the patients. It is a peptide with half-life of 24 to 36 hours and the most sensitive and specific marker for trophoblastic tumours. It gives an indication of tumour volume. Serial measurements are used to monitor progress of disease and response to therapy.

Imaging

Chest radiograph and ultrasound of abdomen and pelvis are mandatory in all cases. Computed tomography of the brain is indicated in symptomatic cases.

Staging

The official International FIGO staging of gestational trophoblastic disease is: stage I—confined to the uterus, II—limited to genital structures, III—lung metastases, IV—other metastases.

Prognosis

Revised WHO scoring system is followed to determine the prognosis (**Table 4**).

Table 4: WHO Scoring System

Prognostic factor	0	1	2	4
Age	<35	>35		
Pregnancy	Mole	Abortion	Term	
Interval	<4 mo	4 to 6 mo	7 to 12 mo	>12 mo
Serum β-hCG	<1,000	<10,000	<1,00,000	>1,00,000
Site of Metastases	Lung	Spleen kidney	Gastroin-testinal	Liver, brain
Size of largest tumour			3 to 5 cm	>5 cm
Number of metastases		1 to 4	4 to 8	>8 cm
Prior chemotherapy			Single agent	Multiple

Total score: 0 to 4, low risk; 5 to 7, intermediate risk; >8, high risk for death.

Treatment

A scheme for management of gestational trophoblastic disease is shown in **Figure 2**. The brief protocol is represented in **Table 5**.

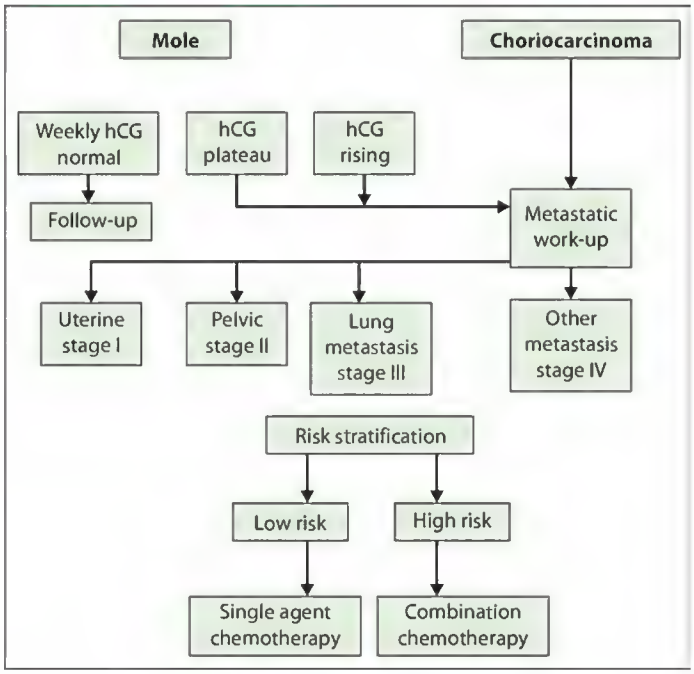


Figure 2: Management of gestational trophoblastic disease.

Hydatidifom mole is treated by suction and evacuation. Hysterectomy is reserved for resistant cases, persistent β-hCG elevation, and choriocarcinoma in excised tissue, metastatic disease, and bleeding or placental site gonadal trophoblastic tumours. β-hCG levels should be done weekly during treatment and chemotherapy should be administered for two cycles after the normal β-hCG level

Patients should be under close follow-up with monitoring of β-hCG levels done weekly for the first six weeks and month if any affected or rise in β-hCG levels denotes resistant disease and warrants change of chemotherapy regimen.

Survival

Low-risk patients have a complete cure. Patients with medium risk have a 98% long-term survival. Prognosis disease treated with combination chemotherapy have 93% survival if they have

Table 5: The Brief Protocols for Gestational Trophoblastic Disease

Patient's Characteristics	Regimen	Schedule and Doses	Regimen	Repeated
Non-metastatic or low risk metastatic	MTX ACT-D	Methotrexate Leucovorin Actinomycin	1 mg/kg IM days 1,3,5,7 0.1 mg/kg IM days 2,4,6,8 10 to 13 µg/kg IV x 5 days	Every 2 weeks Every 12 days
Refractory disease	MAC	Methotrexate Actinomycin Chlorambucil†	0.3 mg/kg IV x 5 days 8 µg/kg IV x 5 days 0.15 mg/kg IV x 5 days	Every 3 weeks
High risk metastatic	EMA-CO	Etoposide Actinomycin Methotrexate Leucovorin Cyclophosphamide Vincristine	100 mg/m² IV days 1-2 0.5 mg IV push days1-2 100 mg/m² IV push, then 200 mg/m² IV over 12 hours day 1 15 mg IM or p.o.q12 h x4, 24 hours after MTX 600 mg/m² on day 8 1 mg/m² IV push on day 8	Every 2 weeks
Refractory disease	EMA-EP	Etopside‡ Cisplatin‡	100 mg/m² IV push day 8 80 mg/m² IV day 8	

† Moy substitute cyclophosphomide 3 mg/kg IV x 5 doys.
‡ Some os EMA-CO except substitute etoposide/cisplotin for vincristine, cyclophosphomide.

not received prior chemotherapy. Long-term survival is 74% for patients who received prior chemotherapy. Relapse after successful therapy does not indicate fatal outcome, even in high-risk group. Complete remission is possible in these patients with chemotherapy with or without surgery.

Follow-Up

Because of the potential to recur, patients should be followed up with β-hCG estimations. Patients are advised contraception for a year after completion of chemotherapy because raised β-hCG levels due to pregnancy may mask relapse and follow-up is then discontinued during pregnancy and then continued 3 weeks after delivery.

OVARIAN CANCER

Ovarian cancer is the most common cause of cancer death from gynaecologic tumours in the United States. Early disease causes minimal, non-specific, or no-symptoms making at least 70% of patients to present in an advanced stage.

Therefore, it is described as 'silent killer'; however, recent improvements in identification of the women at high risk for ovarian cancer, as well as improved imaging techniques, increase the likelihood of early detection. Many histological types exist, though more than 90% are epithelial tumours. The remaining are either stromal or germ cell tumours.

Pathophysiology

The commonly observed risk factors are increasing age and fertility. One common thing associated with all these factors is increased ovulation (which in turn causes rapid proliferation, and aberrant repair might generate a malignant clone). Most theories hypothesise that ovarian cancer begins with the de-differentiation of the cells overlying the ovary, which will be incorporated into it during ovulation and then proliferate. Ovarian cancer arises from coelomic epithelium. The other cancers arising from coelomic epithelium are fallopian tube carcinoma and primary peritoneal carcinoma.

Genetic factors might also play an important role in an estimated 10% of the patients. It has site-specific inheritance pattern and the patients are relatively young (30 to 50 years). Other risk factors include breast carcinoma (BRCA mutation - 60% risk of having ovarian cancer).

Pathology

The major pathological variants are described in **Table 6**. The most common histological type of epithelial ovarian cancer is serous type.

Table 6: Classification of Ovarian Neoplasms

Tumours of epithelial origin	Serous, mucinous, endometroid, clear cell
Germ cell tumours	Dysgerminomas, carcinoma, endodermal sinus tumour (yolk sac), teratomas-immature (embryonal)
Stromal tumours	Gonadoblastoma, Sertoli-Leydig cell, tumours, sex cord
Mesenchymal tumours	
Metastatic	Krukenberg
Miscellaneous	Fibromas, lymphoma

There is a small subgroup of patients who can present with borderline ovarian tumours also called as epithelial ovarian cancer with low malignant potential. These tumours present at younger age and surgery is the main stay of treatment.

Mode of Spread

Ovarian carcinoma can spread by local extension, lymphatic invasion, intra-peritoneal implantation (most common and recognised characteristic), haematogenous dissemination, and trans-diaphragmatic passage.

Clinical Features

The signs and symptoms of ovarian cancer are non-specific. Most patients present with symptoms of several months duration. Symptoms include abdominal/pelvic pain, vaginal bleeding, bloating, abdominal distension, irregular menses, or change in bowel habits. Majority of the patients present in advanced stage (III or IV). Palpable abdominal mass and ascites are the commonly described presenting features.

Diagnosis

Routine pre-operative tests include complete blood count (CBC), chemistry panel (including liver function tests), and a cancer antigen 125 assay (CA-125).

Cancer antigen-125

It is quite sensitive and all the women in reproductive age with complex cyst of more than 8 cm should undergo CA-125 monitoring. If the titres are rising, it is almost diagnostic of ovarian cancer. It is also useful to monitor the response to therapy. It should be remembered that it may be within normal limits in 50% of women with early ovarian cancer. If a patient presents with a raised CA-125 prior to surgery it should be used for follow-up after treatment. However, this is controversial, as treatment for biochemical relapse and for clinical relapse does not alter the natural history of disease.

Other markers

Include α-fetoprotein, β-hCG, and LDH whenever germ cell tumour is one of the differential diagnoses especially in younger women.

Imaging

Transvaginal USG (TVS) is recommended whenever there is dilemma. However, routine imaging is not required in all patients in whom ovarian cancer is highly suspected pelvic and abdominal CT scan is warranted in all cases prior to therapy to monitor the response. Chest radiographs are considered routine but CT scan of the chest is seldom indicated.

Staging

Ovarian cancer is surgically staged and the FIGO system is shown in **Table 7**.

Table 7: FIGO Staging System for Ovarian Cancer

Stage I: Growth limited to the ovaries

- Ia : Growth limited to one ovary, no ascites, no tumour on external surface, capsule intact
- Ib : Growth limited to both ovaries, no ascites, no tumour on external surface, capsule intact
- Ic : Tumour either stage Ia or Ib but with tumour on surface of one or both ovaries, ruptured capsule, ascites with malignant cells or positive peritoneal washings

Stage II: Growth involving one or both ovaries, with pelvic extension

- IIa : Extension and/or metastasis to the uterus or tubes
- IIb : Extension to other pelvic tissues
- IIc : Stage IIa or IIb but with tumour on surface of one or both ovaries, ruptured capsule, ascites with malignant cells from positive peritoneal washings

Stage III: Tumour involving one or both ovaries, with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastases equal stage III

- IIIa : Tumour grossly limited to pelvis, negative lymph nodes but histological proof of microscopic disease on abdominal peritoneal surfaces
- IIIb : Confirmed implants outside of pelvis in the abdominal peritoneal surface; no implant exceed 2 cm in diameter and lymph nodes are negative
- IIIc : Abdominal implants larger than 2 cm in diameter and/or positive lymph nodes

Stage IV: Distant metastasis, pleural effusion must have a positive cytology to be classified as stage IV; parenchymal liver metastasis equals stage IV

Prognostic Factors

Stage at presentation and volume of the disease after surgery are the most important risk factors. Patients with limited disease are classified as having low risk for recurrence if they have grade 1 or 2 disease, no tumour on external surface of the ovary, negative peritoneal cytology, no ascites, and tumour growth confined to the ovaries. They will be labelled as high risk if they have any of the above features. The other factors include CA-125 levels, age, performance status, and histological subtype (mucinous and clear cell having poor prognosis).

Treatment

Surgery and chemotherapy are the main modalities with radiation having a minimal role.

Surgical care

The standard care for ovarian cancer includes a primary staging and cyto-reductive or de-bulking surgical exploration (primary and secondary look). The staging procedure should include peritoneal cytology, multiple peritoneal biopsies, omentectomy and pelvic and para-aortic lymph node sampling.

Chemotherapy

For post-operative treatment, chemotherapy is indicated in all patients with ovarian cancer except those surgical-pathological stage I disease with low-risk characteristics. The single most active agent is platinum analogue (cisplatin and carboplatin) followed by taxanes. Other agents include alkylating agents (Cyclophosphamide, Ifosfamide, Melphalan) anthracyclines (Liposomal Doxorubicin, Adriamycin), gemcitabine, etoposide and topotecan. The present standard of therapy is a combination of taxanes with platinum analogues (T + P) showing maximum benefit compared to any other regimen.

Stage I: Total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) is the treatment of choice. Intra-peritoneal cisplatin or P32/pelvic radiation are rarely used in view of their higher toxicity, recurrence rates and availability of better and safer surgical alternatives.

Stage II/III: Options include aggressive primary cytoreductive surgery followed by chemotherapy (T + P) or neo-adjuvant chemotherapy followed by surgery. This choice is case to case dependent.

Stage IV: At present the intent is palliation and any of the above mentioned agents can be used. Single agent sequential is better in terms of quality of life of the patient compared to combination chemotherapy and the survival results are almost same. Other investigational agents are angiogenesis inhibitors and small molecular tyrosine inhibitors whose efficacy is yet to be proven.

Prognosis

Prognosis remain poor with 5-year survival rates for stage I, II, III, IV of 73%, 45%, 21%, and 5% respectively. Though in the early stages of treatment, a survival advantage was seen with the advent of taxanes and platinum-based chemotherapy, the situation in high-risk patients is far from satisfactory.

Prevention

Oral contraceptives (for general population) and prophylactic oophorectomy (for genetically predisposed patients) have been

tried as primary prevention modalities with the latter showing promising results. Secondary prevention, including routine pelvic examination, CA-125 levels and TVS, does not alter the cancer related mortality.

SEX CORD STROMAL TUMOURS

Commonest in the category is granulosa cell tumour, followed by Sertoli-Leydig cell tumours. They have excellent prognosis as they present in early stage (owing to hormonal effects like precocious puberty, virilisation, post-menopausal bleeding). Surgery is the treatment of choice (unilateral salpingo-oophorectomy in reproductive and pre-menarche females and TAH with BSO in menopausal women). Chemotherapy has a minimal role and whenever tried it is either with BEP (bleomycin, etoposide and cisplatin) or CAP (cyclophosphamide, adriamycin and cisplatin).

Other agents have minimal response rates. It can be tried prior to surgery to down stage or as a palliative treatment in stage IV disease. Hormonal agents like progestins also palliate symptoms in some patients and few reports suggest that they may prevent relapses in high-risk patients.

GERM CELL TUMOURS

These are uncommon in elderly and usually present in young women with an early stage disease. Most of the tumours are dysgerminomas. They are bilateral and often spread to retroperitoneal lymph nodes, they are highly radio and chemo sensitive, and either modality can be used in adjuvant setting for early stage disease after surgery. The remainder are predominantly unilateral with haematogenous metastases on occasions. Fertility can be preserved in vast majority of the patients with conservative surgical approaches and post-operative chemotherapy (BEP- the commonest regimen). Except for stage 1A, chemotherapy is indicated for all patients. Most patients have excellent prognosis even in advanced stages of disease.

VAGINAL CANCER

Primary cancer of the vagina constitutes 1% to 2% of the malignant neoplasms of the female genital tract; cure rates of even advanced cases should now be comparable with those of cervical cancer due to improved techniques of radiation therapy.

Eighty-four per cent of carcinomas involving the vagina are secondary, usually from cervix (32%), endometrium (18%), colon and rectum (9%) or vulva (6%). Endometrial carcinoma and choriocarcinoma commonly metastasise to the vagina, whereas tumours from bladder or rectum invade the vagina directly.

Radical surgery has been the mainstay of treatment. Radiotherapy may be effective in selected patients. The overall prognosis for patients with vaginal melanoma is poor because most cases present with deeply penetrating lesions at the time of diagnosis.

VULVA CANCER

Vulva cancers are usually squamous cell carcinomas diagnosed after the age of 60 years. The clinical presentation is usually a mass lesion which is treated with surgical excision. Pelvic node dissection and radiotherapy are used in advanced stages. Mitomycin C, bleomycin, cisplatin, and 5-FU are active but there is no definitive role for chemotherapy. Other cutaneous neoplasm like melanoma can also occur in this region. Paget's disease of the vulva can often present as a red inflamed pruritic mass.

FALLOPIAN TUBE MALIGNANCIES

These are the rarest of all gynaecological malignancies that are present in an early stage with symptoms pertaining to obstruction (pain) or mass (lump on abdomen). Majority of them are adenocarcinomas. The staging system, treatment and prognosis are very similar to carcinoma ovary.

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21.13 Soft Tissue Sarcomas

Avinash Deo

INTRODUCTION

Sarcomas are mesenchymal tumours. These are divided into two groups: (i) bone sarcomas, and (ii) soft tissue sarcomas (STS). Soft tissue sarcomas are sarcomas of muscles, tendons, fat, fibrous tissue, synovial tissue, vessels, and nerves. Soft tissue sarcomas are the commonest sarcomas. The group is heterogeneous in terms of histology and biological behaviour.

AETIOLOGY

The aetiology of most STS is unknown. Genetic factors, radiation, lymphoedema, and exposure to chemicals have been associated with STS. They do not appear to arise from the mature cell types they resemble. This is evident from the occurrence of sarcomas in areas where normal counterparts are absent, e.g. synovial sarcoma in the head and neck, and occurrence of sarcomas without a normal counterpart, e.g. peripheral neuroectodermal tumour.

Conditions with Predisposition to Soft Tissue Sarcomas

Soft tissue sarcomas have been associated with retinoblastoma, Li Fraumani syndrome, neurofibromatosis, Gardner's syndrome, naevoid basal cell carcinoma syndrome and tuberous sclerosis, which are conditions associated with mutations in tumour suppressor genes. Many of these sarcomas occur in radiated field, e.g. occurrence of head and neck STS in survivors of retinoblastoma.

Radiation

Radiation is probably the most convincing documented aetiological agent for STS. The sarcomas associated with radiation (in decreasing frequency) are osteosarcoma, malignant fibrous histiocytoma (MFH), and angiosarcoma or lymphangiosarcoma. Radiation-associated sarcomas have a reputation for originating close to the penumbra of radiotherapy fields. These have a poor prognosis.

Lymphoedema

Angiosarcomas have been associated with lymphoedema following breast cancer surgery and filarial lymphoedema has been associated with lymphangiosarcoma.

Chemicals

Phenoxyacetic acids, dioxin, and agent orange have been associated with STS. The association has not been convincingly documented. Thorotrast, vinyl chloride, and arsenic have been associated with angiosarcomas of the liver.

GENETICS

Cytogenetic anomalies are seen in a high proportion of STS particularly the high grade tumours. However, these are not consistent. Two anomalies worth mentioning are: (a) t(11;22)-(q24;q12) in Ewing's sarcoma/peripheral neuroectodermal tumour, and (b) t(X;18)(p11;q11) seen in synovial sarcomas. These are useful for the diagnosis. Other anomalies include t(11;22) (p13;q12) in desmoplastic round cell tumour; t(12;22) (q13;q12) in malignant melanoma of soft tissue; and t(2;13) (q35;q14) in alveolar rhabdomyosarcoma.

PATHOLOGIC CLASSIFICATION (TABLE 1)

The pathologist has a major contributory role in the management of STS, as therapy for STS depends on the size, grade, and resection margins of the tumour. Clinical trials of therapy of STS have clubbed subtypes. Though subtypes have a bearing on prognosis and behaviour, these are not important for the treatment planning, more because of lack of information than for any other reason. Soft tissue tumours may be benign or malignant. Some of the tumours have a borderline behaviour. The ratio of benign to malignant tumour is 100:1. Confusion between malignant and benign types may occur on small biopsies. It is important that the pathologist be provided with an adequate sample. Grade is determined from the cellularity, differentiation, pleomorphism, amount of necrosis, and number of mitoses in the tumour. There is a significant amount of discordance between experts about the diagnosis of sarcoma and its grade. Immunohistochemistry is a useful tool for the diagnosis of STS. The most useful immunohistochemical markers are the intermediate filaments (e.g. vimentin, keratin, desmin, leucocyte common antigen, S-100 protein). Cytogenetics and fluorescence *in situ* hybridisation (FISH) are also being used.

Table 1: Histopathological Types of Soft Tissue Sarcoma

Alveolar soft part sarcoma
Angiosarcoma
Dermatofibrosarcoma protuberans
Epithelioid sarcoma
Extra-skeletal chondrosarcoma
Extra-skeletal osteosarcoma
Fibrosarcoma
Gastrointestinal stromal tumour (GIST)
Leiomyosarcoma
Liposarcoma
Malignant fibrous histiocytoma
Malignant hemangiopericytoma
Malignant mesenchymoma
Malignant schwannoma
Malignant peripheral nerve sheath tumour
Peripheral neuroectodermal tumours
Rhabdomyosarcoma
Synovial sarcoma
Sarcoma, not otherwise specified (NOS)

Soft tissue sarcomas are commonest in the lower extremity (30%) followed by viscera (19%), retroperitoneal or intra-abdominal (15%), upper extremity (13%), and trunk (10%). Malignant fibrous histiocytoma is the most common histologic type (40%) followed by liposarcoma (25%). The metastatic

behaviour of sarcomas depends on grade, size, and site of origin. Metastasis are more common as the size and grade increases. Low grade tumours less than 5 cm seldom metastasise. The site of metastasis depends on the site of primary tumour. The extremity lesions metastasise to the lungs while the retroperitoneal or visceral lesions commonly metastasise to the liver.

CLINICAL FEATURES

Soft tissue sarcomas (STS) usually present as a large, often painless mass. The histological type varies with the site (**Table 2**). The distal extremity sarcomas are noticed earlier by the patient and hence present at an earlier stage. Sarcomas of the retroperitoneum grow to a large size before they are noticed, and hence, present at an advanced stage. This is also true to an extent about sarcomas of the proximal lower extremity. Sarcomas may present with pressure symptoms, e.g. neurovascular symptoms in extremity and retroperitoneal sarcomas (involvement of lumbar plexus).

Weight loss is uncommon. Factors associated with a poor prognosis include age older than 60 years, tumours larger than 5 cm or high-grade histology. Positive margins are associated with an increased risk of local relapse. The features of common sarcomas are listed in **Table 3**.

Table 2: Soft Tissue Sarcoma by Anatomical Site

Site	Common Tumours
Head and neck	Rhabdomyosarcoma, angiosarcoma
Chest wall	Liposarcoma, myogenic sarcomas
Gastrointestinal	Leiomyosarcoma, gastrointestinal stromal tumour (GIST)
Genitourinary	Leiomyosarcoma, rhabdomyosarcoma (tests), malignant mixed müllerian, endodermal sinus tumour (both uterus)
Retroperitoneum	Liposarcoma, leiomyosarcoma
Extremity	Malignant fibrous histiocytoma, liposarcoma, synovial sarcoma, fibrosarcoma

INVESTIGATIONS

Imaging Studies

The aim of imaging studies is to evaluate operability. This includes defining the extent of local disease, involvement of neurovascular bundles and other critical structures, and evaluation for metastasis. The imaging modalities include magnetic resonance imaging (MRI) and computed tomography (CT). Magnetic resonance imaging is preferred for extremities, while CT for retro-peritoneum and for evaluation of lungs for metastasis. Positron emission tomography is upcoming and useful for prediction of response to chemotherapy.

Biopsy

Biopsy is necessary for confirming the grade, histological type, and evaluation of margins in a resected specimen. It may be an open biopsy or a needle biopsy. Both the techniques are acceptable. Tissue may also be used for immunohisto-chemistry, electron microscopy, cytogenetics and FISH, in addition. Fine needle aspiration cytology (FNAC) is not appropriate for the diagnosis of STS and it may be used for the confirmation of recurrences. Frozen section is accurate for the diagnosis of malignancy but not for histological subtyping and grading.

Table 3: Features of Common Sarcomas

Tumour	Clinical Features	Remarks
Malignant fibrous histiocytoma	Commonest extremity STS; subtypes described but not found to be distinct on gene profiling Peak incidence in the 7th decade	Complex karyotype genes involved not known
Liposarcoma	Peak incidence from 50 to 65 years Commonest sites are thigh and retroperitoneum Three common types: well-differentiated or undifferentiated, myxoid or round cell and pleomorphic	Undifferentiated liposarcoma is characterised by ring or giant marker chromosomes on cytogenetic analysis
Fibrosarcoma	Usually in the 4th to 6th decade as a painful, deep-seated mass Thigh and trunk are the most common sites	—
Leiomyosarcomas	More than half are located in retroperitoneal or intra-abdominal sites Present insidiously, and reach a large size	—
Angiosarcomas	Lymphangiosarcoma occur in areas with lymphoedema Haemangiosarcomas are usually located in the skin or superficial soft tissue	—
Synovial sarcoma	Young adults, typically found in the para-articular areas of the tendon sheaths and joints, may also be encountered in regions without apparent relationship to synovial structures Higher risk of lymph node metastasis	t(X;18)(p11;q11)SYT-SSX1, SYT-SSX2 exhibits more favourable responses to chemotherapy than most other histologic subtypes
Malignant peripheral nerve sheath tumour	Oedema of the extremeties difficulty in movement of the limb having the tumour and soreness localised to the lymph Biopsy, MRI and CT scan are helpful	Treatment is similar to other sarcomas and is based on the age and type of tumour and vascularity

STAGING

American Joint Committee on Cancer (AJCC) staging system for STS is given in **Table 4**.

TREATMENT

Soft tissue sarcomas can be grouped into four groups for treatment, viz. (i) low-grade tumours (stage I); (ii) high-grade tumours (stage II and III); (iii) unresectable disease; and (iv) metastatic and recurrent disease. The aim of therapy is three-fold; to get local control, to get systemic control, and to get functional preservation.

Table 4: American Joint Committee on Cancer Staging of Soft Tissue Sarcomas

Tumour grade
GX : Grade cannot be assessed
G1 : Well differentiated
G2 : Moderately differentiated
G3 : Poorly differentiated
G4 : Poorly differentiated or undifferentiated

Primary tumour
TX : Primary tumour cannot be assessed
T0 : No evidence of primary tumour
T1 : Tumour 5 cm or less in greatest dimension
T1a : Superficial tumour
T1b : Deep tumour
T2 : Tumour 5 cm or larger in greatest dimension
T2a : Superficial tumour
T2b : Deep tumour

Nodes
NX : Regional lymph nodes cannot be assessed
N0 : No regional lymph node metastasis
N1 : Regional lymph node metastasis

Metastasis
MX : Distant metastasis cannot be assessed
M0 : No distant metastasis
M1 : Distant metastasis

Stage I: Low-grade tumour
G1, any T, N0, M0
G2, any T, N0, M0

Stage II: All small high-grade tumours; superficial large high-grade tumours
G3 or G4, any T1, N0, M0
G3, any T2, N0, M0

Stage III: Large deep high-grade tumours
G3 or G4, any T2, N0, M0

Stage IV: Presence of lymph node or distal metastasis
Any G, any T, N1, M0
Any G, any T, N0, M1

Management of Low-Grade Tumours

Low-grade small tumours tend to be locally aggressive and rarely metastasise. Surgical excision with a 1 cm tumour free margin is adequate for low-grade tumours less than 5 cm. In case the tumour is greater than 5 cm or the margins are less than 1 cm, radiation may be considered.

Management of High-Grade Tumours

The options available for high-grade localised tumours include surgery, radiation (pre-operative, intra-operative, and post-operative) and chemotherapy. Pre-operative radiotherapy is associated with a higher incidence of wound complications but requires a lower dose and a lower volume. Post-operative therapy is free of wound complications but the dose and the volume are higher. A higher treatment dose and volume may be associated with greater risk of radiation associated long-term functional compromise. Intra-operative radiation may be administered as external beam, or brachytherapy. The issue of the best modality to radiate a STS has not yet been resolved. The data on chemotherapy is equivocal but the trials have been small, lack the power to detect small difference and were all conducted without the use of granulocyte-colony stimulating factor (G-CSF) support. The consensus is that the effect of chemotherapy if at all is moderate and the need of chemotherapy needs to be decided on a case to case basis. Doxorubicin and dacarbazine with or without ifosfamide should be used. The dose of chemotherapy can be increased by the use of G-CSF with the hope to get a better outcome.

Unresectable Disease

The tumour size may be reduced by administration of pre-operative chemotherapy or radiotherapy and resection attempted if possible.

Stage IV Disease

If the regional nodes are involved, or if there is a low volume metastasis to a single organ, resection with post-operative chemotherapy and radiation is an option. If this is not possible, palliative therapy should be considered.

Special Situations

Gastrointestinal stromal tumours

Gastrointestinal stromal tumours (GISTs) respond to imatinib which should be used in case of residual disease following surgery or in patients with recurrence.

Uterine and ovarian sarcomas

Ovarian and uterine sarcomas are treated with surgery, radiation and chemotherapy. Endodermal sinus tumour is sensitive to hormonal therapy (progestins, tamoxifen and gonadotrophin releasing hormone analogues).

Retroperitoneal tumours

Retroperitoneal tumours are large and the intra-abdominal structures put a limitation on the amount of radiotherapy that can be administered. These are usually treated with a multi-modality approach involving surgery, chemotherapy and radiation. The outcome of these tumours is poor compared to other STS.

RECOMMENDED READING

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21.14 Cancer of Unknown Primary Site

Hemant Malhotra

INTRODUCTION

Cancer of unknown primary site (CUPS) or occult primary malignancy (OPM) represents a group of heterogeneous tumours that share a unique clinical feature: "early" apparent metastatic disease with no identifiable site of origin at the time of presentation. Thus, OPM patients present with usually widespread metastatic disease for which no primary site can be detected after a good medical history, detailed clinical examination, and extensive investigations. The primary site may either have a slow growth or may possibly become involute and, therefore, unlikely to manifest itself. About 3% of all cancer patients suffer from cancer of unknown primary origin.

The majority of CUPS/OPM are adenocarcinomas or undifferentiated tumours; less commonly, squamous cell carcinoma (SCC), melanoma, sarcoma, and neuroendocrine tumours can also present with a primary site of origin that cannot be determined. In approximately 15% to 25% of patients, the primary site cannot be identified even at post-mortem examination.

The prognosis for patients with OPM is poor. In the pre 2000 era, as a group, the response rates were 8% to 39% (mean 20%). The complete response rates were less than 1% and the mean survival was approximately 6 months (range 4 to 15 months in various studies) survival beyond 2 years was rare. With the availability of newer chemotherapeutic drugs (paclitaxel, docetaxel, gemcitabine, irinotecan) and newer targeted agents (gefitinib, erlotinib, bevacizumab), the one year overall survival has increased to 35% (range 25% to 50%) and about 13% (range 5% to 18%) of patients are alive at 2 years.

Large studies have shown that carcinoma of the lung and pancreas are the most common primary carcinomas that initially present as OPM. Other common malignancies such as colorectal, breast, and prostate cancers infrequently present as OPM. With the advent of two new advanced diagnostic modalities, one radiological and the other molecular, in the last decade, the number of patients with true OPM is decreasing. The positron emission tomography (PET) and molecular profiling of the tumour by DNA microarray technology, are extremely useful additions in the diagnostic armamentarium for this group of cancers.

HISTOLOGICAL CLASSIFICATION

According to routine light microscopy, cancers of unknown primary origin are divided into 4 major subtypes.

1. Adenocarcinomas well to moderately differentiated
2. Poorly differentiated carcinomas and adenocarcinomas
3. Squamous cell carcinomas
4. Undifferentiated neoplasms

The majority of the cases are adenocarcinomas, with poorly differentiated tumours being the next most frequent pathology (**Table 1**). Squamous cell carcinoma is a special minor subtype involving mainly the cervical nodes, and undifferentiated neoplasms are frequently re-classified to major histologic categories (i.e. carcinoma, lymphoma, melanoma, and sarcoma) because of the improvements in histopathology techniques. As regard to the organ of origin of the tumour, the majority of primaries are from either lung or pancreas (**Figures 1 and 2**). Clinical characteristics of the major OPM histologic types are depicted in **Table 2**.

Table 1: Proportions of Reported Histological Diagnoses in OPM

Author	Number of OPM Patients	Adeno-carcinoma (%)	Undifferentiated to Poorly Differentiated Carcinoma (%)	Squamous Cell Carcinoma (%)	Other* (%)
Muir	26,050	47.7	22.0	19.5	8.8
Holmes	686	28.0	16.0	10.0	46.0
Abbruzzese	657	58.2	29.4	5.8	6.7
Le Chevalier	302	45.0	27.5	15.0	12.5
Buda	332	65.0	14.0	21.0	

**includes undifferentiated neoplasm, other specified and unknown histotypes.*

CLINICAL FEATURES

Epidemiology—Demographics

Occult primary malignancy (OPM) comprises approximately 3% of human cancer. The average annual age-adjusted incidence is 7 to 12 cases per 100,000 population per year and as a cause of death, it is reported to be the fourth most common among cancer-related deaths in developed countries. Demographics of OPM patients generally mirror those of the general cancer population, with a mean age of 59 years at diagnosis (range 20 to 89 years) and a marginally higher frequency in males. Squamous cell carcinomas are twice as frequent in males as in females, while there is a compensatory shift in the frequency of adenocarcinomas. In children, OPM represents less than 1% of diagnosed solid tumours.

Natural History

Early dissemination, clinical absence of primary tumour, unpredictable metastatic pattern, and aggressiveness constitute the fundamental characteristics of these tumours. Several studies report that autopsy has failed to identify the primary site in 15% to 25% of OPM cases. Between the identified occult primaries, lung and pancreas constitute the majority, while other common malignancies represent smaller proportions (**Figures 1 and 2**).

The clinical presentation in cases of OPM depends on the predominant site of metastatic involvement. Regarding the organ sites affected, most patients (60%) have more than two sites affected at presentation, with lymph nodes being the most frequently involved. Liver, lung, bones, and pleura constitute common metastatic sites, whereas relatively high frequencies of odd localisations of metastases have been observed. General deterioration and weight loss are the most common symptoms, while digestive and respiratory symptoms, liver enlargement,

Table 2: Clinical Characteristics of the Major Occult Primary Malignancies Histologic Types

	Mean Age (Range)	Major Sites Involved	Specific Clinical Characteristics	Main Treatment Effectiveness	5-year Survival Rate (%)
Adenocarcinoma (well-to-moderately differentiated)	58	Liver, lung, bones	The most frequent type in adults; poor prognosis	Chemotherapy palliative	4
		Axillary lymph nodes only (subtype)	Females; relatively good prognosis	Loco-regional effective	60
		Peritoneum only (subtype)	Females; relatively good prognosis; response to chemotherapy and survival similar to ovarian cancer	Platinum-based chemotherapy effective	12
Poorly-differentiated carcinomas	37 (17 to 70)	Lymph nodes of midline distribution, lung	Rapid tumour growth, favourable response to chemotherapy	Platinum-based chemotherapy effective (57% ORR)*	13 to 16
Squamous cell carcinoma	60	Cervical lymph nodes	Male:female ratio of 6:1	Loco-regional or platinum-based chemotherapy effective	30
Embryonal malignancies	8 (1 to 17)	Bone marrow, bone lesions, lymph nodes, lung	Predominated type in childhood	Carboplatin-doxorubicin-ifosfamide-based chemo-therapy regimens effective	17

ORR = Overall response rate.

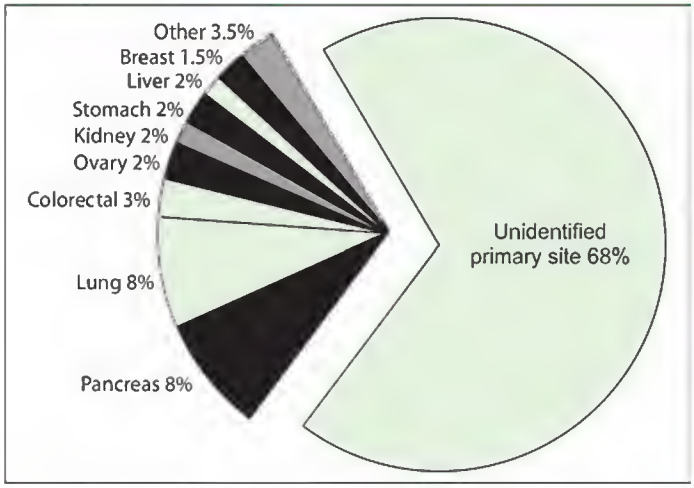


Figure 1: Distribution of identified primary tumour sites reported among 2,114 cases with OPM.

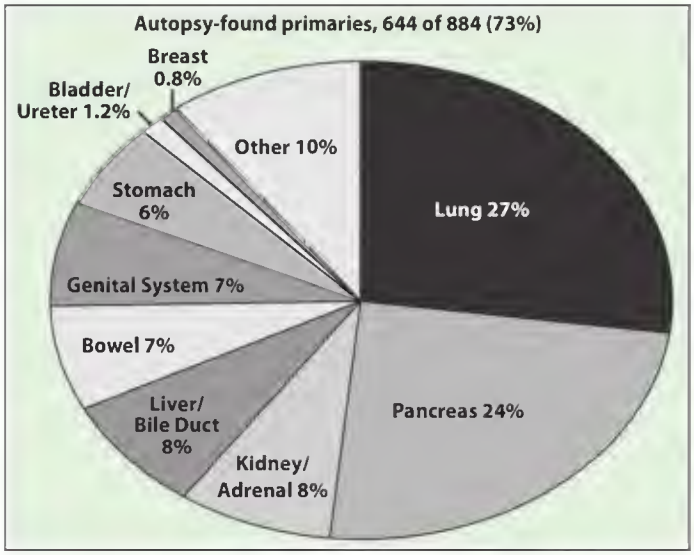


Figure 2: Distribution of identified primary tumour sites reported among 884 cases with occult primary malignancy at autopsy.

ascites, skin nodules, and bone pains suggest the sites of predominant metastatic involvement.

PROGNOSIS

The overall prognosis in patients with OPM is poor, with a mean survival of 5 to 10 months. Fewer than 25% of patients survive up to one year, but survival differs among clinicohistological subgroups (**Table 2**). Significant prognostic factors recognised in OPM are: histopathology, organs involved, tumour burden, gender, and performance status (**Table 3**). The prognostic significance of histological type can be attributed to the chemosensitivity of the underlying occult primary in each category. In poorly-differentiated carcinomas, several chemosensitive tumours may be included, whereas adenocarcinomas usually represent chemotherapy-resistant primaries.

Table 3: Prognostic Factors in Occult Primary Malignancy

	Favourable Factors	Unfavourable Factors
Pathology	Poorly differentiated carcinoma Squamous cell carcinoma Neuroendocrine carcinoma	Adenocarcinoma
Organs involved	Lymph nodes (except supraclavicular)	Liver, lung, bones
Tumour burden		≥three sites
Gender	Female	Male
Performance status	0 to 1	>1
Alkaline phosphatase	≤1.25 N	1.25 N

Lymph node metastatic topography deserves separate mention, since several distinct subgroups of prognostic significance have been recognised. Cervical nodes with squamous cell cancer, axillary nodes with adenocarcinomas in females, and lymph nodes with undifferentiated carcinomas constitute presentations of a favourable prognosis. Supraclavicular lymph node involvement has been defined as a bad prognostic factor.

DIAGNOSIS

Pursuing the Anatomical Location or Searching for Clues to Treatable Tumours?

The search for the identification of the occult primary has always challenged clinicians. The argument in favour of pursuing the anatomical location of the primary is the belief that localising the primary might result in a more specific and effective treatment. In a minority of OPM patients, a primary site of origin can indeed be identified after extensive diagnostic evaluation, but exhaustive investigations have been criticised because of a low yield and a lack of influence on patients' prognosis. Such a strategy has never been found to have any therapeutic implications or to be of survival benefit to the patient. On the contrary, it costs the patient a longer hospital stay, with the experience of painful and distressing investigations and the health care system an unacceptable cost-effectiveness ratio.

Regarding the identification of treatable subgroups, a careful consideration of the clinical presentation of the disease with an optimal re-evaluation of the biopsy specimen provides the best clue. Immunohistochemistry and, in exceptional cases, molecular genetic and cytogenetic studies may help the diagnosis. This way, the well-recognised clinico-pathological subsets of treatable and potentially curable tumours can easily be identified, and any histological misclassifications can be clarified.

Proposed Diagnostic Strategy

As a rule, a reasonable diagnostic approach to OPM patients is to avoid excessive diagnostic procedures without compromising clinically useful diagnostic efficacy.

Based on the initial clinical presentation and pathology report, the diagnostic strategy for a probable OPM should be divided into the standard and optional diagnostic procedures (**Table 4**).

Table 4: Investigations for the Diagnosis of OPM

Standard diagnostic investigations	
Pathology	Histopathologic review of the biopsy material with the use of immunohistochemistry
Laboratory tests	Full blood count, routine biochemistry, faecal occult blood testing, urine test
Imaging studies	Chest radiograph, CT of abdomen and pelvis, PET
Optional or symptoms/signs-oriented investigations	
Imaging studies	CT of head and neck region in cervical node metastasis
	Mammography for axillary lymph node metastasis
Endoscopies	ENT pan-endoscopy, bronchoscopy, proctoscopy, colposcopy
Surgery	Mastectomy in axillary cases, cytoreductive laparotomy for peritoneal carcinomatosis

The standard diagnostic procedure for the majority of these patients is proposed to include the histopathologic review of biopsy material with the use of immunohistochemistry, full blood count, routine biochemistry, faecal occult blood testing, urine testing, chest radiograph, and computed tomography (CT) of abdomen and pelvis. It must be emphasised that immunohistochemistry staining for common leucocyte antigen, CEA, cytokeratin, and vimentin is considered today a routine pathology procedure for these tumours. For the subgroups of the cervical node; epidermoid carcinomas and the axillary adenocarcinomas in females, more specific initial investigational procedures are advisable; those include ear-nose-throat panendoscopy and head and neck CT in cases of cervical lymph nodes and mammography in axillary lymph node metastases in women. Other recommended optional investigations are the high specificity α-fetoprotein (AFP), β-human chorionic gonadotrophin (β-hCG), and prostate-specific antigen (PSA) serum tumour markers in men to exclude extra-gonadal germ cell tumour or prostate cancer, and symptoms or signs oriented endoscopies. Surgical diagnostic procedures have not gained a wide acceptance.

Evaluation of Diagnostic Methods

Physical examination

The physical examination must always be a thorough one and should include head and neck, thyroid, and rectal examination. In women, breast and pelvis; in men, prostate and testicles examination should never be overlooked.

Imaging studies

Although chest radiography has always been a prerequisite for the diagnosis of OPM, its usefulness in the differential diagnosis between primary and secondary disease in lungs has been disputed.

CT is considered today as one of the most valuable imaging tests in OPM cases. It has a clearly proven impact on OPM diagnosis, offering an additional diagnostic accuracy of 20% in cases previously characterised as OPM. CT also helps in the evaluation of tumour mass and provides guidance to biopsy procedure.

In the past 5 years, F-18 fluorodeoxyglucose (FDG) PET/CT has become one of the more frequent imaging modalities in the management of patients with cancer of unknown primary origin. FDG-PET/CT detects more sites of metastasis than other modalities, and in 20% to 40% of cases it discloses the site of the primary tumour. Its exact role is yet to be defined because of a lack of prospective clinical trials comparing the performance of PET/CT with conventional anatomic imaging modalities.

Endoscopy

Endoscopies should always be symptoms or signs oriented investigational procedures in OPM cases.

Surgery

Surgery as a diagnostic procedure has a definite role in biopsy sampling. In cases of women with adenocarcinomas of the peritoneum, cytoreductive laparotomy has a therapeutic rather than a diagnostic benefit.

Pathology

Histopathology is the cornerstone in the diagnostic procedure of OPM. A good biopsy specimen is of great importance, especially in cases of poorly differentiated tumours, and for the application of special pathology techniques that can improve the diagnosis of chemosensitive tumours which are subject to mis-diagnosis. The contribution of light microscopy and specialised pathological studies in the diagnosis of OPM is depicted in **Figure 3**.

Immunohistochemistry is the most useful diagnostic tool and the central axis of the initial basic investigation, especially in

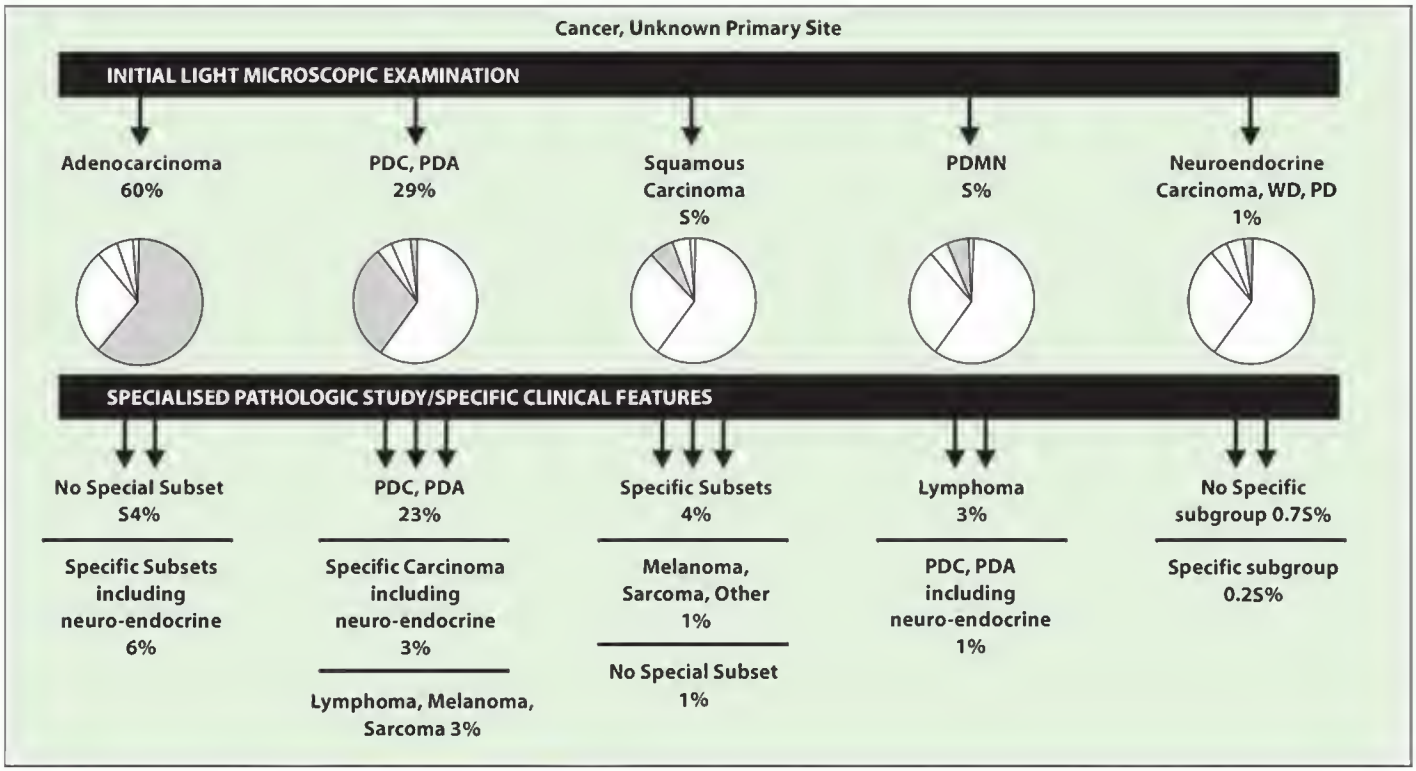


Figure 3: Rale and diagnastic yield af variaus pathalagical tests in OPM.

PDC = Paarly differentiated carcinama; PDA = Poarly differentiated adenacarcinama; PDMN = Paarly differentiated malignant neaplasm; WD = Well differentiated; PD = Poarly differentiated.

cases of poorly differentiated carcinomas. Immunoperoxidase staining has now become widely available and can be reliably applied on routinely fixed paraffin-embedded biopsy materials. Immunocytochemistry can also be applied on cytological preparations in cases of malignant perfusions. Today, with the help of a wide range of immunohistochemistry markers, the misdiagnosis of other malignancies, such as lymphomas, extragonadal germ cell tumours, malignant melanomas, and undifferentiated sarcomas as OPM is rather rare.

Advanced diagnostic tests

Electron microscopy can be a useful diagnostic tool in 15% of undifferentiated OPM not otherwise identified by light microscopy, offering an additional diagnostic accuracy in one-third of these cases. It is a well-reputed diagnostic method for the poorly differentiated neuroendocrine tumours and amelanotic melanomas recognising core granules, electron-dense secretory granules, and premelanosomes. It can also contribute to the diagnosis of undifferentiated squamous cell carcinoma (desmosomes attached to tonofilaments), adenocarcinomas (acinar spaces, tight junctions, and microacini) and sarcomas (myofibrils, dilated rough endoplasmic reticulum, extracellular osteoid). Disadvantages of electron microscopy are the special handling procedure, the experienced personnel, and the expensive equipment required.

Molecular genetic and cytogenetic studies can offer today additional diagnostic information toward the identification of special tumour types that have specific genetic markers. Fluorescence *in situ* hybridisation (FISH) using the chromosomal marker i(12p), which is highly non-random for germ cell tumours, has been proven an excellent diagnostic tool in atypical extragonadal germ cell tumours presenting as undifferentiated OPM. Genetic analysis can also contribute to the diagnosis of a number of tumours with specific chromosomal aberrations, usually seen in soft tissue sarcomas and lymphomas. Nasopharyngeal undifferentiated carcinomas can be distinguished from undifferentiated epidermoid tumours by detection of Epstein-Barr virus genome with polymerase chain reaction analysis.

Serum tumour markers

Males should always have the high-specificity tumour markers β-hCG, AFP, and PSA tested to exclude treatable extragonadal germ cell tumours and prostate cancer amenable to endocrine treatment. In children, testing for urinary catecholamines can produce valuable diagnostic clues, as high urine levels are diagnostic of neuroblastoma (**Figure 2**).

TREATMENT

A reasonable treatment approach for OPM patients is to individualise the treatment, taking into consideration the most appropriate modality for each case, whether loco-regional, systemic, curative, palliative, or supportive.

Loco-Regional Treatment

Being by definition a metastatic disease, OPM leaves only limited room for loco-regional treatment practices, radiotherapy, and surgery.

Loco-regional treatment of curative orientation should be considered in cases of isolated axillary node metastases in females and squamous cell metastases in cervical nodes, especially in $< N_2$ stages. For higher stages (N_3), combination modality treatment with radio-chemotherapy is proposed as a more reasonable approach, offering a better response rate

and survival. Loco-regional radiation therapy has a role in palliation.

Systemic Treatment

Although curative in few cases of OPM, chemotherapy constitutes the mainstream of treatment practices for the majority of patients with this systemic metastatic disease.

Potentially Curable OPM Subgroups

The better-defined, potentially curable sub-population is young adults, primarily males, with poorly differentiated carcinomas having as dominant tumour sites the mediastinum, retroperitoneum, lungs, or peripheral lymph nodes. In these patients, a 16% actuarial 10-year survival has been achieved.

Another well-documented subset of patients with favourable response to platinum-based chemotherapy and improved prognosis is women with peritoneal carcinomatosis. Cure is also possible for the rare cases of children with OPM, if treated with chemotherapy regimens effective against embryonal malignancies.

An indicative synopsis of effective treatment approaches in patients with OPM is presented in **Table 2**.

Adenocarcinomas: Supportive, Palliative, or Investigational Treatment Approach?

Unfortunately, the favourable subsets of OPM constitute a minority. The large majority of adenocarcinomas of unknown primary origin (AOPM) still remain resistant to clinically established chemotherapy. The regimens used so far have been empirical and of palliative orientation and the observed responses in most retrospective studies were moderate, with no definite impact on survival. Quality of life is a major point in these cases and should be taken very seriously into consideration because of the poor performance status and prognosis of these patients.

Future Treatment Perspectives

With the availability of newer chemotherapeutic drugs like the taxels (paclitaxel and docetaxel), gemcitabine, vinorelbine, irinotecan and oxaliplatin and targeted agents like bevacizumab, gefitinib and erlotinib, there have been significantly more response and 1- and 2-year survivals in these patients. Two versus three drugs combinations are being evaluated in clinical trials.

Biological Profile of the Tumour

The search for genetic damage has taken a central role in cancer research in the last decade. A unique biological profile is also suggested by the observations that show an extremely high overexpression of several tumour markers and oncoproteins in these tumours (**Figure 4**).

More and more research is now focused on molecular profiling of patients with OPM (**Figure 5**). Commercially available DNA microarray chips can now be used for molecular profiling and exact characterisation of the tumour such that tumour-specific chemotherapy can be offered rather than empiric therapy. Gene expression microarray (GEM) analysis has demonstrated that molecular signatures

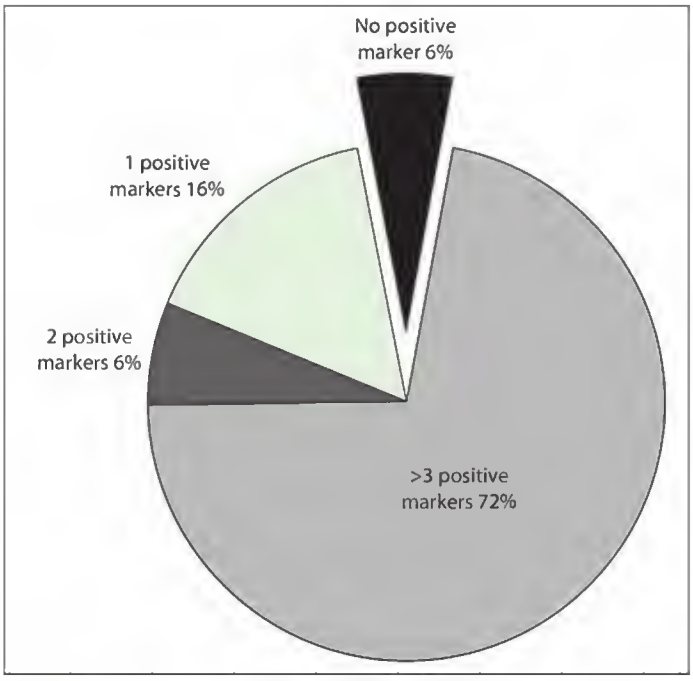


Figure 4: Multiple over-expression of 6 serum tumour markers (CEA, CA 19-9, CA 15-3, CA 125, HCG, AFP) evaluated in 58 OPM cases.

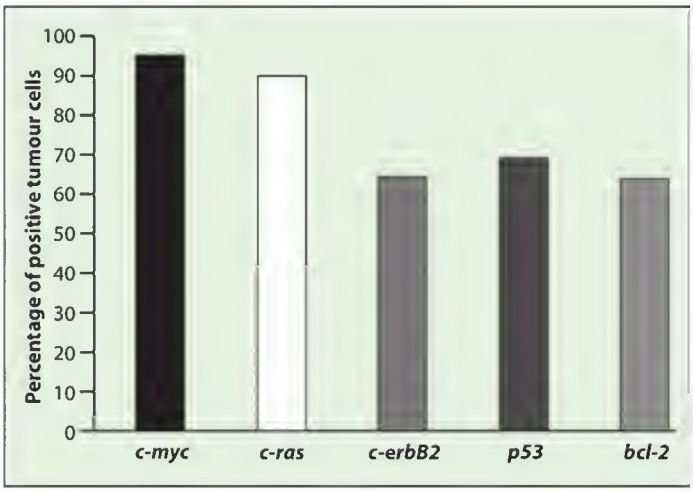


Figure 5: Immunohistochemical detection of oncoproteins in OPM (c-myc, c-erbB-2 and ras were studied in 26 cases, p53 and bcl-2 in 47 OPM cases).

can aid in tumour classification and propose foster primaries. The improved diagnosis by the GEM method possibly influences the management in 50% to 60% of cases. Genomic profiling and cancer classification tools represent a promising analytical approach to assist with the management of OPM patients. It is proposed that molecular profiling diagnosis be considered when the primary clinical algorithm has failed to provide a diagnosis.

CONCLUSIONS

The heterogeneous-in-origin tumours that present clinically as OPM share common clinical features of early metastatic dissemination from an occult primary. A limited diagnostic evaluation toward the detection of the primary tumour and a thorough clinicopathological evaluation for clues to identify the

well-recognised, treatable subgroups are recommended. As a significant therapeutic improvement has not been achieved for the majority of patients with metastatic adenocarcinomas, innovative treatment approaches with the introduction of new classes of drugs into trials are warranted. Findings suggestive of a unique biological profile of OPM have recently been evidenced and justify further research for the genetic and biologic identity of these aggressive tumours that express an absolute metastatic phenotype.

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21.15 Paraneoplastic Syndromes

Senthil Rajappa, D Raghunadharao

INTRODUCTION

Paraneoplastic syndromes or non-metastatic manifestations refer to the signs and symptoms produced by the tumour at sites distant from the primary or metastasis. These syndromes occur in 2% to 20% of all malignancies. However, this may be an under estimation considering the fact that there is under-reporting of these syndromes. No race or sex predilection is reported. Cancers and their related paraneoplastic syndromes may affect people of all ages. These syndromes may be the presenting feature of a malignancy and may help in identifying a possible primary. The signs and symptoms of paraneoplastic syndromes may result from several mechanisms. These are most commonly due to release of physiologically active substances like cytokines, enzymes and hormones, production of antibodies against antigens, which are shared by the tumour and normal tissues or interference with metabolic or synthetic pathways. Increased understanding of the molecular mechanisms of paraneoplastic syndromes may help in an early diagnosis, design of therapies, monitor responses and predict outcomes. Paraneoplastic syndromes may affect almost all organ systems of the body.

CLINICAL SIGNIFICANCE OF PARANEOPLASTIC SYNDROMES

Certain paraneoplastic syndromes are typically associated with certain malignancies, and hence, may help in identifying the primary, e.g. opsoclonus-myoclonus syndrome in neuroblastoma.

Certain paraneoplastic syndromes secrete proteins which may be used as tumour markers to track disease responses and progression, e.g. α-fetoprotein in testicular cancers.

In some situations, the underlying disease may not be treated but the symptoms of the paraneoplastic syndromes may need attention, e.g. metastatic carcinoid tumours.

Paraneoplastic syndromes may confer poor prognosis in certain malignancies, e.g. hyponatraemia in small cell lung cancer (SCLC).

Paraneoplastic syndromes may sometimes precede and can help identify an early relapse, e.g. α-fetoprotein in germ cell tumours.

Many paraneoplastic syndromes may run a clinical course independent of the malignancy, e.g. immune-mediated neurologic syndromes.

ENDOCRINE PARANEOPLASTIC SYNDROMES

Endocrine paraneoplastic syndromes result from the production of peptide hormones or cytokines, which are referred to as 'ectopic' hormones by the tumour. These syndromes include hypercalcaemia of malignancy, Cushing's syndrome, syndrome of inappropriate anti-diuretic hormone secretion (SIADH), hypoglycaemia, oncogenic osteomalacia, as well as production of growth hormone, gonadotrophins, calcitonin, prolactin and thyrotrophic substance.

Hypercalcaemia of Malignancy

Hypercalcaemia is a major metabolic abnormality and an oncological emergency that can occur in 10% of all individuals diagnosed with cancer. The most common cause of hypercalcaemia of malignancy is multiple myeloma (33%) followed by breast and bronchogenic carcinoma. Hypercalcaemia can be classified as that resulting from bone destruction, i.e. osteolysis or humoral hypercalcaemia of malignancy (HHM). Parathyroid hormone-related protein (PTHrP) produces endocrine and paracrine effects and is responsible for HHM. Factors released by or in response to bone metastasis namely receptor activator of nuclear factor kb ligand (RANKL), tumour necrosis factor-alpha (TNF-α) and IL-1 can cause paracrine effects. However, both may result in bone resorption resulting in hypercalcaemia. Determining the stage of the disease and the antineoplastic options are paramount to manage the hypercalcaemia.

Hypercalcaemia may present with renal, gastrointestinal (GI) , neurologic or cardiac manifestations. Patients who are symptomatic should be treated irrespective of the absolute level of calcium. A corrected serum calcium level of 11 to 12 mg% is referred to as mild hypercalcaemia, 12 to 14 mg% as moderate and more than 14 mg% as severe hypercalcaemia.

Therapies for hypercalcaemia are directed at either increasing the renal excretion of calcium or by inhibiting osteoclast activity. Hydration and diuresis although helpful, must be administered with caution in order to prevent fluid logging and pulmonary oedema. Specific measures like bisphosphonates (zoledronic acid) and steroids especially in haematologic malignancies need to be instituted. Calcitonin or gallium nitrate are reserved for those patients who do not respond to the above measures. Anti-tumour therapy should be employed early for best results.

Ectopic Adrenocorticotrophic Hormone Syndrome

This syndrome was first reported by Brown in a patient with SCLC. Some tumours have overaction of *c-fos* oncogene due to loss of a tumour suppressor gene leading to increased production of propiomelanocortin (POMC), which is a precursor of adrenocorticotrophic hormone (ACTH) and many other proteins in the steroid hormone synthesis cascade. Ectopic ACTH syndrome production is most commonly associated with SCLC. Myopathy, muscle wasting, hyperpigmentation and hypokalaemia are more common in ectopic ACTH production compared to Cushing's syndrome. Additional abnormalities include glucose intolerance and metabolic alkalosis.

Distinguishing between pituitary adenoma, ectopic ACTH production and primary adrenal disorders is the primary focus of the diagnostic work-up. Laboratory evaluation reveals

excessive cortisol production by 24-hour free cortisol measurement and lack of suppression after administration of dexamethasone. The levels of ACTH are unaltered by metyrapone and corticotrophin releasing hormone (CRH) stimulation tests unlike a pituitary adenoma. Specific treatment is directed at the underlying tumour.

Syndrome of Inappropriate Anti-Diuretic Hormone Secretion

Hyponatraemia can occur in 10% to 30% of patients with SCLC. SIADH occurs as a result of overproduction of anti-diuretic hormone (ADH) or ADH-like substance by the tumour. Drugs like vincristine, cisplatin and cyclophosphamide may also cause SIADH. The cardinal features of SIADH are water intoxication and hyponatraemia including decreased serum osmolality, euvolaemia, inappropriate elevation of urine osmolality with elevated urine sodium with normal renal, thyroid and adrenal function. Many patients are asymptomatic. Those with sodium level of <125 mEq/L and developing hyponatraemia rapidly are more likely to be symptomatic.

Water restriction (500 to 1000 mL per day) is the most important measure in treating SIADH. Hypertonic saline and diuretics are reserved for patients who have life-threatening convulsions or coma. It is important to raise the sodium level gradually. Demeclocycline is used for patients where fluid restriction and treatment of the malignancy are ineffective.

Paraneoplastic Gonadotrophin Secretion

β-Human chorionic gonadotrophin is the most commonly elevated in testicular cancer, hydatiform mole and choriocarcinoma. Rarely other cancers like breast, lung, gastric and renal cell carcinoma can produce elevated β-hCG. The usual manifestations are gynaecomastia in men and oligomenorrhoea in women. Due to the sharing of the alpha subunit between thyroid stimulating hormone (TSH) and hCG, there may be manifestations of hyperthyroidism. β-hCG also helps in monitoring response to therapy.

Other Endocrine Syndromes

Oncogenic osteomalacia is characterised by osteomalacia, hypophosphataemia, hyperphosphaturia, normocalcaemia, normal parathyroid hormone (PTH) levels and decreased vitamin D levels as a result of a phosphaturic substance or decreased conversion of 1,25 dihydroxy vitamin D. It is associated with mesenchymal tumours, like haemangiomas and haemangiopericytoma.

Calcitonin may be produced in excess by SCLC, carcinoids, and breast cancer. Hypoglycaemia is associated with an insulinoma. It may also be associated with a variety of unusual mesenchymal tumours and GI cancers, which are typically large and involve the liver. It arises due to the production of insulin-like growth factor (IGF 1 and 2).

NEUROLOGIC PARANEOPLASTIC SYNDROMES

Most neurological paraneoplastic syndromes (**Table 1**) begin acutely or subacutely and progress over weeks to months before stabilisation. It usually precedes the diagnosis of cancer. Syndromes that have a relentless or fluctuating course are less likely to be paraneoplastic.

Due to the rare occurrence of these syndromes exact incidence is unknown except in certain situations. *Myasthenia gravis* is associated with 10% to 15% of cases of thymoma, Lambert-Eaton myasthenic syndrome (LEMS) in 3% of SCLC and peripheral neuropathy in 10% of monoclonal gammopathies and 50% of osteosclerotic myeloma.

Table 1: Paraneoplastic Neurological Syndromes

Syndromes of the central nervous system
Encephalomyelitis
Limbic encephalitis
Brainstem encephalitis
Subacute cerebellar degeneration
Opsoclonus-myoclonus
Optic neuritis
Cancer-associated retinopathy
Melanoma-associated retinopathy
Stiff person syndrome
Necrotising myelopathy
Syndromes of the peripheral nervous system
Subacute sensory neuronopathy
Acute sensorimotor neuropathy
Guillain-Barré syndrome
Brachial neuritis
Subacute/chronic sensorimotor neuropathies
Neuropathy and paraproteinaemia
Neuropathy with vasculitis
Autonomic neuropathies
Chronic gastrointestinal pseudo-obstruction
Acute pandysautonomia
Syndromes of the neuromuscular junction and muscle
Myasthenia gravis
Lambert-Eaton myasthenic syndrome (LEMS)
Dermatomyositis
Acute necrotising myopathy

The nervous system can be involved in one of the three ways:

1. Paraneoplastic disorder may damage a non-neural organ/tissue with secondary effects on the nervous system, e.g. hypercalcaemia from tumour-related production of PTHrP can lead to encephalopathy.
2. Paraneoplastic disorder affecting non-neural organ or tissue may lead to structural damage to nervous system, e.g. hypercoagulability may lead to cerebral infarction due to venous or arterial thrombi.
3. It may directly affect the nervous system without involvement of the other organs, e.g. encephalomyelitis, LEMS or *Myasthenia gravis*.

Tumours express antigens are normally present exclusively in the nervous system. These shared antigens are referred to as onconeural antigens and can be isolated in most paraneoplastic neural syndromes. When the tumour cells undergo apoptosis and are phagocytosed by dendritic cells, the onconeural antigen is recognised by the immune system. This results in the production of cross-reacting antibodies leading to an immune attack, which in rare cases may even obliterate tumour.

These syndromes are associated with evidence of inflammation on the cerebrospinal fluid (CSF) analysis as evidenced by pleocytosis and presence of oligoclonal bands, which represent the antibodies. Neuro-imaging is rarely contributory and helps to exclude metastasis. Many patients have serum and CSF antibodies, e.g. anti-Yo, anti-Hu, anti-Ri. Some classical syndromes like paraneoplastic encephalomyelitis and certain

antibodies can be typical of certain malignancies while many may be non-specific. Although immune-mediated mechanisms have been implicated in most neurologic paraneoplastic syndromes, plasmapheresis, immunoglobulins and immunosuppressive therapy are rarely beneficial.

Encephalomyelitis

Encephalomyelitis is a general term used for paraneoplastic syndromes with intense inflammatory response, perivascular lymphocytic cuffing affecting the brain and spinal cord. This includes paraneoplastic cerebellar degeneration, limbic encephalitis and transverse myelitis. There is no known treatment and the disorder runs a subacute course. Limbic encephalitis is characterised by subacute onset of behavioural and mental changes. It is associated with small cell lung, breast and uterine cancers. Paraneoplastic cerebellar degeneration is characterised by acute or subacute onset of cerebellar dysfunction and widespread loss of Purkinje fibre layer. It is associated with small cell lung and breast cancer and Hodgkin's disease.

Paraneoplastic opsoclonus is manifested by high amplitude, involuntary, chaotic, conjugate, saccadic eye movements often associated with myoclonus and ataxia. It occurs in 2% of childhood neuroblastomas. Unlike in adults, opsoclonus-myoclonus in children responds to corticosteroids although some residual neurological defects may persist.

Subacute Neuronopathy

Subacute neuronopathy may be sensory or motor. Subacute sensory neuronopathy is characterised by loss of sensations in the extremities. It is more common in women and is associated with SCLC. Subacute motor neuronopathy is associated with Hodgkin's disease and presents with progressive lower extremity weakness. Unlike other neurologic syndromes, it is commonly diagnosed after the malignancy and runs a chronic non-debilitating course. Anti-neuronal antibody (anti-Hu) directed against the nucleoprotein of the dorsal root ganglia have been isolated. There is no effective treatment for either disorder.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the myoneural junction characterised by proximal muscle weakness. Of the 60% of patients with underlying cancer, two-thirds have SCLC. LEMS is caused by antibody to the voltage-gated calcium channel leading to decreased acetylcholine release into the myoneural junction. Unlike Myasthenia gravis, bulbar involvement is uncommon but can be associated with dysautonomia in 50%. Repetitive nerve stimulation shows decrement of the compound muscle action potential at low stimulation rate and increase at high stimulation rates.

In contrast to other syndromes, LEMS responds to plasmapheresis, intravenous immunoglobulins, immunosuppression and treatment of underlying cancer. Drugs like 3,4-diaminopyridine that increase neurotransmitter release can be used as maintenance therapy.

Peripheral Neuropathy

Peripheral neuropathy occurs in 5% of patients and can be sensory, motor or mixed type. It is reported in lymphomas, plasma cell dyscrasia and cancer of the lung, breast and colon. The demyelinating type may occur acutely as in Guillain-Barré syndrome or have a more chronic course. Axonal neuropathy is more commonly associated with lung cancer and responds to the treatment of the underlying malignancy.

HAEMATOLOGIC PARANEOPLASTIC SYNDROMES

Anaemia

Anaemia is one of the most frequently encountered abnormality in cancer patients with a multitude of causes. These include bone marrow involvement, blood loss, nutritional deficiencies, infections, myelofibrosis and treatment-induced. Although iron stores are adequate, there is impaired iron utilisation. The exact mechanism of this under utilisation of iron is unknown but some studies have shown low levels of erythropoietin. Treatment of the malignancy or erythropoietin supplementation may reverse the anaemia.

Pure red cell aplasia (PRCA) is a rare syndrome with selective loss of red cell precursors. Thymomas have been found in 50% of PRCA and thymectomy results in reversal in 25% to 30% of cases. PRCA can also be associated with lung and breast cancers and haematological malignancies.

Antibody-mediated haemolytic anaemia is frequently associated with β-cell neoplasms like chronic lymocytic leukaemia (CLL) and lymphomas. Microangiopathic haemolysis is an uncommon complication of cancer most commonly seen in mucin-producing adenocarcinomas, especially gastric cancer.

Erythrocytosis

Inappropriate production of erythropoietin by tumours like renal cell carcinoma, hepatoma, adrenocortical tumours, uterine tumours and haemangioblastoma may lead to polycythaemia. Other possible causes include tumour-derived peptides, androgenic hormones or other peptides with erythropoietic effects.

Granulocytosis

Marked granulocytosis or leukaemoid reaction commonly accompanies breast, lung, gastric cancers, lymphomas and brain tumours. The mechanism is supposed to be the release of colony stimulating factors (G-CSF, GM-CSF, IL-3 and IL-1). Leukaemoid reaction may be confused with chronic myeloid leukaemia at times.

Coagulopathy

Coagulopathy associated with malignancy may result in thrombosis or bleeding. These haemostatic abnormalities are an important cause of death in cancer patients. Cancers associated with DIC are acute promyelocytic leukaemia, pancreatic, gastric, lung, breast and colon cancers with mucin secreting tumours of the GI tract being the most frequent. The pathogenesis of the prothrombotic state in cancer is complex and probably, multifactorial. Prothrombotic factors in malignancy include the tumour production of procoagulants [i.e. tissue factor (TF) and cancer procoagulant (CP)], inflammatory cytokines, and the interaction between tumour cells, blood (i.e. monocytes/macrophages, platelets) and endothelial cells. Other mechanisms of thrombus promotion include some general responses of the host to the tumour (i.e. acute phase, inflammation, angiogenesis), decreased levels of inhibitors of coagulation, and impaired fibrinolysis. In addition, the prothrombotic tendency of cancer patients is enhanced by anti-cancer therapy, indwelling central venous catheter, and by haemodynamic compromise (i.e. stasis).

Non-bacterial thrombotic endocarditis is associated with numerous cancers, most commonly GI and lung. It is

characterised by the deposition of fibrin and platelets on the leaflets of the left heart valves. These fibrin vegetations lead to arterial embolisation, infarction, and sudden death.

RENAL PARANEOPLASTIC SYNDROMES

Although renal manifestations of systemic cancer may result from direct infiltration, metabolic complications and drug-induced renal damage, some syndromes are specific and paraneoplastic in nature.

Glomerular Disorders

Membranous nephropathy characterised by nephritic range of proteinuria, hypertension and microscopic haematuria is associated with cancers of the stomach, lung and colon. It usually occurs during or after the diagnosis of malignancy. Immune complexes are thought to play a role in membranous nephropathy as evidenced by subepithelial deposits on immunofluorescence and electron microscopy. The antigens may be foetal antigens or tumour-associated antigens, which lead to the production of cross-reacting autoantibodies. The nephrotic syndrome responds to the treatment of malignancy. Other glomerulopathies include focal and segmental glomerulosclerosis in CLL, immunoglobulin (Ig) A nephropathy in lung cancer and rarely, rapidly progressing glomerulonephritis with lymphoma.

Microvascular Lesions

Haemolytic uraemic syndrome has been reported with giant haemangiomas, acute promyelocytic leukaemia, gastric and pancreatic cancers or treatment with mitomycin C. Renal vasculitis with cryoglobulinaemia has been rarely reported.

CUTANEOUS PARANEOPLASTIC SYNDROMES

A wide range of cutaneous syndromes may be associated with internal malignancy. The appearance of skin lesions may be of extreme value in detection and management of cancer because skin is readily accessible for examination and biopsies. Secretion of cytokines like keratinocyte growth factors, interleukins, insulin like growth factor and triggering of an immune response to antigens expressed in the tumour and skin are thought to be responsible for cutaneous syndromes. These lead to increased proliferation, improper differentiation and hyperkeratosis of skin leading to the various manifestations.

Acanthosis Nigricans

It is characterised by hyperpigmented, grey brown, velvety-soft thickening of the skin on the nape of the neck, axilla, palms, soles, perineal and intertriginous areas and may be associated with pruritus. Acanthosis associated with tumour is of sudden onset and progressive and 50% to 65% are associated with gastric-carcinoma. Other malignancies include breast cancer, lymphoma, and squamous cell cancers. Successful treatment of the underlying malignancy may not lead to alleviation of symptoms.

Dermatomyositis

Dermatomyositis is an inflammatory proximal myopathy associated with characteristic skin changes. The rash accompanies or precedes the onset of myopathy. Skin manifestations include heliotrope rash, periorbital oedema, Grotton's sign (violaceous papules over the knuckles with scaling), photosensitivity, and subcutaneous calcifications. Associated malignancies include lung, breast, lymphoma, ovarian, and GI tract. Topical and systemic corticosteroids may be helpful in alleviating symptoms.

Erythemas

Several erythemas may be associated with cancer. Erythema gyratum repens is a condition characterised by erythematous gyrate bands then occur in a wave like pattern with pruritus. It is almost always associated with a malignancy, most commonly lung cancer followed by breast or GI cancer. Lesions typically regress with treatment of cancer.

Paraneoplastic Pemphigus

It is characterised by persistent painful erosions of the oral mucosa, lips and conjunctiva. It occurs with sarcomas and lymphoma. Other manifestations include erythema and blistering of the trunk and extremities. Treatment with steroids and azathioprine results in occasional responses and treatment of the malignancy often leads to improvement in the skin lesions.

MISCELLANEOUS PARANEOPLASTIC SYNDROMES

Anorexia and Cachexia

Cancer anorexia cachexia syndrome is the most common paraneoplastic syndrome consisting of anorexia, weight loss and wasting. Cancer cachexia may be associated with a hyper, hypo or eumetabolic state. Multifactorial derangements in biochemical pathways lead to cachexia. Patients who have more than 10% of weight loss have poorer survival. The central control of appetite may be altered by release of serotonin. Tumours produce factors that alter the perception of smell and taste of food leading to poor intake. This further aggravated problems like dysphagia and odynophagia as a result of local tumour effects. Maldigestion and malabsorption may result from obstruction of biliary or pancreatic pathways. Pharmacological approaches to improving nutritional status in cancer patients include appetite stimulants, anabolic steroids, corticosteroids and progestational agents. Unfortunately, most of these are not of proven benefit.

Hypertrophic Osteoarthropathy

This clinical syndrome is characterised by clubbing and periostitis of the long bones. Incomplete forms have been recognised including clubbing alone, isolated periostitis and pachydermia associated with minor manifestations like synovial effusions, seborrhoea, folliculitis, hyperhidrosis, hypertrophic gastropathy and acro-osteolysis. Hypertrophic osteoarthropathy (HOA) may be primary or secondary. It is associated with pulmonary, cardiac, liver, intestinal, mediastinal and miscellaneous problems. The most common disorders are non-small cell lung cancer (adenocarcinoma), lung metastasis, hepatocellular carcinoma, oesophageal cancer, thymoma and other non-malignant pulmonary conditions. The treatment of HOA is disappointing. Successful treatment of the underlying disease is associated with regression of the abnormalities. However, lung cancer associated HOA is usually diagnosed late, making successful treatment difficult. Patients with pain are treated with non-steroidal anti-inflammatory drugs.

RECOMMENDED READINGS

1. DeVita. *Cancer: Principles and Practice of Oncology;* 6th Ed. Lippincott, William and Wilkins PA; 2001.
2. Martin Abeloff. *Clinical Oncology;* 3rd Ed. Churchill Livingstone; 2004.

21.16 Cancers in the Predisposed Host

K Pavithran

Cancer is a genetic disease, caused by alterations, loss, or amplification of genes that are important for normal cellular functions, including many proto-oncogenes and tumour suppressor genes. Cancer develops in a multi-step process, resulting from multiple genetic events. Predisposition to cancers occurs due to hereditary factors, immunodeficiency states (primary or secondary—acquired immunodeficiency syndrome or post-transplant setting), chemotherapy or radiotherapy.

HEREDITARY CANCER PREDISPOSITION SYNDROMES

Familial occurrence of cancer has been recognised for many centuries. Genes whose alterations result in hereditary predisposition to cancers have been classified as oncogenes or tumour suppressor genes. A minority of human cancer predisposition syndromes result from inherited mutations of oncogenes (e.g. *RET, MET, KIT*). The majority of cancer predisposition syndromes are due to inherited defects in tumour suppressor genes. Major cancer predisposition syndromes are given in **Table 1**.

Table 1: Cancer Predisposition Syndromes

Syndrome	Gene
Hereditary breast and ovarian cancer syndrome	*BRCA1, BRCA2*
Familial adenomatous polyposis	*APC, MYH*
Hereditary non-polyposis colon cancer syndrome	*hMSH2, hMLH1, hMSH6*
Multiple endocrine neoplasias (I, II)	*MEN1, RET*
Familial retinoblastoma	*RB1*
Neurofibromatosis I, II	*NF1, NF2*
von Hippel-Lindau syndrome	*VHL*

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Hereditary breast and ovarian cancer syndrome (HBOC) is inherited in an autosomal dominant fashion with a penetrance of approximately 85%. Germ-line mutations in BRCA1 and BRCA2 account for about 90% of cases of inherited HBOC. HBOC patients develop breast cancer at an early age and are at elevated risk for cancers in other organs (e.g. pancreas, stomach, fallopian tube and prostate cancer in male BRCA carriers. Cancers arising in BRCA1 mutant patients are usually high-grade invasive ductal carcinomas.

Neurofibromatosis Type I

Neurofibromatosis type 1 (NF1) is inherited in an autosomal dominant fashion, with a penetrance of 100% for neurofibromas.

HEREDITARY NON-POLYPOSIS COLON CANCER (LYNCH SYNDROME)

Hereditary non-polyposis colon cancer is the most common cancer syndrome and is inherited in an autosomal dominant fashion with a penetrance of about 90%.

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) is a highly penetrant, autosomal dominant disorder. The hallmark of FAP is the presence of at least a hundred (and often over a thousand) adenomatous polyps in the colorectum. A subset of these polyps will progress to malignant colon cancer. The cancer risk for FAP patients is virtually 100% by the age of 40 years.

IMMUNODEFICIENCY AND CANCER

Neoplasms are the second most common cause of mortality (after infections) among patients with primary and acquired immunodeficiencies.

Carcinomas After Allografting

Compared with the general population, the risk of developing cancer after organ transplantation is increased three- to five-fold. The risk of post-transplant carcinomas after bone marrow transplantation is influenced by the patient's inherent susceptibility to carcinogenesis and use of radiotherapy. The incidence of cancer in solid-organ transplant recipients increases greater than 1% per year after transplant such that about 20% of patients will experience a cancer within 10 years following transplantation. Many of these cancers involve the skin (squamous cell carcinoma, basal cell carcinoma, melanoma and Merkel cell carcinoma).

Lymphoproliferative Diseases (LPD) After Allogenic Organ Transplantation

The term 'post-transplant lymphoproliferative disease' (PTLD) are lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a transplantation recipient. The incidence of PTLD is approximately 1% for renal and 2% for hepatic transplants, but varies from 2% to 10% for heart, heart-lung, and bone marrow transplants and 20% of small bowel transplants. The interval from time of transplant to onset of PTLD is highly variable and depends on the type of allograft (arise more quickly in patients who have received a bone marrow or stem cell transplant), Epstein-Barr virus status (in EBV positive patients PTLD usually develops within the first year), and the immunosuppressive regimen used (more with high-dose cyclosporine). Majority (>90%) of PTLD in solid organ recipients are of host origin whereas majority of PTLD in bone marrow allograft recipients are of donor origin. The clinical presentations of PTLD vary considerably. PTLD has been grouped into four morphological categories, namely early lesions, monomorphic PTLD, polymorphic PTLD, and classical Hodgkin's lymphoma-like PTLD. The most common symptoms are non-specific, including fever, lymphadenopathy, weight loss, abdominal pain, and splenomegaly.

The initial treatment for PTLD involves modification of immuno-suppression. Using or changing immunosuppression to sirolimus can induce complete responses. Early-onset lesions and polymorphic are more likely to respond to reduction

in immunosuppression. In those who fail to respond to modification of immunosuppression, chemotherapy forms the backbone of therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituixmab. Single agent rituximab produces response rates of around 60%.

ACQUIRED IMMUNODEFICIENCY SYNDROME-RELATED MALIGNANCIES

Individuals with human immunodeficiency virus (HIV) infection are at increased risk for developing various neoplasms. The clinical course of specific malignancies is often markedly altered in the setting of HIV-positive infection as compared to the HIV-negative counterpart.

Acquired immunodeficiency syndrome (AIDS) defining neoplasms are: (1) kaposi's sarcoma (KS), (2) aggressive β-cell non-Hodgkin's lymphoma (NHL), both peripheral and primary central nervous system (CNS) lymphomas, and (3) cervical cancer. A number of other cancers also occur with increasing frequency in HIV-infected patients, including Hodgkin's disease (HD), multicentric Castleman's disease, angiosarcoma, multiple myeloma, lung cancer, and seminoma. Introduction of highly active antiretroviral therapy (HAART) for HIV infection has resulted in fewer AIDS complications, including malignancies.

Kaposi's Sarcoma

Kaposi's sarcoma (KS) is the most common HIV-associated tumour. KS is an angio-proliferative lesion caused by human herpes virus 8 (HHV-8).

AIDS-related KS

Co-infection with HIV increases the risk of KS by more than 100,000 times, and the clinical course can be more aggressive than that of classical KS. KS lesions typically arise on the skin or mucous membranes as flat deep purple plaques. Other sites that are commonly involved are lymph nodes and gastrointestinal (GI) tract. Skin lesions most commonly appear on the legs and face. Diagnosis is usually established by skin punch biopsy. As per the AIDS Clinical Trials Study Group (ACTG), patients are classified as "good risk" or "poor risk" according to the extent of tumour, immune status as measured by CD4+ T-cell count and evidence of HIV-associated systemic illness. KS is not yet curable. Treatment is only palliative in nature. HAART is fundamental to the oncologic therapy of AIDS-KS. If HAART does not result in immunologic and virologic response, additional therapies are required like surgical excision, cryotherapy, photodynamic therapy, intra-lesional injection (e.g., vinblastine), topical 9-cis-retinoic acid, carbon dioxide laser therapy and radiotherapy. Systemic drug therapy is usually with immunotherapy (interferon) or cytotoxic chemotherapy (liposomal anthracyclines or paclitaxel) or combination chemotherapy (doxorubicin, bleomycin, and vinca alkaloid).

Acquired Immunodeficiency Syndrome-Related Lymphoma

AIDS-related lymphoma (ARL) is the second most frequently occurring AIDS-associated malignancy. The risk of developing NHL in the HIV-infected population increases by nearly 100 times the risk in the non-HIV infected population. Introduction of HAART has reduced the incidence of ARL by up to 50%. EBV and HHV-8 has a role in the pathogenesis of ARL.

Predominant related ARLs are—Burkitt's lymphoma, diffuse large β-cell lymphoma, primary effusion lymphoma (PEL); also termed body-cavity lymphoma and plasmablastic lymphoma (PBL) of the oral cavity.

Patients with ARL and AIDS associative Non-Hodgkin's lymphoma (NHL) usually present in advanced stage, have a high incidence of B symptoms and majority of them have some extranodal disease and in one-third of the cases all disease is extranodal. The GI tract is a common site of extranodal involvement. Prognosis depends upon the CD4+ cell count. In the pre-HAART era, survival was very poor, currently the median survival is more than 2 years.

Optimal therapy is not well defined. Treatment consists of standard-dose chemotherapy. Routine CNS prophylaxis is advised for these patients as there is a high predilection for leptomeningeal involvement (15% to 20%). All patients should receive prophylaxis for *Pneumocystis jirovecii* pneumonia regardless of the CD4+ count. Data regarding the use of rituximab is conflicting, as rituximab was associated with excessive toxicity in some series, however, one recent report shows, it is very effective. HAART therapy is continued during the period of chemotherapy unless contraindicated.

Primary effusion lymphoma

It accounts for about 4% of all HIV-associated NHLs. It is caused by HHV-8 infection with a predilection for the serous body cavities. Primary effusion lymphoma occurs as a late manifestation of HIV infection. Patients have a poor clinical outcome and a shorter overall survival (6 months). Combination chemotherapy is the mainstay of the treatment along with HAART.

Plasmablastic lymphoma

It is a rare AIDS-associated NHL, with predilection for the mucosa of oral cavity. It has also been reported in other sites, such as stomach, cervical lymph nodes, lungs, orbit, and paranasal sinuses. The treatment of PBL is not well defined and patients have been treated heterogeneously with chemotherapy and/or radiotherapy.

Human papillomavirus (HPV) associated cancers in AIDS

HPV associated cancers in AIDS include cervical cancer and anal cancer.

Cervical cancer

Immunosuppression and HPV co-infection play a major role on the pathogenesis of the disease. HPV16, 18, 45, and 31 are commonly associated with invasive cervical cancers; that are usually more aggressive and have a higher recurrence rate. The management is similar to patients from the general population without HIV infection. The use of HAART does not seem to have an impact in patient outcome. Rigorous cervical cancer screening programmes in HIV infected patients could have an impact in reducing the incidence and mortality rates in the HPV/HIV infection setting.

Anal cancer

Anal cancer is also associated to oncogenic types of HPV and its incidence has dramatically increased among HIV patients. Chemoradiotherapy (fluorouracil and mitomycin) produces a similar response to those of the general population, with a survival rate of 55% to 75% and preservation of the sphincter in 60% to 90% of cases. The use of screening techniques, such as anal Papanicolaou smear and anoscopy and biopsy are necessary to diagnose intraepithelial lesions or true invasive

cancers and any person diagnosed with anal squamous cell carcinoma must be evaluated for HIV infection.

CANCERS FOLLOWING CHEMOTHERAPY

Many of the cytotoxic agents are potentially mutagenic and carcinogenic, the degree varies among different drugs. Now more and more people are getting cured of their disease after radiotherapy and/or chemotherapy, this has led to therapy-related secondary malignancy, developing years after primary therapy.

After chemotherapy, secondary malignancies are mainly secondary acute myeloid leukaemias (AML). Secondary lymphatic leukaemias are very rare (about 5%). Most of these secondary leukaemias appear in the first 10 years after chemotherapy, especially after alkylating agents or nitrosourea derivatives. Of the alkylating agents, melphalan is thought to be the most leukaemogenic. Risk factors for secondary malignancies include the cumulative dose of the cytostatic agent, age over 40 years, the combination of chemotherapy and radiotherapy.

Based on their characteristics, secondary leukaemias can be divided into two types; secondary leukaemia after administration of alkylating agents, or after therapy with topoisomerase-II inhibitors (epipodophyllotoxin—etoposide) (**Table 2**).

The cumulative 10-year incidence of secondary leukaemia varies greatly, depending on the underlying disease. For example, after curative treatment for Hodgkin's disease, incidence is cited at 1.5% to 10%, and peaks about 4 to 8 years after therapy.

Table 2: Clinical Characteristics of Secondary Acute Myeloid Leukaemia

	DNA-damaging Agents	Topoisomerase II Inhibitors
Latency (in years)	4 to 6 years (range: 1 to 20 years)	1 to 3 years (range: 0.5 to 4.5 years)
Presentation	Antecedent myelodysplastic syndrome	Abrupt, no prodrome
Genotype	Losses, deletions (-5,-7)	Translocations 11q23-based; t(8;21); t(15;17)
Phenotype	M6 and M7 (with myelofibrosis)	Monocytic (M4 and M5)
Prognosis	Less favourable	Favourable

SECONDARY CANCERS FOLLOWING RADIOTHERAPY

Radiotherapy can also induce tumours, with chemotherapy and/or radiotherapy-associated secondary malignancies. Following radiotherapy, it is primarily solid tumours that develop; secondary leukaemias are rare. Following criteria are suggested to diagnose post-irradiation secondary tumour: (1) tumour must have arisen within a previous radiation field, (2) secondary malignancy should differ histologically from the primary, irradiated tumour, (3) if the secondary tumour is leukaemic, the latency period should be more than 2 years, and if it is a solid tumour, more than 6 years, and (4) amount of statistical data should be large enough so that a possible association can be reasonably assumed.

The interval between irradiation and development of a secondary tumour varies. Leukaemias may develop as early as 2 years post radiation, with incidence peaking 5 to 10 years after radiotherapy. Thereafter, risk decreases with time. For solid tumours, intervals of at least 6 years are usual. The risk increases with increasing radiation dose and decreasing age. Children are more prone to develop secondary cancers than adults. Patient who receives neck radiation are at risk for the subsequent occurrence of thyroid cancer. Children who receive prophylactic cranial irradiation for acute lymphatic leukaemia are at increased risk of brain tumours.

EVALUATION OF PATIENTS AT RISK FOR SECOND MALIGNANT NEOPLASMS

In the past history, one should ask for the risk factors like: (1) history of treatment with radiation therapy, an alkylating agent, and/or a topoisomerase-II inhibitor, (2) history of hereditary retinoblastoma (unilateral with a positive family history or bilateral), (3) carrier of ataxia-telangiectasia, (4) post-surgical chronic lymphoedema, and (5) oestrogen treatment.

In the present history, ask for any pain in the previously irradiated area, pallor, bleeding tendencies (e.g. blood in stool, inter-menstrual bleeding). This should be followed by a detailed physical examination. Examination of irradiated patients will help in the early identification of thyroid nodules and skin cancer. Annual mammography should be initiated, not later than 10 years after breast irradiation.

Investigations including radiographs of any painful area or mass in a previously irradiated area, stool examination for occult blood (any patient who received any abdominal irradiation), Pap smear, urine cytology (in any patient with haematuria and a history of bladder irradiation and/or treatment with a cyclophosphamide or ifosfamide), mammogram, depending upon the clinical situation are recommended. All patients who have been treated with an alkylating agent or a topoisomerase-II inhibitor should have a complete blood count every 6 to 12 months for a minimum of 12 years after diagnosis.

Transplant recipients should be warned as to the dangers of sun exposure. They should undergo full skin examination by their transplant care provider. Studies have demonstrated a benefit to systemic retinoid chemoprophylaxis in transplant recipients.

FOLLOW-UP

All former cancer patients should remain under a physician's care indefinitely. For children, there are special after-treatment follow-up clinics in major cancer centres. This helps in regular monitoring of these patients and in giving advises. They should be counselled regarding the potential for the adverse effects of tobacco use, including the potential to interact with the adverse effects of their prior therapy, such as irradiation of the oropharynx, oesophagus, and/or lungs.

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21.17 Oncological Emergencies

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INTRODUCTION

Emergencies in cancer can be catastrophic. Oncological emergencies are often a part of the initial presentation of a cancer patient. The management of oncological emergencies needs understanding of the disease process. The goals of therapy have to be clear and have to be based on the biology of the underlying neoplasm. Many seeming hopeless situations in fact have a good outcome if treated appropriately. Oncological emergencies result from the mass effect of the tumour and the effect of metabolites secreted by the tumour. The common oncological emergencies are listed in **Table 1**.

Table 1: Oncological Emergencies

Metabolic emergencies
Tumour lysis syndrome
Hypercalcaemia
Hypoglycaemia
Lactic acidosis
Hyperuricaemia
Syndrome of inappropriate ADH secretion (SIADH)
Urological emergencies
Haemorrhagic cystitis
Priapism
Haematological emergencies
Haemolytic uraemic syndrome
Febrile neutropaenia
Cardiac and vascular emergencies
Cardiac tamponade
Thrombosis and pulmonary thromboembolism
Emergencies due to pressure effects of the tumour
Superior vena cava syndrome
Spinal cord compression
Intestinal obstruction

SYNDROME OF INAPPROPRIATE ADH SECRETION

Ectopic production of antidiuretic hormone (ADH) by tumours results in water retention, hyponatraemia, and increased urinary osmolarity. About three-fourth of the patients with syndrome of inappropriate ADH secretion (SIADH) have small cell cancer of the lung. It is also associated with the use of vincristine, cyclophosphamide, ifosfamide and melphalan and with brain metastasis. The symptoms of SIADH are those of hyponatraemia and water intoxication. The diagnosis is made by a euvolaemic hyponatraemia in the absence of hypothyroidism, renal dysfunction, or Addison's disease. Tumour-associated SIADH is differentiated from other causes of SIADH by exclusion, though the differentiation has little bearing on the therapy. The treatment of the primary is the cornerstone of the therapy. Radiation is administered for brain metastasis. Fluid restriction, demeclocycline (300 to 600 mg twice daily) and hypertonic saline are administered as required.

TUMOUR LYSIS SYNDROME

Tumour lysis syndrome (TLS) is a complex of metabolic derangements resulting from the kidney's inability to handle products of cell lysis. Potassium, phosphates, and purine metabolites are the major intracellular components that are toxic when released into the extracellular space. These are eliminated by the kidney. The kidney has a finite capacity to eliminate these compounds. The excretory capacity of the kidney may be overwhelmed if these compounds are released too rapidly in large amounts, or when the kidney function is compromised. Hyperkalaemia poses the greatest immediate risk to the patient with TLS. Uric acid is formed from xanthine by the action of xanthine oxidase and is the end-product of purine catabolism. Uric acid precipitates in the tubules leading to renal impairment and compromises the ability of the kidney to excrete potassium. Hyperphosphataemia results secondary to hypocalcaemia due to calcium chelation. Hypocalcaemia worsens the effects of hyperkalaemia. Tumour lysis is most commonly seen in high-grade haematological malignancies (e.g. acute leukaemias and high-grade lymphomas). It is most commonly seen after therapy but may occur spontaneously. Patients with a large tumour burden, patients with pre-existing metabolic derangements like hyperuricaemia and hyperkalaemia and patients with impaired renal function are prone to TLS. Prevention is the best treatment for TLS. Established TLS is a life-threatening condition. Patients should be adequately hydrated (3 litres per day) and initiated on 300 mg of allopurinol per day. Most favour alkalinisation of the urine. The treatment of established TLS is that of the derangements it causes. Allopurinol should be administered to prevent formation of uric acid. Allopurinol has no effect on uric acid which is already formed. Hydration and diuresis eliminate pre-formed uric acid. Recombinant urate oxidase can destroy uric acid and may be considered in patients who are refractory to allopurinol and hydration. Hyperkalaemia is treated with potassium restriction, hydration, diuresis, glucose-insulin drip, beta-2 agonist aerosols and dialysis. Hyperphosphataemia is treated with phosphate restriction and dialysis.

SUPERIOR VENA CAVA SYNDROME

The superior mediastinum is a space through which tubular structures pass from the neck to the thorax. Lymph nodes draining the lung are found in the fatty tissues. As the superior mediastinum has rigid walls, structures passing through it are prone to compression by space occupying pathologies. The commonest cause of superior mediastinal syndrome is lung cancer followed by lymphomas. Superior vena cava syndrome (SVCS) due to catheter-induced thrombosis is being seen more often with the increasing use of venous access devices.

The common manifestations of SVCS include dyspepsia, swelling of the face and upper extremities, cough, chest pain and dysphagia. Examination shows distended neck

veins and chest wall oedema, plethora of face, and oedema of the arms.

Radiograph of the chest is normal in only 15% of the patients. Computed tomography (CT) is performed to define the extent of disease and invasion of adjacent structures including the great vessels, bronchus, and the spinal cord. Venography is indicated if a surgical bypass is contemplated. The investigations to establish diagnosis include sputum cytology, examination of pleural fluid, bronchoscopy, thoracoscopy, mediastinoscopy, lymph node biopsy, and bone marrow biopsy. There is no increased risk of bleeding in areas drained by the SVC because of increased pressure. Invasive procedures can be carried out safely if the need arises.

The treatment of SVCS is disease-specific. SVCS is seldom a dire emergency. Patients with small cell cancer of the lung with SVCS should be treated with chemotherapy and radiation. The response rate exceeds 95%. About 70% of the patients remain free from the disease despite relapses in other parts. Patients with non-small cell lung cancer with SVCS have a poor outcome compared to those without SVCS. They should be treated with radiotherapy. Patients with SVCS due to lymphoma should be treated with chemotherapy with radiation being used for patients who have large mediastinal masses. Catheter-induced SVCS may be treated with thrombolytic agents early (< 5 days) in the course of the disease. Catheters of patients with prolonged symptoms should be removed and this should be done under cover of heparin. All patients of SVCS should be given head elevation and oxygen therapy. Diuretics can reduce oedema but dehydration increases the risk of thrombosis. Anti-coagulants are not of proven use and may interfere with diagnostic procedures. Percutaneously transluminal angioplasty with stent insertion may be considered in patients to provide symptomatic relief pending diagnosis and in patients who cannot be offered therapy. Stenting is superior to radiation.

HYPERCALCAEMIA

Hypercalcaemia is seen in about 10% to 20% of the patients with malignancy. It is commonly seen with multiple myeloma, breast cancer, lung cancer, kidney cancer, and head and neck cancer. Hypercalcaemia results from bone resorption from metastasis or from the effect of factors secreted by the tumour on calcium metastasis. Patients who are asymptomatic with serum calcium levels less than 13 mg/dL do not need aggressive treatment. Volume repletion, limitation of immobilisation, and treatment of the primary may bring down the calcium levels. All symptomatic patients and those patients with serum calcium more than 13 mg/dL should be treated. Hydration brings down the calcium by 2 mg/dL. Though the fall is modest, hydration forms a critical part of treatment of hypercalcaemia. Dehydration leads to an impaired ability to eliminate calcium by the kidney. One to two litres of 0.9% saline may be administered over 2 hours with 20 to 40 mg frusemide. Bisphosphonate (zolendronate 4 mg over 15 to 30 minutes) results in normalisation of serum calcium by 4 to 10 days. The fall lasts for 4 to 5 weeks. Other active agents include gallium nitrate, calcitonin, and plicamycin.

SPINAL CORD COMPRESSION

Though about 1% to 6% of the cancer patients have spinal cord compression, only 1 in 500 patients present with spinal cord compression. Cancers associated with spinal cord compression are breast cancer, multiple myeloma, prostate cancer, lung cancer, and nasopharyngeal cancer. The thoracic spine is involved in about 66% of the cases and the lumbar spine in about 20%. Cervical spine and sacrum are rarely involved. Prostatic and colorectal carcinomas show a predilection for the lumbar spine.

The compression usually occurs due to the extension of disease from a vertebral metastasis. Lymphomas and neuroblastomas can compress the spine by transforaminal extension of para-vertebral mass. Myelopathy of spinal cord compression results from physical damage to the cord and cord oedema due to impaired venous drainage.

Spinal cord compression presents with low back pain. The pain is worse on getting up in morning and may increase on coughing and sneezing. Radiation indicates root involvement. Pain is followed by neurological symptoms. Symptoms of neurogenic bladder occur late.

Magnetic resonance imaging (MRI) is the most important investigation in patients with suspected malignant spinal cord compression. CT-guided myelography may be performed where MRI is contraindicated. Plain radiographs lack sensitivity. The immediate treatment consists of glucocorticoids. Dexamethasone 6 to 10 mg is the drug of choice. The compression may be relieved by radiotherapy or surgery.

RAISED INTRACRANIAL PRESSURE

Normal brain function requires a normal intracranial pressure (ICP). Increase in brain volume like that seen with tumours can be offset by a decrease in the cerebrospinal fluid (CSF) volume, but the compensatory mechanism has its limits. Patients manifest central nervous system (CNS) dysfunction once this limit is breached. ICP may increase due to increase in volume of intracranial structures or an imbalance between production and resorption of CSF. Tumours, brain oedema, extra-axial mass lesions of dura and subdura, intracranial haematoma and subdural empyemas result in an increase in the intracranial contents and rise in the ICP. Malignancy-related increases in CSF volume are rare due to increased production. Absorption of CSF may be hampered by obstruction to the flow of CSF, due to mass lesion along the path of flow described above or by the involvement of the meninges by meningitis or carcinomatosis.

The commonest cause of increased ICP is brain metastasis. Lung cancer, breast cancer, melanoma, choriocarcinoma, renal cell carcinoma, and papillary cell carcinoma of the thyroid are the common causes of metastasis to the brain. Some malignancies like acute lymphoblastic leukaemia have a tendency to involve the meninges. Primary brain tumours particularly those with a periventricular predilection can cause raised ICP. Iatrogenic causes of raised ICP include radiotherapy and meningitis. Cancer patients are immunodeficient and prone to herpes simplex virus (HSV) encephalitis, cryptococcal meningitis, cerebral toxoplasmosis, aspergillosis, and candidiasis. Dural venous sinus thrombosis, either spontaneous or as a result of L-asparaginase therapy, presents with only symptoms of raised ICP in one-third of the cases.

Raised ICP manifests as headache, vomiting, and somnolence which progresses to coma. Focal neurological deficit gives a clue

to the location of the mass. Examination shows papilloedema in about 50% of the patients. Gadolinium-enhanced MRI is the investigation of choice. An unenhanced CT is a quick and readily available alternative that is adequate to determine obstruction to the flow of CSF, uncal, transtentorial and transfalcian herniation and the presence of haemorrhage into a tumour.

The patients should be nursed with their head slightly elevated; dehydration should be corrected using isotonic fluids and corticosteroids administered unless a CNS lymphoid malignancy is suspected. Dexamethasone 24 to 40 mg per day is usually used. Mannitol (0.75 to 1g/kg initial dose followed by 0.25 to 0.5 g/kg every 3 to 6 hours as a 20% to 25% solution) can reduce ICP. The effect of mannitol is transient. Therapy should be stopped if osmolarity exceeds 300 mOsml/L. The fastest method to reduce ICP is intubation and hyperventilation. The target pCO_2 is 25 to 30 mm Hg. Lower levels compromise cerebral blood flow. Obstructive hydrocephalus is neurosurgical emergency treated with external ventriculostomy or placement of a third ventriculostomy. A ventriculo-peritoneal shunt should be avoided as there is a risk of peritoneal seeding. Appropriate therapy for the primary disease should be carried out.

MALIGNANCY-ASSOCIATED HAEMOLYTIC URAEMIC SYNDROME

Haemolytic uraemic syndrome manifests as microangiopathic haemolytic anaemia, thrombocytopaenia, and renal failure. The causes of malignancy-associated haemolytic uraemic syndrome include adenocarcinomas particularly those of the gastrointestinal tract, chemotherapy drugs, and stem cell transplant. Drug-induced haemolytic uraemic syndrome is most commonly seen with mitomycin C and fluorouracil. Other implicated agents include cytosine arabinoside, bleomycin, cisplatin, daunomycin, deoxycoformycin, estramustine, gemcitabine, immunotoxins, and semustine. The outcome of malignancy-associated haemolytic uraemic syndrome is poor. The incriminated agent if any should be withdrawn. Plasma exchange may be attempted but its efficacy is not as much as in idiopathic variety. Cryosupernatant which is free of von-Willebrand factor may be a better replacement than plasma.

HYPERURICAEMIA

Hyperuricaemia may be seen in absence of TLS. It is common in high-grade tumours like acute leukaemias and non-Hodgkin lymphoma. Hyperuricaemia results from increased uric acid production from increased cell turnover. The management of hyperuricaemia is similar to that in patients with TLS.

HAEMORRHAGIC CYSTITIS

Haemorrhagic cystitis presents as suprapubic discomfort, dysuria, frequency and urgency of micturition with haematuria. It is seen with ifosfamide, cyclophosphamide (high dose) and pelvic radiation (cervical cancer, bladder cancer and rectal cancer). Chemotherapy-induced haemorrhagic cystitis is prevented by the use of mesna in an appropriate dose. Radiation cystitis requires discontinuation of radiation. Gross haemorrhage can result in urinary retention due to large clots. Severe haemorrhage is treated with continuous infusion with haemostatic agents (0.5% to 1% silver nitrate or 1% alum) into the bladder. Formalin (1% to 5% solution) may be instilled cystoscopically for 3 to 10 minutes in life-threatening haemorrhage. Other agents which have been tried are prostaglandins, oral conjugated oestrogens or hyperbaric oxygen. Open cystostomy with bladder packing may be used if other measures fail.

PRIAPISM

Priapism may complicate the course of 10% of the patients. Priapism results from penile metastasis. It may also be seen in haemolymphatic malignancy with high counts. The therapy involves analgesics and treatment of the underlying malignancy.

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21.18 Supportive Care in Cancer

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INTRODUCTION

The success story of treatment of cancer in the last decade is largely contributed by the rapid advances in supportive care. This has led to more aggressive chemotherapy with intention to cure, bone marrow transplant in haematological malignancies and palliative therapy for incurable advanced stage cancer patients. The main types of supportive care are directed towards management of following conditions.

ANAEMIA ASSOCIATED WITH CANCER

Anaemia in cancer patients could be due to the bone marrow infiltration, bleeding, hypersplenism, haemolysis, defective iron utilisation, treatment related (extensive radiotherapy or chemotherapy) and diminished nutritional status with deficiencies. 40% of patients with non-myeloid malignancies have anaemia. Overall incidence of anaemia during chemotherapy or radiotherapy is 54% with highest in patients with lung (71%) or gynaecological cancer (65%) and it increases with the number of chemotherapy cycles. Anaemia has a negative impact on the quality of life (QoL) and is an important factor in cancer-related fatigue.

Grading of Anaemia

Treatment-related anaemia is graded according to the National Cancer Institute – Common Toxicity Criteria of Adverse Events (CTCAE v3)

Grade 0 : Haemoglobin within normal limits

Grade 1 : Lower normal level of haemoglobin 10 g/dL

Grade 2 : 8 to less than 10 g/dL

Grade 3 : 6.5 to less than 8 g/dL

Grade 4 : Less than 6 g/dL

Grade 5 : Death

Evaluation of Anaemia

Drug history, haemogram, peripheral blood smear with reticulocyte count, serum iron, transferrin saturation with ferritin levels, Coomb's test, folate and vitamin B12 status and bone marrow examination. Occult blood test in stool, urine routine examination, and evaluation of renal function are the common tests for its diagnosis.

Indications for the Use of Erythropoiesis Stimulating Agents (ESAs)

1. In non-haematological malignancies erythropoiesis stimulating agents (ESAs) are used for the treatment of symptomatic chemotherapy-induced anaemia in adult patients to prevent repeated transfusions and their hazards and improve quality of life. If the Hb level increases by 1 g/dL in 4 weeks then the dose may remain same or reduced by 25% to 50% but if the haemoglobin (Hb) rise is less than 1 g/dL above baseline, the dose should be increased. If the Hb rise is less than 1 g/dL above baseline after 8 to 9 weeks or if Hb 13 g/dL then treatment with ESAs should be discontinued.
2. Amongst haematological malignancies low-risk myelodysplastic syndromes and post-allogeneic transplantation are indications. There is no difference between different ESAs in relation to effectiveness and safety and they should not be used in patients with poorly-controlled hypertension. The relative risk of thromboembolic events increases with ESAs.

NEUTROPAENIA

Neutropaenia in cancer patients is due to bone marrow infiltration from disease or treatment-related (chemotherapy and radiation therapy). The implications are life-threatening infections and delay in treatment. The risk associated with neutropenia increases with its duration and grade. It occurs more in patients older than 65 years, patients with poor performance status, chronic obstructive pulmonary disease, diabetes mellitus, and existing renal or cardiac dysfunctions. Timely intervention reduces morbidity and mortality. Neutropaenia grading scale as per recommendations of the World Health Organization (WHO) is given below:

Grade I : Not significant = 1500 to 2000 ANC(ANC – absolute neutrophil count)

Grade II : Minimal = 1000 to 1500 ANC

Grade III : Moderate = 500 to 1000 ANC

Grade IV : Severe = less than 500 ANC

Febrile Neutropaenia

It is defined as single oral temperature of 38.3°C or 38.0°C over 1 hour with less than 500 neutrophils/mm^3 or less than 1,000 neutrophils/mm^3 with a predicted decline to 500/mm^3 over the next 48 hours. The absence of granulocytes, disruption of mucociliary barriers and shifts in inherent microbial flora along with anti-microbial usage predispose the neutropaenic cancer patients to infections. History taking, physical examination, obtaining cultures, and starting antibiotics empirically are the key. Primary sites of infection are the alimentary tract (i.e. mouth, pharynx, oesophagus, intestine, and rectum), sinuses, lungs, genito-urinary tract, and skin.

The first approach is empiric intravenous monotherapy with either a carbapenem or an extended spectrum anti-pseudomonal cephalosporin followed by combination of aminoglycoside plus an antipseudomonal penicillin. If there is no remission of fever within 48 hours, consider vancomycin depending on potential infecting organisms. Vancomycin can be started upfront in case of catheter-related infections or where there is substantial mucosal damage. If still no remission occurs in next 48 hours then start empirical antifungals. Risk assessment should be performed as part of the initial evaluation. Risk factors are mentioned in **Table 1**.

For lung infiltrates consider additional empiric coverage for atypical pneumonia pathogens (fluoroquinolone, macrolide, or doxycycline) and empiric trimethoprim/sulfamethoxazole or pentamidine for patients allergic to sulphur or patients at high risk for *Pneumocystis jirovecii* pneumonia, Rimantadine, Amantadine during influenza season can be considered.

Table 1: Multinational Association of Supportive Care in Cancer (MASCC) Scoring Index

Burden of illness : No or mild symptoms	5
Burden of illness : Moderate symptoms	3
Burden of illness : Severe symptoms	0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status at the time of onset of fever	3
Age <60 years	2

Using the MASCC-Risk Score: scores ≥ or 21 are at low risk of complications.

Fungal infections are common in neutropaenic patients so empiric use of fluconazole was common. *Candida albicans* have recently been surpassed by non-albicans species which are resistant to fluconazole. Empiric antifungal therapy previously involved amphotericin B at the expense of greater toxicity. The newer lipid formulations of amphotericin B are less toxic. Voriconazole is approved for use in invasive aspergillosis. Primary antifungal prophylaxis involves fluconazole 400 mg daily or itraconazole 400 mg daily.

The use of growth factors for the treatment of febrile neutropaenia is not recommended always except in settings where there is septicaemia, tissue infection, co-morbidities, and prolonged neutropaenia. They reduce duration of neutropaenia but do not alter morbidity and mortality. The granulocyte colony stimulating factor (G-CSF) is given at a dose of 5 µg/kg per day till stable ANC recovery. Pegfilgrastim is a single dose colony stimulating factor and is equally effective.

VENOUS THROMBOEMBOLISM (VTE)

Venous thromboembolism (VTE) represents one of the most important causes of morbidity and mortality in cancer patients with highest incidence in metastatic brain, lung, uterus, bladder, pancreas, stomach, and kidney cancer. The absolute risk depends on tumour type, site and stage, administration of chemotherapy or hormone therapy, surgical intervention, the presence of indwelling catheters, age, pre-chemotherapy platelet and leucocyte count, immobilisation, and previous history of VTE.

Prophylaxis with unfractionated heparin, low molecular weight heparin (LMWH) or fondaparinux in hospitalised cancer patients confined to bed with acute medical complication is recommended. Use of vena caval filters are advocated for recurrent pulmonary embolism. Long term treatment with LMWH is safe and more effective than oral anticoagulation with vitamin K antagonists.

CANCER RELATED FATIGUE

Definition of cancer related fatigue (CRF) (in the 2010 NCCN CRF guidelines) is a distressing persistent subjective sense of physical emotional and/or cognitive tiredness to exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Patient with various types of cancer receiving different types of treatment report the frequency of CRF ranging from 70% to 100%. Persistent CRF is reported by 30% to 40% of cancer survivors. It is a multi-dimensional syndrome and several mechanisms coexist in its pathophysiology.

The first step in the management of fatigue is to identify the potentially reversible contributors. Causes and remedy are mentioned in **Table 2**. After that clinicians may choose to select from amongst the established and investigational drugs used for the symptomatic pharmacologic management of CRF. Methylphenidate has been the most frequently used. Exercise may be beneficial in reducing CRF. Psychological interventions include cognitive behavioural therapy, education or counselling, and supportive or expressive therapy.

Table 2: Frequent Contributors to Fatigue and Suggested Treatments

Mood disorders	Anti-depressants
Endocrine	Thyroid, testosterone replacement
Dehydration	Fluid replacement
Pain	Opioids, adjuvant analgesics
Infections	Antimicrobials as appropriate
Anaemia	Blood transfusion as appropriate
Cachexia	Nutritional and pharmacological interventions
Chemotherapy	Dose and drug modification as appropriate

CANCER PAIN

Incidence of Pain

Over 80% of cancer patients with adjuvant metastatic disease suffer from pain, caused mostly by direct tumour infiltration. Approximately 20% of pain in cancer patients may be attributed to the effects of surgery, radiotherapy, or chemotherapy. The pain may be nociceptive, neuropathic, or a combination of both. The pain management is based on WHO step ladder pattern as given below:

Treatment of mild pain (WHO analgesic ladder-step I): Mild pain (Numerical Rating Scale [NRS]: 1-4) is treated with non-opioid analgesics such as acetaminophen/paracetamol or NSAIDs with or without adjuvants (medicines which are primarily not analgesics but aid in analgesia) like sedatives and steroids.

Treatment of moderate pain (WHO step II): Moderate pain (NRS: 5-7) have been treated with a combination of step I plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol, or propoxyphene.

Treatment of severe pain (WHO step III): Severe pain (NRS: 8-10) is best managed by a strong opioid and step I. Morphine is most commonly used via oral route. Transdermal Fentanyl is best reserved for patients whose opioid requirements are stable.

Scheduling and Titration

All patients should receive round-the-clock dosing with provision of a 'breakthrough dose' to manage transient excerbation of pain which is breakthrough pain. The 'breakthrough dose' is usually equivalent to +10% to 15% of the total daily dose.

Alopaecia

It is undoubtedly one of the most distressing complications of chemotherapy. Hair loss starts from the first cycle and peaks up at 2 months. Regrowth occurs once chemotherapy ends. However, the texture may vary. Anthracyclines, taxanes, and cyclophosphamide are major culprits. Chemotherapy-induced alopecia (CIA) is traditionally categorised as acute diffuse hair loss caused by dystrophic anagen effluvium. The major approach to minimize CIA is by scalp cooling though robust data are missing. Minoxidil was able to reduce the severity or shorten the duration of CIA, but could not prevent CIA.

Chemotherapy Induced Nausea and Vomiting

Another distressing consequence of cancer chemotherapy is nausea and vomiting. Antineoplastic drugs with high emetogenic potential are cisplatin, cyclophosphamide greater than1500mg/m^2, dacarbazine, lomustine, streptozocin. Combination protocols are most dangerous. Chemotherapeutic agents induce nausea and vomiting through central mechanisms (stimulation of chemoreceptor trigger zone) and peripheral gut mucosal receptors through 5-HT receptors. Clinically, three forms of chemotherapy induced nausea and vomiting (CINV) are recognised. Anticipatory CINV occurs before patients receive chemotherapy and is mediated by cortical mechanisms. Acute CINV is seen up to 24 hours post-chemotherapy and nausea and vomiting developing more than 24 hours after chemotherapy up to day 5 is termed as delayed nausea and vomiting.

To prevent CINV, a three drug regimen including single doses of a 5-HT3 receptor antagonist [ondansetron (32 mg) or palonosetron (0.25 mg)], dexamethasone (12 mg) and aprepitant 125 mg day 1, 80 mg day 2 and day 3 (a neurokinin 1 receptor antagonist) given before chemotherapy is recommended. The combination of dexamethasone and aprepitant is also suggested to prevent delayed nausea and vomiting on the basis of its superiority to dexamethasone alone. The ideal approach to the treatment of anticipatory emesis is maximum effective control of acute and delayed emesis.

Diarrhoea

Causes of diarrhoea in cancer patients are injudicious use of antibiotics, co-morbid infection, partial intestinal obstruction, surgery (post-gastrectomy, short-bowel syndrome), acute or chronic radiation toxicity, and chemotherapy.

Chemotherapy-induced diarrhoea (CID) can cause significant morbidity and mortality and at times severe enough to require a dose reduction or a delay, or a discontinuation of chemotherapy. 5-FU (5-flurouracil), irinotecan, and capecitabine are most notorious in this respect. The incidence of all grades of diarrhoea during chemotherapy has been reported to be as high as 82%, with up to one-third of patients experiencing severe (grade 3 or 4) diarrhoea (**Table 3**). Newer oral tyrosine kinase inhibitors have diarrhoea as one of the side effects.

Chemotherapy-induced diarrhoea (CID) can result in life-threatening dehydration, electrolyte imbalances, renal insufficiency, nutritional deficiencies, and affects quality of life. Diarrhoea is also associated with an increased risk of infectious complications in patients with chemotherapy-induced neutropaenia.

Acute medical management of CID includes loperamide or diphenoxylate as first-line agents. Subcutaneous octreotide is recommended for intractable grade 2 diarrhoea and may be considered for grade 1 CID that does not resolve with high-dose loperamide. Hospitalisation is recommended for patients with grades 3 and 4 CID. In-hospital care includes rehydration, antibiotic therapy, and octreotide. A chemotherapy dose reduction is generally advised for patients who have experienced grade 3 or 4 diarrhoea in a previous chemotherapy cycle. Patients should be advised to take low residue diet and ample fluids and avoid caffeinated beverages and alcohol.

Table 3: Chemotherapy Induced Grades of Diarrhoea – National Cancer Institute

Grades	0	1	2	3	4
	None	<4 stools per day	4 to 6 stools per day nocturnal stools	>7 stools per day but less than 10 or incontinuous	>10 stools per day

Dihydropyrimidine dehydrogenase (DPD) plays a central role in 5-FU metabolism, and DPD deficiency is well documented as possibly resulting in severe 5-FU-associated toxicity. The morbidity associated with irinotecan chemotherapy may also be reduced by screening candidates for uridine diphosphate glucuronyl transferase polymorphisms.

Supportive care in oncology has made substantial strides in clinical medicine in the last decade. A working knowledge of the common conditions and their prevention and management will help improve quality of life of cancer patients.

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Section 22

Psychiatric Medicine

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22.1 Basic Considerations in Psychiatry

Ashit Sheth

Psychiatric disorders may occur from disturbances of one or more of the following interrelated factors like biological factors, learnt behaviour, psychological adaptation, and social and environmental conditions. Subjective reports of the patient and other informants form the cornerstone for psychiatric diagnosis and management. There may be no demonstrable physical signs for diagnosis. Proper diagnosis can be reached only through accurate history taking, mental status examination and physical examination.

PSYCHIATRIC HISTORY

The psychiatric history is a record of the patient's life. The doctor should communicate empathy and respect to the patient. Identifying data of the patient covers demographic details of patient such as age, sex, marital status, occupation, and religion. It also includes source of information, and their reliability.

The chief complaint states the reason why the patient is consulting a psychiatrist. It should be recorded in the patient's or the informant's own words. A history of present illness is most helpful in making a diagnosis.

The nature of onset, acute or gradual; the presence or absence of precipitating events; the course and duration of the illness (fluctuating, continuous or episodic); and the impact of the illness on the patient's personal, occupational and social life.

The details of nature of behavioural changes (e.g. irritability, bizarre behaviour) and the presence of physical (headache, vomiting, and fever) and psychological symptoms (forgetfulness, personality changes, confusion) suggestive of organic brain damage should be looked into.

Any history of substance abuse or excessive consumption of prescription drugs (pain killers, cough syrup, etc.) should always be asked for.

Past illness includes details of past episodes of both psychiatric and medical illnesses. Inquire into previous history of similar episodes, hospitalisation, medication, suicide attempts and substance use. Also, collect information about previous treatments and their response.

General medical history includes available information on medical illnesses, injury or trauma, reproductive history, history of neurological disorders, drug allergies and sensitivities. A careful record should be made of present medications taken for physical or mental problems.

A personal history to include the nature of delivery, milestones, presence of neurotic traits in childhood (thumb-sucking, nail-biting, bed-wetting), personality as a child, and behaviour during schools should be asked for; behaviour during adolescence, sexual knowledge and practices, history of sexual abuse, marital history, other sexual relationships and occupational history.

Family history includes details of mental illnesses, epilepsy and mental retardation in the family (preferably for three generations), consanguinity in family, family relationships and support that the family can give to the patient.

Premorbid personality of the patient prior to the onset of illness needs to be assessed. Especially look for mood fluctuations, suspiciousness, being aloof, excessive fantasy thinking and aggressive behaviour.

MENTAL STATUS EXAMINATION

Besides a history, signs can be delineated by performing the mental status examination of patient. The latter is the description of the patient's appearance, speech, actions and thoughts during the interview.

Attitude and Appearance

It includes overall physical impression reflected by posture, poise and grooming. Signs of anxiety, e.g. wide eyes and perspiring forehead, convey valuable insight into the patient's mental state. A paranoid patient's attitude will be uncooperative, guarded or hostile.

Consciousness

Consciousness is the state of awareness. Disturbances in consciousness include disorientation in time, place or person, clouding of consciousness, stupor, delirium, and coma.

Disturbances of attention include distractibility, hyper vigilance and trance.

Emotion

It is a complex feeling state with psychic, somatic and behavioural components. It has two aspects namely mood and affect. Mood is a pervasive or sustained emotion that colours a person's perception of life. Affect is an objective observation of the underlying mood state.

Some common disturbances of mood and affect are given in **Table 1**.

Motor Behaviour

It is the capacity to initiate action as expressed through a person's behaviour.

The various types of motor behaviour disturbances are given in **Table 2**.

Thought

Disorders of thought can be of form, possession, stream or content.

Formal thought disorder or loosening of associations is said to occur when there is illogical thinking, deviations in the train of thinking or incoherent mixture of words and phrases and a lack of association between one thought and another.

Table 1: Common Disturbances of Mood and Affect

Dysphoria: unpleasant mood
Euthymia: normal mood
Irritability: easily prone to anger
Euphoria: subjective feeling of happiness
Elation: happiness that is communicable to the examiner
Depression: feeling of sadness
Anxiety: feeling of apprehension
Agitation: anxiety with motor restlessness
Panic: intense attacks of fear associated with other autonomic and psychic features of anxiety
Depersonalisation: feeling of unreality concerning oneself or one's environment
Apathy: dulled emotional tone associated with indifference
Blunted affect: lack of intensity of affective response and absence of reactivity of affect
Labile affect: sudden changes and shifts, in emotions, unrelated to external stimuli

Table 2: Types of Motor Behaviour Disturbances

Negativism: active or passive opposition to commands or suggestions
Automatic obedience: excessive co-operation with any command and obeying of commands automatically
Catalepsy: maintaining the same posture for long periods of time
Waxy flexibility: body positions are maintained in which they are placed, however uncomfortable or odd they might be
Echopraxia: imitation of actions of others
Stereotype: repetitive fixed pattern of physical actions or speech
Somnambulism: sleepwalking
Compulsion: uncontrollable impulse to perform an act involuntarily
Stupor: is defined as absence of motor behaviour

Stream of thought

Flight of ideas is excessive speech with a rapid shift from one idea to another without reaching the goal. Circumstantially it is the tendency to digress from the main theme or addition of unnecessary details but ultimately reaching the desired goal.

Content of thought

Disturbance in this consists of delusions, obsessions, hypochondriac beliefs and phobias. Delusions are false, unshakable beliefs, not consistent with the patient's intelligence and cultural background. Delusions can be of the following kinds: persecutory, grandiose, self-referential, control, nihilistic or somatic, based on the predominant content of the delusion.

Obsessions are repetitive, intrusive thoughts, ideas or impulses that are recognised by the patient as irrational but which are associated with inability to control them. Hypochondriacal beliefs manifest as an excessive preoccupation with health and a belief that one suffers from a disease in the absence of any organic pathology. Phobia is an irrational fear of an object, activity or situation with an avoidance of the feared object.

Perception

Perceptual disorders can be broadly classified as hallucinations or illusions. Hallucinations are false sensory perceptions not associated with external stimuli. These can be auditory, visual, tactic, olfactory or gustatory. Illusions are false-sensory perceptions of real external stimuli. Sensory distortions are distortions in size or shape of a real external object, e.g. micropsia or macropsia.

Memory

Memory is tested by following simple methods:

Immediate: 'Repeat these numbers after me: 7, 3, 1, 8, 6'

Recent: 'I want you to remember these three things: a cocker spaniel, a red pencil, and a refrigerator. Keep them in mind. I'll ask you to repeat them after a few minutes'. 'What did you eat for dinner last night? What did you have for breakfast?'

Long-term: 'What was your address when you were in grade school? Who was your teacher in fifth grade?'

Hint: Asking overlearned facts such as birthdates or social security numbers does not accurately test long-term memory.

Disturbances of memory

Amnesia: Partial or total inability to recall experiences.

Paramnesia: Falsification of memory due to problems in recall, e.g. confabulation unconscious filling of gaps in memory by imagined experiences that the person believes in *Deja vu*: Incorrect visual recognition of an event or situation as having occurred earlier.

Orientation

Orientation is judged by asking the patient about day, date, month, year, identifying the immediate relatives. Disturbance of orientation occurs in organic brain syndrome.

Intelligence

It is the problem solving ability of an individual.

General level of intelligence is judged at the time of history-taking. Intelligence is reflected in patient's performance at school or at his job. Intellectual abilities are generally affected in dementia.

Insight

It is the awareness that the person is psychologically ill and he requires help.

It is assessed by asking the patient the relevant questions about his perception of his illness. Following questions would elicit the level of insight

Whether patient feels that he is ill?

Whether patient is psychologically or physically ill?

Whether he is willing to take treatment for his problem?

Insight is generally lost in psychosis—schizophrenia, mania, sometimes in depression.

CLASSIFICATION OF PSYCHIATRIC DISORDERS

Classification is required in psychiatry, as in other branches of medicine, so that doctors and others can communicate easily about the nature of patient's problems and about prognosis and treatment, and research can be conducted with comparable groups of patients. Psychiatric disorders were traditionally classified as organic or functional (based on aetiology). However, this has now become redundant as more

organic factors are emerging as causation of major functional disorders. Another system of classification was to divide functional disorders into psychosis and neurosis. Though these terms have survived over a period of time, a host of new nomenclatures now dominate the current classification systems - ICD-10 (International Classification of Disease, 10th Edition) and DSM IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition). The ICD-10 (formulated by the World Health Organization) classifies mental and behavioural disorders.

Organic Factors Including Symptomatic Mental Disorders

This includes the various types of dementias, delirium or acute confusional states due to various causes, psychotic conditions because of brain disease or systemic disease and personality and behavioural changes of a similar aetiology. This block comprises a range of mental disorders grouped together.

On the basis of their common demonstrable aetiology in cerebral disease, brain injury or other insults leading to cerebral dysfunction. The dysfunction may be primary, i.e. because of disease or insult to the brain, or secondary, i.e. because of the effect of other systemic disorders, like endocrine or metabolic disorders.

Mental and Behavioural Disorders Due to Psychoactive Substance Abuse

This group consists of disorders attributable to the use of one or more psychoactive substances. This includes intoxication, dependence syndromes, withdrawal states, psychotic disorders and amnestic syndromes related to alcohol, cannabis, opiates and other psychoactive drugs.

Schizophrenia, Schizotypal and Delusional Disorders

The schizophrenic disorders are characterised by disorders of thinking and perception and inappropriate or blunted mood. Patients may have bizarre delusions and hallucinations and demonstrate thought disorders (manifested by incoherent speech). All these phenomena occur in clear consciousness.

Schizotypal disorder is characterised by eccentric behaviour and anomalies of thinking and affect that resemble schizophrenia though characteristic abnormalities of schizophrenia such as persistent delusions and hallucinations are absent.

The delusional disorders include a variety of disorders in which long-standing delusions constitute the only conspicuous feature which cannot be classified as organic, schizophrenic or mood-related. Acute and transient psychotic disorders are a group of psychiatric disorders that have an acute onset (within two weeks), a rapidly changing and variable clinical picture and the presence of associated stress. These are usually short-lasting and have a good outcome.

Mood Disorders

Here the basic disturbance is a change in mood to depression or elation. All the other symptoms related to activity, social behaviour and thinking can be understood on the basis of the mood disturbance. Persistent and recurrent depressive mood is classified as major depressive disorder. Depression with lesser intensity and long duration is classified as dysthymic disorder. The other type of mood disorder is characterised by episodes of mania and/or depression. When there are repeated manic episodes or at least two episodes of mania and depression, the disorder is called bipolar affective disorder.

Neurotic, Stress-Related and Somatoform Disorders

These disorders have been grouped together because of their historical association with the concept of neurosis and the association of a substantial proportion of these disorders with psychological causation.

They consist of anxiety disorders, i.e. phobic anxiety disorders, panic disorders, generalised anxiety disorders, obsessive compulsive disorders and adjustment and stress-related disorders, dissociative disorders and somatoform disorders.

Behavioural Syndromes Associated with Physiological Disturbances and Physical Factors

These include eating disorders, non-organic sleep disorders and sexual dysfunctions not due to an organic cause.

Disorders of Adult Personality and Behaviour

These include a variety of behaviour patterns which tend to be persistent and are the expression of an individual's lifestyle and mode of relating to self and others. It consists of the following subgroups:

- Specific personality disorders
- Enduring personality change
- Habit and impulse disorders which include pathological gambling, fire-setting and kleptomania, gender identity disorders, disorders of sexual preference and other disorders such as factitious disorder (Munchausen's syndrome).

Disorders of Childhood and Adolescence

These include mental retardation and developmental disorders.

SPECIAL DIAGNOSTIC TESTS

There are a number of tests and evaluation procedures that help in the complete assessment of a mentally ill individual.

Psychological Tests

These help in providing information about intelligence, personality, adjustment and underlying psychopathology. Neuropsychological tests focus exclusively on assessing organic brain damage and the various lobe functions. Commonly used psychological tests include the following.

Intelligence tests

Wechsler adult intelligence scale (revised) and the Stanford-Binet tests of intelligence are useful in diagnosing and assessing mental retardation and may facilitate other diagnosis. Intelligence tests can be verbal or performance-based.

Personality tests

The commonly used tests are the Minnesota multiphasic personality inventory (MMPI), multiphasic questionnaire (MPQ) and the Catell's 16-PF (16 personality factor). The BAI (Bell's Adjustment Inventory) also gives an idea about the patient's adjustment in various areas.

Projective tests

The commonly used tests are Rorschach ink blot test, sentence completion tests, the thematic appreciation test and the object sorting test. Projective tests are unstructured tests

which facilitate the subject to respond in ways that reflect fantasies and individual modes of adaptation. Conscious and unconscious attitudes may be deduced by the subject's responses. Specific responses are found in various psychiatric conditions such as schizophrenia affective disorder and help in arriving at a diagnosis or tapping hidden conflicts.

Tests for Organic Brain Damage

These assess memory, problem-solving and lobe functions. These tests are helpful in dementias, amnesias and other organic dysfunctions. Some of these tests are the Bender-Gestalt test, Wechsler memory scale, PGI memory scale, and neuropsychological batteries such as Halstead Reitan battery and Luna Nebraska battery.

Electrophysiological investigations

Electroencephalography, evoked potentials and event-related potentials are now being used as aids in psychiatric diagnosis. Characteristic latency and wave abnormalities are seen in schizophrenia and affective disorders. Sleep EEG in affective disorders to detect REM and NREM abnormalities and smooth pursuit eye movement recording in schizophrenia are being increasingly used as diagnostic aids.

Imaging

Computed tomography (CT scan), positron emission tomography (PET) and nuclear magnetic resonance imaging (MRI) are particularly useful in dementias and other organic psychiatric conditions and have limited use in the study of conditions such as obsessive compulsive disorders.

Neuroendocrine tests

Dexamethasone-suppression test (DST) is used to confirm a clinical impression of major depressive disorder.

Urine testing for substance use

A variety of substances (e.g. alcohol, barbiturates, benzodiazepines, heroin, cannabis, cocaine, etc.) can be detected in patient's urine if the urine is tested in a specific period after ingestion. This is important as substance abuse can mimic a number of psychiatric disorders.

RECOMMENDED READINGS

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22.2 Anxiety Disorders

Uday Chaudhuri

Anxiety is a normal emotion under circumstances of threat. It is thought to be part of the evolutionary 'fight or flight' reaction of survival. The idea of anxiety as a psychiatric disorder is evolving rapidly. It is characterised by the concept of core symptoms of excessive fear or worry.

In comparison to major depression, which is characterised by core symptoms, the depressed mood or loss of interest, anxiety disorder have considerable symptom overlap with major depression symptoms surrounding core features, particularly sleep disturbance, problems in concentrating, fatigue and psychomotor and arousal symptoms. This is outlined in **Figure 1**.

Each anxiety disorder also has a great deal of symptom overlap with other anxiety disorders.

WHAT THEREFORE, IS AN ANXIETY DISORDER?

All these disorders seem to maintain the core features of same form of anxiety or fear coupled with some form of worry, but their natural history overtime shows them to morph from one into another, to evolve into full syndrome expression of anxiety disorders symptoms.

Associated symptoms of anxiety with brain regions and circuits that regulate them are depicted in **Figure 2**.

Anxiety disorders have core features of fear and worry that cut across the entire spectrum of anxiety disorders sub-types, from generalised anxiety disorder to panic disorder, social anxiety disorder, post-traumatic stress disorder, and obsessive compulsive disorder.

A great deal of progress has been made in elucidating the role of amygdala is the fear response and the role of cortico-striatal-thalamic-cortical circuits is the symptom of worry (**Figure 2**).

Numerous neurotransmitters are involved in regulating those circuits that underlie anxiety disorders. GABA is a key neurotransmitters, as well as benzodiazepine anxiolytic that act on this neurotransmitter system. Serotonin, norepinephrine, alpha 2 delta ligands, voltage gated calcium channels, are important regulators of anxiety circuits. The symptoms commonly attributed to these neurotransmitters and part of anxiety disorder are given in **Table 1**.

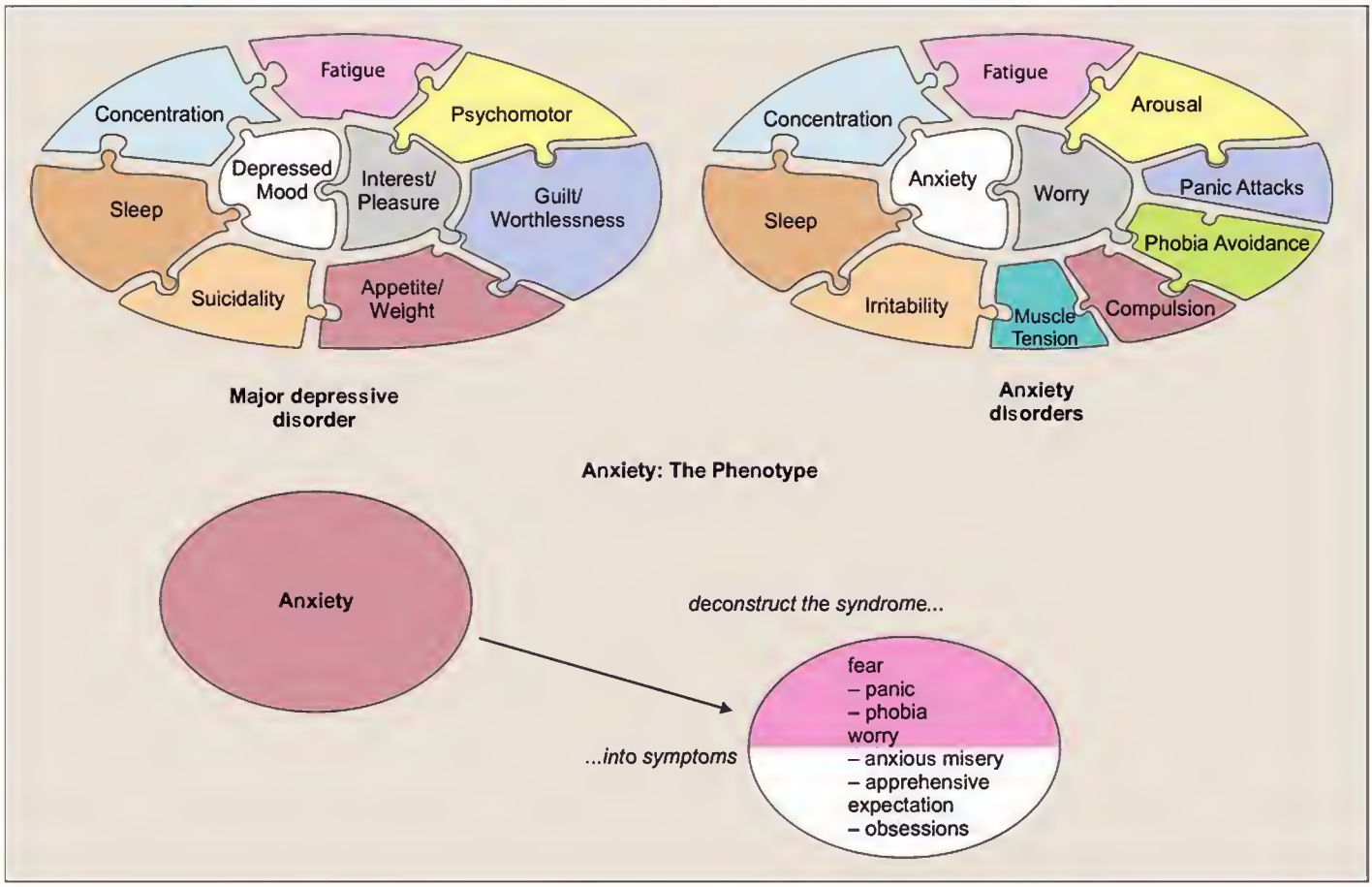


Figure 1: Overlap of MDD and anxiety disorders.

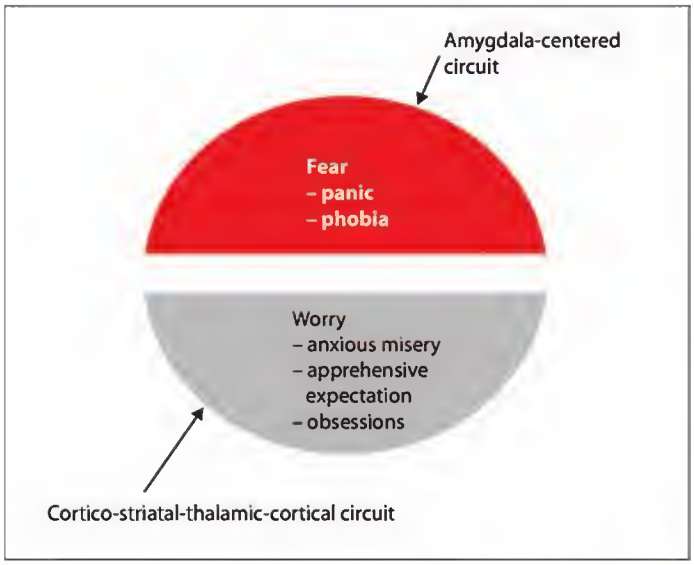


Figure 2: Associated symptoms of anxiety with brain regions and circuits that regulate them.

Table 1: Symptoms of Anxiety Disorder

Psychological
Apprehension
Fear of impending disaster
Irritability
Depersonalisation
Somatic
Tremor
Sweating
Palpitations
Chest pain
Breathlessness
Headache
Dizziness
Diarrhoea
Frequency of micturition
Initial insomnia
Poor concentration

Anxiety disorders are amongst most common psychiatric condition in 15% to 20% of medical clinic patients.

Anxiety, as a symptom, can be a part of other psychiatric disorders (particularly depression), or a consequence of physical illness such as thyrotoxicosis or be drug-induced (e.g. caffeine). Anxiety disorders may be associated with a comorbid disorder like substance abuse disorder.

Symptoms can be psychological, physical or a mixture of both (Table 1). Intervention is required when symptoms become disabling and interfere with functioning. Certain medical conditions which mimic anxiety disorder are given in Table 2.

Table 2: Medical Conditions which may Mimic Anxiety Disorder

Hyperthyroidism
Phaeochromocytoma
Hypoglycaemia
Paroxysmal arrhythmias
Alcohol withdrawal
Temporal lobe epilepsy

There are several disorders within the overall spectrum of anxiety disorders, each with its own characteristic symptoms generalised anxiety disorder (GAD), panic disorder, social anxiety disorder (SAnD), obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) (Tables 3 to 7).

Table 3: Generalised Anxiety Disorder (GAD)

Signs and symptoms	Excessive anxiety; at least 6 months; difficult to control worry/hypervigilant Associated with 3 or more: Restless/on edge, easily fatigued, concentration problems, irritability, muscle tension, sleep disturbance Causes significant distress Often physical complaints like dizziness, tachycardia, tightness of chest, sweating, tremor
Causes	Neurotransmitter dysregulation: NE, 5-HT, GABA Autonomic nervous system activation; locus caeruleus/NE release/limbic system One year prevalence rate: 1%; lifetime prevalence rate 5% Familial association Over half: onset in childhood
Rule outs	Anxiety disorder due to a medical condition (hyperthyroidism; phaeochromocytoma) Substance-induced anxiety or caffeine-induced anxiety disorder Other anxiety disorders: panic disorder, OCD, etc. DSM-IV criteria help rule out
Labs/Tests/Exams	Self-rated scales: Beck anxiety inventory (BAI); state trait anxiety inventory Observer-rated scale: Hamilton anxiety rating scale (HAM-A) Psychiatric evaluation Physical examination Routine lab tests; thyroid function tests
Interventions	Pharmacologic: benzodiazepines very effective (diazepam, lorazepam); non-benzodiazepines: buspirone Beta-blockers: propranolol CBT Deep muscle relaxation Individual and family therapy Education

Table 4: Obsessive-Compulsive Disorder (OCD)	
Signs and symptoms	Obsessive – recurrent, intrusive thoughts that cause anxiety or compulsions – repetitive behaviours (hand washing, checking) that reduce distress/anxiety and must be adhered to rigidly Driven to perform compulsions Time consuming (>1 hour per day), interfere with normal routine Recognises thoughts/behaviours are unreasonable
Causes	Genetic evidence Neurobiological basis: orbitofrontal cortex, cingulated, and caudate nucleus Neurochemical: serotonergic and possibly dopaminergic Association between OCD and Tourette's and others Lifetime prevalence of 2.5% Women >men Average onset: 20 years Childhood: 7 to 10 years
Rule-outs	Other anxiety disorders: phobias Impulse control disorders Obsessive-compulsive personality disorder Body dysmorphic disorder Depression Neurological disorder
Labs/Tests/Exams	Yale-brown obsessive compulsive scale (Y-BOCS) Psychiatric evaluation Mental status examination Neurologic examination
Interventions	Pharmacologic: SSRIs (fluoxetine: higher doses); fluvoxamine; clomipramine Beta-blockers: propranolol Behaviour therapy: exposure and response prevention Deep muscle relaxation individual and family therapy Education

Table 5: Post-Traumatic Stress Disorder (PTSD)	
Signs and symptoms	Traumatic event (self/family) witness others; threat of harm or death or actual death and helplessness Re-experiencing event 'flash-backs' (triggers: sounds/smell) Hypervigilance (unaware re-enactment related to trauma) Persistent anxiety/outbursts Acute (<3 months); chronic (≥3 months); delayed (>6 months)
Causes	Rape, torture, child abuse, disaster, murder, war, etc. Physiologic/neurochemical/endocrinological alterations Sympathetic hyperarousal Limbic system (amygdala dysfunction) 'Kindling': neuronal excitability Risk factor: previous trauma Lifetime prevalence – 8% (US)
Rule-outs	Acute stress disorder Obsessive-compulsive disorder Adjustment disorder Depression panic disorder Psychotic disorders Substance-induced disorder Psychotic disorder due to a general medical condition Delirium
Labs/Tests/Exams	PTSD scale (clinician administered) Psychiatric evaluation Mental status examination Neurologic examination CAGE, SMAST Physical exam, routine blood studies No laboratory test can diagnose
Interventions	Debriefing (rescuers, etc.) Individual or group psychotherapy CBT EMDR (eye movement desensitisation and reprocessing) Pharmacotherapy: antidepressants – SSRIs, SNRIs, MAOIs, TCAs; antipsychotics; anxiolytics; mood stabilisers Family and community support/art therapy/psychodrama

Table 6: Panic Disorder (PD)	
Signs and symptoms	Excessive panic; at least 6 months; difficult to control worry/hypervigilant Associated with 3 or more symptoms : restless/on edge, easily fatigued, concentration problems, irritability, muscle tension and sleep disturbance Causes significant distress Often physical complaints: dizziness, tachycardia, tightness of chest, sweating, tremor
Causes	High level of anxiety since childhood Autonomic nervous system activation; locus caeruleus/NE release/limbic system One year prevalence rate: 1%; lifetime prevalence rate: 5% Familial association
Rule-outs	Medical disorder, substance abuse, misinterpretation of bodily/mental experiences, drug-induced, hyper-vigilance; chronic worry
Labs/Tests/Exams	Self-rated scales: beck anxiety inventory (BAI); state trait anxiety inventory Observer-rated scale: Hamilton anxiety rating scale (HAM-A) Psychiatric evaluation Physical examination Routine lab tests; thyroid function tests
Interventions	Cognitive therapy, SSRIs

Table 7: Social Phobia (SP)	
Signs and symptoms	Excessive panic; at least 6 months; difficult to control worry, hypervigilant Associated with 3 or more symptoms: restless/on edge, easily fatigued, concentration problems, irritability muscle tension, sleep disturbance Causes significant distress Often physical complaints: dizziness, tachycardia, tightness of chest, sweating, tremor
Causes	Strong genetic loading High level of anxiety since childhood Autonomic nervous system activation; locus caeruleus/NE release/limbic system One year prevalence rate: 1%; lifetime prevalence rate: 5% Familial association
Rule-outs	Schizophrenia Patient comfortable with social isolation Presence of hallucinations and delusions Depression Patient does not want to face people as he feels inadequate and guilty Presence of other symptoms of depression Lab tests fear of humiliation in interpersonal situations
Labs/Tests/Exams	Self-rated scales: Beck anxiety inventory (BAI); state trait anxiety inventory Observer-rated scale: Hamilton anxiety rating scale (HAM-A) Psychiatric evaluation Physical examination Routine lab tests; thyroid function tests
Interventions	Cognitive therapy, SSRIs, social skills training

DIFFERENTIAL DIAGNOSIS

Anxiety is usually transient as a part of 'adjustment disorder' and subsides without treatment. Generalised anxiety (chronic anxiety associated with worry) is an important cause of medically unexplained somatic complaints. Phobic anxiety is characterised by avoidance of feared situation (e.g. social situation, specific situation, public speaking – generalised avoidance in agoraphobia) and it is a common association with panic disorder.

MANAGEMENT

It includes a combination of psychological, pharmacological and psychosocial intervention. A holistic approach is required as it interferes with all three conditions of health: physical, mental and social well-being.

Psychological Intervention

Psycho-education and family education, reassurance, relaxation training, health maintenance activities, and cognitive behaviour therapy (CBT) are some of the common psychological approaches.

Pharmacological Intervention

It involves short time therapy with benzodiazepines (not more than 2 to 4 weeks) and as and when required a treatment of acute anxiety spell.

Long-term therapy with selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) and some tricyclic antidepressants (TCAs) like imipramine and clomipramine. Buspirone has also got a role in the treatment of anxiety.

Management of Anxiety Disorder Subtypes

Generalised anxiety disorder

Today, first line treatments include SSRIs (selective serotonin reuptake inhibitors, namely fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram and escitalopram) and SNRIs, (selective serotonin and norepinephrine reuptake inhibitors (SNRI), venlafaxine as well as benzodiazepines and buspirone. Some prescribers are reluctant to give benzodiazepines for anxiety disorders in general for GAD in particular owing to the long-term nature of GAD and the possibility of dependence, abuse potential and withdrawal reaction with benzodiazepines. Benzodiazepines can be useful to 'top up' an SSRI or SNRI. Benzodiazepines can also be useful for occasional intermittent use when symptoms surge and relief is needed quickly.

If a GAD patient is not doing well after several weeks or months of treatment switching to another SSRI/SNRI or buspirone or anxiolytic with a benzodiazepine can be considered. Failure to respond to first line of treatment can lead to trail of the novel alpha 2 delta ligands, gabapentin or pregabalin. One also can try sedative antidepressants such as mirtazapine, trazodone, or tricyclic antidepressants or even sedating antihistamines such as hydroxyzine.

Adjunctive treatments that can be added to first or second line treatment for GAD include hypnotics for continuing insomnia, atypical antipsychotics in low dose for severe, refractory and disabling symptoms unresponsive to aggressive treatment and cognitive behaviour therapy.

Panic disorders

Panic attacks occur in many conditions, not just panic disorder, and panic disorder is frequently comorbid with other anxiety disorder and with major depression.

First line treatment included SSRIs and SNRIs as well as benzodiazepines. To note benzodiazepines are often used as second line options, during treatment initiation with an SSRI/SNRI, for emergent use, during a panic attack, or for incomplete response. Second line treatments include the novel alpha 2 delta ligands, gabapentin and pregabalin as well as tricyclic antidepressants.

Mirtazapine and trazadone can be helpful in some cases as augmenting agents to first line treatment (SSRIs/SNRIs), when there is partial response to treatment. The MAO inhibitors are much neglected in psychopharmacology in general, and for the treatment of panic disorder in particular. However, MAOIs can have purposeful efficacy in panic disorder in specialised setting, where various agents have failed.

Various adjunctive treatments are important in panic disorder. Atypical antipsychotics for severe and treatment resistant cases, cognitive behaviour therapy to augment psychopharmacotherapy and to modify cognitive distortions.

22.3 Bipolar Mood Disorders

Lakshman Dutt, Rakesh Sanghadiya

INTRODUCTION

Mood disorders encompass a large group of disorders in which pathological mood and related disturbances dominate the clinical picture. The term mood disorders (also known as affective disorders) refer to sustained emotional states, not merely to the external expression of a transitory emotional state.

Mood disorders are best considered as syndromes consisting of clusters of signs and symptoms sustained over weeks to months and which represent marked departure from a person's habitual functioning and tend to recur often in periodic or cyclical fashion.

EPIDEMIOLOGY

Lifetime prevalence of mood disorders is; unipolar major depressive disorder (5% to 17%), bipolar I disorder (0% to 2.4%), bipolar II disorder (0.3% to 4.8%), cyclothymia (0.5% to 6.3%) and hypomania (2.6% to 7.8%).

TYPES OF MOOD DISORDER

Manic episode

Manic episode or bipolar affective (mood) disorder, current episode hypomanic, (with or without psychotic symptoms), current episode mild or moderate depression (with or without) somatic symptoms, current episode severe depression (with or without psychotic symptoms).

Depressive Episode

Depressive episode, mild (with or without somatic syndrome), moderate depressive episode (with or without somatic syndrome); severe (with or without psychotic symptoms), recurrent depressive disorder (moderate with or without somatic syndrome); recurrent depressive disorder (severe with or without psychotic symptoms); cyclothymia and dysthymia as per ICD-10 listing.

Recurrent depressive disorder is also referred as unipolar depression. The other method to classify mood disorder is into major depressive disorder; bipolar I disorder, bipolar II disorder, bipolar III disorder, and bipolar IV disorder.

Age and Sex Distribution

Most consistent finding in all studies on the prevalence and incidence of unipolar major depression is that it was almost two-fold more common among women than men. The gender difference begins in early adulthood, is most pronounced in people between ages of 30 and 45 and also persists in elderly. The possible reasons for increased vulnerability of depression in females are increased stress sensitivity, maladaptive coping strategies and multiple social roles and substance use disorders most frequently seen in males masking depressive symptoms have been suggested for the explanation of the gender difference. Gender ratio in bipolar depression is approximately 1:1.

Average age of onset of unipolar depression is between 30 and 35 years, and that of average age of onset of bipolar disorder is around 20 years of age. The prevalence of unipolar depression and bipolar I disorder did not show significant variation based on race and ethnicity. Major depressive disorder and bipolar illness are most frequent among divorced, separated and widowed individuals. Single women have lower rates of depression than married women do; but the opposite is true for men. Although the relationship between depressive symptoms and low socio-economic class is well documented, most studies found a weak correlation between major depressive disorder or bipolar illness and low socio-economic class. Urban communities are more stressed and at risk for depression than rural ones. Most western studies show that major depression was more common in urban population than its rural counterpart.

Despite the fact that more than two-thirds of patients with recurrent major mood disorders show irregular seasonal patterns individually and statistically, spring and fall are the peak time for depression just as summer is for mania. There is a condition known as 'seasonal depression' seen in cold countries where there is less of sunlight because of prolonged winters.

AETIOLOGY

Of the biological amines, norepinephrine (NE) and serotonin (5 HT) are the two neurotransmitters most implicated in the pathophysiology of mood disorders. The correlation suggested by basic science studies between the down-regulation of beta-adrenergic receptors and clinical anti-depressant response is probably the single-most compelling piece of data indicating the direct role for the noradrenergic system in depression. Depletion of serotonin may precipitate depression and some patients with suicidal impulses have low cerebrospinal fluid (CSF) concentration of serotonin metabolite and low concentration of serotonin uptake sites on platelets. The data suggest that dopamine levels are decreased in depression and increased in mania.

Other neurotransmitters like GABA and neuroactive peptides, particularly vasopressin and endogenous opiates, have been implicated in the pathophysiology of mood disorders.

Neuroendocrine Regulation

Major neuroendocrine axes of interest in mood disorder are adrenal, thyroid and growth hormone axis. Other neuro-endocrine abnormalities that may be implicated in patient with mood disorder include decreased nocturnal secretion of melatonin; decreased prolactin release in response to tryptophan administration, and decreased basal level of follicle stimulating hormone (FSH) and luteinising hormone (LH).

Genetic Factors

Adoption, linkage and twins studies also show data supporting the genetic basis for the inheritance of mood disorders.

Cognitive Theory

Depression results from specific cognitive distortion present in persons prone to depression. Those distortion, referred to as

depressogenic schemata are cognitive template data in ways that are altered by early experiences.

Learned helplessness is also another theory for depression.

DIAGNOSIS

In addition to diagnostic criteria for major depressive disorder and bipolar disorders, DSM-IV TR includes specific criteria for mood episodes.

DSM IV TR criteria for major depressive disorder

Bipolar ½: Schizopolar disorder.

Bipolar I disorder

DSM IV TR criteria for manic episodes

Bipolar I½: Depression with protracted hypomania.

Bipolar II disorder

Criteria for bipolar II disorders include one major depressive disorder (MDD) episodes and one hypomanic episode.

Bipolar II½: Depression superimposed on cyclothymic temperament.

Bipolar III disorder

Depression plus induced hypomania.

Bipolar III½: Prominent mood swings occur in context of substance or alcohol use or abuse.

Bipolar IV disorder

Depression superimposed on hyperthymic temperament.

Diagnosis episodes of depressive disorders and manic episode are given in **Tables 1 and 2**.

Table 1: DSM IV TR Criteria for Major Depressive Disorders

Five (or more) of the following symptoms need to be present for a 2 weeks period and represent the change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest.

- Depressed mood most of the time
- Marked decreased interest or pleasure in all
- Significant weight loss when not dieting or weight gain
- Insomnia or hypersomnia
- Psychomotor agitation or retardation nearly every day
- Feeling of worthlessness or inappropriate guilt
- Fatigue or loss of energy
- Decreased ability to think or concentrate
- Recurrent thought of death

The symptoms do not meet criteria for mixed episode.

The symptoms caused clinically significant distress or impairment in social, occupational or other important area of functioning.

The symptoms are not due to direct physiological effects of substance or a general medical condition.

The symptoms are not better accounted for by bereavement.

MENTAL STATUS EXAMINATION

Depressive Episode

General features

Generalised psychomotor retardation is most common although psychomotor agitation may also be seen especially in older patient.

Classically a depressed patient has a stooped posture, no spontaneous movements and a down-cast aerated gaze.

Table 2: DSM IV TR Criteria for Manic Episode

A distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least one week (or any duration if hospitalisation is necessary).

During the period of mood disturbance three or more of the following symptoms have persisted (four if mood is only irritable) and have been present for a significant degree.

- Inflated self-esteem or grandiosity
- Decrease need for sleep
- More talkativeness
- Flight of ideas or subjective experience that thoughts are racing
- Distractibility
- Increase in goal directed activity
- Excessive involvement in pleasurable activities

The symptoms do not meet criteria for mixed episode.

The mood disturbance is severe to cause marked impairment in social occupational or other areas of functionary.

The symptoms are not due to direct physiological effects of substance or general medical condition.

Mood affect and feelings

Depression is the key symptom although 50% of patients deny depressive feeling, family members often bring these patients for treatment because of social withdrawal and generalised decreased activity.

Speech

Depressed patients show decrease in rate and volume of speech, they respond to questions with single words and exhibit delayed response to questions.

Perceptual disturbances

Depressed patient with delusion or hallucination are said to have major depressive disorder with psychotic features.

Delusions and hallucinations that are consistent with a depressed mood are said to be mood congruent that include those of guilt, sinfulness, worthlessness, poverty, failure persecution.

Thoughts

Depressed patients have negative views of world and of themselves. They may have delusion/ideation of hopelessness, helplessness, suicidal ideations, guilt and shame and are preoccupied with loss of sleep; weakness and fatiguability.

Impulse control

About 10% to 15% of all depressed patients commit suicide and about two-thirds have suicidal ideations.

Manic Episodes

General description

Manic patients are excited, talkative sometime amusing and frequently hyperactive. At times, they are grossly psychotic and disorganised and require physical restraints and intramuscular sedative drugs.

Mood, affect and feelings

Manic patients are euphoric but they can also be irritable. They also have a loco frustration. Tolerance which may lead to feeling of anger and hostility. They may be emotionally labile.

Speech

Manic patients are difficult to interrupt. As the mania gets more intense, speech becomes louder, rapid and filled with jokes, rhymes and plays on words; sometimes loosening of association or flights of ideas may also be present.

Perceptual disturbances

Mood congruent manic delusions are often concerned with great wealth, extraordinary abilities or power.

Thought

Manic patient's thought content includes themes of self-confidence and self-aggrandisement.

Sensorium and cognition

Grossly, orientation and memory are intact, although some manic patients may be so euphoric that they answer incorrectly. Kreplin called the symptom 'delirious mania'.

Impulse control

About 75% of all manic patients are associative or threatening. Manic patients do attempt suicide or homicide.

Judgment and insight

Impaired judgment is a hallmark of manic patients. They may break laws about credit cards, sexual activities, finance and sometimes involve their families in financial ruin.

Reliability

Manic patients are notoriously unreliable in their information because lying and deceit are common in mania.

TREATMENT OBJECTIVES

Bipolar disorder is a lifelong illness. Therefore, maintenance treatment is the core of management. Treatment of choice should be made by collaborative effort between patients and physician. The goal of acute therapy is to stabilise acute episodes with the goal of remission. The goal of maintenance therapy is to optimise protection against recurrence of episode. Concurrently attention needs to be devoted to maximising patient functioning and minimising sub-threshold symptoms and adverse effects of treatment.

Treatment Options of Mood Disorders

Drugs used in treatment of mood disorders are described in Table 3.

Table 3: Drugs Used in Treatment of Mood Disorders

Drugs	Uses	Adverse effects
Lithium	Acute and prophylactic treatment of mania/ hypomania and bipolar depression	Cognitive dysfunction Tremor Gastrointestinal Weight gain Foetal abnormalities
Valproate/ Divalproex	Acute mania and maintenance treatment of bipolar disorder? Bipolar depression	Drug-drug interaction Foetal abnormalities
Carbamazepine	Acute and prophylactic treatment of mania	Drug-drug interactions Laboratory monitoring is required
Oxcarbazepine	Acute treatment of mania	—

Lithium

Lithium is indicated in treatment as well as prophylaxis of bipolar disorders as for manic episodes. Maintenance therapy prevents or diminishes intensity of subsequent episode in those patients with a history of mania. However, blood lithium monitoring is required frequently as it is highly renal toxic drug. Therapeutic blood level is 0.6 to 1.2 mEq/dL of blood. So the drug is to be adjusted accordingly and renal functions are required to be monitored. A watch has to be kept on developing symptoms of lithium toxicity.

Valproate/Divalproex

This is indicated for the treatment of manic episodes. Effectiveness for long-term use in mania has not been systematically evaluated. Long-term usefulness for individual patients should be continuously re-evaluated.

Olanzapine

It is indicated for short-term treatment of acute mania episodes associated with bipolar I disorder. Effectiveness for long-term treatment of acute mania has not been systematically evaluated. Risk and benefit in long-term use (>4 weeks) should be periodically re-evaluated for the individual patient.

Other Anti-Convulsants

Gabapentin, levetiracetam, tiagabine and topiramate are the other anticonvulsants that can be used. Their efficacy is not yet proven.

Atypical Anti-Psychotics

There is convincing evidence for efficacy in acute treatment of mania, especially for olanzapine, risperidone, aripiprazole, ziprasidone and quetiapine. Onset of action is within 2 to 4 days. There is strong evidence for maintenance efficacy (both mania and depression) for olanzapine.

American Psychiatry Association guidelines for mood disorders are given in Table 4.

Table 4: American Psychiatry Association Guidelines for Mood Disorders

1. Initiate either lithium or divalproex plus a second-generation anti-psychotic
2. For less ill patient, monotherapy with lithium, divalproex or anti-psychotic may be sufficient
3. For mixed episode, divalproex or anti-psychotic is preferred over lithium
4. Atypical anti-psychotics are preferred over typical anti-psychotics
5. Carbamazepine or oxcarbamazepine are alternative to lithium or divalproex
6. For breakthrough episode, first optimise the maintenance medication dose
7. Consideration adding on anti-psychotic
8. If this does not work, consider adding lithium, divalproex, carbamazepine or oxcarbamazepine
9. Clozapine or electroconvulsive therapy should be considered for treatment refractory patients

Treatment Options of Bipolar Depression

Drugs used in treatment of bipolar depression are given in Table 5.

Emerging Trend Pharmacotherapy of Acute Mania

This includes combination treatment with lithium and divalproex as corner stones of treatment. Increasing use of atypical anti-psychotics for acute treatment and for maintenance (Figure 1).

Table 5: Drugs Used in Treatment of Bipolar Depression

Lamotrigine in acute treatment of bipolar depression
Olanzapine for bipolar-I depression
Olanzapine plus fluoxetine in bipolar I depression
Paroxetine has very low switch rates
SSRIs: fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram
Bupropion and esitalopram
SNRIs: venlaflexine, milnacipran, duloxetine

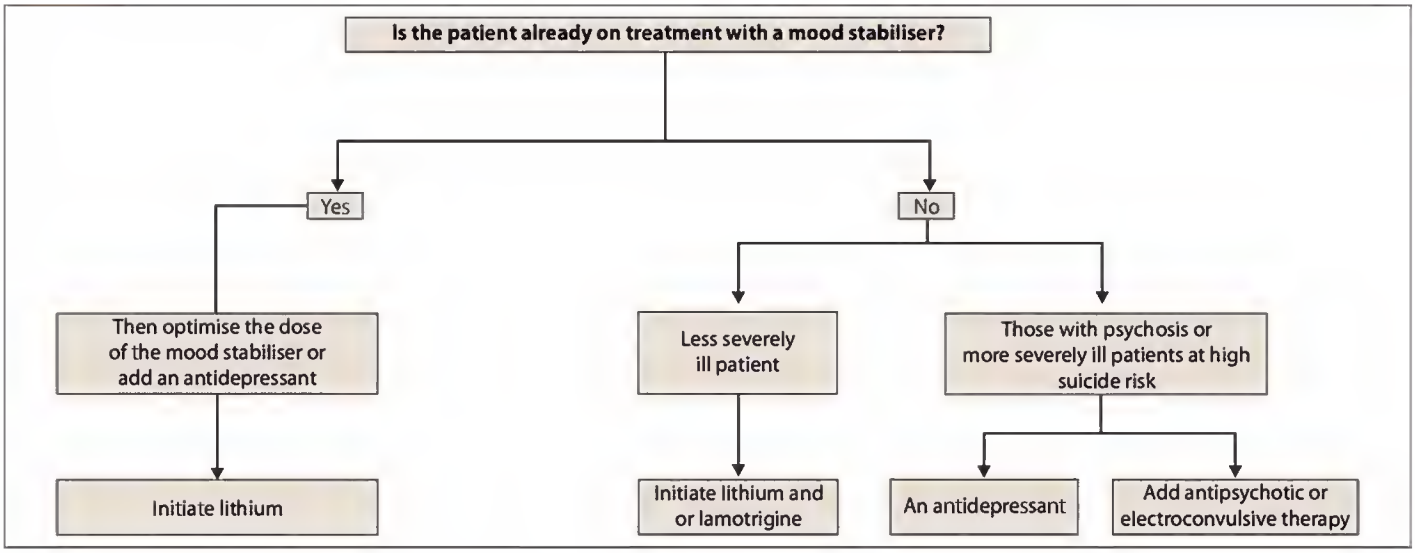


Figure 1: Approach to the patient with Bipolar depression.

22.4 Somatoform Disorders

Vihang N Vahia, Amit Kulkarni

INTRODUCTION

Until late 1970s, the phenomenon of expressing emotional distress and seeking attention through the manifestation of physical symptoms used to be considered a gender- and culture-specific phenomenon. It was hypothesised to be a frequent occurrence and be restricted to certain social strata. In the year 1980, the term somatoform disorders (SDs) was introduced to designate syndromes that are present with multiple pain or other physical symptoms associated with significant dysfunction and social or occupational impairment, where physical examination or laboratory tests failed to explain the symptoms. Clinicians need to differentiate exclusively physical from mixed physical and psychiatric aetiology. Most patients of SD present with mixed aetiology. The crucial task then, is to identify physical and psychological factors that may cause, contribute, complicate, contaminate, co-exist or complement each other. Resentment against doctors, doctor shopping and persistent demands for investigations are common.

The term 'somatoform disorders' incorporates a variety of diverse clinical presentations of physical symptoms that share the diagnostic prerequisite of absence of a physical aetiology to explain emergence of the presenting symptoms. The symptoms tend to be chronic, at times mimic delusional or obsessional features. Despite the prevalence of the non-organic physical illness being lesser than some other psychiatric syndromes, it constitutes higher fraction of medical service utilisation. The diagnosis is valid only in the absence of any other mental or physical disorder or direct effect of a substance that may otherwise explain the symptoms.

Current nomenclature identifies eight categories: (1) somatisation disorder, (2) undifferentiated SD, (3) conversion disorder, (4) pain disorder, (5) hypochondriasis, (6) body dysmorphic disorder, (7) somatoform autonomic dysfunction, and (8) SD not otherwise specified.

AETIOLOGY

Precise aetiology and pathophysiology of somatisation is not known. Physiological stimulation or excitement mediated arousal of sympathetic nervous system leads to rise in blood pressure, tachycardia, gastric hypermotility, muscle tension and pains like tension headaches. Thus sub-syndromal depression and anxiety may have aetiological significance. Heightened awareness of body sensations, along with a cognitive or subjective bias, generates a conviction of being medically ill.

Multiple Hypotheses

Somatic symptoms may be learned illness behaviour to dominate or manipulate relationships.

Psychoanalysts

Psychoanalysts consider SDs as manifestations of repressed anger, impulses, guilt, intrapsychic conflicts or low self esteem.

Developmental Theories

Early parental separation, traumatic childhood, sexual abuse, presence of somatisation in parents and restrictive parenting are implicated in emergence of SD.

Biological Theories

These include bifrontal impairment of cerebral hemispheres and non-dominant hemisphere dysfunction, heightened awareness and misinterpretation of normal body sensations, serotonin and endorphin hypothesis and familial and genetic theories.

PREVALENCE

Precise prevalence for various SDs is not known. Available data indicates prevalence rates to vary between 0.1% and 6%, depending upon the category and surveyed population. A Belgian study ranked SD as third commonest psychiatric disorder after anxiety and depression.

MORTALITY/MORBIDITY

The SDs are not potentially fatal. However, high rates of suicide, side-effects related to use of multiple drugs, polypharmacy and indiscreet drug use merit caution. Medications may be prescribed or surgery could be advised for a misdiagnosed physical illness.

Gender

Female to male ratio varies between 2:1 and 10:1 for various categories of SD except hypochondriasis where it is 1:1.

Age of Onset

Most cases are present with the history of SD in childhood, adolescence or early adulthood. Onset of unexplained physical symptoms in middle-age ought to prompt search for other psychiatric or physical disorders.

GENERAL PRINCIPLES OF MANAGEMENT

The most common primary presentation of SD is some intriguing physical symptoms. Multiple investigations and doctor shopping are frequent. Symptoms may mimic serious medical illness like myocardial infarction or acute abdomen. Tricyclic antidepressants and second generation antidepressant (e.g. duloxetine) drugs have been used with variable success. Pimozide was once recommended as the treatment of choice for mono-symptomatic presentations. Benzodiazepines and narcotic analgesics should be avoided.

Psychosocial interventions include psychoeducation of the patient and his family, good doctor-patient relationship, reassurance that the symptoms are not life-threatening and avoiding repeated investigations, reassurance by quoting other cases of spontaneous improvement is often effective, regular non-invasive medical assessment would reduce anxiety and help-seeking behaviours, and avoiding excessive dependence on the doctor or drug.

CATEGORIES OF SOMATOFORM DISORDER

Somatisation Disorder

Clinical presentation and diagnosis

Somatisation disorder (SOMD) presents multiple physical symptoms beginning before the age of 30 years. DSM IV requires the presence of symptoms for at least 6 months, whereas ICD-10 (WHO) requires minimum duration of 2 years for diagnosis of SOMD. Clinical presentation must include four pain symptoms, related to at least four different sites or functions (common sites of pain are head, back, abdomen, chest, limbs, rectum and joints. Symptoms may be induced during menstruation, sexual intercourse or urination); two unexplained gastrointestinal symptoms other than pain (like nausea, bloating, diarrhoea, indigestion, intolerance to several foods); one sexual or menstrual complaint other than pain (like sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy); and one pseudo-neurological complaint (like aphonia, paresis or paralysis, hypoaesthesia or anaesthesia, blindness or inability to move).

Patients are symptomatic for several years but refuse to accept the medical verdict of absence of any physical illness. Symptoms induce appreciable impairment in functioning. Unlike the factitious disorders, symptoms are not intentionally produced or feigned.

Alcohol, substance use or abuse of prescribed drugs are common co-morbidities.

Management

Do not brush off the patient. Realise that presenting symptoms are a façade of serious emotional turmoil that lies within. A good therapeutic alliance facilitates continuing care by one doctor only. Discourage frequent visits. Give assurance by partial physical examination with minimum investigations. Therapeutic intervention in the form of explaining or educating the patients and their family about the temporal relationship between onset of stress and occurrence of symptoms and that the symptoms do not have a physical correlate is known to help resolution of symptoms. Management of demonstrable mood events with antidepressant medication is advised.

Course and prognosis

This is a chronic and debilitating disorder with fluctuating course. Acute symptoms may last for 6 to 9 months; residual symptoms tend to persist for up to 1 year. Most patients seek help within a year of onset of the symptoms. Persistent symptoms, especially sexual symptoms, may induce marital discord.

Conversion Disorder

Clinical presentation and diagnosis

This disorder is characterised by presentation of sudden physical symptoms following severe conflict or stress. Patients characteristically present with one or more symptom or deficits affecting voluntary motor or sensory functions. The list of possible symptoms include pseudoseizures, impaired coordination, paralysis, lump in the throat, aphonia, urinary retention, loss of pain or touch sensation, double vision, tunnel vision, blindness, deafness and hallucination. Clinical presentations have variable combinations. The symptoms are not intentionally produced or feigned. Severity of the impairment attributed to the symptoms warrant medical evaluation. Many patients seem to be indifferent (*La belle* indifference) rather than be pained by the symptoms or the extent of impairment. Conversion symptoms may be associated with symptoms of other psychiatric disorders.

Management

Management has to be individualised. Some patients remit spontaneously or with resolution of the conflicts. Environmental manipulations by a non-judgemental and non-confrontational therapist help. Some patients benefit from antidepressant drugs. Behaviour therapy or psychotherapy is aimed at helping the patient to cope with stress or modify the stress inducing stimuli. Avoid benzodiazepines or use only for short duration.

Course and prognosis

This is a complex disorder. Initial presentations remit within a short duration despite non-specific treatments. However, recurrence is frequent.

Pain Disorder

Clinical presentation and diagnosis

Irrespective of the age, gender, culture, aetiology, duration and past history, pain is associated with anxiety, discomfort and social, occupational or some other impairment. Diagnosis of pain disorder implies that the severity of pain and distress is out of proportion to the physical condition and that psychological factors are judged to have contributed to onset, severity, exacerbation or maintenance of pain. This diagnosis is valid only in the absence of other physical condition such as dyspareunia or other psychiatric disorders. It may be classified as acute if present for less than 6 months or chronic when persistent for longer duration.

Pain disorders present with one or two symptoms that become a major focus in the life of the patient. Work, school, family and social obligations may be ignored or abandoned to be able to spend long hours visiting medical services. Some chronic cases may reveal familial patterns of chronic pain, depression and alcohol use.

Management

Minimal but all indispensable investigations to rule out any possible physical condition are vital. Diagnosis of exclusion, i.e. psychogenic pain as no physical cause could be identified, may be misleading. Establish diagnosis after demonstrating a temporal relationship between onset and maintenance of pain and some stress or vicarious benefits. Effective doctor-patient relationship needed with regular reassurance to the patient. Behaviour therapy, biofeedback, psychotherapy that explores interpersonal or other conflicts, have all been reported to have varying benefits. Advocate gradually increasing the activities. Tricyclic antidepressant drugs, like amitriptyline, imipramine and dothiepine in small doses, have been popular. Exact mechanism of action is not clear, but is hypothesised to enhance pain threshold. Their analgesic action is independent of their antidepressant action. Amongst the newer antidepressant drugs, duloxetine, (see section on Psychopharmacology) is currently marketed for pain disorder.

Course and prognosis

Acute pain resolves early. However chronic pain has variable onset and tends to persist. Pain may not resolve if there is presence of comorbid general medical condition causing longer duration of acute pain, untreated associated psychiatric disorder.

Hypochondriasis

Clinical presentation and diagnosis

Hypochondriasis is defined as preoccupation of having developed or the possibility of developing a serious physical disease. Medical examination would reveal absence of a new disease even if it may confirm a pre-existing illness. All attempts to convince the patient of absence of any serious illness are rejected, often resulting in severe distress and doctor-shopping (medical or alternative therapists and faith-healers). Subjective conviction of presence of undiagnosed illness may mimic an overvalued idea or an obsession. However, the belief is not of delusional intensity and is not restricted to personal appearance. Duration of the symptoms should be at least 6 months in the absence of any other psychiatric disorders.

Management

Team approach of mental health consultant and primary care physician discourages doctor-shopping. Psychoeducation about the meaning of the symptoms may allay fears of a serious illness. Concentrate on symptom relief without confronting the patient. Most patients should be reassured with minimal investigations to rule out a serious illness. Explore gradually underlying psychiatric co-morbidity or the emotional turmoil that lies within. Management of co-morbid anxiety or depression is absolutely essential.

Course and prognosis

This is a chronic relapsing disorder. Only about 50% of cases show some improvement. Waxing and waning symptoms and being not convinced of the absence of a physical illness cause significant impairment.

Body Dysmorphic Disorder (Dysmorphophobia)

Clinical presentation and diagnosis

The disorder presents with a preoccupation with an imagined defect in personal appearance or excessive concern for a slight or insignificant physical anomaly. The preoccupation induces considerable personal and occupational impairment. Common complaints relate to flaws of face or hair, nose, eyes, eyelids, eyebrows, lips, ears, breasts, genitals, wrinkles, asymmetry of the face, swelling or excessive hair or similarly perceived anomalies of any other body part.

Many patients avoid social contacts to escape criticism of their presumed anomaly. These symptoms may compel the patient to spend long hours before a mirror, install special lights or use magnifying lens to scrutinise the perceived anomaly.

Management

This disorder is difficult to treat. Attempts to deal with symptoms with rational approach are often not successful. Cosmetic surgeries help some patients, but then some patients often report dissatisfaction or even worsening.

Course and prognosis

The disorder commences in adolescence or childhood. They tend to withdraw and spend time scrutinising the appearance. The disorder tends to run a chronic course with few symptom-free intervals.

Somatoform Autonomic Dysfunction

This category of SD is described in the international classification of disorders. Patients present with physical symptoms related to an organ which is innervated or controlled by the autonomic nervous system. Cardiac, gastrointestinal, respiratory and some genitourinary symptoms fall into this category. The symptoms may be associated with objective signs of autonomic arousal like palpitations, sweating, flushing and tremors. Some patients present with idiosyncratic symptoms like fleeting aches and pains, burning, heaviness, tightness, sensation of being bloated or distended. Characteristically, the symptoms affect but do not indicate dysfunction of the target organs.

Autonomic arousal related anxiety is observed in these patients. Antidepressant drugs and non-drug therapies as applicable for other categories of SDs are indicated here. Caution against the use of benzodiazepines, sedating drugs and narcotic analgesic drugs is emphasised.

Undifferentiated Somatoform Disorder

This is a residual category. The term is applied to persistent somatoform symptoms that do not meet the full criteria of SOMD. The disorder is common at primary care where patients may present with only one circumscribed symptom. It is important to rule out improper history that may confound the diagnosis.

Chronic fatigue, loss of appetite and gastrointestinal or urinary symptoms are the frequent presentations. Symptomatic management is usually not effective. Management strategies for SOMD are applicable here.

Somatoform Disorders Not Otherwise Specified

This is a residual category. The term is applicable for conditions that do not meet the diagnostic criteria for other forms of SDs. Pseudocyesis, chronic fatigue or hypochondriacal symptoms that are not of psychotic intensity but cause impairment, in the absence of any other mental or physical disorder are some examples.

LABORATORY INVESTIGATIONS

It is prudent to recommend minimal investigations and resist repeated tests. However, it is essential to rule out uncommon general medical condition especially while dealing with persistent symptoms. Tests to rule out thyroid dysfunctions, phaeochromocytoma, porphyria, substance use and occult alcoholism may be considered. Imaging studies and invasive procedures are usually not contributory.

INPATIENT CARE

The SOMDs rarely require hospitalisation. Severe conversion disorders, co-morbid substance use or iatrogenic complications due to invasive or surgical procedures may mandate hospital care.

OUTCOME

The SDs may be mild and transient or severe and chronic. Early treatment, supportive social environment, higher education, absence of ongoing stress, willingness to accept non-physical aetiology and participate in psychoeducation therapy to understand pathophysiology and develop adaptive skills are associated with better prognosis.

RECOMMENDED READING

1. American Psychiatric Association. Somatoform Disorders in Diagnostic and Statistical Manual of Mental Disorders; 4th Ed. Washington DC: American Psychiatric Association; 2000: pp 485-511.
2. World Health Organization. F 45 Somatoform Disorders. ICD 10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines. World Health Organization; 1992: pp 162-70.

22.5 Psychotic Disorders and Schizophrenia

R Thara

These are a group of psychiatric illnesses that alter a person's ability to think clearly, make good judgments, respond emotionally, communicate effectively, understand reality and behave appropriately. When symptoms are severe, people with psychotic disorders have difficulty staying in touch with reality and are unable to meet the ordinary demands of daily life. Psychotic disorders have major implications in clinical care and public health.

SCHIZOPHRENIA

Several historical writings describe the mentally unsound. The term *unmada* (denoting insanity) first appeared in *Atharvaveda*, believed to be written around 1500 BC. A thousand years later, *Samhitas*, documented clinical sub-varieties of *unmada*. In *Ayurveda,* conditions such as *vatanmada*, *pithanmada* and *kaphonmada*, corresponding to psychosis and depressive states, have been described. Ancient Greeks and Romans were aware of mental health issues. This is evident from writings of Aretaes (AD 1) and Soranus (AD 100), who described the 'insane' as people who are free to wander about, availing themselves of the healing properties of facilities such as medicinal baths and temples along with the physically ill. Thus, in ancient times, schizophrenia was a recognised disorder. The empirical approach to this disorder had its beginnings in the eighteenth century.

Two names associated with the modern history of schizophrenia are Emil Kraepelin and Eugene Bleuler. Through systematic observation, Kraepelin documented that this disorder has its beginnings in early life and takes an essentially downhill course culminating in an intellectually deteriorated state. He used the term 'dementia praecox' for this condition. In 1911, Eugene Bleuler in Zurich, Switzerland, found that not all patients failed to improve. On the basis of his observation of patients' reactions to personal and social influences, he preferred to call the disorder 'schizophrenia', or 'schizophrenic psychoses'.

Schizophrenia affects 0.5% to 1% of the population. Described as the 'greatest disabler of youth', it is universal in its distribution throughout the world. It affects men and women, rich and poor, literate and illiterate. The high-risk age for schizophrenia is between 15 to 35 years. It can, however, occur in children and the elderly.

Signs and Symptoms

Usually, a slow change in the person's personality is an indication of the onset of schizophrenia. A sudden development of abnormal behaviours may also be the first manifestation of a break down.

Hallucinations

The person has sensory perceptions without a stimulus. This may be a voice or voices talking or calling to him, commenting, instructing and sometimes telling him to do awful things – 'I hear a female voice all the time, threatening to kill me'. He may respond to these voices and appear as if talking to self. Other types of hallucinations are visual, gustatory, tactile or olfactory.

Delusions

These are false beliefs that no amount of reasoning will distort. These may be in the form of suspiciousness, directed against one or many people. The person may feel persecuted and feel that someone is out to get him; e.g. 'my food tastes bad, I think it is poisoned' or 'people are following me when I walk on the road'. He may feel afraid or become violent as if trying to protect himself from a persecutor.

Sometimes the person may imagine himself to be a great man or even God – 'I am the son of Jawaharlal Nehru' (grandiose delusions). At times, the person is convinced that objects or people or events are controlling his thoughts and actions – 'My movements are being watched and controlled by a space satellite'. Other delusions refer to the individual's body, to physical or paranormal explanations.

Other essential symptoms to make a diagnosis of schizophrenia include disorganised speech or behaviour and negative symptoms like affective flattening, amotivation, alogia and apathy.

Persons with schizophrenia are also known to experience neuropsychological deficits during the course of the illness. Cognitive impairment is characterised by deficits in attention, learning, memory and executive functions. These deficits have been demonstrated to be associated with dysfunctions in the frontal, temporal and parietal lobes of the brain.

International Classification of Diseases WHO (ICD-10) has given diagnostic guidelines to make diagnosis of schizophrenia which states that (Reproduced from ICD-10; WHO):

1. Duration of symptoms should be at least one month or more which are present for most period of time of the day.
2. One very clear-cut symptom or two or more symptoms if symptoms are not very clear from the group (a) to (d) or two or more symptoms from group (e) to (h). Group of symptoms in (i) is for simple schizophrenia:
3. (a) Thought echo, thought insertion or thought withdrawal and thought broadcasting;
   (b) Delusions of control, influence, or passivity; clearly referred to body or limb movements or specific thoughts, actions or sensation, delusional perception;
   (c) Hallucination voices giving a running commentary on the patient's behaviour, or discussing the patient among themselves or other types of hallucinatory voices coming from some part of the body;

(d) Persistent delusions of other kind that are culturally inappropriate and completely impossible, such as religious or political identity, super human powers and abilities (e.g. being able to control the weather or being in communication with aliens);

(e) Persistent hallucinations in any modality when accompanied either by fleeting or half-formed delusions without clear affective content or by persistent overvalued ideas or when occurring every day for weeks or months on end;

(f) Breaks in interpolations in train of thoughts, resulting in incoherence or irrelevant speech or neologism;

(g) Catatonic behaviour such as excitement, posturing, or waxy-flexibility, negativism, mutism, stupor;

(h) Negative symptoms such as marked apathy, paucity of speech, blunting or incongruity of emotional responses, usually resulting into social withdrawal and lowering of social performance, it must be clear that these are not due to depression or to neuroleptic medication; and

(i) A significant and consistent changes in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and a social withdrawal.

Subtypes of Schizophrenia

Several subtypes of schizophrenia, based on the clinical picture, have been described in the International Classification of Diseases (ICD 10, WHO) as well as the Diagnostic and Statistical Manual (DSM, fourth revision). The common subtypes are listed in **Table 1**. To make the diagnosis of subtype, first a diagnosis of schizophrenia should be made based on the above criterion and subtype to be diagnosed. For all subtypes the duration criteria of one month of persistent symptoms will be essential.

Table 1: Subtypes of Schizophrenia

Paranoid
Catatonic
Simple
Undifferentiated
Hebephrenic
Residual

Paranoid schizophrenia (diagnostic guidelines ICD 10)

(a) Delusion of persecution, reference, exalated birth, special mission, bodily change or jealousy;

(b) Hallucinatory voices that threaten the patient or give commands or auditory hallucinations without verbal form such as whistling, humming or laughing; and

(c) Hallucinations of smell or taste or of sexual or other bodily sensations; visual hallucinations may occur but are rarely predominant.

Catatonic schizophrenia (diagnostic guidelines ICD-10)

One or more should dominate the clinical picture:

(a) Stupor (marked decrease in reactivity to the environment and in spontaneous movements and activity) or mutism;

(b) Excitement (apparently purposeless motor activity, not influenced by external stimuli);

(c) Posturing (voluntary assumption and maintenance of inappropriate or bizarre postures);

(d) Negativism (an apparently motiveless resistance to all instructions or attempts to be moved or movement in opposite direction);

(e) Rigidity (maintenance of rigid posture against efforts to be moved);

(f) Waxy flexibility (maintenance of limbs and body in externally imposed position); and

(g) Other symptoms such as command automatism (auromatic compliance with instructions) and perseveration of words and phases.

Simple schizophrenia (diagnostic guidelines ICD-10)

Slowly progressive with negative symptoms specified in (i) above without any history of hallucinations, delusions or other or of psychotic episode with significant change in personal behaviour manifest as marked loss of interest, idleness and social withdrawal over a delusion, or other, or of psychotic episode with significant change in personal behaviour manifest as marked loss of interest, idleness and social withdrawal over a period of at least one year.

Undifferentiated schizophrenia (diagnostic guidelines ICD-10)

This category should be reserved for disorders that:

(a) Meet the general criteria for schizophrenia; and

(b) Are either without sufficient symptoms to meet the criteria for only one of subtypes, or with so many symptoms that more than one of paranoid, hebephrenic or catatonic subtypes are met.

Hebephrenic schizophrenia (diagnostic guidelines ICD -10)

General criteria for the diagnosis of schizophrenia must be satisfied. It should normally be diagnosed for the first time only in adolescents or young adults. Two or three months of continuous observation is necessary, affective changes are prominent shallow and inappropriate mood with giggling and self-absorbed smiles, delusions and hallucinations are fleeing and fragmentary, behaviour irresponsible and unpredictable. Thought is disorganised, volition is lost and has prolonged course and poor prognosis.

Residual schizophrenia (diagnostic guidelines ICD-10)

(a) Prominent negative schizophrenic symptoms, i.e. psychomotor slowing, under-activity, blunting of affect, passivity, and lack of initiative, poverty of quantity or content of speech, poor non-verbal communication by facial expression, eye contact, voice modulation and posture, poor self-care and social performance;

(b) Evidence in the past of at least one clear cut psychotic episode meeting the diagnostic criteria of schizophrenia;

(c) A period of at least one year during which the intensity and frequency of florid symptoms such as delusions and hallucinations have been minimal or subsequently reduced and the negative schizophrenic syndrome has been present; and

(d) Absence of dementia or other organic brain disease or disorder and of chronic depression or institutionalism sufficient to explain the negative impairments.

It is a chronic stage in which there is clear progression from an early stage to a later stage of long-term irreversible (though not necessarily) negative symptoms.

DIFFERENT TYPES OF PSYCHOTIC DISORDERS

Although schizophrenia and bipolar disorders are the major categories, a number of other categories are delineated.

Schizoaffective Disorder

People with this illness have symptoms of schizophrenia, as well as a serious mood or affective disorder, such as severe depression, mania (a disorder marked by periods of excessive energy) or bipolar disorder (a disorder with cyclical periods of depression and mania).

Schizophreniform Disorder

People with this illness have symptoms of schizophrenia, but the symptoms last less than 6 months.

Brief Psychotic Disorder

People with this illness have sudden, short periods of psychotic behaviour, often in response to a very stressful life event. Recovery is often quick, usually less than a month.

Delusional Disorder

People with this illness have delusions involving real-life situations that could be true, such as being followed, being conspired against, or having a disease. These delusions persist for at least one month.

Shared Psychotic Disorder

This illness occurs when a person develops delusions in the context of a relationship with another person who already has his or her own delusion(s).

Substance-Induced Psychotic Disorder

This condition is caused by the use of or withdrawal from some substances, such as alcohol and crack cocaine, that may cause hallucinations, delusions or confused speech.

Psychotic Disorder due to a Medical Condition

Hallucinations, delusions or other symptoms may be the result of another illness that affects brain function, such as a head injury, brain tumour, epilepsy, encephalitic, etc. causing abnormal and psychotic like behaviour.

Acute and Transient Psychotic Disorders

There is acute onset of delusions, hallucinations and incoherent speech. Complete recovery occurs within one to three months.

Culture-Bound Syndromes

Recurrent, locality specific patterns of aberrant behaviour.

GENERAL SYMPTOMS OF A PSYCHOTIC DISORDER

Prior to the onset of a psychotic break down, certain prodromal symptoms make their appearance. These are listed in **Table 2**.

Table 2: Common Prodromal Features Before First Episode of Psychosis

Reduced concentration, attention
Reduced drive and motivation
Depressed mood
Sleep disturbance
Anxiety
Irritability
Social withdrawal
Suspiciousness
Deterioration in role functioning

Symptoms vary from person to person and may change over time. The common symptoms are listed in **Table 3**. The major symptoms of psychotic disorders are hallucinations and delusions.

Table 3: Common Symptoms of Psychotic Disorders

Hallucinations
Delusions
Disorganised or incoherent speech
Confused thinking
Strange, possibly dangerous behaviour
Slowed or unusual movements
Loss of interest in personal hygiene
Loss of interest in activities
Problems at school or work and with relationships
Cold, detached manner with the inability to express emotion
Mood swings or other mood symptoms, such as depression or mania

Hallucinations are unusual sensory experiences or perceptions of things that are not actually present, such as seeing things that are not there, hearing voices, smelling odours, having a 'funny' taste in the mouth and feeling sensations on the skin even though nothing is touching the body.

Delusions are false beliefs that are persistent and organised, and that do not go away after receiving logical or accurate information. For example, a person who is certain his or her food is poisoned, even if it has been proven that the food is fine, is suffering from a delusion.

EPIDEMIOLOGY

Relevant epidemiological data about acute psychotic illnesses, psychotic disorders due to general medical condition or substance use are lacking.

CAUSES

The exact cause of psychotic disorders is not known. Many factors may play a role. Some psychotic disorders tend to run in families, suggesting that the likelihood to develop the disorder may be inherited. Environmental factors like stress, drug abuse, and major life changes may play a role. In addition, people with certain psychotic disorders may have an imbalance of certain chemicals in the brain. They may be either very sensitive to or produce too much of dopamine. The imbalance of dopamine affects the brain's reaction to stimuli like sounds, smells and sights which leads to hallucinations and delusions. Cultural, socio-political factors and certain medical conditions may influence symptom formation.

There are no laboratory tests to specifically diagnose psychotic disorders, except those that accompany a physical illness, such as a brain tumour, the physician may use various tests, such as blood tests and X-rays, CT scan, MRI of brain to rule out physical illness as the cause of the symptoms.

PREVENTION

There is no known way to prevent most psychotic disorders, but many of the related symptoms can be prevented with early detection and treatment and can help decrease the disruption to the person's life, family and friendships. Avoiding drugs and alcohol can prevent psychotic disorders associated with these substances.

AETIOLOGY

Schizophrenia is now believed to be a disorder of the brain. Genetic factors, early developmental problems and biochemical imbalances are hypothesised to precipitate the illness. The exact nature of genetic factors is not known. It is commonly accepted that there is a genetic vulnerability to develop the illness. People with schizophrenia are known to be particularly sensitive to effects of stress. Those who are introvert, shy, have difficulty in making friends may be more prone to develop this disorder. No one is born with schizophrenia, but some are born with a predisposition to develop the illness.

PREVALENCE AND INCIDENCE OF SCHIZOPHRENIA

Prevalence of schizophrenia is almost the same all over the world. In a recent review of 1,721 prevalence estimates in 46 countries, the reported point and lifetime prevalence is 4.6 and 4 per 1,000 respectively. The most striking feature in this report was the higher rate in the developed countries of the world. There were no gender differences or between urban and rural sites. Migrants, those living in very deprived environments, some ethnic minorities, and children with one or both parents afflicted by schizophrenia are more susceptible to develop the illness.

The incidence rate of schizophrenia all over the world is around 0.5 per thousand. The debate whether it is different in the third world is on-going. A recent review of the incidence of schizophrenia showed an asymmetrical distribution of incidence rates around the world, with many high rates skewing the distribution. The incidence of schizophrenia varies in a five-fold range, between 7.7 and 43.0 per 100,000. Males have a significantly higher incidence of schizophrenia compared with females (male to female risk ratio = 1.4).

COURSE AND OUTCOME

Most people get better with treatment. Some people, who had one episode of the problem, may never have another attack. Many people however, are likely to have one or more recurrences of the problem. In a small group of patients, especially those who do not respond to medication, the symptoms are likely to persist continuously (**Figure 1**).

Outcome in schizophrenia is multi-dimensional. Clinical symptoms and social and occupational functioning are taken into account while assessing the outcome. Sometimes parameters such as quality of life, extent of burden on the caregivers also has to be considered. International, multi-centric studies have shown that availability of effective medicines, better community care, increasing awareness about the illness, greater family support and community tolerance, better job opportunities in the unorganised sectors of employment, especially in the rural areas, and ensuring regular intake of medicines by family members seems to have improved the outcome in a substantial number of persons with schizophrenia. The International Pilot Study of Schizophrenia showed that persons in developing countries had a better outcome than those living in developed nations. This has since then been replicated in several other studies. A twenty-year follow-up of 90 first-break schizophrenia patients showed that only 5 of the original 90 persons with schizophrenia included in the study were continuously ill. Social functioning was good in patients and many held jobs. Greater family support and community tolerance, better job opportunities in the unorganised sectors of employment, especially in the rural areas, and ensuring regular intake of medicines by family members could all be playing a part.

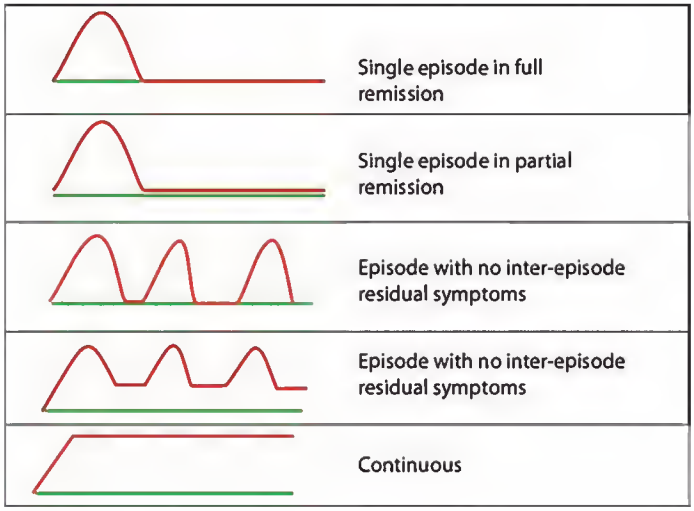


Figure 1: Course of schizophrenia.

TREATMENT

The goals of care are to identify the illness early, treat the symptoms, provide skills to the family, maintain improvement over a period of time, prevent relapses and reintegrate the ill person in the community. The treatment of schizophrenia has three main components. First, there are medications to relieve symptoms and prevent relapse. Second, education and psychosocial interventions help patients and families cope with the illness and its complications, and help prevent relapses. Third, rehabilitation helps patients reintegrate into the community and regain educational or occupational functioning.

Medical Treatment

Medical treatment is the most important and must be adhered to strictly. Anti-psychotic drugs help control acute symptoms and some symptoms of the chronic state, such as apathy and social withdrawal. Although medications do have some side-effects, the beneficial effects of the medications far outweigh the adverse effects. Occasionally, electroconvulsive therapy or shock treatment (ECT) is advised during an acute phase of schizophrenia, but usually in conjunction with drugs.

The most commonly used drugs in the treatment of schizophrenia are known as anti-psychotics or neuroleptics. Conventional or typical neuroleptics are those that have been in use for several decades. Unconventional or atypical anti-psychotics have been recently introduced and their mechanism of action is different from that of conventional drugs. Anti-psychotics can be taken orally, in the form of a syrup or tablet and some are available as injections.

Typical/conventional anti-psychotics

These include phenothiazines, butyrophenones and thioxanthines which act by blocking a particular kind of receptor in the brain called the D2 receptor. There is reliable evidence that in the acute phase of the illness, these drugs are effective in controlling the positive symptoms (delusions, hallucinations and thought disorder). About 60% to 75% of patients improve in 6 to 12 weeks. The common drugs used

extensively in many developing countries are chlorpromazine, haloperidol, thioridazine and trifluoperazine. The problem with this group of drugs is that they have both short- and long-term side-effects which could range from the mildly unpleasant to the potentially debilitating. Despite side-effects, the low cost, availability and years of experience in using these drugs make them still suitable for developing countries.

Depot injections

These are slow-release forms of antipsychotics, administered through injections about once every six weeks. Because of the convenient dosage schedule, many patients comply better with depot injections than tablets, but the side-effects experienced with the former are often worse than those with oral medication. Atypical drugs are not currently available as depot injections.

Atypical/unconventional anti-psychotics

These are indicated for patients who do not respond to conventional antipsychotic drugs. Drugs in this group are clozapine, olanzapine, risperidone, aripiprazole, quetiapine and sulpiride. The primary advantages of atypical anti-psychotics are their effectiveness in dealing with the negative symptoms (such as apathy, social withdrawal and blunted emotions) and some behavioural problems, as well as the relatively lower occurrence of side-effects. Their high cost, however, limits their use in most developing countries.

Psychosocial Rehabilitation

Psychosocial rehabilitation is another vital component of the management of schizophrenia. It is basically a set of techniques aimed at reducing symptoms and decrease impact of illness, improve skills and capability of the person and increases family support in day-to-day management, disabilities. Recent years have witnessed tremendous progress in rehabilitation measures all over the world which includes social skills training, group therapy, cognitive retraining and vocational rehabilitation.

Cognitive retraining focuses on remediation of cognitive deficits such as problems in attention, concentration etc. By using different types of computerised and non-computerised tests, the impairment of cognitive functions can be assessed and some of these tests can also be used to reduce the deficits.

RECOMMENDED READINGS

1. Comprehensive Textbook of Psychiatry. Editors: Harold Kaplan and Benjamin Sadock. Williams and Wilkins, Baltimore, USA.
2. International Classification of Diseases ICD10 Classification of Mental and Behavioural Disorders = Clinical description and diagnostic guidelines WHO; AITBS Indian Edition; 2007.

22.6 Delirium, Dementia, and Other Cognitive Disorders

Venu Gopal Jhanwar

OVERVIEW

Cognition includes memory, language, orientation, judgment, conducting interpersonal relationships, performing actions (praxis), and problem solving. The organic problem may be a primary brain disease or a secondary manifestation of some general disorder. All of the cognitive disorders show some degree of impaired thinking depending on the site of involvement, the rate of onset and progression, and the duration of the underlying brain lesion. Emotional disturbances (e.g. depression) are often present as significant comorbidities.

In the text revision of the fourth edition of Diagnostic Statistical Manual of Mental Disorders (DSM-IV-TR), three groups of disorders – delirium, dementia, and the amnestic disorders are characterised by the primary symptom common to all the disorders, which is an impairment in cognition (as in memory, language, or attention) (**Table 1**). Although other psychiatric disorders can exhibit some cognitive impairment as a symptom, cognitive impairment is the cardinal symptom in delirium, dementia, and the amnestic disorders.

In the past, these conditions were classified under the heading 'organic mental disorders' or 'organic brain disorders'. Traditionally, those disorders had an identifiable pathological condition such as brain tumour, cerebrovascular disease, or drug intoxication. Those brain disorders with no generally accepted organic basis (e.g. depression) were called functional disorders. This century-old distinction between organic and functional disorders is outdated and has been deleted from the nomenclature. Every psychiatric disorder has an organic (i.e. biological or chemical) component, thus the terms functional and organic are not used in DSM-IV-TR.

Table 1: Classification

Delirium
Dementia
Amnestic disorder
Personality changes due to a general medical condition
Substance-induced hallucinosis

CLINICAL FINDINGS

The manifestations are many and varied, and include problems with orientation, short or fluctuating attention span, loss of recent memory and recall, impaired judgment, emotional liability, lack of initiative, impaired impulse control, inability to reason through problems, sexual acting-out, attention problem, aggression, depression, anxiety, irritability, confabulation, impaired intellectual functions, visual and auditory hallucinations, delusions and impaired sleep.

It is important to differentiate between delirium and dementia on the basis of clinical presentation. Delirium is an acute state because of underlying medical conditions which may show complete recovery whereas dementia is a progressive disease.

DELIRIUM

Delirium, a term used to describe an acute confusional state, is a transient global disorder of attention, with clouding of consciousness. Onset is usually rapid. Often goes unrecognised despite clear evidence that it is usually the cognitive manifestation of serious underlying medical or neurologic condition.

Many terms are used to describe delirium, including encephalopathy, acute brain failure, acute confusional state, and post-operative or intensive care unit (ICU) psychosis. Delirium has many clinical manifestations, but essentially it is a relatively acute decline in cognition that fluctuates over hours or days. Onset is usually rapid. The mental status fluctuates (impairment is usually least in the morning), with inability to concentrate, maintain attention, and sustain purposeful behaviour. There is a marked deficit of short-term memory and recall. Anxiety and irritability are common. Amnesia is retrograde (impaired recall of past memories) and anterograde (inability to recall events after the onset of the delirium). Perceptual disturbances (often visual hallucinations) and psychomotor restlessness with insomnia are common.

Delirium is a common disorder; 15% to 45% of hospitalised patients, particularly elderly, are prone to develop delirium. The average duration is about 1 week, full recovery in most cases. Dementia and pre-existing cognitive dysfunction serve as major risk factors for delirium, and at least two-third cases of delirium occur in patients with co-existing underlying dementia.

As the diagnosis of delirium is clinical and made at the bedside, a careful history and physical examination is mandatory when evaluating patients with possible confusional states. Screening tools can help in identifying patients with delirium, such as the Confusion Assessment Method (CAM), the Mini-Mental State Examination (MMSE).

The first aim of treatment is to identify and correct the aetiologic medical condition. Routine laboratory tests may include serum electrolytes, serum glucose, blood urea, serum creatinine, liver function tests, thyroid function tests, complete blood count, serum calcium, phosphorus, magnesium, vitamin B12, folate, blood cultures, blood gas analysis, urinalysis, and cerebrospinal fluid analysis. Discontinue medications that may be contributing to the problem. EEG, CT and MRI evaluations may be helpful in diagnosis.

The two major symptoms of delirium that may require pharmacological treatment are psychosis and insomnia. Most commonly used drug for psychosis is haloperidol and risperidone. Depending on age, weight, and physical condition of patient, the initial dose of haloperidol may range from 2 to 4 mg intramuscularly, repeated in an hour if the patient remains agitated. As soon as the patient is calm, oral

medication in liquid concentrate or tablet form should begin. Use of other antipsychotics, such as paliperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, may be considered for delirium management, but clinical trial experience with these agents for delirium is limited. Insomnia is best treated with short-acting benzodiazepines (e.g. lorazepam 1 to 2 mg at bedtime). Benzodiazepines with long half should be avoided unless they are being used as part of the treatment for the underlying disorder (e.g. alcohol withdrawal).

Table 2: Aetiology of Delirium and Other Cognitive Disorders

Disorder	Possible Causes
Intoxication	Alcohol, sedatives, analgesics, psychedelic drugs and stimulants
Drug withdrawal	Withdrawal from alcohol, sedative-hypnotics, corticosteroids
Medications	Anti-cholinergic medications, anti-depressants, digoxin, H2-blocking agents, salicylates, and a wide variety of other over-the-counter and prescribed medications
Long-term effects of alcohol	Wernicke-Korsakoff syndrome
Infections	Septicaemia; meningitis and encephalitis due to bacterial, viral, fungal, parasitic, or tuberculous organisms or CNS syphilis; acute and chronic infections due to the entire range of microbiologic pathogens
Seizure disorders	Ictal, interictal, and postictal dysfunction
Endocrine disorders	Thyrotoxicosis, hypothyroidism, adrenocortical dysfunction (including Addison disease and Cushing syndrome), phaeochromocytoma, insulinoma, hypoglycaemia, hyperparathyroidism, hypoparathyroidism, panhypopituitarism, diabetic ketoacidosis
Respiratory disorders	Hypoxia, hypercapnia
Metabolic disturbances	Fluid and electrolyte disturbances (especially hyponatraemia, hypomagnesaemia and hypercalcaemia), acid-base disorders, hepatic disease (hepatic encephalopathy), renal failure, porphyria
Nutritional deficiencies	Deficiency of vitamin B1 (beriberi), vitamin B12 (pernicious anaemia), folic acid, nicotinic acid (pellagra); protein-calorie malnutrition
Trauma	Subdural hematoma, subarachnoid haemorrhage, intracerebral bleeding, concussion syndrome
Cardiovascular disorders	Myocardial infarctions, cardiac arrhythmias, cerebrovascular spasms, hypertensive encephalopathy, haemorrhages, embolisms, and occlusions indirectly cause decreased cognitive function
Neoplasms	Primary or metastatic lesions of the central nervous system, cancer-induced hypercalcaemia
Collagen-vascular and immunologic disorders	Autoimmune disorders, including systemic lupus erythematosus, Sjögren syndrome, and AIDS
Degenerative diseases	Alzheimer' disease, Pick' disease, multiple sclerosis, parkinsonism, Huntington chorea, normal pressure hydrocephalus

DEMENTIA

Dementia is defined as a progressive impairment of cognitive functions occurring in clear consciousness (i.e. in the absence of delirium). It is an acquired persistent and progressive deterioration in cognitive abilities that impairs the successful performance of activities of daily living. Memory is the most common cognitive ability lost with dementia.

Global impairment of intellect is the essential feature, manifested as difficulty with memory, attention, thinking, and comprehension. Other mental functions can often be affected, including mood, personality, judgment, and social behaviour. The disorder can be progressive or static, permanent or reversible. Approximately 15% of people with dementia have reversible illnesses if treatment is initiated before it becomes irreversible.

Prevalence is approximately 5% in the general population older than 65 years of age and it doubles every 5 years; reaching 30% to 50% in the general population older than 85 years of age.

Table 3: The Most Common Causes of Dementia in Individuals Older than 65 Years of Age

- Alzheimer's disease
- Vascular dementia
- Mixed vascular and Alzheimer's dementia
- Other illnesses that account for approximately 10%
  - Pick's disease
  - Lewy body dementia
  - Huntington's disease
  - Parkinson's disease
  - Normal pressure hydrocephalus (NPH)
  - Alcoholic dementia
  - Infectious dementia, such as HIV or syphilis

ALZHEIMER'S DISEASE

Alois Alzheimer first described the condition in 1907 that later assumed his name. The final diagnosis of Alzheimer's disease (AD) requires a neuropathological examination of the brain; nevertheless, dementia of the Alzheimer's type is commonly diagnosed in the clinical setting after other causes of dementia have been excluded from diagnostic consideration.

Some of the risk factors for AD are older age, family history, lower education level, and female gender. Education, cognitive exercises, and social support may be protective.

The classic gross neuroanatomical observation of a brain from a patient with AD is diffuse atrophy with flattened cortical sulci and enlarged cerebral ventricles. The classic and pathognomonic microscopic findings are senile plaques, neurofibrillary tangles, neuronal loss (particularly in the cortex and the hippocampus), synaptic loss (perhaps as much as 50 per cent in the cortex), and granulovascular degeneration of the neurons. Neurofibrillary tangles are composed of cytoskeletal elements, primarily phosphorylated tau protein, although other cytoskeletal proteins are also present.

The neurotransmitters that are most often implicated in the pathophysiological condition of AD are acetylcholine and norepinephrine, both of which are hypothesised to be hypoactive in AD.

The diagnosis of dementia is based on the clinical examination, including a mental status examination, and on information from the patient's family, friends, and employers. Symptom compromises of memory loss and at least one other cognitive domain, most commonly aphasia (typically, word finding difficulty), apraxia (inability to perform motor tasks, such as cutting a loaf of bread, despite intact motor function), agnosia (inability to recognise objects), and impaired executive function (poor abstraction, mental flexibility, planning, and judgment). The diagnosis of dementia requires a significant decline in function that is severe enough to interfere with work or social life. Work-up is directed at identifying any potentially reversible causes of dementia. However, such cases are indeed rare.

PHARMACOTHERAPY

Clinicians may prescribe benzodiazepines for insomnia and anxiety, anti-depressants for depression, and anti-psychotic drugs for delusions and hallucinations.

Donepezil, rivastigmine, galantamine, and tacrine are cholinesterase inhibitors used to treat mild-to-moderate cognitive impairment in AD. They reduce the inactivation of the neurotransmitter acetylcholine and, thus, potentiate the cholinergic neurotransmitter, which in turn produces a modest improvement in memory and goal-directed thought.

Donepezil is well tolerated and widely used. Tacrine is rarely used, because of its potential for hepatotoxicity. Memantine (NMDA antagonist) protects neurons from excessive amounts of glutamate, which may be neurotoxic. The drug is sometimes combined with donepezil.

Starting doses, respectively, of donepezil, galantamine, and rivastigmine, are 5 mg orally once daily (maximum 10 mg once daily), 4 mg orally twice daily (maximum 12 mg twice daily), and 1.5 mg orally twice daily (maximum 6 mg twice daily). The doses are increased gradually as tolerated. The most bothersome side-effects include diarrhoea, nausea, anorexia, weight loss, and syncope.

Nonpharmacologic Approaches

Behavioural problems in demented patients are often best managed with a nonpharmacologic approach. Initially, it should be established that the problem is not unrecognised delirium, pain, urinary obstruction, or faecal impaction.

VASCULAR DEMENTIA

Dementia associated with cerebral vascular disease can be divided into two general categories: multi-infarct dementia and diffuse white matter disease (also called *subcortical arteriosclerotic encephalopathy* or *Binswanger's disease*). Individuals who have had several strokes may develop chronic cognitive deficits, commonly called *multi-infarct dementia*. The strokes may be large or small (sometimes lacunar) and usually involve several different brain regions. The occurrence of dementia depends partly on the total volume of damaged cortex, but it is also more common in individuals with left-hemisphere lesions, independent of any language disturbance. Patients typically report a history of discrete episodes of sudden neurologic deterioration.

Risk factors for vascular dementia are those for stroke, i.e. older age, hypertension, cigarette use, atrial fibrillation, diabetes mellitus and hyperlipidemia. Physical examination usually shows focal neurologic deficits such as hemiparesis, a unilateral Babinski reflex, a visual field defect, or pseudobulbar palsy. Recurrent strokes result in a stepwise progression of disease. Neuroimaging studies show multiple areas of infarction. Thus, the history and neuroimaging findings differentiate this condition from AD. However, both AD and multiple infarctions are common and sometimes occur together.

Treatment of vascular dementia must be focused on the underlying causes, such as hypertension, atherosclerosis, and diabetes. Recovery of lost cognitive function is not likely to occur, although fluctuations with periods of improvement are common.

PICK'S DISEASE

The Pick's disease constitutes approximately 5% of all irreversible dementias. It is most common in men, especially those who have a first-degree relative with the condition.

In contrast to the parietal-temporal distribution of pathological findings in AD, Pick's disease is characterised by a preponderance of atrophy in the frontotemporal regions. These regions also have neuronal loss, gliosis, and neuronal Pick's bodies, which are masses of cytoskeletal elements. Pick's bodies are seen in some postmortem specimens but are not necessary for the diagnosis.

LEWY BODY DISEASE

Lewy body disease is a dementia clinically similar to AD and often characterised by hallucinations, parkinsonian features, and extrapyramidal signs. Lewy inclusion bodies are found in the cerebral cortex, amygdala, cingulate cortex, and substantia nigra. Dementia can precede or follow the appearance of parkinsonism. Patients with DLB are extremely sensitive to dopaminergic medications, which must be carefully titrated; tolerability may be improved by concomitant AD medications.

HUNTINGTON'S DISEASE

It is a subcortical type of dementia, characterised by more motor abnormalities and fewer language abnormalities than in the cortical type of dementia. The dementia of Huntington's disease exhibits psychomotor slowing and difficulty with complex tasks, but memory, language, and insight remain relatively intact in the early and middle stages of the illness.

It is an autosomal dominant, degenerative brain disorder. A DNA repeat expansion (CAG repeat) of the mutant gene on chromosome 4 forms the basis of a diagnostic blood test for the disease gene. The clinical hallmarks of the disease are chorea, behavioural disturbance, and frontal executive disorder.

PARKINSON'S DISEASE

An estimated 20% to 30% of patients with Parkinson's disease have dementia, and an additional 30% to 40% have measurable impairment in cognitive abilities. High association of depression is also seen.

HIV-RELATED DEMENTIA

Encephalopathy in HIV infection is associated with dementia and is termed acquired immune deficiency syndrome (AIDS)

dementia complex, or HIV dementia. An estimated 75% of patients with AIDS have involvement of the central nervous system (CNS) at the time of autopsy. The development of dementia in people infected with HIV is often paralleled by the appearance of parenchymal abnormalities in MRI scans. Other infectious dementias are caused by *Cryptococcus* or *Treponema pallidum*. Dementia is usually seen in advanced stage of HIV infection.

HEAD TRAUMA-RELATED DEMENTIA

It is characterised by emotional lability, dysarthria, and impulsivity. There will be a positive history of head injury in past.

Potentially Reversible Dementia or Conditions where Progress of Dementia can be Arrested

Available data reveals that up to 23% of patients qualify for the group of 'potentially reversible' dementias and that includes medication related dementia, psychiatric disorders specifically depressive disorders (pseudo-dementia), surgical brain lesions, i.e. normal pressure hydrocephalus, tumours, chronic sub-dural haematoma, metabolic disorders such as hypothyroidism, hypo-parathyroid, vitamin B12 deficiency, CNS infections (like late stage of neuro-sphylius, HIV, etc). In an Indian report 18% cases of dementia were found to be because of (untreated/poorly treated) neuro-infections and B12 deficiency. It is very important to look for these conditions as further damage can be minimised with proper and timely intervention.

AMNESTIC DISORDERS

These include a variety of diseases and conditions that present with an amnestic syndrome. The syndrome is defined primarily by impairment in the ability to create new memories.

Three Variations of the Amnestic Disorder Diagnosis, Differing in Aetiology

1. Amnestic disorder caused by a general medical condition (e.g. head trauma)
2. Substance-induced persisting amnestic disorder (e.g. caused by carbon monoxide poisoning or chronic alcohol consumption)
3. Amnestic disorder not otherwise specified for cases in which the aetiology is unclear

Thiamine deficiency, hypoglycaemia, hypoxia (including carbon monoxide poisoning), and herpes simplex encephalitis, tumours, cerebrovascular diseases, seizures, electroconvulsive therapy (ECT), and head trauma can cause amnesia.

22.7 Substance Related Disorders

SM Channabasavanna

INTRODUCTION

The term 'substance abuse' refers to the abuse of both alcohol and other drugs.

Categories of substances, commonly liable to abuse for their mind altering properties, include alcohol, cannabinoids, opioids, sedative/hypnotics, inhalants, hallucinogens, cocaine, amphetamines and similarly acting agents (stimulants), and nicotine. Abuse and dependence is also described with caffeine (a stimulant), anabolic steroids and nitrous oxide. Non-dependence producing substances that are abused include anti-depressants, analgesics, antacids, laxatives and vitamins. Specific categories of substances liable to abuse and dependence are discussed separately.

EPIDEMIOLOGY

Lifetime prevalence rates for alcohol use in the general population in India vary from 24% to 74% among males and from 10% to 58% among students. In a recent National Household Survey of alcohol and other drugs among 40,697 males between 12 years and 60 years, 21% reported current alcohol use. A recent study carried out in Karnataka reported alcohol use during the last year by 5.8% of female respondents.

Until the 1980s, apart from alcohol, substances of abuse were predominantly of plant origin cannabis and raw opium. In the last 20 years beside heroin use (the adulterated form is 'brown sugar'), other drugs that have emerged as drugs of abuse include synthetic and semisynthetic opiates, benzodiazepines, antihistaminics and inhalants. Surveys among college students report that 1.5% to 19% use drugs other than alcohol and tobacco, most commonly cannabis, psychotropics and opiates. The National Household Survey reported any current illicit drug use in 3.6% of the surveyed population, cannabis use in 3% and opiate use in 0.7%. However, there are regional differences in substance abuse patterns, with cannabis in Southern India, raw opium in the North West, injecting of opiates escalating in the 1990s in the North-East regions and spreading to the metropolitan cities. It is also important to remember that substance use, especially illicit use, is often a hidden phenomenon and does not show up clearly in conventional epidemiological studies.

While most substance abusers have a 'drug of choice', polysubstance abuse is the most commonly observed pattern, determined by availability and cost. Most of the opiate and cannabis users start their drug taking with tobacco and alcohol, and progress to other drugs of abuse. Although drug abuse was traditionally thought of as a 'student problem', it is now seen in all social strata, with vulnerable groups, such as non-student youth, industrial and transport workers, slum dwellers and migrant populations, becoming increasingly affected.

RANGE OF SUBSTANCE RELATED DISORDERS

Substances can cause problems due to intoxication, overdose, dependence or withdrawal and can have a wide range of physical, psychological, occupational and social adverse consequences. Harmful use is defined as a pattern of use causing damage to physical and mental health. Specific mental disorders induced by substances include delirium, amnestic disorders, dementia, psychosis, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders.

Dependence

This is a pattern of use characterised by a compulsion to use the substance; development of tolerance (need to increase the dose of the substance for the same effect, or reduced effect with the same quantity of the substance); a stereotyped pattern of use, primacy of substance use over other activities; repeated withdrawal symptoms (which occur with abrupt cessation or reduction of use), relief drinking or use of substance (drinking or using substance to overcome withdrawal symptoms) and reinstatement after abstinence (relapse to old substance use patterns).

Withdrawal symptoms may be psychological (intense craving, irritability, mood changes) or physiological (tremors, sweating, sleep disturbances, nausea). Severe withdrawal may be associated with seizures and delirium, as in the case of alcohol and sedative/hypnotics.

AETIOLOGY

Current models of dependence describe it as a result of multiple interacting factors that influence drug-taking. Drug availability, social acceptability and peer pressure are common determinants of initial experimentation with drugs. Personality and biological predisposition influence the perception of drug effect and the changes produced in the central nervous system (CNS) by repeated drug use. The pharmacological properties of the drug also determine whether use will lead to dependence.

An explosion in knowledge of the neurobiology of addiction has helped greatly in understanding mechanisms like tolerance and withdrawal and holds promise for newer pharmacological interventions. Pathways and structures critical for the reinforcing action of a number of dependence producing drugs like opioids, amphetamine and cocaine, as well as alcohol and nicotine, have their origins in the dopaminergic neurons with cell bodies in the ventral tegmental area and their projections to the nucleus accumbens and the related structures that make up the 'extended amygdala'. This area has inputs from the forebrain, midbrain and hypothalamus. Dopamine release in this area is critical for the reinforcing effects of substances. Many other neurotransmitters are also involved and mediate the effects, side-effects and withdrawal effects of the substance. For example, alcohol (ethanol) exerts its action by enhancing the inhibitory action of the gamma-amino butyric acid (GABA) neurotransmitter and

reducing the excitatory action of the glutamate neurotransmitter. By its blocking action at the *N-m*ethyl-*D-a*spartate (NMDA) receptor, ethanol can indirectly alter the release of other neurotransmitters like serotonin, dopamine, norepinephrine, glutamate, aspartate and GABA. The brain reward systems also interact with systems regulating response to stress – the hypothalamic-pituitary adrenal axis and the extrahypothalamic corticotrophin-releasing factor system. Chronic substance use leads to a dysregulation in homeostasis across these systems and counter adaptive responses.

SCREENING FOR SUBSTANCE USE DISORDERS

A good assessment forms the cornerstone in the accurate diagnosis and management of substance use disorders. Eliciting a history of substance use must be part of general history taking in every patient presenting to any medical set up, especially in emergency and trauma settings (**Table 1**). Assessment of substance use disorders must be carried out just as the assessment of any other medical disorder. Any labelling of an individual, as an 'addict' or 'alcoholic', should be avoided. An empathic biopsychosocial approach focussed on motivating the individual to stop or modify his/her substance use pattern is most useful in clinical practice.

Table 1: History-Taking for Substance Use

Various drugs used
Age at initiation
Factors for initiation
Maintaining factors
Quantity/frequency of use
Route of administration
Last use
Physical, behavioural and psychological effects of use
Physical, behavioural and psychological effects of stopping
Consequences of continued use (physical, psychological, occupational, financial, social)
Features of dependence
Past attempts at abstinence
High-risk behaviour
Motivational level to stop or reduce use of substance
Link with presenting problem (e.g. injury, insomnia, gastritis)

Investigations in Substance Use Disorders

Assessment in substance use disorder should include assessment of health damage. In addition to routine investigations, those appropriate to each category of substance (e.g. tests of liver function in alcohol dependence) must be carried out. Testing for human immunodeficiency virus (HIV) and hepatitis B are essential in the context of high-risk sexual behaviour and intravenous drug use. Drug screening in body fluids particularly urine, blood, breath (alcohol) are useful strategies for confirmation of substance use in clinical settings, for medicolegal purposes and monitoring adherence to treatment. Psychological and cognitive assessments are often required for the assessment of personality, co-morbid psychiatric disturbances and cognitive impairment.

BROAD PRINCIPLES OF MANAGEMENT

The general approach to the management of substance use disorders includes management of intoxication, detoxification, management of associated physical and psychological complications, motivating the person to change, pharmacological intervention, psychosocial interventions including behavioural counselling, psychotherapy, involvement of family and participation in support groups. After care and prevention of relapse are critical components of care for dependence, as it is typically a chronic disorder prone to relapses. Community-based approaches, including camp approaches and self-help groups, are useful strategies. Harm minimisation (reducing harmful consequences of continued use) is also a well-recognised management strategy for difficult-to-manage substance use disorders.

Traditionally, broad approaches to substance abuse prevention have included supply reduction (policies and activities aimed at minimising the availability of alcohol and other drugs to people) and demand reduction (aimed at decreasing the internal need or demand for substances by people).

Alcohol Abuse and Dependence

Early problems related to alcohol often go unrecognised and untreated until dependence sets in and it is often only in this situation that medical intervention is offered. About one in two persons who drink have problems related to alcohol use. Alcohol contributes to more than 60 different health conditions in any given society. It contributes to at least 15% to 20% of mortality, mainly through accidents and injuries. Heavy and regular alcohol use is also associated with increased disability, suicide and psychosocial problems. A significant relationship is emerging between alcohol use, high-risk sexual behaviour and vulnerability to HIV/AIDS.

Pharmacology of Ethanol

The ethanol content of different alcoholic beverages varies with spirits, such as whisky, brandy, rum and gin, and distilled liquors, such as arrack containing 35% to 50% alcohol, wines about 12% alcohol and beers ordinarily contain 4% to 5% alcohol. The higher the alcoholic content of the beverage, higher is the blood alcohol concentration (BAC). Alcohol is absorbed largely from the proximal part of the small intestine, although modest amounts are absorbed from the stomach and large intestine, and small amounts from the mucous membranes of the mouth and oesophagus. Drinking on an empty stomach, gulping drinks, consuming carbonated drinks, such as soda along with the alcohol, all enhance absorption. Presence of fats, proteins and carbohydrates in the diet, presence of congeners can slow down absorption. Congeners found in alcoholic beverages, especially illicitly brewed alcohol (such as methanol, butanol, aldehydes, esters, histamines, phenols, tannins and heavy metals such as iron, lead and cobalt) can contribute to organ damage.

Blood alcohol peaks 30 to 60 minutes after consumption on an empty stomach. While absorption patterns are similar, higher blood alcohol levels are achieved for the same dose in women (lesser body water) and persons with a higher fat content.

The alcohol quantity across different alcoholic beverages can be uniformly expressed as 'standard drinks' or standard units. One standard unit is equal to 30 mL of spirits, 60 mL of wine, or half a bottle of beer. Each standard drink is equal to about 10 gm of ethanol. It takes approximately 1 hour for 1 unit of alcohol to be completely metabolised by the body.

Only 2% (at low alcohol concentrations) and 10% (at high alcohol concentrations) is excreted through the lungs, urine and sweat, the greater part is metabolised to acetaldehyde.

Alcohol is metabolised primarily through the cytosolic pathway by alcohol dehydrogenase to acetaldehyde, which in turn is rapidly destroyed by acetaldehyde dehydrogenase (ALDH) in the cytosol and mitochondria. Another metabolic pathway is through the microsomal ethanol oxidising system, which accounts for about 10% of the metabolism at high blood alcohol concentrations. Low doses of acetaldehyde may cause stimulation and behavioural reinforcement. Accumulation of acetaldehyde in the liver, brain and body tissues may result in body damage.

Behavioural Effects

Behavioural effects are given in Table 2.

Table 2: Behavioural Effects at Different Blood Alcohol Concentrations

BAC (mg/dL)	Behavioural Effects
<80	Euphoria, feelings of relaxation, increased self confidence, reduced alertness, excessive talk, clumsiness in motor movements
>80	Noisiness, moodiness, impaired judgement and driving ability
100-200	Blurred vision, gait unsteadiness, gross motor incoordination, slurred speech, aggressive or quarrelsome behaviour, loud talk
200 to 300	Amnesia for the experience
300 to 350	Coma
350 to 600	Death

Systemic Effects With Chronic Alcohol Use

Table 3 outlines the various systemic effects of alcohol abuse.

Biological Vulnerability

Studies suggest that the heritable risk for the development of alcohol dependence is 50% to 60%. There have been many studies to support the heritable nature of alcoholism, including family, twin and adoption studies, which indicate a four-fold increase in the risk for developing alcoholism in children of alcoholics. Genetic variations in the alcohol metabolising enzyme [antidiuretic hormone (ADH) and ALDH] can alter the risk for alcohol dependence. Molecular genetic studies using restriction fragment length polymorphisms (RFLP) suggest an allelic association of the D2 (dopamine) receptor gene, located on the q22-q23 region of chromosome 11 to chronic use. Recent research has also focused on genes regulating GABA and glutamate neurotransmission, as well as genes that regulate the serotonergic system.

Neurotransmitter Changes

Different neurotransmitters are also known to alter alcohol consumption patterns. Dopamine may contribute to the motivation and reinforcement of alcohol consumption. Serotonin levels appear to be lower in the brains of alcohol dependents compared to controls. It may promote alcohol's intoxicating and rewarding effects. Glutamate (an excitatory neurotransmitter) receptors in the brain are inhibited by alcohol and this may account in part for the cognitive dysfunction associated with alcoholism. Alcohol also acts on the inhibitory GABA receptor, especially the GABA receptor, which may mediate the sedative effects of alcohol. Alcohol-induced changes in GABA receptor function may contribute to alcohol dependence and tolerance, and abnormalities in the GABA system may predispose to alcoholism. In addition, various neuromodulators affected by alcohol include endogenous opioid peptides (which may mediate alcohol reinforcement and excessive alcohol consumption), adenosine (which may mediate many of alcohol's acute and chronic effects on the CNS such as incoordination, intoxication and sedation).

Table 3: Systemic Effects of Alcohol Abuse

Nutritional and metabolic effects
- Vitamin deficiencies – B1 (beriberi or Wernicke-Korsakoff's syndrome, B3 (pellagera), B6 (peripheral neuropathy), folate and vitamin A
- Metabolic – hypoglycaemia, ketoacidosis, hypocalcaemia, hypophosphataemia, hypomagnesaemia

Gastrointestinal effects
- Acute or chronic gastritis – evasive/hemorrhagic/non-erosive atrophic
- Mallory-Weiss lesion
- Malabsorption syndrome
- Alcoholic liver disease and cirrhosis
- Pancreatitis

Cancers
- Head and neck, oesophagus, stomach, liver and pancreas

Haematological effects
- Anaemia-microcyte hypochromic (secondary to blood cover), megaloblastic (secondary to folate deficiency)
- Mild thrombocytopaenia and granulocytopaenia

Cardiovascular effects
- Hypertension
- Cardiomyopathy
- Arrhythmia
- Risk factor for haemorrhagia stroke and coronary artery disease (CAD)

Impaired immune respirator
- Secondary infections viz. pneumonia and tuberculosis

Musculoskeletal system
- Myopathy
- Osteoporosis

Sexual dysfunction
- Erectile dysfunction
- Testicular atrophy and sterility

Nervous system
- Acute intoxication
- Sleep disturbances
- Peripheral neuropathy
- Seizures
- Delirium tremens
- Wernicke-Korsakoff's syndrome
- Cognitive impairment
- Cerebellar degeneration

Psychiatric complications
- Depression
- Delusional disorder
- Psychosis resumes of schizophrenia
- Personality disorder

Foetal alcohol syndrome
- Low birth weight
- Hyperactivity
- Subnormal intelligence
- Facial abnormalities (short palpebral fissures, short upturned nose, mid-facial hypoplastia, low nasal bridge, thin upper lip)

Social complications

Psychosocial Theories

Social factors, such as broken families, single parent families, parental 'models', peer pressure, availability of alcohol and cultural sanction of drinking, all contribute to the development of alcohol abuse and dependence. Psychological vulnerability, including stress, low self-esteem, poor coping and poor communication skills may predispose to alcoholism. Alcoholism has also been described as a learnt behaviour, with the temporary relief from anxiety with alcohol acting as a reinforcer, perpetuating alcohol use. Thus, alcohol dependence may be aptly described as a biopsychosocial disorder, with a complex interplay of environmental, genetic and psychosocial factors.

Assessment of Alcohol Related Problems

Thirty to forty per cent of patients presenting to the physician for physical illness are likely to have problem alcohol use. Thus, it is advisable that every patient is routinely asked about alcohol and nicotine consumption, patterns of use, including frequency, quantity and related physical and psychosocial problems. This will facilitate early identification as well as reduce the stigma associated with self-reporting alcohol use. The index of suspicion of alcohol complicating the presenting problem should be higher in certain conditions, listed in the accompanying Table 4.

Table 4: High Index of Suspicion of Alcohol as a Contributory/ Causative Factor

Adult onset seizure
Young stroke
Poorly controlled hypertension
Young onset or poorly controlled diabetes
Hepatitis, cirrhosis
Peripheral neuropathy
Pancreatitis
Parotid gland enlargement
Cancer
Gastrointestinal symptoms of undermined cause
Sleep disturbances
Unexplained falls or accidents
Poorly controlled gout
Confusion or cognitive impairment
Non-specific somatic symptoms
Work-related problems such as absenteeism

Alcohol can also interact with a wide variety of medications such as anaesthetics, antihypertensives, antihistaminics, anticonvulsants, antibiotics, analgesics, antidepressants, antipsychotics and sedatives. Patients on such drugs must be asked about alcohol consumption, educated about the interaction and advised to stop or modify alcohol intake as necessary.

There are useful screening tools, such as the Michigan alcohol screening test (MAST) and the CAGE questionnaire, which can help in picking up alcohol problems. The CAGE consists of asking about whether the person has had difficulty cutting down, been annoyed by criticism about his drinking, experienced guilt because of drinking, or needed an eye-opener. Two or more 'yes' responses suggest a problem with drinking. A more recent schedule from the WHO, the alcohol use disorders identification test (AUDIT), measures alcohol consumption quantities, drinking behaviour and related problems. Each of the ten questions is rated on a scale from 0 to 4. A cut-off of eight or more indicates problem drinking.

While screening tools are helpful in identifying problems related to alcohol, a clinical interview with the patient and significant others is invaluable in reaching a diagnosis and making a comprehensive assessment.

Laboratory Assessment

Several biochemical and haematological parameters can help the physician to assess the damage caused by alcohol (values strongly suggestive of heavy drinking indicated in brackets).

Complete haemogram for evidence of anaemia or acute infection, liver function tests and prothrombin time to assess liver dysfunction, lipid profile, blood sugar, urea and electrolytes when patient is acutely ill, serum uric acid, electrocardiogram, echocardiogram to assess cardiac status, chest X-ray to rule out pulmonary tuberculosis, bronchitis and CT scan if head injury is suspected. Carbohydrate-deficient transferrin (20 gm/dL or more) is also helpful in screening for alcohol abuse and for follow-up monitoring.

Management

Early intervention

Research has shown that early, brief intervention can be very effective. A trial period of reduction of drinking or abstinence and review of the presenting problems can be suggested. For patients with a serious problem or a potential risk of serious problems with alcohol (dependent use, strong family history of dependence, serious physical illness, including hepatic dysfunction, cognitive impairment, psychiatric illness, physiological states, such as pregnancy, serious social crises, e.g. threat of job loss or separation from spouse), abstinence must be strongly advised. An empathic rather than aggressive approach, a clear statement of the physician's medical concern, involvement of the significant others in counselling and a joint agreement with the patient regarding the treatment goal have been shown to have significant results in early stage drinkers, as well as motivate alcohol dependents for longer and more intensive treatment programmes. Monitoring health and drinking state at follow-up is crucial to maintain the gains of treatment.

For dependence

For patients with dependence, treatment consists of handling withdrawal-related syndromes and long-term treatment. Withdrawal, if moderate or severe, is best treated pharmacologically, because there is evidence of neurotoxicity associated with abrupt withdrawal of alcohol from the brain. While outpatient and inpatient detoxification have similar outcomes, inpatient detoxification is preferable in cases with serious physical or psychiatric illness, at risk for seizures or delirium, failed-outpatient detoxification, poor social supports and severe craving.

Steps in the management of the dependent alcoholic include:

- Thorough physical examination and investigations for nutritional impairment, electrolyte imbalance, cardiac, hepatic, gastrointestinal and neurological impairment.
- Adequate nutrition and rest.

- Oral or parenteral B-complex can be provided, including 50 to 100 mg thiamine, for 7 to 10 days.
- Symptomatic treatment of underlying problems such as gastritis, diarrhoea or dehydration.

Detoxification

Drugs commonly used to control withdrawal symptoms are the long-acting benzodiazepines (diazepam 5 to 10 mg or chlordiazepoxide 25 to 50 mg 6 hourly) to ameliorate the withdrawal symptoms. Short-acting benzodiazepines (lorazepam 1 to 2 mg or oxazepam 15 to 30 mg repeated four hourly) are preferred in the presence of hepatic damage. The drug dose can be reduced by 20% on subsequent days and gradually tapered over a week to ten days. Other drugs used for detoxification include anticonvulsants, such as carbamazepine, phenytoin, gabapentin, alpha-adrenergic agents such as clonidine, and beta-blockers such as propranolol.

Delirium tremens can be effectively managed with supportive care, correction of fluid and electrolyte imbalance, antibiotics in the presence of infection, high doses of benzodiazepines along with parenteral B-complex. Antipsychotics, such as haloperidol in low doses (2.5 to 5 mg) may be helpful in controlling agitation, but must be used with caution as they may reduce seizure threshold. Alcohol withdrawal seizures do not need long-term anticonvulsant treatment.

Following detoxification, the patient's motivation is strengthened through individual, group and family counselling, which includes educating about alcoholism, interventions to deal with interpersonal, marital, sexual problems, vocational counselling, helping the patient develop better skills of communication, assertiveness (e.g. handling peer pressure), problem solving and coping with stress. The family is supported and helped to provide a supportive environment to the patient to facilitate recovery. For women alcoholics, gender-sensitive treatment programmes addressing psychological and family issues more intensively, need to be provided. Self-help groups, such as the alcoholic anonymous (AA) and Al-Anon, for families are perceived as useful by many patients. Treatment of less severely dependent alcoholics has also been successfully carried out in rural areas through camps.

Pharmacotherapy for long-term treatment

This includes the use of anticraving agents. Acamprosate, a specific glutamate antagonist, in doses of 1 to 2 gm/day in three divided doses, has been associated with modest but statistically significant outcome on parameters such as number of drinking days, time to first drink and frequency of heavy drinking. It is reasonably well-tolerated and free of any significant adverse side-effects except diarrhoea. Naltrexone, an opiate antagonist, in doses of 50 to 150 mg per day has also found to reduce craving and improve abstinence in alcohol-dependent subjects.

For long-term treatment, disulfiram is still the most commonly used drug in India, in the usual dose of 250 mg per day, after informed consent. Disulfiram does not reduce craving. It acts as a deterrent to drinking, as it inhibits alcohol dehydrogenase, leading to an accumulation of acetaldehyde after alcohol consumption. The disulfiram-ethanol reaction is characterised by flushing, nausea, vomiting, tremulousness, fall in blood pressure. Disulfiram is contraindicated in patients with severe heart disease, hepatic dysfunction, seizures, stroke, uncontrolled diabetes and psychiatric illness. It is not advisable to prescribe disulfiram without the patient's consent in view of the potentially serious effects of the disulfiram-ethanol reaction. Supervised disulfiram therapy ensures better compliance and clinical outcome.

Topiramate, a sulphamate fructopyranose derivative which facilitates GABA function and antagonises glutamate function has been shown to decrease drinking in doses of 200 to 300 mg per day. Major concerns with topiramate include reports of renal calculi and word recall difficulties.

Current research is focused on examining the efficacy of combination treatments (e.g. naltrexone and acamprosate, acamprosate and disulfiram) in the outcome of alcohol dependence.

Ondansetron, a 5-HT_3 antagonist (in doses of 4 µg/kg) have been found to have some benefit in early onset severe forms of alcohol dependence associated with multiple-drug dependency and criminality. Specific serotonin reuptake inhibitors (such as fluoxetine, sertraline) have not been found to have any significant effects on the core symptoms of alcohol dependence. However, antidepressants and mood stabilisers may be required for co-morbid anxiety and mood disorders and short-term anti-psychotics for alcohol-related psychotic disorders.

Concurrent medical conditions

Concurrent medical conditions must be appropriately treated.

Monitoring and Follow-Up

Alcoholism, like other chronic illnesses such as hypertension or diabetes has a chronic, relapsing course. While 50% to 60% of patients significantly reduce their drinking or abstain for 6 months, relapse is frequent. Follow-up, therefore is mandatory and is very useful in bringing the patient back into treatment. In addition, as end stage problems are more resistant to treatment, the focus needs to shift to early detection and intervention for alcohol-related problems.

CANNABIS

Cannabis is obtained from *Cannabis sativa* or the Indian hemp and consumed orally as *'bhang'* (dried leaves of the plant), or smoked as *'ganja'* (from the flowers and upper leaves), or *charas* (from the resinous tops) through cigarettes, beedis or chillums. The active ingredient is delta-9-tetrahydrocannabinol (THC), but more than 400 compounds have been isolated from the plant. Though all these compounds are not psychoactive, they have potential physiological effects. The THC is rapidly absorbed from the lungs into blood and then rapidly concentrates in tissues (this may subsequently be released leading to 'flashbacks'). It is primarily metabolised in the liver, and 11-hydroxy THC is one of the psychoactive metabolites. The long half-life (50 hours) can lead to cumulative side-effects. An endogenous cannabinoid-like ligand, 'anandamide', has been isolated within the brain. Recent studies suggest that cannabis use is substantially influenced by genetic factors. Cannabinoids exert many of their actions by influencing several neurotransmitter systems and their neuromodulators including acetylcholine, dopamine, GABA, histamine, serotonin, norepinephrine, opioid peptides and prostaglandins. Cannabinoids enhance the formation of norepinephrine, dopamine and serotonin.

Physiological side-effects include conjunctival injection, bronchodilatation followed by bronchoconstriction, bronchial irritation, decrements in pulmonary vital capacity, mild postural hypotension, dry mouth, occasional diarrhoea, increased appetite and drowsiness. Angina may be precipitated by those with a history of coronary insufficiency. Other adverse effects, less conclusively proven, include reduced testosterone, spermatozoal abnormalities, impaired foetal growth and development with cannabis use in pregnancy, immune response abnormalities, chromosomal abnormalities and inhibition in DNA, RNA and protein synthesis. A link between heavy cannabis use lung cancer and cortical atrophy is suggested but not established.

Cannabis intoxication is characterised by euphoria, impaired thinking, concentration, perceptual and psychomotor function. A 'toxic psychosis', with confusion, delusions, hallucinations, emotional lability, amnesia, disorientation, depersonalisation and paranoid symptoms can occur. This may resolve in a few hours to several days. A psychosis with both manic and schizophrenic symptoms without confusion known as 'cannabis psychosis' has also been described, but not as clearly validated as the toxic psychosis. In chronic users an 'amotivational syndrome' characterised by withdrawal, apathy, lethargy and lack of motivation has been described, predominantly from India. Heavy cannabis use is known to occur in schizophrenia and can exacerbate the condition.

Tolerance and Dependence

Habitual users rapidly develop tolerance to the psychoactive effects of cannabis. Tolerance to physiological effects occurs at different rates, e.g. tolerance to tachycardia develops earlier than tolerance to conjunctival injection. Withdrawal symptoms in heavy cannabis users are milder than in alcohol or opiate withdrawal and characterised by tremor, nystagmus, nausea, vomiting, diarrhoea, irritability, anorexia and sleep disturbances.

Management

Cannabis use can be determined through physical examination for signs of intoxication and urinary cannabinoid screening. Control of the effects is largely symptomatic. Treatment of unpleasant adverse reactions, usually anxiety, consists of calm and gentle reassurance in a warm and supportive atmosphere. Short-term use of anxiolytic agents, such as benzodiazepines, may be necessary in some instances when anxiety symptoms are prominent or severe. Short-term use of low doses of anti-psychotic medication may be required when the patient has significant psychotic symptoms. The subsequent focus is on maintenance of abstinence, problem solving, improvement of self-esteem and involvement in alternative pleasure seeking activities.

OPIOIDS

Many of the opioid drugs, because of their analgesic and sedating properties have a wide application for medical use. Their euphoriant effect, in addition to these properties, makes them liable for misuse. Opioids can be smoked or consumed orally (raw opium, propoxyphene, codeine containing cough syrups), 'chased' (melted on a silver foil and fumes inhaled) in the form of heroin or brown sugar, injected (heroin, morphine, pentazocine, pethidine, buprenorphine). Opiate use can be initiated either through peer pressure, following prescription for pain relief (e.g. postoperative analgesia) and increased accessibility (physicians and nurses).

Opioids bind to different types of receptors in the body, including the CNS, primarily the μ receptors, as well as kappa and delta, which mediate different effects of the drugs. Various neurotransmitter alterations, including that of acetylcholine, serotonin, GABA, norepinephrine and dopamine, may contribute to the development of tolerance and dependence, which varies across different drug types. It has been suggested that a polymorphism of the μ receptor gene may be implicated in the development or protection from opioid addiction.

Opiate overdose can occur either as a suicidal attempt or accidentally and is characterised by respiratory depression, miosis, bradycardia, decreased body temperature, reduced responsiveness and if untreated can lead to death because of respiratory depression and cardiovascular arrest.

Other effects of opiate intoxication include nausea and vomiting, decreased pain perception, and sedation. Adulterants, especially in street drugs, such as 'brown sugar' can contribute to CNS damage, including peripheral neuropathy, amblyopia, myelopathy and leucoencephalopathy. Sharing of injecting equipment, including needles and syringes, and unsterile injecting practices, lead to increased risk for abscesses, cellulitis, endocarditis, hepatitis and HIV infection. In certain parts of India, HIV seropositivity is reported in as many as 50% of intravenous drug users. Tuberculosis is also a serious problem in this group.

Dependence and Withdrawal

Dependence to opiates occurs more rapidly than with other drugs. Mortality in opiate abusers is high and 25% are likely to die within 10 to 20 years of active use, with death resulting from suicide, homicide, accidents or infection. Use of other substances, especially alcohol, cannabis and benzodiazepines, commonly occurs in opiate users. A switch between different types of opiates is common because of restriction of availability.

Withdrawal symptoms due to opiates tend to be opposite to the acute effects. Drugs with shorter half-lives, such as heroin and morphine produce earlier withdrawal symptoms. Withdrawal symptoms generally subside after 5 to 8 days, but a protracted abstinence syndrome with mild symptoms (autonomic dysfunction, papillary dilatation, sleep disturbances) can persist for 6 months and can contribute to relapse.

Management

Opiate overdose is a medical emergency. Management consists of supportive treatment, especially respiratory support and specifically by intravenous or intramuscular administration of the narcotic antagonist naloxone in an initial dose of 0.2 mg, repeated after 3 to 10 minutes if no response occurs. If there is no response after a cumulative 4 to 5 mg, toxicity with non-opioid CNS depressant should be suspected.

Withdrawal is a self-limiting condition. Clonidine, an alpha-adrenergic agonist in doses of 5 mg per kg (up to 0.3 mg three to four times a day) with blood pressure monitoring can decrease autonomic dysfunction in most patients undergoing opiate withdrawal. The other principle is to substitute with another opiate in detoxification, as there is some level of cross-tolerance across different drugs. Thus, buprenorphine, a partial agonist, can be prescribed in doses of 2 to 4 mg per day in three

divided doses (sublingually), for 7 to 10 days and tapered over 10 to 15 days. Alternatively, propoxyphene, 6 to 9 capsules in three divided doses can be given for a similar duration. Methadone, 10 to 25 mg twice daily, increased to control withdrawal symptoms, and reduced by 10% to 20% per day subsequently is used in some countries, but not available for use in India. Symptomatic treatment is required for sleep disturbances, diarrhoea and bodily pains, but judicious prescription for the minimum period must be done to avoid abuse.

Following detoxification, maintenance of abstinence requires improving motivation through counselling, group therapy and involvement of the family. Abstinence maintenance can be achieved through changes in lifestyle and a focus on productivity through rehabilitation. Self-help groups, also provide the much needed peer support to abstain from opiates.

Long-term pharmacotherapy for opiate use includes the use of naltrexone, an opiate antagonist, in doses of 50 to 100 mg per day for at least 6 months. Considering the high relapse rates associated with opiate use, recent literature has suggested the use of 'harm minimisation' methods, which includes supply of disposable needles to users, educating about safe injecting practices and substitution with oral rather than injectable preparations, for people unwilling to give up their drug habit. Sublingual buprenorphine in doses of 2 to 4 mg per day or once in 2 to 3 days is recommended for maintenance, to encourage opiate users to give up street drugs and injecting drug use. Methadone, a long-acting opiate, as well as levoacetyl methanol are prescribed in several countries as substitute drugs that are legally accessible and safer, but not available in India. Prescription monitoring and judicious use of opiates are important strategies to limit opiate misuse.

SEDATIVE, HYPNOTIC AND ANXIOLYTIC ABUSE

While barbiturates were earlier commonly abused, currently benzodiazepines (especially diazepam and shorter acting benzodiazepines such as lorazepam and alprazolam) are more liable to abuse. Such abuse often occurs following prescription of these drugs for conditions such as insomnia. These drugs act primarily through the GABA system. Intoxication resembles alcohol intoxication and is characterised by slurred speech, incoordination, unsteady gait, nystagmus, impaired attention and memory and sometimes stupor or coma. Longstanding use may lead to cognitive impairment and an amnestic disorder. Withdrawal states are characterized by sweating, tachycardia, tremors, insomnia, nausea, vomiting, hallucinations, illusions, agitation, anxiety and sometimes seizures. Severe benzodiazepine dependence must be detoxified under inpatient supervision because of the risk of seizures and delirium during withdrawal. Treatment consists of supportive management and initial stabilisation with the drug at the same dose, and subsequent reduction by 30% on the second and third day. Subsequent tapering must be done slowly with 10% to 20% reductions weekly. If a short-acting benzodiazepine is being abused (e.g. lorazepam), a useful strategy is to shift to an equivalent dose of a longer-acting drug (e.g. diazepam) and taper as discussed earlier. Propranolol, clonidine and carbamazepine have been used as adjuncts.

INHALANT ABUSE

Abuse of volatile solvents, such as petrol, paint thinners, shoe polish, glue and typewriting whitener, are common especially among adolescents from slums and street children. Solvents are commonly used by 'bagging' (emptying the solvent into a plastic bag, holding it to the nose and inhaling), 'huffing' (soaking a rag in the mixture and stuffing it in the mouth and inhaling), sniffing and snorting or direct spraying into the oral cavity. Solvents act primarily as CNS depressants. Inhalants are associated with many potentially serious adverse effects. The most serious of these is death, which can result from respiratory depression, cardiac arrhythmias, asphyxiation, aspiration of vomitus, accident, or injury (e.g. driving while intoxicated with inhalants). Chronic inhalant users may have numerous neurological problems. The CT and magnetic resonance imaging (MRI) reveal diffuse cerebral, cerebellar and brainstem atrophy with white-matter disease, a leucoencephalopathy. Neurological signs and symptoms may include hearing loss, peripheral neuritis, headache, paresthesias, cerebellar signs, persisting motor impairment, Parkinsonism and lead encephalopathy. Other serious adverse effects associated with long-term inhalant use include irreversible hepatic disease or renal damage (tubular acidosis) and permanent muscle damage associated with rhabdomyolysis. Additional adverse effects include cardiovascular and pulmonary symptoms (e.g. chest pain and bronchospasm) as well as gastrointestinal symptoms (e.g. pain, nausea, vomiting, and haematemesis).

Management consists of appropriate medical care. In addition, vigorous treatment is needed for adolescent patients who progress from experimentation to inhalant abuse or dependence. Comprehensive management includes detoxification, a peer counselling system, assessment of physical, cognitive and neurological deficits, building on existing strengths, developing new strengths, attention to personal and family issues and assistance in returning back to the community.

HALLUCINOGENS

Typical drugs in this category include lysergic acid diethylamide (LSD), phencyclidine (angel dust), ketamine (a short-acting anaesthetic), mescaline (from peyote cactus), 'magic' mushrooms (containing psilocybin), methylene-dioxyamphetamine and methylene-dioxymethamphetamine (MDMA). These drugs may be administered orally or intravenously or are occasionally smoked. Hallucinogenic drugs bind to multiple synaptic receptors in the brain. Hallucinogenic potency is associated with binding affinities at the serotonin type 2 [5-HT_2] receptor where these drugs act as partial agonists.

Acute effects of LSD include hyperacusis, synesthetic experiences (stimulation of one sensory modality is perceived as sensation in a different modality, as when a sound produces a sensation of colour), changes in body image and time space perceptions. Hallucinations, intense emotions, panic-like symptoms and paranoid reactions are common. Phencyclidine and ketamine cause mood changes, intense anxiety, perceptual disturbances, paranoid reactions and motor stereotypes. The MDMA deaths have been associated with drug-induced compulsive dancing, hyponatremia, and hyperthermia. Bad trips or 'flashbacks' (the

re-experiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were earlier experienced while on the drug) are typical of hallucinogen abuse. These are characterised by marked anxiety, dysphoria, paranoid ideations and intense perceptual disturbances. Persistent psychosis may rarely be induced by hallucinogens.

Hallucinogen overdose requires prompt life-support measures, including treatment of coma, convulsions and respiratory depression in an intensive care set up. Treatment for hallucinogen-related perceptual disorders is palliative. Long-acting benzodiazepines, such as clonazepam, anticonvulsants (valproate and carbamazepine), may be useful. Anti-psychotic agents should only be employed in the treatment of hallucinogen-induced psychoses. Co-morbid conditions, associated with hallucinogen abuse-panic disorder, major depression and alcohol dependence, must also be treated.

COCAINE

Cocaine, extracted from the leaves of the coca plant (*Erythroxylon coca*) is a stimulant and local anaesthetic. Cocaine is used intranasally ('snorting'), orally, intravenously or through inhalation. It has potent pharmacological effects on dopamine, norepinephrine and serotonin neurons in the CNS. Compulsive use of cocaine follows quickly after accidental or experimental use. Acute effects include stimulation of mood, disinhibition, increased cardiac rate, blood pressure and body temperature. Deaths due to respiratory depression, cardiac arrhythmias and seizures have been reported following snorting and intravenous cocaine use. Chronic use may cause paranoid symptoms, visual and auditory hallucinations. Severe depression may accompany drug withdrawal.

Cocaine overdose should be managed in an intensive care unit and supportive care and specific management of complications done. Psychosocial approaches include behaviour modification, supportive psychotherapy, group therapy, family therapy and self-help groups.

AMPHETAMINES

Stimulant drugs, such as amphetamine, methamphetamine (used in the treatment of hyperactivity in children), diethylpropion, benzamphetamine and phentermine, are commonly abused for their fatigue reduction, alerting and euphorigenic properties. These drugs are used orally or injected. The MDMA (ecstasy) is a substituted amphetamine popular with adolescents at rave parties. Amphetamine acts on the dopaminergic neurons in the mesolimbic area, stimulating dopamine release and inhibiting its reuptake. Toxicity is characterised by hypervigilance, grandiosity, psychomotor agitation and socially inappropriate behaviour. Physical signs include mydriasis, hypertension, perspiration and vomiting. Cardiovascular abnormalities can occur. Chronic use can lead to a schizophrenia-like psychosis. Withdrawal is characterised by dysphoria and anhedonia.

Treatment is symptomatic. Antipsychotics such as haloperidol 5 mg, may be required for psychotic symptoms and fluoxetine 20 mg for dysphoria. Comprehensive psychosocial treatment is required.

NICOTINE

Nicotine dependence is the most prevalent, most deadly, most costly, yet most potentially treatable of the substance dependencies. Nicotine is commonly smoked as cigarettes or beedis, or orally consumed as chewing tobacco, khaini or gutka. Cultural acceptance of tobacco use and its licit status makes it one of the biggest preventable hazards. The CNS effects are mediated through nicotinic cholinergic receptors. Tolerance, dependence and a withdrawal syndrome contribute to the strong control exerted by nicotine on smoking behaviour. Withdrawal is characterised by craving, depression, irritability, insomnia, anxiety, poor concentration, restlessness and increased appetite. Though most symptoms peak in 1 or 2 days and subside within 3 to 4 weeks of stopping, craving for tobacco products and increased hunger can persist for longer periods.

More than 4,000 chemicals have been identified in cigarette smoke, and nearly 3,000 in smokeless tobacco. These include chemicals with antigenic, cytotoxic, mutagenic and carcinogenic properties. Common among the carcinogens in cigarette smoke are tar, aromatic hydrocarbons and other poisonous substances such as carbon monoxide, hydrocyanic acid, aromatic amines and various aldehydes. Large population studies have found a strong association between cigarette smoking and atherosclerotic cardiovascular disease, cancer and chronic obstructive pulmonary disease. Smoking is also associated with increased occurrence of gastric and duodenal ulcers, delays healing of such ulcers and increases risk of recurrence. In women, smoking may delay conception and smoking during pregnancy is associated with increased risk of spontaneous abortion, foetal death, neonatal death and sudden infant death syndrome. Prevalence of smoking is higher in persons who are depressed. Passive smoking (involuntary smoke inhalation) is recognised as a cause of lung cancer and coronary heart disease in nonsmokers. Parental smoking in the home is associated with an increased risk of acute respiratory illnesses, middle ear discharges, chronic respiratory problems and lung function impairment in children.

Family, twin and adoption studies suggest a strong genetic contribution to the development of tobacco dependence. As with other drugs, the addictive effect of nicotine is linked to the release of dopamine. Dopamine gene polymorphism (DRD2 A1 allele) is more prevalent in smokers than non-smoking controls and associated with a younger age of onset and more unsuccessful quit attempts. It is hypothesised that the presence of the A2 allele of the DRD2 gene may be negatively associated with tobacco smoking or offer protection against smoking. Action of nicotine on various other neurotransmitters may contribute to the perceived effects for the user: acetyl choline with arousal and cognitive enhancement; serotonin with mood modulation and appetite suppression; norepinephrine with arousal; vasopressin with improved memory and beta-endorphin with reduction of anxiety and tension. Polymorphisms in the serotonergic transporter gene, genetic variations in the nAChR sub-units offer supportive evidence for these mechanisms. Recent genetic research suggests that in smokers, CYP2A6 which is responsible for metabolising nicotine metabolises nicotine rapidly causing heavier smoking. Light smokers carry a mutation of this gene and are unable to metabolise nicotine rapidly. They are thus less prone to get habituated or progress to heavier smoking.

Nicotine intoxication is characterised by abdominal pain, dizziness, headache, nausea, pallor, palpitation, sweating,

vomiting and weakness. Intoxication is rare and treatment is supportive.

The common factors for tobacco addiction are the withdrawal symptoms. Typical physical symptoms during withdrawal include craving, irritability, anxiety, poor concentration, restlessness, sleep disturbance, decreased heart rate and increased appetite or weight gain.

In helping people quit tobacco, the physician needs to address the physical withdrawal symptoms, the psychological dependence and the environmental cues that maintain tobacco use. The benefits of quitting tobacco are well established. Cessation produces immediate and long-term physical, psychological and economic benefits. Among smokers, within days of quitting, the sense of smell and taste may improve. One year after stopping, there is a substantial reduction in risk for myocardial infarction. Total mortality among former smokers decreases to that of nonsmokers 15 years after quitting. Cessation also reduces the risk for tobacco related cancers, myocardial infarction, cerebrovascular disease and chronic obstructive pulmonary disease.

While many smokers attempt to spontaneously quit, relapse rates are very high and fewer than 5% are able to abstain after the first cessation.

MANAGEMENT

Treatment of nicotine addiction is as cost effective as treatment of hypertension and hypercholesterolaemia. Many patients who visit the physician are especially responsive to advise to stop smoking or chewing tobacco. Guidelines for intervention are provided in **Table 5**. Intervention consists of a tobacco use assessment in every patient who presents to the physician, including a query about chewing tobacco, especially in women. Education about risks of tobacco use and individualised advise should be provided for such patients. Specific intervention includes setting a quit day and stopping suddenly ('cold turkey') or nicotine replacement therapy (NRT) through nicotine gums, nicotine transdermal patches, or sprays. The nicotine gum which is the more easily available NRT comes as 1 mg, 2 mg and 4 mg. The tobacco use must be stopped while using the gum. The gum is used one piece at a time on a fixed schedule. The gum can be prescribed for 4 to 6 weeks and then tapered over 2 to 3 months. The anti-depressant bupropion is also used as first-line therapy in smoking cessation. Its postulated mechanism of action is reduction in craving through its effect on dopamine and noradrenaline. For bupropion treatment, the drug is started while the person is still smoking and the quit date is set about 2 weeks after the initiation of the drug. In doses of 300 mg per day combined with counselling 1 year quit rates of 24% to 33% have been demonstrated. Clonidine may be useful in control of withdrawal symptoms. Individual counselling, group therapy and behaviour therapy strategies, including skills of handling craving, eliminating cues for smoking (e.g. carrying a cigarette or a matchbox or lighter), and other techniques to avoid relapse (e.g. handling stress), are also useful. Co-morbid conditions, such as depression, require treatment. A combination of pharmacological and psychosocial strategies works better than either alone.

Table 5: High Index of Suspicion of Alcohol as a Contributory/ Causative Factor

Adult onset seizure
Young stroke
Poorly controlled hypertension
Young onset or poorly controlled diabetes
Hepatitis, cirrhosis
Peripheral neuropathy
Pancreatitis
Parotid gland enlargement
Cancer
Gastrointestinal symptoms of undermined cause
Sleep disturbances
Unexplained falls or accidents
Poorly controlled gout
Confusion or cognitive impairment
Nonspecific somatic symptoms
Work-related problems such as absenteeism

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22.8 Psychiatric Emergencies

JK Trivedi

Emergency psychiatry is a sub-specialty of psychiatry that has evolved over the last few decades and is defined as disturbance in thought, mood and/or action which causes sudden distress to an individual (or to significant others) and/or sudden disability, for which immediate management is required.

Mostly psychiatric emergencies are seen in emergency room of a hospital but these can also present in any psychiatric set up.

Psychiatric emergencies do not mean that patients are suffering from only psychiatric disorder. The consultation may be due to medical conditions or conditions unrelated to medical field, like rape, violence, disaster, etc.

An important task of the attending physician is to determine the cause of the mental disturbance. Thus, the assessment should include an interview, mental status examination, physical and neurological examination and when necessary, relevant laboratory investigations. Psychiatric history should always be obtained from both the patient and the informant(s).

BASIC PRINCIPLES OF APPROACH AND MANAGEMENT

Initial Evaluation

Seriousness of the condition should be assessed and 'TRIAGE' system should be followed in emergency room to prioritise cases like emergency, acute and not acute.

Initial Measures

Many a times the patient is uncooperative. Empathetic, confident and composed attitude shown by the physician can reassure the patient and relatives. A quiet and secluded room is useful. When necessary, restraints may be needed to hold a patient for proper management. Personal safety should be ensured and security staff called when necessary. Hospitalisation should be considered when necessary. Precise psychiatric diagnosis in psychiatric emergency services may be less important than appropriate dispositions. Medico-legal cases need to be registered separately and local police should be informed.

COMMON TYPE OF PSYCHIATRIC EMERGENCIES

Common types of psychiatric emergencies are listed in **Table 1**.

VIOLENT AND AGGRESSIVE BEHAVIOUR

Foreshadowing behaviours or warning signs of impending violent behaviours include increased psychomotor activity, clenching of fists and jaw, pacing, slamming doors, banging their fist on a wall, jumpy and easy to startle, sitting on the edge of the chair and clutching the armrest and verbally abusive patient.

Common psychiatric disorders associated with violent behaviour are listed in **Table 2**.

Table 1: Common Types of Psychiatric Emergencies

- A new psychiatric disorder with acute onset
- A chronic psychiatric disorder with relapse
- An organic psychiatric disorder
- Iatrogenic emergencies
  - Side-effects or toxicities of psychotropic medications
  - Psychiatric symptoms due to toxicity/poisoning
  - Side-effects of non-psychotropic medications presenting with psychiatric symptoms
- Alcohol or other substance abuse
  - Withdrawal
  - Overdose
  - Complication
- Deliberate harm to self or others
- Delirium
- Catatonia
- Prominent anxiety symptoms, like panic attacks
- Dissociative disorder (stupor, hyperventilation, pseudoseizure, trans-possession states)
- An abnormal response to stressful situation
- Seizure disorder

Table 2: Common Psychiatric Disorders Associated with Violent Behaviour

- Psychosis
  - Schizophrenia
  - Delusional disorder
  - Acute psychosis
- Mania
  - First episode
  - Bipolar
- Substance use disorder
- Organic brain disorder
  - Post-ictal states
  - Any systemic condition leading to intracranial pathology and/or delirium
  - As a part of behavioural and psychological symptoms of dementia (BPSD)
- Personality disorder
  - Borderline
  - Anti-social
- Sometimes depression (as murder-suicide)
- Dissociative disorder (trans-possession)
- Acute stress reaction
- Adolescents (behavioural problems)

Management of Aggressive and Violent Patient

The physician should gather maximum information before facing the patient. The physician should be empathic, firm and patient. A direct confrontation may escalate the situation. Some rapport building exercise like addressing the patient by his name should be tried which will help in making the diagnosis. If possible, physical examination should be done without putting oneself in

undue danger. Physical restraint will be necessary if verbal commands are ineffective. Restraint should be done in supine position by at least 5 persons, one for each limb and one for head. Leather restraints are the safest and surest type of restraints. The restraints should be checked periodically for safety and comfort. After the patient is under control, one restraint at a time should be removed at 5-minutes interval until the patient has only 2 restraints on. Both the remaining restraints should be removed at the same time, because it is inadvisable to keep a patient in only one restraint. Intoxicated persons should be restrained in left lateral decubitus position to avoid aspiration.

Pharmacological Intervention

Benzodiazepines (BZD)

Lorazepam is a good choice when treating an acute episode of agitation, especially when aetiology is not clear, such as when a patient with a history of schizophrenia may actually be withdrawing from alcohol.

Doses: 2 to 4 mg slow intravenously (1 to 2 mL), rate 2 mg (1 mL)/min. It may be repeated if necessary up to 10 mg per day. Vital signs should be monitored.

Neuroleptics

Haloperidol 5 to 10 mg intramuscularly can be repeated every half an hour to one hour till the patient is calm (maximum 15 to 30 mg per day). Patient should be monitored for extra-pyramidal side-effects.

Yet another approach is to use a combination of injectable haloperidol and promethazine as they can be mixed in the same syringe. This combination can also be sequentially used with iniectable lorazepam.

Atypical antipsychotics

Olanzapine is effective in reducing acute agitation in patients with schizophrenia, bipolar disorder, schizo-affective disorders and dementia. It exhibits less extra-pyramidal side-effects than haloperidol. Optimal dose in adult is 10 mg intramuscularly. Recommended dose in dementia is 2.5 mg. All the above-mentioned drugs may be given orally if the patient accepts the drug orally. After controlling the acute excitement appropriate long-term management should be started. A combination of injectable olanzapine and lorazipam can also be used in severely agitated patients.

Electroconvulsive therapy as such is not a treatment for excitement or violence *per se*. When used, there should be a clear indication for its use and that should be recorded in the case file.

SUICIDAL ATTEMPTS

Suicide is self-inflicted deliberate self-harm resulting in death with evidence that the person is intended to die.

Suicidal attempt is self-injurious behaviour or unsuccessful suicidal act with non-fatal outcomes. Suicidal patient is one who unsuccessfully attempts suicide or demonstrates suicidal ideation, or harbours suicidal intent, or threatens to commit suicide.

Common Causes of Suicide

Common causes of suicide include depression, schizophrenia, drug dependence, bipolar disorder, adjustment disorder and personality disorder.

Management of Suicidal Patients

It obviously lies in preventing the act. In the emergency room, a patient should be assessed in an empathetic manner. They should be asked about suicidal thinking, intent and plans. A definite diagnosis should be made before starting treatment in such cases.

Hospitalisation

For patients who are at high risk for suicide. They should be regularly monitored and treatment should be started according to the underlying disorder. Patients who are not severely suicidal can be sent home after instituting appropriate medications for the underlying disorder. Relatives of the patient should be informed about the danger and they should be asked to keep a close watch on the patient. The patient should not have access to large amount of medications and drugs should be given under supervision.

Pharmacotherapy

BZDs, non-benzodiazepine hypnotics and quetiapine (in low doses) may be given for sleep disturbance and anxiety symptoms. Anti-depressants are to be given in depression. Lithium may be given when indicated as it has got anti-suicidal role. Anti-psychotics are to be prescribed for psychosis.

Electroconvulsive therapy (ECT)

It is reserved for severely suicidal, with catatonic, symptoms. It acts faster. Any underlying physical disorder should be treated.

Long-term therapy

After the management of acute problem, maintenance therapy and other therapies should be started.

EXTRA-PYRAMIDAL SIDE-EFFECTS OF NEUROLEPTICS

Acute Dystonia

This is an abnormal posture produced by sustained involuntary contraction of muscles of different body parts. It may present as trismus, oculogyric crisis, torticollis, blepharospasm, etc. It is a very painful condition and fatalities may occur if the laryngeal muscles are involved. History should be present of taking a neuroleptic/anti-dopaminergic agent.

Treatment consists of antihistaminics like promethazine: 50 mg intravenoulsy/intramuscularly and anti-cholinergics like benzatropine 1 to 2 mg intravenoulsy/intramuscularly. Oral drugs should be started after the acute crisis is over. Trihexyphenidyl (6 to 10 mg per day in divided doses) may be given for this purpose.

Akathisias

It consists of inability to remain seated and is commonly associated with repetitive shifting of weight, pacing or rocking the trunk when standing. There is an inner sense of restlessness. The treatment is propranolol 40 to 80 mg per day. Benzo-diazepine may be given.

Neuroleptic Malignant Syndrome (NMS)

It is uncommon but potentially fatal. It occurs in 0.5% of patients who are on neuroleptics. It is characterised by mental status changes, confusion, disorientation, rigidity, autonomic instability and temperature dysregulation. Laboratory findings include raised CPK-MM, increased white blood cells, myoglobinuria and altered liver function tests.

Management of NMS

Discontinue the neuroleptic medication immediately. Supportive care (intensive care unit care is preferred) with rehydration should be given to manage vitals. Dantrolene sodium 2 to 3 mg per kg intravenously 3 to 4 times per day or bromocriptine is started with 2.5 mg thrice a day and with gradual increment to maximum daily dose of 60 mg. For management of psychiatric symptoms in such patients after resolution of ICF, depot preparations of anti-psychotics and other high potency conventional anti-psychotics should be avoided.

STATE OF ACUTE ANXIETY AND PANIC

Anxiety is characterised by a feeling of fear accompanied by somatic signs of autonomic nervous system hyperactivity.

Primary psychiatric condition causing anxiety includes generalised anxiety disorder, panic disorder depression, phobia substance abuse, PTSD, acute stress reaction and sometimes schizophrenia.

Medical problem causing anxiety should be differentiated from primary psychiatric disorder. Medical conditions that may present with anxiety symptoms are:

1. Cardiovascular—angina, arrhythmias, valvular diseases
2. Metabolic—hyperthyroidism, hyperadrenalism, hypoglycaemia, hypocalcaemia
3. Haematological—anaemia
4. Respiratory—asthma, COPD
5. Secretory tumours—carcinoid, insulinomas, phaeochromocytoma
6. Iatrogenic—sympathomimetic, stimulants, dopaminergics, anti-cholinergics drugs

Treatment

Provide safe and protective environment and consult physician for medical conditions if any for acute stress, when immediate relief is required lorazepam is given, oral BZDs, alprazolam can also be given.

Primary panic disorder requires maintenance therapy. Serotonin selective re-uptake inhibitors are the treatment of choice. Tricyclic anti-depressants and alprazolam, etc. may be given.

LITHIUM TOXICITY

Lithium toxicity presents with tremor, dysarthria, ataxia, altered sensorium and incoordination. Treatment of lithium toxicity follows the following outlines: stopage of lithium, assessment of serum level of lithium, hydration of the patient, and management of physical complications.

STUPOR

It is defined as a clinical syndrome of akinesis and mutism, but with relative preservation of conscious awareness. It is often associated with catatonic signs and symptoms. Stupor is not a diagnosis but a symptom that is seen in a number of clinical conditions, both psychiatric and physical. The common causes of psychiatric stupor are catatonic schizophrenia, depressive stupor and dissociative stupor. Among the medical disorders, organic cerebral diseases constitute a major cause of stupor. Energetic management is required as the nutrition and hydration are compromised due to poor intake. Stupor accompanied by catatonic symptoms should be treated by ECT.

Hysterical Stupor

This is of sudden onset, preceded by a stressful stimulus.

Treatment

Understanding and resolution of stressful environment factor (remove the attention of relatives) is important. Therapy should be supportive. Medications to treat co-morbid anxiety or depression should be given.

DELIRIUM

It is a disturbance in the state of consciousness; characterised by confusion, disorientation, restlessness, affective lability and perceptual disturbances (visual, auditory). It occurs with relatively acute onset and is associated with distractibility, short-term memory impairment and decreased attention span.

Delirium invariably results from an acute organic disturbance although rarely it may be mimicked by certain psychiatric disorder like brief psychotic episode or mania.

Common Causes of Delirium

Common causes of delirium are given in **Table 3**.

Table 3: Common Causes of Delirium

Infection
High grade fever cerebral malaria septicaemia
Meningitis
Encephalitis
Acquired immunodeficiency syndrome
Metabolic disorders
Electrolyte imbalance
Hypo-/hyperglycaemia
Hepatic encephalopathy
Uraemia
Acidosis
Porphyria
Endocrinal imbalance
Hypothyroidism
Hyperthyroidism
Cushing's syndrome
Addison's disease
Vitamin deficiency
Wernicke-Korsakoff's syndrome
Seizure disorder
Head injury
Substance use disorders
Alcohol (intoxication/withdrawal)
Sedatives
Hypnotics
Drug-induced
Anti-cholinergics
Sympathomimetics
Miscellaneous
Systemic lupus erythematosus
Para-neoplastic syndrome
Hyperviscosity syndrome
Toxins

Management

Agitated patients must be protected from harm. Physical restrains may be necessary in some cases. After safety is ensured, a physical and mental status examination should be done. Relevant laboratory tests should be performed. Identification of cause and its immediate correction; e.g. 50 mg of 50% dextrose intravenously for hypoglycaemia, oxygen for hypoxia, 100 mg of vitamin B1 (thiamine) intravenously for thiamine deficiency; intravenous fluids for fluid and electrolyte imbalance. For agitation, BZDs (diazepam 10 mg or lorazepam 2 mg intravenous) or antipsychotic (5 mg haloperidol intramuscularly) or olanzapine may be given. Supportive medical and nursing care is provided. Specific treatment of the underlying cause of delirium should be initiated once the diagnosis is established.

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22.9 Psychotherapy

Vidyadhar Watve

DEFINITION

Strupp defined psychotherapy as 'systematic use of a human relationship for therapeutic purposes of alleviating emotional distress by affecting enduring changes in a patient's thinking, feelings, and behaviour'.

TYPES OF PSYCHOTHERAPIES

Psychoanalysis

Psychoanalysis was introduced by Sigmund Freud.

Principle

To uncover unconscious processes responsible for the problem.

The process lasts for an hour; frequency is 3 to 5 sessions/week, and continues leaning away from the analyst. The patient associates freely narrating anything which comes to his mind, (free association) his fantasies and his dreams. Analyser makes the patient aware of his unconscious processes. The therapy sessions go on for many years. The patient brings about change in his maladaptive behaviour by gaining insight. Intelligent patients with mild-to-moderate psychopathology may benefit from this therapy.

Disadvantage

It is time consuming and expensive. It does not allow simultaneous use of medications.

Psychoanalytically Oriented Psychotherapy

The basic concepts are derived from psychoanalysis. This is less intensive than psychoanalysis. The psychoanalytic psychotherapist is more active and helps patient to understand his inner subjective world to gain understanding of the psychological problem. Each session lasts for an hour, frequency is reduced and may continue for a long time; may or may not allow simultaneous use of medications.

Patients are seen once or twice a week. Patient meets a psychiatrist. The goal is to support the day-to-day problems without leading with unconscious factors; uses various techniques like, ventilation, guidance, environmental manipulation, counselling. Medications are permitted and healthy dependence between patient and the therapist is allowed. However, a greater emphasis is placed on day-to-day reality issues.

These therapies have limitations and have not stood the test of time against other therapies.

Behaviour Therapy

Behaviour therapy (BT) is the application of principles of learning to reduce or culminate maladaptive behaviour and promote desired behaviour in a client. Maladaptive behaviour is reduced by extinction process punishing (punishment, aversion therapy) or by reinforcing desirable behaviour. There are several BT techniques, e.g. aversion therapy, token economy, systematic desensitisation, flooding and assertiveness training. BT is useful in treatment of mental retardation, chronic schizophrenia, agoraphobia, simple phobia, alcoholism and depression.

Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT), developed by Aaron Beck, is based on the hypothesis that the behaviour is determined by the way in which a person thinks about himself and his role in the society. Maladaptive behaviour is secondary to his distorted thinking which can lead to changes in his mood. The therapy is aimed at changing person's distorted thinking so that it changes his mood and behaviour. CBT is extensively used in depression, substance use disorders, schizophrenia, mild-to-moderate depression, anxiety disorders, personality disorder and bipolar disorder. Sessions are planned and frequency is decided. Therapist actively guides the person to understand and deal with distorted thinking. CBT is scrutinised scientifically and found to be effective in majority of psychiatric disorders.

Interpersonal Psychotherapy

This therapy is based on the concept that psychiatric problems disturb interpersonal relationship and aims to improve interpersonal skills. Patient is seen once weekly for twelve to fourteen weeks. The therapy is used in non-bipolar disorder and non-psychotic depression on outpatient basis. Anti-depressants are used along with this therapy.

Group Therapy

Patients with similar problems or different problems can be treated together to save time and cost. In addition, a patient in group therapy gets immediate feedback from other patients. Group therapy also offers an advantage of observing about his relational abilities and problem behaviour to a variety of people. Sharing emotional problems and learning new skills in a group encourages the coping behaviour. The direct dependency on the therapist is reduced. Alcoholics anonymous (AA) is an example of a large peer-run group for clients who are having alcohol related problems.

Hypnosis

This therapy consists of producing altered state of consciousness through various methods of induction. In these states, the patient is amenable to suggestion, which can bring about change in his behaviour. Hypnosis can be used in many disorders like anxiety disorders, nicotine dependence, sexual disorders and dissociative states.

Biofeedback

A patient is attached to biofeedback machine which gives information through sound or light about his physiologic functions, mainly related to muscular tone, brainwaves (ECT) and autonomic nervous system (e.g. pulse/blood pressure). The goal of treatment is to reduce arousal and anxiety by altering

feedback (sound or light). It is used to manage the tension states associated with migraine, hypertensions and tension headaches.

PERSONALITY DISORDERS

General Considerations

Hippocrates' description of four temperaments is one of the earliest descriptions of personality types and disorders, viz. melancholic (pessimistic), sanguine (optimistic), choleric (irritable) and phlegmatic (apathetic). The term personality is used to describe a person's characteristic behaviour in response to his or her inner and outer experiences.

Definition

A personality disorder is diagnosed when an individual has personality traits, which are inflexible, maladaptive and cause subjective distress and impairment in functioning.

Patient with personality disorders are seen by clinicians in outpatient as well as indoor settings. In the general population, the prevalence is between 10% and 15%.

Aetiology

Earliest theories were mainly psychoanalytic emphasising the contribution of external factors, such as pathological or inadequate parenting.

Subsequent advances in genetic and neurobiology research has identified genetic predisposition in different personality disorders as well as various neurobiological abnormalities such as malfunction of serotonin system.

Available data now suggest that, like other psychiatric disorders, personality disorders result from a complex interaction between all these factors.

Classification of Personality Disorders

At present, 10 individual personality disorders are identified (DSM IV TR). A skilled interview by experienced clinicians is the mainstay of personality disorder diagnosis. The following is the brief description of each of different personality disorders.

Paranoid personality disorder

Persons with paranoid personality disorder are characterised by long-standing suspiciousness and mistrust of persons in general. They refuse responsibility for their own acts and feelings and assign responsibility to others. They are often hostile, irritable, and angry. Persons with paranoid personality disorder are affectively restricted and appear to be unemotional. They pride themselves on being rational and objective, but such is not the case. They lack warmth and are impressed with, and pay close attention to, power and rank. It is more common among men than women.

Schizoid personality disorder

Schizoid personality disorder is diagnosed in patients who display a lifelong pattern of social withdrawal. Persons with schizoid personality disorder seem to be cold and aloof; they display a remote reserve and show no involvement with everyday events and the concerns of others. They appear quiet, distant, seclusive, and unsociable. They may pursue their own lives with remarkably little need or longing for emotional ties, and they are the last to be aware of changes in popular fashion. The life histories of such persons reflect solitary interests and success at non-competitive, lonely jobs that others find difficult to tolerate. Their sexual lives may exist exclusively in fantasy, and they may postpone mature sexuality indefinitely. Men may not marry because they are unable to achieve intimacy; women may passively agree to marry an aggressive man who wants the marriage. Persons with schizoid personality disorder usually reveal a lifelong inability to express anger directly.

Schizotypal personality disorder

Persons with schizotypal personality disorder are strikingly odd or strange, even to laypersons. Patients exhibit disturbed thinking and communication. Although frank thought disorder is absent, their speech may be distinctive or peculiar, may have meaning only to them and may often need interpretation. Like patients with schizophrenia, those with schizotypal personality disorder may not know their own feelings and yet are exquisitely sensitive to, and aware of, the feelings of others, especially negative affects like anger. These patients may be superstitious or claim powers of clairvoyance and may believe that they have other special powers of thought and insight. Their inner world may be filled with vivid imaginary relationships and child-like fears and fantasies. They may admit to perceptual illusions or macropsia and confess that other persons seem wooden and all the same.

Because persons with schizotypal personality disorder have poor interpersonal relationships and may act inappropriately, they are isolated and have few, if any, friends.

Anti-social personality disorder

Anti-social personality disorder is an inability to conform the social norms that ordinarily govern many aspects of a person's adolescent and adult behaviour. Although characterised by continual anti-social or criminal acts, the disorder is not synonymous with criminality. Patients with anti-social personality disorder can often seem to be normal and even charming and ingratiating. Their histories, however, reveal many areas of disordered life functioning. Lying, truancy, running away from home, thefts, fights, substance abuse and illegal activities are typical experiences that patients report as beginning in childhood. Suicide threats and somatic pre-occupations may be common.

These patients are extremely manipulative and can frequently talk to others into participating in schemes for easy ways to make money or to achieve fame or notoriety. These schemes may eventually lead the unwary to financial ruin or social embarrassment or both. Those with this disorder do not tell the truth and cannot be trusted to carry out any task or adhere to any conventional standard of morality. Promiscuity, spousal abuse, child abuse, and drunk driving are common events in their lives. A notable finding is a lack of remorse for these actions; that is, they appear to lack a conscience.

Borderline personality disorder

Patients with borderline personality disorder are characterised by extraordinarily unstable affect, mood, behaviour, object relations, and self-image. They almost always appear to be in a state of crisis. Mood swings are common. Patients can be argumentative at one moment, depressed the next, and later complain of having no feelings. The behaviour of patients with

borderline personality disorder is highly unpredictable and their achievements are rarely at the level of their abilities. The painful nature of their lives is reflected in repetitive self-destructive acts. Such patients may slash their wrists and perform other self-mutilations to elicit help from others, to express anger, or to numb themselves to overwhelming affect.

Because they feel both dependent and hostile, persons with this disorder have tumultuous interpersonal relationships. They can be dependent on those to whom they are close and when frustrated can express enormous anger toward their intimate friends. Patients with borderline personality disorder cannot tolerate being alone and they prefer a frantic search for companionship, no matter how unsatisfactory, to their own company.

Histrionic personality disorder

Persons with histrionic personality disorder are excitable and emotional, and behave in a colourful, dramatic, extroverted fashion. Accompanying their flamboyant aspects, however, is often an inability to maintain deep, long-lasting attachments. Persons with histrionic personality disorder show a high degree of attention-seeking behaviour. They tend to exaggerate their thoughts and feelings and make everything sound more important than it really is. They display temper tantrums, tears, and accusations when they are not the centre of attention or are not receiving praise or approval. Seductive behaviour is common in both sexes. Sexual fantasies about persons with whom patients are involved are common, but patients are inconsistent about verbalising these fantasies and may be coy or flirtatious rather than sexually aggressive. Their need for reassurance is endless. They may act on their sexual impulses to reassure themselves that they are attractive to the other sex. Their relationships tend to be superficial, however, and they can be self-absorbed, and fickle. Their strong dependence needs make them overly trusting and gullible.

Narcissistic personality disorder

Persons with narcissistic personality disorder are characterised by a heightened sense of self-importance and grandiose feelings of uniqueness. Persons with narcissistic personality disorder have a grandiose sense of self-importance; they consider themselves special and expect special treatment. Their sense of entitlement is striking. They handle criticism poorly and may become enraged when someone dares to criticise them, or they may appear completely indifferent to criticism. Persons with this disorder want their own way and are frequently ambitious to achieve fame and fortune. Their relationships are fragile, and they can make others furious by their refusal to obey conventional rules of behaviour. Interpersonal exploitiveness is common place. They cannot show empathy, and they feign sympathy only to achieve their selfish ends. Because of their fragile self-esteem, they are prone to depression. Interpersonal difficulties, occupational problems, rejection and loss are among the stresses that narcissists commonly produce by their behaviour—stresses they are least able to handle.

Avoidant personality disorder

Persons with avoidant personality disorder show extreme sensitivity to rejection and may lead a socially withdrawn life. Although shy they are not asocial and show a great desire for companionship, but they need unusually strong guarantees of uncritical acceptance. Such persons are commonly described as having an inferiority complex. Hypersensitivity to rejection by others is the central clinical feature of avoidance personality disorder, and patients' main personality trait is timidity. When talking with someone, they express uncertainty, show a lack of self-confidence and may speak in a self-effacing manner. They are apt to misinterpret other persons' comments as derogatory or ridiculing. The refusal of any request leads them to withdraw from others and to feel hurt. In the vocational sphere, patients with avoidant personality disorder often take jobs on the sidelines. They rarely attain much personal advancement or exercise much authority but seem shy and eager to please. These persons are generally unwilling to enter relationships unless they are given an unusually strong guarantee of uncritical acceptance. Consequently, they often have no close friends or confidants.

Dependent personality disorder

Persons with dependent personality disorder are characterised by a pervasive pattern of dependent and submissive behaviour. They cannot make decisions without an excessive amount of advice and reassurance from others. They avoid positions of responsibility and become anxious if asked to assume a leadership role. They prefer to be submissive. When on their own, they find it difficult to persevere at tasks but may find it easy to perform these tasks for someone else. Because persons with the disorder do not like to be alone, they seek out others on whom they can depend; their relationships are thus distorted by their need to be attached to another person. In folie a deux (shared psychotic disorder), one member of the pair usually suffers from dependent personality disorder; the submissive partner takes on the delusional system of the more aggressive, assertive partner on whom he or she depends. Pessimism, self-doubt, passivity and fears of expressing sexual and aggressive feelings all typify the behaviour of persons with dependent personality disorder. An abusive, unfaithful or alcoholic spouse may be tolerated for long periods to avoid disturbing the sense of attachment.

Obsessive-compulsive personality disorder

The essential feature of the disorder is a pervasive pattern of perfectionism and inflexibility. Persons with obsessive-compulsive personality disorder are preoccupied with rules, regulations, orderliness, neatness, details and the achievement of perfection. These traits account for the general constriction of the entire personality. They insist that rules be followed rigidly and cannot tolerate what they consider infractions. Accordingly, they lack flexibility and are intolerant. They are capable of prolonged work provided it is routinised and does not require changes to which they cannot adapt.

Persons with obsessive-compulsive personality disorder have limited interpersonal skills. They are formal and serious and often lack a sense of humour. They alienate persons, are unable to compromise, and insist that others submit to their needs. They are, however, eager to please those whom they see as more powerful than they are, and they carry out these persons' wishes in an authoritarian manner. Because they fear making mistakes, they are indecisive and ruminate about making decisions. Although a stable marriage and occupational adequacy are common, persons with obsessive-compulsive personality disorder have few friends. Anything that threatens to upset their

perceived stability or the routine of their lives can precipitate a great deal of anxiety otherwise bound up in the rituals that they impose on their lives and try to impose on others.

Passive-aggressive personality disorder

Persons with passive-aggressive personality disorder are characterised by covert obstructionism, procrastination, stubbornness and inefficiency. Such behaviour is a manifestation of passively expressed underlying aggression. In DSM-IV-TR the disorder is also called negativistic personality disorder.

Depressive personality disorder

Persons with depressive personality disorder are characterised by life-long traits that fall along the depressive spectrum. They are pessimistic, anhedonic, duty bound, self-doubting and chronically unhappy.

Sadistic personality disorder

Sadistic personality disorder is not included in DSM-IV-TR, but it still appears in the literature and may be of descriptive use. Beginning in early adulthood, persons with sadistic personality disorder show a pervasive pattern of cruel, demeaning, and aggressive behaviour that is directed toward others. Persons with this disorder like to humiliate.

TREATMENT

Personality disorders are evident since adolescence or young adulthood; but they come to the attention of the clinician usually when these individuals develop a psychiatric disorder like major depression, anxiety disorder, schizophrenia or substance abuse. This is mainly because individuals with personality disorder do not recognise their maladaptive traits as undesirable or needing to be changed.

Treatment is difficult, therefore, and unlikely to result in the development of a fully healthy personality. Psychotropic drug therapy is of limited use but psychotherapy, especially cognitive behavioural therapy, has shown encouraging results demean persons in front of others and have usually treated or disciplined persons uncommonly harshly, especially children. In general, persons with sadistic personality disorder are fascinated by violence, weapons, injury, or torture.

RECOMMENDED READINGS

1. Dewan MJ, Steenbarger BN, Greenberg RP. *The Art and Science of Brief Psychotherapies: A Practitioner's Guide*. Washington, DC: American Psychiatric Publishing Inc; 2004.
2. Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry;* 9th Ed. Philadelphia: Lippincott Williams and Wilkins; 2003.

22.10 Biological and Somatic Treatments of Psychiatric Disorders

E Mohan Das

The ever-growing knowledge regarding the biological basis of psychiatric disorders has helped in the discovery of new and improved treatment modalities. Following is a brief overview of the common somatic treatments in psychiatry.

ANTI-PSYCHOTICS

The anti-psychotic era began with the discovery of chlorpromazine by Charpentier and its introduction to psychiatry by Delay and Deniker in 1952.

Classification

Anti-psychotic agents are classified as typical and atypical anti-psychotics. The dosage, mode of action and adverse reactions are shown in **Tables 1 and 2**.

Additionally, a recent criterion added to the definition is its efficacy in treating the negative symptoms of schizophrenia. From pharmacologic point of view atypical anti-psychotics are serotonin dopamine antagonists (SDA), multi-acting receptor-targeted anti-psychotics (MARTA), partial dopamine receptor agonists or dopamine system stabilisers, and combined D_2/D_3 receptor antagonists (**Tables 2 and 3**).

Mechanism of Action

Conventional anti-psychotics act by blocking the post-synaptic D_2 receptor. D_2 occupancy of 60% to 75% is needed for anti-psychotic action, and more than 80% or occupancy results in extrapyramidal symptoms EPS. The different dopaminergic pathways explain the effects and side-effects of anti-psychotics (**Table 3**). Mode of action of SDA is shown in **Table 4** (serotoninergic receptor antagonism). In addition to the post-synaptic dopaminergic antagonism, it antagonises the $5HT_{2A}$ serotoninergic receptor.

Therapeutic Indications

Anti-psychotic drugs have multiple uses in psychiatry in different dosages. These are used in treatment of psychosis like acute psychotic episodes; schizophrenia, delusional disorders acute and transient psychotic disorders, and schizoaffective disorders. These groups of drugs are also used in acute manic and hypo-manic states and also in organic brain syndromes with psychosis.

The atypical anti-psychotics are approved by US FDA for treatment of an acute manic episode, and some are approved for the maintenance treatment of bipolar disorders, depression when associated with psychotic symptoms.

Table 1: Typical Anti-Psychotics

	Potency	Dose (mg/day)	Adverse Effects			
			Sedative	Hypotensive	Anticholinergic	EPS
Phenothiazines						
Aliphatic:						
Chlorpromazine	Low	300 to 800	High	High	Medium	Low
Triflupromazine	Low	100 to 150	High	High	Medium	Low
Piperazine:						
Trifluoperazine	High	6 to 20	Medium	Low	Low	High
Fluphenazine	High	1 to 20	Medium	Low	Low	High
Perphenazine	Medium	8 to 40	Low	Low	Low	High
Prochlorperazine	Medium	40 to 150	Low	Low	Low	High
Piperidine:						
Thioridazine	Low	200 to 700	Low	High	High	Low
Mesoridazine	Low	75 to 300	Medium	Medium	Medium	Medium
Thioxanthines						
Chlorprothixine	Low	50 to 400	Medium	Medium	Medium	Low
Thiothixine	High	6 to 30	Low	Low	Low	High
Flupenthixol	High	3 to 15	Low	Low	Low	High
Butyropheraphenones						
Haloperidol	High	6 to 20	Low	Low	Low	High
Trifluperidol	High	1 to 8	Low	Low	Low	Low
Penfluridol	Medium	20 to 60	Low	Low	Low	High
Dihydroindole						
Molindone	Medium	50 to 100	Medium	Low	Medium	High
Diphenylbutylpiperidine						
Pimozide	High	1 to 10	Low	Low	Low	High
Dibenzoxazepine						
Loxapine	Medium	60 to 100	Medium	Medium	Medium	High

The other indications are to use in low dosages in anxiety disorders, borderline personality disorder, eating disorders, impulse control disorders, aggression and self-injurious behaviour in mental retardation and autistic spectrum disorders, and also along with stimulants in attention deficit disorders especially with co-morbid oppositional defiant or conduct disorder. They are used to treat substance-induced psychotic disorders, to control psychotic symptoms in dementia and other organic psychosis and in delirium.

Anti-psychotics are used in the treatment of tic disorders (including Tourette's syndrome), hemiballismus, and Huntington's disease. Anti-psychotics are also used in treatment of Nausea, emesis, intractable hiccups.

Adverse Effects

The common side-effects of anti-psychotics are the extra-pyramidal syndromes that include Parkinsonism, dystonia, akathisia, neuroleptic malignant syndrome (NMS) and tardive dyskinesia (TD) (all these side-effects are minimal with atypical anti-psychotics). The other side-effects include hyper-

Table 2: Atypical Anti-Psychotics

	Dose (mg/day)	Adverse Effects			
		EPS	Anticholinergic	Prolactin	Weight gain
Serotonin dopamine antagonists					
Benzisoxazole					
Risperidone	1 to 16	Low to moderate	Low to moderate	Moderate	Moderate
Benzisothiazolyl					
Ziprasidone	40 to 160	0 to Low	Low	Low	0 to Low
Multi-acting receptor-targeted antipsychotics					
Dibenzodiazepine					
Clozapine	300 to 900	0 to Low	High	0 to Low	High
Thienobenzodiazepine					
Olanzapine	5 to 30	Low	Moderate	Low	High
Dibenzothiazepine					
Quetiapine	300 to 800	0 to Low	Low to moderate	Low	Moderate
Partial dopamine agonist					
Quinolonone					
Aripiprazole	15 to 30	0 to Low	Low	0 to Low	0 to Low
D2/D3 antagonists					
Substituted benzamides					
Amisulpride	400 to 1200	Low to moderate	Low	High	Low
Sulpiride	200 to 1200	Low to moderate	Low	High	Low to moderate

Table 3: Dopaminergic Pathways Targeted by Anti-Psychotics

Pathway	Role	Action
Mesolimbic pathway	Dopaminergic excess in this pathway produces positive symptoms	Reduces dopaminergic transmission to alleviate positive symptoms
Mesocortical pathway	Hypodopaminergic state in this pathway produces negative symptoms	Atypicals potentially increase dopamine content here to alleviate negative symptoms
Nigrostriatal pathway	Involved in the fine tuning of motor function	D_2 blockade causes Parkinsonism Dystonia Akathisia Neuroleptic malignant syndrome Tardive dyskinesia (? dopaminergic super sensitivity)
Tuberoinfundibular pathway	Neuroendocrine regulation	D_2 blockade causes Hyperprolactinaemia Amenorrhoea, galactorrhoea, loss of libido in females, impotence, loss of libido, gynaecomastia, low sperm count, feminisation in males

Table 4: Mode of Action of Serotonin Dopamine Antagonists (SDA)

Post-synaptic dopaminergic mechanism
- In limbic area reduces positive symptoms

5HT2A (serotoninergic) antagonism
- Releases serotoninergic inhibition of dopamine
- In hypodopaminergic state in frontal areas—reduces negative symptoms
- In nigrostriated region reduces SPS

prolactinaemia; anticholinergic effects like dry mouth, visual blurring, and constipation; α_1 adrenergic blockade causing postural hypotension, palpitation; miscellaneous effects like drowsiness, lethargy, confusion, seizures, sialorrhoea (clozapine), corneal/lenticular pigmentation, retinal degeneration (thioridazine), and hypersensitivity reactions like skin rashes, urticaria, photosensitivity, and cholestatic jaundice. ECG changes and cardiac arrhythmias are also seen and QT prolongation is noted with ziprasidone, sertindole, thioridazine and pimozide. Clozapine is reported to cause eosinophilic myocarditis and sudden death. Some of the atypical antipsychotics may cause treatment emergent obsessive compulsive disorder (OCD). Though potentially fatal, the incidence of agranulocytosis with clozapine is very low (0.38%). The atypicals like clozapine and olanzapine run a higher risk of weight gain, elevated blood sugar, and elevated levels of cholesterol, lipoproteins and triglycerides and the risk of metabolic syndrome. There are reports of increased cerebrovascular events in geriatric patient prescribed atypicals especially risperidone and olanzapine.

ANTIDEPRESSANTS

Antidepressants are a heterogeneous group of compounds primarily used for the treatment of depression. The introduction of monoamine oxidase inhibitors and imipramine opened the floodgates for the development of newer drugs in the antidepressant armamentarium.

Classification and Mechanism of Action

The antidepressants are classified based on the neuroreceptor targets on which they act modulating the levels of neurotransmitters like serotonin, norepinephrine and dopamine. There are several different pharmacologic actions for more than two-dozen antidepressants (**Table 5**). The immediate clinical response with most antidepressants is due to the increase in levels of the monoamine neurotransmitters. The antidepressants however exert their full clinical response only in a delayed manner. The delayed therapeutic effect probably is by the desensitisation or down regulation of the neurotransmitter receptors. The final common pathway of action of all antidepressants is probably by gene expression and neuroplasticity through the activation or deactivation of vital genes like the brain-derived neurotrophic factor (BDNF) gene among others.

Therapeutic Indications

Antidepressants are mainly used for the treatment of mood disorders; major depression and dysthymia; bipolar depression (SSRIs and bupropion are preferred to TCAs due to the low risk of switch to mania); depression due to general medical condition, premenstrual dysphoric disorder (PMDD) and substance-induced depression; generalised anxiety disorder (GAD); OCD; panic disorder; post-traumatic stress disorder (PTSD); and social phobia. Other indications include eating disorders, insomnia, parasomnias, neuropathic pain, migrainous and nonmigrainous headache, smoking cessation and cocaine detoxification (bupropion), ADHD (atomoxetine, imipramine) attention deficit hyperactivity disorder, irritable bowel syndrome (IBS), impulse control disorders, borderline personality disorders, paraphilias, premature ejaculation, behavioural disturbances in dementia, autism, nocturnal enuresis (TCA), respiratory disorders (SSRI), peptic ulcer (doxepin), movement disorders, chronic fatigue syndrome.

MOOD STABILISERS

Mood stabilisers are drugs used for the acute and maintenance treatment of bipolar disorder. The major mood stabilisers include lithium, anticonvulsants, and atypical anti-psychotics; though some others like calcium channel blockers (CCB) and omega-3 fatty acids exert mood stabiliser effect (**Table 6**).

Lithium

Lithium has proven efficacy in the acute and maintenance treatment of bipolar illness. About 80% of acute mania responds to lithium and it is 70% to 80% effective in the prophylaxis of manic and depressive episodes. Lithium is also effective in the acute treatment of bipolar depression and is a first-line choice though not approved for the same. Lithium is highly renal toxic. It is effective in serum level of 0.6 to 1.2 meq/litre and a constant blood monitoring of serum lithium level along with renal functions are required in patients where lithium is used.

Anticonvulsants

The anticonvulsants usually used as mood stabilisers include valproate, carbamazepine, lamotrigine, gabapentin and topiramate, of which the latter two drugs have not been approved for acute or maintenance treatment but have some evidence regarding its efficacy as a mood stabiliser. Valproate and carbamazepine are approved for the acute treatment of mania, while lamotrigine is approved for the maintenance treatment of bipolar disorder. Valproate and carbamazepine are preferred to lithium in dysphoric mania and mixed state (carbamazepine nowadays is a second-line choice in mania) and are efficacious in the prophylaxis of bipolar disorder though not US FDA approved for the same. Lamotrigine has more impact on the depressive phase of bipolar and has little antimanic property and is not approved for the acute treatment of mania. It is also used as an off label drug for acute treatment of bipolar depression.

Controlled trials also show that valproate, lamotrigine and lithium are efficacious in rapid cycling bipolar disorder. The other anticonvulsant used as putative mood stabilisers include oxcarbazepine, tiagabine, zonisamide, and levetiracetam.

Anti-Psychotics

Almost all atypical anti-psychotics have shown mood stabiliser action, though clozapine is reserved for refractory bipolar disorder. Risperidone, ziprasidone, olanzapine, quetiapine, and aripiprazole are mood stabilisers approved for the treatment of acute mania. The combination of olanzapine with fluoxetine is the only approved treatment for acute treatment of bipolar depression. Aripiprazole and olanzapine are also approved for the maintenance treatment of bipolar disorder. The typical anti-psychotic chlorpromazine also has received approval for the acute treatment of mania. Haloperidol has shown equal efficacy as atypicals in the control of mania especially as adjuvant.

Table 5: Antidepressants/Therapeutic Indication and Adverse Events

Antidepressant Class (Dosage Range in mg/day)	Therapeutic Indication	Adverse Effects
Tricyclics (TCA) Tertiary amines Imipramine (100 to 300) Amitriptyline (100 to 300) Clomipramine (100 to 250) Doxepin (100 to 300) Dosulepin (dothiepin) Secondary amines Nortriptyline (50 to 200)	Major depression, depression due to general medical condition, generalised anxiety disorder (doxepin), panic disorder, OCD (clomipramine), eating disorder, pain disorder, nocturnal enuresis (imipramine), peptic ulcer (doxepin), narcolepsy, nightmare, PTSD, ADHD, sleep walking, sleep terror, premature ejaculation (clomipramine), movement disorder (clomipramine)	Anti-cholinergic effects, nausea, vomiting, sedation, induction of mania, confusion, autonomic effects, cardiac effects, myoclonus, seizure (clomipramine, amoxapine), parkinsonism and NMS (amoxapine), rashes, weight gain, impotence, SIADH. Rare: hepatitis, jaundice, agranulocytosis, leucopaenia, ataxia, peroneal palsies, and paraesthesia
Tetracyclics Mianserin (30 to 100) Amoxapine (100 to 400)		
Monoamine oxidase inhibitors (MAOI) Irreversible, nonselective Isocarboxazid (30 to 60) Phenelezine (15 to 90) Tranylcypromine (20 to 60) Irreversible, MAO B selective Selegiline (20 to 60) Moclobemide (300 to 600)	Major depression, atypical depression, depression due to general medical condition, panic disorder with agoraphobia, PTSD, social phobia, pain disorder, and eating disorder	Orthostatic hypotension, insomnia, weight gain, sexual dysfunction, tyramine-induced hypertensive crisis, paraesthesia, myoclonic jerks, muscle pains, induction of mania, psychotic symptoms Rare: hepatotoxicity, cardiotoxicity, non-tyramine-induced hypertensive crisis
Selective serotonin reuptake inhibitors (SSRI) Fluoxetine (20 to 80) Fluvoxamine (100 to 300) Paroxetine(20 to 60) Sertraline (50 to 200) Citalopram (20 to 60) Escitalopram (10 to 20)	Major depression, atypical depression, dysthymia, bipolar depression, depression due to general medical condition, OCD, panic disorder, PTSD, GAD, eating disorders, premenstrual dysphoric disorder (PMDD), borderline PD, paraphilias, ADHD, behavioural control in dementias and autism, pain disorder, premature ejaculation and syncope	Sexual dysfunction (50% to 80%), nausea, vomiting, diarrhoea, dyspepsia, weight loss or gain, headaches, anxiety (fluoxetine), insomnia or sedation, nightmares, EPS, seizures, anticholinergic effects, SIADH, increased prolactin levels, serotonin syndrome, apathy syndrome and SSRI withdrawal
Norepinephrine reuptake inhibitor (NRI) Reboxetine (4 to 12) Atomoxetine (0.5 to 1.2)	Major depression, dysthymia, social phobia ADHD, drug of choice of adult ADHD	Urinary hesitancy, headache, dizziness, dry mouth, decreased libido, insomnia Nausea, diarrhoea, vomiting, anorexia, dizziness, mood swings, urinary hesitancy, sexual dysfunction
Serotonin norepinephrine reuptake inhibitor (SNRI) Venlafaxine (75 to 375) Duloxetine (30 to 120) Milnacipran (50 to 250)	Major depression, GAD, panic disorder, OCD, social phobia, agoraphobia, ADHD Major depression, diabetic peripheral neuropathy Major depression, pain disorder	Nausea, somnolence, dry mouth, dizziness, nervousness, constipation, asthenia, anorexia, sexual dysfunction, diastolic hypertension (venlafaxine), and withdrawal syndrome
Norepinephrine dopamine reuptake inhibitor (NDRI) Bupropion (150 to 450)	Major depression, bipolar depression, smoking cessation, cocaine withdrawal	Headache, insomnia, nausea, upper respiratory complaints, seizure, hallucinations, delusions, catatonia and delirium
Noradrenergic and specific serotoninergic antidepressant (NaSSA) Mirtazapine (15 to 45)	Major depression, anxiety disorders	Somnolence, dry mouth, increased appetite, constipation, weight gain, dizziness, nightmares, neutropaenia (0.3%), ALT elevation
Serotonin antagonist/reuptake inhibitors (SARI) Trazodone (75 to 600) Nefazodone (100 to 600)	Major depression, insomnia, PTSD, panic disorder, agitation in elderly Major depression, panic disorder, OCD, PMDD, pain disorder	Sedation, orthostatic hypotension, dizziness, dry mouth, headache, gastric irritation, arrhythmias, neutropaenia, priapism
Selective serotonin reuptake enhancer Tianeptine (12.5 to 37.5)	Major depression	Epigastric pain, dry mouth, anorexia, nausea, vomiting, constipation, flatulence; insomnia, drowsiness, nightmares

Table 6: Mood Stabilizers

	Lithium	Valproate	Carbamazepine	Lamotrigine
Half-life	24 hours	8 to 17 hours	24 hours initially, later 12 to 17 hours	25 hours
Starting dose	300 mg bid or tds	20 mg/kg (250 tds)	200 mg bid	25 mg od
Dose range	900 to 1800 mg	750 to 4200 mg	400 to 1600 mg	100 to 500 mg
Onset of action	5 to 14 days	5 to 14 days	5 to 14 days	5 to 14 days
Metabolism	Nil	Hepatic	Hepatic	Hepatic
Serum level	0.6 to 1.2 meq/L (acute)	45 to 25 µg/mL	4 to 12 µg/mL	Not established
Adverse effects	Nausea, diarrhoea, vomiting, tremor, nephrogenic diabetes insipidus, hypothyroidism, cognitive effects, acne and toxicity	GI irritation, nausea, sedation, tremor, weight gain, alopecia, vomiting, diarrhoea, ataxia, polycystic ovarian disease, hepatotoxicity, and agranulocytosis	Rashes, Steven Johnson syndrome, ataxia, vertigo, GI irritation, diplopia, task performance problems, aplastic anaemia, agranulocytosis, pancreatitis, and hepatic failure	Dizziness, ataxia, somnolence, diplopia, headache, nausea, vomiting, rashes, toxic epidermal necrolysis, and Steven Johnson syndrome
Major indications	Acute treatment of mania, maintenance treatment of bipolar	Acute treatment of mania, seizure disorder	Acute treatment of mania, seizure disorder	Bipolar depression, maintenance treatment of bipolar, seizure disorder

Other Mood Stabilisers

Benzodiazepines (especially clonazepam) are used as adjuvants in the treatment of mania. CCBs are used for the control of mania and ultradian bipolar (mood cycling in less than 24 hours). The omega-3 fatty acids also have putative mood stabiliser action and are used in the treatment of mania.

ANXIOLYTICS

Anxiolytics are drugs specifically used to treat and prevent the various anxiety disorders. They are indicated for short-term treatment and long-term prophylaxis of these disorders.

Classification

The drugs used include benzodiazepines, antidepressants, azapirones, sedative antihistaminics, β-blockers, anticonvulsants, anti-psychotics and miscellaneous agents like inositol.

Benzodiazepines

Benzodiazepines are generally used for the emergency and short-term management of anxiety disorders though of late they are recommended for long-term treatment of anxiety. These drugs are used alongside antidepressants and help in allaying the somatic symptoms of anxiety. These drugs activate all three binding sites of the GABA-BZD receptor (subtype of the $GABA_A$ receptor), which results in chloride influx and decreased neuronal excitability. The other indications of benzodiazepines include mixed anxiety and depressive disorder, insomnia, alcohol withdrawal, depression, bipolar disorder, akathisia, agitation, and seizure disorders. The common adverse effects include drowsiness, dizziness, ataxia, falls and fractures (in elderly), disinhibition and respiratory depression (more if combined with alcohol). They are associated with paradoxical aggression, cognitive impairment, hepatic dysfunction, probable teratogenicity, dependence, tolerance and withdrawal syndrome (**Table 7**).

Azapirones

The azapirones like buspirone, gepirone and ipsapirone act via partial agonism of $5HT_{1A}$ receptors and buspirone is beneficial in the treatment of the cognitive symptoms of anxiety. Buspirone is used in GAD, panic disorder, social phobia, and PTSD. They have a delayed onset (2 to 4 weeks) of action. They lack abuse potential and the side-effects include headache, nausea, dizziness and rarely restlessness and insomnia. Buspirone is usually started 5 mg three times a day and then raised every 2 to 4 days, the effective dose range being 15 to 60 mg per day.

Table 7: Benzodiazepines

Drug	Dosage range (mg/day)	Equivalent dose (mg)	Elimination half-life (hours)
Long-acting			
Diazepam	6 to 80	5	20 to 80
Chlordiazepoxide	10 to 150	10	5 to 30
Clonazepam	1 to 4	0.25	18 to 60
Clobazam	30 to 80	5	12 to 60
Intermediate-acting			
Alprazolam	1 to 4	0.5	12 to 15
Lorazepam	2 to 4	1	10 to 20
Oxazepam	30 to 120	15	5 to 20
Temazepam	10 to 30	10	8 to 22
Short-acting			
Triazolam	0.5 to 2	0.25	1.5 to 5

Other anxiolytics

Hydroxyzine, the H_1 antihistaminic, has shown effect at 50 mg per day dosage in GAD. The β-blocker propranolol is used in social phobia (performance anxiety), panic disorder, GAD and PTSD. The usual approach is to use 10 to 40 mg of propranolol half an hour before an anxiety-provoking situation. Anticonvulsants like valproate, carbamazepine, tiagabine, phenytoin, pregabalin and levetiracetam are used for the treatment of GAD, PTSD, social phobia and panic disorder. The atypical anti-psychotics are used in PTSD and to augment antidepressants in OCD. Inositol has been used in the treatment of panic disorder (**Table 8**).

Table 8: Pharmacotherapy of Anxiety Disorder

Disorder	First-Line	Alternatives
OCD	SSRI Clomipramine	Venlafaxine, clonazepam, mirtazapine, anti-psychotics, buspirone, IV clomipramine, anticonvulsants, pindolol, MAOI
Panic disorder	SSRIBZD (immediate control) Certain TCAs	MAOI, anticonvulsants, venlafaxine, mirtazapine, nefazodone, inositol
PTSD	SSRI Serotonergic TCA	Mirtazapine, venlafaxine, MAOI, anticonvulsants, antipsychotics, clonidine, trazodone, propranolol
GAD	SSRI Venlafaxine BZD (immediate control) Certain TCAs	Buspirone, anti-psychotics, hydroxyzine, propranolol, anticonvulsants
Social phobia	SSRI MAOI	RIMA, clonazepam, venlafaxine, reboxetine, propranolol, anticonvulsants, buspirone

ELECTROCONVULSIVE THERAPY

Cerletti and Bini introduced electroconvulsive therapy (ECT) in 1938. It is one of the safest, most effective and yet the most controversial of all treatment modalities in medicine.

Mechanism of Action and Therapeutic Indications

electroconvulsive therapy uses an electrically-induced generalised seizure activity to treat psychiatric disorders (**Table 9**). A wide variety of mechanisms including neuropsychological, neurophy- siological, neurochemical and neuroendocrine are proposed to explain the therapeutic action of ECT. They are effective in the short-term control of various psychiatric disorders listed in **Table 10**.

Technique and Course

Modified ECT is done under short acting general anaesthesia (thiopentone or methohexital) and muscle relaxation (succinyl choline). Brief pulse stimulation is used to produce seizures and is preferred to sine wave stimulation and a seizure of at least 25 seconds is needed for therapeutic effect. The electrode placement is either unilateral (on nondominant hemisphere) or bilateral (bitemporal or bifrontotemporal). Bilateral placement has more rapid clinical response while unilateral placement has lesser cognitive side-effects. ECT is usually given three times a week and the course of ECT varies with the disorder being treated. In catatonia a course consists of 3 to 5 treatments, in depression 6 to 12 treatments, in mania 8 to 20 treatments and in schizophrenia more than 15 treatments.

Contraindications and Adverse Effects

electroconvulsive therapy has no absolute contraindication but it should be used with caution in cerebral aneurysms, intracerebral haemorrhage, raised intracranial tension, recent myocardial infarction and cardiac arrhythmias. Arrhythmias, severe hypertension, phaeochromocytoma and impending retinal detachment. The mortality with ECT is about 0.002% and the common adverse effects include headache, confusion, delirium, and memory disturbance (returns to normal by 6 months). Other adverse effects include fractures, nausea, vomiting and muscle soreness.

Table 9 : Mechanism of Action of Electroconvulsive Therapy

Neurophysiological mechanism
- Anticonvulsant theory
- ↓ Cerebral blood flow
- ↓ Cerebral metabolism
- ↑ Slow wave activity

Neurochemical changes
- ↑ 5HT2a receptors
- ↑ 5HT1a receptor sensitivity
- ↑ Synthesis and utilisation of NE
- ↓ β-receptor
- ↓ α2 adrenoceptor
- ↑ α1 receptor
- ↑ Synthesis and turnover of DA
- ↑ mRNA of D1 and D2 receptors
- ↓ Glutamatergic activity
- ↑ GABAergic function
- ↑ Endogenous opioids
- ↑ Density of specific opioid receptors
- ↓ Melatonin level

Intracellular
- ↑ Brain derived neurotrophic factor (BDNF)

Neuroendocrine
- ↑ Prolactin, corticotrophin, cortisol, oxytocin, vasopressin, β-endorphin

Neuropeptides
- ↑ Thyrotrophin releasing hormone
- ↑ Neuropeptide Y
- ↑ Somatostatin

Table 10: Therapeutic Indications of Electroconvulsive Therapy

Major depressive disorder
- Suicidal or homicidal ideas/attempts
- Stupor
- Psychotic symptoms
- Marked psychomotor retardation or agitation
- Refusal to take food or fluids

Catatonia
- Psychiatric disorders
- Neurologic disorders

Mania
- Life-threatening physical exhaustion
- Treatment resistance

Acute schizophrenia
- Marked positive symptoms
- Catatonia
- Affective symptoms

Pregnant women with suicidal ideas and depression
Geriatric and medically ill patients who cannot take drugs safely
Atypical psychosis
OCD
Delirium
NMS
Hypopituitarism
Intractable seizures
On-off phenomenon of Parkinson's disease

EMERGING TREATMENTS

The emerging biological treatments include repeated transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and magnetoconvulsive therapy (MCT). rTMS involves the use of a magnetic field to inhibit cortical neurons. This is being tried in treatment resistant depression, treatment resistant auditory hallucinations and negative symptoms of schizophrenia. In VNS an implanted pulse generator is used to deliver stimulation of vagus and it has shown 40% response in treatment resistant depression. MCT is a method whereby a varying magnetic field is used to induce a more controlled seizure than what is possible by ECT and can help specific targeting for better response and lesser side-effects.

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Pulmonary Medicine

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23.1 Respiratory System—Structure and Functions

SK Chhabra

PULMONARY ANATOMY

The lungs perform the main function of gas exchange—the uptake of oxygen and expulsion of carbon dioxide, and several other functions including maintenance of acid-base, water balance, defence against invading foreign particles, micro-organisms and generation of several biological active substances and enzymes, and are also involved in metabolism of certain drugs besides providing a portal for administration of certain drugs.

The lungs are lined by the visceral pleura and separated from the chest wall by the parietal pleura, the pleural space being only a potential space with a little fluid to allow smooth movement. The air passage from the nose up to the larynx is called the *upper respiratory tract* and that below is the *lower respiratory tract*.

Upper Respiratory Tract

The *nose* is lined by ciliated columnar epithelium and is richly supplied by blood and nerve endings. It performs the function of olfaction or smelling and filtration, warming, and humidification of inhaled air. The four *paranasal sinuses*, lined by stratified ciliated columnar epithelium, are air-containing cavities in the skull bones found in relation to the nasal cavity. These reduce the weight of the skull and play a role in the voice resonance and temperature regulation.

The pharynx is located posterior to the nasal and oral cavities and has three parts: nasopharynx, oropharynx, and laryngo-pharynx. The lining mucosa changes from ciliated columnar to stratified in the lower part. It is richly supplied by lymphoid tissue that aggregates to form the adenoids in the nasopharynx and lingual, Eustachian and palatine tonsils. The muscles of the pharynx coordinate the swallowing so that aspiration into the larynx is avoided. The *larynx* consists of three articulating cartilages: the thyroid, cricoid, and the arytenoids. The vocal cords extend from arytenoids posteriorly to the thyroid cartilage anteriorly. These are lined by squamous epithelium and the rest of the larynx is lined by ciliated columnar epithelium. Most of the intrinsic muscles of the larynx are supplied by the recurrent laryngeal nerves.

Lower Respiratory Tract (Figure 1)

The airways can be divided into conducting, transitional and respiratory passages according to the nature of function performed. The *conducting airways* include the trachea and the larger cartilaginous bronchi and the more distal membranous, non-cartilaginous bronchioles. These do not take part in gas exchange. The *transitional airways*, consisting of respiratory bronchioles and alveolar ducts, provide a passage as well carry out gas exchange while the most distal zone, the *respiratory zone*, consisting of the alveolar sacs and the alveoli, is responsible for gas exchange.

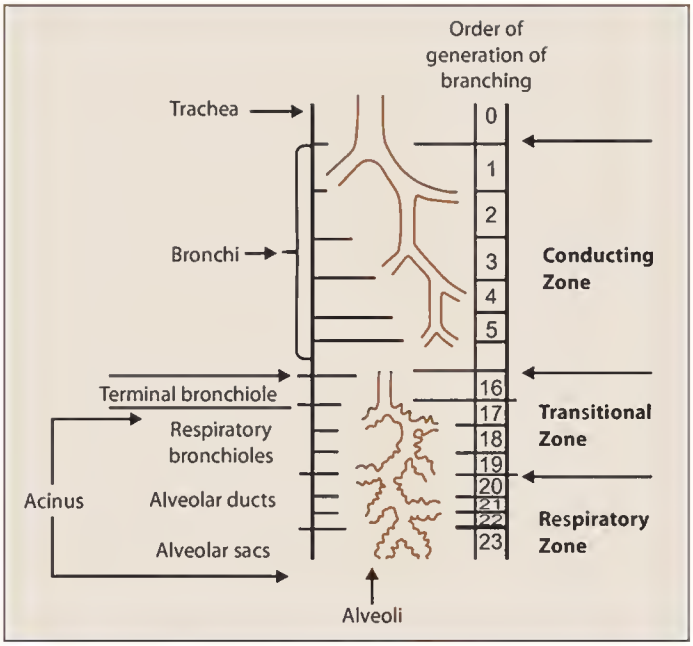


Figure 1: Organisation of the lower respiratory tract.

Conducting Airways (Trachea, Bronchi, and Bronchioles)

The larynx continues as the trachea at the cricoid cartilage enters the thoracic inlet and ends at the carina by dividing into the right and the left main bronchus. Its length varies from 10 to 12 cm; C-shaped cartilages, incomplete posteriorly, encircle it anteriorly and provide stability. It contains rapidly adapting irritant receptors in the epithelium that act as cough receptors and mediate reflex bronchoconstriction. The muscles of the posterior tracheal wall contain slowly adapting stretch receptors that regulate the rate and the depth of breathing. The right main bronchus is wider and is more directly in line with the trachea as compared to the narrower and more horizontal left main bronchus that arises at a sharper angle to the left. The cartilage rings of the bronchi are complete. The two main bronchi give off segmental bronchi (10 on the right and 8 or 9 on the left side) which divide repeatedly finally losing cartilage to become bronchioles, the most distal of which are called the terminal bronchioles (**Figure 2**).

Transitional and Respiratory Zone

The respiratory bronchioles, alveolar ducts, alveolar sacs, and the alveoli constitute the respiratory zone. The respiratory bronchioles, usually up to 3 in order, give rise to up to 9 generations of alveolar ducts. The walls of the respiratory bronchioles contain a little smooth muscle that is also present around the opening of the alveolar ducts. The alveoli are the actual gas exchange area and are present as small outpouchings on the respiratory bronchioles and the alveolar ducts and aggregate to form alveolar sacs at the terminal ends of the alveolar ducts (**Figure 3**). The average number of alveoli is approximately 350×10^6. The total surface area is approximately 40 to 80 m^2.

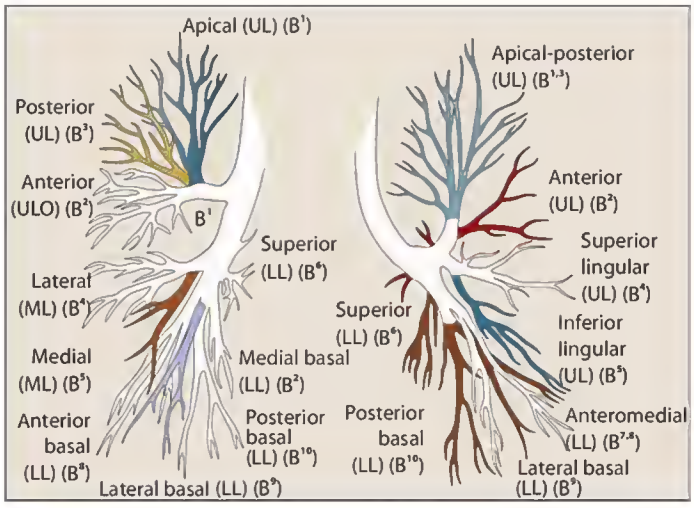


Figure 2: The bronchial tree.

UL = Upper lobe; ML = Middle lobe; LL = Lower lobe.

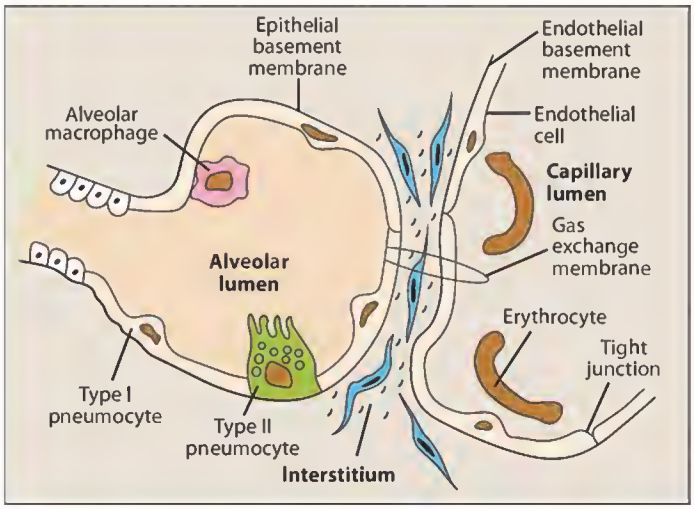


Figure 3: Structure of the alveolus showing the gas exchange membrane and pulmonary interstitium. The alveolar epithelial cells, epithelial basement membrane, pulmonary interstitium, endothelial basement membrane and the endothelial cells constitute the alveolocapillary membrane across which gas exchange occurs.

The part of the lung distal to one terminal bronchiole is called an '*acinus*' and distal to alveolar duct, the '*primary lobule*'. Three to five terminal bronchioles and their acini are bounded by the interlobular septae. This unit is called the '*secondary lobule*'.

Small pores in the alveolar walls, called the *pores of Kohn* provide additional channels of communication between the adjacent alveoli, sometimes even across the segmental boundaries. Additional parallel paths (bronchiolo-alveolar and inter-bronchiolar) or channels may also exist.

Microscopic Anatomy

The trachea is lined by pseudostratified ciliated columnar epithelium rich in goblet cells. The submusoca beneath it contains a few lymphocytes and plasma cells, mast cells (especially in asthmatics), longitudinally arranged elastic fibres and mucosal glands, smooth muscle, nerves and lymphatics. The mucous glands are also present in the larger and medium-sized bronchi. The secretions of these glands contain glycoprotein, lysozyme and lactoferrin.

The mucosa of the main bronchi is similar but becomes thinner and flatter as the airways continue distally. In the respiratory bronchioles, it is cuboidal while in the alveoli, flat and thin cells, the type 1 pneumocytes (90%), provide the surface for gas exchange and have embedded type 2 cuboidal pneumocytes (10%). These latter cells have microvilli and characteristic vacuolar bodies called the lamellar bodies that release the surfactant, a vital lining material that lowers the surface tension of the alveoli at smaller volumes and prevents their collapse. Type 1 cells are more prone to acute lung injury whereas type 2 are more resistant to lung injury and proliferate and differentiate into type1 after lung injury. The mucosa of the large airways contains several types of cells. The *ciliated* cells contain numerous cilia and microvilli on their surface. The cilia move in the direction of the oropharynx providing an escalator for mucous and secretions. The movement of cilia of adjacent cells is co-ordinated to provide an effective wave that moves upwards. The *goblet* cells secrete mucin and are predominantly present in the more proximal airways becoming sparse distally. The *clara* cells with a secretory function and a role in surfactant synthesis are present in larger numbers in the smaller bronchi and the bronchioles. *Serous* cells also perform a secretory function while *basal* cells and *intermediate* cells serve as undifferentiated precursor cells. *Brush* cells are present all over the airways and possibly perform a fluid absorptive function. The *Kulchitsky* or APUD (amine precursor uptake and decarboxylation) cells present in the larger bronchi up to the subsegmental level, may serve a physiological role as chemoreceptors but may also be the precursors for carcinoid and oat cell tumours.

Circulating monocytes migrate into the alveoli traversing the gaps in the capillary endothelial cells to form the alveolar macrophages that provide a phagocytic function as well as an active source of several cytokines and oxidants, and also serve the purpose of antigen-processing.

The alveolocapillary membrane consisting of the alveolar epithelium, its basement membrane, interstitial tissue with a few collagen and elastic fibres and unmyelinated fibres, basement membrane of the capillaries and their endothelium separates the alveolar air from the capillary blood.

Defence, Metabolic and Other Functions

The lungs are equipped with local non-immunological and immunological defence mechanisms that include physical barriers, reflexes including cough and bronchospasm, secretions, and cellular components. The nose and upper respiratory tract filter out large particles in the inhaled air and only particles less than 10 micron manage to reach the lower airways. The mucociliary escalator beats in a coordinated manner to move the trapped particles upwards towards the larynx. The cough and reflex bronchospasm serve to expel inhaled material and limit deeper access.

The bronchial secretions contain substances such as lysozymes, interferon, lactoferrin, etc. having bacteriostatic action as well as the ability to inhibit viral replication. Specific immunological defence mechanisms include lymphocytes, both T and B cells and the macrophages. Lymphocytes are responsible for humoral and antibody-mediated and cell-mediated immunity. Among the immunoglobulins, the predominant are the IgA and IgG. Secretory IgA is of particular importance in respiratory

secretions as it blocks bacterial adherence preventing colonisation and also provides antiviral immunity.

As the lung receives the entire cardiac output, it also serves as a chemical filter for the systemic circulation, protecting against deleterious effects of high levels of several vasoactive substances such as serotonin and norepinephrine. The lung also has a role in the metabolism of bradykinin, endothelin and other peptides.

The lung plays an important role in the maintenance of systemic vascular resistance through the activation of angiotensin II. Other substances that are released from the lung including endothelins and nitric oxide are also involved in the regulation of vascular tone. The lung is a major site for the synthesis and metabolism of eicosanoids.

Blood Supply

The lung receives its blood supply by a dual system, the bronchial arteries supplying oxygenated blood while the pulmonary arteries bring deoxygenated blood for gas exchange. The bronchial arteries are branches of descending aorta but may have other origins. These run along the bronchi and reach as far as the terminal bronchioles. These supply the bronchi, nerves, walls of pulmonary vessels, and intrapulmonary lymph nodes. The veins of the bronchial circulation may drain into the pulmonary veins, left atrium and into the azygous and hemiazygous systems and thence to the right atrium.

The pulmonary artery arises as the outflow of the right ventricle at the pulmonary valve, and divides below the arch of aorta into the right and left branches. These enter the respective hila, although variations are there in the branching pattern, in general these accompany the bronchial tree. The pulmonary trunk and its main branches are elastic arteries and the distal smaller arteries are muscular. The pulmonary circulation is a low-pressure high-capacitance system that accommodates the entire cardiac output. The pulmonary capillaries drain into the pulmonary venous system that finally drains into the left atrium as pairs of pulmonary veins from either lung.

Lymphatics

The lungs are provided with an extensive lymphatic network that maintains fluid balance and provides defence. They drain the fluid from the interstitium. The lymphatic capillaries drain into collecting lymphatics with smooth muscle in their walls and have valves to ensure one-way drainage towards the hilar and the mediastinal lymph nodes. The lymphatics are arranged into a superficial plexus beneath the visceral pleura and a deep plexus in the bronchovascular connective tissue sheath of the airways, the two communicating via lymphatics in the interlobular septa. The branches of the lymphatics accompany the bronchioles and smaller pulmonary arteries and veins. There are no lymphatics in the alveolar walls. The lymph finally flows into the right mediastinal or the thoracic duct. Lymphoid tissue is also present in the lungs along the tracheobronchial tree and also along the vasculature. It participates in antibody and cell-mediated immune responses (**Figure 4**).

Innervation

The afferent pathways originate from sensors in the bronchial epithelium, submucosa, interstitium, and the smooth muscle. Both myelinated and unmyelinated C-fibres are present, the latter being especially prominent in the interstitium where they are thought to be responsible for the J-reflex in response to interstitial oedema. The myelinated fibres serve the stretch and irritant receptors. These fibres travel in the vagus nerve to terminate in the vagal nuclei in the medulla transmitting afferent sensations.

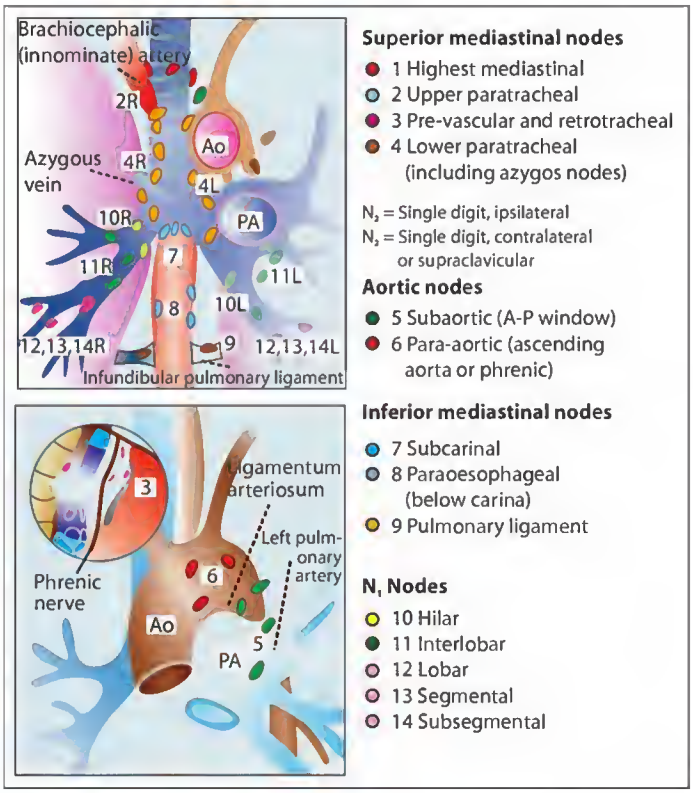


Figure 4: Classification of regional lymph node stations adopted by the American joint committee on cancer (AJCC) and the Union Internationale contre le cancer.

Courtesy: Mountain CF, Dresler CM, Regional lymph node classification for lung cancer staging, Chest 1997; 111: 1718-23.

The efferent pathways reach the lungs through the sympathetic and parasympathetic nervous system. Pre-ganglionic fibres to the sympathetic nerves arise from the upper four or five thoracic paravertebral ganglia while the pre-ganglionic parasympathetic nerves arise from the brainstem motor nuclei associated with the vagus nerve. Post-ganglionic sympathetic fibres terminate near the airway smooth muscle and the glands. The cholinergic activity dominates normally to maintain the bronchomotor tone. Beta-adrenoceptors, mainly the beta-2 subtypes, are present widely throughout the tracheobronchial tree.

ELEMENTARY CONCEPTS IN RESPIRATORY PHYSIOLOGY

Ventilation

The respiratory drive is generated from the medullary centres and transmitted to the diaphragm and the intercostal muscles, the former being responsible for almost 80% of the ventilation. The descent of the diaphragm and expansion of the chest wall create a negative pleural pressure that lowers the alveolar pressure below the atmospheric, thus creating a pressure gradient for air to flow into the lungs. Expiration is a passive process. The upper zones receive more ventilation and the lower zones receive more perfusion.

Airway resistance is the combination of mechanical factors that cause impediment to the flow of air from nose to the alveoli and

back. Due to a tremendous increase in total cross-sectional area, as the bronchial tree divides distally, the resistance is greatest in the larger airways and diminishes distally. Compliance is the property of the lungs to expand in response to an applied change in pressure. Compliance is highest around the resting end-expiratory position and reduces at very high and very low lung volumes. Low compliance indicates a stiff lung.

Gas Exchange

At rest, an adult person utilises 250 mL of oxygen per minute and exhales about 200 mL of carbon dioxide. The diffusion into the blood depends on the pressure gradient across the alveolocapillary membrane and the surface available for gas exchange, as well as the chemical combination rate with haemoglobin, and inversely varies with the length of the passage and the thickness of the membrane. This ability of the lungs to transfer oxygen is called the diffusion capacity (**Figure 5**).

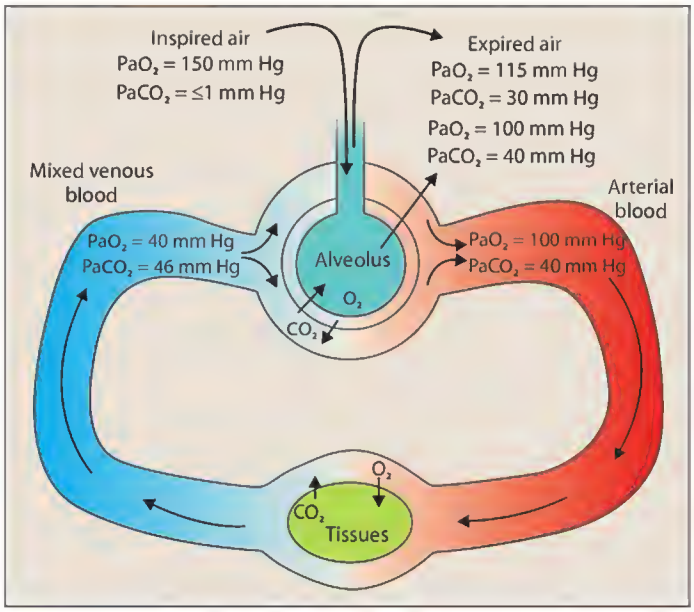


Figure 5: Pulmonary gas exchange.

Gas Transport

Oxygen is transported in blood largely bound to the haem portion of haemoglobin and to a much smaller extent dissolved in the blood, 0.0031 mL per mm PaO_2. The PaO_2 of alveolar air is about 100 mm Hg and that of systemic venous blood is about 40 mm Hg. The extent to which the binding sites on haem are occupied is described as 'saturation' of haemoglobin (SaO_2). When all the sites are occupied, haemoglobin is said to be 100% saturated. The amount of oxygen bound to haemoglobin is determined by the complex relationship between PaO_2 and the degree of saturation and is described by the *oxyhaemoglobin dissociation curve*, which is S-shaped, with the saturation reaching a plateau at the top, indicating that further increase in PaO_2 do not result in an increase in haemoglobin saturation. At a PaO_2 of 60 mm Hg, the haemoglobin is 90% saturated. A PaO_2 of 90% to 100% will result in almost fully saturated haemoglobin. The oxygen dissociation curve shifts to the left with an increase in the pH or a decrease in the $PaCO_2$ or temperature, or 2,3 diphos phoglycerate (2,3-DPG) making it harder to unload (or easier to bind) O_2 for any given PaO_2 while it shifts to the right when the above factors change in the opposite direction making it easier to unload (or harder to bind) O_2 (**Figure 6**).

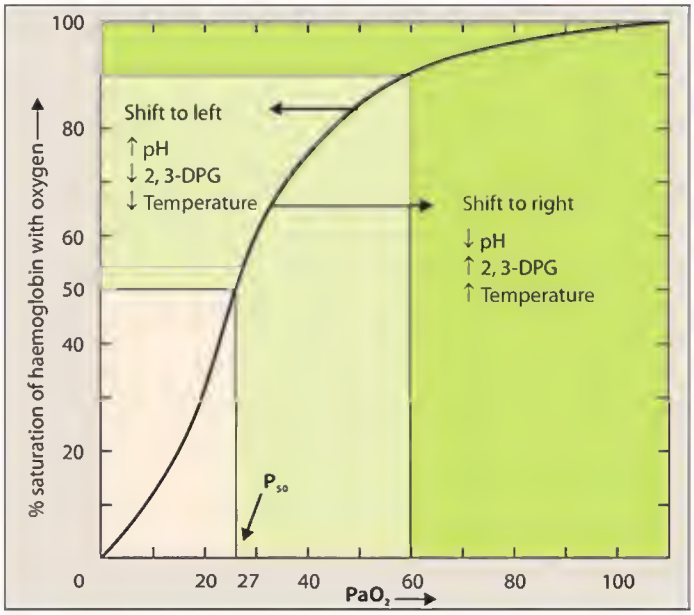


Figure 6: Oxygen-haemoglobin dissociation curve.

The oxygen content of arterial blood (CaO_2) is the sum of the bound and dissolved oxygen. Each gram of haemoglobin can carry 1.34 mL O_2 when fully saturated.

Thus, the CaO_2 = (1.34 × haemoglobin level × SaO_2) + (0.0031 × PaO_2).

The actual delivery of oxygen to tissues is also dependent on the local blood flow that in turn depends on the cardiac output and the local regulation of blood flow in the particular tissue. Disturbances in PaO_2, cardiac output or haemoglobin will thus affect oxygen delivery to the tissues. The PaO_2 falls to approximately 40 mm Hg after O_2 extraction occurs at the tissue-capillary level.

CO_2 is carried in the venous blood in three forms: dissolved (10%), as bicarbonate (60%), and in combination with proteins as carbamino compounds (30%). Combination of CO_2 with water to form carbonic acid (H_2CO_3) in the red cells is catalysed by the enzyme carbonic anhydrase and the latter dissociates into H^+ and HCO_3^-. While HCO_3^- diffuses out, H^+ cannot, as the cell membrane is relatively impermeable to cations. Thus, to maintain electrical neutrality, Cl^- ions move into the cell from the plasma (chloride shift). The deoxygenated haemoglobin has a greater affinity for CO_2 than oxygenated haemoglobin (the Haldane effect). Thus, in the tissues, loading of CO_2 is facilitated.

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23.2 Pulmonary Disorders—A Clinical Approach

Jyotsna M Joshi

Clinical approach to a patient with pulmonary disease consists of history taking and clinical examination. A systematic clinical approach is necessary for making an initial clinical diagnosis. A casual approach, on the other hand, results in wasteful investigations or initiation of hasty empirical treatment.

HISTORY

A thorough history can provide 80% of the diagnosis while a poor history results in misdiagnosis or a missed diagnosis. For example, without a history of asbestos exposure, asbestosis may be misdiagnosed as idiopathic pulmonary fibrosis (IPF). Similarly, a case of cough-variant asthma is likely to be subjected to several investigations if history of atopy is not elucidated. Previous treatment history in cases of tuberculosis (TB) is important to request drug susceptibility tests for possible drug resistance. A case with pulmonary symptoms should be questioned about the cardinal symptoms of pulmonary disease (cough, sputum, haemoptysis, breathlessness, wheeze, chest pain) and fever.

Cough

Cough may be characterised as acute (lasting less than 3 weeks), subacute (lasting 3 to 8 weeks), or chronic (persisting beyond 8 weeks).

- Acute cough may develop because of acute respiratory infection (ARI), upper or lower respiratory tract infection (URTI or LRTI) and pneumonia, exacerbation of asthma or chronic obstructive pulmonary disease (COPD) and pneumothorax.
- Sub acute cough most often results from allergic or bacterial rhinosinusitis.
- Chronic cough can have many causes, but airway diseases (asthma, COPD) and interstitial lung diseases (ILDs) account for most cases.

Cough is the only manifestation of asthma (cough variant asthma) in up to 50% of the patients with the disease. Drug [e.g. like angiotensin converting enzyme (ACE) inhibitor]. Induced Post-nasal drip, and gastro-oesophageal reflux disorder (GERD) are other important causes of unexplained cough. ACE inhibitors cause a non-productive cough, which may begin within hours to months after the initiation of therapy and resolution may occur within 1 to 12 weeks after the cessation of therapy. Post-nasal drip syndrome is the most common cause of chronic cough in non-smoking, immunocompetent adults who have a normal chest radiograph. Chronic cough in patients with GERD is likely to be a vagally-mediated reflux mechanism. Heartburn and regurgitation suggest a GERD-induced chronic cough, but these features may be absent in 'silent' GERD.

Sputum

Cough may be associated with sputum (mucoid or purulent). Acute onset cough associated with purulent sputum is seen in ARI like URTI, LRTI, or pneumonia. However, rusty sputum is characteristic of pneumococcal pneumonia. Chronic cough with mucoid sputum (>25 mL/day) is a symptom of COPD while copious mucoid sputum (>100 mL/day) or bronchorrhoea is characteristic of bronchoalveolar carcinoma and rarely asthma. Copious purulent sputum is often foul smelling or blood-tinged with cough is seen in bronchiectasis, lung abscess or broncho-pleural fistula. Cough with anchovy sauce sputum, a feature of pleuro-pulmonary amoebiasis while clear salty or peppery tasting expectoration is characteristic of pulmonary hydatid disease.

Haemoptysis

Haemoptysis is defined as the coughing up of blood derived from the lungs or bronchial tubes. Most cases are minor and treatable or self-limited. Haemoptysis has several causes. However, in up to 30% of the patients, no cause of haemoptysis can be found. Various definitions of the severity of haemoptysis have been proposed. Haemoptysis is conventionally classified as minimal (blood-streaked sputum), moderate less than 200 mL per day and severe if blood loss is greater than 200 mL per day. It is important to recognise massive haemoptysis quickly, because without urgent treatment, up to 80% of the patients may die. The detailed causes and management of haemoptysis is given in chapter 6, section 2.

Dyspnoea and Wheeze

Breathlessness or dyspnoea is the subjective feeling of uncomfortable or difficult breathing. Dyspnoea is most commonly caused by respiratory and cardiac disorders. Causes, such as asthma, congestive heart failure (CHF), COPD, pneumonia, cardiac ischaemia, ILDs, and psychogenic account for 85% of the patients with dyspnoea. Other causes may be upper airway obstruction, a neuromuscular condition or metabolic acidosis. Dyspnoea may be acute or chronic, and with or without associated wheeze. When dyspnoea lasts for more than a month, it is considered as chronic dyspnoea. Dyspnoea associated with wheeze indicates presence of diseases that cause airway obstruction, such as asthma, COPD and bronchiectasis. Dyspnoea may be progressive or non-progressive. The rate of progression can be ascertained by grading dyspnoea at onset and at the time of examination. Various grading systems are used for evaluating dyspnoea but the Modified Medical Research Council (MMRC) grading system is the most commonly used (**Table 1**). Alternatively, effort tolerance (ET) as stated by the patient (e.g. 'one flight of stairs' or 'few feet on flat ground') may be used instead of dyspnoea grade. Paroxysmal nocturnal dyspnoea (PND), orthopnoea (more breathless on lying down), and platypnoea (more breathless on sitting or standing) must also be asked for. PND is associated with CHF, orthopnoea may occur in CHF and all pulmonary disorders except emphysema and hepatopulmonary syndromes, which are associated with platypnoea.

Table 1: Dyspnoea Severity Modified Medical Research Council MMRC Scale

Grade	Level of Activity
0	Not troubled by breathlessness except on strenuous exercise
1	Short of breath when hurrying or walking up a slight hill
2	Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
3	Stops for breath after about 100 m or after a few minutes on the level
4	Too breathless to leave the house, or breathless when dressing or undressing

Chest Pain

Chest pain can be a symptom of pulmonary, cardiac, gastro-oesophageal, and musculoskeletal problems. However, chest pain that is localised, sharp stabbing in nature, and worsens on breathing is indicative of pleuritic pain. Pleuritic pain may occur due to pleuritis associated with pleural effusion, pneumothorax, pneumonia, pulmonary embolism and lung cancer. Persistent pleural pain in a case of pleural effusion/thickening indicates malignancy.

Additional History

History of pedal oedema and facial puffiness helps in establishing episodes of right heart failure in chronic pulmonary cases. Rarely, these symptoms may be due to nephrotic syndrome, due to renal amyloidosis in chronic suppurative pulmonary disorders, or anaemia/hypoproteinaemia associated with malnutrition. Additionally, patient must be questioned about history of rhinitis/sinusitis in airway diseases like asthma and bronchiectasis, history of dysphagia/hoarseness of voice in suspected lung malignancy, history of joint pains, skin rashes and Raynaud's phenomenon in connective tissue disorders, etc.

Past history of major medical or surgical illness must be elucidated including previous drug history, particularly ACE inhibitor, beta-blockers, methotrexate, amiodarone, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). Family history of asthma, cystic fibrosis, TB, and cancer must be asked for. Personal history includes occupation, diet, bowel and bladder habits and addictions, particularly tobacco smoking. Smoking history must be quantified; also given in chapter 6, Section 23.

With increased awareness of sleep-related disorders, patients must be specifically questioned about sleep quality, snoring (loud habitual, crescendo decrescendo), nocturnal choking or gasping and excessive day time sleepiness (EDS); all of which indicate obstructive sleep apnoea syndrome (OSAS).

GENERAL EXAMINATION

General examination is important and contributes to diagnostic decision-making in several ways. A crude measure of body fat is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in metres). World Health Organization (WHO) defines, underweight as a BMI <20 kg/m^2, normal 20 to 25 kg/m^2, overweight ≥25 kg/m^2, and obesity as a BMI of >30 kg/m^2 and extreme obesity if BMI >40 kg/m^2. Over weight or obesity is common in patients with OSAS. Low BMI in COPD indicates the presence of 'pulmonary cachexia' or 'pulmonary sarcopaenia', a systemic manifestation of COPD.

Pulse, respiratory rate, temperature, and blood pressure have been traditionally considered as the vital signs. Pulse oximetry is now viewed as 'the fifth vital sign'. It is useful to record the baseline saturation of a patient as it may warn the clinician of significant desaturation during an acute illness later. Baseline or exercise desaturation can also aid in diagnosis and oxygen therapy in chronic respiratory disease, like ILD and COPD. Exercise test for this purpose is performed under supervision while the patients are encouraged to walk at their own pace on a flat surface for 6 minutes, alternatively till the target heart rate (200-age) is reached or until limited by shortness of breath or fatigue. Clinically significant desaturation is considered to be any saturation decrease of 4% or more or to a *nadir* of 88%.

General examination findings, like clubbing and pallor, point towards chronic inflammatory diseases and malignancies. Elevated jugular venous pressure (JVP) and pedal oedema in chronic pulmonary cases help to diagnose cor pulmonale with right heart failure. Clubbing is an important clinical finding in a pulmonary case (**Figure 1**). Clubbing is described in 4 grades (**Table 2**). The common causes for finger clubbing are shown in **Table 3**. Presence of enlarged cervical lymph nodes is an important finding, particularly in cases of lung cancer and mediastinal masses. These provide accessible site for fine needle aspiration cytology or biopsy (FNAC/B). Cervical and axillary lymph nodes must be meticulously examined before embarking on expensive and invasive procedures, like computed tomography (CT) and bronchoscopy. The finding of crepitus in the neck is a pointer to the presence of pneumo-mediastinum, engorged neck veins to superior vena cava (SVC) obstruction, and an enlarged thyroid gland explain symptoms of upper airway obstruction. Associated hypothyroidism may explain OSAS and hyperthyroidism may be responsible for worsening asthma control.

Table 2: Grades of Clubbing

Grade	Description
Grade 1	Nail may seem to be loose within the soft tissue (increased bogginess) when palpating the fingernail
Grade 2	Nail extends from the bed (the profile angle) at 180 degrees or greater (normal 160 degrees) demonstrated by 'window sign' or Schamroth sign
Grade 3	Increased curvature of nails with grade 1 or 2 changes, appear like 'parrot beak' or 'drum stick'
Grade 4	Osteoarthropathy (pain and swelling of ankle/wrist joints, elbow/knee joints and hip/shoulder joints with finger clubbing). Osteoarthropathy may be confirmed by showing periosteal new bone formation of long bones.

Table 3: Causes of Finger Clubbing

Respiratory
- Chronic suppurative pulmonary disease—bronchiectasis, lung abscess, empyema
- Malignant lung cancer, malignant mesothelioma
- Idiopathic interstitial pneumonia (IIP) (especially, idiopathic pulmonary fibrosis)
- Pleural fibroma

Cardiac
- Cyanotic heart disease
- Subacute infective endocarditis
- Atrial myxoma

Gastrointestinal
- Inflammatory bowel disease
- Hepatic cirrhosis

Neurological
- Hemiplegic stroke

Metabolic Disease
- Thyroid acropachy

Other
- Familial
- Idiopathic

RESPIRATORY SYSTEM EXAMINATION

Respiratory system examination includes: (a) respiration rate, rhythm and accessory muscles use; (b) upper respiratory tract-nasal discharge, sinus tenderness and examination of the oral cavity; and (c) examination of the chest. Suitable chest examination requires the patient's chest, neck and abdomen to be appropriately exposed. Chest examination is best performed in the sitting or standing position. In patients who have difficulty in sitting, support can be given by someone standing in front and holding his/her hands. In those who are too sick to stand or sit, rolling on one side and then the other for examination of the back helps. Chest examination is performed under the headings of inspection, palpation, percussion, and auscultation (IPPA). The clinical findings are described in terms of areas over the chest (anteriorly—supraclavicular, clavicular, mammary and inframammary, axilla-axillary and infra-axillary, and posteriorly—suprascapular, interscapular, scapular and infrascapular). The corresponding areas of various lung lobes are shown in surface marking in **Figures 2A and B** and help in localising the diseased lobe.

Inspection and Palpation

Inspection and palpation of the chest are performed to assess where disease is bilateral—indicated by equal chest movements (asthma, COPD, ILD) or unilateral—indicated by reduced chest movements and if unilateral; whether associated with increase in hemithoracic volume (bulging of the chest, elevated shoulder, increased spino-scapular distance and shift of the trachea and cardiac impulse/apex beat to opposite side) found in pleural effusion, pneumothorax, hydropneumothorax; reduction in hemithoracic volume (flattening of the chest, depressed shoulder, reduced spino-scapular distance and shift of trachea and cardiac impulse/apex beat to same side) found in collapse, cavity, pleural thickening and no change in volume (no bulging or flattening, both shoulders at same level, equal spino-scapular distance, central trachea, and cardiac impulse/apex beat in the 5th intercostal space in the mid clavicular line) noted in consolidation.

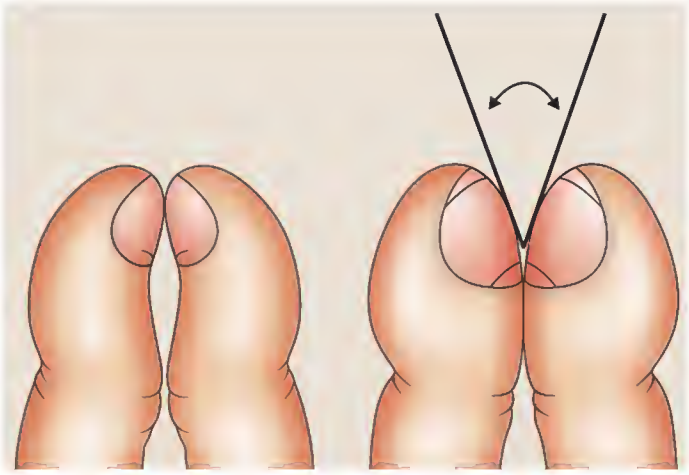
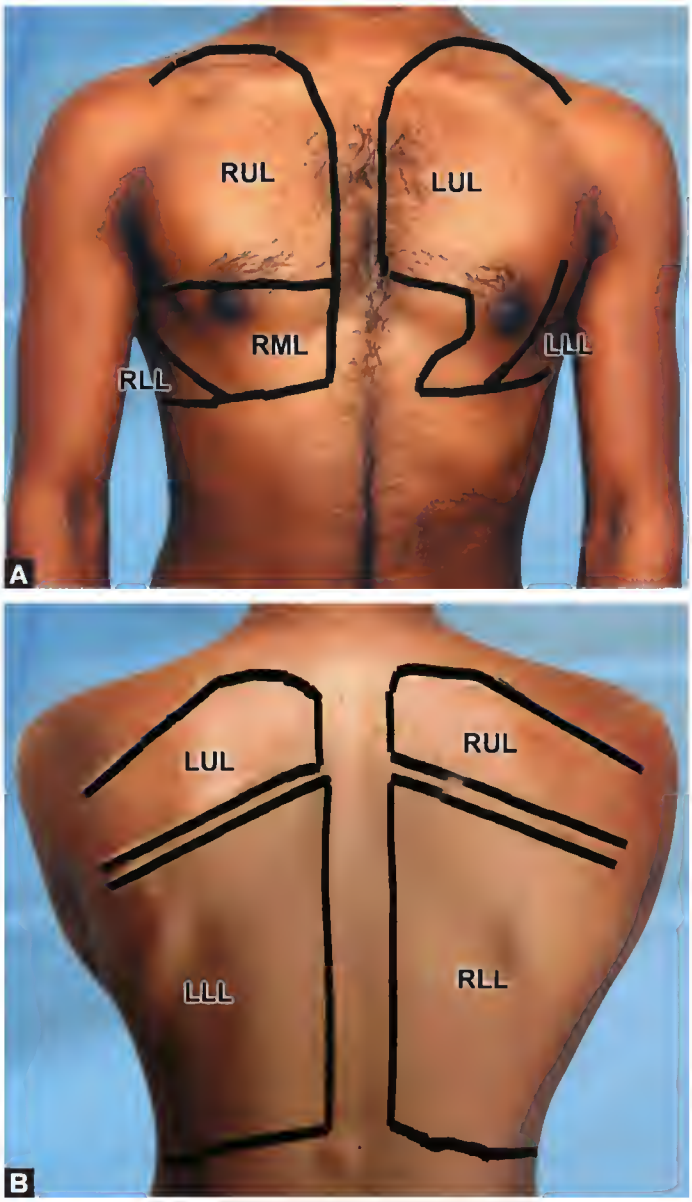


Figure 1: Shamvoth schematic diagram showing a normal finger showing a 'diamond-shaped window' when the dorsal surfaces of the terminal phalanges on opposing fingers are placed together, while the clubbed finger will show no space visible between the opposing nails.



Figures 2A and B: Surface marking of lung lobes over the anterior and posterior chest.

RUL = Right upper lobe; LUL = Left upper lobe; RML = Right middle lobe; RLL = Right lower lobe; LLL = Left lower lobe.

Percussion and Auscultation

Percussion adds to the findings of inspection and palpation. The technique of digital percussion was described by Barth and Roger (1865). The percussion notes vary from tympanic (over the stomach gas bubble—'Traube's space') to dull (over the heart and liver). In pathological cases, hyper-resonant notes are heard in cases of pneumothorax and emphysema, whereas dull notes are produced over consolidation, collapse or pleural effusion. Auscultation via a stethoscope is an integral part of chest examination. Auscultation terms simplified by Forgacs (1978) are established by the International Lung Sounds Association (ILSA). The sounds heard at auscultation are breath sounds (normal or bronchial) and voice sounds (increase vocal resonance/bronchophony or aegophony) and adventitious sounds; continuous sounds (wheezing and rhonchi) and intermittent sounds (coarse and fine crackles). Other adventitious sounds are those that originate in the upper airways (stridor) or in the pleura (friction rub) and interstitium (squawk—inspiratory squeaking sound). The normal breath sounds are the result of turbulent airflow through the larger airways. At the chest wall, the higher frequencies are attenuated by the lung parenchyma resulting in vesicular breath sounds. In the presence of consolidation or collapse with a patent bronchus, these higher frequencies are transmitted, leading to 'bronchial breathing'. Bronchial breathing is usually high pitched (tubular) and heard over consolidation; collapse with a patent bronchus and just above the level of pleural effusion due to collapse (relaxation or passive collapse) of lung. Bronchial breathing may be low pitched (cavernous), heard over an irregular walled cavity or high pitched with metallic intonation (amphoric) heard over smooth walled cavity or broncho pleural fistula. The same mechanism that produces bronchial-breathing allows spoken sounds to be transmitted well as increased vocal resonance (VR)/bronchophony (loud and clear)/aegophony (with a nasal twang) and also whispered sounds 'positive whispering pectoriloquy (WP)'. The breath sounds (and spoken sounds-VR) are reduced or absent when the lung and chest wall is separated by fluid or air, as in pleural effusion or pneumothorax and due to inability of breath sounds to reach the lungs in collapse with obstructed bronchus. **Figure 3** briefly depicts the flow chart of respiratory examination.

MAKING A CLINICAL DIAGNOSIS

The findings of history and clinical examination are analysed to make a clinical diagnosis (**Figure 3**). A summary of findings in various pulmonary disorders is shown in **Table 4**.

A clinical diagnosis must consist of:

1. Pathological diagnosis (What is the lesion?)
2. Anatomical diagnosis (Where is the lesion?)
3. Guess to aetiology (What is the likely cause?)
4. Additional diagnosis (e.g. cor pulmonale, anaemia, jaundice, goitre, etc.)

For example

Left lower lobe collapse due to lung cancer with anaemia, where:

Pathological diagnosis (What is the lesion?): *collapse*

Anatomical diagnosis (Where is the lesion?): *left lower lobe*

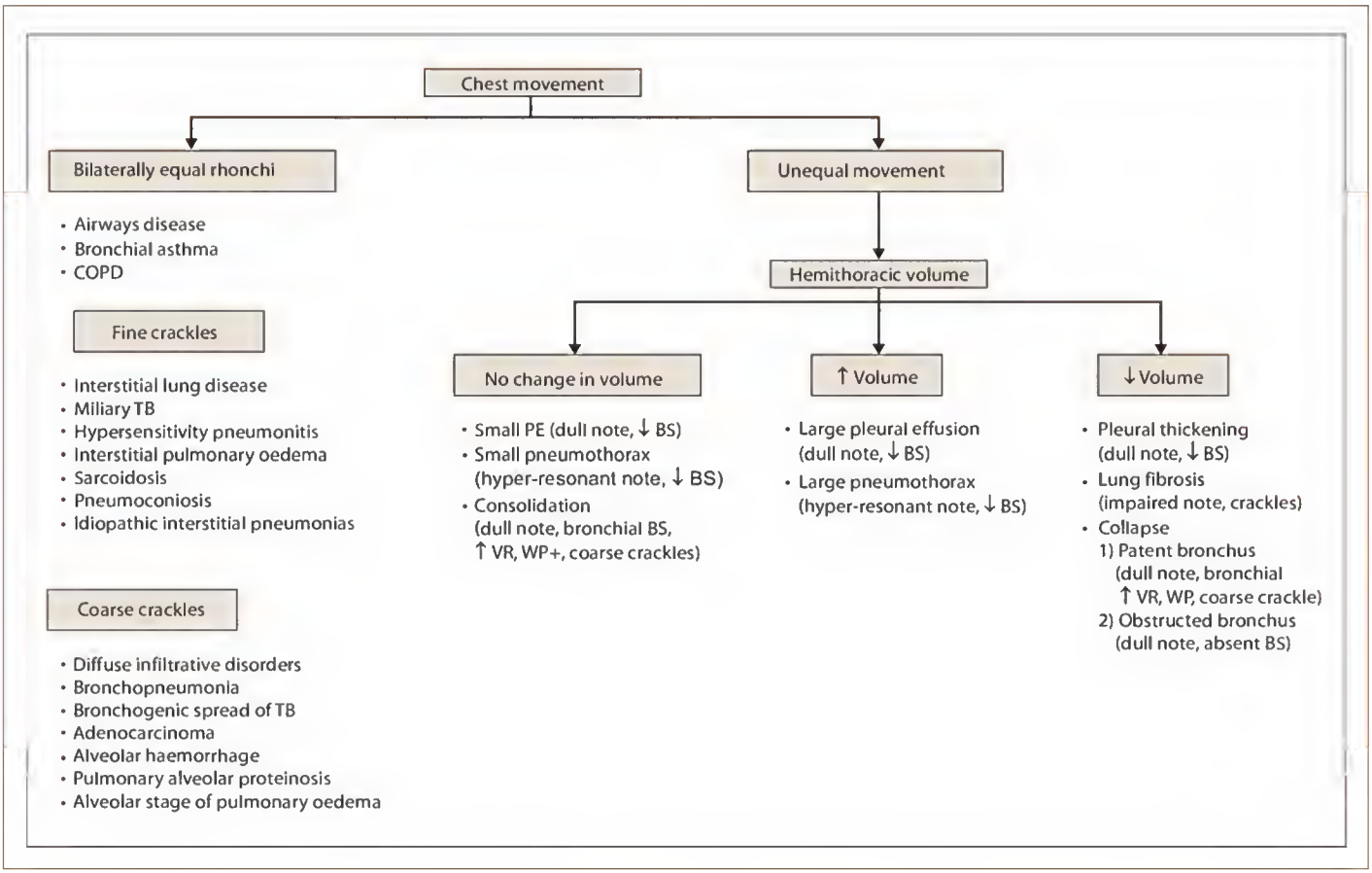


Figure 3: Flow chart of respiratory examination.

COPD = Chronic obstructive pulmonary disease; TB = Tuberculosis; PE = Pulmonary embolism; BS = Breath sounds; VR = Vocal resonance; WP = Whispering pectoriloquy.

Table 4: Clinical Findings in Various Pulmonary Disorders

Disorders	Symptoms	General Examination	Respiratory Examination
Diffuse lung disorders			
Asthma	Dyspnoea, cough, wheeze		Rhonchi
COPD	Cough, mucoid sputum, dyspnoea, wheeze		Emphysematous chest, rhonchi, crackles
Bronchiectasis	Cough, copious mucopurulent sputum, dyspnoea, haemoptysis	Clubbing	Coarse crackles, rhonchi
ILD	Dry cough, dyspnoea, no wheeze	Clubbing	Fine end inspiratory crackles, squawks
Localised lung disorders			
Consolidation	High fever, cough, purulent sputum, chest pain		NCV, dull note, bronchial BS, ↑ VR, WP+, coarse crackles
Collapse (patent bronchus) (also fibrotic/cicatricial collapse)	Cough, sputum, haemoptysis, dyspnoea		↓ Volume, dull note, BS bronchial, ↑ VR, WP+, coarse crackles
Collapse (obstructed bronchus)	Cough, sputum, haemoptysis, dyspnoea		↓ Volume, dull note, BS absent, ↓ VR
Fibrosis	Dry cough		↓ Volume, impaired note ↓ BS, crackles
Pleural effusion	Dry cough, pleuritic chest pain		Dull note, ↓ BS, ↓ VR, shifting dullness +, (initially NCV, subsequently ↑ volume)
Pneumothorax	Dyspnoea, dry cough, pleuritic chest pain		↑ Volume, hyper-resonant note, absent BS, ↓ VR
Hydropneumothorax	Cough (dry or with sputum), dyspnoea, pleuritic chest pain		Hyper-resonant note followed by dull note, shifting dullness, ↓ BS, ↓ VR, succussion splash
Hydropneumothorax with bronchopleural fistula	Cough with copious purulent sputum, posture dependent, dyspnoea, chest pain	Clubbing	Hyper-resonant/dull note shifting dullness, BS-amphoric, ↓ VR, WP+, succussion splash
Pleural thickening (fibrothorax)	Dry cough, dyspnoea		↓ Volume, dull note, ↓ BS, ↓ VR

COPD = Chronic obstructive pulmonary disease; ILD = Interstitial lung disease; NCV = No change in volume; BS = Breath sounds; VR = Vocal resonance; WP = Whispering pectoriloquy.

Guess to aetiology (What is the likely cause?): *lung cancer*

Additional diagnosis: *anaemia*

Based on the clinical diagnosis, further imaging and laboratory tests are performed to make a final diagnosis.

RECOMMENDED READINGS

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23.3 Pulmonary Disorders—Diagnostic Procedures

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INTRODUCTION

In patients with pulmonary disorders, investigations play a very important role in narrowing down the diagnostic possibilities. Broadly, the procedures can be divided into invasive and non-invasive methods (**Table 1**). Though there may be an overlapping between non-invasive and invasive procedures, this classification, to a large extent, helps in improving the understanding about various diagnostic procedures used in pulmonary disorders. In fact, the gold standard for any diagnosis is histopathology, cytology or microbiologic confirmation of the disease. In the last two decades, the use of various diagnostic modalities for obtaining tissue specimens for confirmation of diagnosis in various respiratory disorders has been a very major development in pulmonary medicine.

Table 1: Diagnostic Procedures in Pulmonary Disorders

Non-invasive

- Imaging studies like chest radiograph, ultrasonography (USG) and computed tomography (CT) to assess the anatomy
- Pulmonary function tests to assess physiology and gas exchange
- Microbiological isolation
- Serum markers
- Arterial blood gas (ABG) analysis
- Overnight polysomnography

Invasive

- Fibreoptic bronchoscopy, endobronchial USG
- Thoracoscopy, video-assisted thoracoscopy (VATS)
- Mediastinoscopy
- Definitive tests to confirm the diagnosis by obtaining tissue during bronchoscopy/thoracoscopy/USG and CT-guided procedures

The following sections represent an overview of the various investigative procedures in pulmonary disorders.

NON-INVASIVE DIAGNOSTIC PROCEDURES

Chest Radiography

Chest radiography is the sheet anchor for diagnosis in pulmonary disorders as it is easily available as well as economical. In fact, some clinicians may like to call it an extension of the stethoscope. However, it is important to appreciate that a good clinical examination cannot have any replacement and radiology is complementary and not a substitute for clinical examination.

In the last few years, digital radiography has revolutionised the quality of radiography as compared to the conventional film-based radiography. Normally, a chest radiograph with a postero-anterior (PA) projection is the standard protocol, where the film cassette is placed against the anterior chest wall. However, the patient should be able to sit or stand for the PA view. In critically ill patients or those who are not able to sit up, an antero-posterior (AP) view is performed where the film cassette is placed behind the back. While interpreting the AP view, there is a word of caution; the heart size may be falsely enlarged as the distance between the heart and the cassette increases. Therefore, cardiomegaly on an AP view need not be 'true' cardiomegaly.

The clinicians should analyse the chest radiograph in a systematic order to avoid missing an abnormality and gain maximum information from a standard PA radiograph. One should start with the quality of chest radiograph and positioning of patient, then comment on soft tissues, bony cage, followed by tracheobronchial tree, hilum, mediastinum, lung parenchyma, and costophrenic angles. This should be followed by a comment on cardiac size. The quality of the radiograph is very important. A technically sound radiograph should demonstrate the entire dorsal spine with mid point of right diaphragm at the level of the anterior end of the 6th rib, implying that it is a deep inspiration film, which is very important. A correct positioning of the patient is indicated when medial end of both clavicles is equidistant from the vertebral spinous processes.

It is essential to appreciate that history of the patient, for which the chest radiograph has been performed, is very important. One should always ask for an old chest radiograph for comparison. This also results in avoiding many expensive investigations for a 'lesion' which has been present for many years like the presence of fibrotic strands in the apex in a patient with previous history of tuberculosis (TB).

A few of the common abnormalities on the chest radiograph are pulmonary nodules/masses, cavitary lesions, pneumonia/consolidation, and pleural effusion.

Pulmonary nodules/masses

These could be solitary or multiple. In a solitary lesion, the doubling time is very important. Most malignant lesions have a doubling time between 4 weeks and 24 weeks. In other words, a lesion which has doubled in less than 2 weeks or after 24 weeks is unlikely to be of malignant aetiology. The increase in diameter of more than 25% on the chest radiograph signifies a pathological doubling of the lesion. The other soft pointers toward a benign solitary nodule are significant calcification and smooth margins. However, it is important to note that these soft markers can be deceptive. A nodule in a patient with history of smoking should always necessitate further evaluation. A comparison with old radiographs (if available) is very helpful.

Multiple pulmonary nodules are mainly due to malignant deposits of varied aetiology. Another important term is miliary mottling. These are small nodules of less than 5 mm in diameter. The commonest cause in India is miliary TB. However, the differential diagnosis of miliary mottling includes metastasis, fungal infections, pneumoconiosis, and sarcoidosis.

Cavitary lesions

The two important differential diagnosis are bronchial carcinoma and lung abscess. The common aetiologies of infections in a lung abscess are *Mycobacterium tuberculosis*, *Klebsiella*, *Staphylococcus*, and anaerobes. The presence of air-fluid level suggests the diagnosis of a cavitary lesion (**Figure 1**).



Figure 1: Chest radiograph (PA view) showing a cavitary lesion with an air-fluid level in the right lung.

Pneumonia/consolidation

The important radiological sign of a pulmonary consolidation is air bronchogram, which is a radiolucent bronchi (black) in the background of an opaque lung (white). The other important sign is the opacification of the lung with undulating margins obscuring the underlying blood vessels. A lobar consolidation follows the contours of the lobe and has a sharp margin in the corresponding fissure.

Infections are the commonest cause of consolidation. However, the unusual differential diagnosis including fluid overload, bronchioloalveolar carcinoma, collagen vascular diseases, and pulmonary haemorrhage should also be considered in the appropriate clinical setting.

Pleural effusion

The earliest sign of pleural effusion on the chest radiograph (PA view) is blunting of the lateral costophrenic angle. A minimal amount of fluid (approximately 200 mL) is required to produce appreciable blunting. A large free pleural effusion appears as a dependent opacity with lateral upward sloping of a meniscus-shaped contour. A massive pleural effusion appears as an opaque hemithorax with mediastinal shift to the opposite side. The lateral decubitus view was very important in diagnosing minimal pleural effusion (less than 100 mL), which is not picked up on a routine PA view. With technologies like ultrasonography (USG) and computed tomography (CT) becoming more freely available, this view is used infrequently. However, it is very important to know the importance of this projection, especially in resource-limited setting areas like India where the newer technology is still lacking in the underdeveloped regions of our country.

Intensive care unit (ICU) imaging

With the evolution of advanced critical care in our country, the role of the chest radiograph in this setting needs special mention. In a resource-limited setting like India, chest radiograph is an economical modality to evaluate patients in the ICU. In fact, chest radiograph has become an important diagnostic armamentarium in the ICU setting. It is used to evaluate the position of the monitoring and support equipment like central venous catheter, endotracheal tube, tracheostomy tube, chest tube, pulmonary artery catheter, enteric tube, and intra-aortic balloon pump. The chest radiograph is also an important tool to diagnose pneumothorax, pneumonia, pulmonary oedema, atelectasis, and pleural effusion, which are frequently encountered complications in the management of patients on ventilators and other life-saving devices.

Ultrasonography and Computed Tomography

These techniques have improved the diagnostic armamentarium in respiratory diseases tremendously.

Ultrasonography is a good investigative modality for the peripherally placed lesions in the lung. USG guided procedures help to secure biopsy specimens for tissue diagnosis. The major indication of USG is to detect minimal pleural effusion which is not picked up on PA view and to differentiate between pleural thickening *vis-à-vis* an effusion. The presence of septation in the fluid is a pointer that the effusion is exudative, though final confirmation is obtained on examination of the fluid. A large collection of fluid or pus in the pleural cavity can be drained with USG guidance. Similarly, USG is most useful to drain multiple localised collections of fluid in the pleural cavity.

Computed tomography is another very important investigation which is far superior to the conventional chest radiograph, though the basic principles of physics are the same as in chest radiography. One needs to have a clear understanding of the various terminologies used like spiral CT, high resolution CT (HRCT), lung window, and mediastinal window. The mediastinal window helps in assessing the lesions in the major tracheobronchial tree and in the mediastinum like lymph nodes and great vessels. The mediastinal window also helps in commenting on density difference like calcification as well as caseation in intrathoracic lymph nodes (**Figure 2**). The lung window helps in assessing the parenchymal abnormalities in the lung (**Figure 3**).

The problem with the conventional CT is that the patient needs to hold his breath for a clear image on the CT, otherwise there

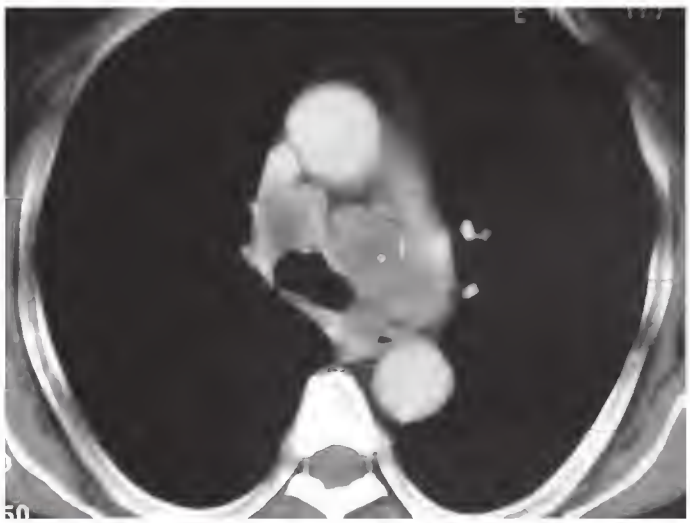


Figure 2: Mediastinal window showing intrathoracic lymph nodes with necrosis.

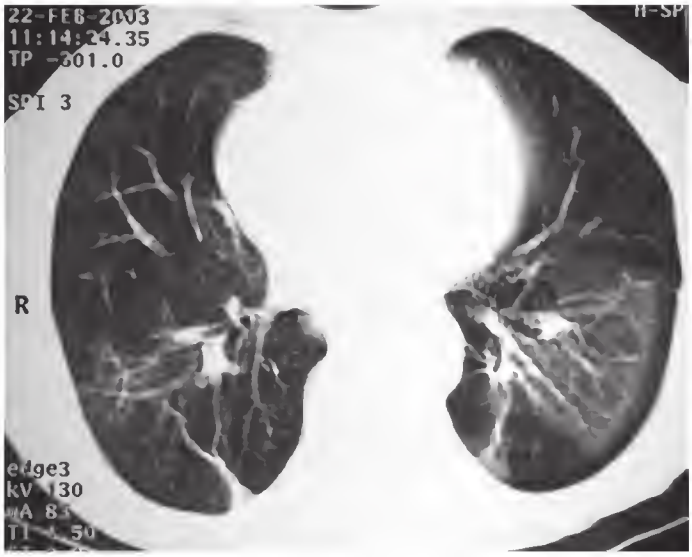


Figure 3: Lung window showing bilateral ground glass opacification.

is blurring of image due to respiratory movement. Moreover, due to respiratory movement, small lesions may be missed. This problem has now been overcome by spiral CT. Spiral CT is a technological evolution where the entire thorax is imaged by holding the breath once only for a few seconds. In fact, even in a dyspnoeic patient, fairly clear images can be obtained, which is not possible on conventional CT machines. As the image acquisition is faster, the amount of contrast required is also less.

A technical advancement over single slice spiral CT is multi-detector row CT (MDCT) or earlier known as multi-slice spiral CT. In MDCT, multiple slices are acquired at the same time. Consequently, the speed of scanning as well as resolution is enhanced significantly. In fact, MDCT allows coronal, sagittal, and oblique imaging at higher spatial resolution as compared to conventional CT. Dynamic MDCT with intravenous contrast or CT pulmonary angiography (CTPA) is becoming the investigation of choice for pulmonary emboli phasing out ventilation-perfusion (V/Q) radionuclide scans. Moreover, three-dimensional anatomy of the tracheobronchial tree can also be constructed using MDCT unlike conventional CT. In fact, the tracheobronchial tree is visualised as clearly as bronchoscopy. This is called virtual bronchoscopy. Research tools are also being developed to employ xenon gas to enhance regional ventilation of lungs using MDCT (Xenon enhanced MDCT or XE-MDCT).

The modality of HRCT (thin transverse slice of 1 to 2 mm *vis-à-vis* the normal slice thickness of 10 mm) is extremely helpful in diagnosis of diffuse lung parenchymal disease. These scans can be performed on both conventional and MDCT. Therefore, it is important to appreciate that HRCT and MDCT are not synonymous.

To summarise, the broad diagnostic indications for CT include further evaluation of lung, mediastinal, and hilar abnormalities in the presence of non-diagnostic radiographs. It is also important in evaluation of mediastinal lymphadenopathy, diffuse lung disease, lung tumours, haemoptysis with non-localising chest radiograph, and pulmonary embolism.

The only limitation is its cost in a resource-limited setting like India. The hazards of radiation exposure to the patient should also be kept in mind, especially in a pregnant woman.

Magnetic Resonance Imaging

The primary advantage of MRI over CT is the lack of ionising radiation. It is also important to realise that as far as respiratory imaging is concerned, MRI offers no diagnostic advantage over CT. In fact, MRI is an inferior modality to assess lung parenchyma as compared to CT. However, the evolution of newer MRI scanners with dynamic gadolinium-enhanced imaging and ultrafast proton will result in increased utility of MRI in evaluation of lung diseases, especially in perfusion abnormalities like pulmonary embolism in pregnant females. The use of hyperpolarised gas imaging with helium and xenon are also being evaluated in malignant lung pathology. The assessment of diaphragm abnormalities, chest wall motion assessment, and breathing mechanics is potentially feasible for clinical usage in future with the advent of advanced ultrafast proton imaging MRI scanners.

Pulmonary Function Tests

Pulmonary function tests are important to assess the physiological function of the lungs. These include tests of respiratory mechanics and pulmonary gas exchange. The standard protocol involves a computerised spirometer and additional facilities for measuring carbon monoxide (CO) diffusion as a measure of diffusion capacity reflecting gas exchange. Of course, the acid-base disorders also reflect on the physiological function of the lungs, but they are outside the purview of this chapter. Ideally, PFT values have to be compared with the predicted values in a population which need to be epidemiologically established in every country. In India, most centres with PFT machines have to depend on the western data for normal values, which may not be representative of our country due to different body habitus.

Basically, respiratory mechanics involve compliance of lung and chest wall on one hand and airway resistance on the other. The direct measurements of lung compliance and airway resistance involve estimation of oesophageal pressure, pleural pressure and trans-diaphragmatic pressure, which is not feasible for day-to-day clinical practice. The practical measure of lung compliance in PFT is measurement of lung volumes, whereas the practical corollary for airway resistance is based on forced expiration manoeuvres by patients. In restrictive lung diseases, PFT demonstrates decreased vital capacity (assumed to be same as forced vital capacity (FVC) for practical purposes), whereas obstructive disease is reflected by decreased forced expiratory volume in one second (FEV1).

For interpretation, we look at the ratio of FEV1/FVC to differentiate between restrictive and obstructive lung disease rather than FEV1 alone. The reason is simple. In a patient of restrictive lung disease as FVC is reduced, consequently FEV1 is also reduced as the lungs have 'less air to be expelled'. Therefore, if one looks at FEV1 only, PFT of a patient with restrictive airway disease may give a false impression of obstructive airway disease due to reduced FEV1. However, when we look at the ratio of FEV1/FVC; as both values are reduced, the FEV1/FVC ratio is normal. On the other hand, in obstructive airway disease, there is air trapping and FVC is increased whereas due to obstruction in the airways, FEV1 is decreased; hence FEV1/FVC ratio is reduced.

Another important difference to understand is between peak expiratory flow rate (PEFR) and FEV1. PEFR can be easily

measured at home and is a very important objective parameter for asthma patients to know whether the disease is under control or is worsening so that they can report to the hospital at the right time. However, PEFR is always effort dependent, and hence, the patient should do it 2 to 3 times and note the best value. However, FEV1 done as part of PFT is relatively effort independent and gives a better reflection of the airway obstruction.

The assessment of respiratory muscle function is important to diagnose neuromuscular disorders affecting the respiratory system and occasionally in restrictive lung disease patients when restriction is extraparenchymal in the chest wall. Briefly, the respiratory muscle function is measured as PE_{max} (indicating maximum expiratory muscle pressure) and PI_{max} (indicating maximum inspiratory muscle pressure). Though expiration is a passive process, abdominal muscles play an important role. On the other hand, inspiration is an active process and the diaphragm is an important inspiratory muscle. Logically, expiratory muscles are most active at end-inspiration (PE_{max}) when the lung volume is maximum; whereas inspiratory muscle act at lower lung volumes, i.e. end-expiration (PI_{max}).

The pulmonary gas exchange parameter practically used in day-to-day clinical practice is carbon monoxide diffusing capacity (DLCO). It is a sensitive test to assess the integrity of the alveolo-capillary membrane. It is classically reduced in interstitial lung disease. However, it is also dependent on the surface area of the alveolo-capillary membrane. In other words, if patient has significant reduced surface area as in emphysema or pneumonectomy, DLCO would be reduced. Therefore, to remove this confounding factor, transfer coefficient (K_{CO}) is a more reliable parameter which represents the uptake of CO per litre of effective alveolar volume.

A more detailed assessment of the physiology of compliance of respiratory apparatus as well as the exact level of airway obstruction (from larynx to terminal airways) can be performed by studying the flow-volume curves or loops and measurements of static and dynamic compliance and airway resistance (R_{aw}) which is readily determined by body plethysmography and specific conductance (SG_{aw}) which is inverse of R_{aw} divided by lung volume at which the measurement was made. Another modality of assessment of respiratory function is the exercise test, which helps to quantify the exercise performance and objective assessment of disability due to disease, where clinically a patient may have recovered. For example, in miliary TB even after complete clinical and radiological recovery, a proportion of patients, despite successful treatment, develop exercise limitation that is detected on exercise test. These tests need a detailed understanding of the respiratory physiology and mechanics for a correct interpretation and their day-to-day use is quite limited. Nevertheless, they are very important for operational research to understand the basic pathophysiology of various respiratory disorders.

Microbiological Techniques

These techniques have a very important role in the diagnosis of infections of the respiratory system. However, it is very important to understand that in our country all microbiology laboratories may not be equipped with facilities for some of the advanced microbiological investigations; therefore the treatment of a critically ill patient should not wait for the outcome of these investigations. The clinicians should empirically cover for the prevalent organisms. On the other hand, if the clinical setting does not support the results of a microbiological investigation, we need to re-check for any contamination of the sample.

Sputum is the most commonly accessible material for a microbiological investigation. The collection of the sputum is very important, otherwise the report may be non-contributory and only add to the cost of care to the patient. It is very important to differentiate sputum from saliva. Grossly, a good sputum sample is thick (semi-solid), which is coughed out deeply from the lungs and is at least 2 mL. Microscopically, a good sputum sample should have less than 10 squamous epithelial cells and more than 25 neutrophils per low power field. If the patient is unable to produce adequate sputum, then it should be 'induced' with hypertonic saline given through a nebuliser mask. The transportation of the sample to the laboratory is equally important and should be done as early as possible.

The role of blood culture is also very important, but again the collection of blood for culture is more vital. All clinicians should be conversant with the correct technique of collecting a blood sample; otherwise the results can be misleading in the management of patients.

There are newer antigen markers in sera/sputum for atypical pneumonia organism like *Mycoplasma*, *Legionella* which can rapidly diagnose these infections.

The role of Ziehl-Neelsen (carbol-fuchsin) staining in the sputum smear for diagnosis of *M. tuberculosis* has been well established over the years. However, newer staining techniques like fluorochrome (auramine-rhodamine) staining are more sensitive as well as time conserving for identifying the mycobacteria.

The culture of mycobacteria on Lowenstein-Jensen medium is a time consuming process and is not of much value as far as immediate patient management is concerned. It takes 6 to 8 weeks for the culture to be reported. Newer culture methods like BACTEC radiometric system yield relatively earlier results.

Polymerase chain reaction

M. tuberculosis ribosomal RNA in respiratory tract specimens can now be identified within 24 hours. In fact, the rapid tests do not replace acid-fast staining, which provides an index of contagiousness, or mycobacterial cultures, permit drug susceptibility testing.

Tuberculin skin test

Tuberculin skin test (TST) (Mantoux test) is another investigation which is frequently done to diagnose latent TB infection (LTBI). However, its diagnostic reliability is always in relation to the clinical context and a positive TST (more than 10 mm induration) in the absence of clinical symptoms should not be considered diagnostic of active TB in our country because of false positivity due to Bacillus Calmette-Guérin (BCG) immunisation. A lower threshold of 5 mm is used to diagnose LTBI in human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS).

Interferon gamma release assays

Interferon gamma release assays are used to diagnose LTBI. Their diagnostic utility in active TB has not been established. These tests include quantiferon-TB Gold (QFT-G), quantiferon-TB Gold in- tube test (QFT-GIT) and T-spot TB test. Early secreted antigen target-6 kDa protein (ESAT-6), culture filtrate protein-10 (CFP-10) and TB7.7 are three antigens used in these tests. The patient makes one visit to the health care facility and results are available in 24 hours.

Nuclear Medicine Imaging

The role of positron emission tomography (PET) and PET-CT using radiopharmaceutical fluoro-2-deoxy-D-glucose (FDG-PET) in the evaluation of focal lung lesions, especially solitary pulmonary nodule is emerging. The low false-negative rate of FDG-PET helps in excluding malignancy and allows follow-up of benign lesions as compared to CT.

Serum Markers

There are some serum markers which are helpful in the diagnosis of pulmonary disorders. Increased angiotensin-converting enzyme (ACE) levels in blood are most frequently used in the evaluation of sarcoidosis. However, increased ACE levels are not specific for sarcoidosis. Some of the other pulmonary conditions with increased ACE levels include emphysema, occupational lung diseases, and lung cancer.

Other serum markers useful in the diagnosis of pulmonary disorders include anti-neutrophil cytoplasmic antibody (ANCA) levels in blood for the diagnosis of Wegener's granulomatosis (WG). Proteinase 3 ANCA (PR3 ANCA) is more specific for WG.

Alpha 1-antitrypsin deficiency resulting in early-onset panacinar emphysema is diagnosed by estimating serum levels of alpha-1-antitrypsin. The presence of high levels of immunoreactive trypsinogen (IRT), a pancreatic protein is being used as a screening modality in infants with cystic fibrosis (CF). The mutation observed in CF patients result from deletion of three base pairs in CF transmembrane conductance regulator nucleotide sequence. This deletion causes loss of the amino acid phenylalanine located at position 508 in the protein. This mutation is referred to as ÄF508, which signifies severe clinical manifestations in patients of CF.

The role of tumour markers is also evolving in patients with lung cancer. Tissue polypeptide specific antigen (TPS) and cytokeratins CYFRA 21-1 are useful serum markers for the diagnosis of non-small cell lung cancer. Neuron specific enolase (NSE) is a useful tumour marker for monitoring course of patients with small cell lung cancer.

Arterial Blood Gas Analysis

The measurement of arterial blood gas analysis (ABG) is an extremely important tool to assess the pH, oxygen, carbon dioxide, and bicarbonate levels in blood. These parameters reflect the exact gas exchange occurring in lungs and integrity of the ventilatory control mechanism. Arterial blood gas analyses also reflects the various pulmonary-renal interactions occurring to maintain the normal acid-base physiology in the body.

Polysomnography

This is an overnight test performed in the sleep laboratory to diagnose apnoea. Cardio-respiratory, thoraco-abdominal, and electroencephalography parameters and oxygen saturation are recorded. Apnoea-hypopnoea index (AHI) > 5 events per hour are used to diagnose obstructive sleep apnoea.

INVASIVE DIAGNOSTIC PROCEDURES

Pleural Fluid Analysis

Diagnostic thoracocentesis and analysis of the pleural fluid is an essential procedure in the evaluation of a patient with pleural effusion. The evaluation includes biochemical, microbiological, and cytopathological analysis.

Enzymes and Cytokines

In recent years, adenosine deaminase (ADA) and interferon-gamma (IFN-γ) have emerged as important diagnostic tools in the diagnosis of tuberculous pleuritis. In a patient with pleural effusion, an elevated level of ADA (> 36 IU/L) in the pleural fluid is suggestive of TB. In fact, there are two isoenzymes of ADA: ADA1 and ADA2. The pleural fluid in tuberculous pleurisy primarily contains ADA2. However, for all practical purposes, the total level of ADA is measured in the fluid. Among the cytokines, studies have suggested that elevated pleural fluid IFN-γ can be used as a marker for the diagnosis of TB. In fact, it is now well documented that significantly higher IFN-γ: interleukin lukin-4 ratio in the pleural fluid compared to peripheral blood in patients with pleural tuberculosis.

Though elevated levels of IFN-γ in the pleural fluid are more sensitive for TB, ADA estimation is a cost effective investigation in the resource-limited setting of our country where the prevalence of TB is high.

Bronchoscopy

Fibre-optic bronchoscopy (FOB) is an outpatient procedure and is used to visualise the tracheobronchial tree. The role of FOB has also been established in diffuse lung disease. Fibre-optic bronchoscopy is also useful in obtaining histopathological, microbiological (Gram's stain, acid-fast bacilli stain, fungal stain, cultures), and cytological samples for the confirmation of diagnosis. The various techniques used with FOB are endobronchial brushings, washings, and biopsy. This technique is important in a proximal lesion of the tracheobronchial tree-like bronchogenic carcinoma. On the other hand, broncho-alveolar lavage (BAL) provides samples from the peripheral airways and alveoli. In patients with miliary TB, it has been shown that significantly higher levels of IL-4 are present in the peripheral blood as compared to BAL.

In patients with diffuse lung disease, BAL is an important tool in association with transbronchial lung biopsy. A newer technique is transbronchial needle aspiration to sample the sub-carinal mediastinal lymph nodes.

Endoscopic bronchial ultrasonography (EBUS) is also becoming a very useful adjunct to evaluate mucosal and sub-mucosal lesions in the tracheobronchial tree. Endoscopic bronchial ultrasonography also increases the diagnostic sensitivity in obtaining fine needle aspiration cytology (FNAC) or biopsy of suspicious lesions.

The use of rigid bronchoscopy had become restricted to the management of exsanguinating haemoptysis or in small children. However, with the advent of tracheobronchial stents, the use of rigid bronchoscopy is again gaining ground. The other

newer therapeutic uses of bronchoscopy include cryotherapy and laser therapy for bronchogenic carcinoma. Another important therapeutic procedure is removal of aspirated foreign body from the tracheobronchial airways.

Radiologically Guided Procedures

The role of USG/CT-guided FNAC and biopsy of various pulmonary abnormalities is a relatively less invasive modality to establish the diagnosis in these disorders. These procedures are quite safe and can be performed on an outpatient basis by experienced radiologists.

Thoracoscopy and Mediastinoscopy

Just as bronchoscopy is used for the tracheobronchial tree, thoracoscopy is used to visualise the pleura, and mediastinoscopy is used to visualise the structures of the mediastinum. The main advantage is obviously a direct visualisation of the suspicious tissue which can be biopsied for further analysis.

However, these are invasive surgical procedures performed under general anaesthesia with consequent morbidity and mortality. These procedures are generally performed when one has exhausted relatively less invasive means of establishing a diagnosis. In recent years, video-assisted thoracoscopic (VATS) procedures have further improved this technique. The main diagnostic indication of thoracoscopy and VATS are pleural biopsy for undiagnosed pleural effusions and wedge lung biopsy for diffuse lung disease. At the same time, therapeutic procedures in the form of pleurodesis for intractable pleural effusion, bullectomy for large bullae and lung volume reduction surgery for chronic obstructive pulmonary disease can also be performed. Mediastinoscopy is very useful to appropriately stage the lung cancers pre-operatively as the hilum is best visualised by this procedure.

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23.4 Upper Respiratory Tract Infections

DG Jain

INTRODUCTION

Upper respiratory tract infections (URTIs), amongst the most common acute conditions presenting in the outpatient setting, is an important cause of morbidity and economic loss globally. Disease transmission occurs via the inhalation route and direct contact. Viruses are the most frequently implicated aetiological causes but URTIs due to primary bacterial infection or super-infection are also frequently encountered. Viral infections need to be distinguished from bacterial URTIs, as targeted treatment is available for bacterial infections.

COMMON COLD AND INFLUENZA

'Common cold' is an upper respiratory tract infection (URTI) caused by viruses (**Table 1**). The term 'influenza' refers to a severe form of the common cold caused by the influenza virus. A new subtype of swine-origin influenza A (H1N1) virus, which has now taken the form of a pandemic, has segments from four influenza viruses, i.e. North American swine, North American avian, Human influenza, and Eurasian swine. Its incubation period is 1 to 7 days.

Table 1: Five Groups of Viruses Causing Common Cold and Influenza

Influenza viruses
Picornaviruses (Coxsackie, Reo, Echo, and rhinovirus)
Respiratory syncytial virus
Parainfluenza virus
Adenovirus

Clinical Features

Sneezing, rhinorrhoea, nasal congestion, sore throat, non-productive cough, pain in the eyes, and headache are the usual symptoms. Sometimes, constitutional symptoms such as malaise and myalgias may be prominent (influenza or para-influenza virus). Fever is uncommon in adults. Occasionally, conjunctivitis (adenovirus), laryngitis (parainfluenza virus), and skin rash (enteroviruses) may also be present. Physical examination reveals post-nasal discharge, erythema around the nose, and glossy nasal mucous membranes. The pharynx may appear congested and exudates could be present on the tonsils. Jugulodigastric lymph nodes may be enlarged and tender. In influenza, extremes of age and pre-existing medical conditions attract a higher risk of complications like sinusitis, otitis media, croup, bronchiolitis, status asthmaticus, pneumonia, myositis, myocarditis, pericarditis, rhabdomyolysis, seizures, encephalitis, toxic shock syndrome, secondary bacterial pneumonia with or without sepsis.

Diagnosis

Real-time polymerase chain reaction (RT-PCR), or isolation of the virus in culture, or a four-fold rise in virus specific neutralising antibodies are used for confirmation of the diagnosis (before administration of antiviral drugs) from clinical specimens, i.e. nasopharyngeal swab, throat swab, nasal swab, wash or aspirate or tracheal aspirate in case of intubated patients.

Management

Common cold is usually treated empirically due to the non-availability and cost involved in laboratory testing. The mainstay of management is symptomatic and supportive treatment directed at alleviating the symptoms of common cold rather than addressing the aetiological causes. Bed rest, adequate fluid intake, anticholinergic nasal sprays (e.g. ipratropium nasal spray) for rhinorrhoea, saline nasal drops, nasal decongestants (e.g. xylometazoline nasal spray) for nasal obstruction are used for symptomatic relief.

In case of influenza, nosocomial and household spread of disease can be minimised by early institution of infection control measures and isolation of the patient in a well-ventilated isolation room/ward with beds kept at least one metre apart. Prompt treatment should be instituted with a generally well-tolerated antiviral drug (e.g. oseltamivir) to prevent severe illness and death. Antiviral prophylaxis should be provided to health care personnel managing the patient. Supportive therapy includes intravenous fluids, parenteral nutrition, oxygen therapy, ventilatory support, antibiotics for secondary infection, vasopressors for shock, paracetamol or ibuprofen for fever, headache, myalgia. Aspirin/salicylate medication is contra-indicated in influenza as it may cause Reye's syndrome. Patients should be monitored for lower respiratory tract infection and for hypoxia. Close contacts of suspected, probable, and confirmed cases should be advised voluntary home quarantine for at least 7 days after the last contact with the infected person.

RHINITIS

It is defined as inflammation of the membranes lining the nose. Rhinitis is characterised by nasal congestion, rhinorrhoea, sneezing, itching, and/or postnasal discharge. It is classified as allergic and non-allergic (**Table 2**).

Allergic Rhinitis

The inflammation in the nose is immunoglobulin E (IgE)-mediated in allergic rhinitis and is due to acute exposure to the inciting allergens which induce the early symptoms such as sneezing, itching, and clear rhinorrhoea within minutes of exposure. Late phase symptoms (nasal congestion and obstruction) appear 4 to 6 hours after exposure. The nasal mucous membrane appears boggy and pale. Acute infectious rhinitis is usually viral in origin. Secondary bacterial infection involving the sinuses is a common complication in which patients have mucopurulent or purulent nasal discharge, facial pain and pressure, and fever may be present.

Non-Allergic Rhinitis

Patients with non-allergic, non-infectious rhinitis without eosinophilia, and some with vasomotor rhinitis, present with nasal obstruction, rhinorrhoea, and congestion that may be precipitated or exacerbated by certain odours, alcohol, spicy foods, emotions, and environmental factors such as temperature, barometric pressure changes, and bright lights. Chronic nasal obstruction is frequently associated with sleep-disordered breathing.

Table 2: Aetiological Causes of Rhinitis

- **Allergic rhinitis**
  - Seasonal (e.g. pollens)
  - Perennial (e.g. house dust mite)
  - Occupational (e.g. animal antigens)
- **Non-allergic rhinitis**
  - Infectious rhinitis
    - Acute (viral, bacterial)
    - Chronic
      - Specific: bacterial, fungal
      - Non-specific: immune deficiency
    - Atrophic rhinitis (*Klebsiella ozaenae*)
  - Non-allergic, non-infectious rhinitis without eosinophilia
  - Non-allergic rhinitis with eosinophilia syndrome
  - Vasomotor rhinitis
    - Runners (rhinorrhoea predominates)
    - Dry patients (nasal obstruction and airflow resistance predominate)
  - Hormonal
    - Menstruation
    - Pregnancy
    - Hypothyroidism
  - Occupational (e.g. wood dust)
  - Food-induced and gustatory rhinitis
  - Drug-induced rhinitis
  - Antihypertensives
    - ACE-Inhibitors
    - Reserpine
    - Phentolamine
    - Alpha-methyldopa
    - Beta-blockers
  - Chlorpromazine
  - Aspirin and other NSAIDs
  - Oral contraceptives
  - Rhinitis medicamentosa
    - Alpha-adrenergic vasodilators
    - Oxymetazoline
    - Phenylephrine

ACE = Angiotensin converting enzyme; NSAIDs = Non steroidal anti-inflammatory drugs.

Diagnosis

Identification of the aetiological causes is based on the pattern, chronicity, and seasonal variation of symptoms (or the lack of these), history of medication, presence of co-existing conditions, occupational exposure, environmental history and identification of the precipitating factors. Physical examination should also focus on identifying surgically correctable conditions such as deviation of the nasal septum (DNS), polyps, or enlarged turbinates. Allergen skin or *in vitro* testing is useful in detecting allergic rhinitis.

Management

Management of rhinitis includes antihistamines, topical corticosteroids, and avoidance of inciting factors. Second generation, non-sedating oral antihistaminics (e.g. loratadine, cetirizine, fexofenadine) are effective in reducing symptoms of itching, sneezing, and rhinorrhoea. The World Health Organization (WHO) recommends using a combination of a non-sedating anti-histamine with anti-leukotriene for treating allergic rhinitis. Intranasal anti-histaminics (e.g. azelastine), while useful in relieving rhinorrhoea, have a bitter taste and may cause sedation due to systemic absorption. Topical corticosteroids (e.g. budesonide, mometasone furoate, beclomethasone) provide ample relief in patients with allergic rhinitis. Other useful drugs for rhinorrhoea include anti-cholinergic agents (e.g. ipratropium bromide), nasal decongestants (e.g. oxymetazoline). Oral corticosteroids and allergen immunotherapy may be helpful in some patients.

PHARYNGITIS

Pharyngitis is defined as the inflammation of the pharynx, hypopharynx, uvula and tonsils. It is usually infectious in aetiology and majority of the cases are of viral origin. Other causes of pharyngitis include allergy, trauma, toxins and neoplasia. Pharyngitis caused by group A β-haemolytic *Streptococci* is more common in children aged 4 to 7 years. In persons with orogenital contact, gonococcal pharyngitis can occur. Oral thrush caused by *Candida* may develop in immunosuppressed persons.

Clinical Features

Pharyngitis may present with throat discomfort, odynophagia, cough, and constitutional symptoms such as fever, headache, malaise and myalgias. Clinical examination reveals tonsillopharyngeal erythema, exudates and rarely foul smelling grey-white pharyngeal membrane (diphtheria). Swollen tender cervical lymphadenopathy, conjunctivitis (adenovirus), maculopapular rash (infectious mononucleosis) may also be present. Cough, rhinorrhoea, and conjunctivitis are frequently associated in viral pharyngitis. Differential diagnosis includes more dangerous conditions, such as epiglottitis, laryngitis, laryngotracheitis, and peritonsillar abscess.

Diagnosis

Diagnosis is established by throat swab culture and serological testing. Prompt recognition and treatment of group A β-haemolytic streptococcal pharyngitis is of paramount importance as this is associated with the development of rheumatic heart disease.

Management

Treatment of pharyngitis is mainly symptomatic and supportive. Some patients may require antibiotic treatment. Empiric antimicrobial therapy should cover all likely pathogens in the given setting and should be tailored as per the culture and sensitivity report. Anti-fungal and anti-viral agents may be required in certain cases. Viral pharyngitis is mostly a self-limiting disease which resolves spontaneously. However, the clinician should be aware of the potential complications of pharyngitis (**Table 3**).

Table 3: Complications and Sequelae of Pharyngitis

Suppurative
- Sinusitis
- Otitis media
- Epiglottitis
- Mastoiditis
- Peritonsillar abscess
- Retropharyngeal abscess
- Suppurative cervical lymphadenitis
- Pneumonia

Non-suppurative
- Airway obstruction
- Acute inflammatory demyelinating polyneuropathy
- Thrombocytopaenia
- Myocarditis, pericarditis
- Encephalitis, meningitis
- Streptococcal toxic shock syndrome
- Acute rheumatic fever

SINUSITIS

Inflammation of the paranasal sinuses results in sinusitis. Numerous factors predispose to the development of sinusitis (**Table 4**).

Table 4: Conditions Predisposing to the Development of Sinusitis

Anatomic abnormalities of the osteomeatal complex (e.g. deviated nasal septum, concha bullosa, bone spurs)
Allergic rhinitis
Vasomotor rhinitis, rhinitis medicamentosa, cocaine abuse
Nasal polyps
Nasotracheal, nasogastric intubation
Tumours causing obstruction
Dental disease/surgery
Recurrent upper respiratory infections
Immune deficiency (e.g. common variable immunodeficiency)
Cystic fibrosis
Kartagener's syndrome and other immotile cilia syndromes
Tobacco smoking
Environmental pollution

Clinical Features

Patients with acute sinusitis present frequently with persistence of symptoms even after the common cold has subsided, with nasal congestion, mucopurulent or purulent nasal discharge, headache, facial pain or heaviness, and fever. Pain increases in bending forwards. Localised tenderness indicates involvement of a group of sinuses. Maxillary sinuses are more commonly affected. The nasal mucosa appears oedematous with copious secretions. In chronic sinusitis, pain and fever are seldom present and the predominant symptoms are nasal obstruction, purulent nasal discharge, postnasal drip, chronic cough, hyposmia and halitosis. Clinical examination reveals an inflamed, thickened mucosa with polypoidal changes.

Diagnosis

Nasal endoscopy is useful for direct visualisation and for obtaining samples for microbiological and histopathological study. Radiographs of the paranasal sinuses [occipitomental (Water's) view and submentovertical view] and computed tomography are useful to demonstrate sinusitis radiographically. Magnetic resonance imaging is a superior modality for evaluating neoplasms, orbital and intracranial complications, and fungal sinusitis.

Management

Sinusitis is treated by controlling the predisposing factors (**Table 4**), analgesics for fever and pain relief and appropriate antibiotics. Nasal saline spray, topically administered decongestants (xylometazoline), steroids (fluticasone, beclomethasone), and cromolyn sodium, may be used for symptom relief. Surgery is indicated in patients with chronic sinusitis refractory to medical treatment, recurrent sinusitis, large obstructing polyps (**Figure 1**), suspicion of tumour, sinus mucocele, pyocele, intracranial extension, cavernous sinus thrombosis, and fungal sinusitis. Surgical options include functional endoscopic sinus surgery, and Caldwell-Luc operation.



Figure 1: Radiograph of paranasal sinuses showing maxillary sinusitis on the right and a polyp on the left.
Courtesy: Dr. S.N. Gosavi.

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23.5 Bronchial Asthma

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DEFINITION

Bronchial asthma is a chronic airway disorder which can affect people of all age groups. According to the *global initiative for asthma* (GINA), asthma is defined as a chronic inflammatory disorder of airways which is associated with airway hyper-responsiveness. It leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lungs that is often reversible either spontaneously or with treatment. In asthmatic patients, airway inflammation usually persists even during asymptomatic periods. Though symptoms and bronchospasm are intermittent, airway inflammation is persistent. Based on the concept of persistent airway inflammation, two important principles have emerged. First, the disease is chronic, often life-long; second, its severity fluctuates and sometimes there may be prolonged remissions.

EPIDEMIOLOGY

Prevalence of asthma varies considerably within countries and between countries. It is more prevalent in developed countries than developing ones, more in children (15%) than adults (10% to 12%), more in urban than rural areas, reasons of which are not fully understood. Nearly 8% to 10% of the total population suffers from it. In India, the prevalence of asthma has been found to be around 7% in the majority of surveys done. However, it has been reported to vary from 2% to 17% in different study populations, the disease can start at any age, but in a majority it starts before 10 years of age. It is twice as common among boys than girls, whereas in adults the male to female ratio is usually equal.

AETIOPATHOGENESIS

Aetiologic factors of asthma are divided into two groups: inducing factors and trigger factors. Inducing factors induce asthma in susceptible persons and these include genetic factors, obesity, viral infections in early life and exposure to tobacco smoke. Trigger factors such as allergens, vigorous exercise, viral infections, etc. can provoke symptoms in subjects already having asthma. Some factors such as viral infection and occupational sensitisers act as both inducer and trigger factors.

Inducing Factors

Asthma occurs more commonly in relatives of atopic individuals, and therefore, atopy has been recognised as an important risk factor for developing asthma. A distinct gene for atopy on chromosome 11q has been identified. Similarly, a gene at chromosome 5q has been linked to the synthesis of immunoglobulin (Ig)E. Tobacco smoke, maternal smoking during pregnancy or infancy, rhino-syncytial virus infections and exposure to high concentration of allergens during infancy can also induce bronchial asthma.

Trigger Factors

Wide range of factors can trigger symptoms in a patient with asthma, important among these are as follows:

Allergens

Inhaled allergens are the common triggering factors responsible for provoking symptoms of asthma. House dust mite is the commonest allergen. Pollen, mold, animal dander and cockroaches are other common allergens provoking asthma.

Environment

Asthma is usually worse on a cold and dry day, especially when there is a strong wind. Traffic pollution can aggravate symptoms in asthmatic patients. Air pollutants such as sulphur dioxide, ozone, diesel particles can also precipitate asthmatic symptoms. Indoor air pollution is also an important trigger factor. Cooking gas fumes and even passive cigarette smoking can trigger symptoms in asthmatic subjects. Paints, sprays and fumes can also precipitate severe symptoms in patients with asthma.

Infections

Patients often give history of an upper respiratory tract infection before an attack of asthma. These symptoms are usually due to rhinovirus infection. Viral infections are the major triggering factors for asthma exacerbations, but it is uncertain that they play an important role in aetiology of bronchial asthma. Recently, atypical micro-organisms like *Mycoplasma* and *Chlamydia* have also been identified in the mechanism of severe asthma.

Drugs

Beta-blockers and cholinergic drugs used for *Myasthenia gravis* and prostaglandins-2 (PGF-2) used for inducing abortion are known to cause bronchoconstriction in patients with bronchial asthma. Aspirin and nonsteroidal anti-inflammatory drugs are known to trigger asthma in almost 5% of the patients. Aspirin-sensitive asthma is more common in intrinsic variety of asthma, especially those having nasal polyps. Majority of aspirin-sensitive patients tolerate paracetamol quite well.

Food

Food allergens are not so common triggers of asthma. Egg, milk, and wheat are implicated in causing asthma in a few cases. The yellow colouring agents of food such as tartrazine and food preserving agents such as sulphites can also aggravate asthma in some patients, often those who are sensitive to aspirin. Physical characteristics of food such as cold edibles are usually not implicated in aggravation of asthma. However, Indians are reported to be more sensitive and they exhibit bronchoconstriction to edibles such as ice. Diet rich in anti-oxidants such as vitamin C and vitamin A, selenium, magnesium and omega-3 polyunsaturated fats or high in sodium and omega-6 polyunsaturated fats are associated with increased risk of bronchial asthma. Some asthmatics may show aggravation of symptoms to sea food items.

Exercise

Vigorous exercise, particularly on a cold and dry day, will cause symptoms in 80% of the patients with asthma. Exercise related exacerbation is also termed as exercise-induced asthma.

Psychological factors

Stress can influence asthma in some patients. However, it is rarely a major contributor to the severity of asthma.

Occupation

Occupational asthma is caused by a specific agent present at the work place. Occupational asthma affects almost 10% of the young adults. More than 200 agents have been linked with triggering of asthma at work places. Chemicals such as isocyanates, platinum, chrome, nickel, reactive dyes of diazonium salt, pharmaceutical agents, wood dust and cotton dust are among the common causes of occupational asthma.

Gastro-oesophageal reflux

Gastro-oesophageal reflux has been associated with triggering of asthma. Microaspirate of gastric contents and nervous reflex causing bronchoconstriction are common mechanisms proposed to explain GER-induced asthma.

PATHOLOGY

Gross Appearance

Patients dying from acute episodes of asthma have bulky and over distended lungs which fail to deflate when the chest is opened. The airways are thickened and plugged with sticky secretions.

Microscopic Appearance

The main features of asthmatic airways include marked thickening of basement membrane, bronchial smooth muscle hypertrophy and damaged epithelium, much of which is shaded. The bronchial wall contains inflammatory cells and the most important cell is eosinophil. Other cells include neutrophils, lymphocytes and plasma cells. The mucous or bronchial secretions of an asthmatic patient contain eosinophils, eosinophil cationic protein, desquamated airway epithelial cells termed as creola bodies, Charcot-Leyden crystals, and thick thread-like sputum called Curschmann's spirals. The mucus is often impacted in the small airways in severe asthma.

PATHOGENESIS OF ASTHMA

Initial Sensitisation

It is now clear that T-lymphocytes play a key role in asthmatic airway inflammation and sensitisation. There are two types of T-lymphocyte helper (Th) cells. Th1 controls synthesis of Igs such as IgA and IgM whereas Th 2 controls IgE production. Usually, there is a balance between Th1/Th 2 switch.

Exposure to an inducing factor sensitises T cells of a person with genetic susceptibility with bronchial asthma, and it shifts the Th1/Th 2 switch in favour of Th 2 dominance. Once sensitised, these Th 2 cells get into airway mucosa and governs IgE-mediated responses of allergic reaction (**Figure 1**). In a normal individual, when a noxious allergic substance enters the airway, IgA is released. However, in a sensitised person IgE is released. Once sensitised, the dose of the noxious agent that provokes asthma on subsequent exposure is much less.

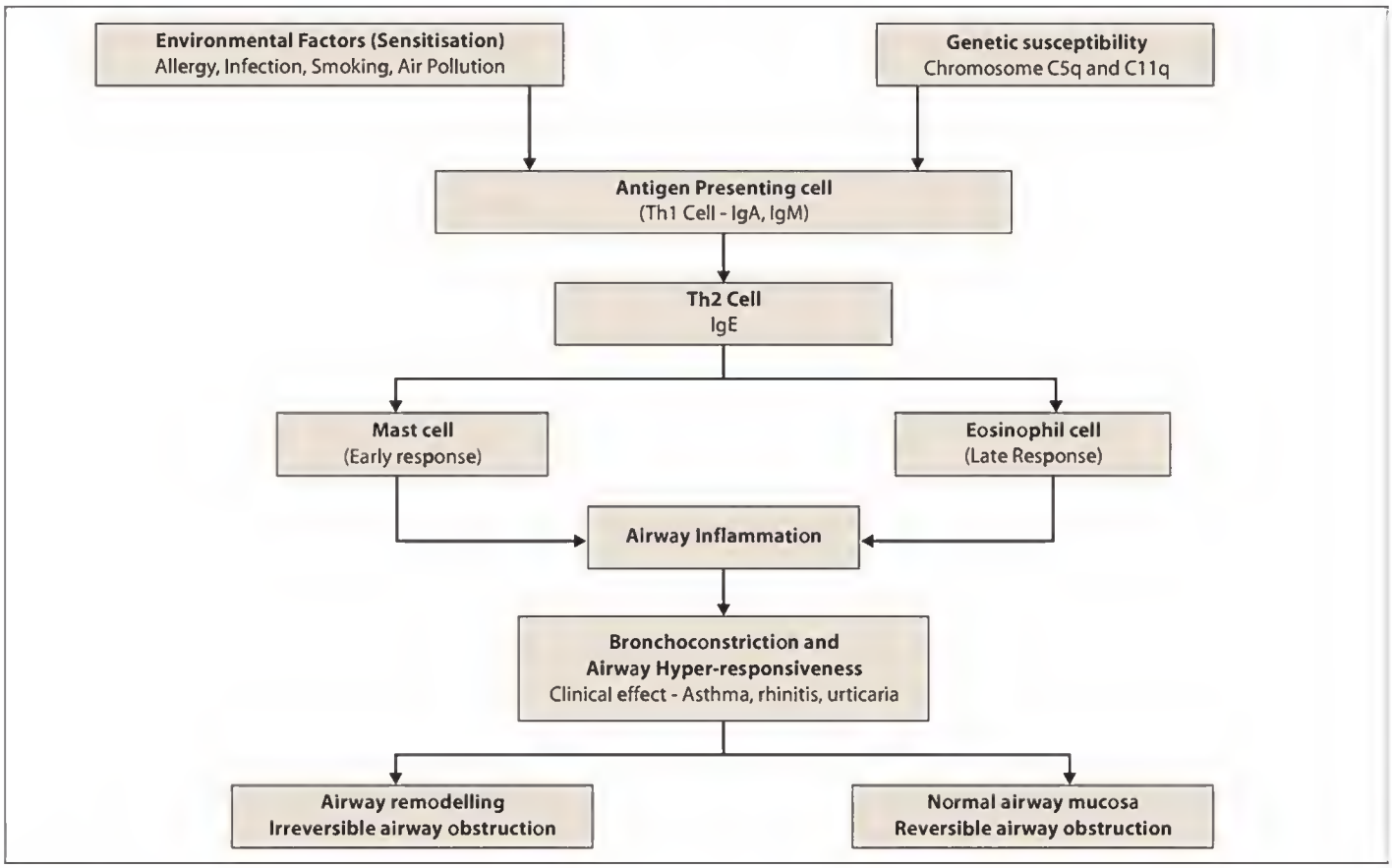


Figure 1: Pathogenesis of asthma.

Ig = Immunoglobulin.

Provocation of Asthma

When an allergen is inhaled by an asthmatic patient, airway obstruction starts within minutes and the peak effect is observed within 20 to 30 minutes. This is an early phase reaction or early response and is due to the direct action of mast cell derived mediators on the smooth muscles of the airways. When inhaled allergens come in contact with mast cells located in airway mucosa, then histamine and arachidonic acid derivatives such as leukotrienes and PGF are released.

In some cases, the reaction soon terminates and resolution starts with the decrease in short-lived mediator concentration. Whereas in many cases, a second phase of airway obstruction occurs 6 to 10 hours later. This is called late phase reaction or late response and it is inflammatory in nature (**Figure 1**).

CLINICAL FEATURES

Symptoms

Episodic breathlessness, wheezing, cough and chest tightness are important symptoms of bronchial asthma. These symptoms show a characteristic pattern of diurnal variability of worsening during night and early morning. It may lead to disrupted sleep due to cough and wheeze. There is an increased mucous production, which is thick, mucoid and difficult to expectorate. History of recurrent episodes of asthma caused by one or more trigger factors is important for the diagnosis of bronchial asthma. However, between episodes, patients usually remain symptom-free. Asthmatics are frequently associated with other atopic conditions, such as eczema, urticaria, allergic rhinitis, and hay-fever.

Physical Examination

Rhonchi are heard as the most prominent sign of asthma, especially during expiration. At the time of asthma exacerbation signs such as increased respiratory rate, flaring of *alae nasi*, use of accessory muscles of respiration, and pulsus paradoxus may be detected. In view of the diurnal variation of airflow obstruction, asthmatic symptoms and signs vary with worsening during night and improvement during day. Therefore, physical examination during day may be normal, and hence, the absence of signs does not exclude the diagnosis of bronchial asthma.

DIFFERENTIAL DIAGNOSIS

Wheezing and dyspnoea are prominent symptoms of asthma, and conditions presenting with these symptoms may pose diagnostic problem. The differentiation of chronic obstructive pulmonary disease (COPD) from asthma can pose clinical difficulty. History of smoking, exertional dyspnoea, and lack of symptoms-free periods favour a diagnosis of COPD, whereas nocturnal worsening, chest tightness, episodic pattern and good response to bronchodilators and steroids favour diagnosis of asthma. Bronchodilator reversibility shown in spirometry is diagnostic of bronchial asthma.

Acute left ventricular failure may cause wheezing and dyspnoea especially during nights. Dyspnoea starting 1 to 2 hours after sleep, history of heart disease, inspiratory crepitations and gallop rhythm supports the diagnosis of left ventricular failure, whereas early morning dyspnoea and response to bronchodilators are characteristic of asthma.

Upper airway obstruction with a tumour or lymphadenopathy is occasionally mistaken for asthma. It usually presents with rapidly progressive airway obstruction and inspiratory stridor. Spirometry shows reduced inspiratory flow and tracings of flow-volume curve becomes flat instead of being curved normally.

Hyperventilation syndrome, foreign body aspiration, bronchiectasis pulmonary tuberculosis and acute pulmonary thromboembolism are also sometimes confused with asthma. Careful history and documentation of variable and reversible airway obstruction can differentiate asthma from these conditions.

DIAGNOSIS

Blood Examination

Usually, patients have an eosinophil count in the range of 5% to 15%, or the absolute eosinophil count is more than 400. Total serum IgE and specific IgE are elevated in bronchial asthma.

Sputum Induction

Sputum examination can provide a useful clue about the severity of airway inflammation. Sputum is induced after administration of hypertonic saline with a nebuliser. In patients with asthma, the number of eosinophils are increased in the induced sputum. Estimation of eosinophilic cationic protein in sputum or urine is also found to be a useful test for assessment of the severity of airway inflammation.

Airway Hyperresponsiveness

Increased airway hyperresponsiveness (AHR) is a characteristic of bronchial asthma. It can be measured by methacholine or histamine challenge test. This test is useful in the diagnosis of asthma when the patient is in remission with normal lung functions.

Chest Radiograph

Radiograph of the chest may show hyperinflation in a patient with asthma. It may also reveal complications of severe asthma such as rib fracture, pneumothorax, and pneumomediastinum.

High Resolution Computerised Tomography of Chest

Routinely, this investigation is not required in patients with bronchial asthma unless some associated lung disease is suspected. High resolution computerised tomography shows areas of thickening of the bronchial wall in patient with severe asthma.

Identification of Trigger Factors

A good history is important in identification of trigger factors. Particular care should be taken in evaluation of environmental factors and occupation of the patient. Household work, especially in the kitchen, is an important provoking factor in many housewives whereas agricultural work such as grain storage, cutting of crops, pesticide spray and exposure to cold during irrigation may be important in rural asthmatics. It is also important to ask about both nocturnal and exercise-induced symptoms.

Skin Prick Test

Sensitivity to a particular antigen can be identified by injecting a small amount of allergens into the skin. Wheal and flare appear at the site of injection of a sensitised allergen. Skin prick test to common inhalant allergens is usually positive in allergic asthma. Allergens can also be identified by estimation of specific IgE in

the blood through radioallergosorbent test (RAST). However, SPT is cheaper and more sensitive than RAST.

Measurement of Lung Functions

Various types of lung function tests are available, but measurements of peak expiratory flow rate (PEFR) by a peak flow meter and forced expiratory volume in one second (FEV1) by a spirometer are most useful in a making diagnosis and assessing the severity of asthma.

Peak expiratory flow rate

Peak expiratory flow rate represents maximal expiratory effort performed after full inhalation. Peak expiratory flow rate is reduced with increasing severity of airway obstruction. It can be measured with a handy tool called peak flow meter. This equipment is very useful in monitoring the severity of asthma and designing a treatment plan on an individual basis. Usually, PEFR values of a patient is compared with the predicted normal values. However, there is a large variation in normal predicted values, and therefore personal best PEFR value is taken as normal reference value. Personal best value is the highest recorded PEFR value of a person taken over a few days during asymptomatic period.

Normally, there is variation in PEFR values taken at different times of the day. The magnitude of variation between morning and evening PEFR values is called PEFR variability and it is proportional to the severity of asthma. Another useful index is PEFR reversibility. After baseline PEFR, beta-2 agonist drugs such as salbutamol or terbutaline are administered through an inhaler or nebuliser. The PEFR noted 15 minutes after the bronchodilator administration, shows the magnitude of reversibility. More than 20% reversibility or variability is diagnostic of bronchial asthma.

Spirometry

Asthma is diagnosed by demonstration of reversible airway obstruction in spirometry. A ratio of FEV1 and forced vital capacity (FVC) less than 0.7 is diagnostic of airway obstruction. After bronchodilator administration, FEV1 increases by more than 12% and 200 mL in asthmatic patients. It is called reversibility of airway obstruction which is characteristic of asthma.

Lung Volumes and Diffusing Capacity

Lung volumes, such as residual volume and total lung capacity, are increased in a patient with asthma. Carbon monoxide diffusing capacity (DLCO) is either normal or increased in the asthma patients. Diffusing capacity of the lung for carbon monoxide is reduced in patients with COPD, therefore, it is useful in differentiating COPD from asthma.

Oximetry

In assessing severity of acute severe asthma, pulse oximetry is a useful tool. It detects hypoxaemia in severe asthma. Normally, oxygen saturation should be more than 90%. Pulse oximetry is also helpful in monitoring oxygen therapy.

Arterial Blood Gas Analysis

Periodic measurement of arterial blood gases proves useful in monitoring of patients with acute asthma. Arterial blood gas analysis give basic information about pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and bicarbonate (HCO_3). In severe asthma, PaO_2 decreases but $PaCO_2$ remains normal. When $PaCO_2$ starts rising, it is an indication of requirement for assisted ventilation.

ASSESSMENT OF SEVERITY

Severity of asthma is highly variable. Assessing the severity of asthma on the basis of one parameter does not represent a true picture. Therefore, GINA guidelines suggest a method of assessing asthma severity on the basis of parameters such as symptoms, activity limitation, lung function tests, inhaler use, and frequency of exacerbations. On the basis of these parameters, asthma is categorised into controlled, partly controlled and uncontrolled as described below.

Indices Determining Control of Asthma

- Day-time symptoms less than twice per week
- Short-acting beta agonist (SABA) inhaler use less than twice per week
- Without any night-time symptoms
- Without limitation of activity
- Normal PEFR and FEV1 values

Controlled

Asthma is said to be controlled if all indices are fulfilled and patient did not have an exacerbation in the last one year.

Partly controlled

Asthma is said to be partly controlled, if any of the indices is more severe than described above or the patient had an exacerbation during the last one year.

Poorly controlled

Asthma is said to be poorly controlled, when more than 3 indices are more severe than described above, or the patient had an exacerbation during the last week.

MANAGEMENT OF ASTHMA

Patient Education

It is aimed to enable asthmatic patient to treat himself under guidance of his doctor. It is achieved by proper education of the patient. Patient education is as important as drug treatment. Every patient with asthma should learn to take medicines regularly, correctly and understand the difference between relieving and preventive medicines. Identification and avoidance of risk factors and triggers involved in asthma are also important components of patient education. Monitoring the severity of the disease by symptom score or peak-flow meter, action plans for a situation like exercise-induced and acute attack, and misconception about the disease should also be addressed.

Identify and reduce exposure to risk factors

Asthma exacerbation can be caused by a variety of trigger factors. Early identification of a trigger factor and preventing its exposure improves asthma control and reduces requirement of medicines.

Assess, monitor and treat asthma

Asthma control is assessed and then patient is treated to achieve the control. Once adequate control is achieved, the patient is monitored regularly to maintain the control.

Manage exacerbation

The aim of treatment during management of an exacerbation is to relieve bronchospasm and hypoxia as quickly as possible.

A future plan is made to prevent recurrence of episodes of exacerbation.

Special Situation

At times, asthma management requires attention to special situations such as allergic rhinitis, pregnancy, aspirin sensitivity, occupational compulsions, and gastro-oesophageal reflux.

DRUG THERAPY

Mode of Administration

Asthma drugs are administered as injection, tablet, syrup, or in aerosol form. Aerosol administration through inhaler devices is the preferred mode of administration. With aerosols, the dose and the side effects of the drug are much less and the therapeutic effect is better. Drugs such as theophyllines and anti-leukotrienes are not available in aerosol form. In order to get optimal therapeutic effect, the technique of aerosol use should be correct.

Devices used for delivering inhaled medications include metered dose inhaler (MDIs), dry powder inhaler (DPIs) and nebulisers (jet nebulisers and ultrasonic nebulisers). With steroid MDIs and DPIs, hoarseness of voice and oral candidiasis are common in some patients. Rinsing the mouth after the use of inhaler, use of a spacer device with MDI and the use of MDIs and DPIs before food are some of the measures to prevent local adverse effects of inhaled corticosteroids. When used with spacer, delivery of MDI drug into airways also improves.

Commonly Used Drugs

Drugs for asthma are divided into two categories: bronchodilators or relievers, and controllers or preventers (**Table 1**). The bronchodilators work quickly and relieve the symptoms and acute attack of asthma rapidly. Beta-2-agonists, anticholinergics, and theophyllines are included in this category. The controller medicines prevent the onset of symptoms by controlling inflammation. Inhaled corticosteroids (ICS), systemic corticosteroids, anti-leukotrienes, and cromones are included in this category. The broad guidelines of asthma management are given in **Figure 2**.

Bronchodilators Drugs

Bronchodilators are the drugs which primarily act on smooth muscles of airways and cause rapid relief of symptoms. There are 3 classes of bronchodilator medicines—β-2 agonists, anticholinergics, and theophyllines.

Beta-2-agonists

The most commonly used bronchodilators are beta-2-agonists. Inhaled preparations are better because even in a small dose they cause equal or better bronchodilatation and the action is much quicker. Salbutamol and terbutaline are short-acting β-2 agonist (SABA) having a duration of action of 3 to 6 hours. Salmeterol and formoterol are long acting β-2 agonists (LABA) having a duration of action over 12 hours.

Short-acting β-2 agonists are very good for the treatment of an attack of asthma and for pre-treating the symptoms associated with exercise. Since long-term regular use of SABA is associated with poor control of asthma, therefore, SABA should not be used on a regular basis. Long acting β-2 agonists are also not used regularly as monotherapy. Since LABA does not control airway inflammation, therefore, it should be used in combination with ICS. However, recently use of LABA in combination with ICS has also been restricted. It has been advised that combination of LABA and ICS should be used only in those patients whose asthma fails to be controlled with controllers such as ICS alone.

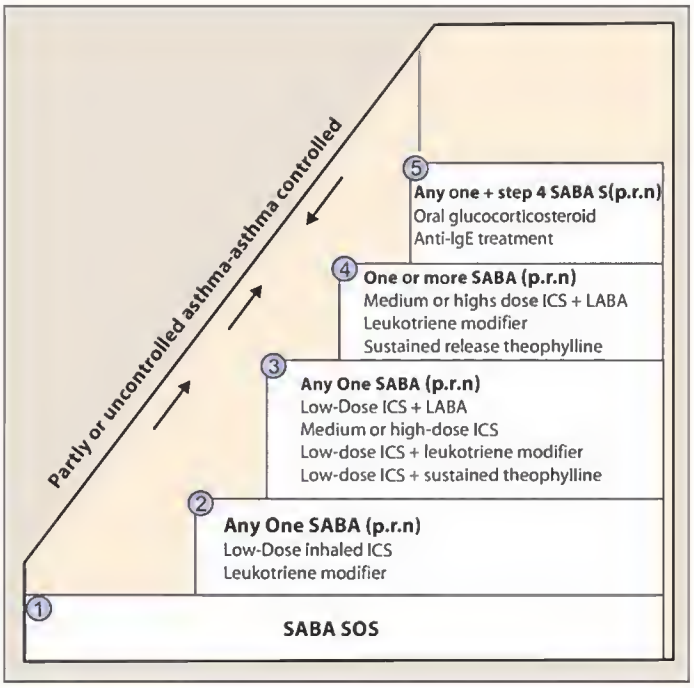


Figure 2: Steps of asthma management based on GINA guidelines. Goal of therapy is to achieve asthma control. SABA is used at all steps.

SABA = Short-acting β-2 agonist; ICS = Inhaled corticosteroids; LABA = Long-acting β-2 agonist; IgE = Immunoglobulin E; p.r.n. = as and when required.

Anticholinergics

Interestingly, *Datura* plant was used as the first inhaled medicine and the *hookah*, the local filtered tobacco inhaler, as the first inhaler device. These two were both discovered and invented in India. With the introduction of more selective anti-muscarinic drugs, interest in these drugs was renewed. Ipratropium bromide is a short-acting muscarinic antagonist of this class. It can be used as reliever therapy in patients who do not respond to beta-2-agonists.

Theophyllines

Two types of formulations of theophylline are available: short-acting and sustained-release. Short-acting theophylline has erratic absorption and therefore, can lead to rise in serum concentration to toxic levels unpredictably. Sustained-release theophylline has more uniform absorption and a longer half-life. It inhibits both early and late asthma reactions after an allergen exposure. It also has some anti-inflammatory properties.

Controller Drugs

Inhaled corticosteroids

Corticosteroids are the most effective controller and anti-inflammatory medicines reducing the number of inflammatory cells and their activation in the airways. It improves lung functions, decreases airway hyper-responsiveness, reduces and prevents symptoms. Inhaled corticosteroids are preferred over tablets or syrup for long-term therapy. Inhaled corticosteroids are safe and effective for long-term treatment of asthma. Beclomethasone, budesonide, fluticasone and ciclesonide are commonly used inhaled steroid preparations.

Systemic glucocorticosteroids

Systemic glucocorticosteroids are important in the treatment of exacerbation of asthma because they prevent its progression.

Table 1: Drugs Used in Management of Asthma

Drug Category and Name	Mode of Administration	Dose	Indication	Side Effects
Beta-2-agonist				
Short-acting β agonists (SABA)				
Salbutamol	Oral, inhalation	2 to 4 mg, 100 to 200 mcg	Reliever	Tremors, tachycardia
Terbutaline	Oral, inhalation	5 mg, 250 to 500 mcg	Reliever	
Long-acting β agonists (LABA)				
Formoterol	Inhalation	4.5 to 9.0 mcg/q 12 hourly	Controller	Mouth-throat irritation
Salmeterol	Inhalation	50 to 100 mcg/q 12 hourly	Controller	Hypokalaemia
Methylxanthines				
Theophylline	Oral	100 to 300 mg/q 8 hourly	Reliever	Cardiac arrhythmias
Aminophylline	Oral and slow IV	250 to 500 mg		Tachycardia
Doxophylline	Oral	400 mg/od		Mouth-throat irritation
				Hypokalaemia, hypotension
				Tremors, death
Anticholinergics				
Ipratropium bromide	Inhalation	40 mcg/qid	Reliever	Dry mouth, blurred vision, Glaucoma, urinary retention
Corticosteroids				
Prednisolone	Oral	20 to 40mg	Controller	Osteoporosis, diabetes
Dexamethasone	Oral	0.5 to 5 mg/qd	Controller	Arterial hypertension
	IV	4 to 20 mg/qd	Reliever	
Hydrocortisone	IV	100 mg bolus–100 mg/q 8 hourly	Reliever	Cataract, glaucoma
Beclomethasone	Inhalation	200 to 2,000 mcg	Controller	Adrenal suppression
Budesonide	Inhalation	200 to 1,600 mcg	Controller	
Fluticasone	Inhalation	100 to 1,000 mcg	Controller	Obesity, muscle weakness
Ciclesonide	Inhalation	80 to 1,280 mcg	Controller	
Mast cell stabilisers				
Sodium cromoglycate	Inhalation	1 mg/dose(2 puffs/q 8 hourly)	Controller	Cough, throat irritation
Ketotifen	Oral	1 to 2 mg/q 12 hourly	Controller	Sedation, dry mouth
Anti-IgE-antibody				
Omalizumab	Subcutaneous	150 to 375mg, 2 to 4/week	Severe allergic asthma uncontrolled with inhaled steroids	Headache, anaphylaxis sinusitis
Leukotriene modifiers				
Montelukast	Oral	5 to 10 mg/day at bed-time	Controller	Well-tolerated
Zafirlukast	Oral			
Zileuton	Oral			

IV = Intravenous; d = Day; od = Once a day.

During exacerbation, a short course of oral corticosteroid (40 to 60 mg prednisolone) is given daily for 5 to 10 days. When the patient symptomatically improves, the oral corticosteroid can be stopped or tapered off but ICS must be continued.

Leukotriene modifiers

The inflammatory cells like mast cells and eosinophils in asthmatic patients produce cysteinyl leukotrienes which are potent bronchoconstrictors. Cysteinyl leukotriene (CysLT1) receptor antagonist drugs like montelukast, pranlukast, zafirlukast and 5-lipoxygenase inhibitor zileuton can prevent such bronchoconstriction, improve symptoms and reduce airway inflammation. These medicines are used as add-on therapy. Leukotriene inhibitors are especially useful in patients with aspirin-induced asthma.

Cromones

Sodium cromoglycate and nedocromil sodium can cause inhibition of mast cell and sensory nerve activation, and therefore, are effective in trigger-induced asthma such as exercise-induced asthma, allergen and sulphur dioxide- induced asthma. These are very safe but have a short duration of action.

Anti-IgE-antibody

IgE mediates important allergen-induced reaction in asthmatic airways. Omalizumab is an antibody which neutralises circulating IgE and inhibits IgE-mediated reactions. This is used only in patients with severe allergic asthma having elevated levels of IgE and who remain uncontrolled with a maximal dose of ICS.

Antigen-specific immunotherapy

The role of antigen-specific immunotherapy in patients with asthma is limited. Proper immunotherapy requires identification of single clinically relevant allergen. Objective evidence suggests that immunotherapy with highly purified allergens is useful in dust mite, pollen and animal dander allergies. Some authorities believe that immunotherapy is more effective in patients having dominant nasal symptoms.

ALTERNATIVE THERAPIES

Majority of alternative or complementary therapies are not useful in asthma. Yoga, hypnosis, and acupuncture have shown small beneficial effects in some studies; however, well-planned randomised controlled trials are lacking.

DIFFICULT ASTHMA

Five per cent of asthmatic patients are difficult to control with the available conventional therapy for asthma. The most common reason for uncontrolled asthma is non-compliance of medication. There are several factors which make asthma more difficult to control, e.g. exposure to high concentration of allergens or exposure to unidentified occupational agents. Viral, bacterial, and mycoplasma infections can sometimes lead to refractory bronchospasm. Uncontrolled gastro-oesophageal reflux and simultaneous use of drugs such as beta-blockers, aspirin, and cyclo-oxygenase inhibitors are also important risk factors of difficult asthma. Refractory asthma is difficult to treat unless primary factors are adequately controlled. Compliance, proper use of inhalers, identification, and elimination of underlying triggering factors are important steps in the management of difficult asthma.

ACUTE SEVERE ASTHMA

This is an extreme stage of severity of asthma formerly termed as status asthmaticus. Clinical features of acute severe asthma include coughing, wheezing, shortness of breath, and chest wall recession (indrawing in the flesh between the ribs and sternum), inability to complete a sentence in one breath, use of accessory muscles, respiratory rate >25 per minute, pulse >110 per minute and presence of pulsus paradoxus.

Pulsus Paradoxus

In normal individuals the systolic blood pressure falls by 2 to 4 mm Hg with normal inspiration and 10 mm Hg with deep inspiration. When systolic pressure falls more than 10 mm Hg during inspiration, the pulse is called as pulsus paradoxus. Presence of pulsus paradoxus indicates presence of severe asthma and in such patients PEFR is usually less than 60% of the predicted or best. Pulsus paradoxus may also be present in other conditions such as cardiac tamponade, constrictive pericarditis, and superior vena cava obstruction.

If the condition worsens, airways become further narrowed and the movement of air decreases. In such situations, sometimes wheezing ceases. It indicates that the airways are extremely narrowed and very little air is moving in and out. This is also called silent chest type asthma.

Features of life-threatening asthma include silent chest, cyanosis, or feeble respiratory effort, bradycardia, hypotension and PEFR <30% of the predicted or best. Patient may be exhausted, confused and lapses into coma. Arterial blood gas analysis shows normal or high $PaCO_2$ (more than 45 mm Hg), severe hypoxia (PaO_2 <60 mm Hg) and a low pH. Acute severe asthma may lead to complications, such as dehydration, acute cor pulmonale and pneumothorax.

TREATMENT

The aim of treatment in acute severe bronchial asthma is to save life. Hypoxia is treated with high concentration of oxygen to maintain oxygen saturation above 90%. Usually, 40% to 60% oxygen is administered. In contrast to chronic obstructive pulmonary disease, carbon dioxide retention is not aggravated by administration of higher concentration of oxygen in bronchial asthma. Short acting β-2 agonist such as salbutamol 5 mg or terbutaline 10 mg are administered via oxygen driven nebuliser. It is repeated as frequently as every 15 to 30 minutes depending on the severity of the asthma. Ipratropium 0.5 mg may also be added to the salbutamol nebuliser solution and repeated every 6 hours. Prednisolone tablet 30 to 60 mg or hydrocortisone hemisuccinate 200 mg through intravenous route or both are given if the patient is very ill. In some patients, intravenous aminophylline 250 mg is administered over 20 minutes. If oral theophylline has been taken in the preceding hours, IV aminophylline should be avoided. Magnesium sulphate given intravenously or with nebuliser is also effective in some patients with acute severe asthma. Sometimes a patient is anxious and perspires, but sedative drugs are contraindicated due to apprehension of respiratory depression.

If any patient does not respond to treatment, one should suspect pneumonitis or pneumothorax. In such a situation, a chest radiograph is useful. The patient should be closely monitored with PEFR every 15 to 30 minutes after starting the treatment, and pulse oximetry to maintain oxygen saturation above 90%. If oxygen saturation is less than 90%, an arterial blood gas analysis should be done and repeated every 2 hours. Assisted mechanical ventilation is required in a patient showing deterioration (**Table 2**). Antibiotics have no role until unless there is an evidence of bacterial pneumonia.

The prognosis of acute severe asthma is good. Mortality is rare, and occurs usually when treatment is delayed or inadequate. Mechanical ventilation may be required.

Table 2: Indication Mechanical Ventilation

Mechanical ventilation is indicated when the spontaneous ventilation is inadequate to sustain life. Initially, some patients may respond to non-invasive ventilation (NIV), therefore a trial of NIV for a period of 1 to 2 hours is a logical approach in selected patients.

Indications

Absolute indication: Cardio-pulmonary arrest, deteriorating consciousness

Relative indications: Hypercapnia, acidosis, progressive deterioration with increasing distress or physical exhaustion

Complications

Hypotension, barotrauma and nosocomial pneumonia

RECOMMENDED READINGS

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23.6 Chronic Obstructive Pulmonary Disease

Surendra K Sharma

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a disease state characterised by progressive development of chronic airflow limitation that is not fully reversible and includes chronic bronchitis, emphysema, and small airway disease. The airflow obstruction in COPD may be partly reversible and some patients may also manifest bronchial hyper-responsiveness. Excluded from this definition is bronchial asthma, which also produces chronic airflow obstruction and at times may be difficult to distinguish from COPD. Chronic bronchitis is characterised by chronic cough with expectoration for at least 3 months of the year for more than 2 consecutive years. Only a minority of patients with chronic cough and expectoration have associated airflow obstruction. Emphysema is defined as the permanent, abnormal distension of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls without fibrosis. Chronic bronchitis and emphysema frequently co-exist since both share common aetiological factors. After many years, chronic bronchitis gets complicated by emphysema.

EPIDEMIOLOGY

In India, COPD is the second most common lung disorder after pulmonary tuberculosis. The disease is frequently encountered in the middle-aged patients and is rare below the age of 35 years. COPD affects males more frequently because of smoking. It is equally prevalent in rural and urban areas. Various aetiological factors responsible for development of COPD are detailed in **Table 1**.

Table 1: Risk Factors for COPD

Tobacco smoking
Air pollution (particularly with sulphur dioxide and particulates)
Occupational exposure to inorganic or organic dusts or noxious gases
Recurrent respiratory infection in childhood
Familial and genetic factors (α_1-antitrypsin deficiency)
Low birth weight

AETIOLOGY

Tobacco Smoking

Tobacco smoking is the single-most important and the most prevalent risk factor for the development of COPD. Tobacco smoke contains numerous vapourised chemicals (92%) and particulates (8%), suspended in gaseous medium. Most of the toxic organic components of smoke are contained in the particulate fraction.

The greater the total tobacco exposure, more the risk of developing COPD. *Hukka* and *bidi* smoking are as harmful as cigarette smoking. Pipe and cigar smokers have higher morbidity and mortality from COPD than non-smokers, although it is lower than cigarette smokers. The cumulative amount of tobacco smoked is related to its adverse affects. This is expressed as pack-years and is calculated by multiplying the number of packs (1 pack = 20 cigarettes) with years of smoking. Since the net weight of tobacco in a *bidi* (150 to 240 mg) is about one-fourth of that in a cigarette, in *bidi* smokers, 'cigarette equivalent pack years' are computed by dividing the 'pack-years' calculated on the basis of smoking *bidis* by four.

Inhaled smoke in conjunction with underlying host susceptibility and environmental factors produces COPD in 15% of smokers. Prolonged cigarette smoking impairs ciliary movement, produces hypertrophy and hyperplasia of mucus-secreting glands. It also inhibits antiproteases and causes neutrophils to release proteolytic enzymes.

Environmental Tobacco Smoke

Although passive smoking and exposure to environmental tobacco smoke have been associated with reductions in pulmonary function, their role in the causation of COPD remains uncertain.

Environmental Pollution

The incidence of COPD is higher in heavily industrialised urban areas. Episodes of exacerbation of COPD correlate with periods of heavy pollution with sulphur dioxide and particulate matter. In India, indoor pollution caused by burning of cow-dung cakes and use of wood for cooking are important contributory factors.

Occupation

COPD is frequently observed in persons who are engaged in occupations exposing them to either organic or inorganic dusts or to noxious gases.

Respiratory Infections

Infections are often the precipitating cause of acute exacerbations of COPD (AECOPD) and contribute significantly to morbidity and mortality. Release of enzymes from the neutrophils found during infections may contribute to the lung damage. Viral respiratory infections in infancy may cause airways obstruction in later life.

Familial and Genetic Factors

Familial aggregation of chronic bronchitis has been well demonstrated and may be partly related to indoor air pollution and passive smoking. Few studies of monozygotic twins have suggested some genetic predisposition to the development of chronic bronchitis, independent of indoor pollution and passive smoking. The protease inhibitor (Pi) alpha-1-antitrypsin (α_1-AT) is an acute phase reactant and a potent inhibitor of serine proteases. Its serum level rises in association with many inflammatory reactions in all individuals except homozygotes. α_1-AT deficiency is the strongest genetic factor causally related to the development of COPD. The deficiency is related to

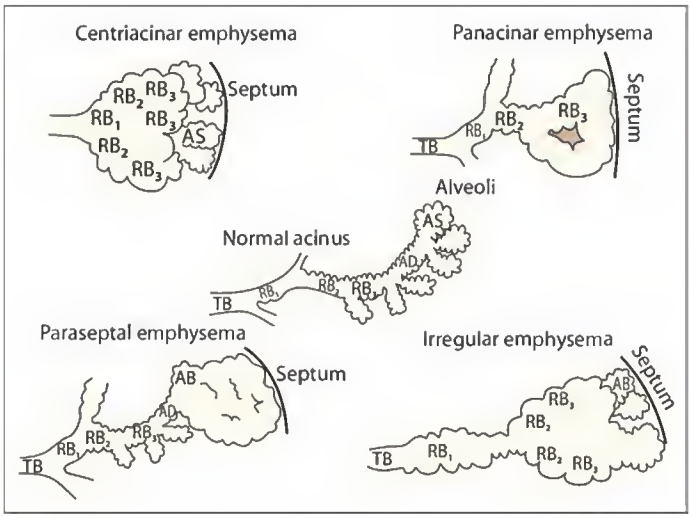


Figure 1: Types of emphysema. Centriacinar emphysema (upper panel left); panacinar emphysema (upper panel right); paraseptal emphysema (lower panel left); irregular emphysema (lower panel right).

TB = Terminal bronchiole; RB = Respiratory bronchiole.
Source: Adapted from Thurlbeck WM. Chronic bronchitis and emphysema - the pathophysiology of chronic obstructive pulmonary disease. New York: American Thoracic Society; 1974.

emphysema only and predominantly affects lower lobes and is panlobular or panacinar, whereas emphysema in cigarette smokers is centrilobular or centriacinar and initially involves the upper lobes. Incidence of α_1-AT deficiency in patients presenting with COPD is 1% to 2% but increases to about 50% in patients with severe disease who are under 40 years of age. The precise mechanism is unclear, in addition to elastase and collagenase, it inhibits several other enzymes. The commonest allele in all populations is PiM and the most common phenotype PiMM.

PATHOLOGY

In patients with chronic bronchitis, there is hypertrophy of the mucus secreting glands. These glands are found in the submucosa of large cartilaginous airways. In patients with COPD the mean Reid index (ratio of thickness of the submucosal glands to that of the bronchial wall) increases to 0.52 (normal 0.44). In COPD, the major site of obstruction is the small airways. Other findings include goblet cell hyperplasia, accumulation of inflammatory cells in the mucosa and submucosa, peribronchial fibrosis, intraluminal mucus plugs and increased smooth muscle. Classification of emphysema is based on the pattern of involvement of acini of the lung distal to the terminal bronchiole (**Figure 1**). *Panacinar* or *panlobular* emphysema involves both the central and peripheral portions of the acinus as compared to *centriacinar* or *centrilobular* emphysema where distension and destruction are mainly limited to the respiratory bronchioles with relative sparing of the peripheral portion of the acinus. *Paraseptal* emphysema involves airspaces at the periphery of the lobule adjacent to the pleura. *Irregular* emphysema involves the acinus irregularly and is almost always associated with scarring. This pattern is often evident in tuberculosis (TB). Pathogenetic mechanisms in COPD are shown in **Figure 2**.

PATHOPHYSIOLOGY

Chronic bronchitis and emphysema frequently co-exist; however, one process may dominate over the other. Both produce airways narrowing but can occur without evidence of obstruction. Airways obstruction is invariably present by the time patient experiences breathlessness. Besides basic disease process in the airways in chronic bronchitis, loss of elastic recoil

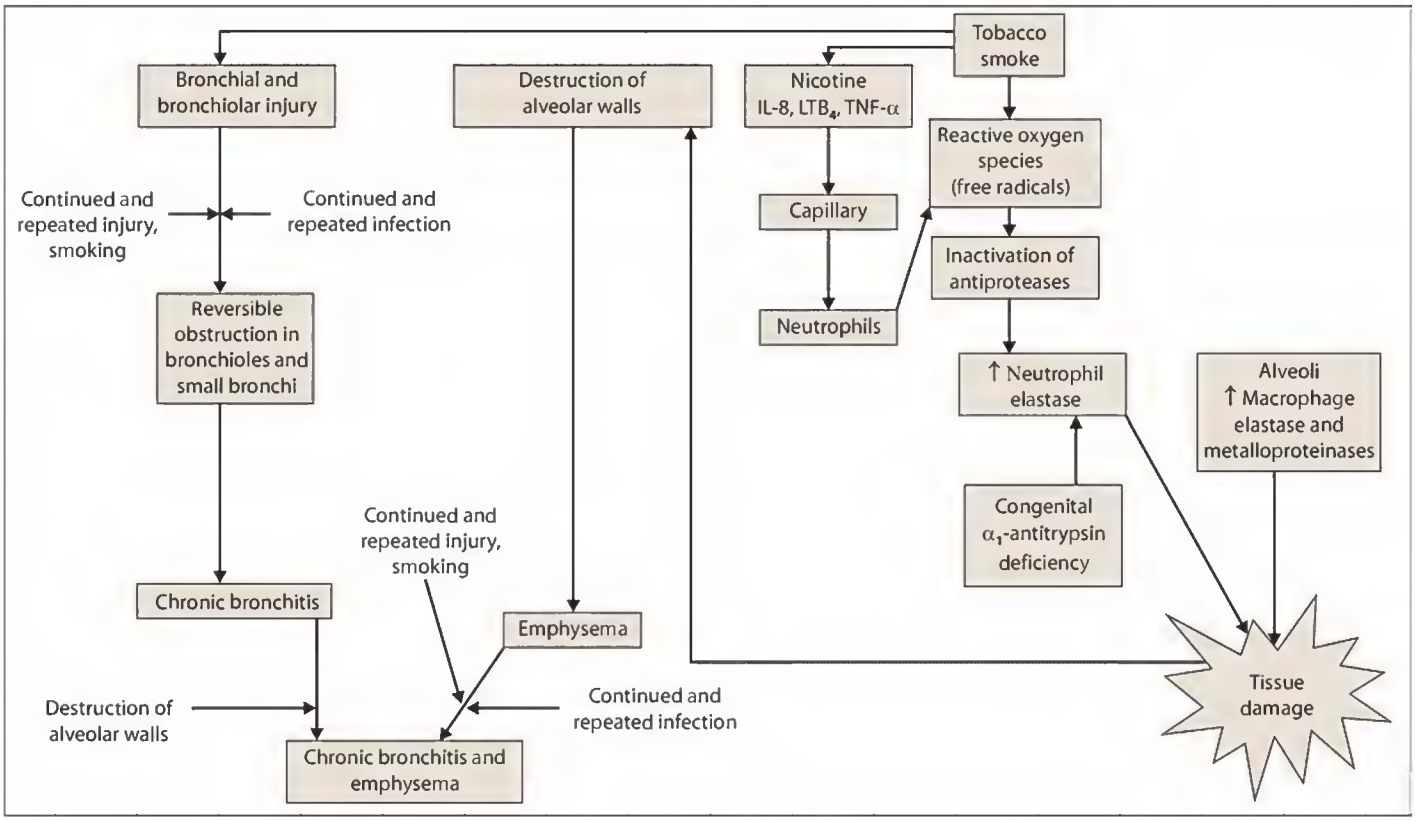


Figure 2: Pathogenesis of COPD. The protease-antiprotease imbalance and oxidant-antioxidant imbalance are additive in their effects and contribute to tissue damage. α_1-antitrypsin (α_1-AT) deficiency can be either congenital or 'functional' as a result of oxidative inactivation.

IL-8 = Interleukin 8; LTB_4 = Leukotriene B_4; TNF = Tumour necrosis factor.

in emphysema through loss of radial support on airways also produces airways narrowing. Patients with COPD experience increased work of breathing due to altered pressure airflow relationship. Because of prolonged time constants for expiration in COPD, lungs are unable to return to their mechanical equilibrium volume [functional residual capacity (FRC)] even during ordinary breathing. As a consequence of this, progressive increase in lung volume shifts tidal breathing to a higher, less compliant portion of the pressure-volume curve of the respiratory system. This results in increased work of breathing. The increased elastic recoil pressure associated with the higher end-tidal volume is known as intrinsic positive end-expiratory pressure (PEEP) or auto-PEEP. This auto-PEEP represents an added threshold load that must be overcome to initiate next inspiration. This contributes significantly to the work of breathing and dyspnoea in patients with COPD. Further, lung hyperinflation also increases the work of breathing as it results in several adverse effects on the inspiratory muscles. The flattening of the diaphragm that occurs in patients with emphysema causes this muscle to operate on unfavourable portion of its length-tension curve. Keeping with the heterogeneous nature of the disease process in the airways and lung parenchyma, non-uniform ventilation, and ventilation-perfusion mismatching are usually observed in COPD. Ventilation-perfusion mismatch produces altered arterial blood gases. The total cross-sectional area of the pulmonary vascular bed is reduced in patients with COPD as a result of anatomic changes, constriction of vascular smooth muscle of branches of pulmonary arteries and arterioles and destruction of alveolar septa with loss of capillaries. Hypoxia is a potent stimulus for pulmonary vasoconstriction. Acidosis due to respiratory failure and secondary polycythaemia from chronic hypoxia augment this pulmonary artery hypertension and right ventricular failure.

CLINICAL FEATURES

Although chronic bronchitis and emphysema frequently co-exist, rarely, features of one type may be predominantly present. **Table 2** provides differentiating features between the two conditions.

Predominantly Chronic Bronchitis

The patient with predominantly chronic bronchitis usually presents with a history of cough and sputum production for many years along with a history of heavy tobacco smoking. Initially, the cough is present only during winter months. Over the years the cough becomes continuous and episodes of illness increase in frequency, duration and severity. With severe degree of airways obstruction, the patient experiences exertional dyspnoea. Occasionally, the patient seeks medical help after the onset of peripheral oedema secondary to overt right ventricular failure. Patients with chronic bronchitis are overweight and cyanotic. Because of this appearance these patients are referred to as 'blue-bloaters'. The percussion note is normally resonant. Medium to coarse crepitations and rhonchi, which change in location and intensity after a deep and productive cough, are heard on auscultation.

Predominantly Emphysema

There is a long history of exertional dyspnoea with minimal cough associated with production of only small amounts of mucoid sputum. The patient appears to be distressed on physical examination. The body build is asthenic with evidence of weight loss. The patient uses accessory muscles of respiration, which serve to lift the sternum in an anterosuperior direction with each inspiration. Patient is tachypnoeic with relatively prolonged expiration through pursed lips. While sitting, the patient often leans forward, extending his arms to brace himself. The neck veins are distended during expiration and briskly collapse with inspiration. The lower intercostal spaces retract with each inspiration; by palpation, the lower lateral chest wall can be felt to move inward. The cardiac impulse, if at all visible, is seen only in the xiphoid and sub-xiphoid regions. Palpation frequently reveals a sustained forward and downward right ventricular impulse in the sub-xiphoid region. The percussion note is hyper-resonant and cardiac dullness is either absent or severely reduced. The upper border of liver dullness is at a lower level. The breath sounds are found to be diminished with faint, high-pitched rhonchi heard towards the end

Table 2: Comparison of Two Types of Chronic Obstructive Pulmonary Diseases

	Predominantly Chronic Bronchitis ('Blue-bloater')	Predominantly Emphysema ('Pink-puffer')
Predominant symptom	Cough	Dyspnoea
Sputum	Copious and purulent	Scant and mucoid
Episodes of bronchial infection	More frequent	Less frequent
Episodes of respiratory insufficiency	Frequent	Often terminally
Chest radiograph	Increased bronchovascular markings at lung bases, large heart	Hyperinflation, bullous changes, small and tubular heart
Lung compliance	Normal	Increased
Airways resistance	High	Normal to slight increase
Diffusing capacity	Normal to slight decrease	Decreased
Arterial blood gases	Abnormality early in course of disease	Normal until late
Pulmonary hypertension		
Rest	Moderate to severe	None to mild
Exercise	Worsens	Moderate
Chronic cor pulmonale	Common	Rare except terminally
Cardiac failure	Common	Rare except terminally

of expiration. A pre-systolic gallop accentuated during inspiration is commonly heard. Patients with this condition have been referred to a as 'pink-puffers' because of maintenance of arterial oxygen tension (PaO_2).

Patients with advanced disease may manifest wasting which is an independent poor prognostic factor in COPD. This could be due to both inadequate dietary intake as well as elevated levels of inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α).

DIAGNOSIS

The diagnosis of COPD must be considered in patients with symptoms of cough, sputum production, or dyspnoea, or history of exposure to risk factors for the disease. The diagnosis requires spirometry.

Pulmonary Function Testing

A post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) less than 0.7 confirms the presence of airflow limitation that is not fully reversible (**Table 3**). Furthermore, an overall increase in lung volumes may be seen depending upon the degree of associated emphysema. Total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) are increased but vital capacity (VC) is decreased in patients with COPD. Peak expiratory flow rate (PEFR) is also reduced and in contrast to asthma, little or no diurnal variation is observed in serial measurements. Carbon monoxide diffusing capacity (DLCO) is normal or slightly impaired in patients with chronic bronchitis and marked reduction suggests co-existing significant emphysema.

Table 3: Comparison of Spirometric Staging Criteria for COPD in the Current ATS-ERS, GOLD, and NCCCC-NICE Guidelines, Using Post-bronchodilator Forced Expiratory Volume in One Second (FEV_1)/Forced Vital Capacity (FVC)*

Stage or Severity	FEV1 as a Percentage of the Predicted Value		
	NCCCC-NICE	GOLD	ATS-ERS
At risk for COPD	†	≥80	≥80
Mild COPD	50 to 80	≥80	≥80
Moderate COPD	30 to 49	50 to 80	50 to 80
Severe COPD	<30	30 to 50	30 to 50
Very severe COPD	†	<50‡	<30

*= *All the guidelines define airflaw obstruction as a criterian far diagnasing COPD as FEV1/FVC ≤0.70; † = Stage not included in guideline; ‡ = FEV1 ≤50% af predicted if chronic respiratary failure with PaO_2 ≤60 mm Hg is alsa present; ATS = American Tharacic Saciety; ERS = European Respiratary Society; GOLD = Global Initiative far Chranic Obstructive Pulmonary Disease; NCCCC = Natianal Callabarating Centre far Chronic Canditians; NICE = Natianal Institute far Health and Clinical Excellence.*

Imaging

There is no characteristic abnormality on chest radiograph, it may be normal or show features of co-existing emphysema. It is also helpful in detecting an alternative disease or complication (**Figures 3 and 4**). Findings in patients with chronic bronchitis may include thickened bronchial walls manifested by tubular or 'tramline' shadows and increased bronchovascular markings. Chest radiograph in patients with predominant emphysema reveals hyperlucent lung fields with loss of peripheral vascular markings, bullae (**Figures 5A and B**), flat and low-level diaphragm and a tubular heart. In late stages, main pulmonary artery and its branches become prominent. High resolution computed tomography (HRCT) can detect emphysema with confidence (**Figure 6**) but is rarely used for routine diagnostic purposes.



Figure 3: Chest radiograph (pastera-anterior view) shawing COPD and old healed pulmanary tuberculasis af the left lung.

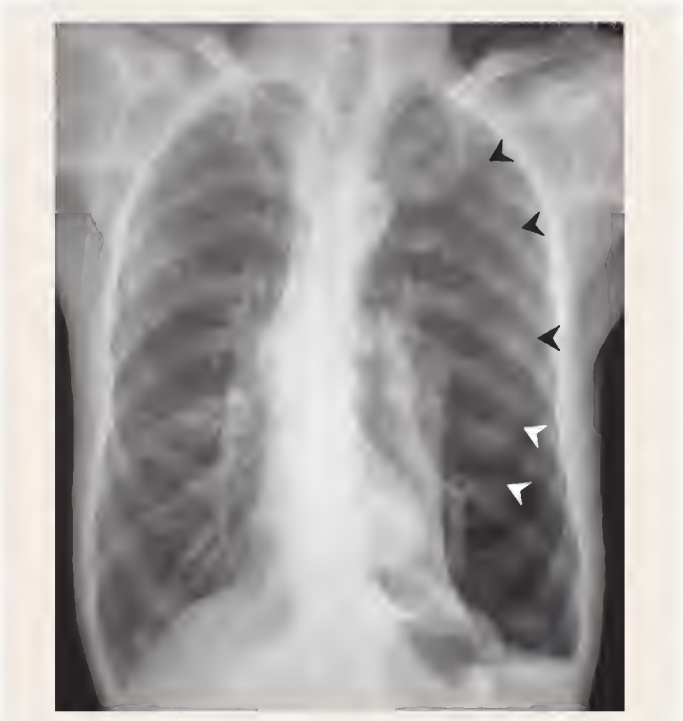
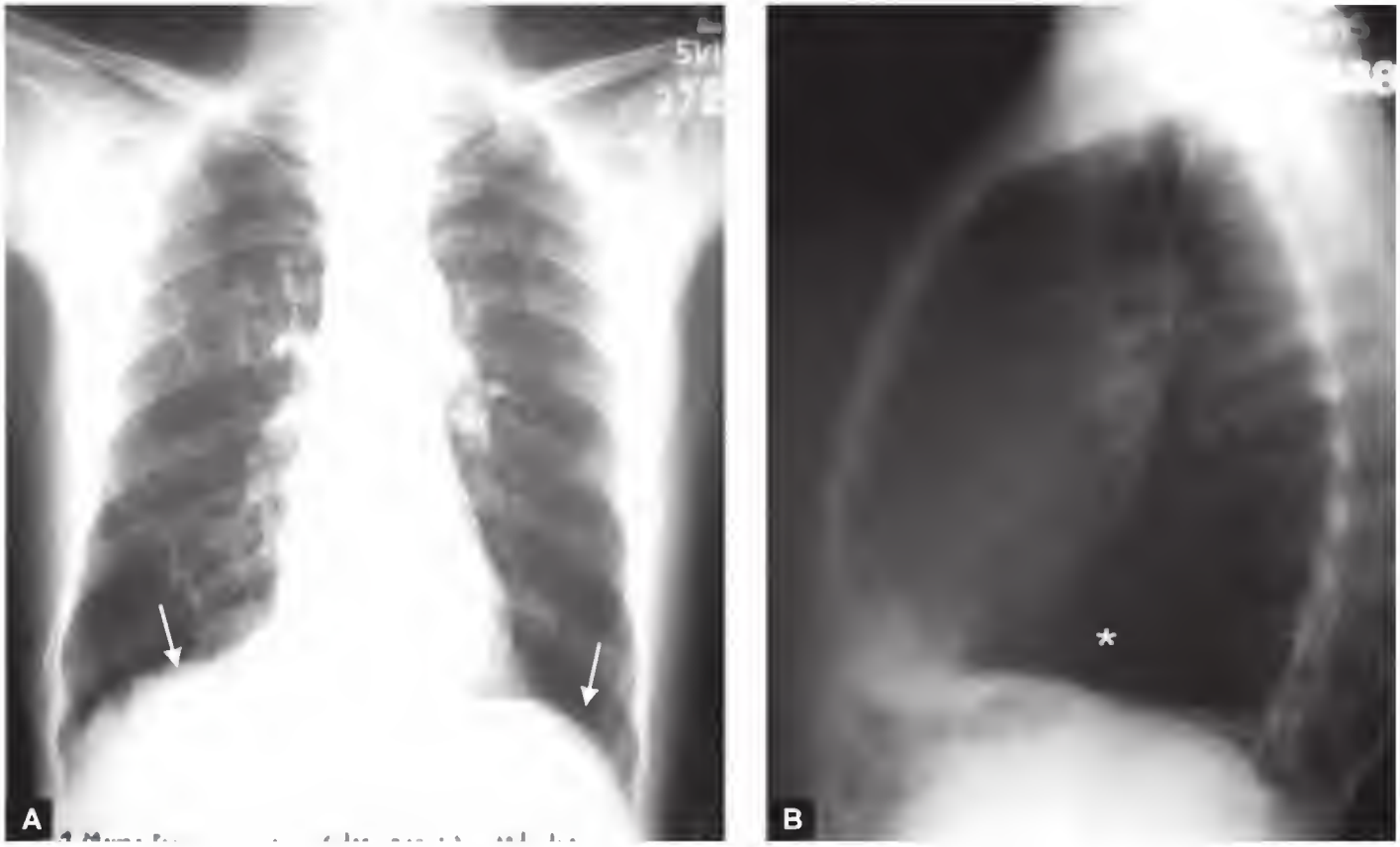


Figure 4: Chest radiograph (pastera-anterior view) shawing COPD with left pneumatharax (arrows point towards lung margin).



Figures 5A and B: (A) Chest radiograph (postero-anterior view) showing hyperlucent lung fields with loss of peripheral vascular markings (bullae) low flat diaphragm (arrows) and prominent pulmonary arterial shadows at both hila and a tubular heart. (B) Chest radiograph (lateral view) showing increased retrosternal lucent zone. Retrocardiac lucency is also increased (asterisk). These findings suggest hyperinflation of the lungs due to bullae.

Other Investigations

Table 4 lists additional investigations that are useful in diagnosing COPD.

Table 4: Other Investigations Useful in Diagnosing COPD

Sputum examination	Culture or molecular tests to identify bacteria, viruses and other pathogens, especially during acute exacerbation
Alpha-1-antitrypsin	Early onset, minimal smoking history or family history
Carbon monoxide diffusing capacity (DLCO)	If symptoms disproportionate to impairment spirometric
Arterial blood gases	If symptoms disproportionate to spirometric impairment and to identify type I respiratory failure (decreased PaO_2) or type II respiratory failure (decreased PaO_2 and increased $PaCO_2$)
Chest radiograph and HRCT	Assessment for suitability of surgery
Electrocardiogram	Assessment of cardiac status, if clinical features of chronic cor pulmonale
2D echocardiography	Assessment of cardiac status, if features of chronic cor pulmonale

COPD = Chronic obstructive pulmonary disease; PaO_2 = Partial arterial oxygen tension; $PaCO_2$ = Partial arterial carbon dioxide; HRCT = High resolution computed tomography.

Complications

Various complications which can occur in patients with COPD are listed in Table 5.

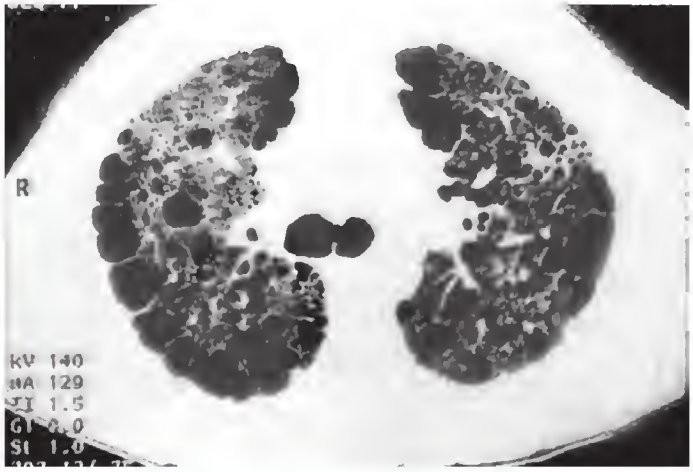


Figure 6: CT of the chest showing paraseptal emphysema involving mainly periphery of the lung.

Table 5: Complications of Chronic Obstructive Pulmonary Diseases

Recurrent episodes of acute exacerbation by viruses and bacteria
Pneumothorax
Secondary erythrocytosis (rare in India)
Weight loss in patients with severe emphysema
Chronic and acute on chronic respiratory failure
Pulmonary artery hypertension
Chronic cor pulmonale
Right heart failure

PROGNOSIS

COPD is usually a progressive disease, punctuated by acute exacerbations and remissions. Eventually it causes respiratory failure, pulmonary hypertension and right heart failure. Death usually ensues within a few years. Few patients with chronic bronchitis do not develop severe airways obstruction and have better prognosis. Six-minute walk distance test and St George's respiratory questionnaire may be used during follow up. **Table 6** lists markers of early disease and prognosis in COPD.

Table 6: Potential Markers of Early Disease and Prognosis in Chronic Obstructive Pulmonary Diseases

Alpha1-antitrypsin deficiency
Cystic fibrosis transmembrane conductance regulator (CFTR) in patients with co-existing cystic fibrosis
MBL-2 genes
Fibrinogen
C-reactive protein, copeptin, serum amyloid A protein (during acute exacerbation)

MANAGEMENT

Stable Phase COPD

Anti-smoking measures

Smoking cessation is the only measure that slows down the progression of COPD and adequate counselling should be done for this. Nicotine replacement therapy in the form of gum, transdermal patch, inhaler or nasal spray, sublingual tablet, or lozenge is helpful in quitting smoking. Use of bupropion, a noradrenergic anti-depressant, is associated with better abstinence rates. Varenicline (a nicotine acetylcholine receptor partial agonist) is helpful in relieving nicotine withdrawal symptoms. Dusty and smoke-laden environment should be avoided and this may involve a change of occupation.

Bronchodilator therapy

Bronchodilators are the mainstay of current drug therapy for COPD (**Figure 7**). As compared to bronchial asthma, the effects of bronchodilator drugs are smaller in patients with COPD because of structural changes in the airways. Bronchodilators produce relaxation of airway smooth muscle, decrease airways resistance, and hyperinflation and improve dyspnoea and exercise tolerance. The main bronchodilators include β_2-agonists, anticholinergic drugs and methylxanthines. The β_2-agonists have been shown to increase ciliary beat frequency and mucociliary clearance, which is impaired in COPD. Anti-inflammatory action of both β_2-agonists and particularly, methylxanthines has also received considerable attention. The β_2-agonists may be given by metered dose inhaler or by mouth. Their excessive use produces tremors and palpitations. Use of metered dose inhalers is associated with fewer side-effects. Patients who have co-ordination problems should use spacers or other ancillary systems for better drug delivery. Regular treatment with inhaled β_2-agonists (salbutamol 200 mg or terbutaline 500 mg 4 to 6 hourly) may be used to treat patients with mild to moderate disease. Long-acting inhaled β_2-agonists (LABAs) (salmeterol and formoterol) are also useful in COPD. Ipratropium bromide, an anticholinergic bronchodilator drug (40 to 80 mg, 6 hourly) should be added in patients with severe airflow obstruction. Tiotropium bromide (18 mg) has a prolonged duration of action and is suitable for once-daily inhalation. Combining inhaled short-acting β_2-agonists (SABAs) and ipratropium bromide produces a greater change in spirometry than either agent alone. Use of LABAs in combination with ipratropium bromide leads to fewer exacerbations than either drug alone.

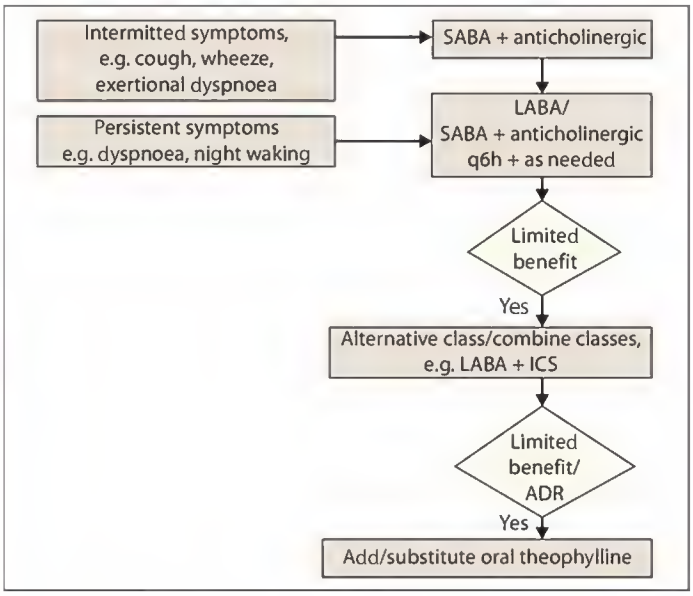


Figure 7: Algorithm for treatment of COPD. Effectiveness of treatment is assessed by response criteria. If forced expiratory volume in one second < 50% predicted and exacerbations of COPD requiring a course of oral corticosteroid or antibiotic occurred at least once within the last year, consider adding regular ICS.

COPD = Chronic obstructive pulmonory diseose; SABA = Short-octing β_2-agonist; LABA = Long-octing β_2-agonist; ICS = Inholed corticosteroids; ADR = Adverse drug reoction.

The role of theophylline or intravenous aminophylline has decreased because of toxicity and lack of efficacy when administered either orally or parenterally. Theophylline blood levels should be measured in those patients who fail to respond or show signs of toxicity. The therapeutic range of blood level is 10 to 20 mg/dL. Insomnia and nervousness occur frequently when levels are in the therapeutic range. Side effects, such as nausea, vomiting, seizures and tachyarrhythmia, occur when blood levels exceed 20 mg/dL. Lower dosages should be given to patients with congestive cardiac failure, liver disease and in elderly patients. Reduced dosage are also required with the concomitant use of ciprofloxacin, erythromycin, propranolol and verapamil. Smokers, patients with thyrotoxicosis, cystic fibrosis and those using phenytoin, barbiturates and rifampicin require higher dosages.

Corticosteroids

Approximately 10% of patients with stable COPD have some symptomatic and objective improvement with oral corticosteroids. There is no evidence that long-term treatment with high doses of inhaled corticosteroids reduces progression of COPD, even when treatment is started before the disease becomes symptomatic. Therefore, their use is not justified in patients with stable COPD in view of the risk of systemic side effects and the cost of using high-dose inhaled corticosteroids for several years.

Oxygen

Use of long-term oxygen therapy (LTOT) is justified from the results of two large trials [US Nocturnal Oxygen Therapy Trial (NOTT) and British Medical Research Council (MRC) study] that showed decreased mortality and improved quality of life (QOL)

in patients with severe COPD and chronic hypoxaemia (PaO_2<55 mm Hg). From these studies, it can be concluded that no oxygen is bad, some oxygen is better, and continuous oxygen is best. Supplemental LTOT has been shown to improve survival, exercise, sleep and cognitive performance in hypoxaemic patients. Oxygen should be administered for at least 15 hours a day. It can be administered by nasal cannula at a rate 1–3 L/min with an aim of achieving PaO_2 of 60 mm Hg. Recent studies have shown that oxygen does not increase survival in patients with less severe hypoxaemia, therefore, the selection of patients is important in prescribing this expensive therapy. Similarly, nocturnal administration of oxygen does not increase survival in patients with COPD who have nocturnal hypoxaemia. Use of oxygen concentrators appears to be cost-effective on long-term basis in patients with COPD. Oxygen concentrators are electrically powered devices for extracting oxygen directly from room air by separating it from nitrogen.

Non-invasive ventilation

The use of non-invasive ventilation (NIV) with a simple nasal mask, when used at home improves oxygenation, reduces hospital admissions in patients with severe COPD and hypercapnia and improves long-term survival. The combination of NIV and LTOT may be more effective.

Treatment of airway secretions

Adequate hydration, expectorants and mucolytic agents are indicated when the secretions are thick and tenacious. Steam inhalation for 10 to 15 minutes several times a day may be beneficial. Postural drainage helps in removing secretions from the bronchial tree.

Nutrition

Nutritional assessment is recommended in patients with COPD. Simple screening includes measurements of body mass index (BMI; kg/m^2) and weight change. Nutritional therapy should be combined with exercise or other anabolic stimuli.

Pulmonary rehabilitation

Pulmonary rehabilitation programme consisting of education, exercise and physiotherapy improves exercise capacity and QOL in severe COPD.

Lung volume reduction surgery

Surgical removal of the most emphysematous parts of the lung improves mechanical efficiency of the respiratory muscle and ventilatory function. Patients with localised upper lobe emphysema appear to do best. Careful selection of patients is essential. Surgical reduction in hyperinflation improves pulmonary functions, exercise capacity and QOL.

Lung transplantation

COPD is an important indication for lung transplantation in the Western countries and is recommended for patients under 65 years of age who have no co-morbid conditions if they have severe disability despite optimum medical management. It is not clear whether single or double lung transplantation is the better choice.

Acute Exacerbation of COPD

A summary of the principles of the management of AECOPD is detailed in **Table 7**.

Table 7: Hospital Management of Acute Exacerbations of COPD

Oxygen therapy: Controlled oxygen therapy monitored by serial arterial blood gas measurements

Bronchodilator therapy: Nebulised salbutamol (5 mg) or terbutaline (10 mg) in combination with ipratropium bromide (500 µg) six hourly

Corticosteroids: Patients treated with systemic steroids have fewer treatment failures, better spirometry and shorter hospital stay

Diuretic therapy: Frusemide (40 to 80 mg) orally or IV according to the extent of oedema. Alternatively, torsemide may be used as it is associated with lesser incidence of hypokalaemia

Appropriate antibiotic therapy: May be initiated in patients that have a change in their sputum characteristics (purulence and/or volume)

Choice should be based on bacteria resistance patterns prevalent locally and includes:

Amoxicillin/clavulanate

*Respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin)

If *Pseudomonas* spp. and/or other *Enterobacter* spp. are suspected, combination therapy should be used

Respiratory stimulants: Doxapram hydrochloride by IV infusion (1.5–4 mg/min) is used only when non-invasive ventilation is either not available or considered inappropriate

Physiotherapy: Chest physiotherapy helps in patients who are drowsy because of carbon dioxide narcosis.

Mechanical ventilation: when the patient is deteriorating despite maximum therapy

**In TB endemic countries to be used only when Mycobacterium tuberculosis has been ruled out.*

Oxygen

In patients with AECOPD, oxygen is administered through nasal cannula, simple face mark or Venturi mask. The goal of oxygen therapy is to maintain PaO_2 at 60 mm Hg.

Treatment of respiratory infection

Up to 25% of exacerbations in COPD are produced by viruses. The major bacterial organisms associated with exacerbations include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*; *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. Choice of antibiotic depends on the clinical condition of the patient and the local patterns of antibiotic susceptibility. Augmentation therapy with α_1-Pi (Prolastin) is associated with a marked reduction in the frequency of lung infections in majority of the patients. The annual use of influenza virus vaccine (trivalent inactivated vaccine 0.5 mL by intramuscular route or live-attenuated intranasal 0.2 mL of vaccine) and the once in life-time inoculation with 23-valent pneumococcal polysaccharide vaccine may provide significant protection (although not an evidence-based recommendation).

Corticosteroids

Recent studies have demonstrated a beneficial effect of systemic corticosteroids in treating AECOPD with improved clinical outcome and reduced length of hospitalisation. Inhaled corticosteroids may slightly reduce the severity of AECOPD.

Assisted ventilation

Significant airways obstruction increases work of breathing. Further, unconsciousness, fatigue and weakness of respiratory muscles contribute significantly to acute ventilatory failure during AECOPD. Correction of reversible factors, such as electrolyte disturbances, abdominal distension or ascites and poor nutrition should be done. Use of sedatives, unless patient is receiving assisted ventilation, is contraindicated.

Non-invasive ventilation

Some patients with AECOPD do not show improvement with medical treatment and develop acute respiratory acidosis, severe hypoxaemia or both. Short-term use of assisted ventilation may be beneficial in these patients. NIV is useful for severely ill patients who do not require immediate endotracheal intubation. Although the best time to start NIV is not established, early intervention when the respiratory rate is >30 per min and the pH is <7.35 may be beneficial. Successful NIV is recommended for co-operative patients who are not sedated, are haemodynamically stable and do not have copious secretions. Guidelines for tracheal intubation are provided in **Table 8**. Mechanical ventilation (MV) is associated with barotrauma, infection and difficulty in weaning. During MV, it is useful to monitor auto-PEEP (intrinsic PEEP), and extrinsic PEEP should be set at 80% of the intrinsic PEEP.

Effect of commonly used medications on important clinical outcomes in COPD is shown in **Table 9**.

Table 8: General Guidelines for Endotracheal Intubation During Acute Exacerbations of COPD

NIV intolerance or failure
Inability to clear copious secretions
Inability to protect airway
Respiratory rate >35/min
Signs of progressive respiratory muscle fatigue
Persistent arterial hypoxaemia with failure to maintain PaO_2 of 55 to 60 mm Hg, or oxygen saturation of <88% to 90% despite maximum medical treatment
Worsening acute respiratory acidosis (pH <7.25) and/or $PaCO_2$ > 60 mm Hg
Deterioration of mental status
Hypotension or shock
Respiratory arrest

COPD = Chronic obstruction pulmonary disease; NIV = Non-invasive ventilation.

Table 9: Effect of Commonly Used Medications on Important Clinical Outcomes in COPD

	FEV_1	Lung Volume	Dyspnoea	HRQoL	Acute Exacerbation	Exercise Endurance
SABA	++++	+++	++++	NA	NA	+++
LABA	++++	++++	++++	++++	++++	+++
Ipratropium bromide	++++	+++	++++	+++	+++	+++
Tiotropium	++++	++++	++++	++++	++++	+++
Inhaled corticosteroids	++++	NA	+++	++++	++++	NA
Theophylline	++++	+++	++++	+++	NA	+++

++++ = Evidence from randomised clinical trials (RCTs), rich body of data; +++ = Evidence from RCTs, limited body of data; FEV_1 = Forced expiratory volume in one second; HRQoL = Health-related quality of life; NA = Evidence not available; SABA = Short-acting β_2-agonists; LABA = Long-acting β_2-agonists.

RECOMMENDED READINGS

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23.7 Pneumonia

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Pneumonia is an accumulation of inflammatory cells and secretions in the alveolar spaces of lung, caused by an infection. The infecting organism, the inflammatory response and the disturbance of gas exchange caused by alveolar involvement are responsible for clinical manifestations.

CLASSIFICATION

Pneumonia has been traditionally classified as *typical* and *atypical*. This is no longer a preferred classification, as clinical and radiological features that were once thought to be indicative of 'typical' or 'atypical' organisms *Mycoplasma pneumoniae*, *Chalmydia pneumoniae*, *Legionella* spp. causing pneumonia, are no longer considered to be specific of any organism.

The more useful classification is according to the probable origin of infection is as follows:

- Community acquired pneumonia (CAP)
- Hospital-acquired and ventilator-associated pneumonia (HAP and VAP)
- Pneumonia in the immunocompromised host

The spectrum of pathogens and, therefore, the antimicrobial treatment varies between the groups.

PATHOGENESIS

The lung, which serves its primary function of gas exchange, is the organ with largest epithelial surface area (approximately 70 m^2) which is in continuous contact with the external environment. In spite of this exposure, lower respiratory tract remains sterile, under normal circumstances.

An infecting organism may reach the lower respiratory tract (a) by aspiration of upper airway contents, (b) by aerosolisation, (c) through blood stream, or (d) from adjacent structures. The first mode is the commonest in the pathogenesis of pneumonia; viral infections, atypical organisms, tuberculosis (TB) and fungal pathogens are examples of aerosol-caused infections. Haematogenous spread is possible in severe bacteraemia. The pulmonary circulation acts as a filter for venous blood, which in some cases allows micro-organisms to lodge in the small vessels of the lungs and cause parenchymal infection. In most cases, infections originate from heart valves or from thrombophlebitis. Because bacteria are released in clusters from the source, they are likely to reach multiple parts of the pulmonary circulation simultaneously, causing dense infections that can cavitate. Haematogenous pneumonias, therefore, are often multifocal, peripheral lesions, that are susceptible to rapid cavitations. The precise mechanism by which the micro-organisms infect the usually sterile lower airways and lung parenchyma are complex, but any situation in which natural defences are impaired will predispose to pneumonia. Colonisation of the upper airway by potential pathogens can occur in normal hosts, especially seasonally or during epidemics with typical bacterial pathogens (i.e. *Streptococcus pneumoniae*). Prevalence of colonisation may increase in areas of crowding or co-housing, such as dormitories or army barracks. An increased incidence of isolation of Gram-negative bacilli from oropharynx has been correlated with increasing severity of the underlying illness of the host. These potential pathogens can be isolated from 2% of healthy hosts, but can be recovered with increasing frequency in patients with co-morbidities. Interestingly, if normal hosts are exposed to high concentration of Gram-negative bacilli in the oropharynx, the bacteria are cleared rapidly, and colonisation does not occur.

Once the colonisation occurs, aspiration of oropharyngeal secretion is the means by which the lower respiratory tract is inoculated. Aspiration of small quantities of oropharyngeal secretions occurs in approximately 50% of normal hosts during sleep and probably occurs more frequently in the setting of altered sensorium, alcohol or sedative drug use. The bacterial concentration of oropharyngeal secretions is very high, of the order of 10 organisms/mL, hence, aspiration of a small volume may provide a very high bacterial inoculum to the lung and once that occurs it depends on the efficiency of normal host defence mechanisms to prevent the development of pneumonia.

PATHOLOGY

Traditionally, pathology of pneumonia has been described as stages of red hepatisation followed by grey hepatisation—signifying congestion with increased vascularity of inflamed tissues and consolidation initially with more red blood cells and then with neutrophils. Because of use of early antibiotics, this natural progression of pathology is perhaps occurring less often these days.

COMPLICATIONS

Complications do occur in pneumonias fairly frequently (**Table 1**). Most common cause of bacterial infection of pleural space is parapneumonic effusion (**Table 2**) and this can create a lot of management problems.

Table 1: Complications of Community Acquired Pneumonia

Pleural infections
Simple parapneumonic effusion
Complicated parapneumonic effusion
Empyema
Lung abscess
Respiratory failure
Sepsis

MICROBIOLOGY

Typical Pathogens

Streptococcus pneumoniae (pneumococcus) is among the leading causes of illness and death from CAP worldwide for

young children, for persons who have underlying chronic systemic conditions and for the elderly. *S. pneumoniae* also causes HAP or pneumonia in immunocompromised host, but the percentage is lower in the latter two groups. *Pneumococcus* is a Gram-positive diplococcus and was re-classified as *S. pneumoniae* because it is genetically related to streptococcus. They are capsulated (the capsule enclosing each pair), non-motile and non-sporing. The importance of *S. pneumoniae* as a cause of pneumonia has acquired a greater clinical significance because non-susceptibility to penicillin has increased significantly over the past decade. Penicillin resistance is associated with resistance to beta-lactams and other classes of antibiotics, such as macrolides, tetracycline, and trimethoprim – sulfamethoxazole. The mode of resistance is not the production of β-lactamases, but alteration in the penicillin binding proteins on the bacterial surface.

Table 2: Comparative Features of Simple and Complicated Para-pneumonic Effusion

	Simple Parapneumonic Effusion	Complicated Parapneumonic Effusion
Appearance	May be turbid	May be cloudy
Biochemical markers	pH >7.30 LDH may be elevated Glucose >60 mg/dL or Glucose pleural/ serum ratio >0.5	pH <7.20 LDH >1,000 IU/L Glucose <35 mg/dL
Nucleated cell count	Neutrophils usually <10,000/μL	Neutrophils abundant (usually >10,000/μL
Gram's stain	Negative	May be positive
Culture	Negative	May be positive

Staphylococcus is a less common aetiology of CAP, but a more important causative organism in HAP. These are Gram-positive cocci appearing in clusters and the most constant association with virulence is coagulase positivity. *Staphylococcus aureus* is coagulase positive. Clinical manifestations are similar to those of CAP from other bacterial aetiologies, although mortality can be higher. Radiological patterns are protean, inclusive of cavity formation. Methicillin-resistant *Staphylococcus aureus* (MRSA) remains more of a concern for HAP, although it has been reported as a cause of CAP. MRSA pneumonia tends to produce significantly greater frequency of bacteraemia and septic shock and is associated with higher mortality.

Klebsiella species (Friedländer's pneumonia) is classically community acquired. But more recently it is being seen in elderly, immunocompromised hosts, and in chronically ill, as HAP. These are ubiquitous, non-motile, Gram-negative rods, that commonly colonise mucosal surfaces of mammals. The organism contains a thick gelatinous capsule, that appears to increase its virulence. The most medically important species of the genus is *K. pneumoniae*. The pneumonia caused by this organism is mostly located in the right upper lobe, and apex of the right lower lobe. Abscess formation and cavitations are also seen. The classic radiological 'bulging fissure' sign is not seen in all patients of this pneumonia, and may also be seen in pneumococcal pneumonia. Occasionally, a patient may recover from the acute phase of *K. pneumoniae* and pass into a chronic phase of infection characterised by cavitations and scarring resembling TB. Spread of plasmid mediated extended spectrum β-lactamases (ESBLs) has been reported in *Klebsiella* (and *Enterobacter* spp.) isolates in some parts of the world. Hence, each institution must establish and monitor the incidence of ESBLs producing organisms.

Haemophilus influenzae is a fastidious Gram-negative coccobacillus, and is a common cause of CAP and HAP identified in patients who require hospitalisation. Aminopenicillin resistance is common, and is due to β-lactamase production. This bacillus is difficult to culture. Most clinical isolates are non-typable strains. It is an exclusively human pathogen. *Haemophilus* pneumonia typically occurs in infants and is accompanied by empyema and sometimes meningitis as well. In older children and adults, the picture is of lobar pneumonia, higher prevalence being seen in patients with chronic obstructive pulmonary disease (COPD).

Adults with chronic lung disease have been reported to have higher rates of *Moraxella catarrhalis* respiratory tract colonisation compared to healthy adults. Both CAP and HAP are common with this pathogen. Although *M. catarrhalis* pneumonia causes a significant pneumonia in elderly patients, fulminant pneumonia, pleural effusion and empyema are uncommon. Most strains of this organism produce an inducible β-lactamase. This β-lactamase is more active against penicillins than cephalosporins and its activity is inhibited by β-lactamase inhibitors.

The Gram-negative bacilli, namely *Pseudomonas aeruginosa, Escherichia coli, Proteus, Serratia, Enterobacter* and *Acinetobacter* are the species that generally cause HAP. These are rare causes of pneumonia in ambulatory patients. *P. aeruginosa* and other members of this species have always been important causes of hospital infection because of their intrinsic resistance to most antibiotics and ability to survive and even multiply at low temperatures and in disinfectant solutions. They may also carry drug resistant plasmids.

Anaerobic Organisms

These are most common aetiologic agents of lung abscess and aspiration pneumonia, and these bacteria are relatively common isolates from empyemas. Risk factors that predispose to anaerobic bacterial pneumonia include aspiration, infection of gingival crevice, necrosis of tissue with abscess formation or bronchopulmonary fistula, infections complicating airway obstruction and infection of dependent pulmonary segment.

Atypical Pathogens

Mycoplasma (smallest living organisms) are a group of bacteria that are devoid of cell walls, and hence, highly pleomorphic (Myco, from fungus like form of branching filaments; plasma, denoting plasticity of their shape). Because of their plasticity, they can pass through bacterial filters and have often been mistaken for viruses. Extrapulmonary manifestations of this infection may include haemolytic anaemia, myocarditis, and diverse neurological syndromes.

Chlamydia pneumoniae is transmitted from human to human without any avian or animal host. It grows poorly in cell cultures. Considerable interest has been aroused recently linking *C. pneumoniae* with atherosclerosis and its clinical effects. However, more work will have to be done to settle this issue. It

is a recognised cause of both CAP and HAP. The preferred diagnostic test is an assay of acute and convalescent specimens to detect a four-fold increase in antibody titres, with supporting evidence based on throat swab polymerase chain reaction (PCR) or culture results. Nevertheless, with limitation and availability of diagnostic tests, treatment most often is empirical.

Legionella pneumophila pneumonia (legionnaires' disease) is an acute pneumonic illness caused by a Gram-negative bacterial organism of the genus *Legionella*. Although rare in immunocompetent adults younger than 30 years of age, legionellosis can be a major cause of lethal pneumonia. Person to person transmission has not been reported and epidemiologic risk factors include recent travel and overnight stay outside home, recent repair of domestic plumbing, recent exposure to hot tub and whirlpool type spas, renal or hepatic failure, diabetes and systemic malignancy. Although the course of illness is variable, the rate of resolution with legionellosis is slower. Clinical features of legionnaires' disease includes high fever, hyponatraemia, central nervous system manifestations, and elevated lactate dehydrogenase levels. Diagnostic tests include urine antigen assay and culture on selective media, which is technically demanding.

Fungal Pneumonias

Recognition of pulmonary infection caused by endemic mycosis is aided by an understanding of the epidemiologic factors associated with exposure to these fungi and the use of appropriate testing. *Histoplasma capsulatum*, a thermal dimorphic fungus is found in nature with a near worldwide distribution, but endemic areas with highest concentration are located in eastern half of the United States of America, and most of Latin America. After inhalation, spores germinate into yeast forms within the lung. Clinical presentations can be an acute, self-limiting disease, acute overwhelming pulmonary infection, chronic upper lobar cavitary disease, and rarely fibrosing mediastinitis. Patients with impaired cell-mediated immunity are at increased risk to develop progressive disseminated *histoplasmosis*. *Blastomycosis* and *coccidioidomycosis* are two other pathogens known to cause pneumonic illness.

Viral Pneumonias

Viral pneumonias are extremely important in two situations – community acquired and in the immunocompromised. Hospital acquired infections are extremely rare. Community acquired viral pneumonias are under-diagnosed and under-treated. Till recently, these were difficult to diagnose, but real-time PCR has changed our ability to diagnose and treat viral pneumonias substantially. The incidence of viral CAP varies. But in patients hospitalised with CAP, about 30% have a viral aetiology, and half of these patients have both bacterial and viral pneumonia. The usual aetiological agents are influenza (A/B), RSV, rhinovirus, parainfluenza, adenovirus, coronavirus [including severe acute respiratory syndrome (SARS)] and metapneumovirus. There is lack of data about Indian patients with viral CAP but there is no reason to suspect that there are any major differences from other countries. A huge community study in Nepal involving only children [utilising World Health Organization (WHO) clinical criteria for diagnosis of pneumonia] found about 40% patients had a viral aetiology. Influenza occurs all the year round in India and this is different from the winter peak seen in western countries.

The diagnosis of viral *versus* non-viral pneumonia is clinically extremely difficult as the two may co-exist. A coryzal illness is common and specifically nasal or laryngeal symptoms and myalgias are more suggestive of viral infections or an obvious viral infection like measles or chickenpox with pneumonia suggests the diagnosis strongly. In an epidemic setting like the SARS epidemic in 2004, and the recent influenza A virus subtype H1N1 epidemic, due to a new strain of swine origin, one can also make a probable diagnosis based on clinical features. A normal or low white cell count makes viral pneumonia more likely but *Chlamydial* or *Mycoplasma pneumoniae* and bacterial pneumonia in the elderly may not show leukocytosis. Plain chest radiology is not sensitive enough to differentiate between bacterial and viral pneumonias. However, a 'pure' (i.e. without any bacterial superinfection) viral pneumonia usually does not present with unilateral lobar consolidation. Apart from a few central laboratories, viral diagnostics are practically unavailable in India. Real-time PCR and fluorescent antibody tests are the most promising tests for the diagnosis, but at the moment are not easily available. Viral cultures are done only in specialised centres. Serology is useful in epidemiological studies but is of no use in clinical management of patients.

Treatment of viral pneumonia focuses on treatment of influenza. Oseltamavir/zanamavir is recommended in any patient with influenza-like illness and risk factors for poor outcome pending reports. Treatment should be started on suspicion as the benefit of antiviral treatment is almost entirely in the early phase. Benefits of treatment for any other community acquired viral infections are unproven. Viral pneumonias in the immunocompromised are not uncommon, especially in the transplant setting. Of therapeutic importance is cytomegalovirus (CMV) as treatment exists for this, but diagnosis is difficult as even PCR/viral culture of CMV from pulmonary secretions does not prove causation. Certain patterns on high resolution computed tomography may suggest viral pneumonias particularly in the immunocompromised patients, e.g. ground-glass and small nodules. Only biopsy or cytological evidence of cytopathic effect is diagnostic of CMV pneumonia.

COMMUNITY ACQUIRED PNEUMONIA

The diagnosis of pneumonia is to be considered in any patient who has newly acquired respiratory symptoms (cough, sputum production, and/or dyspnoea), especially if accompanied by fever and auscultatory findings of abnormal breath sounds and crackles. In a patient with advanced age or an inadequate immune response, pneumonia may present with non-respiratory symptoms, such as confusion, failure to thrive, worsening of an underlying chronic illness or falling down. In these patients fever may be absent, but tachypnoea is usually present, along with an abnormal physical examination of the chest.

Standard postero-anterior (PA) and lateral chest radiographs are valuable in patients whose symptoms and physical examination suggest possibility of pneumonia. Also, the radiograph is an useful tool to exclude other possibilities that can mimic pneumonia. Radiographs can raise the possibility of a necrotising pneumonia (lung abscess), TB, co-existing conditions like bronchial obstruction or presence of pleural effusion. In some patients, history and physical examination may suggest pneumonia, but the radiograph is negative. Clinical relevance of such findings is uncertain, as most studies on CAP

have required the presence of lung infiltrates on a routine chest radiograph, to define the presence of pneumonia. Radiography is also useful for evaluating severity of illness by identifying multilobar involvement.

Once the diagnosis is established, every attempt must be made to ascertain a specific aetiologic diagnosis. The tests include sputum smear Gram's stain, acid-fast stain, sputum culture, blood culture. However, even with extensive diagnostic testing most investigators cannot identify a specific aetiology for CAP, in more than 50% of patients. If an exact aetiology can be identified, then therapy can be focused and also cost-effective. On the other hand, if diagnostic testing leads to delays in the initiation of appropriate therapy, it may have an adverse effect on the prognosis. Also, there is always a possibility of co-infection with an atypical pathogen (which may take a long time to identify). In this case, the value of a focused therapy against the rapidly identified bacteria, is uncertain. But the value of a properly collected and examined Gram's stain of expectorated sputum is still considered helpful for focusing initial therapy in CAP. A lower respiratory tract sample that is not heavily contaminated by oral secretions will typically have <10 squamous cells and >25 neutrophils per low power field. The problems are: (1) not all patients can provide an adequate sample, (2) interpretation is observer dependent, (3) atypical pathogens (which are common either as single or as co-infecting agent) cannot be seen, (4) a positive result for *Pneumococcus* is poorly predictive of the ability to recover that organism from a sputum or blood culture. Routine bacterial cultures of sputum often demonstrate pathogenic organisms, but sensitivity and specificity are poor, and findings should be correlated with the predominant organism identified on Gram stain. However, recovery of organisms from cultures, that are not usually a part of normal respiratory flora may be meaningful. Evidence supporting presence of an atypical pathogen are usually derived by serologic testing, e.g. documenting a four-fold rise in titres to *M. pneumoniae, C. pneumoniae* or *Legionella* spp.

In addition to clinical and radiographic findings (**Figure 1**), routine laboratory tests (complete blood counts, serum electrolytes, hepatic enzymes and renal function) are of little value in determining the aetiology of pneumonia, but may have prognostic significance and influence the decision of hospitalisation. Assessment of oxygen saturation and arterial blood gas (especially in patients with chronic lung disease) are very important tools to assess severity, and document the degree of hypoxaemia and carbon dioxide retention.

The degree of social support available to the patient also influences hospitalisation decision. Absence of a responsible care giver and a primary care physician are strong indications for hospitalisation. Various professional bodies have tried to develop scoring systems based on the risk factors present in a particular patient, but even the expert committees feel that the admission decision remains an 'art of medicine'. Hence, when the overall appearance of the patient seems unfavourable, even if the above-mentioned criteria are not fully met, admitting the patient in hospital is justified, at least until the concerns are resolved.

Chest radiograph, total leucocyte count and C-reactive protein (CRP) are recommended in all patients with pneumonia. Further testing depends on the severity of the disease. In non-severe CAP being treated as an outpatient, further testing is generally not recommended except for sputum Gram's stain and culture in patients with risk factors for resistant bacteria (e.g. bronchiectasis) or sputum for acid-foot bacilli if there is suspicion of TB. In patients with moderate to severe CAP, sputum for Gram's stain and culture, blood culture, and urinary antigen tests for *Legionella* and *Pneumococcus* are recommended. The strength of recommendation for such testing is directly proportional to the severity of the disease. For clinically non-resolving pneumonia, a computed tomography followed by bronchoscopy is generally indicated and is helpful in diagnosing complications like empyema, lung abscess or any unusual pathogens. Rapid antigen tests for influenza-like illness confirmed by real-time PCR is indicated wherever available. There are a plethora of other PCR tests available especially for the diagnosis of viral and 'atypical' organisms from respiratory secretions. But these tests are not routinely used in the non-immunocompromised patients with CAP.

TREATMENT

The first thing to decide is suitability of treating a particular patient at home, at a hospital or in an intensive care unit, depending on the various risk factors (**Table 3**) for pneumonia. Therapy for pneumonia will be either empiric or pathogen-specific (**Table 4**). Even when empiric therapy is to be used, it can be individualised. The presence of other risk factors and the severity of the disease will also influence treatment decisions. For example, underlying COPD or bronchiectasis should lead to consideration for anti-pseudomonal therapy. All patients treated at home should be reviewed within 48 to 72 hours to ensure that there has been no clinical deterioration requiring hospitalisation.

Table 3: Risk Factors for Prognosis of Pneumonia

Advanced age (65 years)
Presence of co-morbidities
COPD, bronchiectasis, malignancy, diabetes mellitus, chronic renal failure, congestive heart failure, chronic liver disease, chronic alcohol abuse, malnutrition, cerebrovascular disease, post-splenectomy, hospitalisation within the past one year
Physical findings
Tachypnoea (30/min)
Hypotension (90/60 mm Hg)
Tachycardia (125/min)
Temperature <35 °C or >40 °C
Disorientation, clouding of consciousness
Laboratory findings
WBC <4 × 10^9/L or >30 × 10^9/L or an absolute neutrophil count below 1 × 10^9/L
Hypoxaemia and/or hypercapnia
Chest radiograph: multilobar involvement, cavity, presence of pleural effusion
Anaemia of (<9 mg/dL)
Organ dysfunction, other than respiratory
Acidosis (pH <7.35)

***C**onfusion, **U**rea (>7 mmol/L), **R**espiratory, **B**lood pressure and Age – is described as CURB65. COPD = Chronic obstructive pulmonary disease; WBC = White blood cell.*

Table 4: Treatment Options in Patients with Community Acquired Pneumonia

Patient Type	Preferred Treatment Options
Out-patients previously healthy	
No recent antibiotic therapy	A macrolide (erythromycin) or doxycycline
Recent antibiotic therapy	A respiratory fluoroquinolone alone (moxifloxacin levofloxacin/gemifloxacin) Macrolide (clarithromycin/azithromycin) plus high-dose amoxicillin, (1 g thrice a day) or an advanced macrolide plus high-dose amoxicillin-clavulanate (1.2 g thrice a day)
Co-morbidities (COPD, diabetes, renal or congestive heart failure or malignancy)	
No recent antibiotic therapy	An advanced macrolide or respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam (regimen selected will depend on nature of recent antibiotic therapy)
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial super infection	A β-lactam or a respiratory fluoroquinolone
In-patients medical wards	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam
Recent antibiotic therapy	An advanced macrolide plus a β-lactam or respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy)
Intensive care unit	
Pseudomonas infection is not an issue	A β-lactam plus either an advanced macrolide or a respiratory fluoroquinolone
Pseudomonas infection is not an issue but patient has a β-lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
Pseudomonas infection is an issue	Either an anti-pseudomonal agent plus ciprofloxacin, or an anti-pseudomonal agent plus an aminoglycoside plus a respiratory fluoroquinolone or a macrolide
Pseudomonas infection is an issue but patient has a β-lactam allergy	Either aztreonam plus levofloxacin or aztreonam plus moxifloxacin or gatifloxacin, with or without an amino-glycoside

Complications need treatment as these arise (cross reference for treatment of empyema, respiratory failure, sepsis). Indications for mechanical ventilation (MV) (either non-invasive or invasive) in the management of pneumonia remains the same as for any other patient with respiratory failure.

HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA

HAP is defined as pneumonia that occurs after the patient has been in hospital for more than 48 hours. Patients who have been endotracheally intubated have a much higher risk of pneumonia. Endotracheal tube and MV and other intubations compromise the host defence mechanism seriously. The infecting organism is more likely to be an antibiotic resistant bacteria, especially when the patient has received frequent courses of antibiotics in the recent past, either at home or in a hospital, or has been on immunosuppressive therapy or haemodialysis (**Table 5**).

A relatively new term health care associated pneumonia (HCAP) is now being used to include any patient who was hospitalised in an acute care hospital for two or more days within 90 days of present infection; resided in a nursing home or long care facility, received intravenous antibiotics, chemotherapy or wound care within 30 days, or attended a hospital or haemodialysis clinic.

Table 5: Risk Factors for Multidrug-resistant Pathogens

Recent antibiotics
Prolonged hospitalisation
Prevalence of antibiotic resistance in the specific hospital unit
Recent hospitalisation (within last 3 months)
Intravenous infusion and antibiotics
Haemodialysis
Immunosuppression

DIAGNOSTIC TESTS

Bronchoscopic samples (protected specimen brush, broncho-alveolar lavage) are more specific, but non-bronchoscopic techniques, mainly tracheal aspirate, are cheaper. Physicians ability to diagnose VAP is often poor, as several pulmonary diseases may present with similar clinical signs. The presence of clinical signs of pneumonia in ICU patients (fever, pulmonary infiltrates in the chest radiograph and purulent pulmonary secretions) is caused by VAP in only about 30% to 40% of cases. Microbiologic findings may help to tailor antibiotic spectra in selected patients, but they should be considered in conjunction with a re-assessment of clinical response within 48 to 72 hours of onset of pneumonia. There is a problem of differentiating colonisation from infection. As a rule, colony forming units (CFU) of $\geq 10^3$/mL or $\geq 10^4$/mL or $\geq 10^5$ of protected brush, alveolar lavage, and tracheal aspirate respectively, are considered to indicate infection.

Depending on the clinical background, it is possible to predict antibiotic resistant bacteria. HAP and VAP are considered to be preventable (**Table 6**) if the quality of care had been optimal. The rates of nosocomial infections, when available, are used to compare units or countries and to assess a quality improvement programme in a given unit. In the context of our country, both *Klebsiella* and *Acinetobacter* are being seen with increasing frequency in the recent years.

Table 6: Recommended Measures for Prevention of Ventilator Associated Pneumonia

Hand disinfection
Microbiologic monitoring
Avoiding of invasive devices
Reduce antimicrobial prescriptions
Avoidance of endotracheal intubation
Non-invasive ventilation whenever possible
Preference of orotracheal intubation and orogastric tubes
Maintenance of optimum ET cuff pressure

PNEUMONIA IN IMMUNOCOMPROMISED PATIENTS

It is a more difficult problem to handle. The causative organisms are many and are unusual pathogens in addition to the common organisms we handle every day (**Table 7**).

Symptoms and Signs

Symptoms and signs are likely to be the same as those found with CAP or HAP in immunocompetent patients, though immunocompromised patients may have no fever or respiratory signs and are less likely to have purulent sputum if they are neutropaenic. In some patients, the only sign is fever.

Table 7: Pneumonia in Immunocompromised Patients

Disorders	Likely Pathogens
Acute leukaemia, aplastic anaemia, cancer chemotherapy	Gram-negative bacteria, *Staphylococcus aureus, Aspergillus sp., Candida sp.*
Diabetes mellitus	*S.aureus*, Gram-negative aerobes
Hodgkin's lymphoma, cancer haemotherapy, corticosteroid therapy	Mycobacteria, viruses (herpes simplex virus, cytomegalovirus), *Strongyloides sp.*, opportunistic fungi *(Aspergillus, Mucor, Cryptococcus spp), Nocardia sp., Toxoplasma sp.*
AIDS	*Pneumocystis jirovecii, Toxoplasma sp,* cytomegalovirus, herpes simplex virus, opportunistic fungi *(Aspergillus, Mucor, Cryptococcus spp),* mycobacteria
Multiple myeloma, agammaglobulinaemia	*S. pneumoniae, H. influenzae, Neisseria meningitidis*

Diagnosis

Diagnosis is established by chest radiograph, blood gases, bronchoscopy and lavage, an induced sputum and blood cultures.

It is to be kept in mind that an abnormal chest radiograph in these patients may not be due to an infection, there may be other reasons like haemorrhage, pulmonary oedema, tumour secondaries, radiation pneumonitis and pulmonary toxicity due to drugs.

Pneumocystis jirovecii is a common cause of pneumonia in immunosuppressed patients, especially in those infected with HIV and in those receiving systemic corticosteroids (see Chapter on HIV).

Chest radiograph showing localised consolidation usually indicates an infection involving bacteria, mycobacteria, fungi, or *Nocardia sp.* (**Figure 1**). A diffuse interstitial pattern is more likely to represent a viral infection, *P. jirovecii* pneumonia, drug or radiation injury, or pulmonary oedema. Diffuse nodular lesions suggest mycobacteria, *Nocardia sp.*, fungi, or tumour. Cavitary disease suggests mycobacteria, *Nocardia sp.*, fungi, or bacteria.

In organ or marrow transplantation recipients with bilateral interstitial pneumonia, the usual cause is CMV, or the disease is idiopathic. A pleural-based consolidation is usually aspergillosis. In AIDS patients, bilateral pneumonia is usually *P. jirovecii* pneumonia. About 30% of patients with HIV infection have *P. jirovecii* pneumonia as the initial AIDS-defining diagnosis, and >80% of AIDS patients have this infection at some time if prophylaxis is not given. Patients with HIV infection become vulnerable to *P. jirovecii* pneumonia when the CD4+ helper cell count is <200/μL.

Treatment

In neutropeenic patients, empiric treatment depends on the host defense, chest radiograph, and severity of illness. Generally,

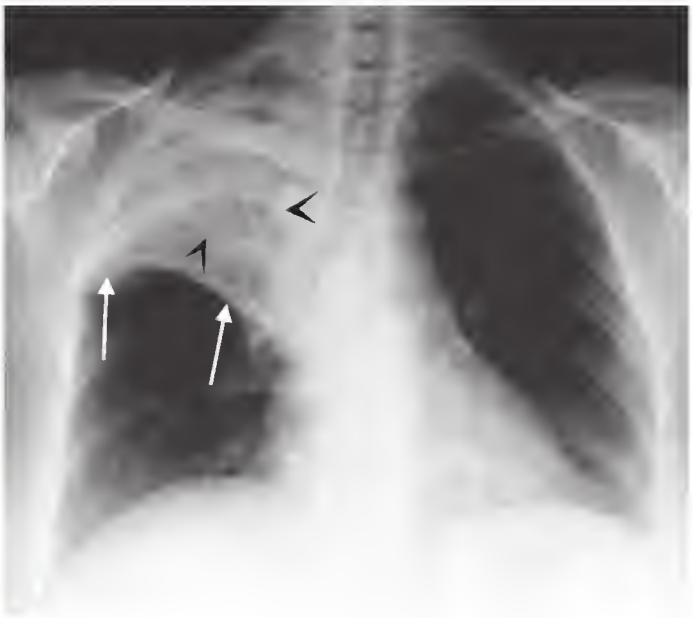


Figure 1: Chest radiograph (postero-anterior view) showing air bronchogram (black arrowheads) and pulled up fissures (white arrows) in case of right upper lobe bacterial pneumonia.

broad-spectrum drugs are needed to cover Gram-negative bacilli, *Staphylococcus aureus*, and anaerobes, as for HAP. If patients with conditions other than HIV do not improve with 5 days of antibiotic therapy, antifungal therapy is frequently added empirically.

Treatment of *P. jirovecii* infection is with antibiotics, usually trimethoprim-sulfamethoxazole or dapsone-trimethoprim, clindamycin-primaquine, atovaquone, or pentamidine. Patients with PaO_2 <70 mm Hg should receive systemic corticosteroids. Prognosis is generally good with timely treatment.

NON-RESOLVING OR SLOWLY RESOLVING PNEUMONIA

Normal resolution of pneumonia is variable and depends on the causative agent and the host response to the invading pathogen. Resolution of fever, white blood cell count, physical signs and radiographic changes usually occur in that order. Non-resolving pneumonia has been variably defined. Radiological resolution of the consolidation is usually achieved in *S. pneumoniae*, CAP by 4 weeks in most patients, but in some, it might take up to 10 weeks. Physicians are often confronted with the problem of non-resolving pulmonary infiltrates in patients receiving antibiotics for CAP.

Atypical organisms, TB and fungal infections need to be excluded, but the main emphasis in clinical practice is to exclude non-infectious causes to explain non-resolving pulmonary infiltrates (**Table 8**).

Table 8: Non-Infectious Mimics of Pneumonia

Neoplasms
Cryptogenic organising pneumonia or bronchiolitis obliterans with organising pneumonia
Hypersensitivity pneumonitis
Eosinophilic syndromes
Pulmonary vasculitides
Alveolar haemorrhagic syndromes
Pulmonary alveolar proteinosis

PREVENTION OF PNEUMONIA

All persons above the age of 50 years should receive inactivated influenza vaccine. Influenza vaccine should also be offered to all patients at hospital discharge and health care workers in in-patient and out-patient settings and in long-term care facilities should receive annual influenza immunisation (not evidence based).

Pneumococcal polysaccharide vaccine is recommended for use in persons aged >65 years and for younger adults with co-morbid diseases like diabetes, cardiovascular disease, lung disease, alcohol abuse, liver disease, cerebrospinal fluid leaks or renal failure. It is also recommended for patients with immune system disorders like sickle cell disease, nephritic syndrome, HIV infection, haematological malignancies and those who are on long-term immunosuppressive therapy.

Older adults may be benefitting from vaccination of children against pneumococcal disease because of decreased pneumoeoccal transmission. A pneumococcal conjugate vaccine is available for use only in children and according to data had resulted in 69% lower incidence of invasive (primary bacteraemic pneumonia with bacterial meningitis) pneumococcal disease in children under 2 years.

RECOMMENDED READINGS

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23.8 Suppurative Pleuro-Pulmonary Diseases

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Suppurative pleuro-pulmonary diseases continue to cause significant morbidity and mortality despite considerable advances made in the diagnosis and management of these conditions. The major suppurative lung diseases are bronchiectasis, lung abscess and empyema.

BRONCHIECTASIS

Introduction and Epidemiology

Bronchiectasis (BE) (*broncos* ~ airways; *ectasia* ~ dilation) is defined as an abnormal, irreversible dilatation of the bronchi. Strictly speaking, it is not a disease *per se* but the end stage of a variety of pathologic processes. Since, the primary clinical manifestations of BE are recurrent, chronic and sometimes refractory infections, it is discussed along with other suppurative diseases of the lung.

Classification

Aetiological

The aetiological classification of bronchiectasis is listed in **Table 1**.

Pathological/radiological

Three main types are described—(i) tubular or cylindrical (**Figure 1**), (ii) varicose and (iii) cystic (saccular) (**Figure 2**) depending upon the appearance of dilated bronchi on imaging. These three types largely represent increasing severity of the disease.

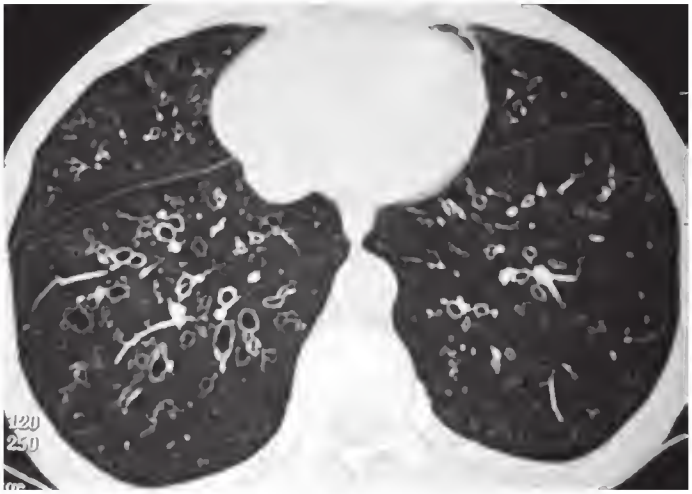


Figure 1: HRCT chest showing tubular bronchiectasis with a central distribution in both lower lobes.

Extent

Bronchiectasis can be either focal or diffuse. Focal or localised disease is typically seen when bronchiectasis results from mechanical bronchial obstruction.

Pathophysiology

Chronic inflammation involving the medium sized bronchi and bronchioles is the hallmark of bronchiectasis. On histopathology,

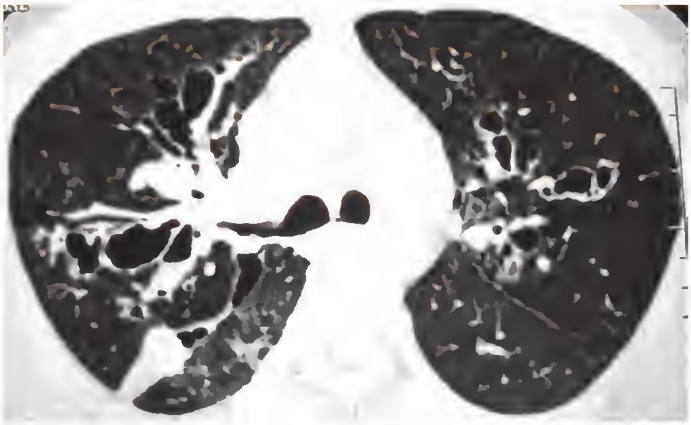


Figure 2: HRCT chest showing varying degrees of varicose and saccular bronchiectasis in both lungs.

there is exudation of neutrophils into the lumina of affected airways as well as infiltration of the bronchial/bronchiolar wall by neutrophils, mononuclear cells and CD4+ T lymphocytes. Recruitment of neutrophils is mediated by proinflammatory cytokines (IL-1β, IL-8, TNF-α and LT B4). Activation of neutrophils leads to damage to the respiratory mucosa and stimulation of mucous secreting glands in the airways. This is followed by a reduction in ciliary beating, impaired mucociliary clearance and ultimately retention of inflammatory secretions. Local immune response to inhaled pathogens becomes deficient and this results in colonisation of the bronchial tree by bacteria like *Pseudomonas aeruginosa*. Thus, infection, inflammation and airway damage perpetuate each other by a vicious cycle.

Clinical Features

The characteristic symptoms of bronchiectasis are chronic cough with expectoration, the sputum being typically copious, thick and purulent. However, the sputum may also be mucoid, mucopurulent or tenacious. This symptom is present in majority (up to 95%) of the patients and the quantity of sputum correlates with the quality of life (QoL). Associated rhino-sinusitis is present in two-thirds of cases. Dyspnoea and chest pain are other common symptoms. Haemoptysis is seen in 30% of patients and can vary from mild blood streaking of sputum to massive haemoptysis. The most common findings on physical examination are crackles (78%) and wheezing (20%). Digital clubbing, a frequent finding in the past, was seen in less than 5% of patients in a recent review.

Investigations

Radiology

Chest radiograph: Chest radiography is a relatively insensitive tool for diagnosing bronchiectasis. Specific findings include ring-like shadows (airways parallel to the X-ray beam), tram lines (airways perpendicular to the X-ray beam) and cystic lesions

(saccular bronchiectasis). However, other findings may be non-specific, e.g. atelectasis, focal area of consolidation and infiltrates.

Table 1: Aetiological Classification of Bronchiectasis

- **Post infectious**
  - Bacterial
    - *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, anaerobes
  - Mycobacteria
    - *Mycobacterium tuberculosis*
    - Atypical mycobacteria (*Mycobacterium avium-complex*)
  - Fungi
    - *Aspergillus* sp. [including allergic bronchopulmonary aspergillosis (ABPA)]
    - *Histoplasma capsulatum*
    - *Coccidioides immitis*
  - Viral
    - Measles
    - Pertussis
    - Adenovirus
- **Congenital**
  - Ciliary dyskinesia
    - Immotile cilia syndrome
    - Kartagener's syndrome
    - Young's syndrome
    - Secondary ciliary dyskinesia
  - Cystic fibrosis (CF) and variants
  - Alpha-1 antitrypsin deficiency
  - Swyer-James-MacLeod's syndrome
  - Tracheobronchomegaly (Mounier-Kuhn syndrome)
  - Congenital cartilage deficiency (Williams-Campbell syndrome)
  - Pulmonary sequestration
- **Abnormal host defence**
  - Immune deficiency
    - Primary
      - Hypogammaglobulinaemia
      - Immunoglobulin G subclass deficiency
      - Complement deficiency
    - Secondary
      - Malignancy
      - Chemotherapy
      - Post-transplant
      - HIV infection
- **Mechanical bronchial obstruction**
  - Foreign body
  - Tumour
  - Lymphadenopathy
- **Sequelae of aspiration or inhalation of toxic gases**
- **Systemic diseases**
  - Collagen vascular diseases
    - Rheumatoid arthritis
    - Sjögren's syndrome
    - Ankylosing spondylitis
    - Relapsing polychondritis
    - Marfan's syndrome
  - Inflammatory bowel disease
- **Miscellaneous**
  - Diffuse panbronchiolitis
  - Yellow nail syndrome

HRCT thorax: High resolution computed tomography (HRCT) scanning is the investigation of choice for diagnosing bronchiectasis and has virtually replaced bronchography. The diagnostic signs are listed in **Table 2**. This is usually done as a non-contrast study using thin sections (1.0 to 1.5 mm window every 10 mm) and a fast scan time (image acquisition time typically of 1 second or less) during full inspiration to reduce artefacts induced by respiration and cardiac pulsation.

Table 2: Diagnostic Signs of Bronchiectasis on HRCT Scans

Major signs

- Bronchial dilatation (abnormal widening of bronchi)
  - Horizontal bronchi: internal diameter of bronchus greater than diameter of its adjacent pulmonary artery (typically 1.5 times or more)—***Signet Ring Sign***
  - Vertical bronchi: Non-tapering or flaring of bronchi towards the periphery—***Tram lines***
- Presence of bronchi in the outer lung fields (within 1 to 2 cm of pleura)

Minor signs

- Bronchial wall thickening
- Mucus impaction in dilated bronchi (with/without plugging of centrilobular bronchioles)
- Crowding of bronchi (volume loss of affected lobe)
- Areas of reduced attenuation (mosaic pattern)

Spirometry

Spirometry with bronchodilator reversibility testing and flow–volume loops should be done in all patients with suspected or proven bronchiectasis. Spirometry often shows an obstructive pattern. Significantly, almost one-third of patients also demonstrate presence of bronchodilator reversibility. Presence of a restrictive defect indicates presence of significant atelectasis, fibrosis or consolidation.

Sputum analysis

Patients with stable bronchiectasis commonly (usually 60% to 80%) have colonisation with micro-organisms in their airways. *Haemophilus influenzae* and *Pseudomonas aeruginosa* are the two most commonly isolated micro-organisms. Patients who have colonisation with *Pseudomonas aeruginosa* tend to have more severe disease.

Specific tests directed at ascertaining aetiology

These are listed in **Table 3,** although a detailed discussion about them is beyond the scope of this chapter.

Table 3: Tests for Detecting Specific Aetiologies of Bronchiectasis

- Paranasal sinus disease (X-ray or CT paranasal sinuses)
- Gastro-oesophageal reflux (barium swallow, 24 hours oesophageal pH monitoring, oesophageal manometry)
- Immune deficiency [Total levels of IgG (and subclasses), IgM, IgE and IgA]
- ABPA [*Aspergillus* skin test, serum precipitins against *Aspergillus fumigatus* and sputum for *Aspergillus fumigatus*]
- Connective tissue disorders (antinuclear antibodies and rheumatoid factor)
- α1-antitrypsin deficiency (serum α1-antitrypsin levels)
- Cystic fibrosis (sweat chloride analysis, nasal potential difference, genotyping)
- Endobronchial abnormalities (Fibre-optic bronchoscopy)
- Ciliary dyskinesias (semen analysis, nasal mucociliary clearance – saccharine test, respiratory cilia sampling followed by electron microscopy

Treatment

Antibiotics

In general, most infective exacerbations are caused by bacteria that are also common aetiological agents for acute

exacerbations of COPD namely *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis* and thus, can be treated by conventional β-lactam antibiotics (penicillins and cephalosporins). Patients with *Pseudomonas aeruginosa* infection may need to be treated differently (including use of parenteral antipseudomonal drugs). Antimicrobial therapy should be guided by sputum cultures which are preferably taken before initiation of treatment since patients may have colonisation with multiple pathogens.

Controversies exist regarding the optimal dose, route and duration of antibiotic therapy.

Dose: Proponents for use of a higher (than usual) dose of antibiotics in bronchiectasis argue that the penetration of antibiotics into the bronchial mucosa and secretions is suboptimal and thus, micro-organisms that are shielded by them (formation of biofilms) do not get eradicated. However, evidence for higher doses is not yet conclusive.

Duration: In general, it is prudent to use antibiotics only during an acute infective exacerbation (generally for a period of 10-14 days). Hence, if clinical worsening is not associated with symptoms suggestive of an infective aetiology (increase in sputum quantity or purulence or fever), it is preferable to avoid using antibiotics. Even during stable disease, antibiotics have been used regularly (continuously or on a monthly basis). However, this has the potential drawback of promoting drug resistance and till conclusive evidence is available to support its role, it cannot be routinely advocated for management of bronchiectasis.

Route: Nebulised antibiotics have shown promise when used in patients with cystic fibrosis (CF) who are colonised by potentially pathogenic micro-organisms like *Pseudomonas aeruginosa* although recent studies have reported similar benefits even among patients with non-CF bronchiectasis. Aminoglycosides (especially tobramycin) are the drugs that have been most commonly used through the inhalational route.

Bronchopulmonary hygiene

Bronchopulmonary hygiene consists of pharmacological and non-pharmacological measures to assist the patient in removal of secretions from his/her respiratory tract.

Physiotherapy: Physiotherapy by postural drainage, chest percussion, forced exhalation and controlled cough is useful in clearing excessive secretions. Mechanical devices that cause chest vibration are also being increasingly used in developed countries.

Mucolytics: These are not recommended for routine use in non-CF bronchiectasis. Nebulised saline, human recombinant DNase and acetyl cysteine all have been shown to be beneficial only in patients with CF.

Surgery

Localised bronchiectasis that is associated with intractable symptoms despite optimal medical management may benefit from surgical resection of the affected segment or lobe.

Bronchodilators

Data on use of inhaled drugs is sparse. Inhaled corticosteroids (ICS), when used in high doses, have been shown (in small randomised trials) to have beneficial effects on symptom related parameters (sputum volume, sputum purulence, cough, dyspnoea) and QoL but without any changes in pulmonary function, number or severity of exacerbations, or microbiological profile of sputum. The benefit may be more marked in those with *Pseudomonas aeruginosa* infection. Therefore, at present their use may be restricted to patients showing significant reversibility of airway obstruction.

Complications

Important complications are recurrent pneumonia, empyema, lung abscess, pneumothorax, cor pulmonale and respiratory failure. Metastatic brain abscesses have also been reported. Secondary amyloidosis is an important long-term complication.

LUNG ABSCESS

Lung abscess is a circumscribed collection of purulent and necrotic material (pus) within the lung parenchyma. Most patients have a predisposition to either aspiration or systemic/local immune suppression.

Pathogenesis

Development of lung abscess can either be a primary (aspiration and bronchogenic spread of infection) or secondary (haematogenous spread to the lung) phenomenon.

The latter usually occurs in patients with an obvious focus of infection elsewhere in the body like endocarditis, liver and other visceral abscesses or suppurative thrombophlebitis. However, lung abscess can develop in patients who have asymptomatic bacteaemia.

In case of lung abscess occurring as a primary phenomenon, the initial process is aspiration of oropharyngeal contents. The aspirate commonly consists of the oropharyngeal flora (predominantly anaerobic bacteria), as well as food debris (and even necrotic periodontal tissue in case of patients with dental caries). Aspiration is followed by development of a pneumonitic process caused by the aspirated anaerobic bacteria. Over a period of 1 to 2 weeks, necrosis ensues and ultimately leads to the formation of a single or multiple cavities. The difference between necrotising pneumonia and lung abscess is only of theoretical interest since the underlying pathogenetic process is the same. In general, lung abscess implies a cavity that is at least 2 cm in diameter while necrotising pneumonia represents multiple, small cavities each of which is less than 2 cm in diameter. The suppurative process, if unchecked, can extend to the pleural space leading to empyema.

There are several factors that predispose to aspiration and lung abscess (**Table 4**); however, aspiration can occur in normal individuals also. When no predisposing factor is apparent, endobronchial obstruction (benign or malignant) should be ruled out.

Microbiology

Although more than 200 different species of micro-organisms constitute the resident flora in the oropharynx (gingival crevices), analysis of the lower respiratory tract secretions in patients with lung abscess reveals that the most virulent among

them (generally 4 to 5 in number) predominate. Anaerobic bacteria like *Prevotella melaninogenicus*, *Fusobacterium nucleatum* and *Peptostreptococcus* spp., are the most commonly isolated micro-organisms. A putrid (foul) odour of sputum is characteristic of anaerobic micro-organisms. Microaerophilic streptococci such as *Streptococcus milleri* are other important pathogens. In addition to anaerobes, aerobic Gram-negative bacilli (GNB) including *Klebsiella pneumoniae, Staphylococcus aureus* and *Pseudomonas aeruginosa* have an important role in the genesis of hospital acquired lung abscesses and their presence is often associated with a poor prognosis.

Table 4: Predisposing Factors for Development of Lung Abscess

Factors predisposing to aspiration
Impaired consciousness
Anaesthesia (general)
Alcohol intoxication
Dental caries
Drug overdose or abuse (narcotics, sedatives)
Head trauma
Metabolic encephalopathy (diabetic coma, hepatic and renal failure)
Neuromuscular diseases
Seizures including post-ictal state
Stroke (cerebro-vascular accident)
Oesophageal disorders
Achalasia and other dysmotility syndromes
Gastro-oesophageal reflux
Stricture (benign or malignant)
Zenker's diverticulum
Immune-suppression
Local
Chronic lung disease
Systemic (Impairment of cell mediated or humoral immunity)
Primary
Secondary
Diabetes mellitus
Malignancy
Chemotherapy
HIV infection
Mechanical bronchial obstruction
Foreign body
Tumour
Lymphadenopathy

Clinical Features

Most patients present with fever and cough with expectoration that is usually copious and foul smelling. Chest pain and haemoptysis are also frequent. Since the typical characteristics of sputum may not be present in all cases especially during the early course of infection, the clinical profile can mimic other diseases like tuberculosis and lung cancer.

Investigations

Radiology

Chest radiograph: Chest radiographs (postero-anterior and lateral views) help to confirm the presence of lung abscess and differentiate it from a pyopneumothorax although at times, this may be difficult and the two may even co-exist. A thick walled cavity with an air-fluid level is the commonly seen abnormality (**Figure 3**). In patients with necrotising pneumonia, consolidation with areas of breakdown in between (cystic lucencies) is seen.



Figure 3: Chest radiograph (PA view) showing a peripherally situated abscess in the left lower lobe with air-fluid level and surrounding consolidation. Few infiltrates are also seen in the left upper zone.

CECT thorax: Contrast enhanced computed tomography (CECT) of the chest (**Figure 4**) helps to define the number and location of abscess(es), as well as other associated features (parenchymal, interstitial, mediastinal or airway abnormalities), if any. In typical cases of lung abscess occurring after aspiration, the location of the abscess(es) is in the dependent broncho-pulmonary segments (superior segment of the lower lobe or posterior segment of the upper lobe when aspiration occurred in the supine position).

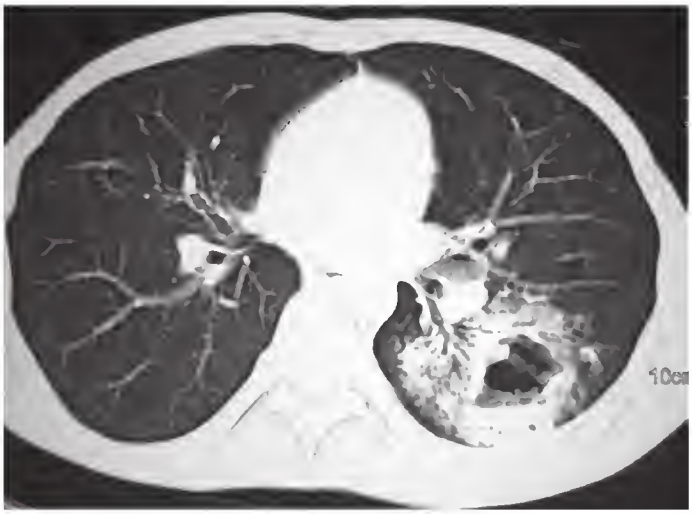


Figure 4: CT chest showing thick-walled abscess in the left lower lobe with air-fluid level and surrounding consolidation (air bronchogram).

Sputum analysis

Anaerobes are isolated in 60% to 80% (and even 100% in certain series) of respiratory tract specimens obtained from patients with lung abscess. Three-fourths of these are polymicrobial (multiple anaerobes or both anaerobes and aerobes).

Anaerobes are ubiquitous commensals of the oral cavity and hence, sputum cultures alone may be of little value in establishing the aetiological agent(s) of lung abscess. However, in routine clinical practice, invasive approaches to obtain lower respiratory tract specimens (transtracheal or transthoracic lung aspiration) are not recommended. A search

for non-conventional aetiological micro-organisms (aerobic GNB, *S. aureus*, *P. aeruginosa*, *Mycobacterium tuberculosis*, fungi, *Nocardia* sp.) should be done in cases of lung abscesses occurring in patients with diabetes mellitus, presenting with non-purulent sputum, multiple abscesses and lack of clinical improvement after 1 week of antibiotic therapy. Lung abscess due to *Rhodococcus equi* is characteristically seen in patients with AIDS. Apart from infectious causes, other causes for lack of response to therapy include presence of a cavitating neoplasm, cystic bronchiectasis and Wegener's granulomatosis all of which can mimic a lung abscess, clinically and radiologically. Such cases should undergo further investigations including bronchoscopy with/without collection of specimens by protected brushing, bronchoalveolar lavage (BAL) and bronchoscopic lung biopsy.

Treatment

Antibiotics

Antimicrobial therapy is the cornerstone of treatment in lung abscess. The optimal duration of antibiotic therapy for most suppurative pleuro-pulmonary diseases including lung abscess is generally 6 to 8 weeks.

Clindamycin has been the preferred drug for treatment of lung abscess in view of its superiority to penicillin in terms of rates of response, duration of fever and time to resolution of putrid sputum. However, lately β-lactam/β-lactamase inhibitor combinations have been proven to be equally effective. Metronidazole is generally ineffective against microaerophilic streptococci limiting its usefulness. A combination of penicillin and metronidazole may be used in situations when there is no access to better antibacterial drugs.

A prospective, open, randomised multicentre trial that compared ampicillin and sulbactam with clindamycin (with/without a 2nd/3rd generation cephalosporin) found that both were well-tolerated and equally efficacious in the treatment of aspiration pneumonia and lung abscess.

Drainage

Postural drainage and chest physiotherapy have been used previously as adjuncts to antimicrobial therapy in an attempt to bring out purulent contents of the abscess cavity. However, this is associated with the danger of inducing sudden emptying of the cavity and the large quantity of expectorated purulent and necrotic material can fill up the airways, as well as the previously uninvolved bronchopulmonary segments with catastrophic consequences.

Percutaneous catheter drainage: In 10% to 20% of patients with lung abscesses who do not respond to medical therapy, percutaneous catheter drainage of the abscess under CT guidance has been used. The usual indications are enlarging cavity and a peripheral location. Obvious risks are creation of a pneumothorax or even pyopneumothorax. Catheter occlusion is another problem especially if the abscess contents are thick and viscid. Overall, complications relating to the procedure occur in approximately one out of 10 cases.

Endoscopic drainage: Endoscopic lung abscess drainage is an alternative to percutaneous catheter drainage for patients with lung abscess in whom conventional medical management (antibiotic therapy) is unsuccessful. Presence of a communication between the lung abscess and the airways is essential for successful insertion of the catheter.

Surgery

Surgical resection is reserved for individuals if the non surgical drainage techniques mentioned above are either not feasible or not available. The rare complication of massive haemoptysis may also mandate surgical intervention.

Outcome and Prognostic Indicators

Complications are generally rare if appropriate and timely antimicrobial therapy is instituted. Complications can be local e.g. empyema, alveolopleural fistulas and recurrent haemoptysis or systemic e.g. metastatic abscesses, infective endocarditis, sepsis and amyloidosis. Predictors of poor outcome are listed in **Table 5**. The overall mortality rate secondary to lung abscess is 5% to 20%.

Table 5: Factors Predictive of Poor Outcome in Lung Abscess

Abscess characteristics
Secondary origin
Large abscess size (>6 cm diameter) and volume
Multiple abscesses
Location in right lower lobe
Host factors
Advanced age
Altered consciousness
Anaemia (haemoglobin <10 g/dL) at admission
Immunosuppression
Malignancy (pulmonary or extra-pulmonary)
Malnutrition and debilitation
Pneumonia
Symptom duration >8 weeks
Microbiological factors—Infection by aerobic organisms alone
Pseudomonas aeruginosa
Staphylococcus aureus
Klebsiella pneumoniae

EMPYEMA THORACIS

Introduction and Epidemiology

Collection of pus in the pleural cavity is known as *thoracic empyema* or *empyema thoracis*. Most empyemas occur as a complication of parapneumonic effusion (PPE). The incidence of thoracic empyema has reduced with the use of effective antibiotics for acute pneumonia.

Pathogenesis

The pleural space is normally sterile and not exposed to environmental (inhaled) pathogens. Pyogenic organisms can gain access to this space by local spread of infection from a focus in either intra- or extra-thoracic areas. Empyema occurring in the absence of clinical and radiological evidence of pneumonia (or other obvious focus of infection) is called primary empyema.

After invasion of the pleural space, suppuration ensues if the invading organisms are able to overcome the natural defence and immune mechanisms. The high concentration of leucocytes in the empyema fluid along with fibrin, cellular debris and bacteria (living or dead) are responsible for its characteristic thick, viscous, whitish-yellow, opaque and turbid appearance (pus). However, pleural invasion by a pyogenic micro-organism does not always progress to empyema. In fact, simple

(uncomplicated) PPE and empyema are two ends of a continuous spectrum (**Table 6**). The formation of PPE can be divided into 3 stages—exudative, fibropurulent and organisation stages. Increased permeability of the visceral pleura is responsible for the development of a sterile exudative effusion in the first phase (simple PPE). The second phase is marked by infection of the exudate, fibrin deposition over the pleura and tendency for formation of loculations/adhesions. In third phases, there is influx of fibroblasts into the pleural space, formation of dense and inelastic pleural peel/fibrous septations.

Table 6: Comparison of Parapneumonic Effusions and Empyema

Fluid Characteristic	Simple PPE	Complicated PPE	Empyema
Visual appearance	Clear	Clear to turbid	Frank pus
pH	>7.2	<7.2	**
LDH	<1000 IU/L	>1000 IU/L	**
Glucose*	>40 mg/dL	<40 mg/dL	**
Neutrophils	Usually <10,000/mL	Usually >10,000/mL	**
Gram stain	Negative	May be positive	Usually positive
Quantity	Minimal (<10 mm on lateral decubitus CXR)	Small to moderate (>10 mm on lateral decubitus CXR but occupying <1/2 hemithorax)	Large (>1/2 hemithorax) OR Any quantity with associated loculations/ thickening of visceral pleura
Free-flowing	Yes	Yes (usually)	Often loculated
Drainage required	Usually no	Yes	Yes

*PPE = parapneumonic effusion; *Fluid glucose <25% blood glucose can be taken as surrogate for absolute value; ** Not applicable.*

Among the biochemical tests in diagnosing PPEs, pH is the most accurate followed by glucose and then lactate dehydrogenase (LDH).

Microbiology

Microbiological profile in thoracic empyema is similar to lung abscess, dominated by polymicrobial isolation from clinical specimens and predominance of anaerobic bacteria. The latter are responsible for 25% to 76% of cases of empyema and in approximately 30% to 35% of cases, there is no associated aerobic infection.

Clinical Features

Patients may present with fever, chest pain, cough, constitutional symptoms or any combination of these. Cough is usually dry unless a large alveolopleural fistula results in copious postural expectoration of pus or there is underlying necrotising pneumonia. On physical examination, specific signs (in addition to those seen in any pleural effusion) include chest wall tenderness and rib crowding.

Investigations

Radiology

Chest radiograph and ultrasound: Typical finding on a PA film is that of a loculated pleural effusion. An air-fluid level may be seen in the presence of an air-leak. In certain cases, it may appear as a rounded pleural mass simulating lung cancer or mesothelioma. Lateral (decubitus or erect) radiographs may be used in addition to PA films. However, the availability of ultrasound has virtually replaced the need for these. Ultrasound is very good modality for evaluation of pleural space and can also be used for diagnostic or therapeutic drainage of loculated empyema.

Contrast enhanced CT (CECT) thorax: Pleural thickening and enhancement on CECT is seen in 80% to 100% of empyemas. The 'split-pleura' sign (presence of thickened enhancing parietal and visceral pleura separated by pleural fluid) is a characteristic finding (**Figure 5**). There is however, no correlation between the extent of pleural thickness and response to treatment.



Figure 5: CECT chest showing the split-pleura sign seen in a patient with bilateral empyema.

Pleural fluid/pus culture

Pleural fluid culture is positive in approximately 60% of cases and much less for anaerobic organisms. Yield may be enhanced by putting pleural fluid samples into blood culture bottles and by taking concomitant blood samples for culture.

Treatment

In contrast to the other suppurative lung diseases (bronchiectasis and lung abscess) wherein antibiotics form the cornerstone of management, antimicrobial therapy alone is inadequate for the treatment of patients with empyema and has to be supplemented with adequate drainage of pus.

Antibiotics

In general, principles of antimicrobial therapy in empyema are the same as those for lung abscess. Appropriate anaerobic cover and adequate duration, both are of paramount importance.

Drainage

Intercostal tube drainage (ICTD) is the most common method for drainage. It is a common belief that relatively large (28 to 36 French) chest tubes are better than smaller bore ones in view of the tendency for chest tubes to get obstructed by the thick fluid. However, correct positioning of the chest tube is more important than its size since studies that have used 8-12 F pigtail catheters under ultrasound or CT guidance have given comparable results to larger bore tubes.

Therapeutic thoracentesis (preferably daily) may be considered as an alternative to ICTD when the latter is either unavailable or contra-indicated due to any reason (e.g. presence of coagulopathy or bleeding diathesis). However, there are no randomised-controlled trials that have compared it with formal drainage.

Fibrinolytics

Incomplete pleural drainage is often seen with ICTD either due to tube occlusion or multiple fibrinous loculations in the pleural space. Use of intrapleural fibrinolytic agents in such individuals may, by lysing fibrin clots and adhesions, facilitate pleural drainage and thus, obviate the need for more invasive surgical interventions.

In a recent Cochrane review, it was concluded that intrapleural fibrinolytic therapy confers significant benefit in reducing the requirement for surgical intervention. Indian studies have also shown intrapleural streptokinase to be a safe and effective adjunctive therapy for patients with empyema and complicated PPE. Fibrinolytics and other biological agents that can be used to enhance drainage of pleural space collection and prevent development of pleural fibrosis (as adjuncts to drainage and antimicrobial therapy) are listed in **Table 7**.

Table 7: Biological Agents for the Treatment of Empyema Thoracis

Fibrinolytics
Streptokinase
Urokinase
Tissue plasminogen activator (Alteplase t-PA)
Single-chain urokinase plasminogen activator
Deoxyribonucleases
Streptodornase
Human recombinant DNase
Antibodies against specific growth factors
Antibody against transforming growth factor (TGF)
Antibody against vascular endothelial growth factor (VEGF)

Surgery

Surgical intervention may be required in as high as 40% of patients with empyema in whom medical management alone is unsuccessful and can be any of the options mentioned below. Although the optimal timing of surgical intervention remains a controversial area, it can be considered as early as seven days after initiation of conservative treatment.

Thoracotomy and decortication: Thoracotomy with decortication has remained the 'gold' standard of surgical management of empyema in the past. However, decortication is a major surgical procedure and is associated with significant morbidity since it involves removal of the fibrous peel covering the visceral and parietal pleura, as well as evacuation of all pus and debris from the pleural cavity. Hence, in the acute stages, decortication should only be done only for control of pleural infection and not for thickened pleura because the latter usually resolves spontaneously with time. If thickening of pleura persists after six months and patient is experiencing significant limitation of activities/restrictive pulmonary defects attributable to the former, decortication should be considered. Marked debilitation, understandably, is a relative contra-indication.

Rib resection and open thoracic drainage: Open thoracic drainage (after resection of segments of 1 to 3 ribs overlying the lower part of the empyema cavity) can be achieved in several ways (**Table 8**).

Table 8: Open Drainage Procedures for Empyema Thoracis

Insertion of one or more short, large-bore tubes into the empyema cavity followed by daily irrigation with an antiseptic solution and collection of the drainage into a colostomy bag placed over the tube(s)
Packing of the empyema cavity with gauze
Open (Eloesser) flap procedure—Creation of a fistulous tract between the empyema cavity and the chest wall that is covered by a skin and muscle flap

The aim in each of them is to allow drainage of the pleural space over a prolonged period of time while allowing the patient to be domiciliary, mobile and at the same time promoting gradual obliteration of the pleural space. Advantages of the two procedures includes chest drainage without tubes and thus, more patient freedom and often more complete drainage.

An important precaution to be taken before undertaking these procedures is to ensure that visceral and parietal pleura adjacent to the empyema cavity have become fused by the chronic inflammation otherwise a pneumothorax will result when the pleural space is in open communication with the atmospheric pressure. Therefore, these procedures cannot be performed early in the course of a complicated PPE/empyema.

Thoracoscopy

Video-assisted thoracoscopic surgery (VATS) is increasingly being used as an alternative to open thoracotomy primarily because it is less invasive and, thus, has less procedure-related morbidity and mortality. VATS allows the operator to break adhesions and loculations in the pleural space, ensure complete drainage of fluid/pus and place ICTD in the most appropriate location, as well as attempt decortication. VATS can be converted to open thoracotomy if it is felt that the desired results cannot be achieved with the former. The biggest disadvantage is lack of its availability. Duration of chest drainage and hospital stay tend to be shorter than those occurring after open thoracotomy with decortication.

TUBERCULOUS EMPYEMA

Tuberculous empyema remains an important entity in India due to the high disease burden of tuberculosis. Tuberculous empyema differs from tuberculous pleural effusions in several aspects (**Table 9**).

Since the immune response is much less than that in patients with tuberculous effusions, there is often a paucity of clinical symptoms and patients may in fact present years after onset of infection. Disease may be suspected after a routine chest radiograph or subsequent to development of an alveolopleural fistula (APF) or empyema necessitates. The characteristic radiological findings include a thick, calcified pleura, rib crowding and loculated collections of pus. Management involves administration of anti-tuberculous therapy (ATT), as well as drainage of pleural space. However, poor penetration of drugs through the fibrotic calcified pleura into the empyema

cavity leads to sub-therapeutic drug concentrations sub-optimal and this tends to promote the development of drug resistance.

Table 9: Comparison of Tuberculous Pleural Effusion and Empyema

Characteristic	Tuberculous Pleural Effusion	Tuberculous Empyema
Incidence	Very common	Relatively rare
Pleural space infection	Localised	Diffuse
Manifestations due to	Exaggerated immune response	Chronic active infection
Visual appearance of fluid	Straw coloured	Frank pus
Predominant cells in fluid	Lymphocytes	Neutrophils
Mycobacterial load	Low (Paucibacillary)	High
Smear for AFB	Rarely positive (<20%)	Strongly positive
Whether drainage required	Usually no	Yes
Residual fibrosis and restrictive defects	Minimal/none	Significant

Another commonly encountered problem is the inability of the trapped lung to re-expand after conservative management and surgical interventions like decortication may be required to achieve this. However, surgery should be undertaken only by experienced thoracic surgeons since patients with tuberculous empyema are poor surgical candidates (**Table 10**).

Table 10: Problems with Performing Surgery for Tuberculous Empyema

- Pulmonary parenchymal involvement
- Malnutrition and generalised debilitation
- Higher risk for post-operative complications
  - Persistent air leak [alveolopleural fistula (APF)]
  - Secondary bacterial infections
  - Respiratory failure
  - Bronchial stump dehiscence
- Technically difficult surgery

High risk patients may be managed conservatively by prolonged tube thoracostomy (or pigtail drainage) along with ATT.

Patients with tuberculous empyema generally fare much worse than those with non-tuberculous empyema. A prospective study to compare the clinical characteristics and outcomes of empyema thoracis due to tuberculous and non-tuberculous aetiologies was carried out recently. Significant differences existed between the two groups (**Table 11**) although mortality rates were similar (approximately 10% in each group).

Overall, amongst patients with empyema, presence of any of the two factors (APF or tuberculous aetiology) was associated with a six-fold risk of having a poor outcome.

Table 11: Comparison Between Tuberculous and Non-Tuberculous Empyema

Characteristic	Tuberculous Empyema (n = 41)	Non Tuberculous Empyema (n = 76)
Prevalence of diabetes mellitus	39.0 %	5.3 %
Mean duration of symptoms	37.5 days	15 days
Prevalence of malnutrition (BMI <18.5 kg/m^2)	56.1 %	28.9 %
Persistent air leak (APF)	78.1 %	22.4 %
Use of intra-pleural streptokinase	4.9 %	23.7 %
Median duration of pleural drainage	55 days	14 days
Median time for resolution of fever	7 days	5 days
Incidence of residual pleural thickening >2 cm	95.1 %	63.2 %

AMOEBIC LUNG ABSCESS AND EMPYEMA

Thoracic amoebiasis (caused by *Entamoeba histolytica*) is an important cause of both empyema and lung abscess. The right lung (lower and middle lobes) is usually affected (>85% of cases). The most common mode of pleuro-pulmonary involvement is by contiguous spread form liver and occurs in 6% to 40% of cases of amoebic liver abscess (ALA). The abscess may communicate with the tracheo-bronchial tree (hepato-bronchial or broncho-biliary fistula) and in such cases, almost all the pus is expectorated out. A combination of elevated right hemi diaphragm, tender hepatomegaly, right pleural effusion and/or right basal pulmonary lesion should alert the physician to the possibility of thoracic amoebiasis. Combination of metronidazole and drainage usually results in good outcome. Mortality ranges from 5% to 16% and is related to poor general condition, advanced age, malnutrition, delayed diagnosis and inadequate treatment.

RECOMMENDED READINGS

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23.9 Pulmonary Tuberculosis

MS Jawahar

EPIDEMIOLOGY

Tuberculosis (TB) is a major public health problem, especially in the developing countries of Asia and Africa. Fuelled by the human immunodeficiency virus (HIV) epidemic and the emergence of drug-resistant TB, it poses greater challenges than ever before. Globally two billion people are infected with the TB bacillus. In 2009, there were 9.4 million new cases of TB and 1.68 million deaths. In 2007, there were an estimated 500,000 new cases of multi-drug-resistant TB (MDR-TB) with India, China and the Russian Federation, accounting for more than 50% of such cases. Extensively drug-resistant TB (XDR-TB) has been reported from 58 countries.

In India, more than 40% of the adult population is infected with TB and about 1.9 million people develop TB disease every year. The prevalence is 299 and the mortality 28 per 1,00,000 population, respectively. The HIV infected population in India was estimated to be about 1.8 to 2.9 million in 2007, almost half of whom are also infected with TB and, thus, are at greater risk of breaking down with TB disease.

PATHOGENESIS

TB is transmitted from person to person by the airborne route. The interaction of *Mycobacterium tuberculosis* with the human host begins when droplet nuclei containing micro-organisms from infectious patients are inhaled. While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction reaches the alveoli where they are phagocytosed by activated alveolar macrophages. The balance between the bactericidal activities of the macrophage and the number and virulence of the bacilli determines the events following phagocytosis.

In the initial stage, either the host's macrophages restrict bacillary multiplication by producing proteolytic enzymes or cytokines, or the bacilli begin to multiply unhindered. If the bacilli multiply, their growth quickly kills the macrophages. Non-activated monocytes attracted by various chemotactic factors ingest the bacilli released from the macrophages.

Soon, two additional host responses develop: a tissue damaging response due to a delayed-type hypersenitivity (DTH) reaction to various bacillary antigens, and a macrophage-activating response which is a cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. It is the balance between the two that determines the form of TB that will develop subsequently.

With the development of specific immunity and the accumulation of large number of activated macrophages at the site of the primary lesion, granulomatous lesions (tubercles) are formed (**Figure 1**). These consist of lymphocytes and activated macrophages, such as epithelioid cells and Langhans giant cells. Initially, the newly developed tissue-damaging response is the only event capable of limiting mycobacterial growth within the macrophages. This response, mediated by various bacterial products, not only destroys macrophages but also produces solid necrosis in the centre of the tubercle. At this point, some lesions may heal by fibrosis and calcification, while others undergo further evolution.

In the majority of infected individuals, local macrophages are activated when bacillary antigens processed by macrophages stimulate T-lymphocytes to release a variety of lymphokines. These activated cells aggregate around the lesion's centre and effectively neutralise the tubercle bacilli. In the centre of the lesion, the necrotic material resembles soft cheese (caseous necrosis).

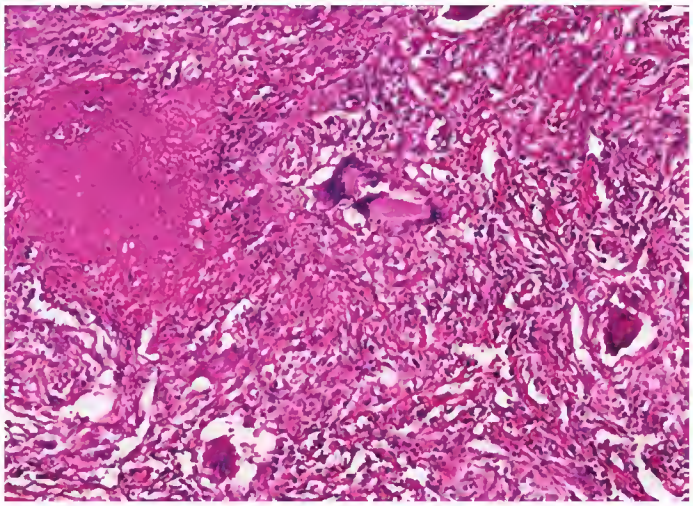


Figure 1: Tuberculous granuloma with caseation, lymphocytes, epithelioid cells, and Langhans giant cells.
Source: http://www.microscopyu.com/galleries/pathology/images/tuberculosis10x02.

In the minority of cases, the macrophage-activating response is weak, and mycobacterial growth can be inhibited only by intensified DTH reactions, which causes tissue destruction. The lesions tend to enlarge and the surrounding tissue is progressively damaged. At the centre of the lesion, the caseous material liquefies. Bronchial walls and blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing a large number of bacilli, is drained through bronchi. Within the cavity, tubercle bacilli multiply rapidly and spread into the airways and the environment through expectorated sputum.

In the early stages of infection, bacilli are usually transported by macrophages to regional lymph nodes, from which they disseminate widely to many organs and tissues. The resulting lesions may undergo the same evolution as those in the lungs, although most tend to heal.

Cell-mediated immunity confers partial protection against *M. tuberculosis*, while humoral immunity has no defined role in

protection. Two types of cells are essential: macrophages, which directly phagocytise tubercle bacilli, and T-cells (mainly CD4+ lymphocytes), which induce protection through production of lymphokines, especially interferon gamma (IFN-γ). Coincident with the appearance of immunity, DTH develops. This reactivity is the basis of the tuberculin purified protein derivative (PPD) skin test.

Risk Factors for Development of Clinical TB

A number of factors predispose to the development of TB. These are listed in **Table 1**.

Table 1: Risk Factors for Development of TB

Risk Factors	Relative Risk
HIV infection	100
Jejuno-ileal bypass	30 to 60
Silicosis	30
Post-organ transplantation status	20 to 70
Recent TB infection (< 1 year)	13
Intravenous drug use	10 to 30
Chronic renal failure/haemodialysis	10 to 25
Immunosuppressive/corticosteroid therapy	10
Gastrectomy	2 to 5
Diabetes mellitus	2 to 4
Malnutrition	2

TB = Tuberculosis; HIV = Human immunodeficiency virus.

CLINICAL FEATURES

TB can affect any organ in the body, but primarily the lungs are involved. Pulmonary TB accounts for 85% of all cases of TB. Since the primary mode of transmission of infection is aerial, the initial seeding of the infecting agent occurs in the respiratory tract. Primary infection can result in either a self-healing primary focus, or less frequently lead to progressive pulmonary disease. In a TB endemic country like India, primary infection occurs in childhood, but in a non-endemic setting it can occur at any age.

The predominant symptoms of pulmonary TB are cough, dyspnoea, chest pain and haemoptysis. Chest pain may be due to pleural involvement or of muscular origin due to the strain of chronic cough. Haemoptysis may occasionally be massive due to erosion of bronchial vessels leading to rapid exsanguination. More often the patient has sputum mixed or streaked with blood. In addition, there may be constitutional symptoms, such as fever, night sweats, anorexia, loss of weight and tiredness. Anyone with cough of two weeks or more, chest pain, unexplained fever or haemoptysis should be suspected of pulmonary TB and investigated.

DIAGNOSIS

The diagnosis of pulmonary TB should always include examination of the sputum for acid-fast bacilli (AFB) with Ziehl-Neelsen staining (**Figure 2**). Even though this technique is more than 125 years old, it still remains the cornerstone for the diagnosis of pulmonary TB. It is a simple and cheap test that will detect 50% of cases of pulmonary TB. Every patient with symptoms suggestive of pulmonary TB should have two sputum specimens examined; one spot specimen and one overnight specimen. However, for the sputum to be positive for AFB, it should contain at least 10,000 bacilli per millilitre of sputum. The

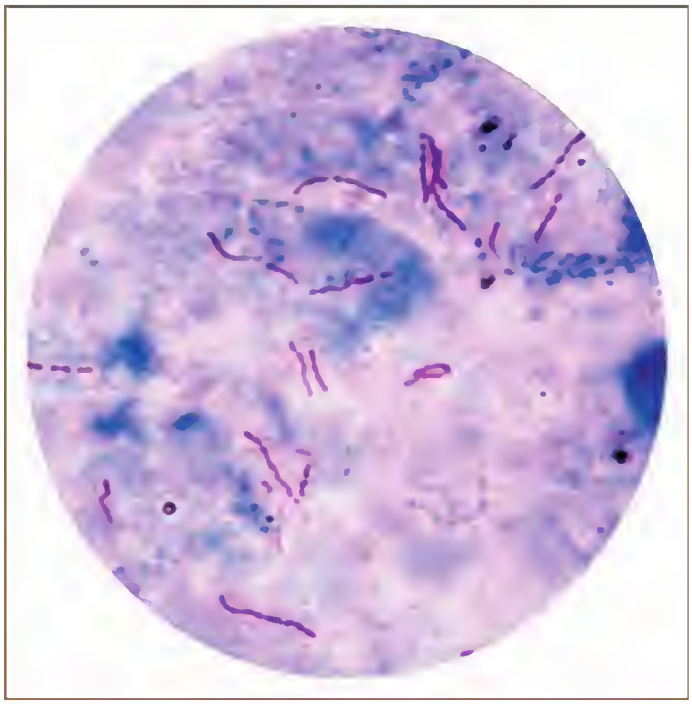


Figure 2: *Tubercle bacilli* viewed with Ziehl-Neelsen staining.

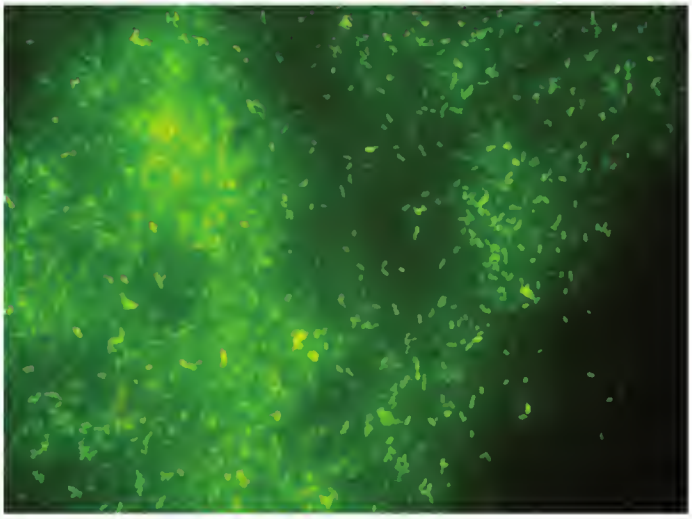


Figure 3: *Tubercle bacilli* viewed under fluorescent microscope.

use of fluorescent microscopy can increase the efficiency of this tool when large numbers of samples are tested (**Figure 3**). Light emitting diode (LED) microscopes are being field tested and may provide cost-effective alternatives in the near future.

When the sputum is less heavily loaded with bacilli, the sputum test may be negative and a chest radiograph may be needed to make the diagnosis (**Figure 4**). Chest radiograph should not be used as the only method of diagnosis for pulmonary TB as it can result in significant over-diagnosis. The interpretation of chest radiographs even by experienced chest physicians is subject to inter- and intra-observer variations. A combination of sputum smear examination and chest radiograph will detect almost all cases of pulmonary TB. It is only rarely that more advanced imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) will be required.

Sputum culture for TB bacilli is a more sensitive method than sputum smear examination. However, it is expensive, more



Figure 4: Chest radiograph (postero-anterior view) of a patient with bilateral pulmonary tuberculosis showing infiltrative lesions of both upper and right middle lung zones.

labour intensive and it usually take 6 to 10 weeks for the results to be available. Sputum culture is of crucial importance when drug resistance is suspected. Recently, automated liquid culture systems have been developed as alternatives to conventional solid media culture. These systems detect products of bacterial metabolism (carbon dioxide production or oxygen consumption with radiometric sensors—BACTEC 460 TB), fluorescent sensors [BACTEC Mycobacteria Growth Indicator Tube (MGIT) 960], colorimetric sensors (MB/BacT system), pressure sensors (ESP culture system II), or redox reagents, such as Alamar blue. These techniques significantly reduce the time for detection, compared with Lowenstein-Jensen culture. The use of liquid culture media in plates and detection of microcolonies and cord formation by inverted microscopy are also a useful tools that are being field tested. By incorporating anti-TB drugs to the media, this technique (termed microscopic-observation drug-susceptibility assay or MODS) can be used for early detection of drug resistance. Another new tool that is being evaluated is the use of mycobacteriophages (FASTPlaqueTB).

Apart from demonstrating the bacilli or detecting its by-products, indirect methods of diagnosis (such as the detection of antigens associated with *M. tuberculosis* or antibodies against it) are also available, though these tools are more often used in the diagnosis of extra-pulmonary TB. However, none of the existing commercial serological tests show adequate sensitivity and specificity to be recommended for diagnostic use.

Nucleic acid amplification (NAA) techniques, such as polymerase chain reaction (PCR), have also been gaining increasing importance again more for the diagnosis of extra-pulmonary TB. However, their use in diagnosis is limited in TB-endemic settings, primarily because of their cost and complexity. A molecular line probe assay is being evaluated in the field by the TB control programmes for rapid detection of rifampicin and isoniazid resistance and, in combination with liquid culture, is expected to provide timely results of drug resistance. The biggest advantage of this technique is that it can be applied directly to clinical specimens, reducing the delay in the diagnosis of drug resistance considerably.

Rapid species identification of culture isolates can be accomplished by molecular probes or high-performance liquid chromatography (HPLC).

The tuberculin (PPD) skin test detects latent TB infection and should not be used as a diagnostic test for TB disease in adults. Of late, IFN-γ release assays have emerged as an efficient alternative to the skin test. There are 2 promising new *in vitro* tests: QuantiFERON-TB Gold uses a whole-blood assay to measure IFN-γ production from sensitised T-cells, whereas the T-SPOT-TB test uses an enzyme-linked immunospot assay to quantify the number of peripheral blood mononuclear cells producing IFN-γ in response to TB-specific antigen stimulation (early secreted antigenic target 6, ESAT-6, and culture filtrate protein-10 (CFP-10). IFN-γ assays do not differentiate between latent and active TB.

TREATMENT

The aims of treatment of TB are to cure the patient, to prevent morbidity and mortality, to prevent transmission of TB to others, to prevent the development of drug resistance and to prevent relapse of TB. All these are achieved by initiating, and ensuring completion of appropriate anti-mycobacterial therapy as early as possible.

The era of TB chemotherapy began with the discovery of streptomycin by Selman Abraham Waksman in 1944 for which he was awarded the Nobel Prize for Physiology or Medicine in 1952. This was followed by para-aminosalicylic acid (PAS) in 1949 and isoniazid in 1952. The introduction of rifampicin and pyrazinamide in the late 1960s made it feasible to shorten the duration of TB treatment considerably and heralded the era of short-course chemotherapy. Much of the path-breaking researchs for the treatment of TB have come from India, mainly from the Tuberculosis Research Centre (TRC), Chennai, and the National Tuberculosis Institute (NTI), Bangalore, and have helped to define the principles of TB chemotherapy.

Current short-course regimens use an initial intensive phase (usually 2 months) of multiple drugs to rapidly reduce the number of TB bacilli; this is followed by a longer continuation phase of fewer drugs that have the ability to kill the more slowly growing organisms. Thus, the first phase of anti-TB treatment focuses on rapid killing of organisms (bactericidal activity). It takes much longer to kill the more slowly growing organisms or 'persistors', and the goal of this phase of treatment is to reach a point of 'sterilisation' (sterilising activity).

Four drugs, isoniazid, rifampicin, pyrazinamide and ethambutol are considered the first-line drugs for the treatment of TB. These drugs are well absorbed after oral administration and peak blood levels are reached in 2 to 4 hours with near-complete elimination in 24 hours.

The treatment regimen of choice for patients with newly diagnosed TB consists of an initial intensive phase of two months with isoniazid, rifampicin, pyrazinamide and ethambutol followed by a continuation phase of four months

with isoniazid and rifampicin. In settings where the initial isoniazid resistance is high or where drug susceptibility tests (DST) are not done, the World Health Organization (WHO) recommends the addition of ethambutol to the continuation phase (**Tables 2 and 3**). Treatment may be given either daily throughout in the intensive phase followed by thrice weekly in the continuation phase or thrice weekly throughout. There is sufficient evidence from clinical trials to show that intermittent treatment regimens (administered three times a week) are as efficacious as daily regimens in the treatment of TB, while being less expensive, having fewer adverse drug reactions and facilitating directly observed therapy.

Table 2: Treatment Regimens for TB Recommended by the WHO

TB Patient Definition	Treatment Regimen	
	Initial Phase	Continuation Phase
Newly diagnosed TB patients	HRZE for 2 months	HR for 4 months
Newly diagnosed TB patients in settings with high initial isoniazid resistance/ DST not done	HRZE for 2 months	HRE for 4 months
Previously treated sputum smear-positive pulmonary TB	SHRZE for 2 months/HRZE for 1 month	HRE for 5 months

TB = Tuberculosis; WHO = World Heolth Orgonizotion; DST = Drug susceptibility tests; H = Isoniozid; R = Rifompicin; Z = Pyrozinamide; E = Ethombutol; S = Streptomycin.

Table 3: Doses of First-line Anti-TB Drugs for Adults

	Recommended Dose			
	Daily		Three times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and Range (mg/kg body weight)	Maximum (mg)
Isoniazid	5 (4 to 6)	300	10 (8 to 12)	900
Rifampicin	10 (8 to 12)	600	10 (8 to 12)	600
Pyrazinamide	25 (20 to 30)	—	35 (30 to 40)	—
Ethambutol	15 (15 to 20)	—	30 (25 to 35)	—
Streptomycin*	15 (12 to18)	—	15 (12 to 18)	1,000

**For potients oged 60 yeors or above ond/or weighing less thon 50 kg-10 mg/kg with maximum of 500-750 mg.*

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For those patients with a history of previous TB therapy, the treatment of choice is determined on the availability of DST results. In the absence of such facility, or while waiting for the results, the patient is treated with an 8-month regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol for 3 months with streptomycin for the first 2 months, followed by isoniazid, rifampicin and ethambutol for 5 months (**Tables 2 and 3**). The regimen is modified if the DST shows resistance to isoniazid and rifampicin.

Role of Corticosteroids

Use of corticosteroids is not recommended in the routine treatment of pulmonary TB. However, they are of value in disseminated TB, such as miliary and meningeal TB, and for the management of pericardial and pleural effusions.

Revised National Tuberculosis Control Programme (RNTCP)

The RNTCP has been in operation since the 1990s. It is based on the WHO's global strategy for TB control and emphasises the importance of standardised treatment regimens administered as 'Directly Observed Treatment, Short Course' as one of the important components. The DOTS strategy, which has its origin in India, is today recognised as the cornerstone of efficient TB management. This is a comprehensive strategy and places the responsibility of curing the TB patient on the health provider system.

Under RNTCP, newly diagnosed patients (pulmonary and extra-pulmonary) are treated with a 6-month regimen of isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for 2 months followed by isoniazid and rifampicin thrice-weekly for 4 months. The patient's response to treatment is monitored with sputum smear examination at 2 and 4 months and at the end of treatment. If the second month sputum smear is positive for *M. tuberculosis*, the intensive phase is extended for one more month.

Previously treated TB patients, comprising of relapse, treatment after interruption or treatment failure are treated with an 8-months regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for 3 months with streptomycin for the first 2 months, followed by isoniazid, rifampicin and ethambutol thrice-weekly for 5 months. In pulmonary TB patients, sputum smear examination is done at the end of the intensive phase, and if it is positive for *Mycobacterium tuberculosis* the intensive phase is extended by one more month. Under RNTCP, newly diagnosed patients (pulmonary and extra-pulmonary) are treated with a 6-month regimen of isoniazid, rifampicin, pyrazinamide and ethambutol thrice-weekly for 2 months followed by isoniazid and rifampicin thrice-weekly for 4 months. The patient's response to treatment is monitored with sputum smear examination at 2 and 4 months and at the end of treatment. If the second month sputum smear is positive for *M. tuberculosis*, the intensive phase is extended for one more month.

During the intensive phase of treatment, every dose is administered under direct observation, while during the continuation phase patients are asked to attend the treatment clinic once a week, when one dose is given under direct observation and the other two doses supplied to the patient for self-administration. A unique feature of the RNTCP is that each patient is allotted a box of medicines that contains drugs for the full duration of the treatment.

COMPLICATIONS

Pulmonary TB that is not adequately and appropriately treated can lead to many complications (**Table 4**), the most important of which is drug resistance. The emergence of MDR-TB and XDR-TB are posing fresh challenges to the global control of this disease.

MDR-TB and XDR-TB

Drug resistance in TB may be either primary (in a patient who has never been exposed to anti-TB drugs) or acquired. Acquired drug resistance is the consequence of inappropriate or irregular therapy. While resistance to a single drug is usually of no major consequence as the resistant bacilli will be killed by the other

Table 4: Complications of Pulmonary Tuberculosis (TB)

Pulmonary	Extra-pulmonary
Development of MDR-TB or XDR-TB	Disseminated TB
Miliary TB	Spread to extra-pulmonary sites, viz. central nervous system and meninges, bones and joints, lymph nodes, genitourinary system, gastrointestinal system, pericardium, skin
Massive haemoptysis	
Cor pulmonale	
Emphysema	
Chronic bronchitis	
Bronchiectasis	
Broncho-pleural fistula	Empyema necessitans
Lung/Pleural calcification	Laryngitis
Aspergilloma	Anorectal disease
Atypical mycobacterial infection	Amyloidosis
	Poncet's polyarthritis

drugs used in the multi-drug treatment regimen, resistance to multiple drugs has major therapeutic implications. MDR-TB is defined as TB caused by bacilli that are resistant to isoniazid and rifampicin, the 2 most potent first-line anti-TB drugs with or without resistance to other drugs. XDR-TB is TB caused by bacilli that are resistant to isoniazid, rifampicin, and also to any of the quinolone group of drugs and any of the injectable second-line drugs, viz. kanamycin, capreomycin or amikacin.

The diagnosis of MDR-TB is a bacteriological diagnosis. Sputum culture and DST should be used to confirm the diagnosis. Incorrect DST results can lead to unnecessary changes of regimen, thus, decreasing the chances of cure.

Treatment of MDR-TB is less effective, more toxic and much more expensive compared to that of drug-susceptible TB. The treatment regimen should include at least four drugs that the patient is known to be susceptible to, or has not previously been exposed to, including an injectable agent and a fluoroquinolone in the initial phase, and at least four of the most active and best-tolerated drugs in the continuation phase. Treatment should be given daily and directly observed. An initial intensive phase of at least 6 months should be followed by a continuation phase of at least 18 months. Treatment should be continued till the sputum cultures remain consistently negative for at least 12 months. The RNTCP now offers a DOTS Plus regimen for patients with MDR TB (**Table 5**). In the initial stages of the treatment, patient should be hospitalised for monitoring treatment and adverse drug reactions. Response to treatment should be monitored with periodic sputum tests. The management of XDR-TB is even more problematical as the choice of effective drugs is severely limited. The treatment regimen should be designed based on the DST results. A treatment regimen using seven drugs (capreomycin, moxifloxacin, cycloserine, ethionamide, ethambutol, pyrazinamide and linezolid) has been recommended.

Pulmonary TB in the HIV Infected Patients

HIV infection is the biggest risk factor for the development of TB. TB can occur at any stage of HIV disease, and its manifestations depend on the level of immunosuppression.

In the early stages of HIV disease, the lungs are most commonly affected, while in the later stages of immunosuppression, extra-pulmonary sites are more often involved. The management of TB in the presence of co-existing HIV infection is challenging. The symptoms of pulmonary TB and other HIV-related respiratory diseases can be very similar. The diagnosis is often more difficult with a greater proportion of smear-negative and extra-pulmonary TB. Radiographic findings may be atypical and may include lower lobe infiltrates and miliary distribution, and cavitary disease may be less likely. While TB patients with concomitant HIV infection may respond as well to standard anti-TB treatment as those who are immunocompetent, deaths during treatment, partly due to HIV itself and partly due to other HIV-related diseases are more frequent. It is also likely that relapse of TB may be higher in HIV-TB patients compared to immunocompetent TB patients.

The combination of anti-retroviral treatment (ART) with anti-TB treatment also presents problems. Apart from the pill burden,

Table 5: Treatment Regimen for MDR-TB Under DOTS Plus of RNTCP

Body Weight (Kg)	Intensive Phase			Continuation Phase		
	Drugs	Dose (mg)	Duration	Drugs	Dose (mg)	Duration
16 to 25	Kanamycin Pyrazinamide Levofloxacin Ethambutol Ethionamide Cycloserine	500 500 500 400 375 250	6 to 9 months	Levofloxacin Ethambutol Ethionamide Cycloserine	500 400 375 250	18 months
26 to 45	Pyridoxine Kanamycin Pyrazinamide Levofloxacin Ethambutol Ethionamide Cycloserine	50 500 1250 750 800 500 500	6 to 9 months	Levofloxacin Ethambutol Ethionamide Cycloserine	750 800 500 500	18 months
>45	Kanamycin Pyrazinamide Levofloxacin Ethambutol Ethionamide Cycloserine	750 1500 750 1000 750 750	6 to 9 months	Levofloxacin Ethambutol Ethionamide Cycloserine	750 1000 750 750	18 months

MDR = Multidrug-resistant; TB = Tuberculosis; DOTS = Directly Observed Treatment Short-course; RNTCP = Revised National Tuberculosis Control programme.

a major handicap is that rifampicin cannot be used along with protease inhibitors. Possible options include deferring anti-retroviral treatment till TB treatment is completed, or at least till the end of the intensive phase of treatment and then to use ethambutol and isoniazid in the continuation phase. If available, rifabutin can be used instead of rifampicin.

Side Effects to Anti-TB Therapy

The adverse effects of anti-TB drugs and their management are described in **Table 6**. These are classified as major or minor. A patient who develops minor adverse effects should continue the TB treatment along with symptomatic treatment. In case of major side effects, the treatment or the responsible drug is stopped, either temporarily or permanently. Patients with major adverse reactions should be managed in a hospital.

with chills and rigours and intense myalgia which typically comes on one to two hours after drug administration. In its milder form it can be managed with antipyretics, but more severe manifestations will warrant the withdrawal of rifampicin from the treatment regimen.

Pregnancy and Breastfeeding

Women of child-bearing age should be advised contraception before starting TB treatment. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy: streptomycin is ototoxic to the foetus and should not be used during pregnancy. A breast-feeding woman who has TB should receive a full course of TB treatment. Mother and baby should stay together and the baby should continue to breastfeed. After active TB in the baby is ruled out, the baby should be given 6 months of isoniazid preventive therapy, followed by BCG (Bacille Calmette-Guérin) vaccination. Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid.

Table 6: Side Effects to Anti-TB Drugs—Syndrome Based Approach to Management

Side Effects	Drugs Probably Responsible	Management
Minor		Continue anti-TB drugs
Orange or red coloured urine	Rifampicin	Reassurance
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin	Give drugs with a small meal or at bed-time
Arthralgia	Pyrazinamide	Aspirin
Itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Anti-histamines
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50 to 75 mg/dL
Major		Stop responsible drug
Skin rash	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop streptomycin, isoniazid, rifampicin, pyrazinamide. Try to identify offending drug by challenging with small doses. Re-introduce other drugs
Deafness, dizziness	Streptomycin	Stop streptomycin. Use ethambutol
Jaundice, hepatitis	Isoniazid, rifampicin, pyrazinamide	Stop isoniazid, rifampicin, pyrazinamide. Use streptomycin and ethambutol. Monitor liver function tests (LFTs). Re-introduce isoniazid, rifampicin, pyrazinamide after LFTs become normal
Visual impairment	Ethambutol	Stop ethambutol
Flu syndrome	Rifampicin	Stop rifampicin
Acute renal failure	Rifampicin	Stop rifampicin
Thrombocytopenia	Rifampicin	Stop rifampicin
Shock	Rifampicin	Stop rifampicin

Adapted from: Treatment of Tuberculosis Guidelines, fourth edition, World Health Organization, 2009, WHO/HTM/TB/2009.420.

The most common of the major adverse reactions is hepatitis and jaundice. Rifampicin induces hepatic enzymes and a transient elevation of the enzymes acetyl aminotransferase (AST) and alanine aminotransferase (ALT) are expected. If this is accompanied by elevated serum bilirubin, hepatotoxic anti-TB drugs (isoniazid, rifampicin and pyrazinamide) should be temporarily withheld and the patient treated with streptomycin and ethambutol. Once the liver function becomes normal, the original regimen may be resumed. Acute renal failure and acute thrombocytopenia warrant the stopping of rifampicin, which should then not be used again in these patients. Flu syndrome is a rare phenomenon usually associated with intermittent rifampicin usage (twice or thrice weekly) and manifests as fever

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23.10 Fungal Infections of Lungs

Ashok Shah

INTRODUCTION

Fungal pneumonias are common nosocomial infections in the immunocompromised host and are often associated with a high morbidity and mortality (**Table 1**). The global human immunodeficiency virus (HIV) epidemic, increased organ transplantation and immunosuppressant use have contributed to the increased occurrence of fungal infections of the lungs. Community-acquired pulmonary fungal infections are also seen, especially in those with pre-existing lung ailments.

Table 1: Classification of Fungal Infections of the Lungs

Allergic
Allergic bronchopulmonary mycoses
Allergic fungal sinusitis
Immunoglobulin (Ig)-E mediated asthma
Bronchocentric granulomatosis
Hypersensitivity pneumonitis
Chronic eosinophilic pneumonia
Saprophytic infestation of airways, cavities and necrotic tissue
Fungal ball, e.g. aspergilloma
Semi-invasive
Chronic necrotising fungosis
Invasive
Acute (necrotising) bronchopneumonia
Tracheobronchitis
Obstructive
Pseudomembranous
Ulcerative
Invasive pleural disease (fungal empyema)

EPIDEMIOLOGY

The aetiologic agents of respiratory mycoses range from yeast-like to dimorphic and filamentous fungi and can be divided into two groups, namely, opportunistic and endemic. The opportunistic fungi are normally commensals but cause disease in an immunocompromised state. These include *Candida* species, *Aspergillus* species, *Cryptococcus neoformans*, and the zygomycetes (*Mucor*, *Rhizopus*). Fungi, previously thought to be non-pathogenic or only sporadically associated with human disease, such as *Candida* (except *C. albicans*), *Fusarium*, *Trichosporon*, and *Malassezia* species, are now emerging as important nosocomial fungal pathogens. The opportunistic fungi have a cosmopolitan distribution and are commonly detected either in immunosuppressed patients or those who are critically ill.

Endemic fungi, on the other hand, are those that can cause disease in normal hosts as well. They are usually restricted in distribution to discrete geographic regions. These are *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, sporotrichosis, and penicilliosis. Pulmonary fungal infections common in India are aspergillosis, cryptococcosis, histoplasmosis, blastomycosis and zygomycosis.

The data on worldwide incidence and prevalence of pulmonary fungal infections are scanty. It was reported that up to 7% patients dying in hospitals have invasive aspergillosis. *Candida* species accounts for 8% to 15% of nosocomial blood stream infections, and are the fourth most common isolate of patients in the intensive care unit (ICU). *Candida* colonisation has also been seen in respiratory samples obtained by bronchoalveolar lavage (BAL), endotracheal aspirate, or protected brush catheter specimens in critically ill non-neutropenic patients. Among the specific patient groups, about 15% of allogenic haemopoietic stem cell transplant recipients develop fungal pneumonia. Approximately 60% and 20% of patients with acquired immunodeficiency syndrome (AIDS) admitted to ICU have *Pneumocystis jirovecii* pneumonia or oesophageal candidiasis, respectively. *Penicillium marneffei* infections are seen in about 30% of people with AIDS in South-East Asia including north-eastern states of India. Endemic fungal infections are commoner in men since oestrogen inhibits transformation of mycelium to the yeast form.

RISK FACTORS

A number of factors may be associated with an increasing incidence of pulmonary fungal infections (**Table 2**). Nosocomial *Aspergillus* species outbreaks have been related to contaminated air or ventilation systems. Recently, many cases of fungal pneumonias have been reported in patients with chronic obstructive pulmonary disease (COPD).

Table 2: Risk Factors for Fungal Pneumonia

Acute leukaemia or lymphoma during myeloablative chemotherapy
Bone marrow transplantation
Solid organ transplantation on immunosuppressive treatment
Prolonged corticosteroid therapy
Acquired immunodeficiency syndrome
Congenital immune deficiency syndromes
Antimicrobial agents and chemotherapy
Presence of indwelling intravascular catheters
Endotracheal tubes and urinary catheters
Neutropenia, in particular associated with fever
Prior haemodialysis
Previous fungal colonisation

CLINICAL PRESENTATION

Acute Pneumonia

In individuals who are neutropenic or immunocompromised, persistent fever (even before the onset of pulmonary findings) may be an early sign of infection. Cough is usually dry, and is associated with pleuritic chest pain. Breathlessness may be marked and respiratory failure may be present. Haemoptysis is seen in patients with invasive aspergillosis or mucormycosis.

Tracheobronchitis

Tracheobronchitis has only been reported with *Aspergillus* species. *Aspergillus* tracheobronchitis is classified into three forms, namely, obstructive, pseudomembranous and ulcerative. Obstructive tracheobronchitis is characterised by thick mucous

plugs full of *Aspergillus* species without macroscopic evidence of bronchial inflammation. The pseudomembranous form typically shows extensive inflammation of the tracheobronchial tree, with a membrane overlying the mucosa containing *Aspergillus* species. The term ulcerative *Aspergillus* tracheobronchitis (UATB) is reserved for patients with limited involvement of the tracheobronchial tree. Patients with UATB have a favourable outcome in lung transplant patients due to surveillance bronchoscopy and prompt initiation of antifungal therapy in the post-transplantation course.

INFECTIONS CAUSED BY YEAST-LIKE FUNGI AND *CANDIDA*

Fungi isolated from sputum may either be commensals, pathogens or saprophytes. Primary *Candida* pneumonia refers to invasive infections limited to the lungs. Secondary *Candida* pneumonia refers to lung involvement due to haematogenous dissemination. The diagnosis of *Candida* pneumonia can be firmly established only on histopathology. This entity, while often documented at autopsy, is usually masked completely by the other manifestations of invasive candidiasis. Classical findings of secondary *Candida* pneumonia are microabscesses with pseudohyphae penetrating blood vessels, lung interstitium and airways.

Aspergillus Infections

Aspergillus species constitute the second most common cause of hospital-acquired fungal infections after *Candida*. It may be seen in up to 30% of patients with haematological malignancies. Lung involvement due to *Aspergillus* species ranges from saprophytic colonisation (aspergilloma) to rapidly invasive and disseminated disease. Allergic bronchopulmonary aspergillosis (ABPA) is the most frequently recognised manifestation of *Aspergillus* associated hypersensitivity respiratory disorder. On histopathology, fungal hyphae can be observed in invasive pulmonary aspergillosis (**Figure 1**).

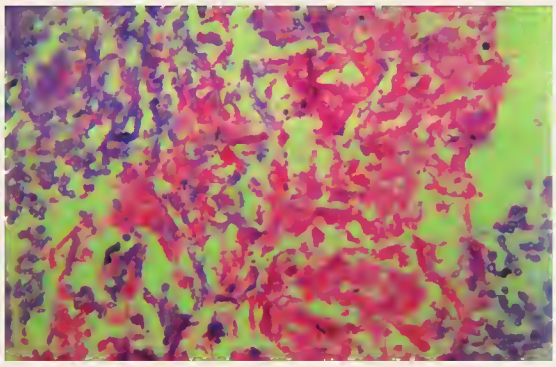


Figure 1: Photomicrograph showing filaments of *Aspergillus* in a patient with invasive pulmonary aspergillosis Haematoxylin, ×40.
Courtesy: Dr Sudhir Jain.

DIAGNOSIS

Diagnosis of pulmonary mycoses is often difficult due to lack of specific pathognomonic clinical syndrome and characteristic radiological features. In our country, the problem is further confounded by lack of dedicated diagnostic mycology laboratories. Patients with pulmonary mycoses are often misdiagnosed as tuberculosis, bacterial diseases, flu-like infections, or any disease of obscure aetiology and thus suffer the complications of unwarranted chemotherapy and/or surgery.

Opportunistic infections should be suspected in patients presenting with leucopenia and/or neutropenia. However, leucocytosis (endemic mycoses), eosinophilia (coccidioidomycosis) may sometimes be encountered. Culture of respiratory tract secretions is crucial to the diagnosis.

Fibre-optic bronchoscopy is useful to obtain samples for smear examination and cultures. Transbronchial lung biopsy is useful for detecting tissue invasion. Bone marrow aspiration and/or biopsy, smear and culture of other specimens like blood, urine, and cerebrospinal fluid are also useful diagnostic aids. A urine fungal culture in men after a prostatic massage helps to identify *Cryptococcus* species.

Serologic tests facilitate rapid diagnosis of fungal infections. Antigen detection using enzyme-linked immunosorbent assay (ELISA) or latex agglutination and molecular methods like polymerase chain reaction are useful in detecting *Candida* species and *Histoplasma capsulatum*. Detection of *Histoplasma* antigen in urine or serum is useful in diagnosis and to evaluate the efficacy of treatment in disseminated histoplasmosis. In invasive *Aspergillus* pneumonia, galactomannan ELISA may be positive in the blood very early, prior to clinical suspicion of invasive fungal infection. On histopathology, caseating or necrotising granulomas with intracellular organisms inside macrophages are seen in infections with *Histoplasma capsulatum* or *Coccidioides immitis*.

Consolidation, nodular shadows, patchy infiltrates, cavitating lesions and pleural effusion are the common findings on the chest radiograph. Mediastinal adenopathy is seen in patients with endemic fungal pneumonias. Miliary mottling may occur in patients with disseminated disease. Computed tomography (CT) scan is useful in the evaluation of non-specific infiltrates in immunocompromised patients. The 'halo sign' on CT is now regarded as an early indicator of invasive pulmonary aspergillosis. A nodular core is present but there is no visible pulmonary parenchyma. This is surrounded by a ground-glass perimeter, through which pulmonary parenchyma is visible. Macronodules including 'infarct-shaped nodules', 'crescent sign' along with cavitation (**Figure 2**) and consolidation may also be seen. An algorithm showing approach to diagnosis is depicted in **Figure 3**.

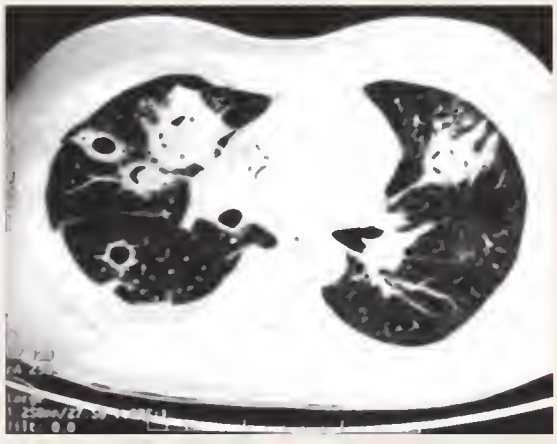


Figure 2: Computed tomography of the thorax showing bilateral 'macronodules' along with a 'crescent sign' on the right side in a patient with invasive pulmonary aspergillosis. An 'infarct-shaped nodule' abutting the pleural surface on the right side is also visible
Courtesy: Dr Puneet Khanna.

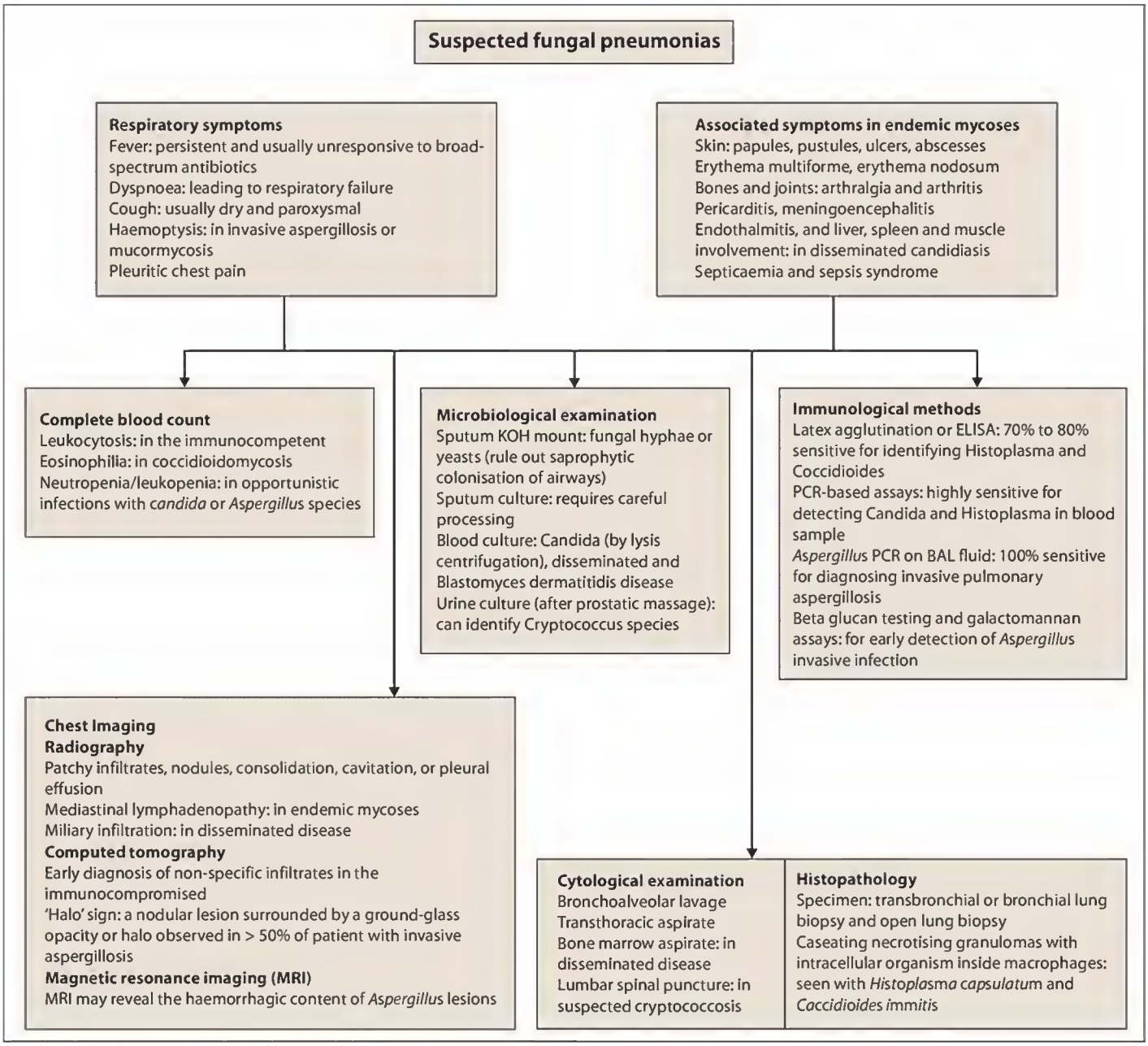


Figure 3: Diagnostic algorithm for patients with suspected fungal pneumonias.

KOH = Potassium hydroxide; ELISA = Enzyme-linked immunosorbent assay; PCR = Polymerase chain reaction; BAL = Bronchoalveolar lavage.

TREATMENT

Spontaneous recovery without treatment usually occurs in endemic mycoses, especially in mildly affected immunocompetent patients. However, early institution of treatment, even when diagnostic tests are underway, is required if dissemination occurs. Antifungal agents (**Table 3**) are the mainstay of the treatment. Due to improved survival rates, as demonstrated in randomised controlled trials, voriconazole is the drug of choice for primary treatment of invasive pulmonary aspergillosis. The recommended duration of therapy is at least 6 to 12 weeks. In immunocompromised patients, it is better to continue antifungal agents throughout the entire period of immune suppression and also until the lesions have resolved. During subsequent immunosuppression, empirical treatment may be of help in the prevention of infection.

Reversing the factors responsible for the immunocompromised state may facilitate successful recovery. In patients with candidiasis, it is important to remove indwelling infected intravenous lines or urinary catheters, especially in the setting of haematogenous spread. Furthermore, rapid tapering of immunosuppressants and corticosteroids should be achieved, lest relentless infection might ensue. Usage of growth factors is helpful in patients with febrile neutropenia. In patients with coccidioidomycosis and mucormycosis, surgical debridement or resection of necrotic tissue is often a necessary adjunct to antifungal treatment. Surgery may also be useful in haemoptysis from a single focus, lesions contiguous with the great vessels or pericardium, and invasion of the chest wall. Another relative indication for surgery is the resection of a single pulmonary lesion prior to intensive chemotherapy.

Table 3: Antifungal Agents Used in the Treatment of Respiratory Mycoses

Drug	Mode of Action	Indications
Flucytosine	Acts directly on fungal organisms by competitive inhibition of purine and pyrimidine uptake and indirectly by intracellular metabolism to 5-fluorouracil after penetrating fungal cells. Inhibits RNA and protein synthesis	Active against *Candida* and *Cryptococcus* species Generally used in combination with amphotericin B
Fluconazole	Selectively inhibits fungal CYP450 and sterol C-14 alpha demethylation	Candidiasis, coccidioidomycosis, blastomycosis/histoplasmosis Maintenance therapy in patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis
Itraconazole	Slows fungal cell growth by inhibiting CYP450 dependent synthesis of ergosterol, a vital component of fungal cell membranes	Fungistatic activity demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis, Histoplasma duboisii, Aspergillus fumigatus, Cryptococcus immitis, Cryptococcus neoformans, Paracoccidioides brasiliensis, Sporothrix schenckii, Trichophyton rubrum*, and *Trichophyton mentagrophytes* Patients with pulmonary and extra-pulmonary aspergillosis who are intolerant of or are refractory to amphotericin B therapy
Voriconazole	Inhibits fungal CYP450 mediated 14 alpha-lanosterol demethylation, which is essential in fungal ergosterol biosynthesis	Primary treatment of invasive aspergillosis Initial therapy for tracheobronchitis Salvage treatment of *Fusarium* species or *Scedosporium apiospermum* infections
Amphotericin B	Exerts antifungal activity, principally by binding to sterols in the fungal cell membrane	Broad spectrum of activity against pathogenic fungi, including yeasts, except *Fusarium* species
Caspofungin	Inhibits synthesis of beta-(1,3)-D-glucan, an essential component of fungal cell wall	Refractory invasive aspergillosis and salvage therapy
Anidulafungin	Inhibits synthesis of beta-(1,3)-D-glucan, an essential component of fungal cell wall	Invasive candidiasis
Micafungin	Inhibits synthesis of beta-(1,3)-D-glucan, an essential component of fungal cell wall	Candidemia, acute disseminated candidiasis

CYP450 = Cytochrome P-450; RNA = Ribonucleic acid; AIDS = Acquired immunodeficiency syndrome.

The principles of management of fungal pneumonias are described in **Table 4**.

As in invasive fungal pneumonias, early institution of treatment for *Aspergillus* tracheobronchitis may help in (i) preventing anastomotic disruptions in lung transplant recipients, and (ii) clearing off ulcerative tracheobronchial lesions. Here too, voriconazole is the drug of choice. The role of aerosolised amphotericin is under investigation. The dosage regimens with various antifungal agents is given in **Tables 5 A to C**.

COMPLICATIONS

Dissemination to other sites and sepsis syndrome are the most common complications of fungal pneumonias. Blood vessel invasion can lead to haemoptysis, pulmonary infarction, myocardial infarction, cerebral emboli, cerebral infarction, or blindness. Fibrosing mediastinitis and broncholithiasis are commonly observed in histoplasmosis. Other complications include bronchopleural or tracheoesophageal fistulas, pericarditis and arthritis.

Table 4: Principles of Management of Fungal Pneumonias

Aetiological Cause	Antifungal Drugs
Candidiasis	Amphotericin B is the mainstay of treatment. Flucytosine may be of benefit when added to amphotericin B Fluconazole use in pulmonary disease not studied but is effective in hepatosplenic candidiasis and candidemia. Anidulafungin is useful in invasive disease
Aspergillosis, Zygomycoses	Amphotericin B is often started empirically in patients who are neutropenic with fever and unexplained pulmonary infiltrates and cannot tolerate an invasive pulmonary procedures. Flucytosine is synergistic with amphotericin B. Rifampicin often added empirically when patient is deteriorating in face of amphotericin B. Itraconazole used to complete the treatment with initial response to amphotericin B; *Mucor* species generally resistant to azoles. Ketoconazole may be antagonistic with amphotericin B
Cryptococcosis	Amphotericin B in patients who are severely ill. Fluconazole in milder cases or after clinical response to amphotericin B. Lifelong maintenance therapy in AIDS due to frequent recurrences when treatment is stopped
Histoplasmosis	Amphotericin B induces rapid response in patients who are severely ill Azoles/triazoles in patients with milder illness
Coccidioidomycosis	Amphotericin B is effective in more than 90% of cases Fluconazole or itraconazole after improvement. Treatment is less effective than in other endemic mycoses

Table 5A: Dosing of Antifungal Agents: Azoles

Fluconazole	
Systemic candidiasis	400 mg po/IV qid; continue for a minimum of 4 weeks and for at least 2 weeks after symptoms resolve
Coccidioidomycosis	400 mg po/IV for 1 day, then 200 to 400 mg po/IVmg; 400 to 800 mg po/IV for patients infected with AIDS
Blastomycosis	400 to 800 mg po/IV
Histoplasmosis	400 to 800 mg po/IV
Itraconazole	
Aspergillosis	200 to 400 mg po for 1 year
Blastomycosis	200 to 400 mg po for 6 months
Coccidioidomycosis	200 mg po bid for 12 to 18 months
Histoplasmosis	Moderate: 200 mg po for 9 months
	Life-threatening: 200 mg po tid for 3 days, then, 200 mg po bid until response
Patients with HIV	400 mg po for 12 weeks (85 to 90% response); then 200 mg po
Paracoccidioidomycosis	200 mg po qd for 6 months
Recommended IV dose	200 mg IV bid for 4 doses, then 200 mg IV for maximum of 14 days (each dose infused over 1 hour)
Voriconazole	
Loading dose	6 mg/kg IV q12 hours infused over 2 hours for 2 doses
Maintenance	4 mg/kg IV q12 hours infused over 2 hours; when able to tolerate po, may switch to 200 mg po q12 hours

Table 5B: Dosing of Antifungal Agents: Amphotericin B

Conventional	0.25 to 1.5 mg/kg per day IV; not to exceed 1.5 mg/kg per day
Test dose	1 mg in 20 mL of D5W infused IV over 20 to 30 min; monitor pulse, respiration rate, temperature and blood pressure q30min for 2 hours
Invasive aspergillosis	0.5 to 0.6 mg/kg per day IV (1 to 1.5 mg/kg per day in patients who are neutropenic for rapidly progressing, potentially fatal infections); cumulative dose of 1.5 to 4 g has been administered over 11 months
Mucormycosis	1 to 1.5 mg/kg per day IV for 2 to 3 months; cumulative dose of 3 to 4 g
Invasive candidiasis	0.4 to 0.6 mg/kg per day IV (1 to 1.5 mg/kg per day for candidemia or rapidly progressing potentially fatal infections); treat for 7 to 14 days in low-risk patients (6 weeks or longer in high-risk patients)
Blastomycosis	0.5 to 1 mg/kg per day IV; cumulative dose of 1.5 g
Coccidioidomycosis	0.5 to 1 mg/kg per day IV (1.5 mg/kg per day in rapidly progressing, potentially fatal infections); treat for 4 to 12 weeks
Histoplasmosis	0.5 to 1 mg/kg per day IV for 7 days; then 0.8 mg/kg IV
Paracoccidioidomycosis	0.4 to 0.5 mg/kg per day IV; total dose of 1.5 to 2.5 g
Cryptococcosis	0.3 to 1 mg/kg per day IV (with or without flucytosine) until response, usually 2 to 4 weeks to several months; then change to fluconazole 400 mg po/IV for 8 to 10 weeks; in patients with HIV infection, follow with indefinite treatment with fluconazole at 200 mg per day
Lipid complex	5 mg/kg per day for aspergillosis at median duration of 25 days; as long as 6 weeks for cryptococcosis in patients with HIV infection; then, 12 week of fluconazole po
Liposomal amphotericin B	3 to 5 mg/kg per day IV for systemic fungal infections (e.g., *Aspergillus*, *Candida*, and *Cryptococcus* species)

Table 5C: Dosing of Antifungal Agents: Echinocandins

Caspofungin	70 mg IV over 1 hour on day 1; 50 mg IV thereafter
Anidulafungin	
Candidemia/candidiasis	200 mg IV on day 1; decrease dose on day 2 and thereafter to 100 mg/d IV; do not exceed infusion rate of 1.1 mg/min
Micafungin	
Candidemia and *Candida* peritonitis/abscesses	100 mg IV once daily
Oesophageal candidiasis	150 mg IV once daily

PROGNOSIS

Disseminated invasive fungal infections of the lungs are associated with a high mortality, often exceeding 80%. The individual prognosis ultimately is linked with the severity and outcome of the underlying disease, and to whether the reversal of factors affecting the patient's immune status is possible.

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23.11 Diffuse Interstitial Lung Disease

SK Jindal

INTRODUCTION

Diffuse interstitial lung disease (ILD) encompasses a group of disorders of diverse aetiologies with common feature of generalised involvement of the lung interstitium. It includes over 200 different diseases which, in spite of their heterogenous nature have several common clinical, radiological and histological manifestations.

AETIOLOGY AND CLASSIFICATION

Interstitial lung disease is broadly grouped as: (1) primary, when the cause is unknown; and (2) secondary, when there is an identifiable disease responsible for the interstitial involvement (**Table 1**).

Table 1: Important Causes of Interstitial Lung Disease

Primary or idiopathic
- Idiopathic pulmonary fibrosis (IPF) or usual interstitial pneumonia (UIP)
- Non-Specific interstitial pneumonia (NSIP)
- Organising pneumonia (OP)
- Respiratory bronchiolitis (RB)
- Diffuse alveolar damage (DAD)
- Desquamative interstitial pneumonia (DIP)
- Lymphocytic interstitial pneumonia (LIP)

Association with diseases of known aetiology
- Infections
  - Tuberculosis
  - Bacterial
  - Fungal
  - Parasitic
  - Viral
- Non-infectious causes
  - Hypersensitivity pneumonitis
  - Pneumoconioses
  - Drug-induced
  - Radiation-induced
  - Malignancies
  - Systemic vasculitides

Association with diseases of unknown aetiology
- Sarcoidosis
- Connective tissue disorders
- Systemic sclerosis
- Rheumatoid arthritis
- Polymyositis-dermatomyositis
- Systemic lupus erythematosus
- Chronic eosinophilic pneumonia

Miscellaneous
- Histiocytosis X
- Eosinophilic granuloma
- Lymphangioleiomyomatosis
- Tuberous sclerosis

Primary Interstitial Lung Disease

Primary ILD is idiopathic in origin. No secondary cause or association is identifiable. It was also known in the past as cryptogenic fibrosing alveolitis or idiopathic pulmonary fibrosis (IPF) or 'lone IPF'. This group of idiopathic interstitial pneumonias (IIPs) based on clinico-radiological and pathological features, is now classified into seven distinct types: (1) usual interstitial pneumonia (UIP), (2) desquamative interstitial pneumonia (DIP), (3) lymphocytic interstitial pneumonia (LIP), (4) non-specific interstitial pneumonia (NSIP), (5) acute interstitial pneumonia (AIP), (6) diffuse alveolar damage (DAD) and (7) cryptogenic organising pneumonia (COP). Some of these IIPs such as the DIP, NSIP and respiratory bronchiolitis associated ILD (RBILD) are characteristically associated with the smoking history.

Secondary Interstitial Lung Diseases

Most forms of secondary ILDs have either a known aetiological cause or an association with another disease of known (or unknown) aetiology. An ILD secondary to another illness factually represents the pulmonary involvement of the primary disease than a separate entity.

The most important association of ILD is seen with different connective tissue disorders (CTDs). Progressive systemic sclerosis (PSS) and rheumatoid arthritis (RA) are frequent causes. Systemic lupus erythematosus (SLE), polymyositis-dermatomyositis syndrome and ankylosing spondylitis are also known to cause pulmonary fibrosis. There is a great degree of overlap between IPF and fibrosis associated with different connective tissue disorders.

Occupational exposure to different inorganic and metal dusts is another important cause. Silica dust causes progressive fibrosis, massive progressive fibrosis can occur in such a short period of few weeks to a few months in case of a heavy exposure. Asbestosis and anthracosis are also associated with pulmonary fibrosis.

Sarcoidosis as a cause of ILD, is now commonly recognised. Interstitial involvement occurs in stage II sarcoidosis along with the presence of hilar and mediastinal lymphadenopathy. It can also occur alone in the absence of lymph node enlargement (stage III sarcoidosis).

Several drugs are known to cause ILDs. The list includes most of the cytotoxic drugs (bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate and BCNU) and several non-cytotoxic drugs (such as nitrofurantoin, non-steroidal anti-inflammatory drugs, opiates, anti-convulsants like carbamazepine and dilantin, anti-arrhythmic drugs, hydralazine, penicillamine and gold salts). Amiodarone lung toxicity is relatively frequent and is considered as a prototype of drug-induced ILD.

Radiation administered for thoracic malignancies, especially when used in a higher dose, is another iatrogenic cause of ILD. Radiation can induce both pulmonary and mediastinal fibrosis. Inhalation of toxic gases and fumes, such as methyl isocyanate and nitrogen dioxide can cause interstitial involvement. In view of a shorter exposure, it is generally self-limiting but chronic

pulmonary involvement from inhalational exposure is also possible.

Hypersensitivity pneumonias (extrinsic allergic alveolitis) of acute, sub-acute or chronic onset which occur on exposure to known environmental or occupational antigens include farmer's lung, byssinosis, air-conditioner's lung, bird-fancier's disease and mushroom picker's disease. They may also occur in individuals working with different chemicals, drugs, pharmaceutical agents and laboratory animals. This is especially so in the industrial workers engaged in the manufacturing/processing of rubber foam, azo-dyes, tetracyclines, ampicillin, antihypertensive drugs and others.

EPIDEMIOLOGY

Interstitial lung disease in India was considered to be rare in the past. An increased awareness, wider availability of high-resolution computed tomography (HRCT) and other diagnostic tests have led to an increased recognition of the problem. ILDs constitute about 10% to 15% of the patients with respiratory diseases, seen at any large hospital in the country. About 50% of the ILDs are idiopathic in origin while others are associated with identifiable diseases, most commonly, a CTD. UIP, also known as IPF is the most common form of IIP.

PATHOLOGY AND PATHOGENESIS

The normal pulmonary interstitium comprises of the anatomical space between the alveolar and the capillary basement membranes. It contains mesenchymal and connective tissue cells, and extra-cellular matrix composed of collagen, elastin and proteoglycans. The interstitial involvement progressively encroaches the alveolar spaces, the terminal bronchioles and also the overlying pleura. It results in a diffuse involvement of the lung parenchyma.

Characteristically, there is cellular infiltration and thickening of pulmonary interstitium and of alveolar walls, as well as the presence of mononuclear cells in the alveolar lumen. The cellular exudate comprises primarily of alveolar macrophages but lymphocytes, neutrophils, eosinophils and plasma cells are also present. Although the total collagen component of lungs remains normal, the ratio of type I to type III collagen is increased. The advanced-stage disease is characterised by extensive fibrosis, obliteration of the lumen of alveoli and formation of multiple cysts, also called as the honeycomb lung.

There is no clear understanding of disease pathogenesis. Chronic inflammation, recurrent epithelial injury and impaired damage repair are some of the possible reasons of pulmonary fibrosis. Several new mechanisms of pulmonary fibrosis have evolved in the last decade. Pulmonary fibrosis is considered to result from an aberrant defence reaction with failure of mechanisms which are normally responsible for repair. It is now recognised that there is persistence and/or repetitive injury responsible for inflammation followed by recruitment of a host of inflammatory cells. The different cytokines and other mediators released by the activated cells, especially macrophages, are able to stimulate fibrosis. Local oxidative lung damage may also result from the reactive oxygen species and proteases released by the inflammatory cells, such as neutrophils and eosinophils. There is increased procoagulant activity, apoptosis, angiogenesis, and fibrogenesis. A genetic predisposition is also likely.

CLINICAL FEATURES

The prototype idiopathic ILD commonly involves the older adults of both sexes in the 6th or 7th decade of life. But ILDs secondary to a connective tissue disorder such as PSS, RA or SLE are more common in the young female patients. Onset is generally sub-acute, although acute forms are also known. In particular, AIP which is frequently fatal, presents with a rapid onset of acute respiratory distress. It rapidly results in diffuse alveolar damage.

Most often, the patients present with progressive breathlessness and dry, unproductive cough which is occasionally accompanied by scanty mucoid expectoration. Constitutional symptoms of malaise, weakness, fatigue, myalgias, fever, arthralgia and weight loss are frequently seen in association with a CTD.

Finger-clubbing is present in about one-third of the patients. Hypertrophic osteoarthropathy is rarely seen. Cyanosis is generally absent at rest but desaturation occurs and cyanosis appears even after mild exercise. Cyanosis may be present even at rest in an advanced state of disease. Physical examination of the chest may reveal tachypnoea, reduced chest expansion and intercostal retractions. Breath sounds are vesicular and quite distinct. Broncho-vesicular or bronchial breathing is heard in the presence of a consolidation, a cavity or an advanced disease. The bibasal dry, end-inspiratory 'velcro' crackles are quite characteristically heard in most patients of IPF. These crackles are attributed to the snap opening up of collapsed alveoli when equalisation of pressure occurs between the alveolar spaces and the proximal bronchiole during inspiration.

Patients with secondary ILDs may also show symptoms and signs of the underlying diseases. Patients with CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia) may present with pulmonary hypertension as a primary manifestation. Pulmonary hypertension and chronic cor pulmonale, chronic congestive failure develop in a long standing disease. Acute exacerbation or an 'accelerated stage' indicates a rapid deterioration without the presence of an identifiable cause.

DIAGNOSIS

Diagnosis of ILD is generally suspected on history and clinical examination. But differential diagnosis from other causes of similar clinical presentation may be needed in some cases. Cardiac failure and pulmonary thromboembolism (PE) are the two important diseases requiring careful exclusion. Cardiac failure is diagnosed on the basis of history, clinical findings, electrocardiogram (ECG), chest radiography and echocardiography. Chronic and silent pulmonary thromboembolism may sometimes pose difficulties when more specific investigations such as the ventilation perfusion scans, contrast enhanced computed tomography and pulmonary angiography are helpful. Algorithm I shows approach to diagnosis (**Figure 1**).

Establishing the Cause of ILD

Following investigations offer a variable help in establishing the cause of ILD.

Chest radiography

The interstitial infiltrates are seen as discrete, linear, nodular or reticulonodular shadows diffusely distributed in both the lungs (**Figure 2**). The individual nodular shadows are usually of less

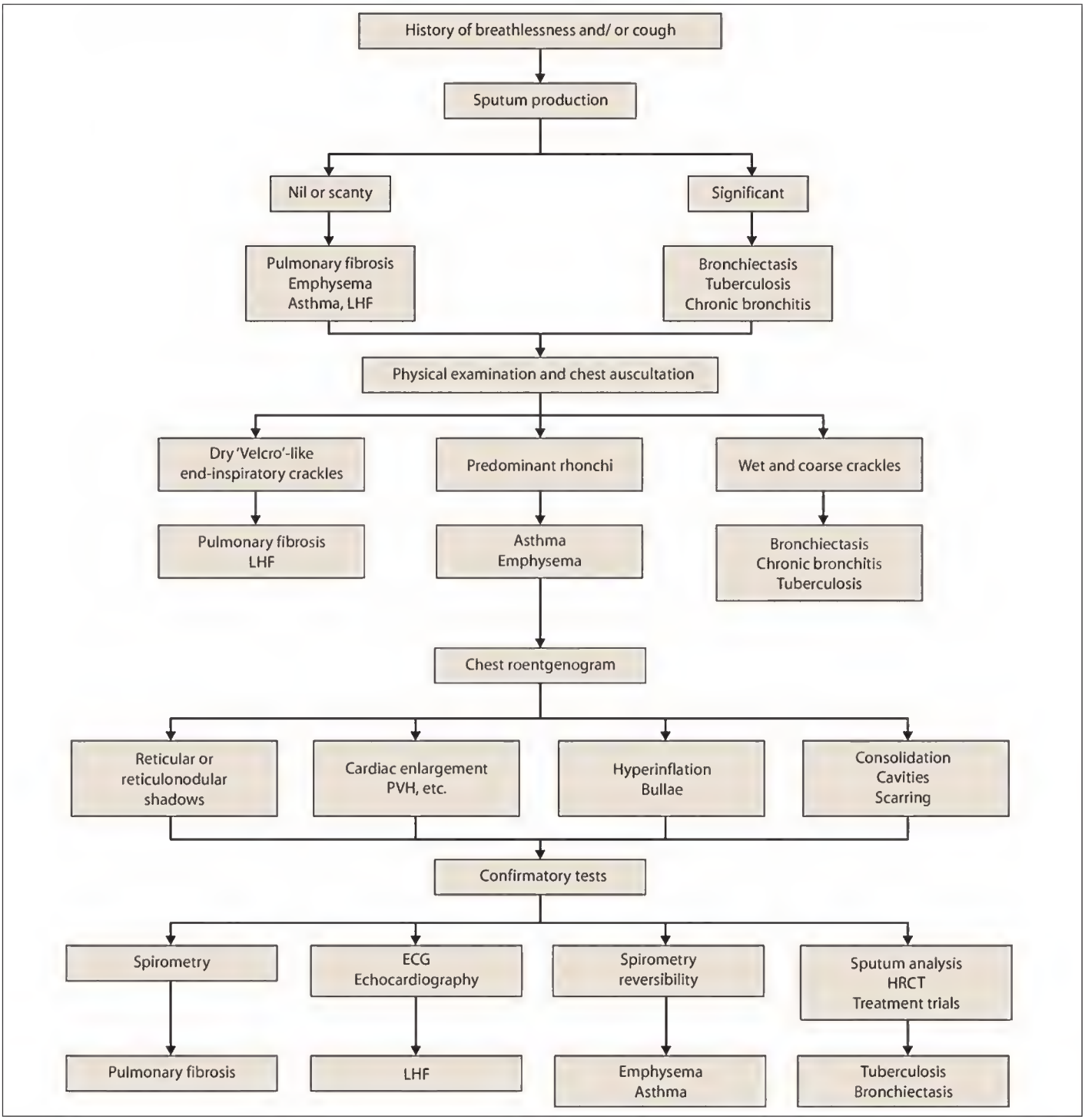


Figure 1: Algorithm for diagnosis of pulmonary fibrosis in a patient with respiratory symptoms.

HRCT = High resolution CT scan; LHF = Left heart failure; PVH = Pulmonary venous hypertension.

than 2 mm in diameter. They may also coalesce and form larger nodules. The shadows are generally bibasilar in distribution in early stages. In later stages, diffuse involvement occurs all over the lungs. Upper lobe involvement suggests diseases, such as pneumoconioses, sarcoidosis and hypersensitivity pneumonias.

Presence of diffuse mottling or ground-glass appearances may suggest an active stage of diffuse alveolitis. Miliary distribution throughout the lung fields is characteristically seen in tuberculosis (TB), pneumoconiosis, and sometimes in sarcoidosis. Occasionally, fluffy alveolar shadows may be present due to the coalescence of interstitial shadows or a complicating infection. A normal chest radiograph does not exclude ILD. In advanced disease, when fibrosis is extensive, the lungs get shrunken and reduced in volume. Small, uniform-sized, quadrangular cystic spaces, representing patent bronchioles, give the typical appearances of a honeycomb lung.

The HRCT offers a much better view of lung parenchymal involvement. The classical picture of bibasilar reticular and/or nodular infiltrates, honeycombing and absence of lymphadenopathy support the diagnosis of IPF (**Figures 3A to C**). Pathology is considered uncertain if radiographic findings are atypical, lung involvement is mild or patchy and/or there is presence of hilar/mediastinal lymphadenopathy. The HRCT is of great use in classifying IPF. The HRCT features of subpleural septal



Figure 2: Chest radiograph showing diffusely distributed infiltrate.

thickening, traction bronchiectasis, and ground-glass attenuation can be considered as definite UIP and lung biopsy can be avoided (**Figures 3A to C**). Diseases, such as sarcoidosis, histiocytosis and lymphangitis have more characteristic patterns. The HRCT is also of some help in making a quantitative assessment of pulmonary fibrosis. Spiral CT gives even a better resolution, especially in a patient with tachypnoea who cannot hold his breath.

Pulmonary function tests

Most ILD demonstrate a restrictive defect on spirometry. Tidal volumes are generally small and both the vital capacity and the total lung capacity are reduced. Expiratory flows are normal or even 'supranormal'. Airway obstruction, characterised by reduced forced vital capacity (FVC) and forced expiratory flows, can occur in patients with hypersensitivity pneumonias, and in smokers. Reduced diffusing capacity (DLCO) and arterial hypoxaemia (reduced PaO_2) may not be present in the early stages. Some degree of arterial hypoxaemia on exercise is almost always demonstrable (all these are given in a algorithm).

Bronchoalveolar lavage (BAL)

Assessment of cellular response in the BAL fluid, although is not conclusive, may help in the differential diagnosis. There is lymphocytic predominance in sarcoidosis and TB, neutrophilic in pulmonary fibrosis. Presence of eosinophils may suggest hypersensitivity reactions or pulmonary eosinophilia. Infective micro-organisms such as the mycobacteria, fungi, or *Pneumocystis jirovecii* can be isolated from BAL fluid. Presence of lymphocytosis in the BAL fluid is shown to predict a better response to corticosteroid therapy. An increase in the alkaline phosphatase/albumin ratio in BAL fluid on a repeated study reflects progression of fibrosis.

Other investigations

Although non-specific, haematological investigations provide useful information. A high erythrocyte sedimentation rate (ESR) of more than 50 mm in first hour occurs in CTD, malignancies, infections, and systemic vasculitides. Unexplained anaemia is seen in diffuse alveolar haemorrhage and CTD. Mild to moderate leukocytosis is common in both primary and secondary ILD.

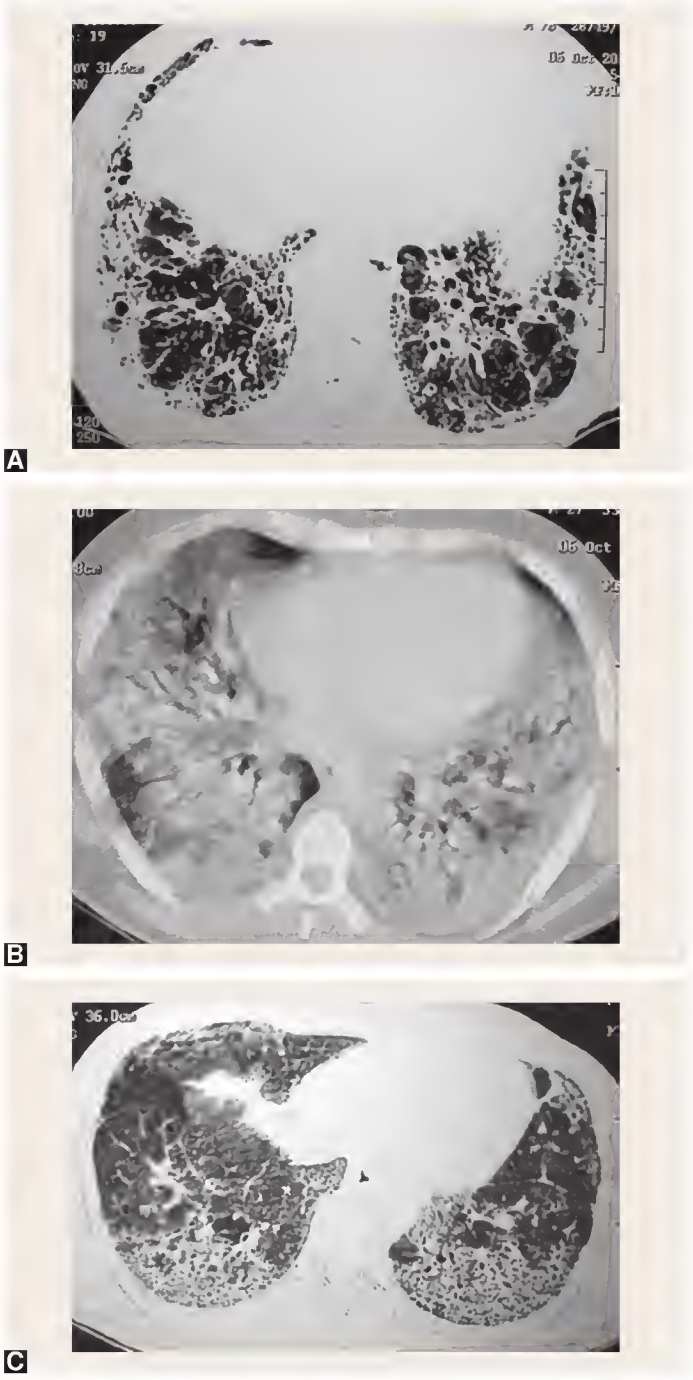


Figure 3A to C: (A) HRCT chest-showing IPF, (B) UIP, (C) and bronchiectasis, suggestive of ILD.

Eosinophilia is more characteristically seen in eosinophilic and hypersensitivity pneumonias, vasculitides, sarcoidosis, and drug-induced lung diseases. Occasionally, there is leucopenia and/or thrombocytopaenia.

Abnormal liver or renal function tests suggest the involvement of these organs. Elevated calcium may be seen in sarcoidosis and malignancies. Increased enzymes, such as creatinine phosphokinase and aldolase, are present in polymyositis and dermatomyositis. Increased serum angiotensin converting enzyme (SACE) in sarcoidosis is quite characteristic but may be seen in silicosis, hypersensitivity pneumonias, and other diseases.

A number of immunological parameters are described in CTDs and other ILDs. Hypergammaglobulinaemia, positive serum

auto antibodies (e.g. the anti-nuclear factor) and circulating immune complexes may be seen. Anti-basement membrane antibodies in Goodpasture's syndrome, anti-neutrophil cytoplasmic antibody (C-ANCA) in Wegener's granulomatosis, Churg-Strauss syndrome and Systemic necrotising vasculitis, and anti-Jo_1 antibody in polymyositis-dermatomyositis are generally considered characteristic.

Radionuclide scanning using Gallium–67, and positron emission tomography (PET) with glucose FDG isotope have a place to identify disease-activity and to predict response to therapy. Similarly, the clearance of aerosolised technetium-99m diethylenetriaminepenta-acetic acid (DTPA) is markedly increased in patients with inflammatory lung diseases including sarcoidosis.

Lung biopsy

Diagnosis of IIPs is fairly specific on clinical features and radiographic characteristics seen on HRCT. Lung biopsy is required only when the findings are atypical, to exclude an infective vasculitides or some other undiagnosed cause of ILD is suspected. It may also help to predict the response to treatment and prognosis of a patient. Patients with usual interstitial pneumonia do worse than those with other histological subsets of IIPs. Transbronchial lung biopsy (TBLB) with the help of fiber-optic bronchoscopy (FOB) is less rewarding, especially in patients with IPF. In sarcoidosis, the positivity rates of TBLB may be as high as 70% to 80%. Many patients of IPF cannot be subjected to TBLB in view of an inadequate biopsy size and risks involved with FOB. Transthoracic or open surgical approach provides a better option to obtain lung tissue. These are summarised in algorithm.

MANAGEMENT

The management of ILD should follow an algorithmic approach (**Figure 4**). In the absence of a satisfactory, definitive treatment of IPF, most objectives (**Table 2**) are achieved with supportive and symptomatic therapy. Several different groups of drugs are employed in its treatment (**Table 3**). Supportive treatment is provided for respiratory failure, pulmonary hypertension, cor pulmonale and congestive cardiac failure, wherever indicated. Long-term pulmonary vasodilators are not shown to prevent the development of pulmonary hypertension. An acute increase in symptoms and presence of fever with or without mucopurulent expectoration raises the suspicion of a respiratory infection necessitating treatment with antibiotics. To assess the response to therapy and to monitor its progress, a clinical, radiological and physiological (CRP) score has been used in the past. It is difficult to frequently repeat invasive investigations, such as the BAL or lung biopsy. It is generally adequate to rely on clinical picture, simple spirometry, and a plain chest radiograph.

Table 2: Objectives of Treatment of ILD

Provide symptom relief
Slow down disease progression
Prevent complications
Improve quality of life
Prolong survival
Prevent treatment complications
End-of-life care – Palliation treatment

Anti-Inflammatory Therapy

Anti-inflammatory therapy has remained the mainstay of treatment. Minimal to significant improvement is reported with the use of anti-inflammatory agents. But their efficacy remains unproven and the toxicities are substantial. The commonly used criteria to start anti-inflammatory therapy include the presence of severe or worsening clinical symptoms, younger age of the patient and shorter duration of illness.

Table 3: Drugs Employed for the Treatment of ILD

Treatment of Primary Disease responsible for a secondary ILD
Treatment of primary ILD
Anti-inflammatory drugs
Corticosteroids*
Azathioprine*
Cyclophosphamide
Anti-fibrotic agents
Colchicine
Pirfenidone*
Pentoxyphylline
D-Penicillamine
TGF-beta antagonist
Interferon-gamma
Anti-oxidant agents
N-acetylcysteine*
Nitric oxide synthase inhibition
Supportive and symptomatic treatments*
Oxygen
Pulmonary vasodilators
Diuretics
Antibiotics (if infection)

*Note: (i) Drugs marked * are generally used in clinical practice; (ii) Trial treatment is given for 3 to 6 months. Taper treatment in case of nil response; (iii) Avoid corticosteroids in the presence of complicating co-morbidities.*

Corticosteroids are the most frequently used anti-inflammatory agents. Their role to provide long-term relief and to prolong survival is doubtful. Prednisolone is administered in a dose of 1 to 1.5 mg/kg for a period of about 6 to 12 weeks. Maintenance daily dose of about 15 to 20 mg is continued for 1 to 2 years or more.

Other immunosuppressive agents, such as azathioprine or cyclophosphamide, administered along with prednisolone are shown to do better. Intravenous cyclophosphamide used as intermittent pulse therapy (1 gm to 1.3 gm per month) is shown to provide some relief. A combination of low-dose corticosteroids and azathioprine is frequently employed for maintenance treatment continued for 2 to 3 years after the disease onset. The role of anti-inflammatory therapy is limited to patients with predominant inflammation. The risks, especially the use of prolonged corticosteroids and other immunosuppressants, often outweigh the benefits of therapy.

Anti-Fibrotic Agents

There is a greater trend to rely on anti-fibrotic drugs for the treatment of ILDs. Of the several anti-fibrotic agents which had been tried, colchicine was considered the safest alternative. It was recommended in a dose of 0.6 to 1.2 mg per day for a period of at least 6 to 12 months. D-penicillamine and pirfenidone are other drugs which have been tried with variable results. Interferon gamma B, TGF-beta and several other agents, initially shown to have promising results, are also equally ineffective in their clinical use.

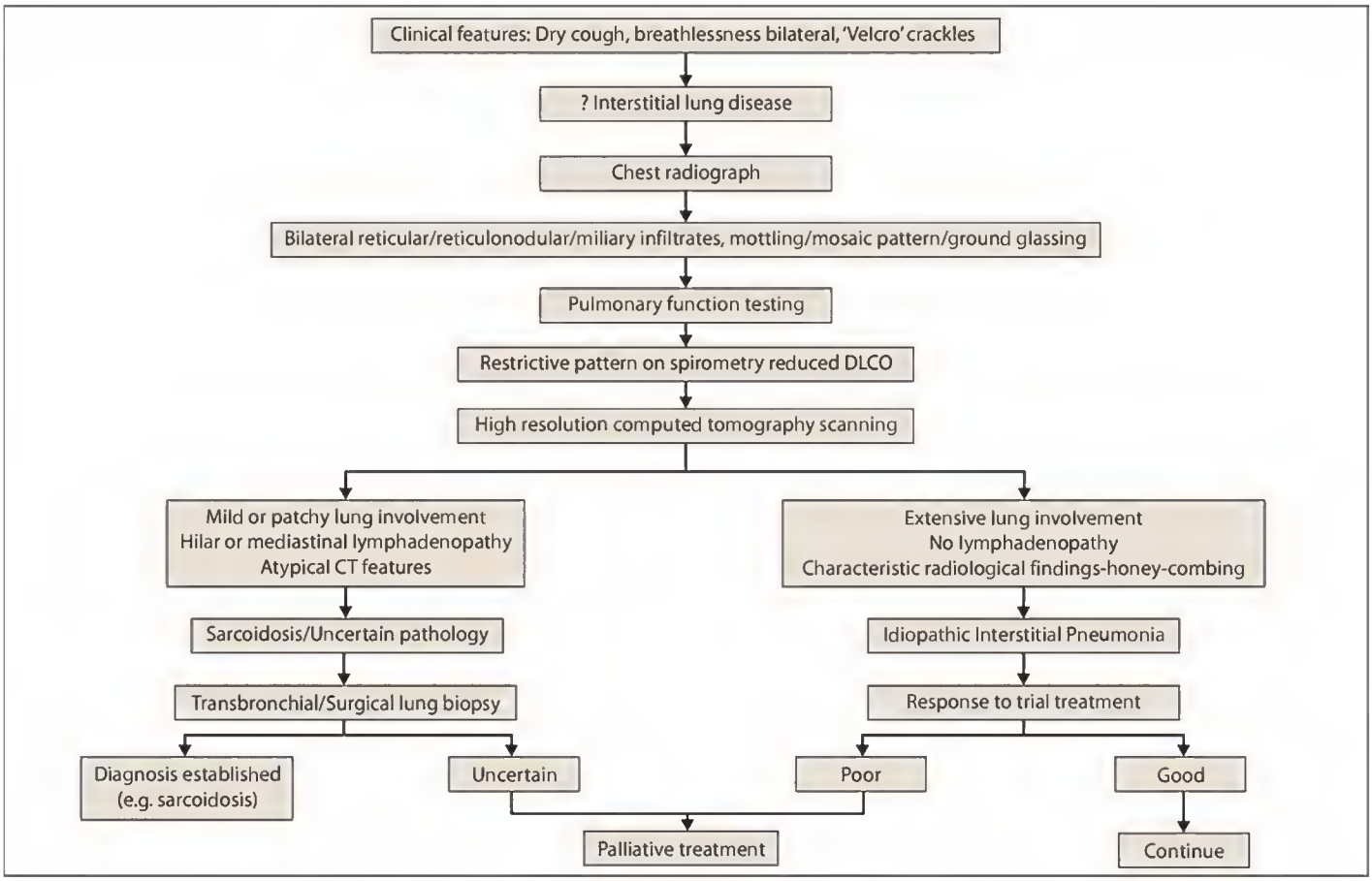


Figure 4: Management algorithm for ILD.

Other Treatments

Anti-oxidants, such as N-acetylcysteine to reduce oxidative stress, are shown to offer some clinical advantage when used along with anti-fibrotic agents. Drugs targeted to prevent or reduce apoptosis, angiogenesis and coagulant activity may find some use in the future. Presently, no drug from these groups is available for clinical use.

It is a better option to resort to symptomatic palliative therapy and withdraw immunosuppressive drugs in case there is no response in the initial 3 to 6 months of use and for end-stage disease.

Lung transplantation is the only hope for the advanced, end-stage disease. Single lung transplantation is recommended in most patients. Five years survival is reported in up to 40% to 60% of the patients. The common post-transplant complications includes the risk of rejection, multiple opportunistic infections in an immunosuppressed host, and organising pneumonias. The lack of availability of organ for transplantation and very high cost involved in the procedure are the limiting factors.

PROGNOSIS

Prognosis of ILDs, secondary to systemic diseases or other causes is determined by the natural course of the underlying disease. Prognosis of primary IIPs is variable. While NSIP, DIP and RBILD respond better, the IPF is progressive and fatal. The survival has not significantly improved in the last 50 years or so from that reported in the 1960s. The median survival of IPF is about 4 years. Acute interstitial pneumonia and acute exacerbation of IPF are rapidly fatal, sometimes in a course of a few weeks or months.

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23.12 Eosinophilic Lung Disease and Tropical Pulmonary Eosinophilia

Farokh E Udwadia

INTRODUCTION

Pulmonary eosinophilia is characterised by pulmonary infiltration with a predominant eosinophilic exudate, almost always accompanied by a significant rise in the peripheral eosinophilic count. In clinical practice, the term pulmonary eosinophilia is often used to denote peripheral eosinophilia with pulmonary shadowing on the chest radiograph without an exact tissue diagnosis always being made. This may be incorrect, as peripheral eosinophilia and the pulmonary infiltrate (which may be non-eosinophilic) in a given patient may have separate aetiological causes. The association of pulmonary shadowing with peripheral eosinophilia has been described by the use of various semantic terms such as Loeffler's syndrome (transient pulmonary infiltrates, lasting for <3 weeks with peripheral eosinophilia), the pulmonary infiltration with eosinophilia (PIE) syndrome, eosinophilic pneumonia and eosinophilia among others. Pulmonary eosinophilia as observed in the tropics is best classified as follows (**Table 1**).

Table 1: Causes of Pulmonary Eosinophilia

Pulmonary eosinophilia due to human filarial infections
Pulmonary eosinophilia due to other parasitic infections
Allergic bronchopulmonary aspergillosis
Hypersensitivity response
Drugs
Pollen
Other fungi
Other antigens
Asthmatic pulmonary eosinophilia
Churg-Strauss syndrome
Cryptogenic eosinophilic pneumonia
Hypereosinophilic syndrome

PULMONARY EOSINOPHILIA DUE TO PARASITIC CAUSES

Filarial Infection

Human filarial infection generally results in endemic filariasis. However, an unusual clinical variant of filarial infection is the most common cause of pulmonary eosinophilia in the tropics. This variant results from a hypersensitivity response, chiefly within the lungs to human microfilariae and is termed tropical eosinophilia.

Other Parasitic Infections

Other parasitic infections that can give rise to pulmonary eosinophilia include infections caused by Ascaris and other nematodes, *Toxocara canis*, *Toxocara cati*, ankylostoma and strongyloidiasis.

PULMONARY EOSINOPHILIA DUE TO NON-PARASITIC CAUSES

Allergic bronchopulmonary aspergillosis (ABPA) is the most frequent and important among the non-parasitic causes. Other causes include hypersensitivity response to drugs, other fungi, pollen and a host of other antigens; asthmatic pulmonary eosinophilia, when not due to ABPA, the Churg-Strauss syndrome, cryptogenic eosinophilic pneumonia, which is usually chronic and occasionally acute (may not always be accompanied by peripheral eosinophilia); and the hypereosinophilic syndrome.

TROPICAL EOSINOPHILIA

Historical Background

In 1943, Weingarten used the term tropical eosinophilia (TE) when describing a syndrome characterised by severe spasmodic bronchitis, eosinophilic leucocytosis, and disseminated mottling of both lungs. He also described the successful treatment of tropical eosinophilia following the use of neoarsphenamine (an arsenical preparation). Further work over many subsequent years has now elucidated the histopathology, the natural history, immunology, and aetiology of this exotic syndrome.

Epidemiology

The syndrome is particularly endemic in India, Sri Lanka, South-East Asia and Africa, and has been reported from filarial epidemic areas worldwide. In India, its endemicity is mostly marked along the Western Coastal Strip around Bombay, Goa, Kerala, the Eastern Coast and in Bengal, Bihar, and Orissa which are also endemic to filarial infection.

Aetiology

Presently, TE is considered to be a variant of human filarial infection resulting from hypersensitivity to microfilariae liberated by *Wuchereria bancrofti and Brugia malayi*. This concept is based on serological, histopathological, therapeutic, and immunological evidence.

Clinical Features

Tropical eosinophilia can involve many organ systems e.g. liver, spleen, lymph glands but chiefly involves the lungs. The pulmonary manifestations include paroxysmal cough, breathlessness, wheeze, scattered auscultatory crackles, pulmonary infiltrates, and an absolute eosinophilic count greater than 3000 to 3500/mm^3. These symptoms are most marked in the night but are often also present in the day. Non-specific systemic features include fever, malaise, and weight loss. The absolute eosinophil count in hyperacute cases can be as high as 50,000/mm^3. The non-pulmonary manifestations of TE include hepatosplenomegaly, lymphadenopathy, muscle pains and muscle weakness, and occasionally, diarrhoea with weight loss.

Radiology

The radiological features vary. Prominent hila with heavy vascular marking at the bases are often observed. Fluffy reticulonodular shadows over the mid zones and bases of the lungs may also be seen. At times, the picture is of miliary mottling indistinguishable from miliary tuberculosis. In 20% of the patients, the chest

radiograph is normal even though the lung histopathology is typical of TE. In the early part of its natural history, TE invariably responds to diethylcarbamazine. Patients who remain untreated, who have a long history or who respond inadequately to diethylcarbamazine, may progress to chronic increasing respiratory disability due to moderately severe pulmonary fibrosis.

Lung Function

Two patterns are observed. A predominant restrictive pattern with low forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV) and a lowered diffusion capacity due to reduced area of membrane available for diffusion. A combination of airways obstruction and restriction where the forced expiratory volume in the first second (FEV1) to FVC ratio being reduced in addition to the restrictive pattern described above.

These findings improve and return to normal after three to four months in patients who respond well to diethylcarbamazine. In patients who frequently relapse and in patients with a long standing history, there is a progressive increase in the restrictive pattern due to moderate pulmonary fibrosis. The degree of pulmonary function impairment in these patients is, however, never as marked as in severe cryptogenic fibrosing alveolitis. Pulmonary hypertension and cor pulmonale in uncomplicated TE do not generally occur.

Histopathology and Natural History

In the early part of its natural history, TE is histopathologically characterised by a dense eosinophilic pneumonia and bronchopneumonia; later (6 months to 2 years after the onset of symptoms), a mixed cell exudate of eosinophils, lymphocytes and mononuclear cells is observed, together with some degree of fibrosis. Breathlessness on exertion is now the predominant symptom. Even later (symptoms >2 years), the eosinophils in the lungs are scanty; the exudate is lymphocytic with mononuclear cells and there may be well marked fibrosis. Increasing respiratory disability is observed in chronic cases. In some long standing cases, the peripheral eosinophilia wanes and the presenting feature is increasing breathlessness on exertion with respiratory disability. If observed for the first time at this late stage, the relation of the clinical feature to TE may not be recognised. Such a patient may then be dubbed as bronchitic or as suffering from idiopathic pulmonary fibrosis. It is noteworthy that histopathological studies have demonstrated the presence of disintegrating fragments of microfilariae in the lung, as also in the liver and lymph nodes when these are involved.

Immunology

In TE, microfilariae from a mature gravid human filarial parasite are periodically released but are promptly trapped within the lungs and thus removed from the circulation. Microfilaraemia in the blood is thus very rarely observed. Within the lungs, microfilariae elicit a strong type I, type III, type IV immunological response. High levels of filarial specific immunoglobulin (Ig)E, IgG, and IgM are found in the lower respiratory epithelial lung fluid. The role of the eosinophil is crucial in this response. The eosinophil serves a dual purpose. It helps to destroy the microfilarial parasite and yet also has a destructive effect on lung tissue due to the release of eosinophil granule components. The latter includes eosinophilic major protein, peroxidases and collagenases, all known to injure lung parenchymal cells.

If microfilariae succeed in running the gauntlet of the pulmonary circulation, they reach the systemic circulation and cause an eosinophilic reaction in the reticuloendothelial system (liver, spleen, lymph glands and rarely, the muscles and the gastrointestinal tract). Thus, though TE chiefly involves the lung, other systems may be involved. The reason for the difference in the immunological response to the same filarial parasite in patients with endemic filariasis and in those with TE remains unknown. Racial and genetic factors are important. Age at which infection occurs and the frequency of exposure may also determine difference in immunological response.

Treatment

Diethylcarbamazine is specific for treatment in a dosage of 5 mg/kg/day administrated preferably for a period of three weeks. About 4% to 5% of the patients even in the earlier part of their natural history respond inadequately and 20% to 40% of patients with a longer duration of symptoms (2 to 5 years) fail to respond. The lack of response to patients with a long standing history is explicable because the drug cannot be expected to act on increasing fibrosis within the lung. It has been suggested that repeated monthly courses of diethylcarbamazine at 2 to 3 monthly intervals for a period of 1 to 2 years may reduce the morbidity of patients with TE who live in endemic zones and who are subject to relapses and repeated infections. The role of corticosteroids in patients with increasing fibrosis is underdetermined but may well merit a try.

PULMONARY EOSINOPHILIA AND OTHER PARASITIC INFECTIONS

Other nematodes (notably ascarial infection), which at some stage in their life cycle go through the lungs can excite an immunological response with clinical features indistinguishable from tropical eosinophilia. In addition, ascarial infection would also respond to diethylcarbamazine. There are a number of physicians who, therefore, consider tropical eosinophilia to be a syndrome having many aetiologies. However to prevent the term TE from becoming a 'catch all' waste paper basket for all patients in the tropics with cough, breathlessness and peripheral eosinophilia, it would be best to define the above symptom complex in relation to aetiology. This can only be possible if cheap easily available tests for human parasitic infections are locally available. Till then, to avoid semantic confusion, it is suggested that the use of the term TE should be confined to a symptom complex which is caused by an unusual hypersensitivity response to the human filarial parasite, responding at least in the early part of its natural history to diethylcarbamazine.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis generally, though not always, occurs against the background of asthma and is due to a hypersensitivity response to inhaled spores of *Aspergillus fumigatus*. These spores thrive within bronchial secretions, from hyphae, liberate antigen thereby exciting an immune response leading to an eosinophilic exudate within bronchial walls and adjacent alveoli. Type I, III and IV reactions are involved and there is an accumulation of antigen- specific antibodies, IgE, IgG, and IgA within the involved lung tissue.

Clinical Features

Clinical features include fever, an exacerbation of asthmatic symptoms, and peripheral eosinophilia (>5x10^9/L). The chest radiograph shows presence of 'shadows' (often migratory) chiefly involving the upper lobes of one or both lungs. Coughing

is often associated with expectoration of viscid brownish pellets of mucus containing the fungus. Bronchial casts may occasionally be coughed up.

Investigations

Sputum or bronchoalveolar lavage (BAL) fluid examination reveals hyphae of *Aspergillus fumigatus* on staining and culture. The chest radiograph shows fleeting pulmonary shadows. Segmental or lobar atelectasis may occur. The skin patch test to *Aspergillus fumigatus* antigen is positive. Serum precipitins (IgG) against *Aspergillus fumigatus* are positive. The total IgE and antigen-specific IgG are raised in the serum.

Repeated episodes of bronchopulmonary aspergillosis lead to destruction of bronchial walls and surrounding alveoli resulting in proximal bronchiectasis and bilateral upper lobe fibrosis. Permanent radiologic abnormalities may include ring shadows due to dilated bronchi, 'gloved-finger' shadows due to secretions in dilated bronchi, 'tram line' shadows due to thickened bronchial walls extending outwards from the hilum. Pulmonary shadows due to ABPA in asthmatic patients are often wrongly diagnosed and treated as tuberculosis.

Treatment

Prednisolone in a dosage of 30 mg/day for five days and then tapered off within 15 days resolves the shadows and relieves symptoms. Attacks may recur necessitating frequent courses of corticosteroids. A small maintenance dose of 5 to 10 mg/day may give better control of asthma and prevent frequent episodes of ABPA. Overall, good control of asthma by conventional therapy is important.

PULMONARY EOSINOPHILIA DUE TO DRUGS, POLLEN AND OTHER ANTIGENS

Pulmonary eosinophilia due to drugs, pollen and other antigens may take the form of peripheral eosinophilia with transient pulmonary shadows and infiltrates (Loeffler's syndrome) or as with hypersensitivity to drugs may lead to fairly extensive eosinophilic infiltrates, with pulmonary shadows that are either diffuse or distributed peripherally. The clinical picture is that of fever, cough and breathlessness coupled with pulmonary shadows. These resolve within weeks of stopping the offending drug. Common drugs causing pulmonary eosinophilia are listed in **Table 2**.

Table 2: Common Drugs Causing Pulmonary Eosinophilia

Antibiotics (e.g. penicillin, minocycline)
Sulpha drugs
Trimethoprim-sulphamethoxazole
Nonsteroidal anti-inflammatory agents
Carbamazepine
Tricyclic antidepressants
Nitrofurantoin
Penicillamine

ASTHMATIC PULMONARY EOSINOPHILIA

Pulmonary eosinophilia may rarely occur in patients with bronchial asthma in whom all tests for ABPA are negative. In patients with intrinsic asthma, this rare form of pulmonary eosinophilia may well be the prevasculitic form of Churg-Strauss syndrome. In atopic patients with extrinsic asthma, eosinophilic pulmonary infiltrates may be due to a reaction to an unidentified allergen. Asthmatic pulmonary eosinophilia responds well to corticosteroids.

Churg-Strauss Syndrome

In Churg-Strauss syndrome a pulmonary vasculitis is associated with pulmonary eosinophilia. The syndrome evolves in three phases. An initial phase of asthma is often present for many years. The second phase is characterised by tissue and peripheral eosinophilia. The lungs are most commonly involved in this phase. The chest radiograph at this stage shows one or more 'shadows' in one or both lungs. These shadows may be flitting in character and when present against the background of long standing bronchial asthma with peripheral eosinophilia suggest the correct diagnosis. The final is the life threatening stage of systemic vasculitis; the lungs, gastrointestinal tract, peripheral nerves and skin being most frequently involved. Mononeuritis multiplex is a frequent presentation. Skin lesions take the form of purpuric lesions, nodules or vasculitic ulcers. Cardiac involvement causes abdominal pain, haematemesis or melana. A chest radiograph in the third phase of the disease most often shows non-cavitating bilateral nodular or confluent shadows. Pleural effusions may be occasionally seen.

The perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) test is often positive. A lung biopsy may be necessary to distinguish the Churg-Strauss syndrome from other forms of pulmonary eosinophilia. Prednisolone in a dose of 1 mg/kg controls the disease. A maintenance dose may be necessary for an indefinite period of time.

CRYPTOGENIC EOSINOPHILIC PNEUMONIA

Cryptogenic eosinophilic pneumonia is characterised by dense pulmonary infiltrates and peripheral eosinophilia with or without a background of asthma. Occasionally, peripheral eosinophilia is absent. The disease is common in females above 35 years of age. The clinical features of breathlessness, cough, fever are associated with pulmonary shadows which are more peripherally distributed (exactly the opposite of the bilateral centrally placed shadows observed in pulmonary oedema). The disease is generally chronic but may rarely be acute in onset. It responds well to corticosteroid therapy (prednisolone in a dose of 1 mg/kg). Recurrence is not uncommon after stoppage of steroid therapy.

HYPEREOSINOPHILIC SYNDROME

Hypereosinophilic syndrome is a systemic disorder of unknown aetiology which generally occurs in males and is characterised by a very high peripheral eosinophilia (>20x10^9/L), fever, weight loss with dense eosinophilic infiltration of the heart, lung, skin, central nervous system, liver, spleen, and other organs. Treatment with oral prednisolone is often effective. The use of vincristine and hydroxyurea may improve prognosis.

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23.13 Occupational and Environmental Lung Diseases

Ashutosh Nath Aggarwal

DEFINITION AND PATHOGENESIS

Pneumoconiosis is a generic term for the lodgement, and subsequent non-specific pulmonary reaction, of any inhaled mineral or organic dust in the lungs irrespective of the effects (excluding malignancy and asthma). These respiratory disorders are a heterogeneous group. They are commonly categorised based on the time of the development of obvious disease (acute or chronic/prolonged exposure) and on the specific agent responsible for the disease. Three broad factors: (a) intensity and duration of exposure; (b) individual susceptibility; and (c) the nature, chemistry and geometric, aerodynamic and surface properties of each specific agent – influence the character and severity of pulmonary reaction to mineral dusts. The particles leading to pneumoconiosis need to be small enough (generally 0.5 to 5 μm) to reach the respiratory bronchioles and get deposited there.

MAGNITUDE OF THE PROBLEM

Over the last few decades, the occurrence and severity of the usual occupational lung disorders have progressively decreased in industrially developed countries. This has largely been brought about by: (a) improvements in work environment; and (b) enforcement of work-related safety legislation. However, working conditions remain far from satisfactory, let alone healthy, in less developed nations, including India. The problem in India is further compounded by: (a) the lack of availability of exact figures relating to prevalence and incidence of occupation-related diseases; (b) inadequate facilities for screening, diagnosis and management of these disorders; and (c) absence of proper mechanisms for notification and worker compensation.

RECOGNITION AND PATIENT EVALUATION

Four important criteria are useful to guide the diagnosis of an occupational lung disease. First, the patient should have been exposed to a known hazardous agent at workplace. Second, the latency between exposure, and onset of clinical manifestations, should be appropriate for the agent suspected to result in lung disease. This duration is highly variable for each offending agent. Third, the worker's clinical features should be consistent with the syndrome related to this exposure. Fourth and final, there should be no other more likely explanation for the clinical manifestations. The last criterion is important because tobacco smoking and other cardio-respiratory illnesses may be equally prevalent in these persons. Other more specific criteria have also been proposed for disorders, such as asbestosis and beryllium lung disease.

Patient evaluation generally begins with a review of type and frequency of the respiratory symptoms. The timing or periodicity of symptoms in relation to occupational exposure is important. All jobs of the patient, from the first to the current, should be looked into, especially for diseases related to chronic exposures. If any significant occupational exposure is found, one should determine (a) the type, amount and duration of exposure, (b) whether there is any time relationship to work or exposure and (c) if the exposure still continues. In addition, the patient should be asked whether ventilation at workplace was adequate and whether any personal protective gear (such as mask) was provided. It is also important to ask if other co-workers have been similarly affected. A complete physical examination should be conducted to detect manifestations of disease and also to identify any complications related to chronic lung disease (such as cor pulmonale).

The usual first investigation is chest radiograph. If available, the chest radiographs should be compared to the previous films. Hyperinflation and other findings consistent with airflow disorders should be noted. If radiographic abnormalities are rather diffuse, then the type and location of these opacities should be described. The radiological severity can be graded from mild to severe, as suggested by the International Labour Organization guidelines (**Table 1**). Computed tomography of chest may also be appropriate for a more detailed evaluation of pleural abnormalities, intrathoracic lymphadenopathy, lung nodules and interstitial disorders. Lung function studies should be performed on all patients, as they provide useful information on the functional status. Single breath diffusing capacity can be estimated for patients with exposure to fibrogenic dusts or exposure resulting in a diffuse infiltrative process and in patients with breathlessness out of proportion to radiologic manifestations.

ACUTE INHALATION INJURY

Although most occupational lung disorders result from prolonged exposures, it is important to recognise that short-term exposures can also be associated with pulmonary manifestations. Inhalation fever and acute toxic injury are the two prototypes of such disorders.

Inhalation Fever

Inhalation fever refers to an acute, self-limiting flu-like syndrome occurring after a single massive exposure to the offending agent. The illness resembles a viral flu and is marked by fever, chills, myalgia and malaise. Symptom onset is rather acute, typically 4 to 8 hours after initial exposure. Common precipitants include: (a) metal fumes (causing metal fume fever); (b) organic dusts and other bioaerosols contaminated with micro-organisms and endotoxins and/or mycotoxins, (causing the organic dust toxic syndrome); and (c) fumes produced by heating plastics (causing polymer fume fever).

Table 1: International Labour Organization Radiographic Classification of Pneumoconiosis

Small opacities (<10 mm in diameter) are defined by their average shape, size and profusion as recorded from standard chest radiographs.

Shape and Size	
Rounded (nodular)	*p* for diameters up to 1.5 mm *q* for diameters >1.5 mm but <3 mm *r* for diameters >3 mm but <10 mm
Irregular (reticular)	*s* if fine *t* if medium *u* if coarse
Profusion	
Category 0	small opacities are absent or less profuse than in category 1
Category 1	small opacities are present but few in number
Category 2	small opacities are numerous
Category 3	small opacities are more numerous with obscure normal radiographic markings

Conglomeration or coalescence of these opacities to produce one or more opacities with diameters greater than 10 mm defines 'complicated' pneumoconiosis or progressive massive fibrosis (PMF). This is categorised based on the size of large opacities (>10 mm in diameter):

Category A	sum of diameters of lesions is not more than 50 mm
Category B	total area occupied by lesions is not greater than the area of the right upper lobe (RUL)
Category C	total area occupied by lesions is greater than the area of the RUL

The intensity of these reactions may be dose-dependant. Pathologically, there is an intense non-allergic neutrophilic pulmonary inflammation. Overall, there is no significant structural damage to the respiratory tract. Peripheral leucocytosis is common. However, chest radiographs and pulmonary function tests typically remain normal. Treatment is largely supportive.

Acute Toxic Injury

Inhalation of irritant or toxic gases, vapours, particulates or aerosols may sometimes cause more severe injury to the respiratory tract. Such exposure can occur in almost any occupation. For instance, various respiratory irritants and asphyxiants can be encountered in mining environments. These include carbon dioxide, carbon monoxide, hydrogen sulphide, methane, nitrogen oxides, and sulphur dioxide. Pulmonary responses to these exposures are variable, and depend upon several factors that include: (a) solubility of substance; (b) particle size; (c) concentration; (d) duration of exposure; (e) chemical properties; and (f) host factors, such as minute ventilation of the exposed individual. Depending on the nature of the offending chemical and the intensity of the exposure, affected persons may develop rhinitis, pharyngitis, laryngitis, tracheobronchitis, bronchiolitis and/or pneumonitis. Compounds that are more water-soluble dissolve easily in the aqueous phase of mucous of the upper respiratory tract and airways, and cause maximal injury in these regions. This results in oedema and ulceration of the nasal passage, posterior oropharynx and larynx. The less water-soluble agents tend to bypass the upper airways and predominantly injure smaller airways and/or the lung parenchyma. With more severe injury, acute respiratory distress syndrome (ARDS) or organising pneumonia with obliterating bronchitis may occur.

Treatment is largely supportive. All victims should be removed from the site of exposure as early as possible. Supplemental oxygen, systemic corticosteroids and bronchodilators are usually prescribed. Patients need to be observed closely for any need for airway protection. If required, early airway intubation may be necessary to prevent the airway from acute laryngeal obstruction. Patients progressing to ARDS will require assisted ventilatory support. Following recovery from the respiratory injury, some patients may have persistent bronchial hyperreactivity manifesting as chronic cough.

COAL WORKER'S PNEUMOCONIOSIS

The development of pneumoconiosis among coal mine workers results from prolonged inhalation and deposition of carbonaceous dust. Dust exposure varies in different parts of the coalmine and is heaviest at the coalface.

Pathology

There are two major categories of coal worker's pneumoconiosis. Simple coal worker's pneumoconiosis is characterised by accumulation of small aggregations of carbon particles, uniformly distributed throughout both the lungs. These lesions (coal macules or coal nodules if large), consist of stellate aggregation of dust and dustladen macrophages around respiratory bronchioles with reticulin fibres and variable amounts of collagen. Complicated coal worker's pneumoconiosis [or progressive massive fibrosis (PMF)] is characterised by the presence of larger (usually more than 1 cm) anthracotic and fibrotic masses in pulmonary parenchyma. These lesions are typically situated in upper lobes, and may cavitate due to ischaemic necrosis.

Clinical and Radiographic Features

Simple coal worker's pneumoconiosis may not be associated with significant clinical symptoms or signs. It often gets detected as micronodular mottling on routine chest imaging. The disorder itself is not disabling, but may progress to complicated coal worker's pneumoconiosis. In contrast to simple coal worker's pneumoconiosis, complicated coal worker's pneumoconiosis is often associated with breathlessness, premature disability, pulmonary function abnormalities and reduced life expectancy.

Coal workers with rheumatoid arthritis may also develop multiple necrobiotic lung nodules up to 2 cm in diameter, often accompanied by subcutaneous rheumatoid nodules. This combination is referred to as Caplan's syndrome. In addition to pneumoconiosis, coal dust exposure increases a miner's risk of developing chronic obstructive pulmonary disease, especially among tobacco smokers. Because coal miners are often also exposed to varying amounts of silica, many patients present with a picture of mixed pneumoconiosis (often termed as anthracosilicosis).

Treatment

There is no specific treatment for coal worker's pneumoconiosis. Prevention, early recognition and treatment of complications (such as airflow limitation, respiratory infections, respiratory failure, cor pulmonale or pneumothorax) remain the cornerstones of medical management.

SILICOSIS

Silicosis is a fibrotic disease of the lungs produced by inhalation and deposition of dust containing free crystalline silica (or silicon dioxide). The importance of silica as a health hazard is due to its ubiquity. Clinically significant exposures can occur during mining, quarrying, and tunnelling of granite or rock with high quartz content. Other industries at risk include sandblasting, manufacture of abrasive detergent, pottery making, brickworks, foundry work, jade polishing, etc.

Pathogenesis

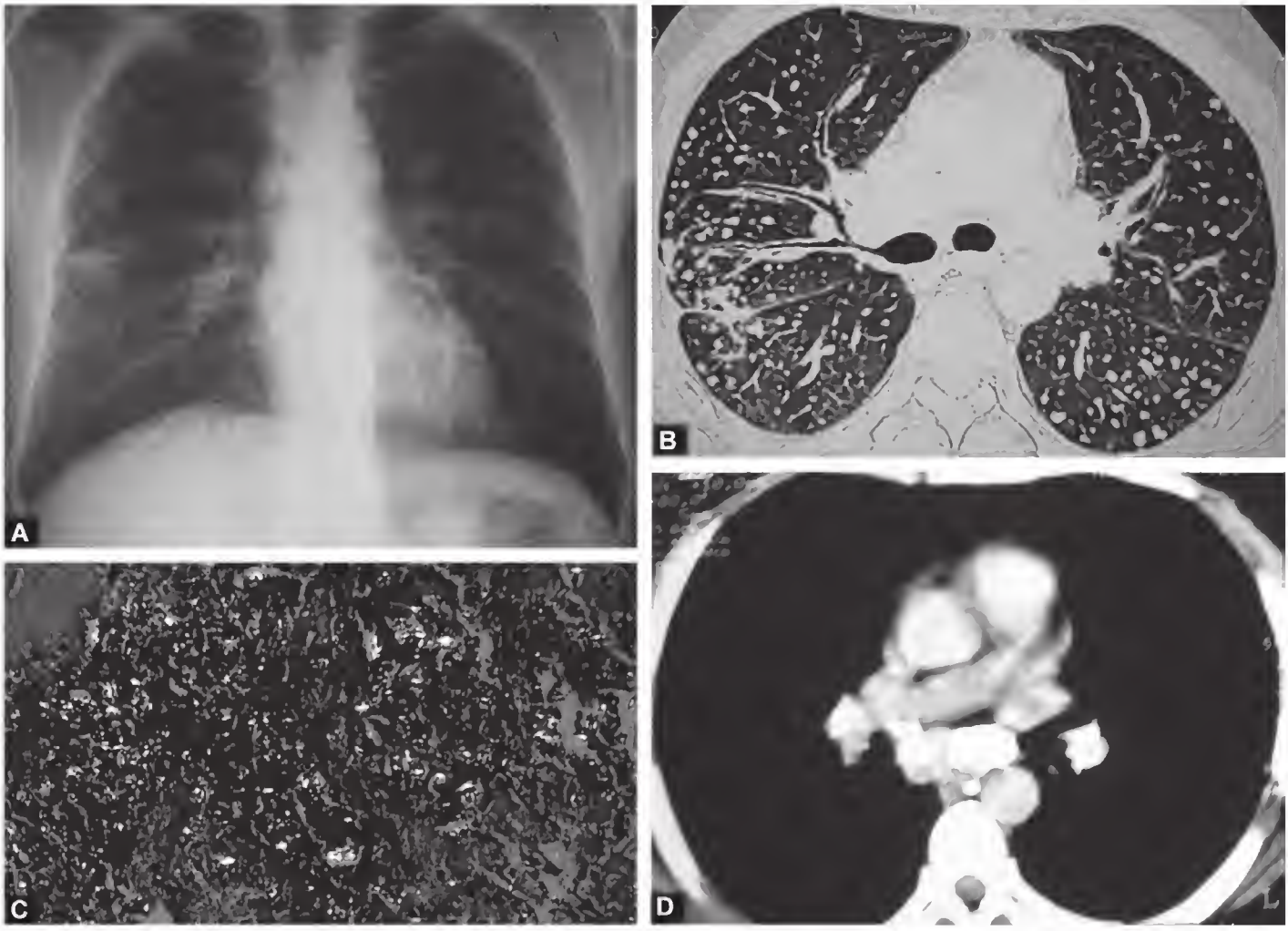
The exact mechanism of lung injury after silica inhalation remains unclear. Alveolar macrophages engulf inhaled free silica, get activated and release cytokines growth factors and oxidants. This stimulates pulmonary parenchymal inflammation, and ultimately leads to fibrosis. Since silica particles cannot be biologically degraded, they outlive the macrophages that ingest them and continue the cycle of lung damage.

Clinical and Radiographic Features

Silicosis can manifest acutely after extreme exposure, but usually manifests in a chronic form requiring many years to develop.

Acute silicosis, and the less common accelerated silicosis, is caused by intense silica dust exposure over short periods (up to two years). In the acute form, mononuclear cells infiltrate alveolar septa, and alveolar spaces fill up with a acellular proteinaceous material. The overall clinical and pathological profile is quite similar to pulmonary alveolar proteinosis, and the condition is often referred to as silicoproteinosis. Severe hypoxaemia is common and hence, this condition is potentially life-threatening.

Chronic silicosis is usually diagnosed after several years of silica exposure. In the initial phase, patients may have no obvious symptoms or may have non-specific, respiratory symptoms. Cough and dyspnoea are common. Radiologically, there is a profusion of small (and typically rounded) opacities predominantly in upper lung fields (**Figures 1A to D**). Enlarged hilar and mediastinal lymph nodes, with a characteristic egg-shell calcification, are common. With continued exposure and disease progression, lung nodules coalesce to form larger masses, and fibrosis and bullae formation set in. This phase is termed as



Figures 1A to D: (A) A typical chest radiograph (postero-anterior view) from a patient with silicosis, showing small round nodules and patchy areas of fibrosis. (B) These features are better appreciated on a chest CT. (C) Histopathological examination of a bronchoscopic lung biopsy specimen under polarised light shows birefringent silica particles within fibrotic nodules. (D) Calcified hilar and mediastinal nodes are also seen on chest CT.

progressive massive fibrosis and is clinically associated with significant lung function impairment and more severe symptoms.

Patients of silicosis are at an increased risk of mycobacterial disease (both typical and atypical), possibly due to functional defects in alveolar macrophages. More recently, silica has also been recognised as a potential human carcinogen.

Treatment

Patients with acute silicosis require oxygen therapy and in severe cases, mechanical ventilation. Whole lung lavage may be beneficial in silicoproteinosis. There is no specific treatment for chronic silicosis and supportive measures need only be prescribed. Patients must be removed from their workplace to prevent further worsening of the disease.

ASBESTOS-RELATED LUNG DISEASE

Asbestos is a collective term for naturally occurring fibrous mineral silicates, widely used for their insulation and fire resistant properties. Major exposures occur during asbestos mining, manufacture/installation of thermal insulation for ships and power stations, production of brake and clutch linings, etc.

Pathogenesis

Asbestos fibres are either serpentine (e.g. chrysotile) or straight (e.g. crocidolite, amosite, tremolite). The former are more commonly used, but the latter penetrate deeper into lungs and are more resistant to breakdown. In contrast to other pneumoconioses, asbestos-related diseases can occur in people with very small or casual exposure as well, and have a latent period of several decades.

Small fibres get deposited in the wall of respiratory bronchioles and are phagocytosed by the macrophages. In contrast for other mineral dust particles, the long asbestos fibres are difficult for macrophages to engulf. The activated macrophages secrete cytokines and chemical mediators of inflammation, which in turn damage the lung parenchyma and lead to fibrosis.

Clinical and Radiological Features

Asbestosis refers to progressive diffuse lung fibrosis resulting from prolonged asbestos exposure. Once initiated, the damage progresses irrespective of removal from continued exposure. Clinical and radiological features resemble those to other interstitial lung disorders with cough, breathlessness, bibasilar crepitations, finger-clubbing and restrictive ventilatory defects being common. Presence of pleural thickening and diaphragmatic or pericardial calcification are useful radiographic findings. Asbestos bodies (asbestos fibres coated with iron-rich protein) may be demonstrated on microscopy from areas of fibrosis.

Pleural manifestations are also common. Benign effusions have the shortest latency (often less than ten years) and may be recurrent. They are typically small and unilateral exudates. Pleural plaques are the commonest radiographic marker of asbestos exposure. Non-calcified plaques are often seen along the chest wall or diaphragm and may be multiple and/or bilateral. They can enlarge to form sheets that get calcified later but are different from the diffuse pleural thickening often associated with lung parenchymal lesions. Persons with asbestos exposure are at a considerably higher risk to develop pleural mesotheliomas, as well as other malignancies involving lung, gastrointestinal tract and kidney (see chapter 1, section 27 also).

OCCUPATIONAL ASTHMA

Asthma is a common occupational disease and may be defined as variable airway obstruction due to a sensitising agent inhaled at workplace. It is common among spray painters, bakers, hairdressers and workers in chemical industries. Typically, asthma-like symptoms occur only at work or immediately thereafter and improve over weekends and during vacations. With continued exposure, however, symptoms may become chronic and loose the obvious relation to workplace exposure. A significant change in forced expiratory volume in one second across work shift is highly suggestive. Lung function testing with specific inhalational challenge to suspected workplace agents may help identify the causative agent. Timely removal from further exposure (e.g. change of job) is helpful in controlling symptoms, especially in the early phase of the disease. Disease control strategies remain otherwise similar to those for non-occupational asthma.

HYPERSENSITIVITY PNEUMONIA

Hypersensitivity pneumonia is also termed as extrinsic allergic alveolitis. It is an inflammatory disorder of the lungs which involves alveolar walls and terminal airways. It is induced in patients by inhalation of certain toxic agents (allergans). The host susceptibility and the allergans, of the organic substances are responsible for subacute or acute pneumonia. The common conditions are farmer's lung, allergic broncopulmonary aspergillosis and others. The hypersensitivity pneumonia are influenced by the weather conditions and the presence of allergans in the atmosphere.

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23.14 Sarcoidosis

VK Vijayan

INTRODUCTION

Sarcoidosis is a systemic disorder of unknown origin characterised by granulomatous inflammation in a variety of organs, most commonly, the lung and affects people of all racial and ethnic groups. Though thought to be uncommon earlier, sarcoidosis cases are increasingly being reported from India during the second half of the last century. This may be due to the increasing awareness of physicians to the clinical entity and also the availability of new diagnostic tools such as thoracic imaging including computed tomography (CT), pulmonary function testing, fibre-optic bronchoscopy and immunological investigations. However, the accurate diagnosis of sarcoidosis and the ability to differentiate it from tuberculosis (TB) are challenges to physicians, especially in countries with high prevalence of TB.

EPIDEMIOLOGY

Sarcoidosis occurs worldwide. It affects persons of all races and both sexes with a wide range of prevalence (1 to 40/100,000). The highest prevalence (>50/100,000) has been reported in Scandinavian countries and the United States (US) African-American population. It appears to be less frequent in Asian countries, South America and Africa but is common in Japan, USA and central Europe. Globally, sarcoidosis shows a predilection for young adults (<40 years) with a slight female predominance and it is rare in children. However, it can occur at all age groups. Socio-economic status does not affect the risk of sarcoidosis. In contrast to Western data, sarcoidosis in India has a later onset by a decade and the disease is more common in men.

AETIOLOGY

The aetiology of sarcoidosis is unknown. It has been suggested that sarcoidosis results from the exposure of genetically susceptible individuals to specific environmental agents. Several studies strongly suggested that the disease could spread by person-to-person transmissions or shared exposure to an environmental agent. An increased incidence of sarcoidosis has been reported in rescue workers from the New York City Fire Department involved in the 2001 World Trade Centre disaster. Mycobacterial and propionibacterial deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) have been recovered from sarcoid tissues. Several non-infectious agents and micro-organisms have been implicated as possible aetiological agents of sarcoidosis (**Table 1**). However, there is no definite proof that any of these agents is involved in the aetiology of sarcoidosis. It has been suggested that sarcoidosis is an end result of immune responses to various ubiquitous environmental triggers. The incidence of sarcoidosis has been reported to be higher in non-smokers. It has also been suggested that sarcoidosis is an autoimmune disease.

Genetic susceptibility to sarcoidosis involves several genes but no single gene responsible for the disease has been demonstrated. Polymorphism of tumour necrosis factor-α (TNF-α) gene, interleukin-1 (IL-1) gene, angiotensin converting enzyme (ACE) gene, and vitamin D receptor gene has been reported to be associated with the expression of the disease. Human leukocyte antigen (HLA) DQB*0602 appears to be associated with progression of disease. HLA DR 11, 12, 14, 15 and 17 appear to confer susceptibility to disease and HLA DR1, DR4 and HLA DQ*0202 seems to be protective.

Table 1: Aetiological Agents Postulated for Sarcoidosis

Infective agents
Viruses
Epstein-Barr virus
Retroviruses
Coxsackie B virus
Cytomegalovirus
Herpes virus
Bacteria
Propionibacterium acnes
Borrelia burgdorferi
Mycobacterium tuberculosis
Cell wall deficient mycobacteria and other mycobacteria
Mycoplasma
Chlamydia
Nocardia
Occupational and environmental exposure
Beryllium
Zirconium
Aluminium
Talc
Pine tree pollen
Clay soil

PATHOGENESIS

The development of sarcoidosis requires three major events: exposure to antigen; acquired cellular immunity directed against the antigen mediated through antigen-presenting cells and antigen-specific T-lymphocytes; and the appearance of the immune effector cells that promote a non-specific inflammatory response (granulomatous inflammation). The characteristic feature of sarcoidosis is the non-caseating granuloma formation. The CD4+ T-cells interact with antigen-presenting cells and initiate granuloma formation. The CD4+ T-cells on activation differentiates into type 1 helper T (Th1)-like cells that secrete IL-2 and interferon-γ and induce macrophages to produce TNF-α production. It has been reported that serum amyloid A regulates granulomatous inflammation in sarcoidosis through toll-like receptor-2. Granulomas contain central collection of macrophages and epithelioid cells surrounded by lymphocytes. Macrophages differentiate into epithelioid cells which fuse to form multi-nucleated giant cells. The granulomatous response resolves during the following 2 to 5 years in more than 60% of patients.

However, it has not been clearly understood why lung disease persists and leads to pulmonary fibrosis in some patients but not in others. Though the pathogenesis of lung fibrosis in sarcoidosis is unknown, it has been observed that there is an increase in matrix metalloproteinases 8 and 9 in bronchoalveolar lavage and sputum specimens from patients with sarcoidosis. It has been postulated that uninhibited protease activity initiates extracellular matrix breakdown and remodelling.

PATHOLOGY

Sarcoid granulomas can be seen in the lung, lymph nodes, mucus membranes, liver, myocardium, central nervous system, skin, joints, and parotid glands. These granulomas are non-caseating, discrete, tight, and compact and may contain inclusion bodies such as Schumann, asteroid, Hamazaki-Wesenberg or crystalline bodies. Unlike tuberculous granulomas, reticulin fibres are preserved in sarcoid granulomas (**Figure 1**). Spontaneous resolution of granulomas can occur in 70% to 90% of the Caucasian subjects and 10% to 15% patients progress to irreversible fibrosis. In the lungs, the granulomas are located close to or within connective tissue sheaths of the bronchioles, subpleural and perilobular spaces and small vessels (a lymphangitic distribution). Granulomata in the lung biopsy specimens have been demonstrated in up to 80% of the patients with stage-I disease without radiological involvement of lung parenchyma.

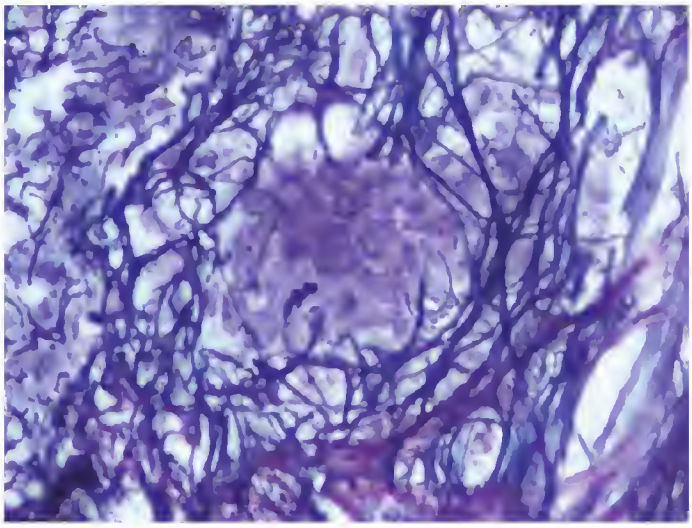


Figure 1: Reticulin surrounding the sarcoid granuloma.

CLINICAL FEATURES

Patients with sarcoidosis may present to different specialities as sarcoidosis is a multi-organ disorder. The clinical feature may vary depending on the ethnicity, duration of illness, site, and extent of organ involvement and activity of the granulomatous process. Many asymptomatic patients (30% to 50%) are discovered when a chest radiograph is obtained for screening purposes.

Constitutional symptoms such as fever, night sweats, fatigue and weakness, anorexia and weight loss have been found to be more common in Indian patients. Sarcoidosis is an unusual cause of fever of unknown origin. Sarcoidosis can present as acute or chronic disease. Acute presentations are frequently seen in Caucasians, and may present with Löfgren's syndrome (bilateral hilar lymphadenopathy, ankle arthritis, erythema nodosum and constitutional symptoms) or Heerfordt's syndrome (fever, parotid gland enlargement, facial palsy and uveitis). Acute sarcoidosis is uncommon in Indian patients. Chronic sarcoidosis has an insidious onset, constitutional symptoms are uncommon and symptoms are related to the organs involved. Pulmonary hypertension (PH) is an important complication of sarcoidosis in 6% to 23% of the patients. Pulmonary fibrosis leading to obliteration of the pulmonary vessels and granulomatous infiltration of the pulmonary arterioles are the proposed mechanisms of PH.

Lung Involvement

Lung manifestations are seen in almost all (>90%) patients. Predominant pulmonary symptoms (30% to 50%) are dyspnoea, dry cough and chest pain. Haemoptysis is rare, clubbing is not usually seen. Localised wheezing due to endobronchial segmental or lobar stenosis mimicking asthma can occur in up to 10% of the patients. Physical findings are observed in less than 20% of the subjects, dry rales are the most frequent signs.

Chest imaging

The chest radiographic findings are classified into four stages (**Table 2**). At the time of diagnosis, most of the patients in the West have stage-I disease whereas majority of the Indian patients present with stage-II disease (**Figure 2**). The characteristic chest radiographic finding is bilateral hilar lymphadenopathy. A 'clinico-radiological dissociation' in which the chest radiographic findings may appear widespread and frightening with minimal symptoms has been described in Indian patients with sarcoidosis.

Other chest radiographic findings include reticular, reticulonodular or focal alveolar opacities, areas of consolidation with air bronchograms, miliary mottling and ground-glass opacities. Calcified lymph nodes resembling egg-shell calcifications can occur in >5% patients with long-standing sarcoidosis. As fibrosis sets in, pleural adhesions to the diaphragm, bullae, cysts and honeycombing are observed in the end-fibrotic stage of the disease. Involvement of larynx, trachea and bronchi can lead to stridor, airway obstruction and bronchiectasis. Pleural effusion, pneumothorax and pleural thickening are uncommon findings. Nasal stuffiness and palatal obstruction or disfigurement from lupus pernio has been described. Contrast-enhanced computed tomography (CECT) demonstrates the lymphangitic distribution. The characteristic CECT findings are ground-glass attenuation (**Figure 3**), central bronchovascular thickening and nodularity (**Figure 4**), thickening of inter-lobular septae, miliary nodules, conglomerate masses, consolidation and architectural distortion, parenchymal and pleural nodules. Contrast-enhanced computed tomography also demonstrates paratracheal, hilar and mediastinal lymphadenopathy.

Table 2: Chest Radiographic Stages in Sarcoidosis

Stage	Finding	Frequency
0	Normal chest radiograph	5% to 10%
I	Bilateral hilar lymphadenopathy (BHL)	50%
II	BHL and pulmonary infiltrations	25%
III	Pulmonary infiltrations without BHL	15%
IV	Pulmonary fibrosis	5% to 10%



Figure 2: Chest radiograph (postero-anterior view) showing bilateral hilar lymphadenopathy and pulmonary infiltrates (stage II sarcoidosis).



Figure 3: CECT chest showing ground-glass attenuation.

Pulmonary functions and gas exchange

Pulmonary function test results are often normal in early stages. The main pulmonary function abnormalities in advanced disease are restrictive ventilatory defect and reduced diffusion capacity for carbon monoxide (DLCO). Airway obstruction is also observed when the bronchial mucosa is involved. Pulse oximetry is often normal when measured at rest but may show desaturation after exertion in patients with extensive lung involvement. Arterial blood gas analysis at rest and during exercise is more sensitive than pulse oximetry. Reversible airway obstruction mimicking bronchial asthma and airway hyper-reactivity have also been reported in Indian patients.

Bronchoscopy

Flexible fibre-optic bronchoscopy (FOB), transbronchial lung biopsy (TBLB), endobronchial biopsy, transbronchial needle aspiration, and bronchoalveolar lavage (BAL) are all useful to obtain tissue sample for the diagnosis of sarcoidosis. The bronchoscopic appearances of sarcoidosis are plaques, nodules, and erythema and cobblestone appearance. Bronchoalveolar lavage reveals lymphocytic alveolitis with an elevated CD4+/CD8+ ratio.



Figure 4: CECT chest showing nodular sarcoidosis.

Cardiac Sarcoidosis

In clinical series, cardiac dysfunction is uncommon (5% to 10%) compared with autopsy studies where a higher prevalence of cardiac sarcoidosis (76%) has been described. Granulomas and scars are commonly found in the left ventricular free wall and the interventricular septum with involvement of the conducting system. Cardinal cardiac manifestations include arrhythmias of all types, conduction abnormalities, congestive heart failure, and sudden death. Other cardiac manifestations include papillary muscle dysfunction, infiltrative cardiomyopathy and pericarditis. Doppler echocardiography may show cardiac dysfunction, especially diastolic dysfunction. Thallium-201 (^{201}Tl) scintigraphy shows segmental areas of decreased thallium uptake and this corresponds to granulomata or fibrosis. The perfusion defects in sarcoidosis decrease in size during exercise and this is in contrast to the findings in cardiac ischaemia ('reversed distribution'). Endomyocardial biopsy may be useful to demonstrate noncaseating granulomas in cardiac sarcoidosis.

Skin Involvement

Skin involvement is common (25%) and the cutaneous manifestations range from small purplish macules, papules to plaques, and subcutaneous nodules. Alopaecia and hypo- and hyper-pigmented areas are also noticed. Sometimes, sarcoidosis can occur in scars and tattoos. Erythema nodosum is a manifestation of acute sarcoidosis and usually lasts for about 3 weeks. Lupus pernio is an indurated, lumpy, violaceous lesion on the nose, cheeks, lips or ears and can be extremely disfiguring and may erode into underlying cartilage and bone.

Neurosarcoidosis

Neurological manifestations are rare (<10%) and include cranial nerve involvement (particularly facial nerve palsy) and hypothalamic and pituitary involvement. Other manifestations include headache, ataxia, cognitive dysfunction, weakness and seizures. Space occupying masses, peripheral neuropathy and neuromuscular involvement occur in chronic sarcoidosis.

Computed tomography and magnetic resonance imaging (MRI) with gadolinium are the diagnostic modalities in neurosarcoidosis. Cerebrospinal fluid examination reveals lymphocytes, elevated protein and increased ACE levels.

Ocular Sarcoidosis

Ophthalmic lesions are common (20% to 30%) and may sometimes be severe resulting in blindness. The most common manifestation is uveitis. Anterior uveitis manifests as painful red eye, blurred vision and light sensitivity and may cause periphlebitis which has been described as 'candle wax drippings'. Acute anterior uveitis usually clears spontaneously within a year or after local therapy with corticosteroids. Posterior uveitis requires systemic treatment. The chronic form of uveitis can lead to glaucoma, cataract and blindness. Conjunctiva can be involved as small, pale, yellow nodules. Keratoconjunctivitis sicca, retinal vasculitis, lacrimal gland enlargement and dacryocystitis are other ocular manifestations. Eye involvement may be asymptomatic and this emphasises the need for ophthalmic investigation including slit-lamp and fundoscopic examination in every patient with sarcoidosis.

Lymphoid System and Spleen

Intrathoracic and peripheral lymph node enlargement is common. Radiographic evidence of hilar lymph node enlargement is seen in up to 90% of the patients. Peripheral lymph nodes are enlarged in about one-third of the patients. Peripheral nodes are firm, discrete, mobile and non-tender. The spleen is frequently enlarged (40% to 80%) in autopsy studies, but clinical symptoms due to splenomegaly are rare. Splenic rupture (spontaneous or traumatic) is an unusual complication of massive splenomegaly.

Hepatic and Gastrointestinal Sarcoidosis

Clinically significant hepatic dysfunction is rare. Liver is palpable in only up to 20% of the patients. However, liver biopsy had revealed granuloma in up to 80% of the patients. Cholestatic pattern of biochemical alterations with minimal increase in aminotransferase concentrations are seen in up to one-third of the patients and manifest as pruritus and jaundice. Occasionally severe disease leading to intra-hepatic cholestasis, portal hypertension and hepatic failure has been reported. Variceal bleeding due to portal hypertension, hepatopulmonary syndrome with refractory hypoxaemia and cirrhosis has been reported in hepatic sarcoidosis in nearly 1% of the patients. The gastrointestinal tract is rarely involved (<1%); the stomach is the commonly involved organ. Other parts involved are oesophagus, appendix, rectum and pancreas.

Renal and Endocrine Systems

The enzyme, 25-hydroxyvitamin D-1α- hydroxylase present in the sarcoid macrophages converts 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D. The overproduction of 1, 25-dihydroxyvitamin D causes increased intestinal absorption of calcium and enhanced bone resorption leading to hypercalciuria with or without hypercalcaemia. This can result in nephrocalcinosis, urolithiasis and renal failure. Kidneys can also be involved directly by a granulomatous interstitial nephritis. Diabetes insipidus may occur due to the involvement of hypothalamus or pituitary glands. Rare endocrine manifestations include hypothyroidism, hyperthyroidism, hypothermia, anterior pituitary gland involvement and adrenal suppression.

Musculoskeletal Manifestations

Arthralgias are more common (25% to 39%) than arthritis in Indian patients. Acute arthritis is rare in Indian patients. Knees, ankles, elbow, wrists and small joints of hands and feet are involved. Muscles can be involved leading to proximal muscle weakness and this has to be differentiated from corticosteroid-induced myopathy.

Other Manifestations

Painless unilateral or bilateral enlargement of the parotid gland (~15%), cystic bone lesions associated with chronic skin lesions, anaemia (4% to 20%), and leucopaenia (40%) are also described. The erythrocyte sedimentation rate (ESR) may be moderately raised. Hypergammaglobulinaemia is common with raised immunoglobulin (Ig)G levels. Other uncommon manifestations reported from India are cirrhosis of liver with portal hypertension, superior vena cava syndrome, breast lumps and transient paralysis of phrenic and recurrent laryngeal nerves. Sarcoid granulomas can also be seen in breast and uterus.

DIAGNOSIS

The diagnosis of sarcoidosis is based on the following criteria: a compatible clinical and/or radiological picture; histological evidence of non-caseating granulomas; and exclusion of other diseases that produce similar histological or clinical picture. Tuberculin skin test (up to 100 TU) is negative in about 60% cases. Sarcoidosis, poses a great diagnostic challenge to physicians in countries where the prevalence of TB is high. If the tuberculin skin test is positive, the diagnosis of TB should be seriously considered in suspected cases of sarcoidosis from countries with high prevalence of TB.

Recommended tests for evaluation of patients with sarcoidosis are listed in **Table 3**. Clinical presentation and thoracic imaging studies may suggest the diagnosis of sarcoidosis. All suspected cases should be confirmed by biopsy to exclude infections or malignant conditions. FOB with TBLB are recommended in most cases as the diagnostic yield is high (80% to 90%), if 4 to 5 samples are obtained. Histological demonstration of granuloma is also possible by bronchial mucosal biopsy even when bronchial mucosa is normal (40% to 60%) and the yield may exceed 90% when there are gross endoscopic findings, such as mucosal nodularity, oedema, or hypervascularity. Bronchoalveolar lavage is a research tool and may help in excluding other causes, such as infectious aetiology.

Other sites for biopsy are visible skin lesions, the lips, and the conjunctiva or enlarged superficial lymph nodes, liver (if serum alkaline phosphatase is elevated). If bronchoscopic procedures or biopsies from other sites have failed to provide a diagnosis, mediastinoscopy, video-assisted thoracoscopic surgery (VATS) or open lung surgery is done occasionally to obtain tissue samples mainly to exclude other intrathoracic disorders.

The presence of non-caseating granulomas on biopsy should not be taken as confirmation of the diagnosis of sarcoidosis. Other granulomatous diseases, especially TB should be excluded to make a diagnosis of sarcoidosis (**Table 4**). In patients with the classical Löfgren's syndrome, biopsies are not usually necessary. Gallium-67 (^{67}Ga) scanning may demonstrate a lambda pattern (uptake in bilateral hilar and right paratracheal lymph nodes) and a 'panda pattern' (uptake in parotid and lacrimal glands).

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) appears to be more accurate and contribute to a better evaluation of extrapulmonary sarcoidosis. Cardiac MRI with gadolinium enhancement and PET have been found to be useful in the diagnosis of cardiac sarcoidosis. Serum ACE activity has no diagnostic value. The Kveim-Siltzbach skin test is not widely available. In addition, difficulties in standardisation and risks of transmissions of infective diseases limit its usefulness.

Table 3: Diagnostic Methods for the Evaluation of Patients with Sarcoidosis

History (occupational and environmental exposure; symptoms)
Physical examination with emphasis on lung, skin, eye, liver, heart, and nervous system
Peripheral blood counts (white blood cells, red blood cells, platelets)
Serum chemistry (calcium, liver enzymes, creatinine, blood urea nitrogen, and angiotensin converting enzyme)
Urine analysis
Chest radiograph (postero anterior view)
High resolution computed tomography (HRCT) and CECT of chest
^{18}F-FDG PET in patients without apparent lung involvement to identify the sites for diagnostic biopsy
^{18}F-FDG PET and MRI with gadolinium to detect cardiac and neurologic involvement
Pulmonary function tests (spirometry, lung volumes, carbon monoxide diffusing capacity and arterial blood gases at rest and after exercise)
Tuberculin skin test
Electrocardiogram (ECG)
Ophthalmic evaluation with slit-lamp examination
Biopsy to obtain histologic confirmation of non-caseating granulomas (with special stains and cultures to exclude tuberculosis, fungal diseases, and malignancy)
Fibre-optic bronchoscopic procedures including bronchoalveolar lavage
Biopsy from skin, lip, lymph node or granulomatous scar
Mediastinoscopy, video-assisted thoracoscopic surgery (VATS), open lung biopsy
Other tests depending on clinical presentation and suspicion of extrathoracic disease

^{18}F-FDG PET = ^{18}F-fluorodeoxyglucose positron emission tomography, MRI = Magnetic resonance imaging.

Table 4: Causes of Granulomatous Lung Diseases Other than Sarcoidosis

Infective agents	**Disease**
Mycobacteria	Tuberculosis, atypical mycobacterial infection
Fungi	Histoplasmosis, coccidioidomycosis
Bacteria	Brucellosis, chlamydia infection, tularaemia
Spirochetes	Treponemal infections
Parasites	Leishmaniasis, toxoplasmosis
Occupational and environmental exposure	
Organic or inorganic agents	Hypersensitivity pneumonitis
	Chronic beryllium disease
	Talc
	Granulomatous disease related to other metals (titanium, aluminium, and zirconium)
	Methotrexate pneumonitis
Other conditions	
Neoplasia	Lymphoma, tumour-related granulomas
Autoimmune disorders	Wegener's granulomatosis, primary biliary cirrhosis, Churg-Strauss syndrome

ASSESSMENT OF ACTIVITY

Though many laboratory and serological markers have been described to assess the activity of sarcoidosis, none of them is useful in clinical practice. Clinical evaluation of the patients based on the mode of onset, the worsening or presence of symptoms and the presence of skin lesions in association with changes in chest radiograph and lung function tests is the best way to assess the activity of sarcoidosis.

TREATMENT

Asymptomatic patients with normal lung function and patients with minimal, well tolerated symptoms and mild functional abnormalities should be observed without treatment because of the potential for spontaneous improvement. These patients require treatment only if symptom develops or lung function deteriorates. The aim of the treatment is prevention of the irreversible loss of organ function and improvement of symptoms for better quality of life. Patients with symptoms can be treated with corticosteroids. Severe ocular, neurosarcoidosis, cardiac sarcoidosis, malignant hypercalcaemia, symptomatic, and/or progressive stage-II and stage-III pulmonary disease require treatment with oral corticosteroids as the first-line treatment. Though corticosteroid therapy may have short-term benefits, there is no evidence that these improve long-term outcome. Pulmonary sarcoidosis is treated with prednisolone (30 to 40 mg/day, gradually tapered to 5 to 10 mg/day over 2 to 3 months). The treatment should be continued for a minimum duration of 12 months. In order to decrease the side effects of hypothalamic suppression, alternate day treatment using equivalent total dosages of prednisolone is also effective. Cardiac or neurological sarcoidosis requires higher doses of steroids. Löfgren's syndrome can be treated with non-steroidal anti-inflammatory drugs. Several patients (~25%) relapse after discontinuation of corticosteroid therapy and some with repeated relapses may require indefinite therapy. Inhaled corticosteroids may reduce symptoms in endobronchial sarcoidosis, but its role in parenchymal sarcoidosis is not well established. Topical steroids have also been found to be useful in some patients with skin sarcoidosis, nasal involvement, or iritis/uveitis.

ALTERNATIVE TREATMENTS

Patients with sarcoidosis requiring long-term corticosteroid therapy and suffering from major side effects of steroids can be offered steroid-sparing alternative treatments. These agents can be used in combination with reduced dosages of steroids or can also be given as a single therapy. Prednisolone requirement has been found to be considerably reduced in patients receiving methotrexate (10 to 25 mg weekly) for six months. Hepatitis and neutropaenia are important adverse effects of methotrexate therapy. Other cytotoxic drugs for sarcoidosis are azathioprine (100 to 150 mg/day) and cyclophosphamide (50 to 150 mg/day). The antimalarial drugs chloroquine and hydroxychloroquine (200 to 400 mg/day for 6 months) have been found to be useful in lupus pernio, nasal sarcoidosis, disfiguring skin sarcoidosis and hypercalcaemia. As hydroxychloroquine is found to be less toxic, it can be used for prolonged periods without retinal damage. Chloroquine has also been reported to be useful in chronic pulmonary sarcoidosis and also in neurosarcoidosis failed on corticosteroid treatment. Other investigational drugs for treatment of

sarcoidosis are minocycline, pentoxifylline, thalidomide, and specific TNF-α inhibitors (etanercept, infliximab). There is an increased risk of TB with infliximab treatment. Patients with end-stage sarcoidosis and cor pulmonale require supplemented oxygen, diuretics, and bronchodilators to relieve airway obstruction. In the end-stage disease, lung transplantation has been successfully performed. Recurrent sarcoidosis has been reported in the lung allograft. However, it is not clinically or radiologically significant.

NATURAL HISTORY AND PROGNOSIS

Sarcoidosis is considered as a benign disease with a tendency to wax and wane either spontaneously or in response to treatment. It has been reported that 60% to 70% of the patients have spontaneous remission and 10% to 30% of the patients have a chronic course. However, this may vary depending on geographical and ethnic differences. Permanent sequelae are seen in 10% to 20 % of the patients. Acute form of the disease (e.g. Löfgren's syndrome) has good prognosis. Mortality in sarcoidosis has been reported to be 1% to 5% and the most common cause of death is respiratory failure. However, the death can frequently be due to myocardial involvement. Adverse prognostic factors in sarcoidosis are lupus pernio, chronic uveitis, onset of disease after 40 years, chronic hypercalcaemia, nephrocalcinosis, black race, progressive pulmonary disease, nasal mucosal involvement, cystic bone lesions, neurosarcoidosis, myocardial sarcoidosis, symptoms that last for more than 6 months, the absence of erythema nodosum, splenomegaly, and involvement of more than three organs.

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23.15 Sleep Related Breathing Disorders

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INTRODUCTION

Sleep is a state of relatively suspended sensory and motor activity, which occurs naturally, is recurring and which is characterised by total or partial unconsciousness with the inactivity of nearly all voluntary muscles. One-third of our lives is spent in sleep. Any changes in the quantity, quality, or pattern of sleep may result in sleep disorders. Over the past 50 years, research into sleep disorders and the clinical advances have lead to more effective treatment of sleep disorders.

Sleep disorders are quite common but are frequently undiagnosed and untreated. The 2nd edition of the *International Classification of Sleep Disorders* (ICSD-2) was published by the American Academy of Sleep Medicine in 2005. This classifies sleep disorders into eight major categories: (1) insomnia, (2) sleep-related breathing disorders (SRBD), (3) hypersomnias of central origin, (4) circadian rhythm sleep disorders, (5) parasomnias, (6) sleep related movement disorders, (7) isolated symptoms and (8) normal variants and other sleep disorders.

Sleep related breating disorders is a general term which includes both obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). Obstructive sleep apnoea results from complete or partial upper airway obstruction, while CSA usually results from reduction in overall respiratory drive.

Apnoea means cessation of airflow for at least 10 seconds. Apnoea can be obstructive (respiratory effort without airflow), central (absence of both airflow and respiratory effort) or mixed. Hypopnoea is a reduction in airflow of 30% from a baseline for longer than 10 seconds and is associated with an oxygen desaturation of more than or equal to 4%. The apnoea-hypopnoea index (AHI), is the total number of apnoeas and hypopnoeas per hour of sleep. An aphoea-hyponoea index of more than 5 is indicative of OSA. The CSA syndrome is an AHI greater than 5 events per hour with more than 50% of the respiratory events classified as central rather than obstructive. Apnoea-hyponoea index is the most commonly used objective clinical measure of sleep apnoea severity.

OBSTRUCTIVE SLEEP APNOEA SYNDROME

Epidemiology

Sleep related breating disorders affects patients regardless of their social or ethnic background. Western data estimates the prevalence of OSA between 0.3% to 4 %, affecting 2% to 4 % of males and 1% to 2% of females, with a large number of individuals still undiagnosed. A population based study in Delhi, India estimated the prevalence of OSA at 2.4 % in males and 1.0% in females.

Pathophysiology

Obstructive speep apnoea is characterised by periodic episodes of complete or incomplete upper airway obstruction. There are three immediate sequelae of OSA that include intermittent arterial blood gas abnormalities, arousals, and large negative swings in intrathoracic pressure. These events result in activation of neurohormones, hypercoagulopathy, oxidative stress, release of inflammatory mediators which lead on to structural alterations of the cardiac chambers. There are a number of anatomic abnormalities associated with OSA like retrognathia, maxillary retropositioning, caudal displacement of hyoid bone, intra-nasal obstruction, macroglossia, enlarged or low placed soft palate, and enlarged lymphoid tissue around the upper airways. Genetic variations, like Pierre-Robinson syndrome, Treacher-Collins syndrome and Down's syndrome may lead to the development of OSA.

Obesity is a major risk factor for OSA, with the neck size being the strongest predictor of OSA. The neck circumference is correlated with the increased dimensions of the parapharyngeal fat pads . The larger upper airway soft tissue of men may be one of the factors contributing to the increased incidence of OSA in males as compared to females.

Clinical Presentation

The signs and symptoms of OSA are many and some of them are listed in **Table 1**.

Table 1: Signs and Symptoms of Obstructive Sleep Aphoea

Question	Yes/No
Snoring	Yes
Witnessed apnoea	Yes
Unrefreshing sleep	Yes
Waking up gasping for air	Yes
Nocturnal reflux	Yes
Nocturia	Yes
Nocturnal sweating	Yes
Sleep talking	Yes
Morning dry mouth	Yes
Morning headache	Yes
Unexpected sleep onset	Yes
Falling asleep while driving	Yes
Routine napping	Yes
Unrefreshing naps	Yes

CARDIOVASCULAR CONSEQUENCES OF OBSTRUCTIVE SLEEP APNOEA

Hypertension

The prevalence of hypertension is greater in patients with OSA and hypertensive patients have higher incidence of OSA. The Wisconsin Sleep Cohort study showed the dose-response association between sleep disordered breathing at baseline and the development of new hypertension 4 years later.

Obstructive Sleep Apnoea and Coronary Artery Disease

Sleep apnoea events induce a state of increased oxygen demand as well as a state of low oxygenation reserve because of the lack of ventilation. This leads to a situation that nocturnal

angina can be triggered by apnoea in Coronary artery diseases (CAD) patients. Coronary artery diseases has been found to be present in one-fourth of OSA patients, with the percentage of patients with CAD being high in patients with moderate to severe OSA. Patients with CAD and nocturnal angina should be considered for sleep study because nasal continuous positive airway pressure (CPAP) reduces nocturnal angina attacks and nocturnal myocardial ischaemia.

Obstructive Sleep Apnoea and Left Ventricular Systolic Dysfunction

The Sleep Heart Healthy Study analysed the association between OSA and various cardiovascular disorders. It was found that an AHI >11 increased the risk of congestive cardiac failure by 2.38%. Haemodynamic, neurohumoral, inflammatory and oxidative stress, endothelial dysfunction and prothrombotic mechanisms are implicated in the development of left ventricular (LV) dysfunction in patients with OSA. The inter-mittent hypoxia caused by apnoea, followed by post apnoea reoxygenation contributes to generation of oxygen free radicals. This causes oxidative stress on the myocardial muscle fibres and plays a role in the development of systolic LV dysfunction. It has also been noted that the proportion of CSA increases from the first to the last quarter of the night.

Obstructive Sleep Apnoea and Arrhythmias

The most frequent arrhythmias seen in OSA are brady-arrhythmias. These include sinus bradycardia, atrioventricular block, complete heart block and ventricular asystole. These bradyarrhythmias are often asymptomatic, as the rhythm disturbances occur only at night. A strong association between OSA and atrial fibrillation has been found and this appears to be independent of gender, hypertension, heart failure or body mass index. Tachyarrhythmias, like ventricular and supra-ventricular tachycardia may occur in OSA.

Obstructive Sleep Apnoea and Stroke

Prospective cohort studies have demonstrated that OSA is associated with a two- to three-fold increased risk of developing a stroke, independent of known cerebrovascular risk factors.

Obstructive Sleep Apnoea and Pulmonary Hypertension

Hypoxaemia and apnoea cause acute elevations in pulmonary artery pressure during sleep but not all pulmonary hypertension can be solely attributed to OSA.

Sleep-Related Breathing Disorders in Pregnancy

The state of pregnancy, till recently, had been considered to be protective against the development of SRBD. Progesterone, though initially causes increased upper airway muscle activity, when primed with repetitive hypoxia, causes the reverse to occur. Progesterone also causes reduction in integrity of vascular endothelium leading to tissue oedema. The increased levels of circulating estrogen associated with pregnancy, cause vascular relaxation, especially in the upper portion of the upper airways. These changes contribute to the development of OSA. A causal link between SRBD and the development of gestational hypertension has been found.

Classification of Central Sleep Apnoea

There are two general categories of CSA – Hypercapnic and Non-hypercapnic. Hypercapnic CSA results from decreased sensitivity of chemoreceptors superimposed on a loss of the voluntary 'wake drive', which results in overall reduction in respiratory drive. Clinically, this presents as alveolar hypoventilation syndrome, which include among others, the obesity–hypoventilation syndrome, neuromuscular failure, chronic narcotic use and idiopathic central hypoventilation (Ondine's curse). These patients are chronic carbon dioxide retainers.

Non-hypercapnic CSA is due to increased sensitivity of the chemoreceptors leading to ventilatory changes, even to trivial changes in PCO_2. Some of the conditions associated with non-hypercapnic CSA include CSR in systolic congestive heart failure (CHF), sleep transition states, periodic breathing at high altitude and the initiation of CPAP therapy.

DIAGNOSIS

Clinical Assessment of Sleep-Related Breathing Disorders

History

This helps to identify the signs and symptoms of SRBD as well as to ascertain the differential diagnosis and to request for appropriate tests for diagnosis. The patient's routine sleep-wake schedule can also be ascertained.

Sleep schedule

The patient's sleep patterns, onset of sleep, awakening including weekdays and weekends is elicited. This data is compared with that of polysomnography.

Sleep problems

There are number of sleep disorders with overlapping symptoms. A thorough sleep history is essential and questions detailing the signs and symptoms of sleep disorders must be asked.

Family and medical history

Risk factors for SRBD include male gender, obesity, middle age or older individuals, crowded airways and anatomic abnormalities like retrognathia or micrognathia, large tongue and low set palate.

Medications

Details of medications being used by the patient, especially stimulants, wake promoting substances, sedatives-hypnotics and other sleep promoting substances must be elicited.

Questionnaires

Sleep questionnaire

Validated sleep questionnaires include the Sleep Disorder's Questionnaire and the Pittsburgh Sleep Questionnaire.

Sleepiness questionnaire

The most widely used questionnaire in clinical practice is the Epworth Sleepiness Scale. Others include the Karolinsky Questionnaire, the Stanford Sleepiness Scale, the Profile of Mood States, the Pictorial Sleepiness Questionnaire, the Berlin Questionnaire, and a number of other visual analogue scales.

Depression questionnaire

Commonly used screening tools include Zung Depression Inventory and the Beck Depression Inventory.

Laboratory Assessment

The current standard technique of diagnosing SRBD is attended laboratory polysomnography (PSG).

Sleep is characterised by three states: wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Non-rapid eye movement sleep consists of 1, 2, 3, and 4 while REM sleep consists of a single stage that is divided into phasic REM and tonic REM sleep. These sleep stages are defined by recordings taken by electroencephalographic (EEG) activity recorded from central and occipital derivations, electrooculographic (EOG) activity from left and right eye and from submental electromyographic (EMG) recordings. Sleep stages are recorded in 30 second epochs. The total length of recording is called the total recording time (TRT). The addition of all the epochs scored in one of the five sleep stages, after sleep onset, is called the total sleep time.

Advancements in PSG recordings have made it possible to collect data other than EEG, EOG, EMG, electrocardiogram (ECG), oxygen saturation and snoring intensity like Oesophageal pH, accessory EMG and nasal pressure. These data are useful in diagnosing conditions like nocturnal acid reflux . Sleep apnoea is graded as mild (AHI 5 to 15), moderate (AHI 15 to 30) and severe (AHI >30), as per the American Academy of Sleep Medicine. After a diagnosis of sleep apnoea is established, a continuous positive airway presure (CPAP) titration is done and the 'split-sleep ' study does away with the conventional two-night sleep study. Infant and pediatric sleep studies are possible with the help of specialised personnel using paediatric specific equipment.

TREATMENT

Treatment options for OSA are outlined in **Table 2**.

Table 2: Treatment Options for Obstructive Sleep Apnoea Syndrome

General measures
Change of position during sleep
Avoidance of alcohol and sedatives
Oxygen therapy
Sleep hygiene
Specific measures
Oral appliances
Continuous positive airway pressure
Bi-level positive airway pressure
Auto-adjusting positive airway pressure
Surgical treatment
Nasal Reconstruction
Uvulectomy
Pillar procedure
Tonsillectomy and/or adenoidectomy
Uvulopalatopharyngoplasty
Laser-assisted pharyngoplasty
Linguloplasty
Genioglossus advancement
Thyrohyoid suspension
Maxillomandibular advancement
Tongue base surgery
Radiofrequency ablation
Tracheotomy

Oral Appliances

Oral appliances are now being considered as first-line treatment for patients with mild to moderate OSA, though previous literature was contrary to this. Oral appliances have been found to be as useful as CPAP in improving subjective sleepiness. A retrospective study done in patients with severe OSA, reporting to a single dental sleep clinic, showed reduction of AHI by 50%. A repeated PSG with the oral appliances in place is essential, in order to make appropriate adjustments.

Continuous Positive Airway Pressure Treatment

Positive airway pressure (PAP) devices act like a pneumatic pump supplying positive pressure to the upper airways, thereby preventing collapse and occlusion during sleep. CPAP has been demonstrated to reduce the AHI and improve subjective and objective sleepiness. Despite its demonstrated efficacy, the adherence to therapy is suboptimal. An estimated 15% to 30% of the patients do not accept CPAP treatment and upto 25% of the patients discontinue the treatment within the first year. Average adherence to PAP has been estimated at 65%. Other PAP delivery modes which may provide greater comfort and better adherence are the auto-adjusting PAP (APAP), Bi-level PAP (Bi-PAP) and flexible PAP (C-Flex). The APAP devices have the ability to simultaneously detect and prevent upper airway obstruction using the lowest possible pressure during sleep. Bi-PAP devices deliver two independently adjusted levels of pressure: high pressure during inhalation and a low pressure during exhalation. C-Flex devices lower the pressure level at the beginning of exhalation, returning to set pressure before exhalation ends. It is thought that the flexible amount of pressure relief causes an increase in comfort to the patient, thereby resulting in better therapeutic adherence. There are ongoing studies on the use of cognitive behavioural therapy and theory based music intervention as means of improving adherence to CPAP therapy.

Surgical Treatment

Once surgical treatment is indicated, conservative procedures must be tried first and only after that, comes the aggressive procedures and second-line treatments. Since the introduction of uvulo-palatopharyngoplasty (UPPP) in 1981, it is the most common procedure for treating OSA.

CLINICAL OUTCOMES AND MORTALITY IN OSA

The various clinical outcomes in patients with OSA are listed in **Table 3**. The risk of death among patients with untreated severe OSA is about three times that of the general population or of those patients with mild OSA. The increased risk of mortality was seen in younger patients, prompting the suggestion that diagnosis and treatment be done early.

Table 3: Clinical Outcomes in Obstructive Sleep Apnoea

Death
Cardiovascular
Non-fatal myocardial infarction
Non-fatal stroke
Heart failure
Arrhythmias
Pulmonary hypertension
Systemic hypertension
Traffic accidents
Daytime sleepiness

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23.16 Pulmonary Embolism and Deep Vein Thrombosis

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DEEP VENOUS THROMBOSIS

Deep venous thrombosis is commoner than generally perceived; one of four patients admitted for a general medical condition to a hospital develops deep venous thrombosis. Incidence in Indian population varies between 8% and 28% in hospitalised patients; 50% and 60% in patients undergoing hip/knee surgeries.

Deep venous thrombosis (DVT) is most common in the lower limbs, particularly in the venous sinuses of the soleus muscle in the calf and in the femoral and iliac veins. It is much less frequent in the upper limbs, but the axillary vein may be involved as a complication of trauma, long venous-infusion catheters, neoplasm or radiotherapy. Virchow's triad attributes venous thrombosis to three factors: relative venous stasis, endothelial injury and increased coagulability (**Table 1**).

Table 1: Predisposing Factors for Deep Vein Thrombosis

Venous stasis
Immobility (bed rest, surgery, limb paralysis), low cardiac output
Varicose veins
Venous injury
Trauma, intravenous cannulation
Increased coagulability
Malignant disease, drugs (e.g. oestrogens, oral contraceptives), dehydration, polycythaemia, nephrotic syndrome, ulcerative colitis, lupus anticoagulant
Inherited coagulation defects
Antithrombin-III, protein C, protein S deficiency, factor V Leiden mutation, anticardiolipin antibodies
Increasing age

Pathology

Normal endothelium is non-thrombogenic. However, change or injury to the endothelium can trigger the activation of platelets finally leading to adhesion and aggregation of platelets. Endothelium can also be activated to release activators of certain coagulation factors (factor X) due to injury or as result of hypoxia following stagnation of blood due to venous stasis. Activated clotting factors lead to fibrin formation. Initially, the thrombus consists mainly of dense layers of platelets and fibrin. Later, the jelly-like mass of fibrin and red cells may become detached to form an embolus. After a few days, inflammatory changes occur in the wall of the vein, the thrombus may undergo lysis and organisation.

Diagnosis

Most patients have no physical signs. DVT and pulmonary thromboembolism (PTE) may occur in healthy people with no predisposing cause. In a patient suspected to have DVT, a detailed history is elicited and careful inspection of the extremity is performed. One would look for redness, warmth, tenderness on calf compression (Moses' sign), measure the leg circumference and try to elicit Homan's sign (calf pain on dorsiflexion of foot with the knee bent). However, very often the patient is completely asymptomatic. Recent evidence suggests that 1% of all asymptomatic calf DVT patients that go home will die of PTE. A high level of suspicion is, thus, necessary to detect patients with increased risk of DVT as shown in Well's DVT scoring system (**Table 2**).

Table 2: Well's DVT Scoring System: Score <0—Low Risk, 1 to 2—Moderate Risk, >3—High Risk

History	Score
Paralysis, paresis or plaster immobilsation of the legs	+1
Major surgery in past 4 weeks, or being bedridden for 3 or more days, or travel lasting longer than 4 hours in the previous 6 weeks	+1
Cancer treatment in previous 6 weeks, or on palliative treatment	+1
Clinical findings	
Entire leg swollen	+1
Calf swollen; in the symptomatic leg, the circumference is 3 cm more than the other leg, measured 10 cm below the tibial tuberosity	+1
Tenderness along deep veins	+1
Pitting oedema (worse in the symptomatic leg)	+1
Collateral superficial veins (non-varicose)	+1
Other alternate diagnosis	
For example: musculoskeletal injuries, haematoma, chronic oedema, superficial phlebitis in varicose veins of the leg, cellulitis of the leg, arthritis of the leg, Baker's cyst	–2

Investigations

Duplex ultrasound

The technique called duplex ultrasound, which includes venous compression ultrasound (CUS) and the Doppler ultrasound, has a high sensitivity (90% to 100%) and specificity (80% to 100%) for diagnosis of DVT in the thigh. It is less sensitive (75%) for detection of DVT in the calf veins.

In CUS, a vein with an indwelling thrombus is not obliterated by external compression; thus, failure to obliterate the femoral vein by external compression is an indirect evidence of femoral vein thrombosis. This method uses a two-dimensional B-mode ultrasound. Doppler ultrasound, on the other hand, uses the Doppler shift method to detect the velocity of flow in an underlying vessel. This combined duplex approach is more accurate than either method alone.

Impedance plethysmography

Impedance plethysmography (IPG) is a reliable method for detecting thrombi in the deep veins of the thigh (sensitivity and specificity ~ 90%). However, IPG can miss thrombi in the calf veins where its sensitivity is less than 70%, as calf thrombi produce relatively little venous obstruction.

Contrast venography

Though it remains the 'gold standard' for confirmation of DVT, contrast venography is an invasive test and involves administration of contrast medium. It is contraindicated in patients with renal insufficiency and is not accurate in patients with recurrent DVT because of the difficulty in visualising an intraluminal defect in veins that have been thrombosed previously. It is seldom used presently.

Treatment

Therapeutic anticoagulation is the mainstay of management of DVT (**Table 3**), which also includes treatment with analgesics for local pain, elastic bandaging and elevation of the leg, prevention of further clotting, and prophylaxis against recurrent pulmonary emboli. The purpose of the bandage is to compress superficial veins and so promote increased blood flow through the deep veins.

Table 3: Therapeutic Anticoagulation in VTE

Initiation
Admit for close observation. Check baseline coagulation profile
Initiate intravenous UFH 80 µ/kg as bolus followed by 18 µ/kg/hr
Monitor ACT/aPTT 6 hourly, titrate infusion to maintain 1.5 to 2 times normal value
Initiate VKA on day 1 of therapy
Check INR on day 3
Heparin (UFH/LMWH) may be stopped after a minimum of 5 days and once INR ≥2 for >24 hours
LMWH in a dose of 1 mL/kg SC q12h may be an alternative, but UFH is preferred in renal failure
Maintenance
Therapeutic anticoagulation is mandatory for 3 to 6 months in all patients with first episode of VTE with a reversible risk factor (e.g. pregnancy/trauma)
Prolonged, i.e. lifelong anticoagulation is required in patients with recurrent (>1) episode, unprovoked first episode (no identifiable risk factor, low risk of bleeding), patients with malignancy

VTE = Venous thromboembolism; UFH = Unfractionated heparin; LMWH = Low molecular weight heparin; VKA = Vitamin K antagonist.

Consequences of DVT may vary from complete resolution of the clot to death due to pulmonary embolism. Morbidity associated with DVT includes post-thrombotic syndrome that includes chronic venous hypertension causing limb pain, ulcers, hyperpigmentation, swelling, dermatitis, venous gangrene, and lipodermatosclerosis. Elastic compression stockings protect against post-thrombotic syndrome by decreasing the incidence to half.

VTE is being recognised as a relapsing disorder in a number of patients, particularly those with thrombophilia, malignancy and in patients with more than one episode of DVT. These patients require long-term anticoagulation. Persistently elevated D-dimer levels (after stopping anticoagulation) or persistent residual venous thrombosis on Doppler help to identify this subset of patients following the first episode of DVT.

Prophylaxis

Almost all critically ill patients and some post-operative patients have significant risk factors for venous thromboembolism. A reasonable strategy is to extend anticoagulation prophylaxis to all immobilised critically ill patients and also to moderately high-risk general surgical patients, unless there are contraindications to such therapy. Prophylaxis for DVT includes pharmacological and/or mechanical prophylaxis (**Table 4**). Certain high risk groups (poly trauma/bariatric surgery) require a combination of both methods.

Table 4: Deep Venousthrombosis Prophylaxis

Methods of prophylaxis	
Mechanical	Graded compression stockings Sequential compression device Venous foot pump
Pharmacological	Low-dose UFH LMWH fixed-dose irrespective of body weight (e.g. Enoxaparin 40 mg SC q24h) Fondaparinux 2.5 mL SC q24h VKA

Patient groups	**Recommendation**
Low risk: <10% Laparoscopic/urologic/gynaecologic surgeries for benign conditions/ minor surgeries lasting <30 min requiring LA/spinal anaesthesia	Early ambulation
Moderate: 10% to 40% Surgery >30 min requiring GA/ medically ill patients	Risk of bleeding: mechanical No risk: UFH/ LMWH
High: 40% to 80% Hip/knee/spinal cord surgeries/ oncosurgeries/bariatric surgeries/ critically ill patients/polytrauma/SCI	Risk of bleeding: mechanical No risk: UFH/ LMWH

UFH = Unfractionated heparin; LMWH = Low molecular weight heparin; VKA = Vitamin K antagonist; LA = Local anaesthesia; GA = General anaesthesia; SCI = Spinal cord injury.

Source: Adapted from ACCP Guidelines, 2008.

PULMONARY THOMBOEMBOLISM

Definition

Pulmonary thromboembolism (PTE) is defined as a condition where there is significant obstruction of a part or whole of the pulmonary arterial tree by a thrombus, migrating from a site outside the lung. PTE is not a disease per se, but is a complication of DVT in most cases. The primary source of PTE is from thrombi arising in the deep veins of the lower extremities (90%). The term venous thromboembolism (VTE) is commonly used to include both DVT and PTE as a continuum of one aetiopathological process.

Epidemiology

PTE is being more frequently recognised due to increasing awareness and advances in diagnostic techniques. The incidence of PTE in India is assumed to be less than in the Western countries. One reason for this may be the lack of diagnostic facilities at most centres in India. In USA, it accounts for about 10% of in-hospital mortality; 10% of these occur in the first hour, timely treatment reduces mortality from 30% to less than 10%.

Aetiology

PTE is a complication of DVT and most commonly results from the detachment of a vascular thrombus from the leg (70% to 80%) or pelvis (10% to 15%). Thrombi which are confined to the veins below the knee appear to pose lower risks than those arising above the knee.

Pathophysiology

Acute alteration in haemodynamics and respiratory physiology occur when massive PTE occludes pulmonary arteries. These effects occur due to physical obstruction and serotonin release due to pulmonary vasoconstriction. On the other hand, pulmonary infarction is less common as the lungs receive dual blood supply from the bronchial circulation. The pathophysiological consequences of PTE are shown in Table 5.

Table 5: Haemodynamic Presentation of Pulmonary Thromboembolism

Massive	Moderate to severe	Mild to moderate
>50% in PV bed	>50% ↓ in PV bed	<50% ↓ in PV bed
↑↑ PVR	↑ PVR	PVR – normal
↑↑ RV after-load	↑ RV after-load	Normal RV after-load
RV failure	RV dysfunction	No RV dysfunction
↓ CO, shock	No shock	No shock

PV bed = Pulmonary vascular bed; PVR = Pulmonary vascular resistance; RV = Right ventricular; CO = Cardiac output.

Clinical Evaluation

The clinical manifestations of PTE are variable and often non-specific. While sudden and unexpected death may result during convalescence after an operation or a prolonged medical illness, PTE can, at times, be totally symptomless. Patients with massive PTE (Figure 1) present with substernal pain that may be indistinguishable from the pain of coronary thrombosis and/or dyspnoea. These patients may be anxious, restless, confused and cyanosed. Signs of shock may supervene. Tachycardia and tachypnoea and a gallop rhythm are frequently evident. Occurrence of other findings such as an accentuated pulmonary component of the second heart sound and rise in jugular venous pressure will depend on the degree of pulmonary hypertension produced. The chest is usually clear. Rhonchi may be heard as a result of secondary bronchoconstriction.

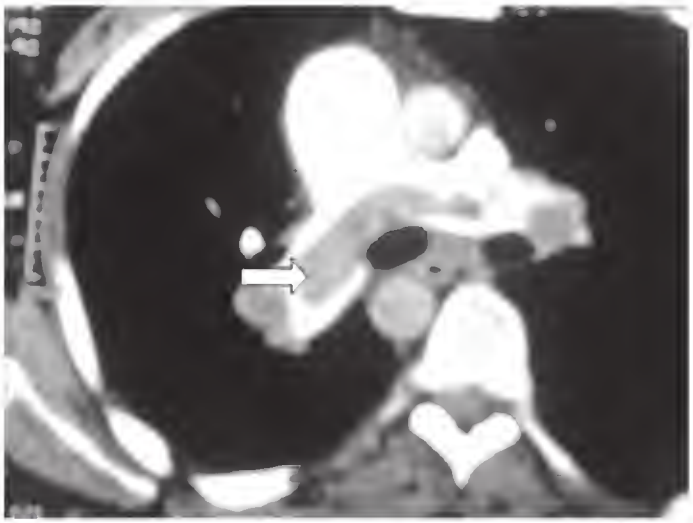


Figure 1: CT pulmonary angiography showing saddle thrombus extending from the main pulmonary artery into right and left branches (arrow).

Many patients with smaller or often recurrent emboli present in a more insidious manner. Dyspnoea may be the only symptom; unexplained dyspnoea should always raise the suspicion of pulmonary embolism. Pleuritic chest pain and haemoptysis indicate pulmonary infarction and their onset may be delayed for a day or more after the initial presentation. A pleural rub may be heard over the affected area. A pleural effusion, small or large, may develop and persist for weeks. Fever is usually present and is persistent when the embolus is of an infective nature. A mild icteric tinge may be evident.

Investigations

Radiographic assessment

The chest radiograph, even in patients with life-threatening PTE, may appear normal. The most frequent radiographic abnormalities in PTE are atelectasis or a pulmonary parenchymal abnormality. The Hampton hump is a classic finding caused by a pleural-based abnormality from pulmonary infarction but its absence cannot be used to exclude PTE. The overall specificity and sensitivity of a chest radiograph, as a diagnostic tool, is very low. Therefore, the major role of the chest radiograph is to exclude other possibilities that may mimic PTE such as pneumonia, pneumothorax and to provide information that could help in the interpretation of radionuclide scans.

Electrocardiogram

The electrocardiogram (ECG) is normal in 70% to 80% of patients with PTE. Sinus tachycardia is the most common ECG abnormality especially when the emboli are small. Right axis deviation and clockwise rotation of the heart may be present. The deep S wave in lead I, a prominent Q wave and inverted T wave in lead III, commonly referred to as the S_1, Q_3, T_3 mimicking inferior myocardial infarction, are highly suggestive of PTE. Depression of the ST segment may occur in lead I and lead II. T waves in leads V_1 to V_4 may be inverted, while the P waves are prominent in lead II and VI (Figure 2).

In an appropriate clinical setting, transient development of incomplete or complete right bundle branch block (RBBB) is strong supportive evidence of PTE. Recurrent episodes of arrhythmias, e.g. sinus tachycardia, atrial flutter or atrial fibrillation may also occur. ECG changes are often transitory, lasting from a few hours to a few days or a week. Thus, serial ECGs are of great diagnostic help. It must, however, be kept in mind that a normal ECG does not exclude the diagnosis of PTE. ECG is also useful for excluding acute myocardial infarction.

Arterial blood gas abnormalities

Hypoxia and hypocapnia is the main arterial blood gas abnormality. However, massive PTE may be accompanied by significant increase in dead space reflecting as hypercapnia and respiratory acidosis, with low end-tidal CO_2.

In most instances, the disturbed blood gas balance will rapidly normalise. This is probably due to an equalising of lung units with low and high V/Q ratios. This happens as a consequence of physiological reflexes causing both hypoxia-induced vasoconstriction to ventilated lung units and bronchoconstriction following hypocapnia to underperfused lung units. However, if there is already an underlying lung disease, such as COPD, these reflexes may fail and the overwhelming V: Q abnormality may persist.

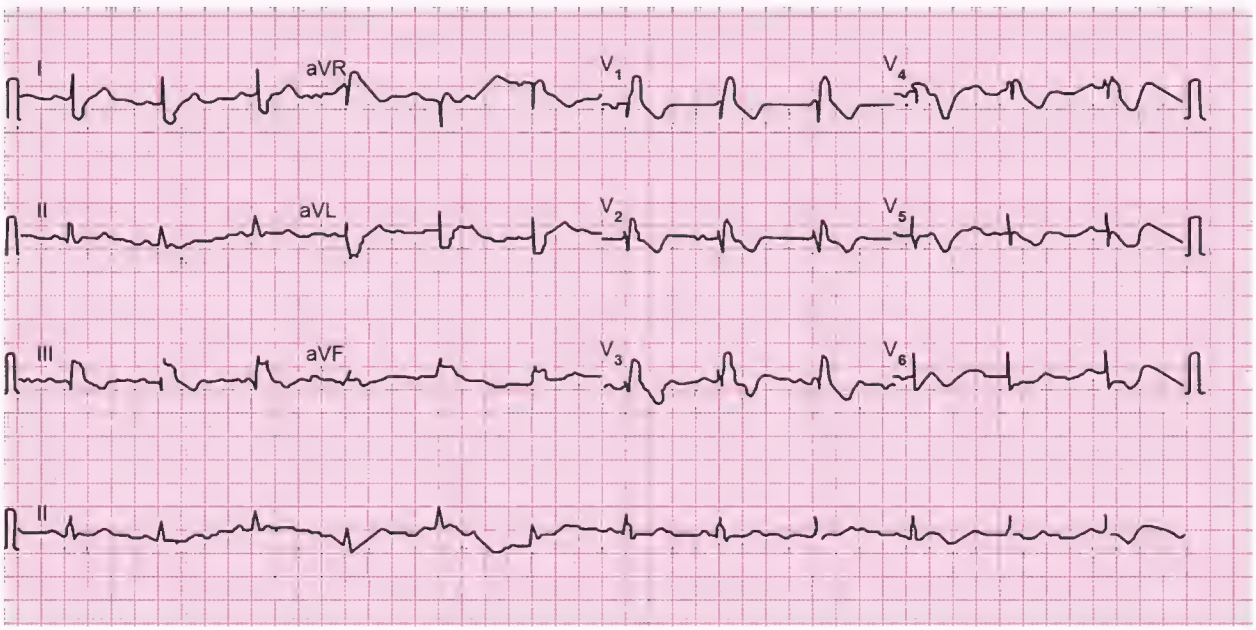


Figure 2: ECG showing $S_1Q_3T_3$ pattern and RBBB in a patient with pulmonary thromboembolism.

Echocardiogram

Two-dimentional-echocardiography (2D-echo) is particularly useful as it reveals abnormalities of right ventricular (RV) dysfunction manifest by RV dilation, hypokinesia, septal flattening or tricuspid regurgitation. The presence of RV dysfunction and pulmonary hypertension on 2D-echo in the right clinical setting strongly suggests a massive PTE (**Figure 3**).

Plasma D-dimer

Plasma D-dimers are fibrin derivatives produced by plasmin-mediated clot degradation. An abnormally elevated level of D-dimer by ELISA method has a high sensitivity (>95%) but poor specificity for identifying patients with PTE. This is because D-dimer may be elevated in a number of other conditions that are often commonly associated with VTE, e.g. pregnancy, sepsis,

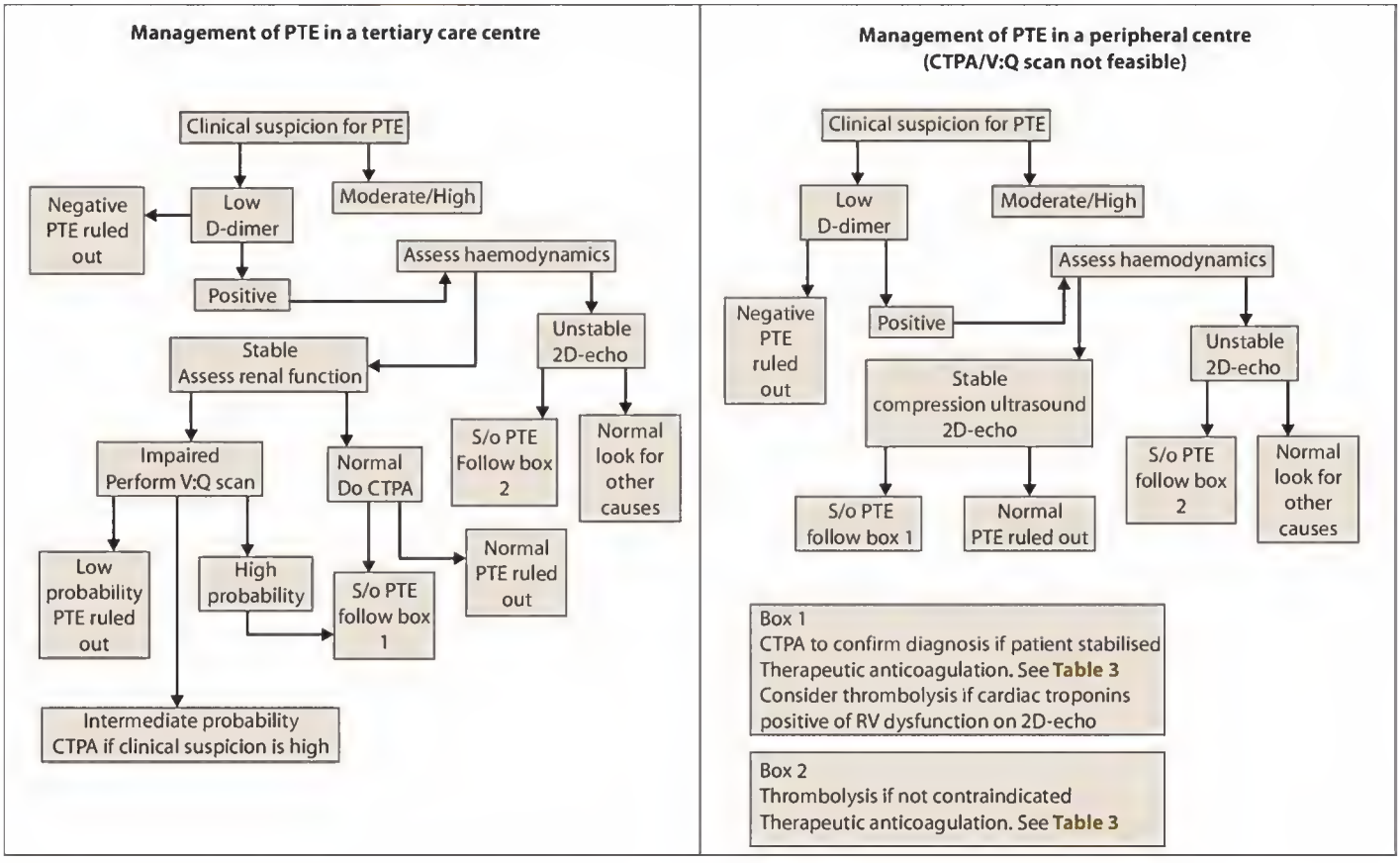


Figure 3: Management of Pulmonary Thromboembolism (PTE).

trauma, recent surgery. Albeit the test has a high negative predictive value, i.e. a normal value can virtually exclude the possibility of venous thromboembolism especially in patients with low clinical suspicion.

Ventilation-perfusion scan

In lung perfusion scan, a suspension of particles of macro-aggregated human albumin labelled with technetium99m is injected intravenously. The area of the lung which is under-perfused shows up a 'cold spot' or 'avascular' area in the scan. A normal perfusion scan virtually excludes the diagnosis of PTE.

In a ventilation scan, radioactive xenon-133 is inhaled and exhaled by the patient, while the gamma camera records its distribution throughout the alveolar gas exchange units. The test is based on the assumption that ventilation is preserved in areas of reduced perfusion due to pulmonary embolism and is abnormal when perfusion defects are due to pulmonary lung disease. V/Q scanning is useful in patients with moderate-to-high clinical suspicion where contrast dye is to be avoided. (**Figure 3** for algorithm for diagnostic strategy).

CT pulmonary angiography

CT pulmonary angiography (CTPA) is a minimally invasive investigation, widely available in most major hospitals, and offers the advantage of direct visualisation of pulmonary emboli within the pulmonary arteries. It also provides information about parenchymal abnormalities that may help in establishing an alternative diagnosis. CTPA is more accurate in detecting central or lobar PTE and less sensitive in detecting subsegmental PTE. Hence, CTPA cannot rule out the possibility of subsegmental PTE and this is the main disadvantage from conventional pulmonary angiography. However, isolated subsegmental PTE is uncommon and in presence of a negative CTPA one can safely withhold anticoagulation and on the other hand, a CTPA showing a PTE (**Figure 1**) may be treated without further tests.

Conventional pulmonary angiography

Formerly the 'gold standard' for diagnosis of PTE, the use of pulmonary angiography has declined with the advent of modern CTPA. It is more often used as an imaging modality as a part of local thrombectomy.

Cardiac markers

Cardiac troponins often elevated in massive PTE are indicative of significant right ventricular dysfunction, thus, helpful in prognostication rather than diagnosis. BNP elevation may indicate RV strain and stretching of RV muscle, which may suggest a serious prognosis. However, it may be elevated in other coexisting conditions like CHF and hence is of little value.

Treatment of Massive PTE

Massive PTE is a life-threatening medical emergency which is often undiscovered until autopsy. Diagnosis heavily relies on clinical suspicion together with CTPA or V/Q scanning. Unfortunately, most patients with massive PTE are clinically unstable and this may delay proper diagnostic evaluation and specific therapeutic intervention. However, the central aim initially is to counter the respiratory and haemodynamic consequences of the embolus till such time as reasonable diagnostic evaluation is possible (**Figure 3**). Echocardiography is an excellent bedside technique, which helps in recognising RV failure and haemodynamic instability, so that proper therapy is instituted in this selected group of patients. After initial supportive measures, most patients may be reasonably stable to be transported to CTPA for further evaluation.

Initial management in the presence of hypotension would include volume resuscitation. However, fluids should be administered cautiously particularly in the presence of marked increase in pulmonary vascular resistance and RV failure, where volume resuscitation may further compromise RV function resulting in more drastic reduction in the cardiac output. Among the vasoactive agents, norepinephrine and dobutamine have been reported to show haemodynamic improvement most consistently. If the patient remains haemodynamically stable, with or without supportive treatment, prompt anticoagulation with heparin should be started (**Table 3**). However, if in spite of initial resuscitation and all supportive measures, the cardiac output is not adequately restored and the patient remains haemo-dynamically unstable, one must consider therapeutic options aimed directly at reducing the embolic burden like intravenous or catheter-directed thrombolytic therapy (can be administered within 14 days of diagnosis of PTE) or surgical embolectomy. Further, thrombolytic therapy may be considered in some cases of PTE with RV dysfunction or elevated cardiac troponin levels. When there are contraindications to its use (**Table 6**) or if the hypotension is refractory despite thrombolytic therapy, embolectomy should be considered. Certain other scenarios such as trapped embolus within the right atrium or right ventricle may necessitate surgery. Approved dosage regimes for thrombolytic therapy in acute PTE are shown in **Table 7**.

Table 6: Contraindications to Thrombolytic Therapy

Absolute	
	Active internal bleeding
	Bleeding diathesis
	Recent GI bleeding/proven peptic ulcer (in last 3 months)
	Previous haemorrhagic stroke/CVA in last 6 months/intracranial tumour
	Recent (<2 months) head injury/any trauma/major surgery
	Severe uncontrolled hypertension (diastolic BP >110 mm Hg)
	Allergy to earlier treatment with streptokinase (use alternate agent)
Relative	
	Pregnancy, post-partum state
	Chronic liver disease
	Cardiopulmonary resuscitation
	Haemorrhagic retinopathy

Table 7: Thrombolytic Treatment of Pulmonary Thromboembolism

Streptokinase	
	250,000 U IV (as loading dose) over 30 minutes followed by 100,000 U/hour for 24 hours
Urokinase	
	4,400 U/kg body weight IV (as loading dose over 10 minutes) followed by 4400 U/kg/hour for 24 hours
Tissue plasminogen activator	
	100 mg IV over 2 hours

Placement of inferior vena caval (IVC) filters may prevent additional, potentially fatal emboli in a selected group of patients with massive emboli. The main indications for using

IVC filters are recurrent PTE despite anticoagulation, patients who develop bleeding on anticoagulation, large free-floating thrombus in the ileofemoral veins, immediately following surgical catheter embolectomy and in high-risk patients where anticoagulation and thrombolytic therapy is contraindicated. More recently, temporary (retrievable) filters have been placed in patients with short-term risk of bleeding. Interestingly, IVC filters are a potential nidus for thrombus formation and often mandate a low level of anticoagulation.

Chronic thromboembolic pulmonary hypertension (CTPH) represents partly a failure of initial treatment of PTE and develops in less than 4% of patients following the first episode, and the incidence increases following recurrent VTE.

In patients with recurring episodes of PTE and no known predisposing factors or in patients with a strong family history of PTE, it is mandatory to do an assay of protein C, protein S, homocysteine and AT-III and look for factor V Leiden mutations. In cases of AT-III deficiency or homozygous factor V Leiden, long-term or even lifelong anticoagulation is recommended. However, all patients should receive heparin prophylaxis during surgery or trauma.

Pregnancy

Physiological changes in pregnancy and post-partum period may predispose to development of DVT in the legs and pelvic veins. VTE was previously observed to be more common in the post-partum period possibly related to earlier practices of prolonged bed rest after delivery or use of oestrogen to suppress lactation. Now, it is equally common to document DVT in all trimesters of pregnancy. Important risk factors include increased parity, obesity, prolonged immobility, operative or difficult instrumental delivery and previous history of VTE. Multiple risk factors are often present during pregnancy. Interestingly, there is a striking propensity for left leg involvement (nearly 80%) when DVT occurs in pregnancy probably due to the tortuous course of left leg venous drainage through the pelvis. Mortality has been reported at 15% in undiagnosed patients and in Western countries, PTE is an important cause of maternal mortality.

Clinical diagnosis of VTE is notoriously unreliable because the physiological changes in pregnancy can complicate the interpretation of the usual signs and symptoms of VTE; elevated D-dimer levels are common in uncomplicated pregnancy. Ultrasound and Doppler studies of the leg veins are the investigations of choice. Diagnostic work-up for thrombophilia is not indicated in all cases of DVT in pregnancy except in selected cases with strong clinical suspicion of hypercoagulable state.

Main aims of management include restoration of venous patency to prevent post-phlebitic syndrome in the future and prevent PTE. Bed rest and elevation of the affected leg promotes venous return and decreases oedema. However, as soon as symptoms permit, the patient should be ambulated as there is no evidence to show that prolonged bed rest prevents detachment of the embolus. Coumarin is not used in pregnant patients as it produces haemorrhagic complications in the foetus and carries the risk of warfarin embryopathy (manifests as skeletal or CNS defects), hence intravenous and subcutaneous heparin or LMWH is the treatment of choice.

Management of Bleeding Caused by Anticoagulant Treatment

In an emergency for rapid reversal of anticoagulation following warfarin treatment, both vitamin K (10 mg IV slowly) and fresh frozen plasma (FFP) must be given to correct the international normalised ratio (INR). Recombinant factor VIIa (rVIIa) can also be used in an emergency as it is effective for a prompt and complete reversal. Protamine is used for immediate reversal of standard heparin (1 mg of protamine for every 100 units of standard heparin if the last dose of heparin was given within 30 minutes and 0.5 to 0.75 mg/100 units of heparin if it was 30 to 60 minutes since the last dose) and LMWH (1 mg of protamine for every 1 mg of LMWH). Protamine does not fully reverse LMWH but can neutralise the antithrombotic effect. Because of the longer half-life of LMWH, a second dose of protamine may be required.

NON-THROMBOTIC PULMONARY EMBOLISM

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare complication of pregnancy wherein amniotic fluid and foetal cells enter the maternal pulmonary circulation and trigger an anaphylactic reaction or complement activation or both. This leads to pulmonary vasospasm and pulmonary hypertension causing hypoxia which damages myocardial and pulmonary capillaries, resulting in LVF and ARDS. This manifests as an acute catastrophe during labour and less commonly following an abortion or amnioinfusion. The patient may develop shock, respiratory distress, seizures, neurological manifestations and even cardiac arrest. Patients who survive this phase may progress to develop uterine atony and disseminated intravascular coagulation (DIC) leading to massive post-partum haemorrhage. Therapy is usually supportive. Steroids may have a role as anaphylaxis is postulated.

Air Embolism

Air embolism is often an iatrogenic complication that occurs frequently during neurosurgical procedures in the sitting position, less commonly during central line insertions, thoracocentesis, haemodialysis, radiographic procedures, penetrating chest injuries, etc. Air may enter the pulmonary circulation causing right ventricular outflow obstruction or alternately enter the cerebral circulation. Typically about 5 mL/kg of air is fatal but in the cerebral circulation, 2 to 3 mL and in the coronary circulation, 0.5 mL may be dangerous. Patients often present with a sudden cardiovascular collapse, dyspnoea or arrythmias. Movement of air through a patent foramen ovale may result in an arterial air embolism that may manifest as a myocardial infarction or stroke. Transoesophageal echo-cardiography/precordial duplex ultrasound or cranial Doppler are useful diagnostic modalities. Placing the patient in the left lateral Trendelenberg's position may preclude the air from moving into the right ventricle. High flow oxygen, attempts at air aspiration from an indwelling CVC, hyperbaric oxygen in the case of Caisson's disease are some of the suggested therapeutic modalities.

Fat Embolism

Fat embolism may occur due to the mechanical dislodgement of fat globules into veins which subsequently move into

cerebral circulation by arteriovenous shunts. These emboli cause microcirculatory defects, platelet aggregation and vasoactive amine release. An alternate theory is that trauma/sepsis causes the systemic release of free fatty acids or chylomicrons which coalesce and cause the above effects. Hence, fat embolism is common following trauma, orthopaedic procedures, parenteral lipid administration and in patients with multiple medical problems. Diagnosis of fat embolism may be defined based on presence of one major (respiratory distress, radiological signs, cerebral signs devoid of other aetiologies and petechial rash) and four minor criteria (pulse >110/m, fever >38.5°C, retinal changes of fat globules, elevated ESR, drop in haemoglobin or platelets, jaundice, renal dysfunction) plus fat microglobulinaemia. Treatment involves management of the orthopaedic condition, DVT prophylaxis, supportive care and steroids.

RECOMMENDED READINGS

1. Antithrombotic and Thrombolytic Therapy; 8th Ed. ACCP Guidelines. *Chest* 2008; 133:381S-545S.
2. Clive Tovey, Suzanne Wyatt. Diagnosis, investigation, and management of deep vein thrombosis. *BMJ* 2003; 326:1180-4.
3. Tapson VF. Acute pulmonary embolism. *N Engl J Med* 2008; 358:1037-52.

23.17 Diseases of Pleura, Mediastinum, Diaphragm and Chest Wall

Alladi Mohan

DISEASES OF THE PLEURA

The visceral pleura that lines the lungs, folds back itself at the hilum to form the parietal pleura which lines the inner thoracic wall, the mediastinum and the diaphragm. The cavity between the visceral and parietal pleura is termed the pleural space and it normally contains a very thin layer of fluid (0.13 mL/kg) which acts as a lubricant. Only the parietal pleura is pain sensitive as it contains sensory nerve fibres, supplied by the intercostal and phrenic nerves.

Pleurisy

Inflammation of the pleura results in pleurisy (or pleuritis). Pleurisy may start as dry pleurisy (**Table 1**), but may later on resolve or develop into wet pleurisy (pleural effusion). Patients with pleurisy present with a localised, sharp, stabbing pain on the affected side that worsens on inspiration, coughing, and sneezing (pleuritic pain). Physical examination may reveal reduced movements on the affected side. A pleural rub may be heard on auscultation.

Table 1: Common Causes of Dry Pleurisy

Epidemic myalgia (pleurodynia, Bornholm disease)
Extension of infection from the underlying lung (e.g. pneumonia)
Tuberculous pleurisy
Chest trauma
Serositis due to connective tissue diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus)
Pulmonary infarction
Pleural malignancy (metastatic, primary)
Radiation injury
Uraemia

Pleurodynia (also called epidemic myalgia, Bornholm disease), caused by Coxsackie B virus infection, is a form of dry pleurisy which may occasionally be complicated with pleural effusion. It occurs in epidemics and commonly affects children and young adults. Patients present with fever, severe incapacitating pleuritic chest pain. On the affected side, movements of the thorax are reduced, the chest wall muscles are tender and a pleural friction rub may be heard. This condition should be differentiated from chest pain due to other causes such as, herpes zoster, intercostal myalgia, costochondritis, and rib trauma. Treatment is symptomatic and supportive and includes relief of pain by administration of analgesics.

Pleural Effusion and Empyema

Abnormal, excess accumulation of fluid in the pleural space is termed as pleural effusion. Presence of pus in the pleural space is termed empyema. Various causes of pleural effusion are listed in **Table 2A**.

Table 2A: Causes of Pleural Effusion

- **Transudate***
  - Congestive heart failure†
  - Constrictive pericarditis†
  - Restrictive cardiomyopathy†
  - Cirrhosis of liver (hepatic hydrothorax)†
  - Nephrotic syndrome†
  - Acute glomerulonephritis†
  - Severe hypoproteinaemia†
  - Myxoedema†
  - Meigs' syndrome (ovarian tumour and usually right-sided pleural effusion)
  - Peritoneal dialysis†
  - Superior vena cava obstruction†
- **Exudate***
  - Inflammatory diseases of pleura
    - Tuberculosis†
    - Bacterial pneumonia
    - Viral infections
    - Fungal infections
    - Parasitic infections
    - Pulmonary embolism†
  - Collagen vascular disease
    - e.g. Rheumatoid arthritis†, systemic lupus erythematosus†
  - Disorders of adjacent structures
    - Oesophageal rupture
    - Diaphragmatic hernia
    - Liver abscess
    - Subphrenic abscess
    - Pancreatitis†
    - Neoplastic diseases
      - Mesothelioma
      - Metastatic†
    - Mediastinitis
    - Chest wall injury
    - Haemothorax
    - Chylothorax
  - Uncommon causes
    - Sarcoidosis†
    - Yellow nail syndrome†
    - Drugs†
      - Nitrofurantoin, dantrolene, methysergide, metoprolol, amiodarone, procainamide, bromocriptine, procarbazine
    - Occupational asbestos exposure†
    - Uraemia†
    - Urinothorax
    - Post-radiation therapy

**Described in Table 2B; †May present with bilateral pleural effusion.*

Clinical Features

Patients with pleural effusion manifest symptoms due to inflammation of pleura, compromise of pulmonary mechanics or interference with gas exchange. Most present with pleuritic chest pain that corresponds to the affected area. Sometimes, pleuritic pain may be referred to the abdomen. Pleuritic pain in the lower chest with ipsilateral shoulder pain indicates diaphragmatic involvement. A dull aching pain may be evident in patients with malignant pleural effusion. Dry cough with minimal scanty sputum and dyspnoea are usually present. History of expectorating copious purulent sputum may suggest an empyema rupturing into a bronchus (bronchopleural fistula). Fever is a prominent symptom in empyema where it may be high grade, remittent and associated with chills and rigors, and in pleural effusions of infective or inflammatory aetiology.

Physical examination reveals: reduced movements; impaired tactile and vocal fremitus; a stony-dull note on percussion. In pleural effusion, the highest point of the stony-dull note is evident in the axilla (*Ellis 'S' shaped curve phenomenon*). Breath sounds may be diminished or absent on the affected side. Aegophony may be heard at the upper level of the pleural effusion. Mediastinal shift to the opposite side may be evident in a large pleural effusion. Classical pleural friction rub, which is coarse, creaky and leathery in character, audible during the latter part of inspiration and the early part of expiration (*to-and-fro pattern*) may be present in the early stages of the disease; it may disappear when the pleural surfaces separate as a result of collection of excessive fluid, but may reappear in the stage of resolution. In empyema, intercostal fullness, bulging, redness and tenderness may be evident. With large pleural effusions, haemodynamic disturbances may be evident.

Diagnostic Evaluation

Chest radiograph

The chest radiograph findings of a pleural effusion range from blunting of costophrenic angle (small effusion) (**Figures 1A and B**) to dense opacification of the entire hemithorax with mediastinal shift to the opposite side (large effusion) (**Figures 2A to E**). Elevation of hemidiaphragm is seen in sub-pulmonic effusion. Encysted or interlobar effusions are better appreciated in the lateral view. Lateral decubitus chest radiograph obtained with the patient lying on the affected side can help in identifying small effusions. Pleural plaques (asbestosis) and pleural calcification (**Figure 3**) may also be present.

Ultrasonography

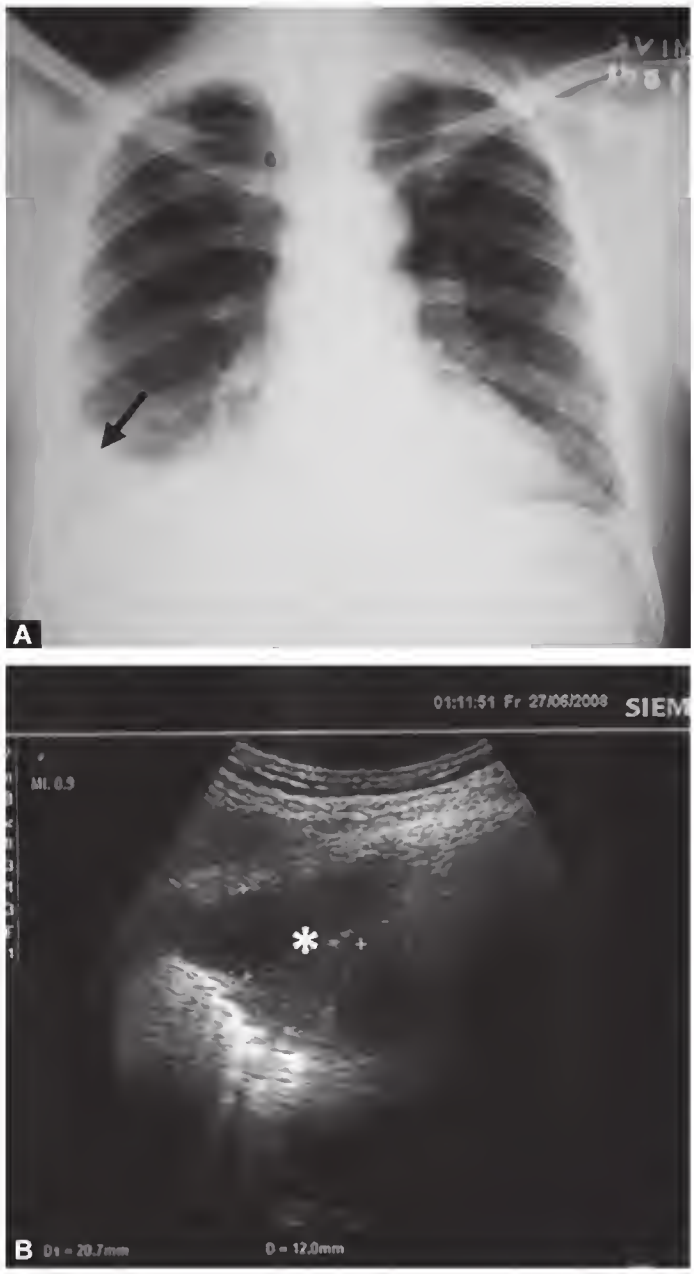
Ultrasonography of the chest is useful for detecting small pleural effusions (**Figure 1**), identifying multiloculated effusions and in localising the site for a diagnostic thoracocentesis.

Computed tomography

Computed tomography (CT) of the chest is useful for delineating loculated pleural effusion or empyema (**Figures 4A and B**), detecting mediastinal or hilar lymphadenopathy or lung lesions, such as tumours.

Thoracoscopy

Video-assisted thoracoscopic surgery (VATS) is a helpful procedure for obtaining tissue and fluid for ascertaining the aetiological diagnosis.

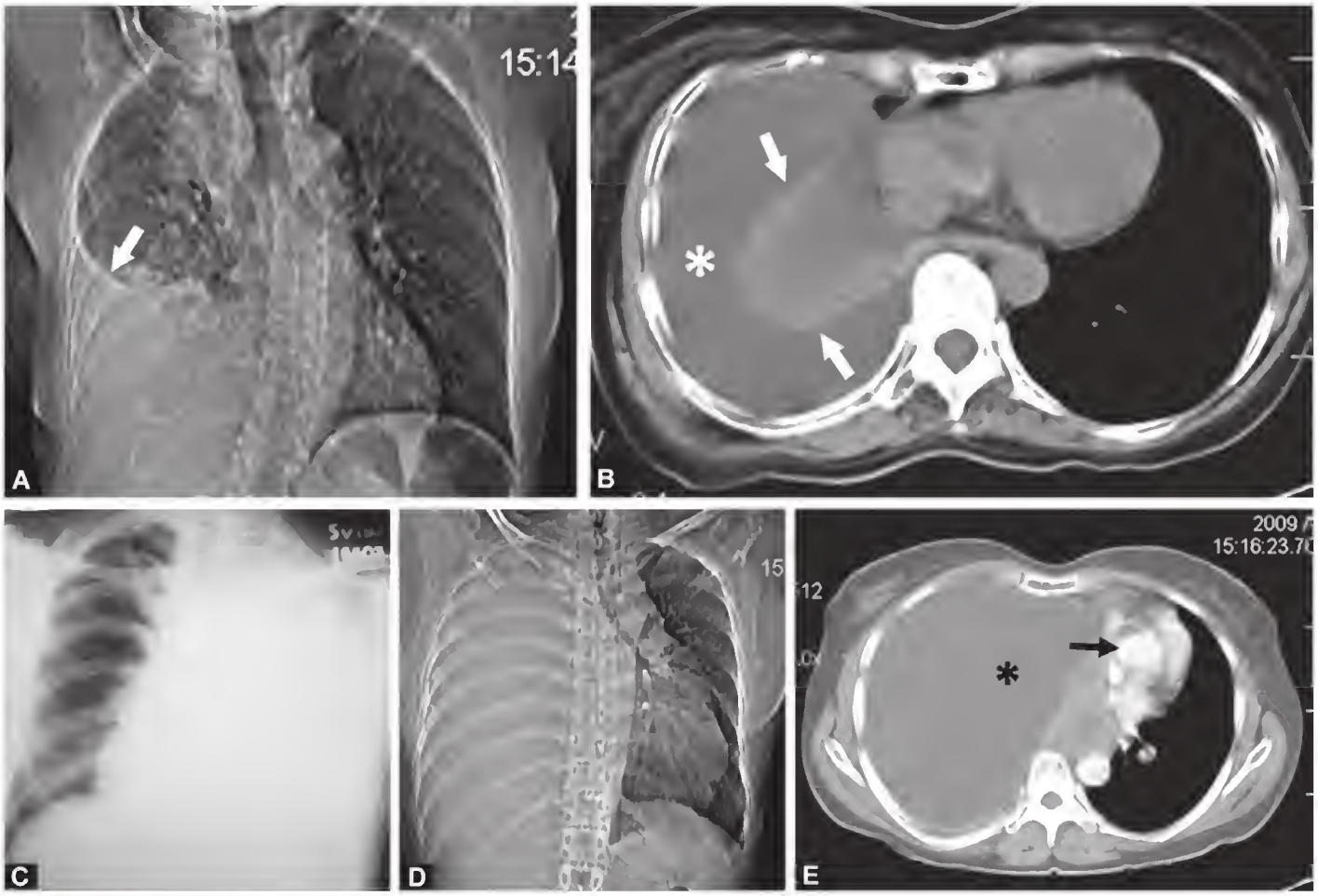


Figures 1A and B: (A) Postero-anterior view of chest radiograph (arrow), and (B) Ultrasonography of chest showing a small right-sided pleural effusion (asterisk). Ultrasonography helps in identifying small pleural effusions, facilitates quantification of the pleural fluid volume and also helps in the detection of loculation and septation.

Diagnostic thoracocentesis

Diagnostic thoracocentesis helps in categorising the pleural fluid as transudate or an exudate (**Table 2B**). A transudative pleural effusion occurs due to systemic factors, whereas an exudative pleural effusion occurs due to alteration in the local factors which influence the formation and absorption of pleural fluid. In acute infections, predominance of polymorphs may be present; in chronic infections, like tuberculosis (TB), lymphocytes predominate. In some cases, eosinophils predominate.

Transudative pleural effusions are usually clear, have low specific gravity, protein levels, lactate dehydrogenase (LDH) levels and very few cells. In transudative pleural effusion, pleural fluid glucose levels run parallel with blood glucose levels; pleural fluid glucose levels are reduced in exudative



Figures 2A to E: (A) Contrast-enhanced CT chest topogram(arrow) showing a moderate right-sided pleural effusion, (B) In the transverse CT (mediastinal window) image of the same patient, pleural effusion (asterisk) and the collapsed lung border (arrows) are also evident, (C) Chest radiograph (postero-anterior view) showing a massive left-sided pleural effusion and complete opacification of the left hemithorax with mediastinal shift to the right side, (D) Contrast-enhanced CT chest topogram of another patient showing a massive right-sided pleural effusion, (E) In the transverse CT (mediastinal window) image of the same patient, massive right-sided pleural effusion (asterisk) and mediastinal shift to the left side (arrow) can be seen.

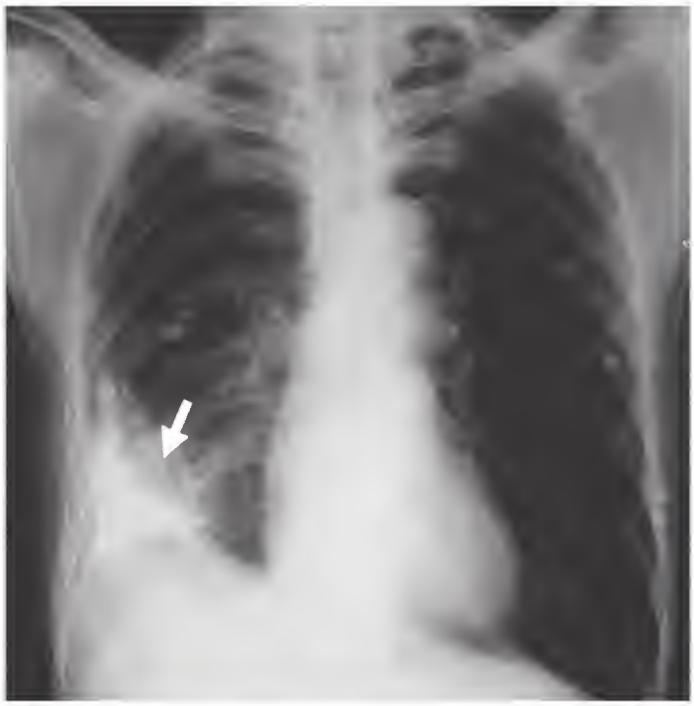


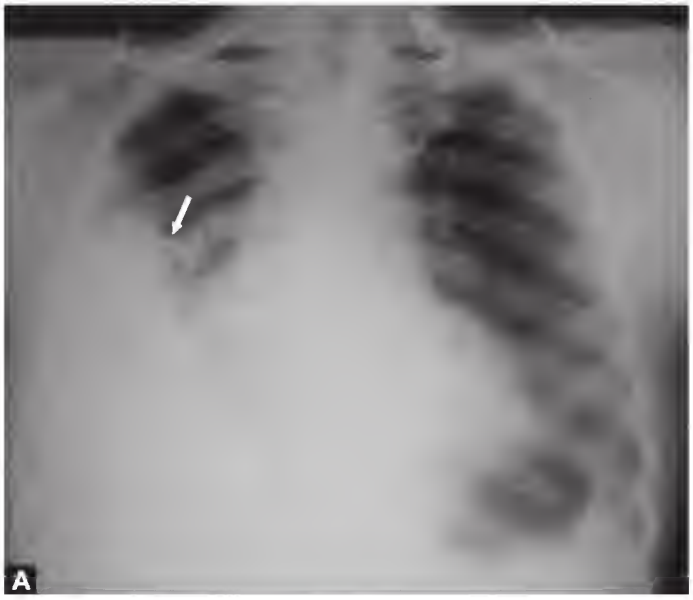
Figure 3: Chest radiograph (postero-anterior view) showing right-sided pleural calcification (arrow) that developed as a sequelae of a tuberculous pleural effusion.

pleural effusion. In rheumatoid pleural effusion, glucose levels may be very low (<60 mg/dL) and cholesterol levels may be high (especially in chronic effusions). In pleural effusions complicating pancreatitis, amylase levels are elevated. Adenosine deaminase (>36 IU/L), interferon-gamma (>112 pg/mL) levels are elevated in TB pleural effusion.

Table 2B: Criteria Used for Categorising a Pleural Effusion as an Exudate

Light's criteria	
	Pleural fluid protein: serum protein ratio >0.5
	Pleural fluid LDH: serum LDH ratio >0.6
	Pleural fluid LDH >two-third of the upper limit of normal serum LDH
Others	
	Pleural fluid protein >3 g/dL
	Pleural fluid LDH >200 IU/L
	Pleural fluid cholesterol >45 mg/dL
	Pleural fluid-to-serum cholesterol ratio >0.3
	Serum albumin-pleural fluid albumin gradient ≤1.2 g/dL
	Pleural fluid-to-serum bilirubin ratio >0.6

Aspiration of frank pus suggests empyema. A milky-white fluid suggests chylothorax or a chyliform (pseudochylous) effusion (**Table 3**). Haemorrhagic pleural effusions may suggest pleural malignancy. Pleural fluid seldom reveals acid-fast bacilli





Figures 4A and B: (A) Postero-anterior view of chest radiograph (arrow) showing a right-sided loculated pleural effusion, (B) Contrast-enhanced transverse CT (mediastinal window) image shows loculated pleural effusion on the right side (arrows).

on smear examination. Culture of pleural fluid for bacteria, mycobacteria or fungi can help in ascertaining the aetiological diagnosis. Cytopathological examination of pleural fluid confirms the presence of malignant pleural effusions. Molecular diagnostic methods such as polymerase chain reaction can be helpful in confirming the diagnosis in certain situations.

Pleural biopsy

Needle biopsy of the pleura using Abram's punch biopsy needle or Cope's needle, radiologically-guided Tru-cut needle biopsy can help in confirming histopathological diagnosis. Sometimes, VATS or open pleural biopsy may be required to confirm the diagnosis.

Management

In pleural effusion due to systemic causes like congestive heart failure, pulmonary embolism, treatment of the underlying cause facilitates the resolution of the effusion. In patients with synpneumonic effusion who continue to run fever, diagnostic thoracocentesis is indicated to rule out empyema.

In India, TB is the most common cause of pleurisy with effusion in young adults. Among middle-aged and elderly subjects who are smokers, malignant pleural effusion should be considered. Under the Revised National Tuberculosis Control Programme (RNTCP), patients with large or massive TB pleural effusion receive directly observed treatment, short course (DOTS), category I treatment and those with small to moderate TB pleural effusions, defined as pleural fluid volume less than 1,500 mL on ultrasonography of the chest, receive DOTS, category III treatment. A short course of prednisolone (0.5 mg/kg daily for 4 weeks) may be helpful in some cases to provide relief from toxaemic symptoms and to facilitate rapid absorption of fluid.

In malignant pleural effusion, treatment is aimed at the underlying malignancy. Rapidly reaccumulating pleural effusion requiring frequent thoracocentesis may require pleurodesis by injecting a sclerosant, such as, sterile talc or tetracycline. Intrapleural streptokinase administration may help if bacterial empyema is loculated; tube thoracostomy is often required in

Table 3: Differentiation of Chylothorax from Pseudochylothorax

Variable	Chylothorax	Pseudochylothorax*
Prevalence	Uncommon	Rare
Aetiology	Usually caused by thoracic duct transection (trauma, surgery); or obstruction (e.g. non-Hodgkin's lymphoma). Other causes: filariasis, lymphangioleiomyomatosis, congenital absence of thoracic duct, yellow nail syndrome	Often post-inflammatory; can be a feature of long-standing pleural effusions (e.g. tuberculosis, rheumatoid arthritis, empyema)
Onset	Acute to subacute	Insidious
Appearance	Milky; sometimes serous or haemorrhagic	Milky; satin-like sheen may be present
Pleural fluid analysis		
Evidence of thickened/calcified pleura	Usually not present	Usually present
Cell count	Lymphocyte rich	Neutrophils predominate
Total proteins	Exudative	Exudative; total protein level usually 4 to 7 g/dL
Lipid profile	Cholesterol 60 to 200 mg/dL; Triglycerides >110 mg/dL; Cholesterol/triglyceride ratio <1	Cholesterol >250 mg/dL; Triglyceride levels usually normal; may be elevated sometimes. Cholesterol/triglyceride ratio >1
Others		
Chylomicrons	Present	Absent
Lipid-laden macrophages	Absent	Present
Cholesterol crystals	Absent	Present (rhomboid shaped)
Addition of ethyl ether to milky fluid	Clears it by dissolving triglycerides	No change
Testing after consumption of butter containing radioiodine-labelled triglycerides; or containing lipidophilic dye (e.g. Sudan III)	Detection of dye/radioactivity	No detection of dye/radioactivity

** Also called cholesterol effusion, chyliform effusion*

such cases. In chronic empyema, Elossier flap procedure, decortication may be required.

Pneumothorax

Definition

Presence of air in the pleural space results in pneumothorax. It may occur spontaneously or as a consequence of iatrogenic injury or trauma to the chest. Spontaneous pneumothorax may develop in otherwise healthy individuals (*primary*) or it can occur as a complication of underlying lung disease (*secondary*), e.g. due to the rupture of a subpleural emphysematous bulla, pleural bleb or as a complication of barotrauma due to mechanical ventilation.

Primary spontaneous pneumothorax

Various types of spontaneous pneumothorax are shown in **Table 4**.

Clinical Features

Primary spontaneous pneumothorax is commonly encountered in males, aged 15 to 30 years; tobacco smoking, tall stature and the presence of apical subpleural blebs are risk factors. Secondary pneumothorax, more common in older individuals affects patients with pre-existing lung diseases. Common presenting symptoms include sudden-onset chest pain on the affected side and breathlessness. In the closed type, breathlessness is mild. In the open type, breathlessness may be more severe and secondary infection of pleura is common. Tension pneumothorax is an acute medical emergency, the patient is severely dyspnoeic; cyanosis, marked tachycardia, profuse sweating may be present.

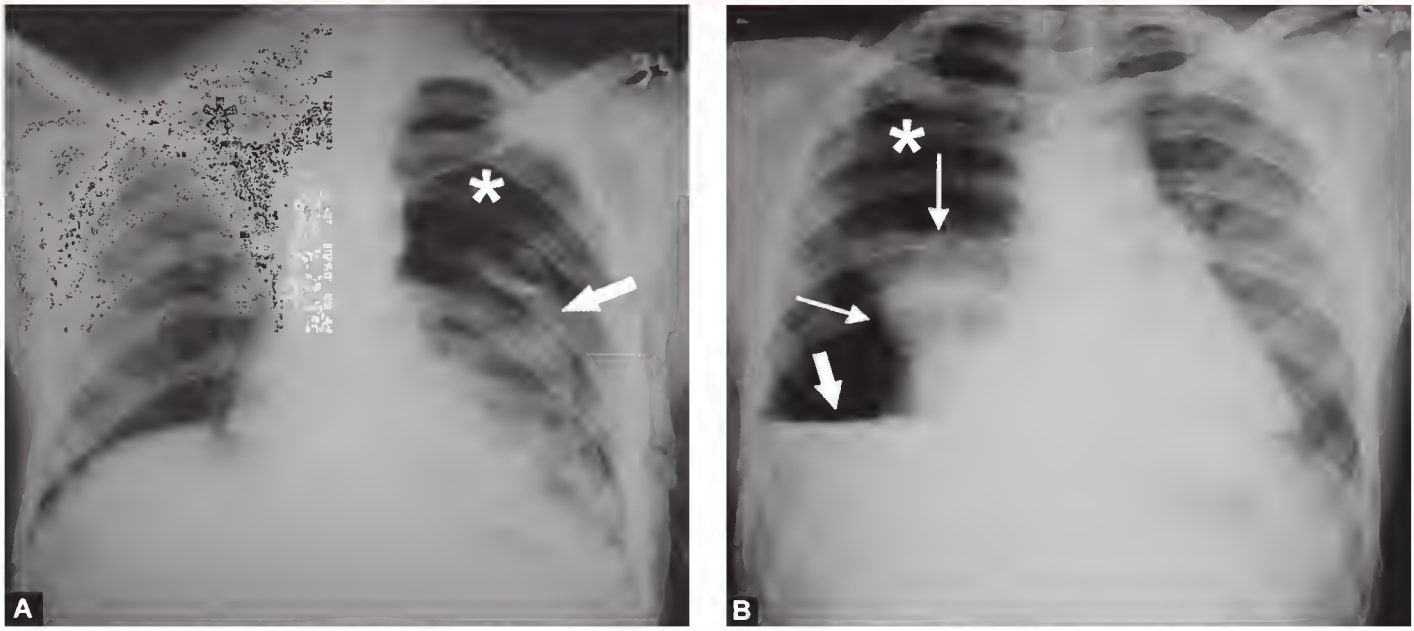
Physical signs vary according to the type and size of the pneumothorax. Mediastinum is shifted to the opposite side. On the affected side, intercostal fullness, diminished movements, hyper-resonant percussion note, reduced or absent breath sounds may be evident. In hydropneumothorax or pyopneumothorax, a horizontal 'fluid level' marks the interface between the liquid and the air. Other important physical signs include amphoric breath sounds (in bronchopleural fistula, tension pneumothorax) succussion splash (hydropneumothorax). Recurrent spontaneous pneumothorax can occur in patients with emphysematous bullae or lymphangioleiomyomatosis.

Investigations

Chest radiograph findings include mediastinal shift to the opposite side, presence of air in the pleural cavity as a translucent shadow along with the sharply defined edge of the collapsed lung (**Figures 5A and B**). Hydropneumothorax and underlying pulmonary disease may also be seen (**Figure 5B**).

Table 4: Types of Spontaneous Pneumothorax

Type	Pathophysiology	Salient Features
Closed	The communication between the lung and pleural space seals off as the lung deflates and does not reopen	The mean pleural pressure remains negative. Air in the pleural space gets reabsorbed spontaneously, the underlying lung re-expands over a few days or weeks. Infection is rare
Open	The communication between the lung and pleural space fails to seal. Air continues to transfer freely between the lung and pleural space. Usually develops following rupture of a tuberculosis cavity, an emphysematous bulla or lung abscess into the pleural space	The mean pleural pressure remains equal to atmospheric pressure; lung cannot expand. Bronchopleural fistula, spread of infection from the airways into the pleural space resulting in empyema are common
Valvular (tension)	The communication between the airway and the pleura acts as a one-way valve allowing air to enter the pleural space during inspiration but not to escape on expiration. This results in large amounts of air being trapped in the pleural space	The intrapleural pressure may become more than the atmospheric pressure. This may cause mediastinal shift towards the opposite side, compression of the opposite normal lung, impairment of systemic venous return and may result in cardiovascular compromise Rarely, in patients with splinting of the mediastinum due to scarring (e.g. sequelae of tuberculosis) or malignancy, a 'tension' pneumothorax may occur without mediastinal shift



Figures 5A and B: (A) Chest radiograph (postero-anterior view) showing a left-sided pneumothorax (white asterisk), collapsed lung border (arrow) in a patient being treated for pulmonary tuberculosis. Parenchymal infiltrates in the right upper zone (black asterisk) are also evident, (B) Chest radiograph (postero-anterior view) showing a right-sided hydropneumothorax (asterisk); collapsed lung border (thin arrows) and a horizontal fluid level (thick arrow) are also seen.

Chest radiograph helps identifying underlying pulmonary parenchymal lesions and in differentiating pneumothorax from large emphysematous bullae and cysts of the lung.

Treatment

The therapeutic approach to the management of a patient with pneumothorax is shown in **Figure 6**. Tension pneumothorax is a medical emergency and requires immediate release of tension in the pleural space using a wide-bore plastic cannula connected to a water-seal drainage system. Tube thoracostomy, appropriate antibiotic therapy and/or anti-tuberculosis treatment may be necessary.

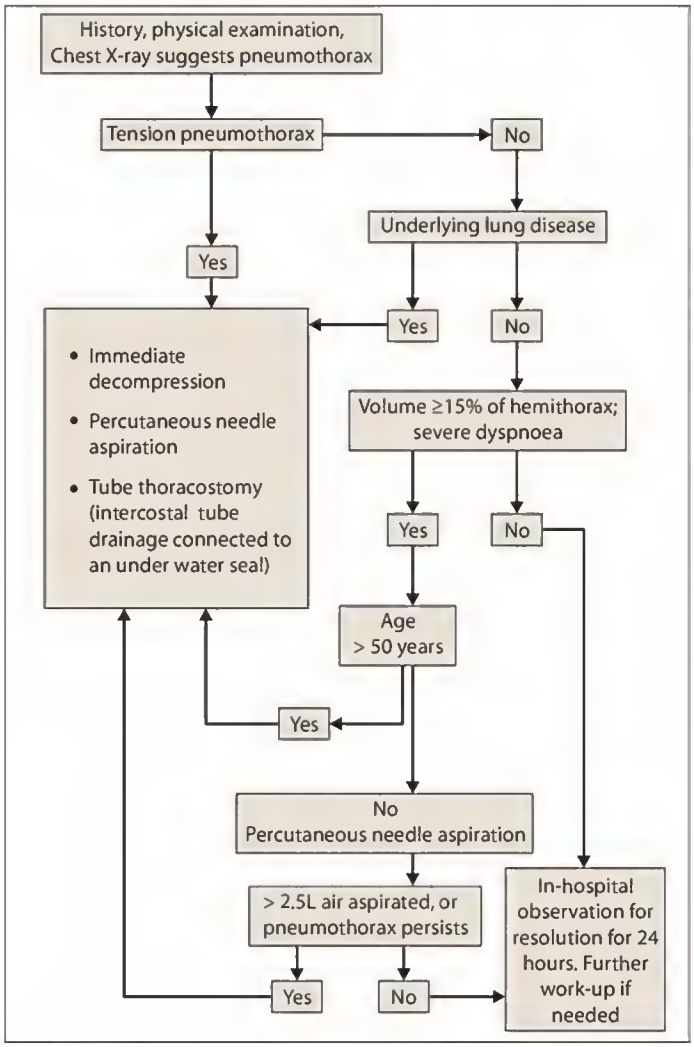


Figure 6: Algorithm for the management of a patient with pneumothorax.

Recurrent pneumothorax

Recurrent pneumothorax in individuals with a low respiratory reserve in whom further recurrence may be hazardous and in those indulging in activities such as flying or diving should be treated by surgical pleurodesis by pleural abrasion or parietal pleurectomy at thoracoscopy or thoracotomy.

TUMOURS OF THE PLEURA

Benign and malignant tumours of the pleura have been described. Metastatic tumours arising from primary tumours of the lung or breast are more common than primary pleural tumours.

Pleural Fibroma

Pleural fibroma is a benign tumour, most commonly encountered in middle-aged persons. The patients are usually asymptomatic and the tumour is incidentally diagnosed on chest radiograph taken for some other reason. Some patients may present with cough, breathlessness, chest pain and constitutional symptoms, such as fever and arthralgias. Digital clubbing and pulmonary osteoarthropathy are prominent features in some patients. Treatment is by surgical resection.

Malignant Mesothelioma

Aetiology

Asbestos exposure is strongly associated with the development of malignant mesothelioma. It occurs in the fourth or fifth decade of life; males are more frequently affected.

Clinical features

Salient clinical manifestations include chest pain, cough, fever, weight loss, anorexia and pleural effusion. Rarely, hoarseness of voice and dysphagia occur.

Diagnosis

The chest radiograph shows moderate to large unilateral pleural effusion or nodular or smooth unilateral pleural thickening. The CT of the chest may show a ring-like extension of tumour on the pleural surface. Diagnostic thoracocentesis, pleural fluid cytology, closed needle biopsy of the pleura, radiologically guided pleural biopsy may help in confirming the diagnosis. However, open biopsy at thoracoscopy or thoracotomy, electron microscopy and immunohistochemical staining may be required to distinguish malignant mesothelioma from metastatic adenocarcinoma.

Course and prognosis

The median survival time ranges between 4 months and 12 months from the time of diagnosis. Regardless of therapy, the prognosis is best for epithelial cell type. The sarcomatous cell type carries a poor prognosis; in the mixed or biphasic types, prognosis falls in between the two other types.

Treatment

Treatment includes surgical debulking (pleurectomy with decortication or extrapleural pneumonectomy) followed by chemotherapy and high-dose radiation therapy to destroy residual tumour cells.

DISEASES OF THE MEDIASTINUM

The mediastinum comprises the area between the two pleural sacs and is arbitrarily divided into anterosuperior, middle and posterior compartments (**Table 5**).

Acute Mediastinitis

Various causes of acute mediastinitis are listed in **Table 6**. Acute mediastinitis is usually secondary to spontaneous or iatrogenic perforation of a thoracic viscous (e.g. oesophagus); or after median sternotomy for cardiac surgery. Rarely, inhalational anthrax can cause primary acute mediastinitis. Patients with oesophageal rupture present with severe chest pain, breathlessness, and look acutely ill. Treatment includes parenteral antibiotic therapy, surgical exploration of the mediastinum and primary repair of the oesophageal tear, drainage of the pleural space and the mediastinum. Patients with mediastinitis following median sternotomy commonly present with wound drainage, sepsis or a widened mediastinum. Mediastinal needle aspiration confirms the diagnosis. Treatment includes parenteral antibiotics, immediate drainage, and debridement.

Table 5: Distribution of Lesions in Various Mediastinal Compartments

Mediastinal Compartment	Common Lesions	Rare Lesions
Antero-superior mediastinum The antero-superior mediastinum extends from the manubrium sterni and the first ribs to the diaphragm. Its posterior border is defined by the anterior aspect of the pericardium inferiorly and curves posteriorly to include the arch of the aorta and great vessels. This compartment encloses the ascending aorta, superior vena cava, azygous vein, thymus gland, lymph nodes, fat, connective tissue, transverse aorta and great vessels	Thymomas Lymphomas Germ cell tumours Lymph node TB	Vascular lesions Mesenchymal tumours Endocrine tumours
Middle mediastinum The middle mediastinum (visceral compartment) is bounded above by the superior pericardial reflection and below by the diaphragm. The posterior border extends to the spine. This compartment encloses the heart and pericardium, trachea and major bronchi, pulmonary vessels, lymph nodes, fat and connective tissue	Lymph node TB Foregut cysts Lymphomas	Pleural cysts Pericardial cysts Neuroenteric cysts Gastroenteric cysts Hydatid disease
Posterior mediastinum The posterior mediastinum (paravertebral compartment) extends from the superior aspect of the first thoracic vertebral body to the diaphragm anteriorly and then posteriorly to the posteriormost curvature of the ribs. It encloses the sympathetic chain, vagus nerves, oesophagus, thoracic duct, various lymph nodes and the descending aorta	Neurogenic tumours	Vascular lesions Mesenchymal lesions Lymphatic lesions

Table 6: Causes of Acute Mediastinitis

Oesophageal perforation
Instrumental (e.g. oesophagoscopy, sclerotherapy) Forceful vomiting (Boerhaave's syndrome)
Trauma
Foreign body
Operative injury
Caustic ingestion
Cancer
Tracheobronchial perforation
Direct extension of infection from retropharyngeal space; odontogenic infection (descending necrotising mediastinitis), pancreatitis, lung, pleura, pericardium, lymph node, paraspinal abscess
Post-sternotomy mediastinitis
Anthrax mediastinitis

Granulomaotus Mediastinitis and Mediastinal Fibrosis

Diseases such as TB, sarcoidosis, silicosis, histoplasmosis, and several other fungal diseases can cause granulomatous mediastinitis. Several conditions, such as drugs (e.g. methysergide), silicosis, multisystem fibrosing disorder, radiation, among others can cause fibrosing mediastinitis. These patients present with signs of compression of some of the mediastinal structures, like superior vena cava syndrome, tracheobronchial obstruction, compression of pulmonary vessels, or nerves.

Pneumomediastinum

Presence of air in the interstices of the mediastinum is termed pneumomediastinum or mediastinal emphysema. Pneumomediastinum commonly results from microscopic alveolar rupture but can also be caused by air escaping from the upper respiratory tract, intrathoracic airways or gastrointestinal tract. Gas producing bacterial infection of the visceral space, outside air reaching the mediastinum following trauma or surgery are other mechanisms. Patients present with sudden severe pain in the substernal region and breathlessness. Subcutaneous emphysema in the suprasternal notch and a crunching or clicking noise synchronous with the heartbeat and best heard in the left lateral decubitus position (*Hamman's sign)* can be heard. The chest radiograph shows air in the mediastinum parallel to the heart and aorta. Treatment of the underlying disorder may provide relief from symptoms. Rarely, needle aspiration or surgical incision may be required to relieve mediastinal compression.

Mediastinal Cysts and Tumours

Mediastinal tumours (**Table 5**), (**Figures 7A to D**), when small, are asymptomatic and may be detected as an incidental finding on the chest radiograph. Patients may present with manifestations due to compression of various mediastinal structures by the mass. These include dyspnoea, cough, stridor, wheezing, haemoptysis, obstructive pneumonia and the middle lobe syndrome (compression of the trachea and the major bronchi); distended, non-pulsatile neck veins, oedema and cyanosis of face, neck and arms (*superior vena cava syndrome*); hoarseness of voice, bovine cough (left recurrent laryngeal nerve); diaphragm paralysis (phrenic nerve); dysphagia (oesophagus) and Horner's syndrome (sympathetic trunk). Patients of intrathoracic lymph node TB or lymphoma may present with systemic manifestations such as fever, weight loss and toxaemia. Chest CT is helpful in localising these lesions. Transthoracic needle biopsy, VATS or media-stinoscopy and biopsy help in confirming the diagnosis.

Thymic tumours

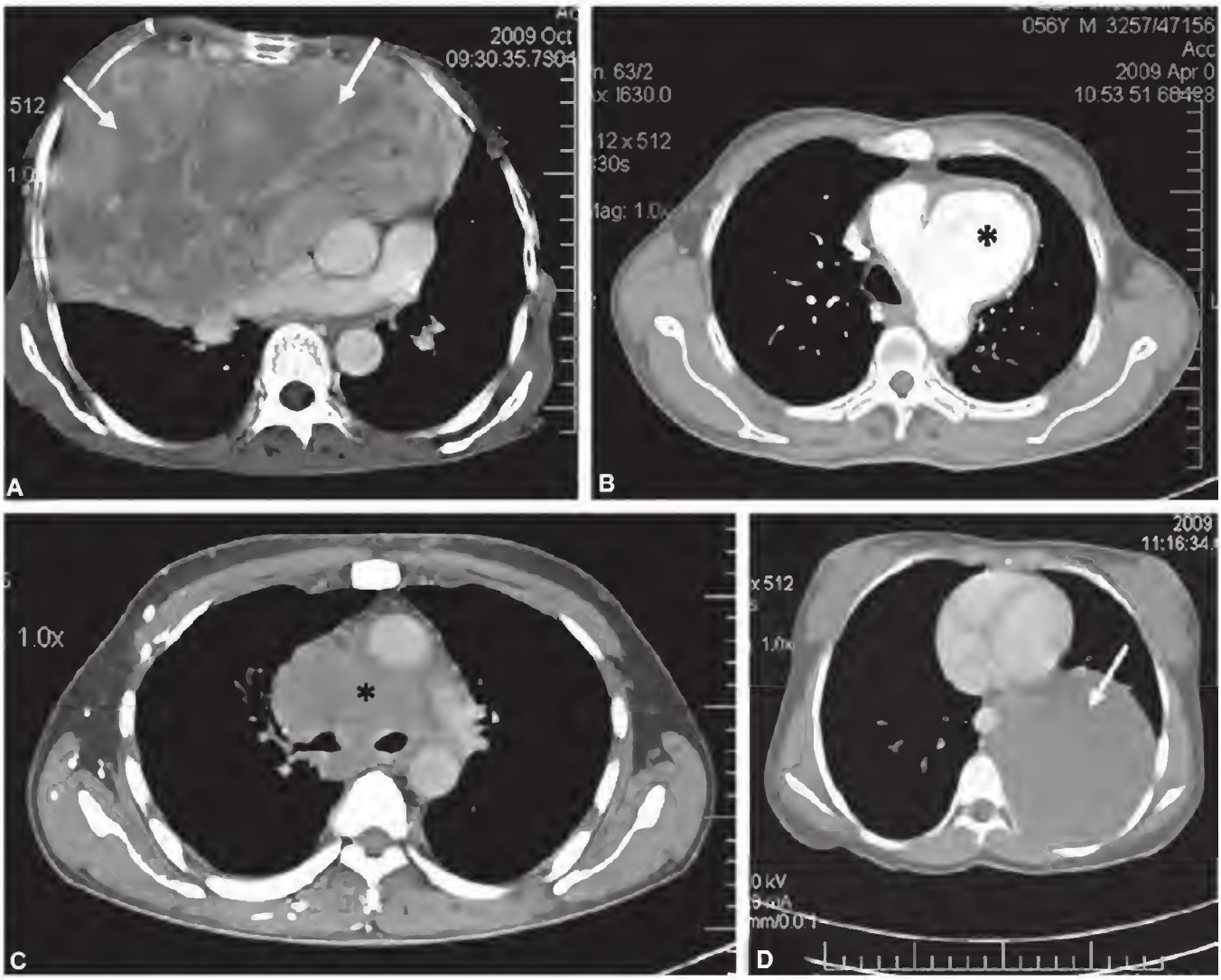
Thymoma is a common anterior mediastinal tumour and is frequently associated with *Myasthenia gravis* and pure red cell aplasia. Surgical resection is indicated as malignant thymomas are difficult to diagnose clinically.

Thyroid lesions

Mediastinal thyroid lesions include a cervical goitre, extending retrosternally into the anterior mediastinum and rarely, primary intrathoracic goitre. The lesion can be recognised by radioactive iodine scanning. Treatment is by resection.

Germ cell tumours

Germ cell tumours include teratoma and teratocarcinoma, seminoma, embryonal cell carcinoma and choriocarcinoma.



Figures 7A to D: (A) Contrast-enhanced CT chest (arrows) showing anterior mediastinal mass, (B) (asterisk) aortic aneurysm mimicking a middle mediastinal mass, (C) (asterisk) middle mediastinal lymph node mass, and (D) (arrow) a posterior mediastinal mass.

Teratomas, the most common germ cell tumours, are common in the anterior mediastinum. In teratomas, structures originating from all three germ cell layers may be found; ectodermal derivatives predominate. When only the epidermis and its derivatives are present, the lesion is termed dermoid cyst. Usually, they do not produce symptoms. Patients become symptomatic when infection sets in or malignant transformation occurs. Calcification is common and teeth may be identified. Chest CT is useful in delineating these lesions. Rarely, mediastinal seminoma and teratoma may be metastatic.

Neurogenic tumours

Neurogenic tumours are located mainly in posterior mediastinum. These tumours appear as dense, round or oval, radio-opaque densities occupying the paravertebral gutter on the chest radiograph. Many neurogenic tumours may be hormonally active.

Others

Rarely developmental cysts, such as, bronchogenic, pericardial or enteric cysts, hydatid cysts, primary carcinoma of the mediastinum, extra-medullary haematopoiesis in patients with chronic haemolytic anaemia can present as mediastinal tumours.

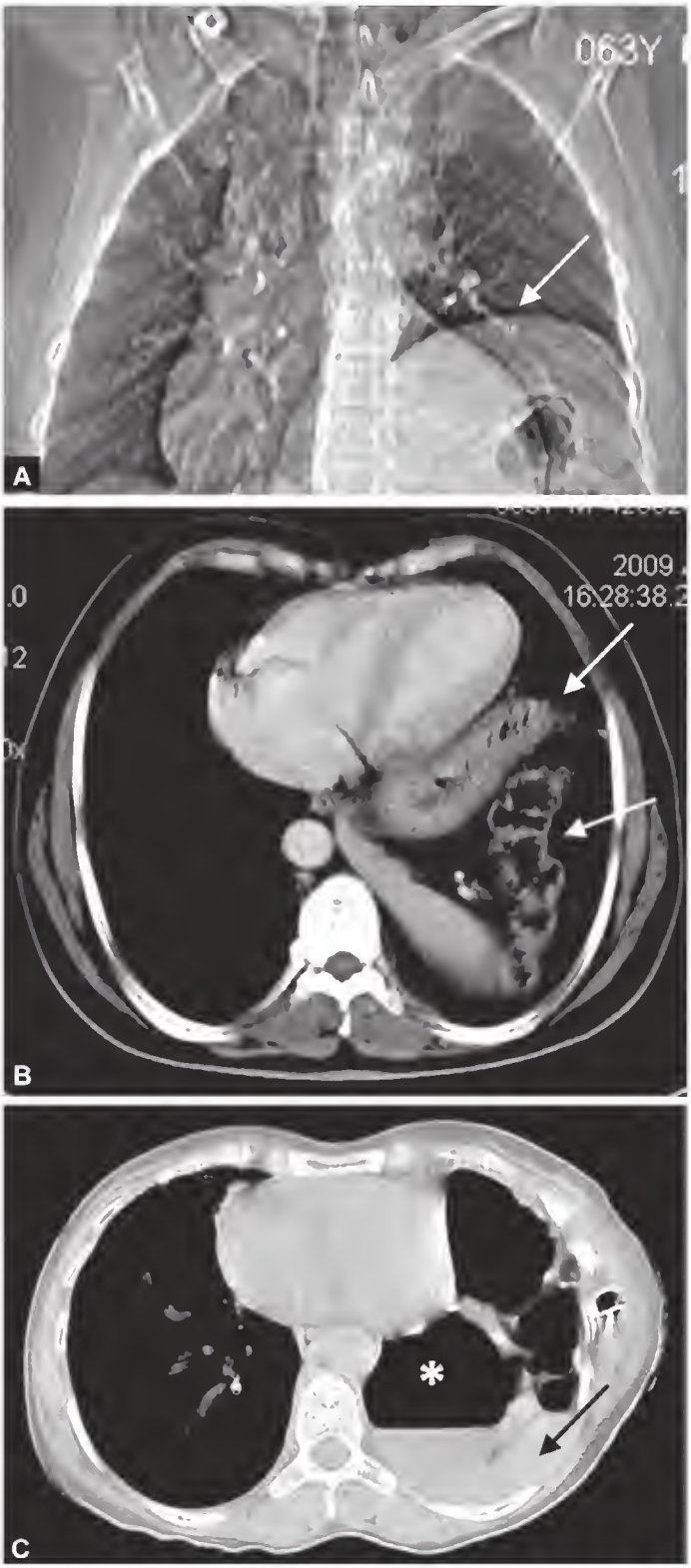
DISORDERS OF THE DIAPHRAGM

The diaphragm is the major muscle of respiration which separates the thoracic and abdominal cavities. Anatomical and neurological disorders affecting it render the diaphragm ineffective in providing adequate intrathoracic pressure resulting in a decrease in the amount of oxygen provided to the alveoli.

Anatomical Disorders

These can be congenital or acquired and result in diaphragmatic hernia. Bochdalek hernia results from herniation through a defect in the posterolaterally located Bochdalek foramen. Herniation thorough the foramen of Morgagni in the anterior midline through the sternocostal hiatus of the diaphragm is less common. Neonates with these conditions present with respiratory distress and need urgent surgical repair. In hiatus hernia, the abdominal contents herniate through the oesophageal hiatus. In sliding hiatus hernia, the gastro-oesophageal junction moves above the diaphragm together with part of the stomach. In rolling or para-oesophageal hiatus hernia, a part of the stomach herniates through the oesophageal hiatus and lies beside the oesophagus, without displacement of the gastro-oesophageal junction.

Eventration of diaphragm (**Figures 8A to C**) develops as a result of congenital or acquired decrease in muscle mass and increase in fibrous tissue and results in elevation of one hemidiaphragm (**Table 7**). Usually, most patients are asymptomatic and no treatment is required for this condition. Traumatic diaphragmatic rupture can occur due to both penetrating and blunt trauma and requires surgical intervention.



Figures 8A to C: (A) Contrast-enhanced CT chest topogram (arrow) and (B) transverse CT showing eventration of diaphragm (arrows), (C) Contrast-enhanced CT chest of another patient showing diaphragmatic hernia on the left side and the migration of stomach (arrow) and spleen (asterisk) into the left side of the thorax.

Table 7: Causes that Result in Elevation of the Diaphragm

Causes of elevation of one hemidiaphragm
Thoracic causes
Phrenic nerve palsy
Splinting of diaphragm (e.g. fractured rib, pneumonia, pleurisy)
Sub-pulmonic effusion
Post-operative (lobectomy, pneumonectomy)
Abdominal causes
Tumours, cysts and other causes of hepatomegaly
Amoebic liver abscess
Subphrenic abscess
Distended stomach
Interposition of colon between liver and right hemidiaphragm (*Chilaiditi syndrome*)
Elevation of both domes of diaphragm
Increased intra-abdominal pressure (e.g. obesity, ascites, pregnancy, abdominal tumours)
Spinal cord injury
Neuromuscular disorders

Disorders of Innervation

The transmission of respiratory stimulus from the brain to the diaphragm via the phrenic nerve can be interrupted by traumatic injury or disease processes, e.g. malignancy, spinal cord disorders, syringomyelia, poliomyelitis and motor neuron disease. Most patients with unilateral diaphragmatic paralysis remain asymptomatic. Bilateral diaphragmatic paralysis can present with severe exertional dyspnoea and marked orthopnea.

Evidence of paradoxical movement on performing the sniff test and observing the diaphragmatic movement on fluoroscopy or ultrasonography is a helpful manouevre in evaluating diaphragmatic paralysis and differentiating it from eventration of diaphragm.

DISORDERS OF THE CHEST WALL

The chest wall is a critical component of the respiratory pump and comprises of the bony structures (ribs, spine), respiratory muscles and nerves connecting the central nervous system with the respiratory muscles.

Several congenital abnormalities, such as pectus excavatum (funnel chest), *pectus carinatum* (pigeon chest) and *Poland's syndrome* (aplasia or hypoplasia of the sternocostal portion of the pectoralis major muscle, syndactyly), *Jeune's syndrome* (asphyxiating thoracic dystrophy) can impair chest wall function. In rickets, widening of the costochondral junctions (rachitic or rickety rosary), horizontal depression along the lower anterior chest (Harrison sulcus) due to pulling of the softened ribs by the diaphragm during inspiration may be seen. In scurvy, the sternum is depressed and scorbutic rosary can be seen. While rickety rosary is knobby and nodular, scorbutic rosary is more angular and has a step-off at the costochondral junction.

Chest wall cold abscess and sinuses can occur due to TB, thoracic actinomycosis. When an empyema goes undetected over a long period of time, it erodes through the chest wall, forms a subcutaneous abscess and spontaneously drains

on to the surface of the body and may present as a chest wall swelling with an expansile cough impulse (empyema necessitans).

Conditions causing kyphosis (spinal deformity with antero-posterior angulation) and scoliosis (lateral displacement or curvature of the spine) can result in severe rib distortion affecting the respiratory function. Fibrothorax as a result of underlying pleural or pulmonary disease also presents with the physiologic manifestations similar to those seen in chest wall disorders. Chest trauma can result in flail chest, usually due to sequential double rib fractures in more than one site or fracture of ribs and the sternum. Because of the rib fractures, there is uncoupling of a part of the chest wall from the rib cage resulting in paradoxical motion.

In ankylosing spondylitis, the anterior chest wall can be affected by enthesitis (inflammation of the muscular or tendinous attachments to bone) of the manubriosternal symphysis and sternoclavicular joints. Fixation of the chest wall through fusion of the costovertebral joints can also develop.

Chest wall tumours can present as a palpable mass with or without pain and systemic symptoms. Large tumours of the chest wall (**Figure 9**) can result in pulmonary restriction. Surgical excision is usually required.



Figure 9: Contrast enhanced CT chest of a patient showing a chest wall tumour (arrows) on the right side.

ACKNOWLEDGEMENT

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23.18 Atelectasis and Pulmonary Fibrosis

Rupak Singla

ATELECTASIS

The term atelectasis is derived from the Greek words *ateles* and *ektasis*, which mean incomplete expansion. Atelectasis is defined as diminished volume affecting all or part of a lung. Several types of atelectasis exist; each has a characteristic radiographic pattern and aetiology.

Classification and Pathophysiology

Atelectasis is divided physiologically into (a) obstructive and (b) non-obstructive.

Obstructive Atelectasis

Obstructive atelectasis, also known as resorptive atelectasis, is the most common type. It results from reabsorption of gas from the alveoli when communication between the alveoli and the airway is obstructed. The obstruction can occur at the bronchial or bronchiolar level. The most important condition producing intrinsic bronchial obstruction is bronchogenic carcinoma (**Table 1**). Other causes of bronchial obstruction include other primary lung and metastatic neoplasms, inflammatory aetiologies (especially tuberculous or fungal infection), aspirated foreign bodies, mucous plugging, a malpositioned endotracheal tube and extrinsic compression of an airway by neoplasm, lymphadenopathy, aortic aneurysm or cardiac enlargement.

Some conditions may decrease deep breathing or suppresses a person's ability to cough, such as large doses of opioids or sedatives, general anesthesia, chest or abdominal surgery, certain neurologic conditions, chest deformities, abdominal swelling, immobility of the body and some tight bandages. Such conditions can cause or contribute to atelectasis because of pooling of secretions, mucous or blood in bronchi. People who smoke or who have lung disorders (e.g. chronic obstructive pulmonary disease, cystic fibrosis) have a greater risk of developing atelectasis.

Following obstruction of a bronchus, the circulating blood absorbs the gas in the peripheral alveoli, leading to retraction of the lung and an airless state within a few hours. In the early stages, blood perfuses the airless lung; this results in ventilation-perfusion mismatch and arterial hypoxaemia. Filling of the alveolar spaces with secretions and cells may occur, thereby preventing complete collapse of the atelectatic lung. With passage of time, the uninvolved surrounding lung tissue distends, displacing the surrounding structures. The heart and mediastinum shift toward the atelectatic area, the diaphragm is elevated and the chest wall flattens.

The rate at which atelectasis develops and the extent of atelectasis depend on several factors. These include the extent of collateral ventilation that is present and the composition of inspired gas. The collateral ventilation is provided by the pores of Kohn and the canals of Lambert. The obstruction may lead to superadded infection in the atelectatic lung. If the obstruction is removed, any complicating post-obstructive infection subsides and the lung returns to its normal state. If the obstruction is persistent and infection continues to be present, fibrosis develops and the lung may become bronchiectatic.

Table 1: Causes of Atelectasis

- **Causes of obstructive atelectasis**
  - Causes within bronchial lumen
    - Neoplasm
      - Benign (adenoma)
      - Malignant (carcinoma bronchus, lymphoma, metastatic breast, thyroid, melanoma, sarcoma, seminoma, renal cell carcinoma, osteosarcoma, chondrosarcoma)
      - Alveolar cell carcinoma
    - Inflammatory aetiology (e.g. tuberculosis, fungal infection)
    - Aspirated foreign body
    - Mucous plug
    - Malpositioned endotracheal tube
  - Causes in the bronchial wall
    - Stricture or Stenosis
  - Causes outside the brochus
    - Neoplasm
    - Lymphadenopathy (hilar/mediastinal)
    - Aortic aneurysm or
  - Cardiac enlargement
- **Causes of non-obstructive atelectasis**
  - Relaxation atelectasis
    - Pleural effusion
    - Pneumothorax
    - Large emphysematous bullae
  - Compression atelectasis
    - Chest wall, pleural, or intraparenchymal masses
    - Loculated collections of pleural fluid
  - Adhesive atelectasis
    - Hyaline membrane disease
    - Acute respiratory distress syndrome
    - Smoke inhalation
    - Cardiac bypass surgery
    - Uraemia
    - Prolonged shallow breathing
  - Cicatrisation atelectasis
    - Idiopathic pulmonary fibrosis
    - Sarcoidosis
    - Pneumoconiosis
    - Collagen vascular diseases
    - Chronic tuberculous and fungal infections
    - Radiation fibrosis
  - Replacement atelectasis
    - Bronchoalveolar cell carcinoma

Non-Obstructive Atelectasis

Non-obstructive atelectasis can be caused by loss of contact between the parietal and visceral pleurae, compression, loss of surfactant and replacement of parenchymal tissue by scarring or infiltrative disease (**Table 1**). Subtypes of non-obstructive atelectasis are described below:

Relaxation or passive atelectasis

This results when a pleural effusion or a pneumothorax eliminates contact between the parietal and visceral pleurae. Generally, the uniform elasticity of a normal lung leads to preservation of shape even when volume is decreased. The different lobes also function differently, e.g. the middle and lower lobes collapse more than the upper lobe in the presence of pleural effusion, while the upper lobe may be affected more by pneumothorax.

Compression atelectasis

This occurs from any space-occupying lesion of the thorax compressing the lung and forcing air out of the alveoli. Such space-occupying lesions include pleural tumours, large pulmonary parenchymal masses, large emphysematous bullae and lobar emphysema. The mechanism is similar to relaxation atelectasis.

Adhesive atelectasis

This results from surfactant deficiency. The surfactant has phospholipid dipalmitoyl phosphatidyl-choline, which prevents lung collapse by reducing the surface tension of the alveoli. Lack of production or inactivation of surfactant, which may occur in adult respiratory distress syndrome (ARDS), radiation pneumonitis, or blunt trauma to the lung, causes alveolar instability and collapse leading to adhesive atelectasis.

Cicatrisation atelectasis

This results from diminution of volume as sequelae of severe parenchymal scarring. A number of conditions can result in pulmonary fibrosis and cicatrisation atelectasis, such as idiopathic pulmonary fibrosis, sarcoidosis, pneumoconiosis, collagen vascular diseases, chronic tuberculous and fungal infections, and radiation fibrosis.

Replacement atelectasis

This occurs when the alveoli of an entire lobe are filled by tumour (e.g. bronchioalveolar cell carcinoma) resulting in loss of volume.

Other Types of Atelectasis

Several other types of atelectasis observed in clinical practice are described below:

Right middle lobe syndrome

This is a disorder of recurrent or fixed atelectasis involving the right middle lobe and/or lingula. The right middle lobe, due to its anatomical separation from the upper and lower lobes and poor collateral channels of ventilation, collapses more frequently and rarely re-expands (Brock's syndrome). It can result from either extraluminal (bronchial compression by surrounding lymph nodes) or by intraluminal bronchial obstruction. It may develop in the presence of a patent lobar bronchus without identifiable obstruction. Inflammatory processes and defects in the bronchial anatomy and collateral ventilation have been designated as the non-obstructive causes of middle lobe syndrome.

Rounded atelectasis

This represents folded atelectatic lung tissue with fibrous bands and adhesions to the visceral pleura. Incidence is high in asbestos workers (65% to 70% of cases), most likely due to a high degree of pleural disease. The mean age at presentation is 60 years and the affected patients are typically asymptomatic.

Platelet atelectasis

This also called discoid or subsegmental atelectasis, this type is seen most commonly on chest radiographs. It probably occurs because of obstruction of a small bronchus and is observed in states of hypoventilation, pulmonary embolism or lower respiratory tract infection. Small areas of atelectasis occur because of inadequate regional ventilation and abnormalities in surfactant formation from hypoxia, ischaemia, hyperoxia and exposure to various toxins. A mild-to-severe gas exchange abnormality may occur because of ventilation-perfusion mismatch and intra-pulmonary shunt.

Post-operative atelectasis

This is a common pulmonary complication in patients following thoracic and upper abdominal procedures. General anaesthesia and surgical manipulation lead to atelectasis by causing diaphragmatic dysfunction and diminished surfactant activity. The atelectasis is typically basilar and segmental in distribution.

EPIDEMIOLOGY OF ATELECTASIS

The incidence and prevalence of atelectasis are not well documented. However, in India, cicatrisation atelectasis following tuberculosis (TB) is extremely common.

Age

The age at presentation depends upon the underlying cause. The mean age at presentation for rounded atelectasis is 60 years.

Sex

Atelectasis has no sex predilection.

Race

Atelectasis has no racial predilection.

Mortality/morbidity

Patient mortality depends on the underlying cause of atelectasis. In post-operative atelectasis, the condition generally improves. The prognosis of lobar atelectasis secondary to endobronchial obstruction depends on the treatment of the underlying malignancy.

CLINICAL PRESENTATION OF ATELECTASIS

Most symptoms and signs of atelectasis are determined by the rapidity with which the bronchial occlusion occurs, the size of the lung area affected, and the presence or absence of complicating infection. Rapid bronchial occlusion with large area of lung collapse causes pain on the affected side, sudden onset of dyspnoea, and cyanosis. Hypotension, tachycardia, fever and shock may also occur.

Slowly developing atelectasis may be asymptomatic or may cause only minor symptoms. Middle lobe syndrome often is asymptomatic, although irritation in the right middle and right lower lobe bronchi may cause a severe, hacking, non-productive cough.

PHYSICAL EXAMINATION OF ATELECTASIS

The physical examination findings show dullness to percussion over the involved area and diminished or absent breath sounds. Chest excursion in the area is reduced or absent. The trachea and the heart are deviated toward the affected side. A monophonic or fixed rhonchus may also be heard over obstructed atelectasis. In upper lobe collapse, these signs may be absent. In cases of post-obstructive pneumonitis, clinical findings of signs of volume loss with a dull note on percussion, tubular bronchial breath sounds, bronchophony, with coarse crepitations may be observed.

INVESTIGATIONS OF ATELECTASIS

Imaging Studies

Chest radiograph

Radiography is the initial investigation for suspected lung atelectasis. Chest radiographs show direct and indirect signs of lobar collapse. These have been described in **Table 2**.

Table 2: Radiographic Signs of Atelectasis

Direct Signs	
	Displacement of septa/fissure
	Loss of aeration leading to radio-opacity
	Crowding of bronchial and vascular markings
Indirect Signs	
	Elevation of hemidiaphragm
	Shift of trachea or mediastinum
	Narrowing of rib cage
	Over inflation of remaining lung
	Shift of hilum

Atelectasis of each segment or lobe of the lung results in a particular pattern of blurring of the normal boundaries (Silhouette sign) of mediastinal structures.

Upper lobe atelectasis may obliterate the superior mediastinal border. The collapsed right upper lobe shifts medially and superiorly, resulting in elevation of the right hilum and the minor fissure (**Figure 1**). Rarely, the right upper lobe may collapse laterally, producing a mass like opacity that may look like a loculated pleural effusion. The minor fissure in right upper lobe collapse is usually convex superiorly but may appear concave because of an underlying mass lesion. This is called the sign of 'Golden S'.



Figure 1: Chest radiograph (PA view) showing collapsed right upper lobe shifting medially and superiorly, resulting in elevation of the right hilum.

Middle lobe collapse obscures the right heart border (positive Silhouette sign) on a postero-anterior (PA) film (**Figure 2**). On lordotic view, a triangular opacity may be observed (**Figure 3**). The lateral view shows a triangular opacity overlying the heart because the major fissure shifts upward and the minor fissure shifts downward (**Figure 4**). On computed tomography, the atelectatic right middle lobe appears as a triangular opacity against the right heart border with the apex pointing laterally and is termed the 'tilted ice cream cone sign'.

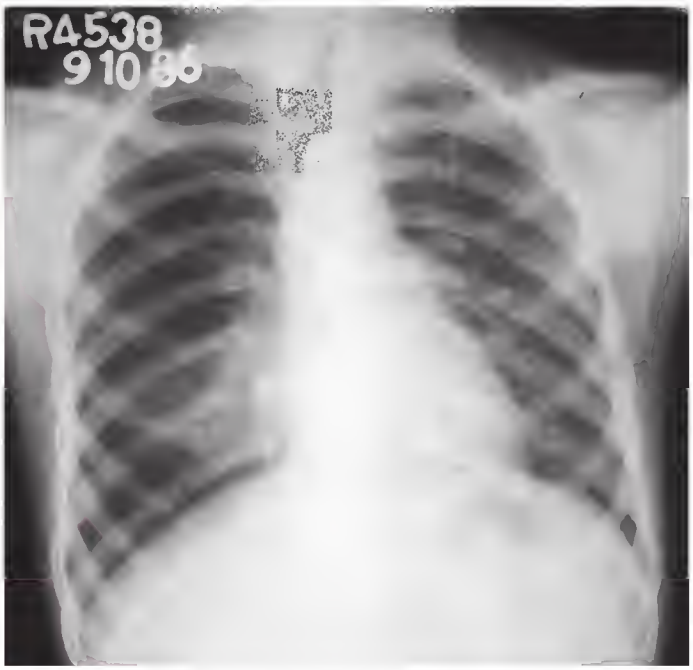


Figure 2: Chest radiograph (PA view) showing right middle lobe collapse obscuring the right heart border (positive Silhouette sign).



Figure 3: Chest radiograph (lordotic view) showing the right paracardiac triangular shadow suggestive of the right middle lobe atelectasis.

Lower lobe atelectasis does not obliterate the cardiac borders, and causes a retro-cardiac triangular opacity (**Figure 5**). On frontal views, the hilum shifts downward, and the rotation of the heart produces flattening of the cardiac waist, which is known as the



Figure 4: Chest radiograph (lateral view) showing a triangular opacity of right middle lobe atelectasis overlying the heart because the major fissure shifting upward and the minor fissure shifting downward.



Figure 5: Chest radiograph (PA view) showing the left lower lobe atelectasis seen as retro-cardiac triangular opacity.

flat-waist sign. On lateral radiographs, opacity makes the posterior third of the left diaphragm indistinct. A CT shows the atelectatic lower lobe in the inferior posterior location.

Complete atelectasis of a lung leads to opacification of the entire hemithorax and an ipsilateral shift of the mediastinum (**Figure 6**). In case of intraluminal growth, there may be sudden cut-off of air in the bronchus called 'bronchial cut-off sign' (**Figure 7**). The mediastinal shift separates atelectasis from massive pleural effusion.



Figure 6: Chest radiograph (PA view) showing complete atelectasis of the left lung leading to opacification of the entire hemithorax and an ipsilateral shift of the mediastinum.



Figure 7: Chest radiograph (PA view) showing sudden cut-off of air in the right main bronchus called 'bronchial cut-off sign'.

Computed tomography (CT)

CT is useful in evaluating the mediastinum, chest wall, hilum, pleura and adjacent lung. CT is also very sensitive for detecting the site of obstruction and whether a neoplasm is responsible for the same. In compressive atelectasis, air-bronchogram is present but not in obstructive atelectasis. CT may also be useful to

demonstrate associated bronchiectasis in chronic atelectasis. With the advent of spiral CT and three-dimensional reconstructions, virtual, three-dimensional images can be obtained and virtual bronchoscopy has become possible.

Magnetic resonance imaging (MRI): In some patients, MRI can provide comparable and/or complementary information.

Other imaging tests: In recent years, B-mode sonographic patterns as well as colour Doppler sonographic patterns of atelectasis have been reviewed. In addition, contrast-enhanced sonography (CES) allows differentiation between compression atelectasis and obstructive atelectasis by different patterns of enhancement.

Laboratory Studies

1. Pulmonary function testing in atelectasis of the lung usually shows a restrictive pattern. In some cases with associated bronchiectasis, a combined obstructive and restrictive pattern may be obtained.
2. On arterial blood gas analysis, atelectasis of a significant size may show hypoxaemia. However, despite hypoxaemia the $PaCO_2$ level is usually normal or low as a result of the increased ventilation.

Flexible Fiber-Optic Bronchoscopy

Flexible fiber-optic bronchoscopy (FOB) can be a useful diagnostic and therapeutic procedure.

1. Bronchoscopy helps in evaluating the cause of bronchial obstruction. In addition, bronchoscopy helps in clearing mucous plugs when they cause bronchial obstruction.
2. Bronchoscopy has its limitations. Because only the sub segmental bronchi are visualised, a distal end bronchial lesion is not accessible through bronchoscope.
3. In an evaluation of middle lobe syndrome, bronchoscope may show an endobronchial aetiology (mucus plugging/broncholithiasis/tumour), although the non-obstructive causes of the syndrome, such as inflammatory processes and defects in the bronchial anatomy and collateral ventilation may be missed.
4. During FOB, the washing, brushing and biopsy specimens of any obstructing mass should be examined for evidence of malignancy.

Complications of Atelectasis

Patients with atelectasis of lobe or segment of lung may have following complications:

1. Acute pneumonia
2. Bronchiectasis
3. Hypoxaemia and respiratory failure
4. Post-obstructive drowning of the lung
5. Sepsis
6. Pleural effusion and empyema

MANAGEMENT OF ATELECTASIS

Medical Care

The treatment of atelectasis depends on the underlying aetiology. Treatment of acute atelectasis, including post-operative lung collapse, requires removal of the underlying cause. In patients with pleural effusion, the pleural aspiration should be done and investigated for biochemistry and cytological examination. Tuberculosis should be treated with anti-tubercular drugs. In pneumothorax, intercostal tube drainage results in expansion of the lung. Immediate repositioning of the endotracheal tube will result in re-expansion of the lung in cases with inadvertent endotracheal tube of the right main bronchus. Large emphysematous bullae might require surgical resection. Chest physiotherapy and FOB might be helpful in patients with mucous plugging of the airways.

If a foreign body is suspected to be the cause for obstructive atelectasis, therapeutic bronchoscopy for its removal is indicated. In case of endobronchial tumour, the obstruction can be relieved by surgery, radiation or chemotherapy. In selected patients, laser therapy or airway stenting may be considered.

Non-pharmacologic therapies for improving cough and clearance of secretions from the airways include chest physiotherapy, including postural drainage, chest wall percussion and vibration, and a forced expiration technique (called huffing).

For post-operative atelectasis, prevention is the best approach by a good perioperative care. Anaesthetic agents associated with postanaesthesia narcosis should be avoided; narcotics should be used sparingly because they depress the cough reflex. Early ambulation and use of incentive spirometry are important. Encourage the patient to cough and to breathe deeply. Post-operative atelectasis is treated with adequate oxygenation and if required, by intubation and mechanical ventilatory support. When these efforts are not successful within 24 hours, flexible FOB should be performed.

In patients with chronic atelectasis, associated fibrosis, destruction and bronchiectasis can result in infection and haemoptysis. This can be prevented by regular chest physiotherapy and postural drainage, vaccines and antibiotics.

Surgical care

Chronic atelectasis with symptoms such as recurrent infections or significant haemoptysis is treated with segmental resection or lobectomy.

PULMONARY FIBROSIS

Pulmonary fibrosis describes the clinical end-point of a multiplicity of diverse pathological processes, ranging from infection to autoimmune diseases, most of which are of unknown aetiology but have characteristic features that allow them to be classified as distinct disease entities (**Table 3**).

Clinical Presentation of Pulmonary Fibrosis

Symptoms

By far, the most common presenting complaint of a patient of pulmonary fibrosis is dyspnoea. Depending upon the underlying cause, it may be acute, as in infections, extrinsic allergic alveolitis; sub-acute as in *Pneumocystis carinii* pneumonia associated with human immunodeficiency virus (HIV); or chronic as in asbestosis, pulmonary sarcoidosis. Cough is a fairly common symptom, and a very non-specific initial finding. Cough can be disabling, particularly in idiopathic pulmonary fibrosis (IPF) and diseases that primarily affect airways, such as bronchiolitis, cryptogenic organising pneumonia and sarcoidosis, in which cases it is also associated with expectoration. Other less common symptoms include chest pain and haemoptysis.

Table 3: Causes of Pulmonary Fibrosis

Post-infections	Drug-induced	Toxins/Poisons/ Organic Dusts	Occupational and Environmental
Post-TB Post-viral mycoplasma Human immunodeficiency virus-related	Nitrofurantoin, Bleomycin, Sulfasalazine, Beta-blockers, Gold, Penicillamine, Amiodarone, Busulfan, Methotrexate, Bromocriptine, Carmustine, Cyclophosphamide, Ergots, Nitrosoureas	Oxygen, Chlorine, Fluorine, Nitrogen dioxide, Paraquat radiation-induced, Fungal spores Animal proteins	Asbestosis Silicosis/Berylliosis Progressive massive fibrosis
Collagen Vascular Diseases	**Vasculitides**	**Inherited Causes**	**Idiopathic Causes**
Rheumatoid arthritis, Systemic lupus erythematosus Sjögren's syndrome Systemic sclerosis	Churg-Strauss syndrome Polyarteritis Nodosa Wegener's granulomatosis	Tuberous sclerosis Neurofibromatosis Ankylosing spondylitis Familial pulmonary fibrosis	Idiopathic pulmonary fibrosis Sarcoidosis Langerhan's cell histiocytosis Lymphangioleiomyomatosis, Amyloidosis Hemosiderosis

Table 4: Radiographic Pattern of Distribution of Pulmonary Opacities in Pulmonary Fibrosis

Upper Zones	Mid Zones	Lower Zones	Generalised
Pulmonary Koch's Sarcoidosis Langerhan's cell histiocytosis Silicosis Progressive massive fibrosis Extrinsic allergic alveolitis	Pulmonary oedema Alveolar proteinosis *Pneumocystis jirovecii* infection	Idiopathic pulmonary fibrosis Asbestosis Collagen vascular diseases Tropical pulmonary eosinophilia Rheumatoid lung disease Primary Sjögren's syndrome	Miliary tuberculosis, cystic fibrosis, metastases, acute respiratory distress syndrome, drug reactions, microlithiasis, lymphangitis carcinomatosis

Signs

Most common findings are crackles. These are usually inspiratory, and occur not only in most patients of pulmonary fibrosis associated with idiopathic pulmonary fibrosis, but also in many other interstitial lung diseases. The crackles are usually audible at the lung bases initially. Gradually, as the disease progresses, crackles extend upto the lung apices. In bronchiectasis, crackles may be inspiratory as well as expiratory.

Radiological Features

Tables 4 and 5 summarise the radiological features of pulmonary fibrosis.

Table 5: High Resolution Computed Tomography (HRCT) Features of Pulmonary Fibrosis

Cystic Disease	Honey-combing	Ground-glass Opacities
Langerhan's cell histiocytosis Lymphangio-leiomyomatosis	Asbestosis Collagen vascular diseases Chronic hypersensitivity Pneumonitis Sarcoidosis Idiopathic pulmonary fibrosis (IPF) End-stage acute respiratory distress syndrome	IPF Alveolar proteinosis Radiation pneumonitis Sarcoidosis

Complications of Pulmonary Fibrosis

Pulmonary fibrosis leads to the development of hypoxia, which in turn produces pulmonary arterial hypertension and right-sided heart failure. Supplemental oxygen therapy may prove beneficial.

Treatment of Pulmonary Fibrosis

As stated earlier, pulmonary fibrosis is an end-stage process and optimal therapy is an area of intense research. Supportive care, physiotherapy, and pulmonary rehabilitation are essentially required for all the patients. Supplemental oxygen inhalation may prove helpful for hypoxaemic individuals. Preventive strategies like vaccination with influenza and pneumococcal vaccines are useful to combat infection with these pathogens and should not be overlooked. Adequate counselling of patients regarding avoidance of exposure to likely offending drugs, toxins, occupational or environmental agents also form an important part of the treatment of pulmonary fibrosis. Corticosteroids and immunosuppressive therapy may be useful in relevant situations. Lung transplantation can be considered in end-stage fibrosis with an unfavourable prognosis.

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23.19 Benign and Malignant Tracheobronchial Tumours

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INTRODUCTION

Lung cancer is the most common cancer globally. During the past two decades, better understanding of the biology, use of systemic chemotherapy and development of biologic therapy for non-small cell lung cancer (NSCLC) has led to modest improvement in the quality of life and overall survival. Currently, adjuvant chemotherapy (4 cycles of platinum-based combination) is considered standard in completely resected NSCLC stage II and IIIA. Role of chemotherapy in resected stage IB NSCLC is not clear at present. Post-operative radiotherapy (PORT) is not indicated for stage I or II NSCLC, and remains controversial in resected stage IIIA (N2) disease. For advanced NSCLC, cisplatin-based doublets (two drugs) combination is preferred in patients with good performance status (ECOG,0- 1), whereas carboplatin-based combinations are preferred in patients with impaired organ functions (kidney, heart). Non-platinum cytotoxic doublets are acceptable for patients with contraindications to platinum therapy. Patients who fail to primary therapy benefit with docetaxel or pemetrexate or erlotinib. A small subset of patients with advanced NSCLC benefit with EGFR inhibitors—tyrosine kinase inhibitors, e.g. geftinib and erlotinib, though effect generally lasts for months. Benefit is seen predominantly in never-smokers, female patients with adenocarcinoma histology and in those with presence of activating mutations in the EGFR-TK domain. Currently, it is not clear if EGFR inhibitors should be used upfront or after chemotherapy or if they can be used as adjuvant in patients with early stage NSCLC. Another biologic agent, Bevacizumab (vascular endothelial growth factor inhibitor), when used with chemotherapy has been found to improve outcome in selected patients with non-squamous cell advanced NSCLC.

BENIGN TUMOURS OF TRACHEOBRONCHIAL TREE

Benign tumours of tracheobronchial tree are rare and account for 0.2% of all the respiratory malignancies (**Table 1**). Clinical presentation includes symptoms of airway obstruction like cough, shortness of breath or wheezing. Because of these non-specific symptoms, patients may be mistaken for asthma or obstructive lung disease and may receive oral corticosteroids, leading to delay in diagnosis. Some patients may also present with atelectasis and secondary pulmonary infection when tumour is detected incidentally. Haemoptysis can also be a presenting symptom.

The chest radiographs may demonstrate collapse of a lobe or an entire lung due to complete obstruction or to hyperinflation of the lung peripheral to a bronchial tumour that causes a ball valve effect. Computed tomography of the chest may demonstrate a tracheal or bronchial mass but it may underestimate the extent of submucosal invasion. Fibre-optic bronchoscopy is useful in: (i) directly visualising the tumour and its extent; and (ii) to take biopsy samples to clinch the diagnosis. Malignant tumours require further investigations to rule out distant metastasis.

Table 1: Benign and Malignant Tumours of Tracheobronchial Tree

Benign tumours of trachea and major bronchi
Bronchial mucous adenomas
Carcinoids
Pleomorphic adenomas
Malignant tumours of trachea and major bronchi
Mucoepidermoid carcinoma
Adenoid cyctic carcinoma
Squamous cell carcinoma
Bronchogenic carcinoma
Small cell lung cancer
Non-small cell lung cancer
Squamous cell carcinoma
Adenocarcinoma
Large cell carcinoma
Bronchoalveolar carcinoma
Other types: adenosquamous type, etc.

Carcinoid tumours are of neuroendocrine origin, found in large bronchi. Histologically, they are composed of cuboidal cells with small and hyperchromatic nuclei arranged in organoid or ribbon-like pattern. On immunohistochemistry, these cells stain positive for neuroendocrine markers like chromogranin and synaptophysin. Typical carcinoids have low mitotic rate with no necrosis. These tumours rarely metastasise. Atypical carcinoids, on the other hand, have higher mitotic activity and necrosis, and have poorer prognosis. Two per cent of bronchial carcinoids secrete serotonin and cause classical features of carcinoid syndrome—diarrhoea, flushing and hypotension. Some of them cause Cushing's syndrome by secreting ACTH.

Treatment of benign tumours consists of segmental resection of trachea or bronchus with or without sleeve resection of corresponding lung parenchyma. Unresectable malignant tumours are managed with radiotherapy or local ablative measures like laser photocoagulation or cryotherapy, although treatment in such cases is mostly palliative.

BRONCHOGENIC CARCINOMA

Lung cancer is the most common malignancy worldwide in males and is also the leading cause of death due to cancer. Almost half of the cases occur in the developing countries. Incidence of lung cancer is declining in industrialized nations (like United States) due to smoking control measures; it continues to rise in developing countries.

INDIAN SCENE

In India, lung cancer is the most common cancer among males (ICMR, 2005). Data from urban and rural population-based cancer registries is shown in (**Table 2**). The Cancer Atlas Programme of ICMR has revealed high incidence of lung cancer in certain pockets in north-east India. The median age at diagnosis is lower in India (54 versus 68 years), with higher male to female ratio (4:1 versus 1.4:1). Only 12% of patients had stage I-II

compared to 36% and squamous cell carcinoma is the predominant histological subtype (Table 3).

Table 2: Age Adjusted Incidence Rates of Lung Cancer in Population-Based Cancer Registries

Registry	Males	Females
Aizwal District	39.3	42.2
Mizoram State	24.9	24.7
Imphal West District	19.2	16.5
Mizoram State excluding Aizwal District	17.0	14.5
Kamrup Urban District	14.8	5.1
Delhi	13.8	3.2
Bhopal	12.3	0.8
Chennai	11.2	3.0
Silchar Town	10.4	1.4
Mumbai	8.9	3.2
Bangalore	8.5	2.8
Ahmedabad	5.5	1.0
Dibrugarh District	5.4	2.7
Sikkim State	5.2	6.2
Barshi	1.9	0.9

Source : Consolidated report of the PBCRs 2001-2004.

Table 3: Lung Cancer: A Comparison Between Indian and Western Data

	Industrialised Nations	India
Age (median in years)	68	54
M:F	1.44:1	4:1
Smoking	92 (male) 80 (female)	64
Stage		
IA	16.4	0.3
IB	10.8	4.6
IIA	1.6	0.9
IIB	5.4	6.1
IIIA	14.6	10.3
IIIB	15.2	35.5
IV	36.2	42.4
Histologic type/Sub type		
Adenocarcinoma (bronchoalveolar)	32	27
Squamous carcinoma	29	34
Large cell carcinoma	9	—
Small cell carcinoma	20	10
Large cell neuroendocrine	2	—
Others	12	25

RISK FACTORS

The various risk factors implicated in lung cancer are given in Table 4.

Smoking

Smoking is the most important risk factor for lung cancer especially for small cell lung cancer (SCLC) and squamous cell carcinoma. The relative risk of developing lung cancer is 30 times higher in smokers than in non-smokers. Only 5% to 10% of all patients with lung cancer are non-smokers. Tobacco smoke contains more than 300 chemicals, of which 40 are potent carcinogens. Nitrosoamines like nicotine-derived nitrosoamine ketone (NNK) and polycyclic aromatic hydrocarbons like benzo a pyrene can induce lung cancer in animal models similar to human lung cancer. Nicotine and inorganic metals like nickel, arsenic and chromium also act as carcinogens. The risk of lung cancer is directly related to the duration and intensity of smoking. Similarly, cessation of smoking is associated with decline in the risk of lung cancer. The relative risk is 16 after 5 years of cessation compared to non-smoker, 8 after 10 years and 2 after 30 years. Passive smoking also increases the risk of lung cancer. Studies indicate that it may contribute to 25% of all lung cancers in non-smokers.

Table 4: Risk Factors for Lung Cancer

- Smoking
- Industrial Carcinogens: accounts for up to 8% of lung cancer related deaths
  - Radionuclides such as uranium, radon in miners, radon derivatives (especially small cell lung cancer)
  - Asbestos, especially with heavy smoking; asbestos fibres include: actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite
  - Silica
  - Arsenic compounds: arsenic trioxide, arsenic pentoxide, arsenic acid and derivatives
  - Organic compounds like polycyclic aromatic hydrocarbons (PAHs), diesel fumes
  - Metals like nickel, chromium
- Fibrosis/Scars: Scars (scar carcinoma, cavitary lesions after tuberculosis) (cavitary carcinoma)
- Dietary Factors
- Genetic Predisposition
  - Risk in relatives of lung cancer patients is increased by factor 2-4
  - Chromosomal Deletions and Mutations: 3p21 deletion, mutations of tumour suppressor gene p53, and Rb, altered oncogene expression (myc in small cell lung cancer; K-ras, Her2/neu in adenocarcinomas)
  - Cytochrome P450
  - DNA repair genes like ERCC and XRCC
  - In East Asia, 40% of lung cancer cases occur in never-smokers and are associated with increased incidence of EGFR mutations.

Development of lung cancer is a multi-step process; initially there is epithelial metaplasia followed by dysplasia, carcinoma *in situ* and then invasive carcinoma.

PATHOLOGY AND CLASSIFICATION

The WHO histological classification of epithelial tumours of lung consists of 42 different histological varieties, but all these varieties can be grouped under two broad types: tumours originating from surface epithelium of bronchi or bronchioli, namely, non-small cell lung cancer and those arising from neuroectodermal cells/APUD (amine precursor uptake and decarboxylation), small cell lung cancer. Both these types differ in their cell of origin, histology, behaviour of growth and spread, natural course, staging and management.

The non-small cell lung cancers (NSCLCs) can be further subdivided into following types based on histological features although they do not differ in staging and treatment.

Squamous cell carcinoma was the most common type three decades ago; adenocarcinoma is currently the predominant type in industrialised nations. In India, squamous cell cancer is still the predominant histologic subtype (Table 3), there is marginal increase in the incidence of adenocarcinoma subtype. Squamous cell carcinomas typically arise from epithelium of proximal segmental bronchi, evolving through stages of squamous metaplasia, dysplasia, carcinoma *in situ* and invasive carcinoma and present as a hilar mass (Figure 1A). Figure 1B shows the CT image of same patient

Adenocarcinomas are typically located in the periphery of the lung and are less amenable to detection by sputum cytology or



Figure 1A: Chest radiograph showing right hilar mass with raised diaphragm.

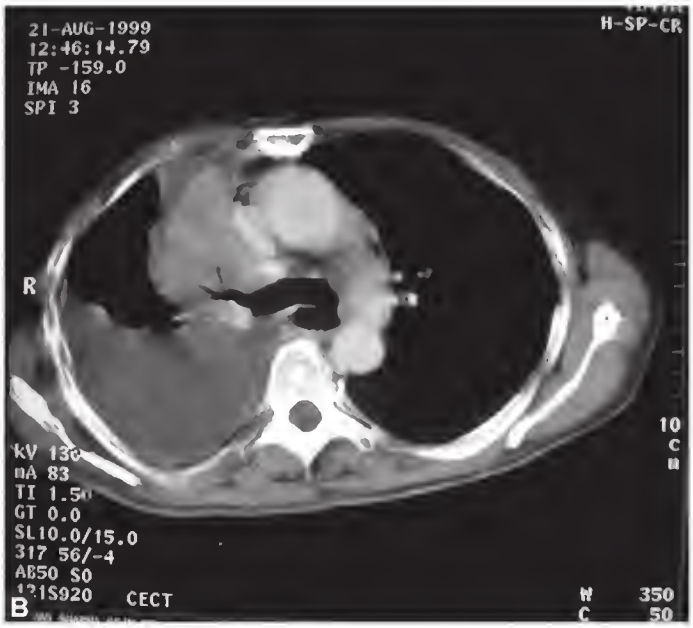


Figure 1B: Computed tomography of the same patient with evidence of right hilar mass and pleural effusion.

bronchoscopy but more approachable for CT-guided needle biopsies. Fourteen different subtypes have been described. Bronchoalveolar carcinoma is special subtype of adenocarcinoma seen more commonly in non-smoking females of Asian origin. This is multi-focal, spreads along the airways (known as lepidic spread) before stromal and angiolymphatic invasion and can hamper with gas exchange at alveolar surface causing dyspnoea. Mucinous variety can be associated with copious mucinous expectoration. Special interest has developed in this variety due to high incidence of epidermal growth factor receptor (EGFR) mutations and response to targeted therapeutic agents like erlotinib and gefitinib.

Large cell carcinomas comprise 15% of all lung cancers and present similar to adenocarcinomas as a peripheral lung nodule. Some of them show neuroendocrine differentiation and when associated with necrosis and high mitotic rate, are called large cell neuroendocrine carcinomas.

Lung cancer is a heterogeneous disease at molecular level. This is evidenced by the fact that a small subset of patients with advanced disease benefit with EGFR inhibitors – tyrosine kinase inhibitors (TKIs), e.g. geftinib and erlotinib, though effect generally lasts for months. Benefit is seen predominantly in never-smokers, female patients with adenocarcinoma histology and in those with presence of activating mutations in the EGFR-TK domain. The two most common mutations in the TK domain, exon 19 deletions and L858R have been associated with best responses. Similarly, pemetrexate is a newer antifolate drug and is effective for patients with advanced NSCLC with non-squamous histology.

MODE OF SPREAD

Lung cancer spreads locally by direct invasion of adjacent structures like chest wall, pleura, diaphragm, trachea, Oesophagus, and great vessels of mediastinum, pericardium and the heart. Lymphatic spread occurs to bronchopulmonary, mediastinal and subcarinal and then supraclavicular lymph nodes. Lower lobe lymphatics drain into posterior mediastinum and subcarinal nodes. Right upper lobe lymphatics drain towards the superior mediastinum and left upper lobe lymphatics drain into the anterior mediastinum as well as superior mediastinum.

Distant metastasis occurs to bone, liver, adrenals and brain and to any site in the body by haematogenous dissemination. Metastasis can also occur to the same lobe or other lobes or contralateral lung. Rare sites like skin and subcutaneous tissue, breast, ovary, testis and thyroid have been reported.

CLINICAL FEATURES

Cough is the most common symptom followed by breathlessness, haemoptysis and chest pain. Breathlessness may occur due to endobronchial obstruction by tumour causing collapse of a lobe or whole lung or pleural effusion. Rarely, breathlessness may be due to lymphangitis carcinomatosis, a condition where lymphatics are infiltrated by tumour (**Figure 2**). Haemoptysis occurs more often in a central lesion. Rapid enlargement of tumour, especially SCLC, can cause obstruction of SVC resulting in facial puffiness, plethora and engorged veins over the neck and chest wall together known as superior vena cava syndrome. Pancoast tumour is a lesion arising from the apical region of the lung (**Figures 3A and B**). It may cause Horner's syndrome due to involvement of sympathetic ganglia or its roots. Brachial plexus involvement may be seen.

Systemic symptoms like weight loss and loss of appetite are common. Symptoms may also occur due to metastatic lesions like bone pain in skeletal metastasis, painful and tender hepatomegaly in liver metastasis. Seizures and features of raised intracranial tension like headache, vomiting and papilloedema can occur in brain metastasis.

A unique constellation of symptoms can develop in lung cancer affecting the neuroendocrine system and skin caused by humoral substances released by tumour tissue, known as paraneoplastic syndromes. Clinical significance of paraneoplastic syndromes lies in the fact that they may precede cancer by months to years and may warn about occurrence. When they occur along with cancer, they may give a clue to underlying disease. Usually they resolve with treatment of the disease but some neurological syndromes may persist. Paraneoplastic syndromes are more commonly seen with SCLC but are also seen with NSCLC. The most common syndrome associated with SCLC is syndrome of inappropriate

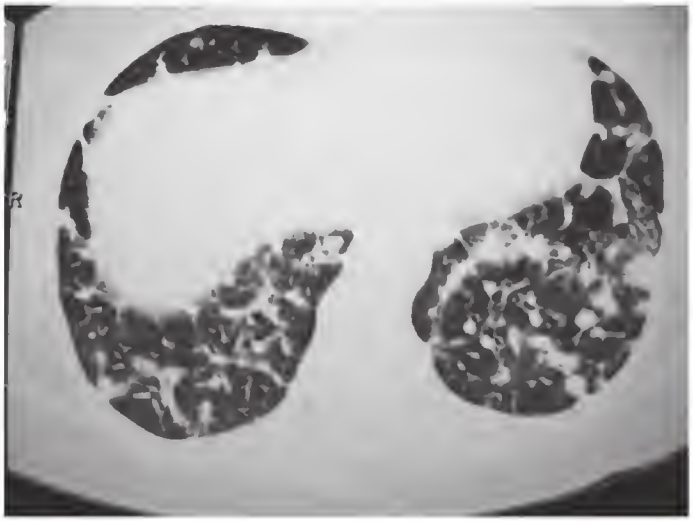


Figure 2: Computed tomography of the chest showing lymphangitis carcinomatosis.



Figure 3A: Chest radiograph showing advanced pancoast tumour with erosion of rib and body of vertebra.

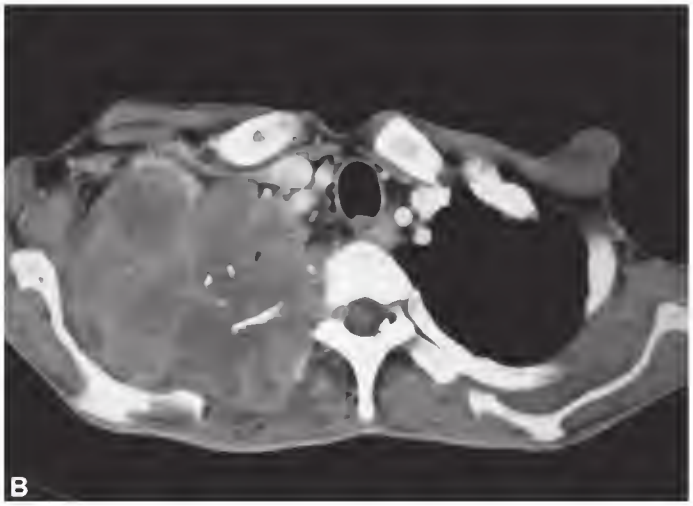


Figure 3B: Computed tomography of the same patient showing first rib and vertebral involvement and apical mass.

secretion of anti-diuretic hormone (SIADH) resulting in hyponatraemia due to secretion of ADH by the tumour. Hyponatraemia is usually asymptomatic but can rarely cause neurological manifestations like seizures and altered mental status. Cushing's syndrome due to secretion of ACTH or corticotropin releasing hormone (CRH) has also been reported and portends a poor prognosis. Lambert-Eaton myasthenic syndrome is characterised by proximal muscle weakness which worsens with exercise. It can be differentiated from myasthenia gravis by electromyogram (EMG) and anti-cholinesterase antibodies. Peripheral neuropathy, limbic encephalitis and paraneoplastic cerebellar degeneration can occur in SCLC.

Hypercalcaemia is more common in squamous cell type of NSCLC. It is caused by secretion of parathyroid hormone related peptide (PTHrP) although hypercalcaemia due to extensive bone metastasis has to be ruled out. Clubbing and hypertrophic osteoarthropathy can occur in NSCLC. Thromboembolic manifestations can also occur. **Table 5** describes clinical features reported in major studies from India.

Table 5: Clinical Presentation: Experience from India (%)

	PGI Chandigarh (%)	AIIMS New Delhi N=907 (%)	Other Centres (%)
Cough with expectoration	88	83 (69.5)	40-94.3
Chest pain	52.2	78.9	16-66.7
Loss of weight	90	88	11.4-77
Breathlessness	Not reported	83.9	24-59
Weakness	90	91.4	4-60
Haemoptysis	69	37.2	28-60
Fever	19.6	68	22-68.6
Anorexia	90	88.8	20.5-70
Hoarseness of voice	29. 9	28.5	9-33
Nausea and vomiting	6	—	25.0
Puffiness of face	19.8	10.5 (SVCO)	2.9-8.3
Dysphagia	20.8	—	2.9-6
Others	30.5	—	—

SVCO = Superior vena cava obstruction.

INVESTIGATIONS

Complete blood count and renal and liver function tests along with electrolytes are recommended in all cases. Chest radiograph may reveal large peripheral lung nodule or central obstructing lesion, collapse or pleural effusion (**Figure 4**). Mediastinal lymphadenopathy and sometimes diaphragmatic palsy or lymphangitis carcinomatosa can be made out. Central lung lesion (near hilum) is mostly seen in small cell or squamous cell cancer. Peripheral lung lesions (distant to hilum, nodular structures) are frequently large cell lung cancer or adenocarcinomas. Diffuse lung disease is usually alveolar carcinoma.

Contrast-enhanced computed tomography (CECT) of chest and upper abdomen will pick up smaller lesions not visible on radiographs and also better define the anatomy of the lesion and its relation to mediastinal structures as well as lymph-adenopathy . It also reveals metastasis to other lobes, opposite lung, liver, or adrenals (**Figure 5**). CT scan has a sensitivity of 60% and specificity of 80% to detect lung cancer. FDG-PET scans ([^{18}F] Flouro-deoxyglucose-Positron emission tomography (FDG-PET scans) is useful in detecting mediastinal lymphadenopathy, visceral and bone metastasis. PET scan has higher sensitivity and specificity (70% and 80%, respectively) and high negative predictive value of 90%. Integrated PET-CT scans further improve sensitivity and specificity to 80% and 95%, respectively. MRI scans are not useful for diagnosis and staging but they may be useful in tumours invading spine, great vessels

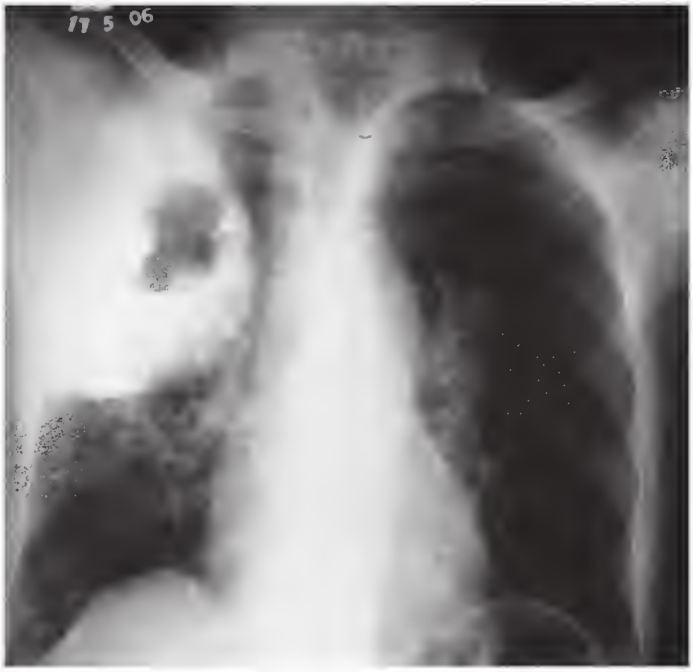


Figure 4: Chest radiograph showing mass lesion with evidence of cavity in squamous cell carcinoma.

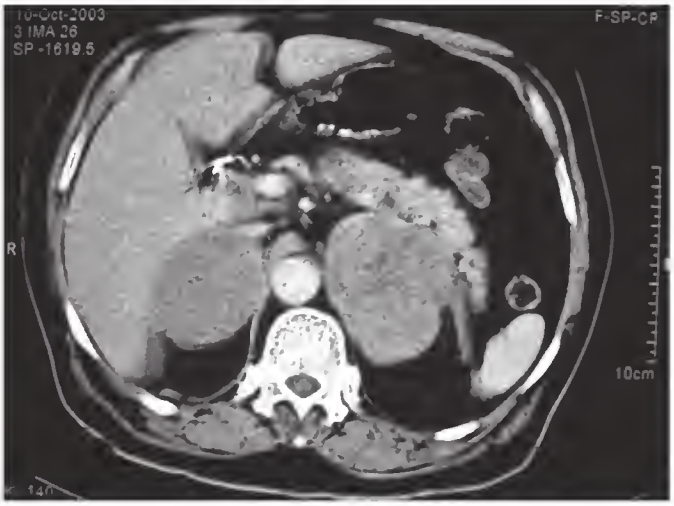


Figure 5: Computed tomography showing left adrenal metastasis.

or brachial plexus. MRI brain is superior to CT scan in detecting intracranial metastasis. Bone scan is used to detect skeletal metastasis.

DIAGNOSIS

Sputum cytology has a sensitivity of 65% in detecting lung cancer, especially in central lesions and with multiple sampling. Pleural fluid cytology helps in diagnosis in 60% to 70% of cases. CT-guided fine needle aspirate helps in diagnosing peripheral lesions with 95% yield. Sometimes, this technique is used to confirm solitary lesion in liver or adrenals. Fibreoptic bronchoscopy helps in visualising more central lesions and also to take biopsy or brush samples. Transbronchial aspirate of lung lesion or mediastinal lymph node can also be done. Video-assisted thoracoscopy (VAT) can be used in diagnosis, staging and interventional procedures like resection or mediastinal lymph node sampling. Mediastinoscopy is used to accurately stage the nodal disease. Thoracotomy and mediastinotomy are rarely performed due to availability of non-invasive imaging (CT and PET-CT) and less invasive procedures.

SOLITARY PULMONARY NODULE

Solitary pulmonary nodule is defined as an asymptomatic lung lesion less than 6 cm in diameter with normal physical examination and normal blood counts and liver function tests (**Figure 6**). It can be benign or malignant. Age greater than 45 years, history of smoking and a doubling time of 30 to 400 days indicate a high probability of malignant lesion. Circular, crescentric or densely calcified lesions are more likely to be benign. Suspicious lesions should be further investigated and the rest should be kept under follow-up. CT-guided needle biopsy yields an accurate diagnosis in 85% to 90% of the cases in peripheral lung lesions. Open biopsy is done in more central lesions. FDG-PET scans are considerably sensitive and specific in identifying malignant solitary pulmonary nodule.



Figure 6: Computed tomography of the chest showing speculated nodular lesion.

STAGING

TNM staging is used to define the extent of disease spread. Recently, International Association for the study of Lung Cancer (IALC, 2009) has proposed revised TNM staging. In this new classification, T1 tumours (0 to 3 cm) have been sub- classified as T1a (<2 cm) and T1b (2 to 3 cm); T2 tumours (>3 cm) to T2a (3 to 5 cm) and T2b (5 to 7 cm) and T2 tumours exceeding 7 cm as T3. Satellite nodule in the same lobe (T4) is now classified as T3 and additional nodules in a different ipsilateral lobe (M1) as T4 and additional nodules in contralateral lung as M1a, pleural and pericardial dissemination (T4) as M1a and distant metastases have been reclassified as M1b in the new staging system (**Table 6**).

TREATMENT

Surgery remains the treatment of choice for patients with stage I and II disease where the lesion is resectable. In Stage IIIA, ipsilateral mediastinal nodes are resectable but generally have a poorer outcome and post-operative adjuvant chemotherapy and/or radiotherapy is required. Stage IIIB lung cancers are unresectable in view of invasion of mediastinal structures or contralateral lymph nodes and stage IV disease is incurable by surgery due to distant metastasis. Resectability and operability has to be determined in each individual patient before planning surgery. Resectability indicates whether the disease can be excised without any residual disease. Some stage IIIA lesions

Table 6: TNM Staging of Non-Small Cell Lung Cancer by IASLC**

Primary Tumour	
TX	Tumour proven by presence of malignant cells in bronchopulmonary secretions but not visualised by imaging or bronchoscopy, or any tumour that cannot be assessed, as in pretreatment imaging
T0	No evidence of tumour
Tis	Carcinoma *in situ*
T1	Tumour ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, and without invasion proximal to a lobar bronchus at bronchoscopy
T1a	Tumour ≤2 cm in greatest dimension
T1b	Tumour >2cm but ≤3 cm in greatest dimension
T2	Tumour >3 cm but ≤7 cm in greatest dimension or tumour with any of the following features: involves the main bronchus ≥2 cm distal to the carina or invades the visceral pleura or associated with atelectasis/obstructive pneumonitis extending to the hilar region but does not involve the entire lung
T2a	Tumour >3 cm but ≤5 cm in greatest dimension
T2b	Tumour >5cm but ≤7 cm in greatest dimension
T3	Tumour >7 cm or of any size with invasion of any of the following: chest wall (including superior sulcus tumour), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus within 2 cm of the (but not involving) the carina; or associated atelectasis or obstructive pneumonitis of the entire lung; or separate tumour nodule(s) in the same lobe
T4	Tumour of any size with invasion of any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; or separate tumour nodule(s) in a different lobe of the lung
Regional Lymph Node Involvement	
Nx	Regional lymph node status cannot be assessed
N0	No demonstrable metastasis to regional lymph nodes
N1	Metastasis to ipsilateral peribronchial and/or pulmonary or hilar nodes and intrapulmonary nodes (including direct extension)
N2	Ipsilateral mediastinal and/or subcarinal
N3	Contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular nodes
Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Metastasis present
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial effusion)
M1b	Distant metastasis

Stage Grouping			
IA	T1a, b	N0	M0
IB	T2a	N0	M0
IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
IIB	T2b	N1	M0
	T3	N0	M0
IIIA	T1,T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
IIIB	T4	N0, N1, N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

*** IASLC = International Association for the Study of Lung Cancer.*

Source: Reproduced from AJCC 7th edition.

are also unresectable. Operability indicates whether the patient is fit to undergo surgery. In general, patients should have normal haemogram, renal and liver function tests and optimal cardiopulmonary reserve which are determined by various modalities like spirometry with diffusion capacity, arterial blood gas analysis, echocardiography and ventilation-perfusion scans. If the post-operative predicted value of FEV_1 or DLCO equals or exceeds 40% of predicted, this is considered to be associated with lesser peri-operative risk. Lobectomy, bilobectomy or pneumonectomy can be performed depending on the extent of the disease. Post-operative mortality rates range from 6% for pneumonectomy to less than 1% for smaller resections.

Radiotherapy (RT) plays a role in locally advanced unresectable disease. External-beam radiotherapy from a linear accelerator is generally used after three dimensional CT planning. A dose of 60Gy to 66Gy is delivered to the primary lesion and 40 to 45Gy to the uninvolved lymph nodes over a period of 6 to 8 weeks when irradiated. Toxicity includes, acute complications like acute radiation pneumonitis (developing within 1 to 6 months of RT), acute oesophagitis and rarely pericarditis, myelitis and brachial plexopathy. Late complications include pulmonary fibrosis (<5%), oesophageal strictures and bronchial stenosis.

Chemotherapy when used alone is not curative in lung cancer but it improves survival when used along with primary modalities like surgery or radiotherapy. Adjuvant chemotherapy benefits patients of stage II and IIIA NSCLC. Neoadjuvant chemotherapy in which a specified number of cycles are administered before surgery or irradiation also appears to be beneficial. Concomitant chemoradiotherapy (CCRT) where radiotherapy is delivered along with chemotherapy has also been intensively investigated. The latter has been found to be beneficial, substantial toxicity has made people to prefer sequential chemotherapy followed by radiotherapy. Chemotherapy is the standard of treatment in stage IV disease. Intent is palliative in this setting. Platinum compounds like cisplatin and carboplatin have become the standard of care. Beside platinum compounds, other active chemotherapeutic agents include gemcitabine, taxanes (paclitaxel, docetaxel) and pemetrexate. The commonly used combinations are carboplatin and paclitaxel, cisplatin and paclitaxel, cisplatin and gemcitabine, and cispaltin and vinorelbine (**Table 7**).

Table 7: Common Chemotherapy Protocols for Non-Small Cell Lung Cancer and Small Cell Lung Cancer

Drugs	Dose	Route		
For non-small cell lung cancer				
Paclitaxel	175 mg/m²	IV	Day 1	Start next cycle
Carboplatin	AUC 6	IV	Day 2	on day 22
Gemcitabine	1000 mg/m²	IV	Day 1 & 8	Start next cycle
Cisplatin	70 mg/m²	IV	Day 1	on day 22
Vinorelbine	30 mg/m²	IV	Day 1 & 8	Start next cycle
Cisplatin	80 mg/m²	IV	Day 1	on day 22
Docetaxel	75mg/m²	IV	Day 1	Start next cycle
Cisplatin	75mg/m²	IV	Day1	on day 22
Second line				
Pemetrexate	500 mg/m²	IV	Day 1	Start next cycle on day 22
For small cell lung cancer				
Cisplatin	75 mg/m²	IV	Day 1	Start next cycle
Etoposide (VP-16)	100 mg/m²	IV	Day 1 to 3	on day 29
Second line				
Irinotecan	60 mg/m²	IV	Day 1,8,15	Start next cycle
Cisplatin	60 mg/m²	IV	Day 1	on day 29

Pemetrexed is a newer antifolate drug that has been approved as first-line treatment for patients with advanced non-squamous, NSCLC in combination with cisplatin, and as single agent for relapsed or chemotherapy refractory NSCLC after platinum-containing chemotherapy, at a dose of 500 mg/m^2. Pemetrexed undergoes intracellular activation by poly-gamma-glutamylation that is essential for its antiproliferative activity. Polyglutamate derivatives mainly inhibit three key enzymes of intracellular folate metabolism, i.e. thymidylate synthase (TYMS), dihydrofolate reductase (DHFR), and glycinamide ribonu-cleotide formyltransferase (GARFT), with TYMS being the most relevant target. Pemetrexed undergoes rapid renal elimination as unchanged parent compound, with a terminal half-life of between 2 hours and 5 hours. All patients on pemetrexate therapy should receive supplement-ation with folic acid and vitamin B12.

STAGE-WISE MANAGEMENT OF NSCLC

Stage I, II and IIIA patients should undergo surgical resection, if they are operable. Adjuvant chemotherapy is beneficial in stage II and IIIA disease. PORT (post-operative radiotherapy) has not been shown to be beneficial till now. Medically, inoperable early stage NSCLCs and unresectable locally advanced NSCLCs are treated with chemo-radiotherapy. A dose of 60 Gy to 70 Gy is administered in a daily fraction of 1.8 Gy to 2 Gy along with a platinum-based chemotherapy regimen. Chemotherapy and radiotherapy can be administered sequentially or concurrently. Concurrent administration has better outcome at the cost of excessive toxicity. Majority of the patients with NSCLC (55%) have stage IIIB or stage IV disease at presentation. Such patients have a median survival of 8 to 10 months with palliative chemotherapy and best supportive care. Chemotherapy helps in prolonging survival in patients with good performance status. In patients with poor performance status, chemotherapy has not been shown to be beneficial. The five-year survival in early operatable stages upto stage IIIA is 50% to 91% while it is less than 7% in late stage (stage IIIB/IV).

TARGETED THERAPY

Epidermal growth factor receptor (EGFR) mediates cancer cell growth, proliferation, invasion, metastasis and cell survival. EGFR is expressed in 40% to 80% of lung cancers making it an attractive target for molecular therapy. They bind to intracellular tyrosine kinase domain of the receptor and inhibit its activity. EGFR tyrosine kinase inhibitors (TKIs) like gefitinib and erlotinib are novel agents which have shown activity in NSCLC. They are especially found to be active in female gender, patients of Asian origin and in never-smokers. Bronchoalveolar subtype has been shown to respond to EGFR tyrosine kinase inhibitors. Mutations in EGFR gene are being studied to predict the response to EGFR TKIs. Side effects are skin rash, diarrhoea and rarely, interstitial pneumonitis. Cetuximab, a monoclonal antibody against EGFR, is also under clinical trial.

Tumour angiogenesis has been an important target in various cancers including lung cancer. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), which is an important molecule mediating angiogenesis. It has shown activity in NSCLC in first-line setting when combined with standard chemotherapy.

PALLIATIVE TREATMENT

Endobronchial obstruction by tumours can be relieved by bronchoscopic removal either mechanically or by special techniques like laser ablation, electrocautery or cryotherapy. It may be followed by endobronchial stenting to prolong patency. Malignant pleural effusions which recur after multiple drainage can be managed by pleurodesis with talc, bleomycin, or doxycycline. Pericardial effusion can be relieved by indwelling catheters.

Radiotherapy can be administered for palliation of symptoms like haemoptysis, chest pain or dyspnoea. Haemoptysis can be controlled in 75% to 85% of patients with radiotherapy.

Bone Metastasis

Approximately 30% to 40% of NSCLC patients develop bone metastases. These are associated with a significant increase in skeletal-related events (SREs), including severe bone pain, hypercalcaemia, pathological fractures and spinal cord compression. These SREs result in impaired mobility, reduced quality of life, and frequently require therapeutic intervention (radiation therapy, surgery and systemic treatments). The normal balance of formation of new bone by osteoblasts and the resorption of old bone by osteoclasts becomes imbalanced and/or uncoupled, leading to the development of lesions that are osteolytic, osteoblastic or a combination of both. Palliative external-beam radiotherapy must be considered to relieve pain, unresponsive to narcotic analgesics. Bisphosphonate therapy (zoledronic acid) has proven efficacy for the treatment of bone metastases from a broad range of solid tumour types, including lung cancer. Symptomatic compression fractures in spine can be treated with vertebroplasty or kyphoplasty. Pathological fractures especially in weight bearing bones require orthopaedic fixation.

Brain metastasis, when solitary can be treated with surgical resection followed by whole brain radiotherapy (WBRT). Small lesions can also be treated with stereotactic radiosurgery using gamma knife. However, many patients present with multiple brain metastases in whom WBRT alone can be offered in addition to corticosteroids.

SMALL CELL LUNG CANCER (SCLC)

Small cell lung cancer constitutes 20% of all lung cancers and its incidence is probably declining in United States. In India, it accounts for 2.4% to 10% of all lung cancer types according to various hospital-based case series. It is strongly associated with smoking and occurs in the same age group as NSCLC. Incidence is higher in males. Clinically, it presents as a rapidly progressive lung mass, with dyspnoea, chest pain, and haemoptysis. They can present with symptoms due to metastasis like bone pain, abdominal pain or headache, vomiting or seizures in case of brain metastasis. SVC syndrome can occur in 10% of individuals. SCLCs usually present as a hilar or central mass and are usually metastatic at presentation (90%). Common sites of metastasis are liver, adrenals, bones (lytic or less commonly blastic lesions involving the vertebrae, ribs, pelvis , skull and long bones), bone marrow, and to brain.

Histologically, the tumour constitutes of dense sheets of small cells with scant cytoplasm, finely granular nuclear chromatin, inconspicuous or absent nucleoli. Frequent mitoses are seen.

Although histopathology is characteristic, immuno-histochemistry helps in difficult cases. Cytokeratin(CK) is positive and markers of neuroendocrine differentiation like CD56, synaptophysin and chromogranin can be demonstrated. TTF-1 is positive in 70% to 80% of the cases.

Only 10% of the patients with SCLC have disease confined to lung at presentation and surgery plays a limited role in SCLC. In contrast to NSCLC, SCLC has been staged into:

1. Limited stage disease
2. Extensive stage disease

Limited stage is defined as disease confined to one hemithorax that can be encompassed in a tolerable radiation field. Patients with ipsilateral malignant effusion, ipsilateral or contralateral supraclavicular lymph nodes or contralateral mediastinal lymph nodes are considered to have limited stage disease. Limited stage disease is treated with concurrent chemotherapy generally 4 to 6 cycles of cisplatin and etoposide(VP-16) and radiotherapy. In patients who may not tolerate concurrent chemo-radiotherapy, both can be given sequentially. Prophylactic cranial irradiation is given to patients who respond well to chemoradiotherapy in order to reduce the risk of brain metastasis.

Extensive stage disease is treated with chemotherapy alone. According to SEER programme database, 2-year and 5-year survival are 12% and 5%, respectively for extensive stage disease.

LUNG CANCER IN ELDERLY

Lung cancer in older patients (≥ 70 years) is an increasing problem. Elderly patients have comorbidities, and have poor tolerance to chemotherapy compared to younger patients. In elderly population of patients with advanced NSCLC, single agent chemotherapy with agents like gemcitabine, vinorelbine, and taxanes is considered standard therapy. Among targeted therapies, the EGFR inhibitors, e.g. erlotinib and geftinib, are most promising agents. Phase II data trials have shown activity and good tolerability in this population.

METASTATIC LUNG CANCER

Lung is the most common site for secondary metastasis. Tumours can spread to lung through haematogenous or lymphangitic routes. Lymphangitic spread occurs by retrograde spread from involved lymph nodes through lymphatic channels in the pleura and diaphragm and the thoracic duct to the mediastinal and the hilar lymph nodes. Widespread dissemination in the lung occurs through pulmonary lymphatics resulting in the picture of lymphangitis carcinomatosa (**Figure 2**). Typically seen in breast cancer and gastric cancer, lymphangitis carcino-matosa presents with progressive dyspnoea, chest signs of crackles and rhonchi in advanced or relapsed primary malignancy. Radiology reveals linear interstitial infiltrates especially in the lower zone and is better appreciated in computed tomography. Steroids and radiotherapy give some relief in symptoms but is ultimately fatal.

Haematogenous route is the more common mode of spread and arises from deposition of tumour cells and invasion of thin-walled capillaries. Breast, renal cell cancer, testicular germ cell tumours, gestational trophoblastic tumours-choriocarcinoma, osteogenic sarcoma and Ewing's sarcoma, soft tissue sarcomas, colorectal cancer, hepatocellular cancer, melanoma, thyroid and head, and neck cancers are common primary tumours to metastasise to lungs. In most cases, lung metastases are asymptomatic and detected as a new lesion in follow-up chest radiograph or computed tomography of chest in a patient with known malignancy. Frequently, lung metastasis is diagnosed along with primary during routine evaluation. Bulky tumour close to hilum or multiple florid metastases as that occurs in choriocarcinoma, renal cell cancer and testicular germ cell tumour can produce dyspnoea. Haemoptysis can occur in metastasis from choriocarcinoma. Pleural effusions or pleural deposits may be seen in some cancers like breast and ovarian cancer.

FOLLOW-UP

A regular follow-up is advised for patients treated with surgery, radiation and/or chemotherapy. On each visit, a detailed history, physical examination, chest radiograph and ultrasound are advised once in 3 months for first 2 years then once in 6 months till 5 years then once a year, indefinitely. For patients with advanced disease treated with palliative intent, symptom-based approach is advised for follow-up. Patients must be advised abstinence from smoking (and to avoid occupational exposure, wherever applicable).

CONCLUSION

More than 80% of lung cancer cases are attributed to smoking. While incidence of lung cancer is on the rise in developing countries, effective smoking control measures have shown a decline in its incidence in industrialised nations. Routine screening for lung cancer is not helpful. Newer diagnostic modalities like PET-CT and mediastinoscopy have improved diagnostic capability. Better understanding of molecular biology of lung cancer has led to development of targeted therapy and newer chemotherapeutic regimens. DNA from lung cancer cells has been sequenced with detection of 22,000 mutations. Identifications of key genes affected by mutations and development of targeted therapy would be important areas of research in future studies.

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23.20 Cor Pulmonale

Sandeep Singh

DEFINITION AND EPIDEMIOLOGY

Cor pulmonale or pulmonary heart disease is a very popular term in medical literature but it has been used rather loosely for many years. It is best defined as an alteration in the structure or function of the right ventricle (RV) secondary to the diseases of lung or its vasculature. Pulmonary artery hypertension (PAH) is the link between the lung dysfunction and the involvement of the RV (hypertrophy and/or dilatation). Congenital heart diseases (CHDs) or primary abnormalities of the left side of the heart leading to PAH are not included in the definition of cor pulmonale.

An updated clinical classification of pulmonary hypertension (PH) has been developed by the experts at the Fourth World Symposium on Pulmonary Hypertension (Dana Point, California, 2008). This classification is considered to be the 'gold standard' today. The definition of cor pulmonale corresponds well with the group of 'pulmonary hypertension owing to lung diseases and/or hypoxia' as per this new classification.

The true prevalence of cor pulmonale is difficult to ascertain as routine physical examination and non-invasive laboratory tests are relatively insensitive to confirm its diagnosis. PAH develops in approximately 25% of patients with advanced pulmonary disease. Cor pulmonale accounts for approximately 5% to 10% of all heart diseases and 20% to 30% of all admissions for heart failure (HF). The development of PAH has important prognostic implications, as it significantly increases the risk of hospitalisation and is associated with reduced survival.

AETIOLOGY

Many conditions can lead to cor pulmonale. **Table 1** provides a list of common diseases that may lead to cor pulmonale. The most frequent cause remains chronic obstructive pulmonary disease (COPD), which accounts for approximately 80% of the cases.

Table 1: Major Causes of Cor Pulmonale

Pulmonary diseases
Chronic obstructive pulmonary diseases
Pulmonary tuberculosis
Interstitial lung diseases
Bronchiectasis
Collagen vascular diseases
Sarcoidosis
Pneumoconiosis
Cystic fibrosis
Bronchiolitis obliterans
Drug-induced lung diseases
Disorders of chronic hypoventilation
Obesity hypoventilation syndrome
Neuromuscular diseases
Thoracic cage deformities
Sleep apnoea syndrome
Primary central hypoventilation

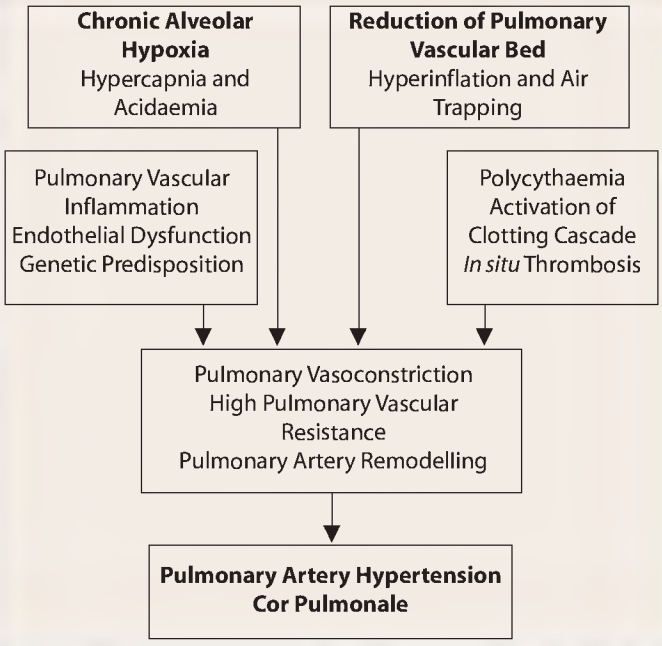
PATHOPHYSIOLOGY

PAH is defined as resting mean pulmonary artery pressure (PAP) of more than 20 mm Hg and during exercise more than 30 mm Hg. Typically, in patients with COPD, PAH appears when airflow limitation is severe and is associated with chronic hypoxaemia. In the initial stages, PAH may only be observed during exercise or sleep. Even in advanced stages, most patients have only modest increase in PAP at rest; the mean PAP varies between 25 mm Hg and 35 mm Hg. Rarely, severe PAH (mean PAP more than 35 to 50 mm Hg) may be observed, even without major airflow limitation. This is labelled as 'out-of-proportion' PAH, and carries poor prognosis with rapid progression to right HF and death.

This is in sharp contrast to the development of PAH due to left heart disease, CHDs, pulmonary thromboembolic disease and primary PAH, where mean PAP is usually more than 40 to 50 mm Hg.

Several pathophysiological mechanisms lead to PAH and subsequently cor pulmonale are shown in **Table 2**.

Table 2: Pathophysiology of Cor Pulmonale in Pulmonary Diseases



Pulmonary Vasoconstriction

Traditionally, chronic alveolar hypoxia is the most important factor leading to pulmonary vasoconstriction and an increased pulmonary vascular resistance (PVR). This hypoxic pulmonary vasoconstriction is an adaptive physiological response, shunting blood away from hypoxic regions to better ventilated parts of the lung. Hypercapnia and acidaemia further exacerbate pulmonary vasoconstriction that would result from a given level of alveolar

hypoxia. Eventually, chronic long-standing hypoxia induces structural changes in the pulmonary vascular bed leading to pulmonary vascular remodelling. In general, the more the abnormal in (PO_2) and (PCO_2) values in patients with COPD, the more severe the PAH and a greater likelihood of cor pulmonale.

Anatomical Factors

The destruction of the capillaries secondary to lung disorders [e.g. emphysema, interstitial lung diseases (ILDs), parenchymal infiltrative diseases] results in overall diminished cross-sectional area of the pulmonary vascular bed. This diminishment occurs progressively as the lung conditions deteriorate. In emphysema, there is destruction of capillaries that course along the alveoli that are being destroyed or coalescing to form bullae. Also, severe emphysema is associated with hyperinflation and air trapping, which results in positive alveolar pressure throughout the respiratory cycle. This causes mechanical compression on the surrounding vessels resulting in increased PVR. This mechanism perhaps assumes more importance in explaining the development of cor pulmonale in patients with severe emphysema who are not hypoxic. In ILDs, there is also decrease in distensibility of pulmonary vascular bed due to the surrounding fibrotic tissue causing higher PVR and PAH.

Haematological Factors

Increased blood viscosity secondary to polycythaemia, and activation of clotting cascade leading to *in situ* thrombosis. This further aggravates PVR.

Endothelial Dysfunction

It has been shown that in COPD there may be endothelial dysfunction resulting in imbalance between the mediators of vasodilation (nitric oxide, prostacyclin) and vasoconstriction (endothelin-1). There is reduction in synthesis and/or release of nitric oxide from the lungs. This is coupled with a reduction in prostacyclin synthesis and excessive expression of endothelin-1. All these factors lead to pulmonary vasoconstriction and higher PVR.

Genetic Predisposition

It has been proposed that pulmonary vascular response to hypoxia may be genetically predisposed. The expression of serotonin (5-hydro-xytryptamine, a potent pulmonary artery smooth muscle cell proliferator) and angiotensin (potent vasoconstrictor) are dependent on the polymorphism of 5-hydro-xytryptamine transporter and angiotensin-converting enzyme genes, respectively.

Inflammation

Role of inflammatory mediators has been increasingly accepted. It has been hypothesised that development of structural and functional abnormalities in COPD is related to inflammatory cells in the pulmonary vascular wall.

PATHOLOGY

The structural basis of chronic and sustained PAH in cor pulmonale include pulmonary vascular remodelling, reduction in cross-sectional area of pulmonary vessels and pulmonary *in situ* thrombosis. The structural changes particularly affect the distal pulmonary arteries and are characterised by medial hypertrophy of small pulmonary arteries, muscularisation of pulmonary arterioles, and initial thickening and fibrosis.

The increased PVR and PAH in cor pulmonale lead to sustained pressure over-load and eventually structural changes in the RV. There is gradual hypertrophy and dilation of right ventricle. Right HF sets in at a point when RV cannot meet the need for increased stroke work without significant increase in right heart filling pressures. This response depends upon the acuteness and severity of pressure over-load. Acute cor-pulmonale occurs after a sudden and severe increase in the after-load [e.g. massive pulmonary embolism (PE)], resulting in RV failure without RV hypertrophy. In comparison, chronic cor pulmonale is associated with more slowly progressive PH that leads to RV hypertrophy and dilation. Usually left ventricle (LV) is not involved in cor pulmonale. However, in advanced cases, the interventricular septum can get displaced towards the LV. This can cause reduction in the LV volume and cardiac output. This ventricle interdependence may play a role in cases with severe PAH and gross RV over-load.

CLINICAL FEATURES

Cor pulmonale has a chronic, long-standing, and slowly progressive course. However, at times acute worsening of stable cor pulmonale with life-threatening complications may occur. This acute decompensation occurs either from the progression of underlying disease or a superimposed acute process causing additional stress on the RV. The precipitating event for decompensation is often a respiratory tract infection.

The clinical detection of cor pulmonale is often difficult due to subtle and non-specific signs and symptoms. Early stages of PH may not have any additional clinical finding. Even later, symptoms suggestive of an underlying pulmonary disease dominate. These include dyspnoea on exertion, chronic cough and expectoration, wheezing, and occasional cyanosis and clubbing of fingers. In addition, patients with severe PAH may experience fatigue, dizziness, or even effort-related syncope. This occurs due to the lack of rise in the cardiac output during exercise. Angina chest pain may be seen due to RV ischaemia or pulmonary artery stretching. Rarely, grossly-enlarged pulmonary artery can cause hoarseness of voice due to compression of the left recurrent laryngeal nerve. In advanced stages, right HF occurs resulting in symptoms similar to that ensues in chronic HF. These include anorexia, right upper quadrant discomfort, ascites, and pedal oedema. Symptoms of left heart involvement in the form of orthopnoea and paroxysmal nocturnal dyspnoea are usually absent. Orthopnoea, when present in patients with isolated right HF reflects an increased work of breathing in the supine position due to compromised excursion of the diaphragm.

The physical examination detects findings of PH and RV hypertrophy. Patients with right HF have tachycardia, tachypnoea, elevated jugular venous pressure (JVP), hepatomegaly, and pedal oedema. Sometimes, pedal oedema may be seen even without right HF. The mechanisms include peripheral vasodilatation associated with hypercapnia, renal vasoconstriction secondary to hypoxia causing sodium retention, and neurohormonal activation.

Cardiovascular examination may reveal prominent 'V waves' in JVP as a result of tricuspid regurgitation. In addition, there may be a prominent 'a wave' reflecting the increased force of right atrial contraction. The RV heave may be palpable along the

lower left sternal border or in the epigastrium. The pulmonic component of the second heart sound is accentuated and may even become palpable. The second heart sound may be narrowly split. Right-sided S3 or S4 gallop may be present. A high-pitched pulmonary systolic ejection sound may be heard in the second and the third left intercostal spaces next to sternum. This is often followed by a soft, localised systolic ejection murmur produced by ejection of the RV stroke volume into a dilated pulmonary artery. Often, tricuspid regurgitation is present resulting in blowing pansystolic murmur in the lower left sternal border which increases with respiration (Carvallo's sign). When prominent PH is present, a soft, decrescendo diastolic murmur of pulmonary incompetence (Graham Steell murmur) may be heard that localised to the second and the third left parasternal area. It must be remembered that all these clinical findings may get masked due to hyperinflation and increased anteroposterior diameter of the chest in patients with advanced COPD.

DIAGNOSIS

Due to the non-specificity of the symptoms and signs, ancillary evaluation may be useful. Pulmonary function data using spirometry is mandatory for the diagnosis of COPD; however, it is not useful in predicting PAP. The common investigations necessary in patients of cor pulmonale include the following:

Chest Radiograph

The findings of chest radiograph largely depend on the underlying pulmonary disease. Characteristic features of PAH include enlargement of central pulmonary arteries and hilar vessels. The peripheral vessels are attenuated in advanced cases resulting in oligemic peripheral lung fields. A right descending pulmonary artery with a diameter greater than 16 mm suggests PAH. The heart may have globular appearance due to the RV enlargement (**Figure 1A**). Some encroachment of the retrosternal space by the enlarged RV may be seen in a lateral view (**Figure 1B**). If hyperinflation of lungs is marked, the overall cardiac silhouette may not be enlarged. In advanced cases, when RV failure sets in, there may be right atrial and RV dilatation on chest radiography.

Electrocardiography

Unfortunately, electrocardiogram (ECG) findings are insensitive for detection of PAH. Only one-third of patients with elevated PVR have signs of cor pulmonale on ECG. There may be right atrial enlargement (p-pulmonale) in severe cases. This results in an increase in amplitude of P wave in lead II, III, aVF to more than 2.5 mm. The QRS vector in the frontal plane often shifts to the right. If lung hyperinflation is present, a low voltage QRS complex is common. Incomplete or complete right bundle branch block may be seen. RV hypertrophy which exhibits tall R waves in lead V1 (**Figure 2**) and prominent S wave in lead V5 and V6 may be seen. In acute cor pulmonale, such as occurs in acute PE, a classical pattern of S wave in lead I and a Q wave and inverted T wave in lead III ($S_1Q_3T_3$) may be seen.

Computed Tomography

A high-resolution computed tomography (CT) of the chest is useful in accurately diagnosing early emphysema and ILDs. Contrast-enhanced CT of the chest is very useful for diagnosing acute PE. Ventilation-perfusion lung scan remains useful for the diagnosis of chronic pulmonary thromboembolic disease.



Figure 1A: Chest radiograph (postero-anterior view) showing globular shaped heart due to right ventricle enlargement, prominent main and right descending pulmonary artery due to pulmonary artery hypertension.

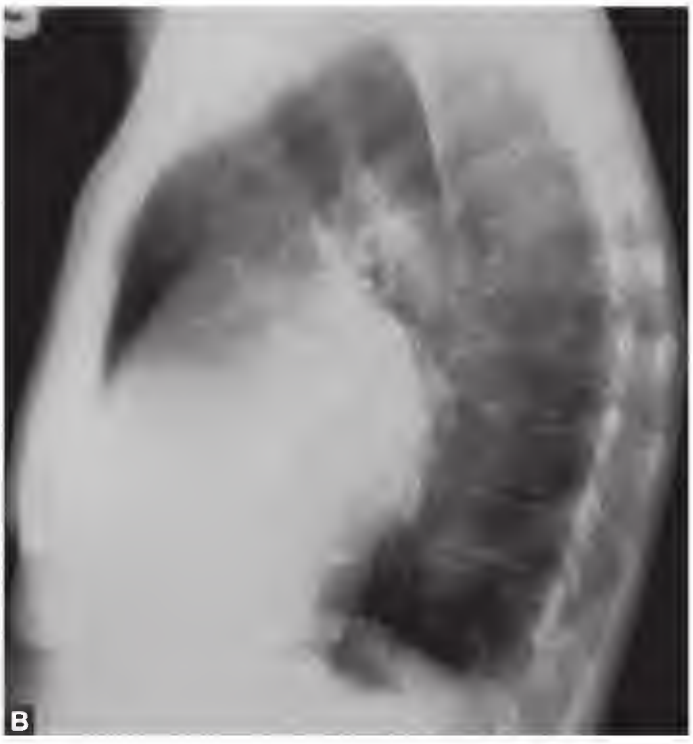


Figure 1B: Chest radiograph (lateral view) showing encroachment of retrosternal space due to right ventricle enlargement.

Echocardiography

Echocardiography is an invaluable tool in the evaluation of most forms of PAH. However, its utility may get limited in patients with COPD because of suboptimal images. Echocardiographic examination also assists in eliminating various non-pulmonary causes of PH, such as LV dysfunction from coronary artery disease or dilated cardiomyopathy, aortic or mitral valve disease and CHD. Two-dimensional echocardiography is useful for measuring right atrium and RV dimensions (**Figure 3**). RV wall thickness as well as its contractility can be assessed. There may be paradoxical movement of interventricular septum into LV

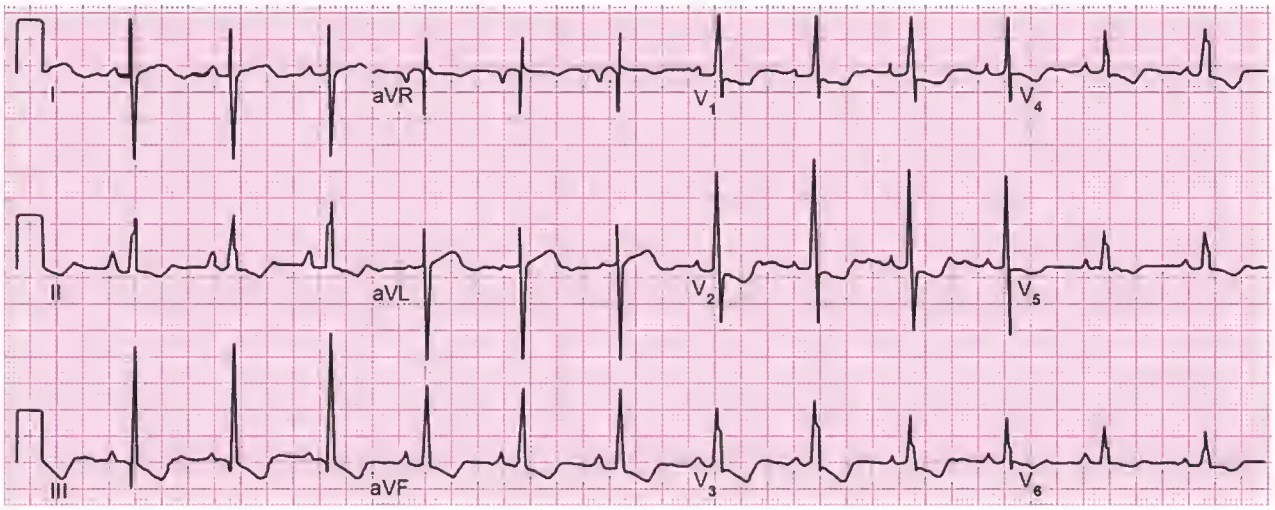


Figure 2: Electrocardiography showing right atrial enlargement (p-pulmonale), right axis deviation and right ventricle hypertrophy.

during systole. At a later stage, dilatation of the tricuspid annulus and RV leads to tricuspid regurgitation. Inferior vena cava may be dilated.



Figure 3: Two-dimensional echocardiography showing enlargement of the right ventricle.

Doppler echocardiography is the best and most reliable method for non-invasive diagnosis of PAH. It allows estimation of the PAP by measuring the jet velocity of tricuspid regurgitation using continuous wave Doppler echocardiography. If sufficient lung hyperinflation prevents an adequate trans-thoracic examination, trans-oesophageal echocardiogram may be useful.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) allows the measurement of volumes and blood flow in the thorax. It may be useful for assessing RV structure and function, particularly in patients who are difficult to image with echocardiography because of severe lung disease. However, its role as a routine diagnostic tool to diagnose PAH in patients with pulmonary diseases needs to be defined.

Right Heart Catheterisation

Catheterisation of the right heart is the 'gold standard' for the diagnosis and quantification of PAH. The haemodynamic definition of PAH includes a mean PAP $\geq$20 mm Hg, with a pulmonary capillary wedge pressure (PCWP) or LV end-diastolic pressure $\leq$15 mm Hg and calculated PVR $\geq$3 Wood units.

It is very useful for excluding the elevated left heart pressure (measured as the PCWP) as a cause of right HF. However, it is an invasive procedure and its use cannot be recommended routinely.

Cardiac Bio-Markers

Natriuretic peptides are released by cardiac myocytes. B-type natriuretic peptide (BNP) and N-terminal BNP levels are elevated in patients with cor pulmonale secondary to RV stretch and may be dramatically elevated in acute PE. Given the high sensitivity of these peptides for moderate to severe PAH, their measurement is recommended.

TREATMENT

The primary treatment must be directed to the specific underlying pulmonary condition leading to cor pulmonale. This chapter focuses on the treatment of cor pulmonale secondary to COPD. General principles of medical treatment includes decreasing the work of breathing by assisting ventilation, use of bronchodilators, steroids as well as treatment of any underlying infection. In the management of chronic cor pulmonale, diet and lifestyle modifications play an important role. These include smoking cessation, salt restriction, and weight loss. Structured pulmonary rehabilitation programmes have been useful. Patients with severe PAH, especially if there is history of syncope, should avoid over-exertion. Blood transfusion is indicated in anaemic patients. Phlebotomy should be performed in patients with severe polycythaemia (haematocrit $\geq$65%). This results in reduction in PVR and PAP and improvement in exercise tolerance.

Oxygen Therapy

Long-term oxygen therapy (LTOT) has convincingly shown to improve the pulmonary haemodynamics in patients with COPD.

Adequate oxygenation relieves pulmonary vasoconstriction and reduces PVR and RV after-load. The RV contractility is improved leading to an increase in its stroke volume and cardiac output. Renal vasoconstriction is also relieved, resulting in an increase in urinary sodium excretion. There is improvement in oxygen delivery to brain, heart, and other vital organs.

Two landmark, prospective randomised trials evaluated the pulmonary haemodynamics in patients with COPD using LTOT. In the British Medical Research Council (MRC), oxygen administration for at least 15 hours a day prevented further rise in PAP. Similarly, in the USA, nocturnal oxygen therapy trial (NOTT), administration of continuous oxygen resulted in favourable pulmonary haemodynamics and improved survival as compared to only nocturnal oxygen therapy. Further, the results of many small scale studies also support that the LTOT convincingly attenuates the progression of PAH. It may even reverse the PAH, however, the PAP seldom returns to normal. The longer the daily duration of oxygen therapy, the better are the pulmonary haemodynamics in these patients. Accordingly, continuous oxygen therapy is strongly recommended.

However, it must be emphasised that at times acute administration of high concentration of oxygen to hypoxic COPD patients can adversely affect breathing, especially if there is hypercapnia. These patients need to be observed more closely in the initial phase of domiciliary oxygen therapy to ensure that the ventilatory drive is not being impaired.

Today, three systems: gas cylinders, liquid oxygen systems, and oxygen concentrators are available for delivery of LTOT at home. Of these, the most attractive is the oxygen concentrator which extracts pure oxygen from the room air and provides a constant supply of oxygen. Recent advances in their designs have made these devices portable as these weigh less, easy to carry and store, and the oxygen supply lasts longer.

Diuretics

Diuretic therapy is the mainstay in the management of chronic cor pulmonale with excessive RV over-load. It alleviates dyspnoea, hepatic congestion, and peripheral oedema. It decompresses the RV by reducing the pre-load, reducing in the ventricle wall stress, and improved myocardial performance. Potentially, reduced shift of interventricular septum towards LV improves LV filling and systemic cardiac output. However, excessive volume depletion should be avoided, since significant contraction in the RV filling volume and pressure in the setting of PH may reduce cardiac output. Another potential complication of diuretic therapy is the development of metabolic alkalosis. This suppresses the ventilation and can result in worsening of hypercapnia.

Digoxin

It is of uncertain benefit in the management of cor pulmonale. Its effects on the RV are unclear. Clinical studies do not support its routine use in patients with cor pulmonale. If needed, it should be given in low doses and monitored carefully. It must also be emphasised that patients with COPD are particularly sensitive to its use. It can result in serious arrhythmias in the setting of hypoxia, acidosis, and electrolyte imbalance.

Pulmonary Vasodilators

These agents have been largely studied in the setting of primary PAH (idiopathic PAH) or PAH secondary to connective tissue disorders. No large scale studies or guidelines are available for their use in patients having PAH secondary to pulmonary diseases.

Inhaled nitric oxide is more potent vasodilator than oxygen. However, if used alone, it worsens ventilation-perfusion imbalance. Also, the delivery of nitric oxide and the cost are potential obstacles for its use. The phosphodiesterase-5-inhibitors (sildenafil), prostacyclin and its analogues (epoprostenol) and endothelin receptor antagonist (bosentan) are specific pulmonary vasodilators and have been successfully used in idiopathic PAH, scleroderma and chronic pulmonary thromboembolic disease. It may be possible that in future, these drugs may be used synergistically with LTOT in patients with cor pulmonale secondary to pulmonary diseases.

PROGNOSIS

Before the widespread availability of LTOT, development of PAH in COPD patients doubled the mortality. However, even with LTOT, the 5-year survival is approximately 30% to 35% with mean PAP >25 mm Hg as compared 60% to 65% in those whose initial pressures are <25 mm Hg. Those patients who develop severe PAH (mean PAP >40 mm Hg) suffer extremely poor prognosis with approximate 5-year survival of 15%.

RECOMMENDED READINGS

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Section 24

Rheumatology

Section Editor: Rohini Handa

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24.1 Basic Considerations of Rheumatology

Rohini Handa

Musculoskeletal (MSK) complaints are frequently encountered in clinical practice. Pain is the most common presenting manifestation. Since a wide variety of conditions may give rise to MSK pains, a systematic approach is necessary to arrive at a diagnosis. Patient history is the single most important source of diagnostic information, followed by a careful physical examination. Laboratory investigations play a supplementary role, rather than primary role. Several MSK diseases resemble each other at the outset and a definitive diagnosis may not be possible at the first patient visit. A distinctive pattern may become discernible only over a period of observation. In such a situation, symptomatic treatment without rushing to give a specific label and close follow-up are quite appropriate.

APPROACH TO A PATIENT WITH MUSCULOSKELETAL COMPLAINTS

The three key points that need address are origin of pain, nature of disease, e.g. inflammatory or non-inflammatory, and pattern recognition.

Origin of Pain (Articular or Non-Articular)

The first task of the clinician who is confronted with MSK pains is to ascertain the exact source of pain by history and examination (**Figure 1**). Not all pains around a joint originate in the joint itself. Adjacent periarticular structures such as bone, ligament, tendon, bursa, or muscle may be responsible (**Table 1**). In general, articular pains tend to be diffuse and deep seated. In contrast, the pain of bursitis is characterised by localised point tenderness away from the joint line. Active (patient moves the joint himself/herself) and passive (physician puts the patient's joint through range of motion) movements also help in making this distinction on the bedside. Articular pain is aggravated by both active and passive movements in contradistinction to periarticular pain, which is more aggravated by active than passive movements. Mechanical symptoms like locking, instability or 'giving way' point to articular origin of pain. The clinician has also to be aware of the possibility of 'referred pain'. For example, hip pain may be referred to the knee.

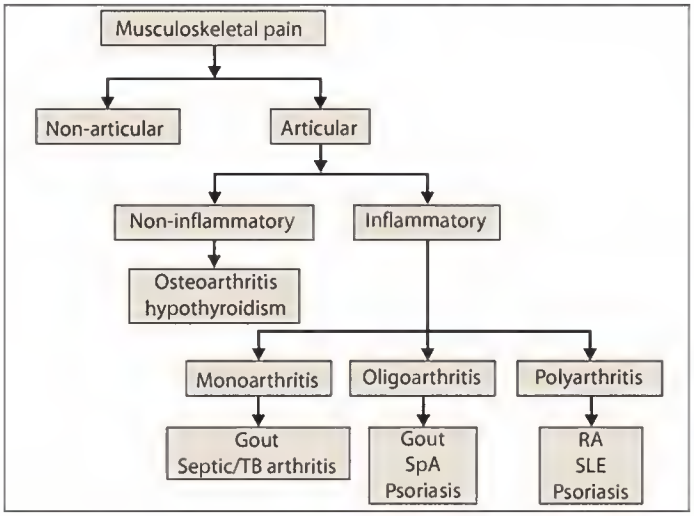


Figure 1: Approach to a patient with musculoskeletal pain.

SpA = Spondarthritides; RA = Rheumatoid arthritis; TB = Tuberculosis; SLE = Systemic lupus erythematosus.

Table 1: Identifying the Site of Musculoskeletal Pain

Arthritis	Joint swelling and tenderness Pain often diffuse, deep seated Pain increases on both active and passive movements
Bursitis	Point tenderness over the anatomical site Pain more on active than passive movements
Tendinitis	Linear, tender swelling of tendon sheath Stretching the tendon induces pain Tendon rub may be palpable/audible
Enthesitis	Pain at tendon insertion site Characteristic feature of spondarthritides
Bone pains	Deep seated Tenderness can be elicited by pressing bones
Muscle pains	Diffuse, not well localised Tenderness on squeezing muscles
Fibromyalgia	Diffuse pain with characteristic tender points
Growing pains	Benign leg pains, typically bilateral, in children of 8-12 years age; usually a diagnosis of exclusion

Arthralgias should be differentiated from arthritis. Arthralgias are joint pains without obvious inflammation; whereas, arthritis is associated with demonstrable features of inflammation like joint swelling and tenderness. Raised temperature and visible redness are usually not seen in chronic arthritides like rheumatoid arthritis (RA) or spondarthritides (SpA). These are more a feature of conditions like acute gout or septic arthritis. Arthralgias are non-specific and seen in several non-MSK conditions, e.g. haematological diseases, post-viral fever, metabolic arthropathy like hypothyroidism, etc. A drug history may be important because some commonly used drugs like statins can cause MSK symptoms.

Nature of Disease (Inflammatory or Non-Inflammatory?)

One of the fundamental concepts in rheumatology is to differentiate inflammatory rheumatic diseases like RA, SpA, lupus, etc. from non-inflammatory disorders like osteoarthritis (OA) since the management is radically different. Inflamed joints stiffen or 'gel' after periods of inactivity and tend to loosen with use. In contrast, non-inflammatory or mechanical joint pain improves with rest and is typically associated with use related pain. **Table 2** outlines the points that help in clinical differentiation. It has to be borne in mind that even patients with inflammatory joint disease can develop mechanical symptoms, for example, secondary OA of knees in a patient with RA.

Table 2: Differentiating Inflammatory from Non-Inflammatory Rheumatic Diseases

	Inflammatory rheumatic diseases	Non-inflammatory rheumatic diseases
Examples	RA, SpA, SLE	OA, trauma, hypothyroidism
Morning stiffness	> 30 minutes	< 30 minutes
Pain aggravation	On resting the joint	On moving the joint
Spontaneous flares	Common	Uncommon
Acute phase reactants like ESR, CRP	Increased	Normal

RA = Rheumatoid arthritis; SpA = Spondarthritides; SLE = Systemic lupus erythematosus; ESR = Erythrocyte sedimentation rate; CRP = C-reactive protein.

Pattern Recognition

Joint pains are a near universal feature of rheumatic or MSK diseases. However, other features like chronology, number/type/sequence of joints affected, symmetry, presence or absence of fever, extra-articular involvement, etc. give rise to a distinctive pattern that helps in making a diagnosis (**Table 3**). For example, an inflammatory polyarthritis in a young woman that is associated with fever and malar rash is highly likely to be lupus. Similarly, an insidiously developing arthritis associated with Raynaud's phenomenon and skin thickening and tightening suggests a diagnosis of systemic sclerosis (SSc). It is worthwhile to remember that on occasions, especially at disease onset, the symptoms and signs may not fit into any one pattern, when the term 'undifferentiated' arthritis is used. Over a period of time, the disease may resolve, evolve into a definitive entity or stay 'undifferentiated'. It is because of this reason that management decisions in rheumatology are based on organ involvement rather than diagnostic labels. Often, features of two or more MSK diseases may be present in the same patient when the term 'overlap syndrome' is employed. The various features that aid pattern recognition are discussed below:

Table 3: Pattern Recognition in Musculoskeletal Diseases

Mode of onset
- Acute
- Insidious

Duration
- Acute or self-limited
- Chronic

Number of affected joints
- Monoarthritis
- Oligoarthritis
- Polyarthritis

Distribution
- Symmetrical or asymmetrical
- Lower limbs versus upper limbs
- Small versus large joints
- Specific joints

Extra-articular features
- Fever
- Mucocutaneous lesions
- Eye
- Nodules

Sequence of involvement
- Intermittent
- Additive
- Migratory

Chronology

The mode of onset and duration of symptoms help in differential diagnosis. Acute onset is seen with septic arthritis, reactive arthritis, viral arthritis, gout or trauma. On the other hand, conditions like RA, SpA and OA tend to be insidious in onset. Based upon duration, MSK complaints may be classified into acute (lasting <6 weeks) or chronic (lasting >6 weeks). Patients with acute, self-limited conditions like viral arthritis may require only a limited evaluation and follow-up. However, patients with symptoms lasting >6 weeks need detailed evaluation. Other groups of patients who merit detailed evaluation irrespective of symptom duration are patients with prominent constitutional/systemic symptoms, e.g. fever, weight loss etc., older patients and patients who exhibit multiple organ involvement.

Number of joints affected

Arthritides are divided into monoarthritis (single joint involvement), oligoarthritis (affecting 2, 3 or 4 joints, also known as pauci-articular disease) and polyarthritis (affecting ≥ 5 joints). The important conditions in each category are listed in Table 4. It is important to know the number of joints affected because it narrows down the diagnostic possibilities, and helps the clinician in embarking upon investigations in a planned manner. Involvement of a single joint should prompt the clinician to consider crystal arthropathy (like gout) or septic arthritis. A good rule of the thumb is to consider every case of monoarthritis as infection of the joint unless proven otherwise. Joint aspiration and synovial fluid analysis are mandatory. Overlooking septic arthritis is a serious error because delay in treatment rapidly results in joint destruction. Synovial fluid should be subjected to gross examination, total and differential leucocyte counts, Gram and Ziehl-Neelsen staining, culture, and crystal studies. Protein and sugar estimations in synovial fluid, unlike CSF or pleural/peritoneal fluids are of no value. Tests for mucin, clot and viscosity are no longer performed. Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* in synovial specimens can be associated with false positives and should never be interpreted in isolation from clinical findings. The normal synovial fluid has a cell count less than 200 WBCs/mm^3, mostly mononuclear. The cell count in non-inflammatory conditions like OA is less than 2000 WBCs/ mm^3 while the count in inflammatory conditions like RA and gout is >2000 WBCs/ mm^3. Septic arthritis is associated with very high counts in range

Table 4: Differential Diagnosis Based on Number of Joints Affected

Monoarthritis	Oligoarthritis	Polyarthritis
Septic arthritis	Gout	Rheumatoid arthritis
Tuberculous arthritis	Juvenile idiopathic arthritis (JIA)	Psoriatic arthropathy
Gout and other crystal deposition diseases	Psoriatic arthropathy	SLE Systemic sclerosis
Spondarthritides	Spondarthritides	Juvenile idiopathic arthritis
Monoarticular presentation of polyarticular disease		Adult-onset Still's disease Inflammatory bowel disease Gout (rarely)

of 100,000/mm³ with >90% polymorphonuclear leucocytes. Synovial fluid crystal identification is the gold standard for diagnosis of gout and other crystal arthropathies.

The SpA constitute the vast majority of oligoarthritides encountered in clinical practise. It is a big group of inter-related conditions where ankylosing spondylitis is the prototypic illness. Other disease entities in SpA include reactive arthritis (including Reiter's syndrome), psoriatic arthropathy, arthritis associated with inflammatory bowel disease and undifferentiated SpA. Clinically SpA should be suspected whenever a young patient less than 40 years (males outnumber females) presents with inflammatory low back pain and asymmetrical, lower limb, large joint oligoarthritis, i.e. asymmetric involvement of hips, knees or ankles. While dealing with low backache (LBA), it is clinically helpful to differentiate between mechanical and inflammatory low backache. Mechanical causes comprise more than 90% cases of LBA. Inflammatory LBA, a typical feature of SpA, worsens after rest or prolonged sitting in the same posture, in contrast to mechanical causes like prolapsed intervertebral disc which improve on rest. Early morning stiffness, buttock ache, enthesitis, dactylitis, peripheral joint synovitis and eye involvement, if present, support the diagnosis of SpA. Sacroiliitis is the characteristic radiologic hallmark of SpA. HLA B27 is present in a varying proportion of patients with SpA depending on the underlying condition. However, HLA B27 can be present in healthy individuals also. The presence of HLA B27 does not mean SpA and conversely, the absence of HLA B27 does not rule out SpA.

Gout presents most often as monoarthritis, less commonly as oligoarthritis and rarely as polyarthritis. JIA and psoriasis can cause both oligoarticular and polyarticular joint disease. Spondarthritides are characterised by inflammatory low back pain in addition to arthritis.

Another clinical feature with discriminant value is sausage digit or dactylitis seen in reactive arthritis or psoriatic arthropathy. Herein, the entire digit is diffusely swollen. This is clinically a very important point of distinction from joint diseases like RA where only the joint gets swollen (fusiform or spindle-shaped swelling) and not the entire digit (**Figures 2A and B**).

The term polyarthritis refers to involvement of more than four joints. It may be due to inflammatory causes like RA, SLE, psoriasis, systemic sclerosis (SSc), juvenile idiopathic arthritis (JIA), rheumatic fever (RF), adult-onset Still's disease, etc. or non-inflammatory causes like OA. Hand examination is crucial in patients with polyarthritis as explained below.

Symmetry

Symmetrical involvement refers to affliction of the same joints on right and left sides. Even in symmetrical involvement, mirror image symmetry is not required. To clarify things, involvement of right 4th, 5th and left 2nd metacarpophalangeal (MCP) joints is deemed symmetrical involvement of MCP joints. RA, systemic lupus erythematosus (SLE), SSc, and nodular OA of hands are typical examples of symmetric polyarthritis. Gout and SpA are typically asymmetric oligoarthritides. Psoriasis can cause either asymmetric oligoarthritis or symmetric polyarthritis. The most important practical point is that a clinician should hesitate to give a diagnosis of RA, if the disease is asymmetrical.

UPPER LIMB VERSUS LOWER LIMB JOINT INVOLVEMENT

This can provide a clue to the differential diagnosis. Joints of both upper and lower limbs are involved in RA, SLE and psoriasis. Predominant involvement of lower limbs is seen in gout, SpA and erythema nodosum, whereas, haemochromatosis preferentially affects joints of upper limbs.

Type of Joints Affected

Small versus large

RA typically affects both small and large joints. In fact, inflammatory, symmetric polyarthritis of small joints of hands like MCP joints and proximal interphalangeal (PIP) joints, is a characteristic feature of RA. Similarly, psoriasis, lupus and SSc affect both small and large joints. In contrast, SpA affects large joints much more than smaller joints. Therefore, the typical pattern of joint involvement in SpA is asymmetric oligoarthritis of large joints of lower limbs. Thus, the pattern in RA and SpA is quite different and distinctive, permitting bedside recognition.

Specific joints

These can give a clue to the nature of arthritic illness, e.g. distal interphalangeal (DIP) joint involvement is characteristic of OA, while DIP joints are spared in RA. Other conditions which give rise to DIP joint involvement are psoriasis and SSc. Involvement



Figures 2A and B: (A) Dactylitis seen in reactive arthritis versus (B) fusiform swelling in rheumatoid arthritis.

of the first carpometacarpal joint is typical of OA, while ankle and shoulder are rarely involved in primary OA.

Spine

Spinal involvement other than cervical spine is rare in RA. In contrast, inflammatory low back pain is a characteristic feature of SpA.

Sequence or Pattern of Involvement

The three common patterns of joint involvement are intermittent, additive, and migratory. Intermittent arthritis is episodic and the patient may be totally asymptomatic in between the episodes. Examples include gout, Behçet's syndrome, Reiter's syndrome, intermittent hydrarthrosis, and palindromic rheumatism. Additive arthritis is one where more and more joints are afflicted with time. This is seen with RA, SpA, psoriasis, OA, etc. Migratory polyarthritis refers to a pattern wherein pain and swelling in a specific joint starts rapidly and subsides in 24 to 36 hours; the arthritis then picks up new joints. The difference from additive pattern is that the previously involved joints in migratory pattern return to normal as new joints become involved, whereas in the former the joint involvement persists. Migratory pattern is seen in rheumatic fever, gonococcal arthritis, viral disease, sarcoidosis, and bacterial endocarditis.

These patterns may not be seen in the classical form due to treatment received by the patient. Also, these patterns may coexist in the same patient. However, when one pattern dominates, it may suggest a particular diagnosis.

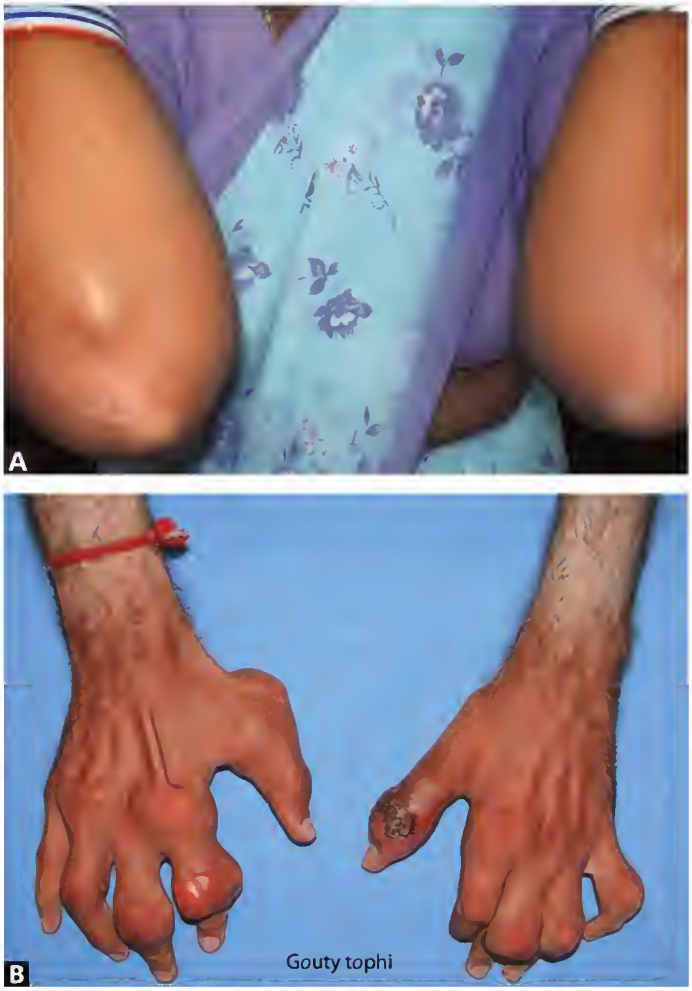
One of the commonly overlooked diagnoses in India is juvenile idiopathic arthritis (JIA), formerly known as juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis (JCA), in children below the age of 16 years. There is a tendency to label all joint pains in children as rheumatic fever (RF) with undue reliance on one laboratory marker, that is, elevated ASO (anti-streptolysin O) titres. The joint pains in RF are migratory, affect large joints and tend to subside over 6-12 weeks, with or without treatment. The major brunt is borne by the heart. In contrast, the arthritis in JIA tends to be additive, persistent, and may involve small or large joints. The presence of deformities strongly militates against a diagnosis of RF, since the arthritis in RF is most often non-deforming.

Extra-Articular Features

Features that may be associated with joint involvement like fever, skin lesions, nodules, etc. play a role in differential diagnosis. Fever along with arthritis narrows down the diagnostic possibilities to SLE, systemic-onset JIA (Still's disease), vasculitis, infective endocarditis, rheumatic fever and adult-onset Still's disease. It is important to realise that although malaise is very common in RA, fever of moderate-to-high grade is not seen with RA and should necessitate a search for other causes.

Mucosal or cutaneous lesions are seen in SLE, psoriasis, Behçet's syndrome, reactive arthritis, SSc, erythema nodosum, vasculitides, gonococcal arthritis, etc. The malar rash of SLE is characteristic and can be appreciated even in dark skinned individuals. Gonococcal infection usually occurs in young, sexually active adults and the skin lesions comprise of a pustule with an erythematous base. Nail changes of psoriasis can easily be masked by nail paint in female patients.

The type of eye involvement may also vary with different eye diseases. RA usually causes keratitis or scleritis in contrast to uveitis seen in SpA. A detailed description of skin/eye manifestations of various rheumatic diseases is beyond the scope of this chapter.



Figures 3A and B: Arthritis with nodules.

Conditions causing nodules in a patient with arthritis include RA, OA (Heberden and Bouchard nodes), tophaceous gout, rheumatic fever, multicentric reticulohistiocytosis, sarcoidosis, erythema nodosum, vasculitides, etc. (**Figures 3A and B**). However, the associated features make the pattern recognition possible. For example, carditis, migratory polyarthritis, erythema marginatum and chorea in RF hold the clue to diagnosis. Rheumatoid nodules are uncommon in Indian patients with RA when compared to Western patients. Similarly, nodular OA of hands is less often encountered in India as compared to Caucasians.

CONCLUSION

Rheumatology is predominantly a clinical subspecialty. Pattern recognition, based on detailed history and thorough physical examination, remains the cornerstone of the diagnostic approach to a patient with musculoskeletal complaints. A good history provides as much as 80% of diagnostic information, with the physical examination and investigations contributing only 15% and 5%, respectively.

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1. Handa R. Approach to a patient with arthritis- mono/oligoarthritis. *Notionol Medicol Journol of Indio* 1999; 12:121-2. *One of the series of 5 orticles by the author thot provide the reoders with o step by step, bedside opprooch to rheumatic complaints.*

24.2 Soft Tissue Rheumatism and Regional Rheumatic Pain Syndromes

Ved Chaturvedi

INTRODUCTION

Soft tissue rheumatism refers to symptoms arising not from the joints themselves, but those that arise from the periarticular structures, such as ligaments, tendons, insertion of tendons at bony sites (entheses), tendon sheaths, bursae and muscles. STR may present clinically in two main forms:

1. Localised (regional) pain syndromes
2. Diffuse pain syndrome or fibromyalgia

Regional rheumatic pain syndromes are a common presentation in general practice. Diagnosis of these pain syndromes is predominantly clinical and depends upon general awareness of these disorders and knowledge of anatomy, especially soft tissue structures. One important point which the author has learnt is to use two colour pens for marking the exact site of pain—red for swelling and blue for pain. The author terms this method as 'Red Blue Marking Method' for regional rheumatic pain syndromes which leads to better symptom localisation. It is more rewarding to do a thorough physical examination and use the simple marking methods than ordering unnecessary tests. The aetiopathogenesis of regional rheumatic pain syndromes is still unclear. Factors implicated include genetic, environmental, occupational, repetitive trauma, psychological, etc. The regional rheumatic pain syndromes are classified by the major anatomical structure involved (**Table 1**). Low backache has been dealt within a separate chapter.

Table 1: Common Regional Rheumatic Pain Syndromes

Shoulder
- Rotator-cuff disorders
- Bicipital tendinitis
- Adhesive capsulitis (frozen shoulder)

Elbow region
- Olecranon bursitis
- Lateral epicondylitis (tennis elbow)
- Medial epicondylitis (golfer's elbow)

Wrist
- DeQuervain's tenosynovitis
- Carpal-tunnel syndrome
- Trigger finger/thumb
- Dupuytren's contracture

Hip
- Trochanteric bursitis
- Iliopsoas bursitis
- Ischial bursitis
- Meralgia paraesthetica

Knee
- Bursitis (pre; infra-patellar, anserine)
- Baker's cyst
- Osteochondritis dissecans
- Traction apophysitis
- Anterior knee pain syndrome
- Patellar instability syndrome

Ankle and foot
- Achilles tendinitis
- Retrocalcaneal bursitis
- Plantar fasciitis
- Bony deformities
- Morton's neuroma
- Metatarsalgia

DISORDERS OF THE SHOULDER REGION

Shoulder pain may have its origin in the glenohumeral joint, acromioclavicular joint or periarticular structures, or be referred from the cervical spine (felt at the supraspinatus region), thoracic outlet, subdiaphragmatic conditions (felt at the tip of the shoulder), or brachial plexus. Rotator cuff disorders (impingement syndrome) are the most common cause of shoulder pain. The spectrum ranges from mild tendinitis of the rotator cuff, with or without inflammation of the adjacent subacromial bursa, to bicipital tendinitis, tears of the rotator cuff and secondary glenohumeral osteoarthritis. Trauma, unaccustomed activities, ageing, vascular compromise, etc. are contributory factors.

Rotator Cuff Disorders

The presentation of rotator-cuff lesions depends on the age of the patient. Young adults often present acutely after forceful activity like throwing or after trauma. In the middle-aged individuals, the onset is more gradual and history of repetitive or strenuous upper limb activity may be present. There may be no precipitating factors in the elderly patients. The patient typically experiences pain on active abduction, and sometimes when lowering the arm. Patients have difficulty in working overhead or lifting and reaching behind their back when dressing. Clinical examination reveals limitation of active movement by pain, and tenderness localised to the rotator cuff and greater tuberosity. The 'supraspinatus' or 'empty can' sign (pain on resisted elevation of the arm to 90° midway between abduction and forward flexion with the thumb pointing downwards in internal rotation) is often positive. Neer's 'impingement sign' (one hand of the examiner forward flexing the patient's arm while the other hand restricting scapular rotation) is positive; the patient develops pain in the overhead position near the end of full flexion. Rotator cuff tears can be partial or complete. Clinical features include shoulder pain on abduction, night pain, varying degrees of weakness of abduction and external rotation, local tenderness and loss of range of movement. The supraspinatus and impingement signs are usually positive: inability to actively maintain 90° of passive shoulder abduction. Magnetic resonance imaging and ultrasound are employed for diagnostic imaging.

Initial management of rotator cuff tendinitis consists of rest, nonsteroidal anti-inflammatory drugs (NSAIDs), and physical treatments including heat application and range of movement exercises (early mobilisation of the shoulder is important in minimising the disability). If symptoms persist for more than 2 to 4 weeks, injection of a depot corticosteroid into the nearby subacromial bursa is often beneficial. Surgery is indicated for intractable pain and severe functional impairment.

Bicipital Tendinitis

Bicipital tendinitis is often related to chronic impingement of the bicipital tendon by the acromion. It usually occurs in association with rotator cuff tendinitis and glenohumeral instability. The pain is felt over the anterior aspect of the shoulder after radiating into the biceps muscles. It is increased by the overhead activities, shoulder extension and elbow flexion. Localised tenderness is present over the tendon in the

bicipital groove. Bicipital tendon pain can be reproduced by resisted supination of the pronated forearm with the elbow 90° flexed, shoulder flexion against resistance. Treatment entails rest, NSAIDs, and physical modalities like hot packs, ultrasound, etc. Some cases require local corticosteroid injection into the tendon sheath parallel to the tendon fibres. Care should be taken to avoid direct injection into the tendon.

Subacromial Bursitis

Chronic subacromial bursitis often occurs in association with rotator cuff tendinitis and chronic impingement. Primary subacromial bursitis due to trauma, infection, rheumatoid arthritis (RA), or other arthritic disorders is rare. Abduction is painful, and there is local tenderness and sometimes fluid distension of the bursa, which is visible just anterior to the acromion with the shoulder extended.

Adhesive Capsulitis

Adhesive capsulitis, also known as frozen shoulder capsulitis, or pericapsulitis, is characterised by progressive, global restriction of shoulder movements associated with pain and functional disability. A period of immobility of the shoulder is the most commonly identified predisposing factor. It is more common after the sixth decade and in females. The condition may also coexist with diabetes mellitus, hypothyroidism, lung carcinoma, myocardial infarction, cardiac surgery and shoulder trauma. Although adhesive capsulitis is often a self-limiting disorder, the extent and rate of recovery are variable. Dynamic sonography, demonstrating limitation of sliding movements of the supraspinatus tendon during abduction of the arm is diagnostic. Treatment of adhesive capsulitis consists of NSAIDs, physical therapy and corticosteroid injections into both the glenohumeral joint and subacromial bursa. Physiotherapy is important. Gentle range of movement exercises, beginning with pendulum exercises and wall climbing with the fingers, and finally active strengthening exercises, are required to restore joint mobility. Operative capsulotomy, with surgical release of the coracohumeral ligament and of subacromial adhesions, is occasionally beneficial in patients with chronic symptoms refractory to conservative treatment.

DISORDERS OF THE ELBOW REGION

Lateral epicondylitis (tennis elbow), medial epicondylitis (golfer's elbow), and olecranon bursitis are the common soft tissue lesions at the elbow.

Lateral Epicondylitis (Tennis Elbow)

It usually afflicts the dominant arm in individuals aged 40 to 60 years. In actual practice less than 5% cases can be attributed to tennis playing. There are no specific precipitating factors for this condition, which results from inflammation of the soft tissues attaching to the lateral epicondyle, especially, extensor carpi radialis brevis tendon. Patients present with pain over the lateral epicondyle and the surrounding area. Grip may be impaired and routine activities like lifting weight, shaking hands may produce pain. Examination reveals tenderness over the lateral epicondyle. Another cardinal sign is increase in pain in resisting wrist dorsiflexion while the elbow is in extension. Symptoms may also be precipitated by extending the elbow with wrist palmar flexed. Physical modalities like heat or cold, NSAIDs and local corticosteroid injections are used for its management. Some patients benefit by elbow splinting also. Refractory cases may need surgical intervention in the form of lateral release of the extensor tendon.

Medial Epicondylitis (Golfer's Elbow)

This is much less common than tennis elbow and results from involvement of the common flexor tendons at the medial epicondyle. Pain over the medial side of elbow on resisted wrist flexion while the elbow is extended in a reliable sign. The management is similar to that of lateral epicondylitis.

Olecranon Bursitis

The subcutaneous olecranon bursa is a frequent site for traumatic, inflammatory, and septic bursitis. Inflammatory olecranon bursitis may be due to RA, psoriatic arthritis, gout or sepsis. Non-septic olecranon bursitis can result from repetitive, minor, or unnoticed trauma to the elbow. It is less disabling as pain is minimal. Local tenderness and swelling are present. Management involves aspiration, NSAIDs, and one or more injections of corticosteroid.

DISORDERS OF THE WRIST AND HAND

DeQuervain's Tenosynovitis

DeQuervain's tenosynovitis of the abductor pollicis longus and extensor pollicis brevis is commonly due to repetitive occupational activity. It is common in females in the age group of 30 to 50 years. It may also occur in association with RA, psoriatic arthritis, and pregnancy, and during the post-partum period. Most patients complain of pain along the radial aspect of the wrist and at thumb base during pinch grip, grasping and other hand activities. Finklstein's test is positive (the thumb is flexed into the palm and wrist deviated ulnarly resulting in pain over the radial side). Treatment consists of heat application, NSAIDs, and splinting.

Trigger Finger or Thumb (Stenosing Digital Tenosynovitis)

The pathological lesion is tenosynovitis of the flexor tendons of the finger or thumb, resulting in fibrosis localised to the annular pulley that overlies the metacarpophalangeal joint. A nodular thickening of the tendon often develops at the site of stenosis, that interferes with the normal gliding of the tendon, resulting in pain over the area of the pulley and 'snapping' or 'triggering' of the finger or thumb. Examination reveals tenderness over the area of the proximal pulley, and often limitation of digital flexion and extension. Management consists of heat application, exercises, NSAIDs and local steroid injections.

Dupuytren's Contracture

This presents as nodular thickening and contraction of the palmar fascia which may lead to flexion contractures of the fingers. The ulnar side is commonly affected. Treatment involves physiotherapy and local steroid injections.

DISORDERS OF THE HIP REGION

It is important to differentiate pain arising from hip joints and adjacent structures from referred pain. Referred pain at the hip can be due to thoracolumbar spine disorders, peripheral vascular diseases and intra-abdominal pathology. The skin over the greater trochanter is innervated by T12 roots, while L1 supply the inguinal region and L2-4 supply the anterior aspect of thigh. Radiculopathies due to spine disorders can, therefore,

mimic hip pain. However, in these illnesses there is no limitation of hip movements. Abdominal problems like inguinal or femoral hernias, ureteric stones, tuberculous abscess, retroperitoneal appendicitis and pelvic inflammatory diseases may also masquerade as hip arthritis. Careful clinical examination makes differentiation possible at the bedside. Thrombosis or aneurysm of aorta and its iliac branches can give rise to buttock, thigh or calf pain that may be confused with hip pain. Examination of peripheral pulses can be rewarding in such a situation. The common rheumatic pain syndromes around the hip include trochanteric bursitis, ischiogluteal bursitis and illopsoas bursitis.

Trochanteric Bursitis

Patients with trochanteric bursitis present with a deep, aching pain over the lateral upper thigh which is often intensified by walking but it may be worse at night, especially when the patient is lying on the affected side. The diagnosis is confirmed with palpation of the posterior aspect of the greater trochanter which elicits local tenderness in this area. Treatment includes rest and local injection of depot steroids.

Ischiogluteal Bursitis

Also called 'weaver's bottom', it results from prolonged sitting on hard surface. The bursa lies over the ischeal tuberosity and helps gliding of the gluteus maximus muscle. The diagnosis is made by the characteristic history and by eliciting tenderness on palpation of the ischeal tuberosity with the patient lying supine with the hip flexed. Treatment consists of using a cushioning seat, NSAIDs, stretching exercises while lying on the cushion. A local depot steroid should be given cautiously due to adjoining sciatic nerve.

Iliopsoas Bursitis

The bursa lies over the anterior surface of the hip joint under the iliopsoas muscle and between the hip joint capsule. Typically, patients present with an inguinal mass which may be painful and may be associated with secondary femoral vein obstruction or femoral nerve compression. Intra-articular pathology of hip joint may be associated with the bursitis.

DISORDERS OF THE KNEE REGION

Knee pain is a common articular complaint. Non-arthritic conditions comprise a large proportion of knee complaints, particularly in younger age groups.

Pre-Patellar Bursitis

Pre-patellar bursitis presents as a painful, red swelling anterior to the kneecap and is seen most often in people who spend a lot of time kneeling. Active knee extension is usually quite painful although passive knee flexion is usually only minimally limited. Infection, gout and repeated trauma are usual factors.

Infra-Patellar Bursitis

The deep infra-patellar bursa lies between the upper portion of the tibial tuberosity and patellar ligament and it is separated from the knee joint synovium by a fat pad. It presents as tenderness in the soft tissues of either side of the ligament just proximal to its insertion on the tibial tubercle.

Anserine Bursitis

The anserine bursa is located about 5 cm below the medial aspect of the knee. Anserine bursitis is a term loosely applied to pain and associated local tenderness in this region. The typical presentation is that of an obese woman presenting with nocturnal pain, and rarely, a palpable mass on upper and medial aspect of tibia.

Gastrocnemius-Semimembranous Bursitis (Baker's Cyst)

Any cause of synovitis in the knee can lead to leakage into the popliteal space when a communication exists between the gastrocnemius-semimembranous bursa. Symptoms consist of fullness and tightness in the popliteal space which increases with walking. A Baker's cyst can be detected clinically by palpation of fullness in the medial-third of the popliteal fossa. Ultrasonography will establish the diagnosis in most of the cases (**Figure 1**). Baker's cysts may dissect into the muscles of the calf, simulating thrombophlebitis. Rupture of a Baker's cyst should be confirmed by Doppler ultrasound.

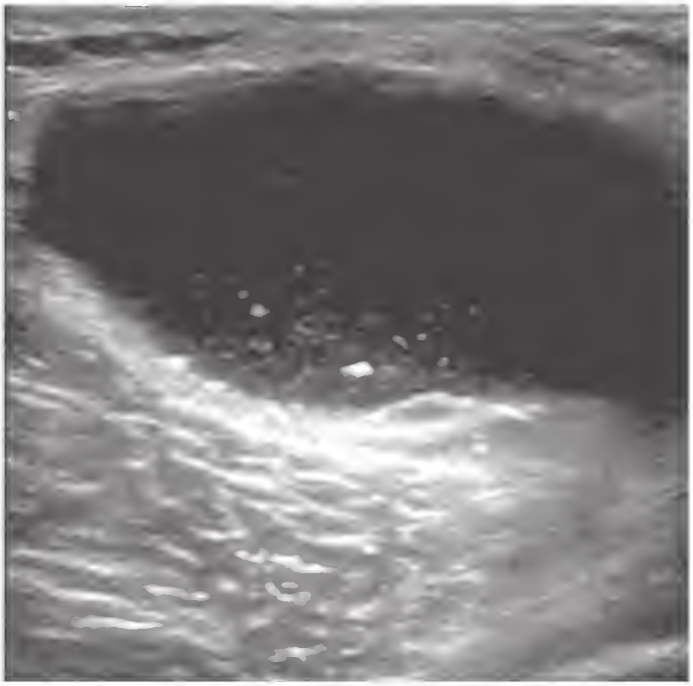


Figure 1: Ultrasound demonstrating Baker's cyst.

Treatment of an intact or ruptured Baker's cyst includes depot steroid injection in knee. Due to close proximity of popliteal vessels, it is wise not to use posterior approach for direct aspiration of the Baker's cyst.

Iliotibial Band Syndrome (Runner's Knee)

The iliotibial band is a fascial band connecting the ilium with the lateral tibia, connecting to the tensor fasciae lata and the gluteus maximus. Repetitive flexion and extension, particularly with high intensity running, can lead to inflammation of the iliotibial band or at its associated bursa overlying the lateral femoral condyle. Examination reveals tenderness localised to the lateral femoral condyle approximately 2 cm above the joint line, pain with weight bearing on the knee when flexed 30° to 40°. Treatment consists of rest, local heat, and depot corticosteroid.

Internal Derangements of Knee

Internal derangements of the knee refer to disruption of the normal functioning of the ligaments and menisci usually due to significant, often athletic trauma. MRI and arthroscopy are helpful in diagnosis.

Patellofemoral Pain Syndrome

Chondromalacia patellae is a term which has been used synonymously with patellofemoral pain. It is most commonly described as poorly localised, anterior knee pain, frequently accompanied by the 'grab' sign (patients cover the entire front of the knee with the band when asked to identify the location of the discomfort). Pain frequently occurs after prolonged sitting with flexed knees, the so-called 'theatre' sign. Treatment modalities include avoidance of overuse, exercises, and anti-inflammatory medications.

DISORDERS OF THE FOOT

The most common causes of heel pain are Achilles tendinitis, retrocalcaneal bursitis, and plantar fasciitis. Achilles tendinitis presents with gradual onset of pain with foot push off. Physical examination reveals tenderness and occasionally thickening of the tendon which can also be detected by ultrasonography (**Figure 2**). Retrocalcaneal bursitis is associated with posterior heel pain and may be associated with tender swelling on both sides of the insertion of the tendon. Localised pain with weight-bearing on the undersurface of the heel is the typical presentation. Spondyloarthopathy, trauma, gout and hypothyroidism are the few known causes. Treatment consists of a heel pad or cushion, rest, local heat, anti-inflammatory agents or in some cases local steroid injection. Plantar fasciitis is the most common cause of subcalcaneal heel pain. Patients usually complain of pain on the undersurface of heel on weight bearing, especially after a period of rest, e.g. on taking the first few steps on awakening in the morning. Localised tenderness may be elicited on the anteromedial part on calcaneum on its plantar surface. Radiographs are often normal. Plantar spurs, if seen, are often not the cause of the heel pain which is due to inflammation of the plantar fascia. Causes include repetitive overuse as in athletes, excessive standing and walking, improper footwear with hard soles, and spondyloarthropathies. Treatment is by means of rest, hot fomentation, NSAIDs, soft footwear with heel cushions, ultrasound therapy, and sometimes local injection of corticosteroids.

Metatarsalgia

Metatarsalgia is the symptom of pain across the plantar surface of one or more metatarsophalangeal joints and may be due to diverse causes including callosities, flat-foot, arthritis, muscle imbalance, fat pad atrophy, Morton's neuroma, hallux valgus or rigidus, tarsal tunnel syndrome, and arterial insufficiency. Tarsal tunnel syndrome most often refers to compression of the posterior tibial nerve as it courses around the medial malleolus. The typical presentation is with dysaesthesias involving the plantar aspect of the foot that is often more prominent at night. The diagnosis of tarsal tunnel syndrome may be confirmed by nerve conduction studies documenting delay in conduction of the posterior tibial nerve across the ankle.

DIFFUSE PAIN SYNDROME AND FIBROMYALGIA

Fibromyalgia is a clinical syndrome characterised by persistent, diffuse pain in the body. This is typically described by the patient as "pain all over the body" including joints, muscles and spine. However, there is no clinical discernible evidence of inflammation at any of these sites, and therefore, this condition is classified as soft tissue rheumatism. This is more commonly seen in young or middle-aged women and the pain is accompanied by a number of other symptoms including: fatigue, depressed mood, sleep disturbance, headaches and social isolation. Clinical examination reveals multiple, soft tissue tender points over bony prominences, muscles and tendons. The American College of Rheumatology (ACR) classification criteria in vogue required tenderness on pressure (tender points) in at least 11 of 18 specified sites and the presence of widespread pain for diagnosis. Widespread pain was defined

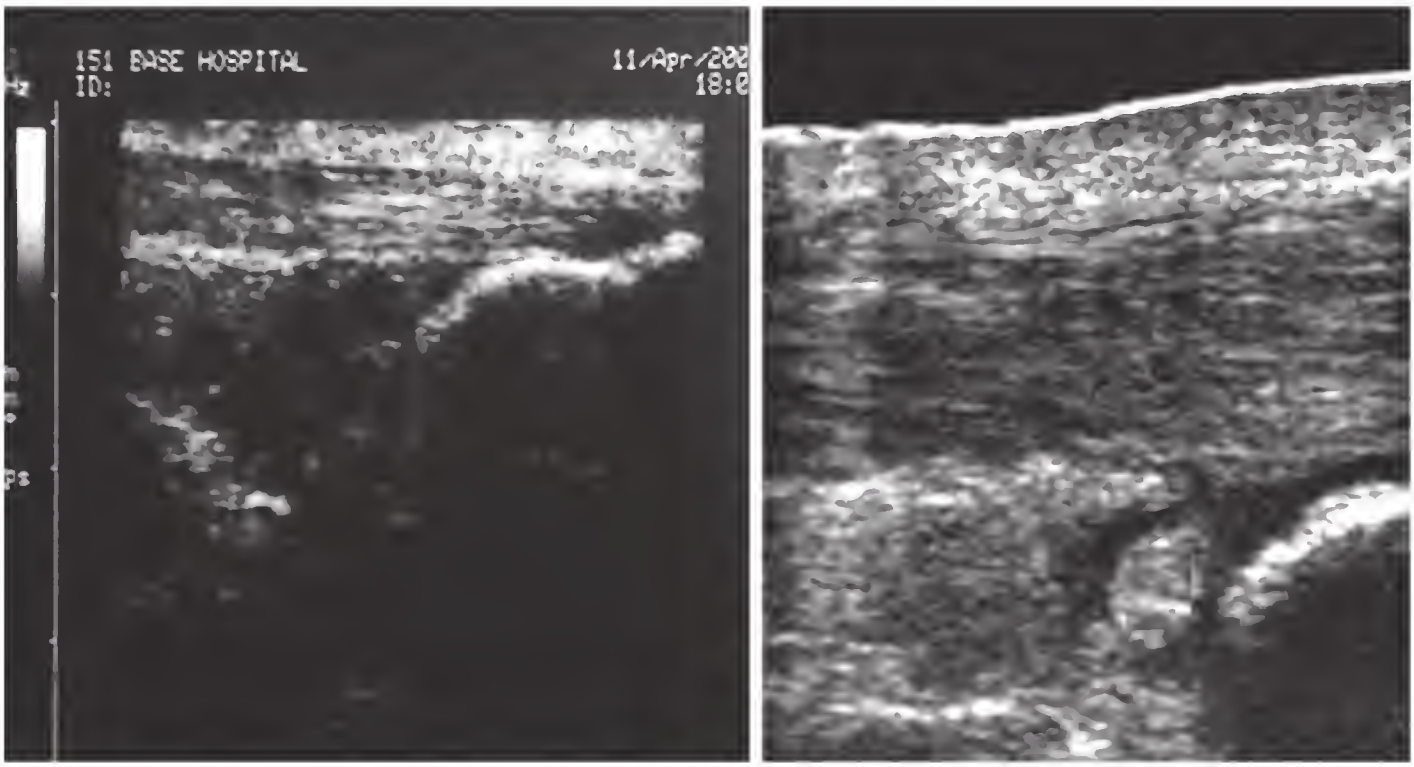


Figure 2: Ultrasound demonstrating Achilles tendinitis.

as axial pain, left- and right-sided pain, and upper and lower segment pain. Recently, the American College of Rheumatology has proposed diagnostic criteria for fibromyalgia that do away with tender point examination and permit a symptom-based diagnosis. A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:

1. Widespread pain index (WPI) >7 and symptom severity (SS) scale score >5 or WPI 3-6 and SS scale score >9.
2. Symptoms have been present at a similar level for at least 3 months.
3. The patient does not have a disorder that would otherwise explain the pain.

The WPI score ranges from 0 to 19 while the SS score ranges from 0 to 12. The successful management of fibromyalgia requires both non-pharmacological and pharmacological measures, with particular emphasis on patient education, in order to explain the nature of the disease and to highlight that joint or bone damage will not occur in this condition, unlike untreated inflammatory arthritis. A suitable programme of graded exercises can be very helpful in maintaining adequate mobility and improving functional capacity. Psycho-behavioural management can also help and these include psychotherapy, hypnotherapy and relaxation response therapy, where available. The drugs that might be useful are analgesics and NSAIDs, tricyclic anti-depressants such as amitryptyline, fluoxetine, gabapentin and pregabalin. For one or two very troublesome tender points not responsive to analgesics or NSAIDs, a local steroid injection may often be helpful.

CONCLUSION

Regional rheumatic pain syndromes, despite being very common in clinical practice, are neither properly recognised nor adequately treated. There are usually no serologic markers or pathognomonic imaging findings. Awareness of the entity and a basic knowledge of regional rheumatic anatomy are sufficient to permit clinical recognition in the vast majority of the cases. Treatment is simple and comprises patient education, NSAIDs, physical modalities like heat, cold, ultrasound therapy, etc. and intralesional corticosteroids.

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24.3 Low Backache

C Panchapakesa Rajendran, S Rajeswari

INTRODUCTION

Low back pain (LBP) is the most common rheumatic disorder accounting for 30% to 50% of rheumatic musculoskeletal complaints encountered by general practitioners. As an ailment, it is second only to the common cold with 70% to 80% of the population experiencing LBP at some point of time. Most often it is a self-limited illness and becomes chronic only in 5% of cases. LBP is the most common pain syndrome in industrial countries with the highest prevalence in persons aged 45 to 65 years. The incidence in the industrial sector in India is 11% in textile workers.

ANATOMICAL CONSIDERATIONS

The functional unit of the lumbar spine consists of two vertebral bodies and an intervertebral disc anteriorly and the facet joints posteriorly (**Figures 1 and 2**). The anterior portion is flexible and serves the functions of shock absorbency and weightbearing. The nucleus pulposus provides shock absorbency to the disc and the annulus fibrosus allows for the flexibility of the functional unit. The posterior portion of the unit protects the neural elements. It acts as a fulcrum and guides the movements for the functional unit. The lower lumbar discs need to bear a load of 1000 kg when stressed with pure compression forces. The posterior segment muscles and abdominal muscles help to dissipate these compression loads. The sacrum and iliac bones function as one unit. The lumbosacral angle also plays a role in determining the posture and degree of spinal curvature. The back is sensitive to 4 to 8 Hz vibrations and whole body vibration produce buckling and slipping of the lumbar discs and degeneration.

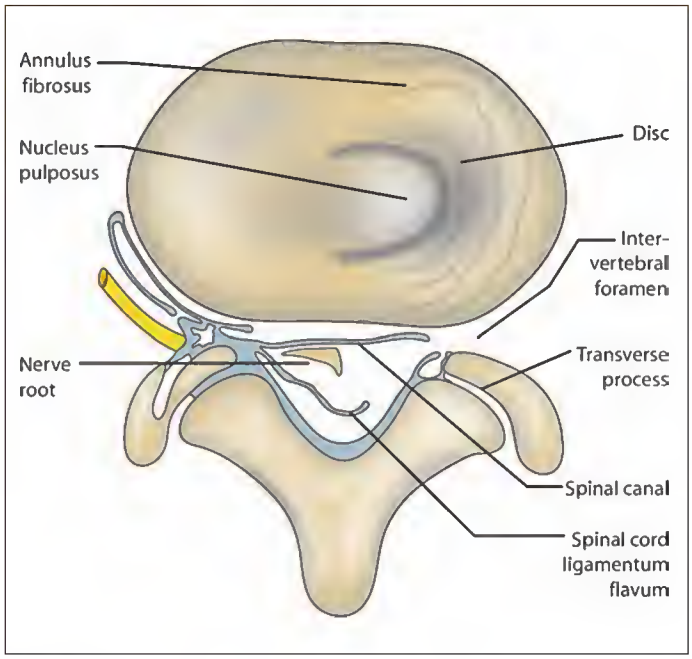


Figure 1: Normal lumbar spinal canal.

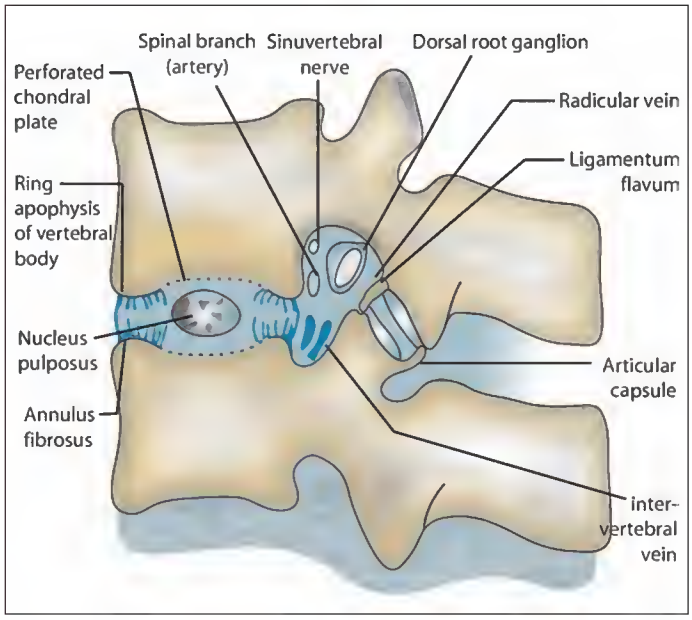


Figure 2: Sagittal section of spine.

AETIOLOGY

Aetiologies of low backache are enumerated in **Table 1**.

Clinical Features and Approach

A detailed history of involved relevant systems, a good social history, and methodical clinical examination are essential for arriving at a diagnosis. LBP can present as acute or chronic pain (**Table 2**). Acute LBP is one where the duration is less than 1 month, subacute from 1 to 3 months, and chronic if the duration is more than 3 months or if pain occurs episodically within a 6 months period. Mechanical causes of low backache account for the majority (90%) of cases while systemic diseases account for only 10%. Acute LBP has a favourable natural history. Most episodes resolve in a few weeks. In one-third of patients, the LBP may last for a month. Chronic LBP of more than 3 months duration is seen only in a minority.

Acute Low Back Pain

It is important to rule out catastrophic conditions enumerated in **Table 3** as they require emergency intervention.

Certain 'Red Flags' (danger signs) of serious disease should be looked out for when dealing with acute LBP. These include history of trauma, fever, incontinence, unexplained weight loss, cancer, long-term steroid use, parenteral drug abuse, intense local pain, human immunodeficiency virus infection, thoracic pain, neurological symptoms, structural spinal deformity, inability to get into a comfortable position associated with a pattern of symptoms not compatible with benign mechanical disease, and lack of response to conservative measures.

'Yellow Flags' are signs which identify patients at risk for chronicity and disability. These include factors like age, physical

fitness, abdominal muscle weakness, smoking, obesity, low educational level, high pain levels and disability, etc. psychosocial factors (like poor cognitive functioning, anxiety, stress, depression, distress, somatisation, etc.), and occupational factors (like manual material handling, bending and twisting, whole body vibration, poor work relationships, social support and job dissatisfaction).

Table 1: Aetiologies of Low Backache

Congenital
- Abnormal vertebral facets
- Sacralisation of L5 transverse process
- Spondylolysis or spondylolisthesis between L5 and S1 vertebrae (Figure 4)

Acquired Inflammatory
- Infective
  - Osteomyelitis, e.g. tuberculosis
  - Discitis
  - Epidural abscess
- Non-infective or rheumatologic
  - Spondyloarthropathies (e.g. ankylosing spondylitis)
  - Trauma to ligaments, muscles, vertebrae or annulus fibrosus with disc prolapse

Vascular
- Abdominal aortic aneurysm dissection
- Epidural haematoma
- Haemoglobinopathies

Neoplastic
- Primary tumours of the spine, e.g. multiple myeloma
- Metastatic

Degenerative
- Disc disease
- Facetal arthropathy
- Spinal canal stenosis

Metabolic
- Osteoporotic vertebral fracture
- Paget's disease

Mechanical
- Poor posture aggravated by
  - Obesity
  - Pregnancy
  - Over work

Referred Pain
- Abdominal viscera (renal, pancreas, posterior duodenal ulcer)
- Pelvic disorders (pelvic inflammatory disease)

Soft Tissue Rheumatism
- Fibromyalgia
- Psychogenic/Malingering
- Miscellaneous
- Whole body vibration
- Computer-related

Chronic Low Back Pain

Patients belonging to this category are those who have not responded to six weeks of conservative management. These patients can be divided into four groups based on the location and radiation of pain as described below:

Localised low back pain

Pain not radiating below the gluteal region forms the largest group in which inflammation, infections, tumour and degeneration have to be ruled out.

Sciatica

Pain radiating below the knee and down the leg and associated with mechanical impingement upon the nerve. A positive straight leg raising test (Figure 3) indicates a herniated intervertebral disc while a positive exercise stress test is in favour of lumbar canal stenosis.

Anterior thigh pain

Conditions like inguinal hernia, hip joint disease, diabetic mononeuropathy, renal calculi, abdominal aneurysm and retroperitoneal tumours have to be ruled out with appropriate investigations.

Posterior thigh pain

It may be due to back strain and referred pain due to damage of muscles in the lumbosacral spine or a high herniated disc (L3-L4 level). Clinical tests to distinguish inflammatory from mechanical back pain should be done (Table 4).

Some special situations are summarised in Table 5.

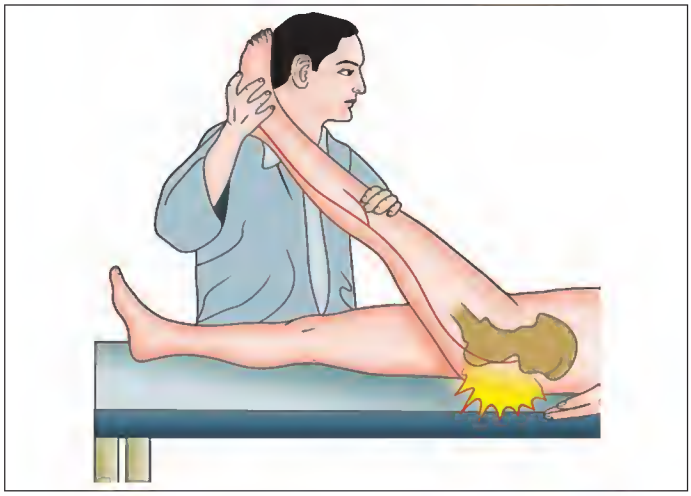


Figure 3: Straight leg raising test. The leg is raised 30° to 70° until radicular symptoms are elicited, when test is positive.

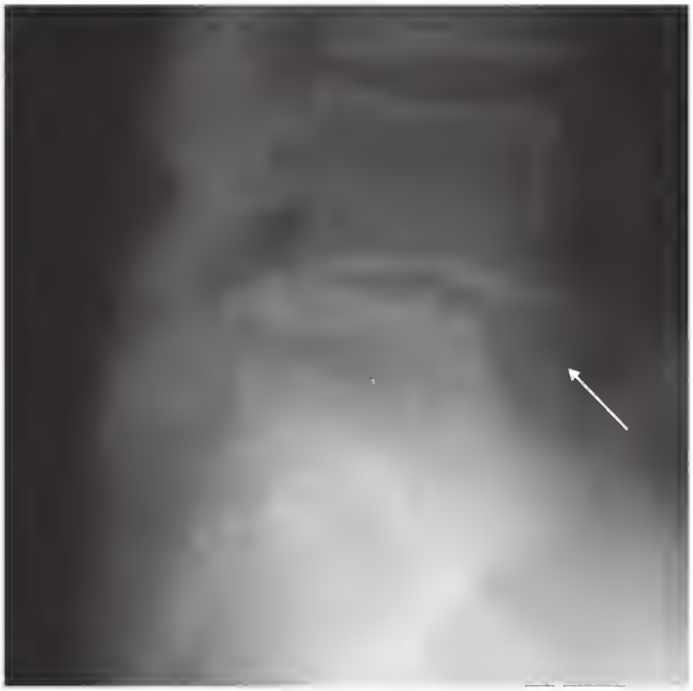


Figure 4: Spondylolisthesis at L5 level.

Table 2: Classification and Features of Low Back Pain

Category	Pathologic Entity	Quality	Location	Onset and Duration	Aggrevating Alleviating Factors	Neurologic Deficit
Superficial somatic (skin, subcutaneous tissue)	Cellulitis	Sharp	Well localised	Acute	Intensified by direct contact	None
Deep somatic	Muscular strain	Sharp	Diffuse	Acute or chronic	Intensified with movement	None
	Arthritis Fracture	Dull Boring	Multiple segments	Chronic	Diminished with rest	None
Radicular	Discogenic	Segmental	Low back	Acute	Aggravated by bending, sitting, Valsalva manoeuvre	None
	Spinal stenosis	Radiating, claudication, paraesthesia	Afferent distribution of affected nerve root	Acute/chronic	Aggravated by lumbar extension, walking, standing relieved by flexion, sitting	Present
Visceral referred	Pancreas, intestine, prostate, endometriosis, abdominal aneurysm	Deep, colicky, boring, tearing	Segmental with radiation inside body	Acute/chronic	Not affected by motion, walking, etc.	None
Nerve root pain	Diabetic femoral neuropathy	Burning paraesthesia, numbness	Radicular		Intensified by sensory stimulation of the damaged nerve	Present
Psychogenic	Depression, conversion reaction, malingering	Variable	Non-dermatomal	Persistent	No consistent correlation	None

Table 3: Catastrophic Conditions Leading to Acute Low Back Pain

Leaking or ruptured abdominal aneurysm
Acute paraplegia due to central herniation of nucleus pulposus presenting as cauda equina syndrome
Epidural haemorrhage
Embolus
Anterior spinal artery thrombosis
Epidural abscess
Spinal cord tumours

Table 4: Differences between Pain due to Inflammatory and Mechanical Causes

Feature	Inflammatory	Mechanical
Age of onset	20-40 years	Any age
Sex	Male > female	Equal
Onset	Subacute	Often acute
Effect of activity	Relieves	Aggravates
Effect of rest	Aggravates	Improves
Radiation to legs	+ diffuse	+ radicular/sclerotomal
Limitation of movements	+ in all directions	+ only in some directions
Neurologic symptoms and signs	Negative	May be present

Table 5: Special Situations

Work related
- Lifting/bending

Childhood and adolescence
- Developmental anomalies
- Infections
- Malignancies
- Carrying heavy school bags

Young adults
- Spondyloarthropathies
- Ligament injuries
- Prolapsed intravertebral discs
- Increased computer usage

Pregnancy
- LBP
- Hyperlordosis
- Muscle stretching
- Pelvic instability
- Myofascial pain

Middle-aged
- Degenerative
- Posterior facet arthropathy

Elderly
- Osteoporosis + fracture
- Degenerative
- Malignancy

INVESTIGATIONS

It needs to be emphasised that investigations play a minimal role in low back pain, especially acute LBA which has a tendency to spontaneous recovery. Investigations may be needed to rule in or rule out 'red flag' conditions. Over reliance on radiographs should be avoided. Evident radiographic abnormalities are often not responsible for back pain. Similarly in chronic LBP, imaging studies should only be obtained if results are likely to influence surgical or medical treatment. However, patients with history of trauma or pointers towards systemic disease need appropriate laboratory investigations and radiological work-up.

Laboratory Investigations

The following laboratory abnormalities reflect a serious underlying pathology. High erythrocyte sedimentation rate, C-reactive protein and low haemoglobin occur in inflammation, malignancy and in systemic disorders. Elevated serum alkaline phosphatase is commonly seen in metastases, osteomalacia and Paget's disease and elevated serum acid phosphatase or prostate-specific antigen in prostatic cancer. The 'M' band in serum electrophoretic pattern is seen in multiple myeloma.

Radiological Investigations

The basic screening procedure is plain radiograph. Additional investigations include computed tomography (CT), magnetic resonance imaging (MRI), myelogram, bone scan, bone densitometry and single photon emission computed tomography (SPECT). CT and MRI are of special value in evaluating the anatomical details (**Figure 5**). MRI is the modality of choice; however, the CT defines the bony architecture of the spinal canal better than MRI. Bone scan is a useful screening procedure for the diagnosis of inflammation, infection and secondaries. Bone densitometry is indicated when osteoporosis is considered. SPECT is performed when a bony abnormality is suspected. In discitis, the tracer uptake has a vertical orientation. In metastatic involvement, the area of increased uptake extends from the vertebral body into the pedicle. Fractures show linear horizontally oriented areas of increased uptake centered in the vertebral body and in the transverse process. Increased uptake centered about the disc space and also seen in and projecting beyond the surface of the vertebral body is noted in degenerative joint disease.

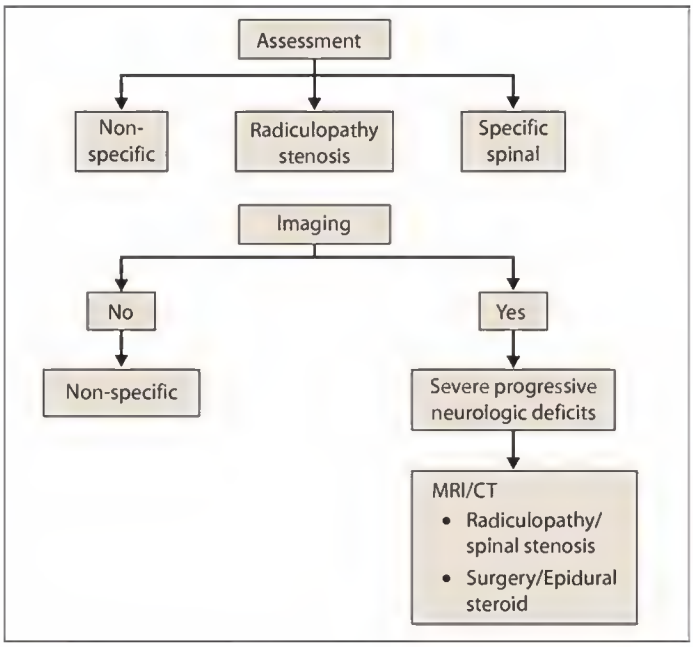


Figure 5: Clinical practice guidelines for diagnosis and treatment of low back pain (LBP).

In chronic LBP, the investigations vary depending upon the subgroups. For localised back pain, plain radiograph, CT or MRI be done. MRI differentiates metastatic spinal fractures from osteoporotic lesions. The investigation of choice for sciatica is MRI. Evaluation of anterior thigh pain includes radiographs for hip arthritis, CT with contrast in abdominal aneurysms, ultrasonogram for ureteric colic due to stone, intravenous urogram for evaluation of the urinary tract and MRI for retro-peritoneal tumours. Posterior thigh pain may need MRI or CT myelogram. Bone biopsy is indicated in rare situations when the diagnosis of the bone pathology is not clear.

The investigations of choice for the catastrophies include an urgent CT or MRI for cauda equina compression and an angiogram for ruptured aortic aneurysm.

TREATMENT

There is no single form of therapy that is effective for all forms of back pain.

Acute Low Back Pain

Cauda equina compression and abdominal aneurysm require emergency surgery, decompression in the former and resuscitation in the latter. Once the above emergencies have been ruled out, acute LBP can be treated conservatively by controlled physical activity, which refers to two days of bed rest, preferably in the semi-fowler position with the knees and hips flexed. Progressive mobilisation and exercise should follow this as the patient's pain improves. *Don't take back pain lying down* is the present trend. Physical modalities employed for mechanical low back pain include interferential therapy (IFT), transcutaneous electrical nerve stimulation (TENS), dry and moist heat, microwave and ultrasound. Functional exercises which replicate function to maximise movement, stability and offer mechanical advantage, rather than traditional ones are advocated. Analgesics (like paracetamol, tramadol, etc.) or non-steroidal anti-inflammatory drugs (NSAIDs) are used for pain relief. Local injections of cortisone or local anaesthetics, narcotic analgesics for severe pain, and muscle relaxants are also used if needed.

Back discipline (e.g. using a straight back support chair, standing on a broad base and flexing the knees while lifting weights) helps prevent recurrences.

Chronic Low Back Pain

Chronic LBP can be managed conservatively by the administration of analgesics, NSAIDs, muscle relaxants including tricyclic anti-depressants, and physical modalities like heat therapy. Early intervention in the form of spinal manipulation therapy and exercises may be more effective than bed rest and analgesics. The Mckenzie method is very effective for non-specific spinal pain.

Smoking should be avoided; obesity should be checked; correct lifting techniques and proper posture maintenance while sitting and standing should be adopted. Exercises include pelvic tilt, knees to chest, hamstring stretch and partial curl to name a few. Psychiatric counselling is given when warranted. Cognitive behavioural therapy has been proved to be useful. If conservative management fails, local or epidural steroids are given. Surgery in the form of decompression or spinal fusion is indicated when the patient develops intractable pain, neurological symptoms or deficit due to disc disease, spinal canal stenosis and unstable vertebral articulation.

Patients with persistent chronic LBP benefit from multi-disciplinary pain clinics where psychosocial approaches by interdisciplinary specialists, including occupational and vocational therapy, ergonomics and biofeedback are utilized. Acupuncture and yoga have proved to be useful (**Figure 6**).

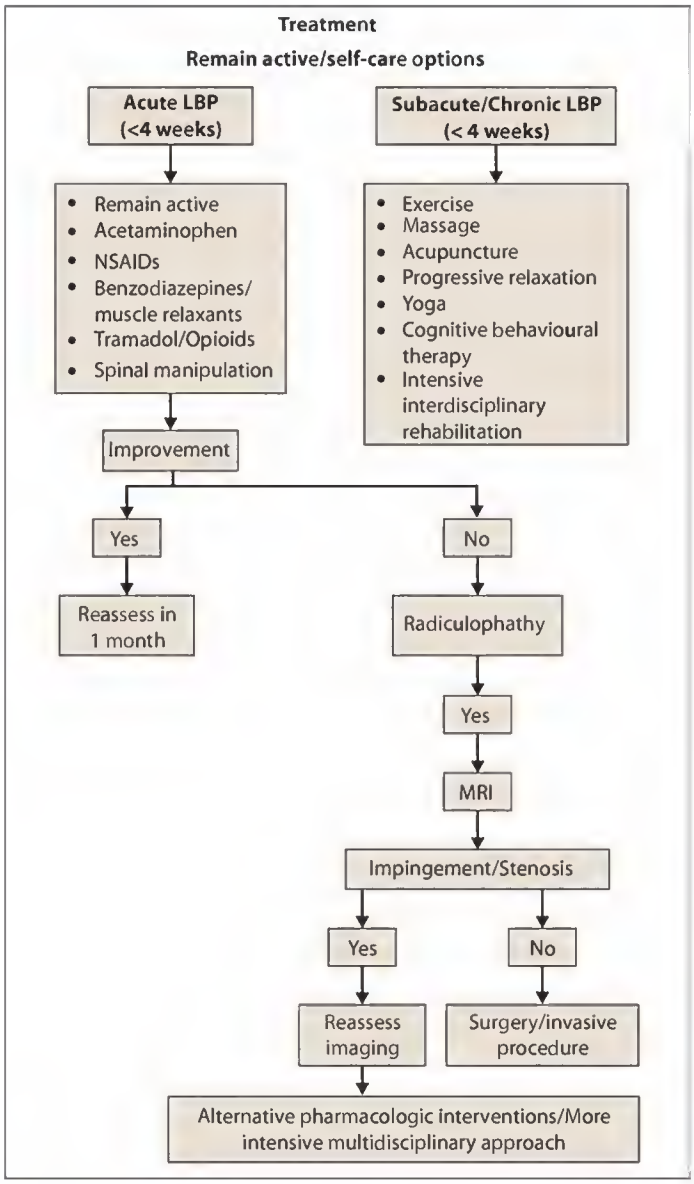


Figure 6: Clinical practice guidelines for diagnosis and treatment of low back pain.

OUTCOME MEASURES

The McGill pain questionnaire is the most commonly employed and its Indian modification in vernacular languages needs to be validated. The other common instruments used for chronic LBP are back specific function (Roland Morris Questionnaire), generic health status (SF-36), pain (Visual Analogue Pain Scale) (**Figure 7**), work disability and patient satisfaction.

The Oswestry LBP Disability Index by Fairbank *et al* interprets 'percentage of disability' as 0% to 20%—minimal; 20% to 40%—moderate; 40% to 60%—severe; 60% to 80%—crippled and 80% to 100%—bed-bound (exaggerated symptoms).

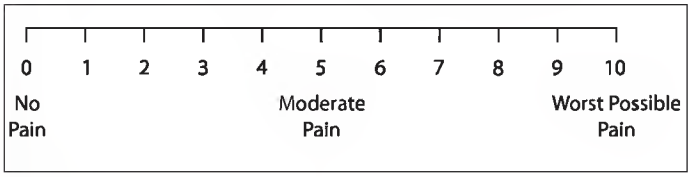


Figure 7: Visual analogue pain scale.

SUMMARY

Dealing with LBP, in general, can be arduous and taxing. Acute LBP is self-remitting in most patients as 90% improve within three months. Most back pains are mechanical in origin. Surgery for LBP is indicated only in 1% of those affected. Referrals to multidisciplinary comprehensive pain centers should be made, only after initial attempts at treatment fail. Chronic LBP may not be curable but can be surely made bearable.

RECOMMENDED READINGS

1. Chou R, Qaseem A, Snow V, *et al*. Diagnosis and treatment of low back pain: A joint clinical practice guidelines from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147: 478-91.
2. Koes BW, Van Tulder MW, Thomas S. Diagnosis and treatment of low back pain. *British Medical Journal* 2006; 332: 1430- 4.
3. Tiwari RR, Pathak MC, Zodpey SP. Low Back Pain among Textile workers. *Indian Journal of Occupational and Environmental Medicine* 2003; 7: 1.

24.4 Osteoarthritis

Siddharth Kumar Das

INTRODUCTION

Osteoarthritis (OA) is characterised by focal loss of cartilage with accompanying periarticular bone response in the form of subchondral bone sclerosis and attempted new bone formation by way of bony over-growths called osteophytes. OA involves all components of the joint, including bone, cartilage, meniscus and synovium. OA clinically presents as joint pain and crepitus in the elderly.

EPIDEMIOLOGY

OA is an important cause of disability and the second most common musculoskeletal problem in the world (30%) after back pain (50%). The reported prevalence of OA in rural India is 5.8%. The major risk factors associated with the knee joint OA are age, female sex, obesity, non-smoker, occupational knee bending, physical labour and chondrocalcinosis. Symptomatic and radiographic OA increases with age. The disease follows a more severe course in women with greater symptoms, more extensive involvement, and increased prevalence of knee and hand joint involvement. In contrast, men have an increased prevalence of hip OA in western countries.

Obesity precedes OA and is not its secondary consequence. Weight reduction is shown to be an effective primary as well as secondary disease prevention strategy (5% reduction in weight decreases the risk for symptomatic OA by 50%). Indians have increased knee OA as compared to Western people. This could be related to excessive squatting in day-to-day activities, especially amongst women. Hip OA is comparatively uncommon in India. Joint trauma, malalignment, meniscectomy and quadriceps weakness are important risk factors. Vitamin D deficiency, possibly acting through production of quadriceps weakness or through undefined mechanisms, has been said to be associated with progression of OA.

Chondrocalcinosis imparts a small risk, independent of age, for the development of knee OA. Chondrocalcinosis was thought to be rare in India. Although no epidemiological data is available, our recent experience suggests that it is not uncommon. Crystals are not proved to be causative but are intimately linked to the development/progression of OA.

Evidences for the genetic basis of OA are increasing. Heberden's nodes have been shown to be clustered in families with a dominant inheritance. Twin studies show 65% concordance for developing OA. Certain familial forms of OA associated with spondyloepiphyseal dysplasias are linked to a point mutation in the gene coding for type II collagen (COL2A1). An endemic variety of secondary OA has been reported from Western Karnataka (Handigodu disease) that in all probability is due to a spondyloepiphyseal dysplasia occurring in a particular community. No specific genetic abnormality has been found so far. Hand joint OA is being linked to HFE gene mutations. However, the common HFE variants C282Y and H63D are not associated with primary OA of the hip or knee. Genetic basis of generalised OA is further strengthened by its association with human leucocyte antigen HLA A1, and B8, and α1 antitrypsin M2 phenotype. Genome wide scans suggest possibility of susceptibility to be linked to chromosome 2q in the IL-1 and IL-1Ra gene region. This cluster may harbour susceptibility for knee OA but not for hip OA.

PATHOGENESIS

Normal hyaline cartilage consists of chondrocytes (1% to 2%) embedded in extracellular matrix composed of water, type II collagen and proteoglycan. The chondrocyte secretes numerous inactive matrix metalloproteinases (MMPs) that include stromelysin, collagenase, gelatinase, etc. which can destroy the whole cartilage framework. These are activated by plasmin and activated stromelysin. Chondrocytes also release tissue plasminogen activator (tPA) that converts blood or chondrocyte-derived plasminogen to active plasmin. This cascade is modulated by tissue inhibitor of MMPs (TIMP) and plasminogen activation inhibitor (PAI). Interleukin-1 (IL-1) plays a pivotal role in OA pathogenesis. It increases the synthesis and secretion of latent or inactive MMPs and tPA; suppresses proteoglycan synthesis and hence, the cartilage repair; decreases TIMP1 and PAI synthesis; and may be involved in proliferation of osteoblast-like cells leading to osteophyte formation. Matrix repair is stimulated by insulin-like growth factor (IGF-1), fibroblast growth factor (FGF) and transforming growth factor-β (TGF-β) which increase proteoglycan synthesis (**Figure 1**). In early stages there is matrix and cartilage degeneration on the one hand and active chondrocyte replication with enhanced biosynthesis on the other hand. This leads to a state of homeostasis, known as compensated OA, in which both repair and degeneration are balanced. After a few years, the reparative process is exhausted resulting in progressive OA.

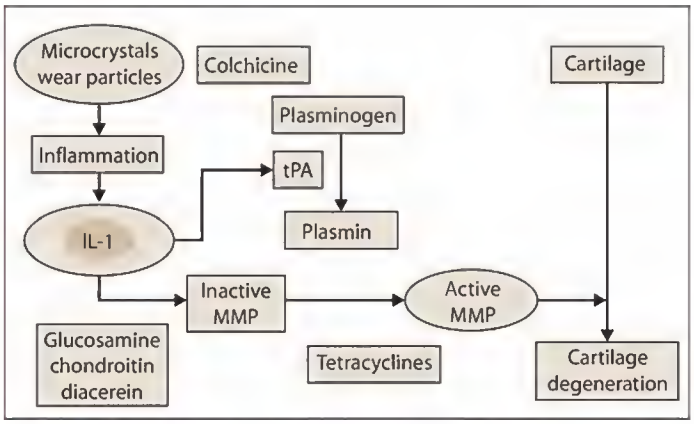


Figure 1: An overview of probable degradative mechanisms involved in OA and possible sites of action of drugs for osteoarthritis.

Previously, OA was considered to be an inherently non-inflammatory disorder. However, about 25% patients of OA of

the knee present with clinical evidence of inflammation that may be secondary to release of IL-1.

The cartilage is devoid of nerve endings. Hence, the pain in OA is believed to originate from the capsule, synovium, periosteum, subchondral bone, ligaments, muscles, etc.

MORPHOLOGY

Earliest identifiable changes are loss of proteoglycans and decreased metachromasia in cartilage. There is focal loss of cartilage, associated with reactive proliferation of chondrocytes to form clusters. Progression of these changes leads to breach of surface integrity, fissures, pitting, flaking of cartilage and development of vertical clefts (fibrillations). These fissures deepen and may expose the subchondral bone, which becomes ivory-like due to thickening and vascularisation (eburnation). Associated bone growth in subchondral region leads to sclerosis, while growth in joint margin leads to the formation of osteophytes.

NATURAL HISTORY

The course of OA is highly variable, with radiological progression seen in one-third to two-third of patients. Improvement is rare. Symptoms may progress, improve, or may even be arrested spontaneously and do not correlate well with radiographic progression.

CLINICAL FEATURES

Pain in or around the involved joints is the cardinal symptom. Usually it starts insidiously as intermittent, localised, deep ache, often aggravated by joint use and relieved by rest, in an asymmetric fashion and then becoming symmetric. The pain becomes persistent and in advanced cases night pain may be very disturbing. Knee joint involvement is typically associated with pain on descending or ascending stairs, squatting for toilet, climbing into autorickshaws, rickshaws, buses, etc. There may sometimes be locking or buckling of knee joint. Hip involvement causes problems of gait and pain in the groin or medial part of thigh.

Stiffness in joints on first awakening (morning stiffness) in OA usually lasts 5 to 30 minutes (average 20 minutes). Stiffness occurring after periods of rest or inactivity (gelling) is frequent and lasts for a few minutes. Functional impairment in OA is variable and depends on associated muscle wasting, weakness, and on radiological severity of the disease.

Signs of OA include bony swelling, crepitus (sensation of bone rubbing against bone on movement), restricted movement, deformity of joint, muscle weakness and muscle wasting. Commonly involved joints in OA are the knee, the hand joints (distal interphalangeal, first carpometacarpal and proximal interphalangeal joints) and spinal apophyseal joints, while hip, acromioclavicular, and sternoclavicular involvement is uncommon. The carpal joints, the elbow, ankle, glenohumeral and the intertarsal joints are rarely involved in OA. A bowleg deformity is seen in over 50% of patients with knee OA. Signs of local inflammation like knee joint effusion may be seen in some patients.

SUBSETS OF OSTEOARTHRITIS

OA for convenience can be categorised into four major subsets, though subsets may overlap with each other.

Nodal Generalised OA (GOA)

Nodal generalised OA is seen 10 times more often in middle-elderly women. It is characterised by Heberden's nodes (bony enlargement of distal IP joint), Bouchard's nodes (bony enlargement at proximal IP joints) and familial clustering (**Figure 2**).



Figure 2: Bouchard and Heberden nodes.

Erosive OA

It is characterised by involvement of the interphalangeal joints of the hands often with florid inflammation and erosive changes that lead to deformities and ankylosis. A small proportion (15%) may evolve into seropositive rheumatoid arthritis (RA).

Isolated Knee Joint OA

It is the most common form of OA where knee may be the only joint involved. It is usually starts unilaterally in the beginning but becomes bilateral over a period of time. Obesity, female gender and knee bending are the important risk factors. It may involve predominantly medial femorotibial, lateral femorotibial or patellofemoral compartment. The involvement of patellofemoral component is tested by eliciting pain when patella is compressed against femur on active extension of knee (Shrug test).

Spinal OA

Apophyseal joint involvement is the only true form of OA of spine. Pain in bending backwards is the typical physical sign of such involvement. Intervertebral disc degeneration with osteophyte formation (**Figure 3**) is considered an integral part of OA. It is common in the lumbar (lumbar spondylosis) and the cervical (cervical spondylosis) regions, the sites of maximum spinal motion. It gives rise to local pain and/or radicular pain. Diffuse idiopathic skeletal hyperostosis (DISH) comprises of flowing calcification along the anterior longitudinal ligaments and disc margins. DISH and OPLL (ossification of posterior longitudinal ligament) are considered to be variant forms of OA.

INVESTIGATIONS

The earliest feature is joint space narrowing, which in the knee is best demonstrated in weight-bearing radiographs (**Figures 4A and B**). Osteophytes are the hallmark of the disease. Subchondral bone sclerosis, subchondral cysts, deformity, loose bodies and calcification [linear due to calcium pyrophosphate dihydrate (CPPD) deposition, spotty due to hydroxyapatite deposition] are the other changes.



Figure 3: Lumbar spondylosis.

Computed tomography is useful in assessing the axial joints. Ultrasound is useful in assessing changes in periarticular structures, like Baker's cysts. Bone marrow oedema, cartilage defects, meniscal tears, osteophytes, subchondral cysts, sclerosis, synovitis and synovial effusions may be seen on magnetic resonance imaging (MRI). MRI and Scintiscan (Tc^{99m} biphosphonate) are, however, not recommended for routine clinical use.

Synovial fluid cell count is less than 2000/mm^3 with mononuclear cell predominance. Synovial fluid may show the presence of crystals in 30% to 70% patients, commonly seen are CPPD. However, hydroxyapatite (HA) or basic calcium phosphate (BCP) crystals may also be detectable.

DIAGNOSIS

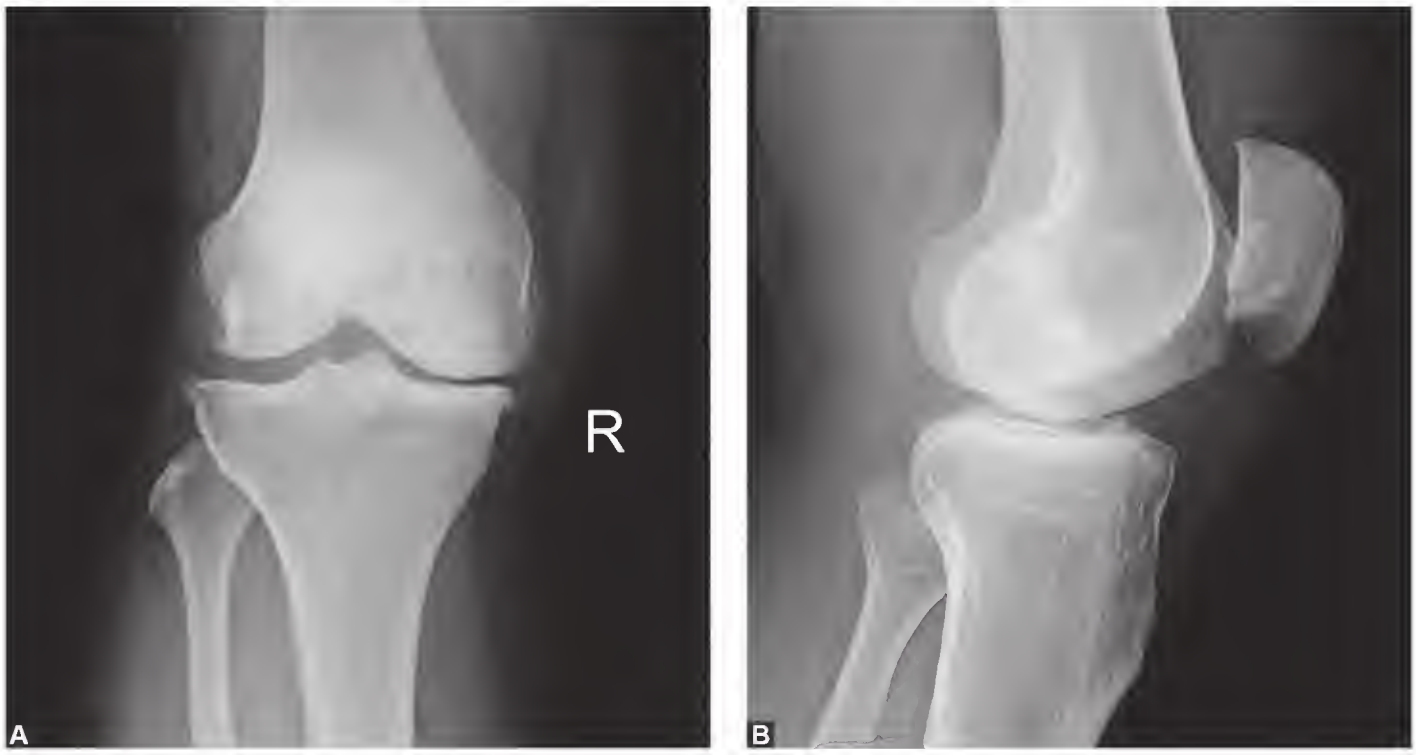
The diagnosis of OA is clinicoradiological. It is well known that early OA may not show radiological changes, while only 50% to 60% of patients with OA by radiograph are clinically symptomatic. Erosive form of OA is particularly difficult to differentiate from RA. A positive rheumatoid factor (RF) and an elevated erythrocyte sedimentation rate help in diagnosing RA. Patients having mixed disease further complicate the picture. OA changes may follow joint damage due to RA. It must be remembered that joints actively involved in RA seldom show osteophytes. The elderly may demonstrate RF positivity even in the absence of RA. Therefore, elderly patients with a positive RF, isolated knee pain and crepitus without hand joint involvement are more likely to have OA rather than RA.

MANAGEMENT

The treatment of OA is aimed at minimising pain, optimising function and reducing disability using a combination of non-pharmacological, pharmacological and surgical therapies.

Non-Pharmacological Management

Patient education and joint protection measures like avoidance of poor posture and limitation of excess joint loading are important. Day-to-day activities may need alteration (e.g. change of toilet seat from the Indian style to Western style; avoiding weight loading movements of the joints, (e.g. avoidance of squatting, sitting on low chairs, sofas, floor and climbing stairs, etc.). Weight reduction is important in obese patients. When the disease is relatively quiescent, low intensity weightbearing activity is safe and beneficial for muscle strength, mobility and a sense of well-being. But when the disease is



Figures 4A and B: Showing osteoarthritis of the right knee with: space reduction in medial compartment (A); chondrocalcinosis seen on lateral view of knee joint (B).

active with significant pain and inflammation, patients should not overstress with exercise. Quadriceps strengthening exercises are important. Supportive devices are often an adjunct to other modalities. Devices like canes, crutches, orthotic shoes and knee braces when used properly, lead to pain relief with improved function. A ¼ inch lateral heel raise or shoe insert is frequently helpful in varus deformity of knees.

Application of superficial heat on periarticular tissue by hot packs and paraffin baths alleviates pain, relieves muscle spasm and decreases joint stiffness. Deep heat by ultrasound and diathermy may damage cartilage and should be avoided. Heat increases inflammation, hence, ice packs are more helpful for acutely inflamed knee or bursae.

Pharmacological Management

Analgesics and nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat the both pain and inflammation in OA. Their use is limited by their gastric and renal toxicity, especially in the elderly. Some studies have shown acetaminophen (paracetamol) 1 g 3 to 4 times a day (maximum 4 g per day) to be equally effective as other NSAIDs in OA with the advantage of fewer gastric side effects. NSAIDs like aspirin and indomethacin which have been implicated in cartilage degeneration are best avoided in OA. Newer selective cyclooxygenase-II (COX-2) inhibitors like meloxicam, celecoxib, etoricoxib, etc. have been shown to be chondroneutral and equally effective with fewer NSAIDs-related side effects. Capsaicin cream on topical application gives relief from pain and tenderness by depleting substance P in sensory nerve endings and may be used. Absorption of locally applied NSAIDs may be erratic but may have a strong psychological value.

Chondroitin and glucosamine

Chondroitin and glucosamine are nutraceutical agents whose use and effectiveness have been debated with conflicting reports in the literature. Glucosamine sulphate is given in doses of 1500 mg per day and chondroitin 1200 mg per day. They may provide symptomatic benefit in some patients with knee OA. It is unclear whether they have a disease modifying role. The sulphate salt of glucosamine marketed by one pharmaceutical company only has been shown to be consistently effective in OA and also been shown to provide disease modification. However, the hydrochloride salt has never been shown to benefit patients.

Diacerein

Diacerein in doses of 50 mg twice daily with meals is being used in OA. Diacerein has a small, consistent benefit in improvement of pain. It is believed to be an inhibitor of IL-1.

Intra-articular treatments

Intra-articular steroids are employed in patients with knee OA who have effusion. Since repeated steroid injections may lead to more cartilage damage, it is recommended that the same joint should not be injected more than 3 times a year. The incidence of joint infection following intra-articular steroids is low. Visco-supplementation with intra-articular hyaluronan injection is a promising therapy, providing symptomatic relief to about 60% to 70% patients with knee OA especially those without effusion. Hyaluronan is given as 3 to 5 (depending on molecular weight) intra-articular injections at weekly intervals. Local reaction may occur in up to 8% patients. Considering that IL-1 is an important cytokine for the development and progression of OA, anakinra has been used intra-articularly. Early studies have shown that its use is safe but a single injection with a half-life of a few hours is not effective in reducing the pain.

Colchicine

One centre from India has reported that patients presenting with significant inflammation with demonstrable CPPD crystals in joint fluid have better symptomatic relief when treated with colchicine. Even in patients not presenting with inflammation, colchicine produces significant symptomatic relief. Colchicine is used in a dose of 0.5 mg twice daily.

Other modalities

Tetracyclines chelate metals and thus inactivate MMPs. Since MMPs are important in the degradative pathway, doxycycline has been used for the management of OA. Chondrocyte transplants directly or in scaffolds, have been shown to regenerate near-normal hyaline cartilage and may be useful for small lesions of the cartilage but are not currently routinely recommended for the treatment of OA.

Surgical Management

Joint replacement must be considered in any patient presenting with end-stage joint disease with pain not responding to conventional treatment. Total knee replacement is opted by patients who are older and have weakness, more difficulty in getting up, more problems in climbing stairs and impaired extension of knee. Total hip and knee joint replacement have improved the quality of life and decreased the morbidity due to OA. Most series report excellent long-term results in over 90% of patients undergoing joint replacements. Other surgical therapies available for OA are loose body removal, osteotomy, arthrodesis, arthroplasty, synovectomy, debridement, etc. with varying grades of efficacies.

PREVENTION

Weight reduction is the only known method of reducing the risk of symptomatic OA. Lifestyle changes, like less squatting and less stair climbing, are likely to help. Some of the therapies described for OA possibly reduce the progression of OA, and hence, are more likely to be beneficial for prevention rather than for treatment. However, one has to realise that if prevention of OA is to be attempted the effort has to start in twenties and thirties, as we know that the seeds of OA are sown early.

RECOMMENDED READINGS

1. *Cochrane Dotobose Syst Rev* 2005; (2):CD002946.
2. Doherty M. *Clinical feature ond subset chorocterisotion.* In: Doherty M, editor. OA, London Wolfe; 1994: pp 61-83.

24.5 Gout and Other Crystal Arthritides

URK Rao

Many crystals are associated with articular syndromes (**Table 1**). In practice, only monosodium urate monohydrate (MSU), calcium pyrophosphate dihydrate (CPPD), and calcium hydroxyapatite (BCP) are commonly encountered.

Table 1: Crystal Associated Arthritides

Crystal	Clinical features
Monosodium urate (MSU)	Acute/chronic gouty arthritis, tophi, renal calculi
Calcium pyrophosphate dihydrate (CPPD)	Acute pseudogout, chronic inflammatory or degenerative arthritis; chondrocalcinosis
Basic calcium phosphate hydroxyapatite (BCP)	Calcific periarthritis, acute/chronic inflammatory or destructive arthritis, soft-tissue calcinosis
Calcium oxalate aluminium phosphate	Acute arthritis in patients on renal dialysis
Cholesterol	Chronic synovial effusions in RA/OA
Cysteine/cystine	Acute arthritis
Charcot-Leyden (lysophospholipase)	Synovial fluid and tissue deposition, with eosinophilia
Xanthine	Acute arthritis (rare), renal calculi

GOUT

Gout is an inflammatory response to the MSU crystals formed secondary to hyperuricaemia. The major clinical manifestations are acute synovitis, chronic erosive and deforming arthritis, tophi, nephrolithiasis, and interstitial nephritis. The epidemiology of hyperuricaemia is different from that of gout. Mean uric acid (urate) concentrations are age and sex related. Prepubertally, in males the mean concentration is around 3.5 mg/dl, with a steep rise to 5.2 mg/dl at puberty. In females, the mean concentration is up to 4.7 mg/dl with rise only after menopause. Hyperuricaemia is defined as a serum or plasma urate concentration greater than 7.0 mg/dl in males and 6.0 mg/dl in females. Gout is seen in only one-tenth of patients of hyperuricaemia. The incidence of gout varies in population from 0.2 to 3.5 per 1000, with an overall prevalence of 2-26 per 1000. Gout is found to have increased prevalence in recent years. It is rare in children and premenopausal females. The peak age of onset in males is between 40 and 50 years.

Pathogenesis of Urate Crystal-Induced Inflammation

Uric acid is a weak acid, present mainly as urate, the ionised form in physiologic fluids. At concentrations greater than 6.8 mg/dl, urate can crystallise as MSU in and around joints. MSU crystals are released into the joint cavity, activate synovial lining cells, recruit and activate mastocytes and peripheral blood monocytes. At the cellular level, inflammation induced by urate crystals is brought by innate immune engagement of the crystals by plasma membrane receptors including toll-like receptors (2 and 4). In turn, they produce various cytokines such as interleukins (e.g. IL-1, IL-8) and chemokines leading to endothelial cell activation. Neutrophils are recruited into the joint cavity, leading to MSU crystal phagocytosis and cell activation. Auto-limitation of active inflammation is brought out by macrophages, neutrophil necrosis and apoptosis.

Risk Factors

Serum uric acid concentration is the single-most important determinant of the risk of developing gout. With normal renal function, its blood concentration depends mainly on the breakdown of nuclear proteins and dietary purine load (**Figure 1**). Provocative factors include alcohol, dietary excesses, surgery, trauma, sepsis, stress, starvation, dehydration and drugs like diuretics, pyrazinamide and aspirin.

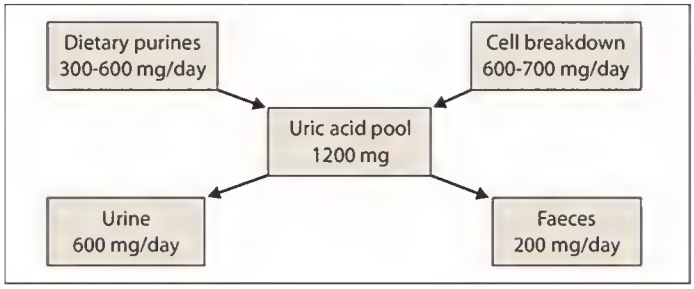


Figure 1: Body uric acid pool.

Classification

Hyperuricaemia and gout may be classified as primary and secondary (**Table 2**). Increased production of uric acid as a cause of gout is seen in only 10-15% of subjects (over-producers) and in 80-90%, uric acid excretion is impaired (under-secretors).

Clinical Features

Gout can occur in four phases.

Asymptomatic hyperuricaemia

Hyperuricaemia may be an incidental finding and may never lead to gout. Conversely, serum uric acid levels may not be elevated during acute gouty arthritis. This is because ACTH released in response to stress is uricosuric. Generally, asymptomatic hyperuricaemia needs close observation with no active treatment. However, growing epidemiological and experimental evidence indicates that asymptomatic hyperuricaemia is capable of directly promoting hypertension and vascular disease. Severe over-production of urate, as may occur with cytotoxic chemotherapy, is associated with high risk of acute renal failure and requires intervention.

Acute gouty arthritis

The big toe (first metatarsophalangeal joint) is the classic site for gout. One-third of patients may get their first attack at another site such as the in-step of the foot, ankle, knee, or hand joints. Sydenham's classic description lists the important clinical characteristics used to diagnose a typical attack. The attack is

acute, it starts in the night, the joint and surrounding tissues are swollen, hot, red, shiny and extremely painful. There is a mild fever with chills. Left untreated, the attack will start to improve in a week or two. The skin over the joint may subsequently desquamate. Atypical manifestations include tenosynovitis, bursitis, cellulitis or mild pain and discomfort without swelling, lasting a day or two. Acute gout in one joint may provoke migratory attacks affecting other joints over subsequent days (cluster attacks). Pauci or polyarticular gout attacks are more common in women, especially with diuretic use.

Table 2: Causes of Hyperuricaemia

Primary hyperuricaemia
- Increased uric acid production
  - Idiopathic (10%)
  - Specific enzyme defects
  - Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency
  - Increased phosphoribosyl pyrophosphate (PRPP) synthetase activity
- Decreased uric acid excretion
  - Idiopathic (90%)

Secondary hyperuricaemia
- Increased uric acid production
  - Increased purine synthesis *de novo*-specific enzyme defects
    - Complete HGPRT deficiency
    - Glucose 6-phosphatase deficiency (type I)
  - Increased turnover of preformed purines
    - Myeloproliferative disorders, e.g. polycythaemia vera, granulocytic leukaemias
    - Lymphoproliferative disorders, e.g. lymphomas, myelomas
  - Others—Macroglobulinaemia (Waldenstrom's)
    - Carcinomatosis
    - Chronic haemolytic anaemia
    - Gaucher's disease
    - Exfoliative psoriasis
- Decreased uric acid excretion
  - Renal, e.g. chronic kidney disease, nephrogenic diabetes insipidus
  - Increased levels of organic acids, e.g. exercise, starvation, ketoacidosis and alcohol drugs, e.g. diuretics, low-dose aspirin, pyrazinamide, cyclosporine, ethambutol
  - Other medical disorders, e.g. hyperparathyroidism, myxoedema, Down's syndrome, lead nephropathy, sarcoidosis

Intercritical gout

After the first attack of gout, the second episode may never occur or occurs after several years. However, in most of the patients, the next few episodes occur within one year. The frequency of attacks and number of sites involved gradually increase with time.

Chronic gout (tophaceous gout)

Development of chronic tophaceous gout depends on uncontrolled hyperuricaemia of long duration, usually more than 10. But tophi or chronic polyarthritis may occur as early as 3 years or as late as 40 years after the first acute attack. Tophi appear as firm, nodular or fusiform swellings. In inflamed tophi, the overlying skin may be erythematous. In ulcerated tophi, white chalky material, the urate crystals, may exude. The common locations of tophi are the great toe, feet (**Figure 2**), hand joints (**Figure 3**) and olecranon. Tophi of helix of the ear, though classic is uncommon. The gout in elderly patients, especially women, may present differently compared to typical gout occurring in middle-aged men (**Table 3**).



Figure 2: Gouty arthritis affecting toes in a 45-year-old male. A tophus can be seen over the base of left great toe.



Figure 3: Gouty arthritis affecting fingers in a 45-year-old male.

Table 3: Typical Gout versus Elderly-Onset Gout

Feature	Typical Gout	Elderly-Onset Gout
Age of onset	Peak in mid 40s	Over 65
Sex	M > F	M = F
Presentation	Acute monoarthritis; lower extremity (base of greater toe, instep of the foot)	Polyarticular upper and lower extremity (finger involvement more common than typical gout)
Tophi	Several years of attack	May occur early
Associated features	Obesity, hyperuricaemia, hypertension, alcohol abuse	Renal insufficiency, diuretic use

RENAL DISEASE

After gouty arthritis, renal disease is the most frequent complication of hyperuricaemia. Urate nephropathy is attributed to the disposition of MSU crystals in the renal interstitial tissue. Other manifestations include acute uric acid nephropathy or uric acid calculi. Calcium oxalate renal stones occur more commonly in patients with hyperuricaemia or gout than in normouricaemic subjects. Renal failure accounts for 10-25% of deaths of gouty patients. Co-existent hypertension may be more important than urate in the pathogenesis of renal failure. It should be remembered that hyperuricaemia may be seen secondary to chronic renal failure without gout.

Obesity, hypertension and hyperuricaemia are important associated disorders. A negative association exists between gout and rheumatoid arthritis (RA) and gout and systemic lupus erythematosus.

Investigations

The synovial fluid is turbid with greatly elevated neutrophils. The synovial fluid should ideally be examined under polarised light. Urate crystals are needle-shaped, generally 5-25 μm in length, intracellular or extracellular in location and negatively birefringent (**Figure 4**). Urate crystals can also be demonstrated in gouty tophi.

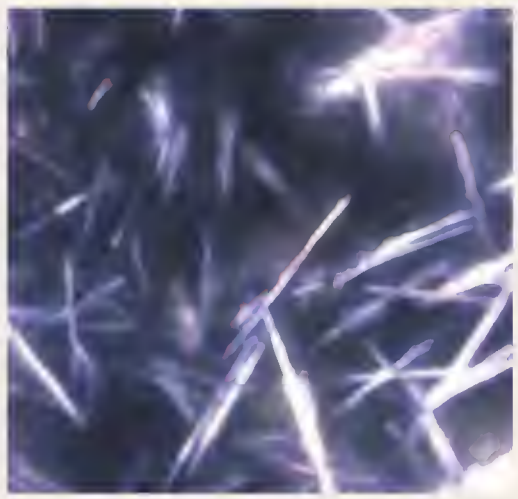


Figure 4: Negatively birefringent needle-shaped monosodium urate crystals.

Hyperuricaemia is confirmed if two or more fasting serum uric acid levels are elevated. Over-producer status can be determined by more than 700 mg in 24 hours urinary urate on a normal diet, or by a single urine sample with increased uric acid/creatinine ratio (normal <0.5). Assessment of renal function, lipid profile and acute phase reactants such as ESR help in the management.

Radiographs may be normal in early disease. In patients with recurrent attacks or chronic gout, radiographs show punched-out erosions with over-hanging edges, mostly para-articular, asymmetrical and eccentric (**Figure 5**).

Diagnosis

Demonstration of urate crystals is the 'gold standard' for the diagnosis of gout. Septic arthritis is an important differential diagnosis of acute gout. Sepsis may co-exist with gout. With less



Figure 5: Radiograph of right foot with soft tissue swelling and erosions with over-hanging edges at first MTP joint.

classic attacks, other conditions to consider are psoriatic arthritis, reactive arthritis, osteoarthritis, traumatic arthritis, pseudogout and palindromic rheumatism. Chronic tophaceous gout and polyarticular gouty arthritis are often mistaken for rheumatoid arthritis.

Treatment

The management of gout is directed towards the treatment of acute gout, prevention of further attacks and identification and correction of factors that contribute to the disease. Weight reduction and reduction of urate concentration by low purine diet should be considered in the long-term management of gout. Crash weight reduction programmes should be avoided. High purine foods are red meat, liver, kidney, sardines, pulses and whole grain cereals. If hypouricaemic agents are used, pulses may be permitted. Beer, lager, port and some wines should be avoided. Drugs such as thiazide diuretics are best avoided. Associated disorders like hypertension and hyperlipoproteinaemia should be controlled.

The drugs used are colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs), xanthine oxidase inhibitors like allopurinol and uricosuric agents, e.g. probenecid and sulphinpyrazone. The sites of action of these drugs are shown in **Figure 6** and the general principles of management of gout are given in **Tables 4 and 5**.

It is important to distinguish the differences between anti-inflammatory therapy for gout and the treatment of hyperuricaemia. Allopurinol is purely a uric acid lowering agent and has no role in the treatment of an acute attack and may even precipitate an acute attack of gouty arthritis. Acute gout is treated with colchicine, NSAIDs or corticosteroids. However, if the patient is already taking hypouricaemic drugs, the same should be continued unchanged during acute attacks. A common

mistake is either to start uric acid lowering agents or to change their dosage at such times. **Table 5** gives details of drugs used to treat gout and **Figure 6** shows the site of action of drugs.

Table 4: Principles in the Management of Gout

Acute gout

- NSAIDs
- Colchicine
- Local or systemic corticosteroids

Recurrent and chronic gout

- *Reverse* factors promoting hyperuricaemia, e.g. diuretics, alcohol abuse
- *Treat* associated problems, e.g. obesity, hyperlipidaemia, hypertension
- *Correct* lifestyle patterns, e.g. avoid high purine diet, excessive exertion, starvation, dehydration
- *Use* drugs to lower plasma urate concentrations, e.g. allopurinol, probenecid
  - Allopurinol should be used in tophaceous gout and patients with renal stones. Probenecid should not be used in the presence of nephrocalcinosis or renal stones
- *Continue* prophylactic doses of colchicine or NSAIDs for a few weeks to months even after normalisation of uricaemia

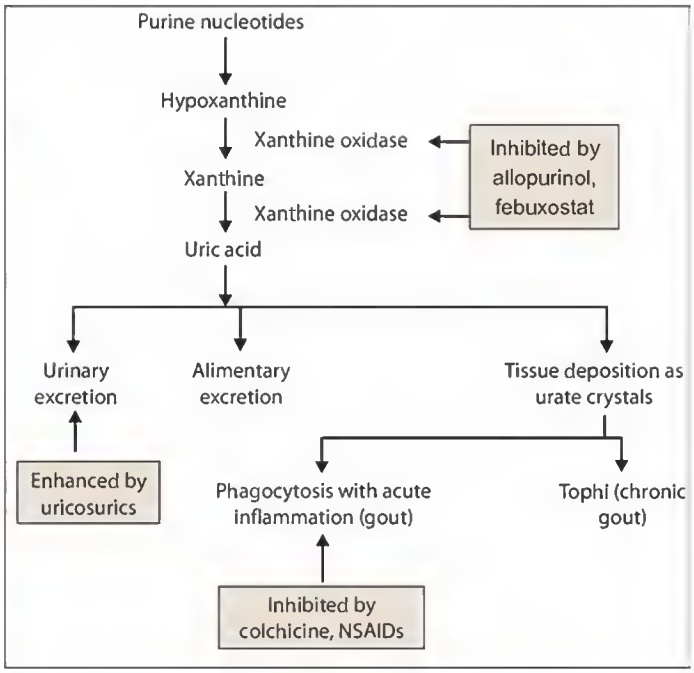


Figure 6: Sites of action of drugs in gout and hyperuricaemia.

Table 5: Important Drugs Used in the Treatment of Gout

	Colchicine	Allopurinol	Probenecid
Uses	Anti-inflammatory agent in acute gout Prophylactic drug to prevent recurrent attacks	Reduce serum and urine urate concentration in hyperuricaemia of tumour lysis, acute uric acid nephropathy, renal calculi of urate and calcium crystals in primary and secondary gout, tophaceous gout	Increases excretion of uric acid by kidney, thereby reducing serum concentration in hyperuricaemia
Mode of action	Inhibits phagocytosis by multiple actions over neutrophil leucocytes	Inhibits xanthine oxidase, its metabolite oxypurinol is active	Competitive inhibition of tubular reabsorption of urate
Dosage	In acute attack, initial dose 1 mg followed by 0.5 mg every 3 hours till desired effect or appearance of side effects; not more than 3-4 mg/day, prophylactic dose 0.5 to 1 mg/day for several months	Once or in divided doses usually up to 300 mg/day (maximum 600 mg/day)	250 mg twice a day in increments up to 1 to 2 g/day in 2 to 3 divided doses
Side effects	Vomiting, diarrhoea, haemorrhagic gastroenteritis; on larger doses myoneuropathy	Hypersensitive reactions, interaction with mercaptopurine and azathioprine; potentiates their effects	Dyspepsia, rash, convulsions, drug interactions; promotes efficacy of frusemide, indomethacin, dapsone, heparin, ampicillin
Special precautions	Dose should be reduced in renal insufficiency	Dose should be reduced in renal insufficiency. Not to start in acute gouty attack, use after inflammation subsides	Not indicated in presence of renal calculi or renal insufficiency and blood dyscrasias

Hyperuricaemia

Asymptomatic hyperuricaemia needs no drug therapy. However, prophylactic allopurinol is used to prevent uric acid nephropathy due to tumour lysis following chemotherapy. The decision to introduce drugs like allopurinol to normalise hyperuricaemia depends in part on the number of previous attacks of acute gout, the degree of hyperuricaemia (serum uric acid >10 to 11 mg/dl requires treatment) and the presence of risk factors. Urate lowering drugs are not indicated after just a single attack of gout but should be considered after a second or third attack. Allopurinol is instituted 10 to 15 days after resolution of inflammation by NSAIDs or colchicine. Anti-hyperuricaemic therapy is usually given indefinitely. **Figure 7** shows the line of action for treatment of gout.

Acute gout

Drug therapy should be initiated as early as possible. When used within the first few hours of an attack, NSAIDs or colchicine give a good response. Though indomethacin is widely used, other NSAIDs like diclofenac, naproxen, etoricoxib, piroxicam, etc. can also be used. Intra-articular steroid therapy terminates the gouty attack. This form of therapy is useful in a situation where NSAIDs cannot be given in adequate doses or are ineffective. Oral steroids may be indicated in severe acute attacks but the response is variable and rebound attacks may occur on their withdrawal.

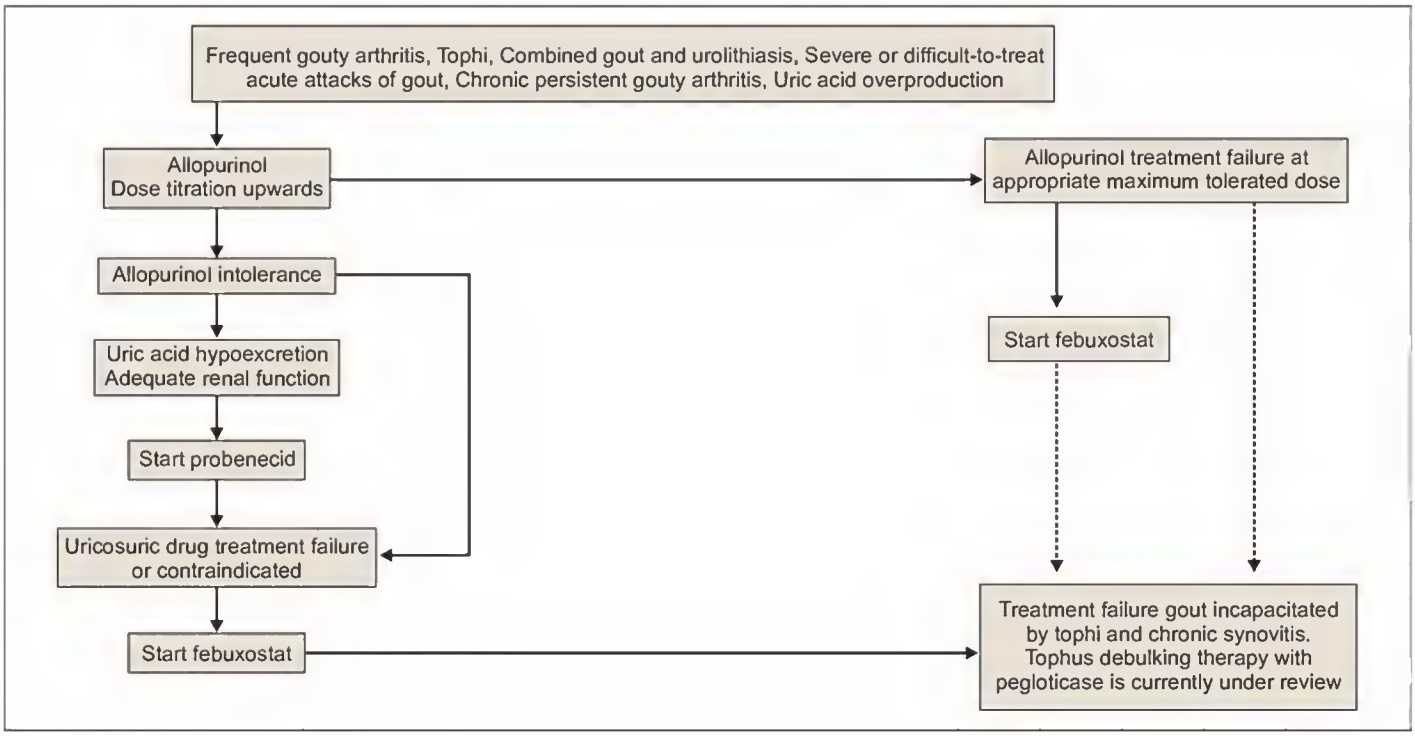


Figure 7: Therapeutic algorithm to reduce the elevated serum uric acid in gout.

Recurrent attacks of gout

Colchicine in low doses (0.5 mg twice daily) is used prophylactically to prevent recurrent attacks.

Tophaceous gout

In treating tophaceous gout, it is mandatory to lower plasma urate concentration to such a degree (<5 mg/dl) as to allow urate to be resorbed from the surface of the tophi. This requires long-term usage of uric acid lowering drugs.

Other drugs

Benzbromarone is a potent uricosuric drug used in patients with no improvement with allopurinol and in renal transplant patients. Side effects include hepatotoxicity. An angiotensin receptor blocker, losartan, used in the treatment of hypertension, has uricosuric effect. It acts by inhibiting renal tubular reabsorption of urate. Fenofibrate, a lipid-lowering drug has uricosuric effect. It is useful in the treatment of patients with hyperlipidaemia and gout.

Recent Advances in the Treatment of Gout

Febuxostat, a xanthine oxidase inhibitor (80-120 mg) has been approved and is available for the treatment of gout. Febuxostat can be used in patients with allopurinol allergy (**Figure 7**).

Recombinant uricase, Rasburicase, which metabolises uric acid, is being used to prevent development of tumour lysis syndrome in patients with malignancy on chemotherapy. Polyethylene glycol conjugated mammalian uricase (pegloticase) causes prolonged reduction of serum urate with resolution of tophi. It has been used in phase III studies in severe refractory gout. Canakinumab, a monoclone antibody which blocks ILg beta, is shown in phase 3 trials to provide rapid pain relief in acute flaves of difficult to treat gout.

OTHER CRYSTALLITIDES

Calcium Pyrophosphate Dihydrate (CPPD) Crystal Deposition Disease

Calcium pyrophosphate dihydrate (CPPD) crystals are frequently encountered in synovial fluid of patients of osteoarthritis (OA) and frequently give rise to inflammatory episodes. It is believed that CPPD crystal deposition is secondary to OA and not the primary event in such settings. A number of times, patients have primary CPPD crystal deposition before the onset of degenerative joint disease. Primary CPPD crystal deposition disease may be inherited as an autosomal dominant trait. Hyperparathyroidism, hypothyroidism, haemochromatosis, amyloidosis, hypomagnesaemia and hypophosphatasia are sometimes associated with it.

CPPD crystal deposition advances with age and 50% of those aged 90 years have radiological evidences of CPPD crystal deposition. About 20% patients with CPPD crystal deposition disease also have hyperuricaemia. Many have associated BCP crystals deposition.

Clinical Presentations

The revised diagnostic criteria of CPPD crystal deposition disease is given in **Table 6**. CPPD crystal deposition may present in several ways.

Acute pseudogout

There is inflammation of one or more joints lasting for several days to weeks. Attacks are abrupt in onset and severe. Any joint may be affected but in nearly half of the patients, the knee is the affected joint. It can occur spontaneously or after a minor trauma, surgery, illness, stroke and myocardial infarction.

Pseudorheumatoid presentation

A low-grade symmetrical polyarthritis associated with morning stiffness, fatigue, synovial thickening, flexion contractures and

Table 6: Revised Diagnostic Criteria for Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

Criteria

Demonstration of CPPD crystals in tissue or synovial fluid by definitive means (e.g. characteristic radiograph diffraction or chemical analysis)

Identification of monoclinic or triclinic crystals showing weakly positive or no birefringence by compensated polarised light microscopy

Presence of typical radiographic calcification

Acute arthritis, especially of knees or other large joints

Chronic arthritis, especially of knee, hip, wrist, elbow, shoulder, or metacarpophalangeal joint, especially, if accompanied by acute exacerbations

The following features help to differentiate chronic arthritis from osteoarthritis:

Uncommon site—wrist, MCP, elbow and shoulder

Radiographic appearance—radiocarpal or patellofemoral joint space narrowing, especially, if isolated (patella wrapped around the femur)

Subchondral cyst formation

Severity of degeneration—progressive, with subchondral bony collapse and fragmentation with formation of intra-articular bodies

Osteophyte formation—variable and inconstant

Tendon calcifications, especially triceps, achilles, obturators

Categories

Definite disease: Criteria I or II (a) plus II (b) must be fulfilled

Probable disease: Criteria II (a) or II (b) must be fulfilled

Possible disease: Criteria III (a) or III (b) should alert the clinician to the possibility of underlying CPPD crystal deposition

elevated ESR may be present in about 5% patients. About 10% patients with CPD crystal depositions may also have rheumatoid factor (RF) in low titres. Many of these patients are misdiagnosed as RA. CPPD deposition is very common, hence, RA may be present by chance in up to 1% patients of CPPD crystal deposition disease. Diagnosis of rheumatoid arthritis would be tenable in presence of high titres of RF and classical erosions.

Osteoarthritis type presentation

This is seen in about 50% of patients, the knees are the most commonly affected joints followed by the wrists, metacarpophalangeal joints, hips, shoulders, elbows and ankles. Shoulder, elbow wrist and metacarpophalangeal joint involvement is uncommon in primary osteoarthritis, and when these atypical joints are involved, it suggests the presence of a primary CPPD crystal deposition disease. Valgus deformity suggests CPPD crystal deposition disease.

Osteoarthritis with secondary CPPD crystal deposition

Patients with primary osteoarthritis usually have knee, hip, first carpometacarpal, distal interphalangeal, sometime, proximal interphalangeal joint and spine involvement (**Figure 8**). Many patients with primary osteoarthritis have radiological chondrocalcinosis. Many more (up to 60-70%) have CPPD crystals demonstrable in synovial fluids. Patients with CPPD crystals in joint fluid have more synovial effusions and more severe radiographic OA and have greater progression of disease. However, this CPPD crystal deposition is believed to occur after the start of primary osteoarthritis. Possibly, CPPD crystal



Figure 8: Calcification of lateral meniscus.

deposition disease and osteoarthritis form a continuing spectrum of disease.

Systemic Symptoms

Systemic features may appear during an acute attack of pseudogout with fever, leucocytosis and elevated ESR and acute phase reactants. Acute neck pain with fever with calcification around odontoid process (Crowned dens syndrome) may mimic pyogenic meningitis. Sometimes a picture resembling septicaemia, high fever with mental confusion and disorientation may be seen.

Neurological Manifestations

Depositions of CPPD crystals in ligamentum flavum and tumour (tophi) like CPPD crystal deposition in the spinal canal may lead to a picture of cervical myelopathy, radiculopathy and spinal canal stenosis. This may sometimes occur in the lumbar area also.

Miscellaneous Presentations

Many people with characteristic calcifications demonstrable on radiographs may be asymptomatic. Patients with back pain may present with a picture suggestive of ankylosing spondylitis with true bony ankylosis. A picture suggestive of Charcot's joint with a destructive arthropathy without neurological deficit may be seen in some patients. A monoarticular degenerative arthritis may sometimes be seen. In some patients, proximal stiffness, pain and elevated ESR may be misdiagnosed as polymyalgia rheumatica.

Diagnosis

The hallmark of the disease is demonstration of CPPD crystals in tissues or joint fluid.

Synovial fluid examination

The synovial fluid from inflamed joints is frequently haemorrhagic. Mean leucocyte concentration is about 20,000 cells/mm with predominant polymorphs. CPPD crystals are more commonly seen than radiological ch ondrocalcinosis. In

patients with acute inflammation, phagocytosed micro-crystals are seen in phagolysomomes. A phase contrast with polarised light examination gives better results. CPPD crystals may be monoclinic and triclinic and some show twining. They have a weakly positive birefringence and show inclined extinction.

Radiological Features

The typical radiological appearance of CPPD crystal deposition is called 'chondrocalcinosis'. This manifests as a linear or punctuate deposits in articular hyaline or fibrocartilageous tissues. Common sites are the knee (linear calcific deposits in femoral condylar cartilage best seen on lateral view), menisci (best seen in AP view, uncommon in India) (**Figures 8 and 9**), symphysis pubis and hips, wrists and spine (calcification of annular ligaments) (**Figure 10**). CPPD crystal deposition disease is characterised by isolated wrist degeneration and isolated patellofemoral joint space narrowing.

Treatment

Like with gout, colchicine in high doses may abort attacks of pseudogout. High-dose colchicine may be toxic, hence, intra-articular corticosteroids may be better. There is no drug treatment to remove CPPD crystals from tissues or joint fluids. Joint aspirations are the only method to remove CPPD crystals from synovial fluid and may help. NSAIDs are commonly used. Long-term oral colchicine may reduce the number and duration of acute attacks. Whether removal of crystals and prevention of acute attacks by colchicine will prevent or slow degenerative joint disease is not known.

Basic Calcium Phosphate (Calcium Apatite) Crystal Deposition Disease

Basic calcium phosphate (BCP) deposition disease is known to cause acute and chronic musculoskeletal symptoms such as bursitis and tendinitis. The recurrent painful periarticular inflammation is associated with radiographically demonstrable periarticular calcifications at multiple sites. Common sites of involvement include the shoulder, greater trochanter of the hip, lateral epicondyle of the elbow and tendinous attachments around the wrist and knee. Microscopic study reveals typical globular bodies with a 'shiny coin' appearance depicting calcium apatite crystals. Calcium and phosphorus metabolism is usually normal.

Apatite crystal-induced inflammation is also observed in patients on chronic haemodialysis and those with scleroderma or dermatomyositis. Apatite deposits can also occur intra-articularly. Erosive arthritis usually of shoulders (Milwaukee shoulder) rarely occurs in elderly women due to apatite crystal deposition.

The management of BCP deposition disease includes therapy with NSAIDs, colchicine, local glucocorticoid injections and physiotherapy.

Calcium Oxalate Crystal Deposition Disease

Calcium oxalate deposition produces an unusual form of arthritis mostly seen in patients with renal failure on dialysis, with chronic bowel disease or in primary oxalosis. Patients present with acute mono- or oligoarticular arthritis involving metacarpophalangeal joints. It may be of asymmetrical onset and associated with tenosynovitis or bursitis. Unlike gout, initial episode may be prolonged and chronic arthritis may develop rapidly. Diagnosis can be established by identifying calcium oxalate crystals which may be calcium oxalate dihydrate (positively birefringent bipyramidal crystal), or calcium oxalate monohydrate.

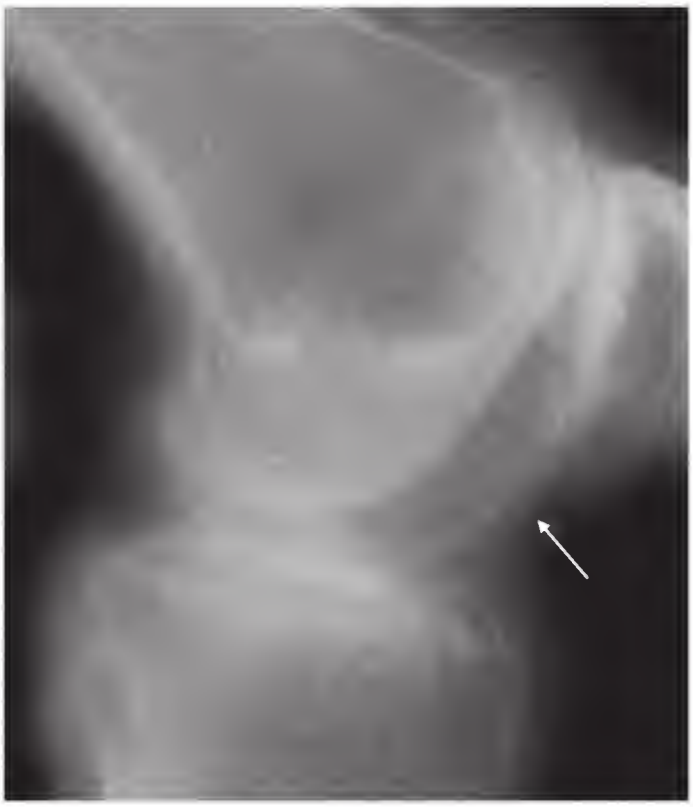


Figure 9: Linear calcification of articular cartilage along femoral condyle.

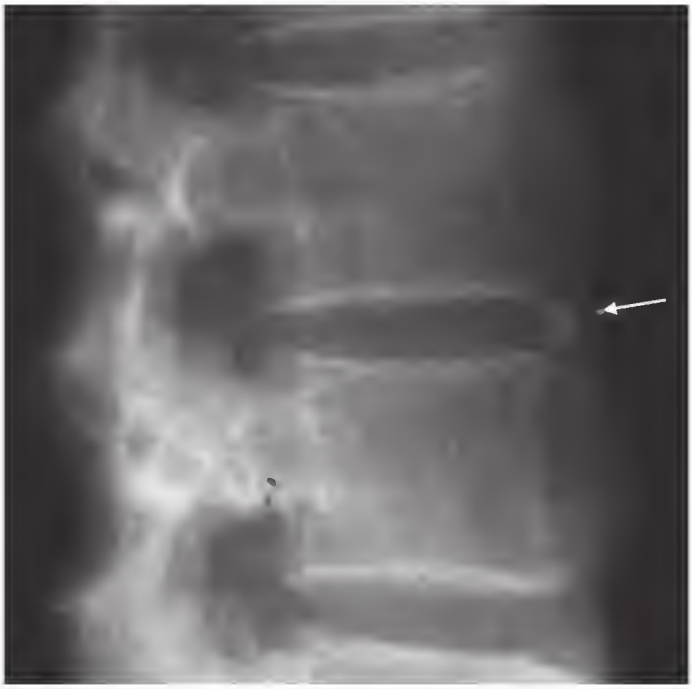


Figure 10: Calcification of annular ligament.

RECOMMENDED READINGS

1. Mc Carthy G. Calcium pyrophosphate dihydrate hydroxyapatite and miscellaneous crystals. In: JH Klippel editor. *Primer on the Rheumatic Diseases*; 13th Ed. New York, Springer; 2008: pp 263-70.
2. Nuki G. Treatment of crystal arthropathy-history and advances. *Rheum Dis Clin North Am* 2006; 32:333-57.

24.6 Rheumatoid Arthritis

AN Malaviya

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory polyarthritis that primarily affects small diarthrodial joints of the hands and feet in a symmetrical pattern. It is a heterogenous disease with variable severity, unpredictable course, and a variable response to drug treatment.

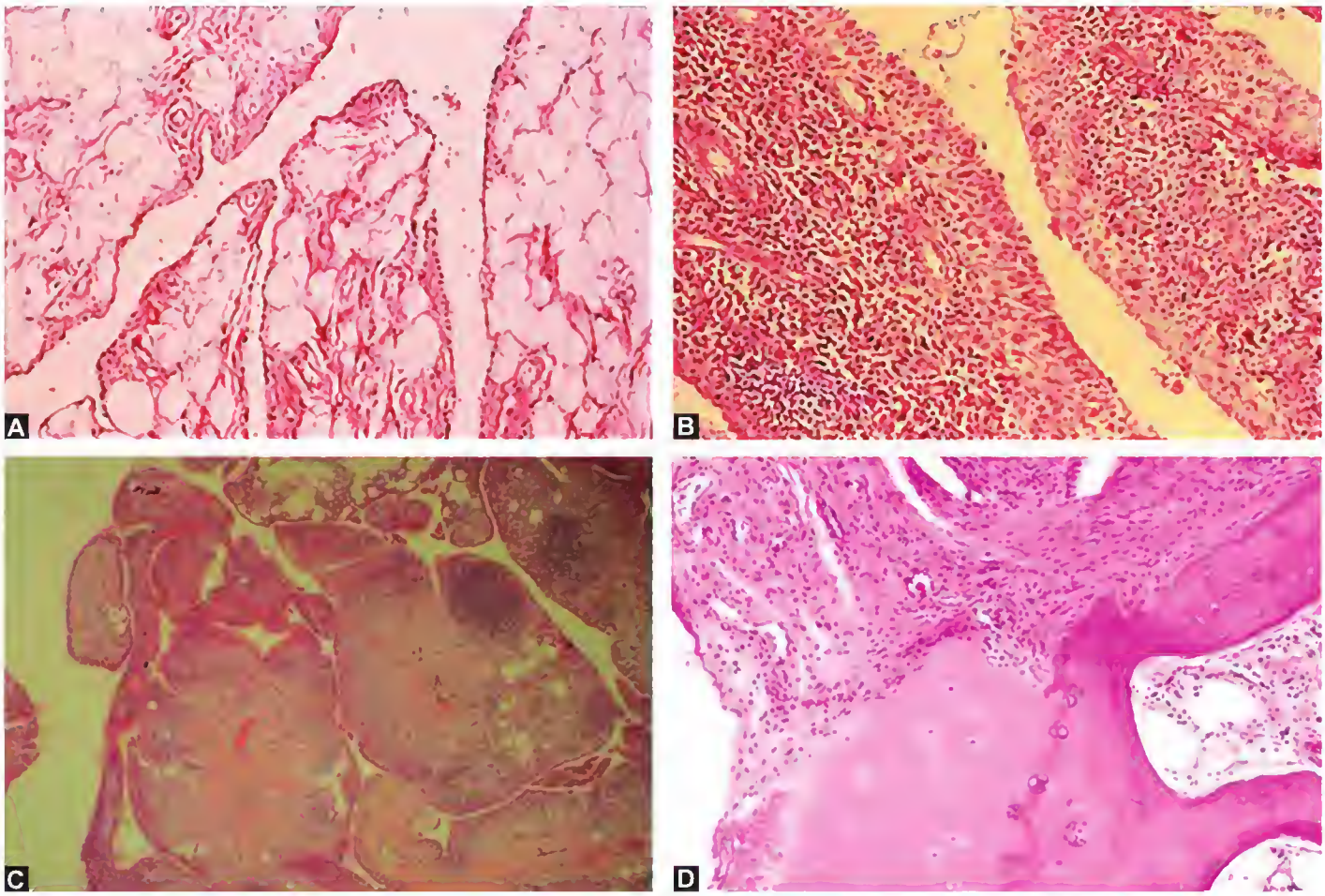
EPIDEMIOLOGY

The disease prevalence worldwide is approximately 0.8% (0.3% to 2.1%) of the population. In India, the prevalence of RA is 0.5% to 0.75%. The peak age of onset is in the fourth and fifth decade of life with more than 75% patients developing disease between 30 and 50 years of age.

GENETIC AND RISK FACTORS

The disease is seen 2 to 4 times more often in first degree relatives. The disease concordance in monozygotic twins is approximately 30% to 50%, while it is similar to nontwin siblings in dizygotic twins. The most important genetic susceptibility locus associated with RA is a class II major histocompatibility complex (MHC) allele of man namely, HLA-*DRB1* and the group of alleles collectively identified as shared epitope (SE). These include HLA-DR4 (DRβ1*0401) and other closely related alleles (DRβ1*0101, and several others). Among Indians, genetic susceptibility to RA with highest relative risk is with DRB1*0405, followed by DRB 1*0401 and those with DR4 haplotypes on DQB1*0302 region. Interestingly certain HLA-DR alleles may be protective against RA, e.g. DRB1*1502 and DRB1*0403 among Indian RA patients.

Nongenetic risk factors include gender and tobacco. Women are affected with RA 2 to 4 times more often than men. Role of hormones, pregnancy and related physiological alterations, foetal-maternal interactions have been implicated. Recently, a link between RA and smoking has been established. Smoking causes repeated insult to the mucosa of the airways causing



Figures 1A to D: (A) Photomicrograph of normal synovium that consists of 1 to 3 cell layer thick discontinuous intima without basement membrane. (B) Villous hyperplasia of synovium and chronic mononuclear inflammatory infiltrate in RA. (C) Lymphoid aggregates in the sub-synovium. (D) Typical pannus formation consisting of fibrovascular tissue protruding from the inflamed synovium into the articular cartilage. Figures A, B and D: Reproduced from the Clinical Slide Collection on the Rheumatic Diseases, 2009 American College of Rheumatology with permission.

Courtesy: Prof. Subimal Roy, Pathologist, Sir Ganga Ram Hospital, New Delhi.

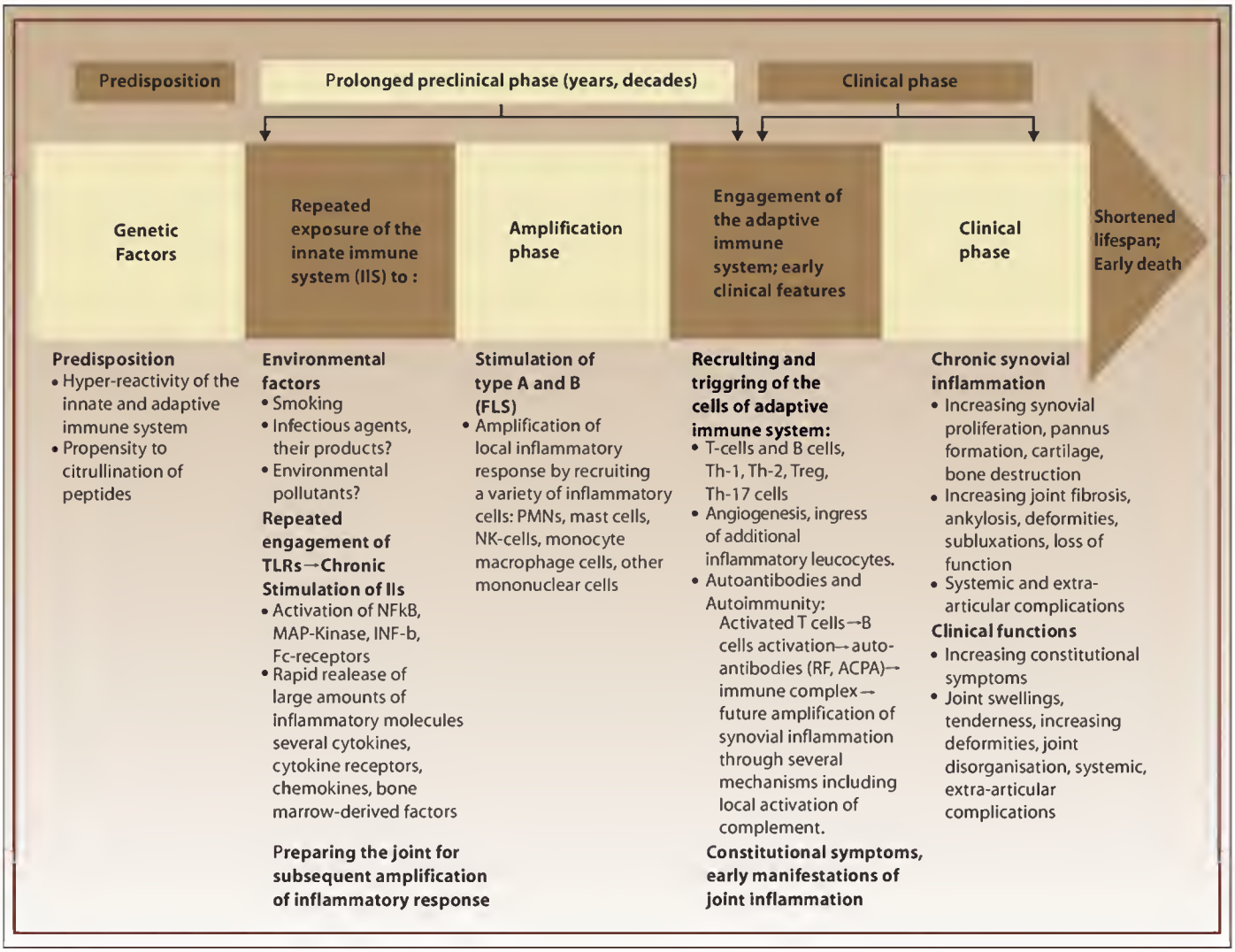


Figure 2: Natural history and immunopathogenesis of RA.

persistent low-grade inflammation that activates innate immune system through engagement of toll like receptors.

AETIOLOGY

The exact cause of RA still remains unknown. Infectious agents or their products have been implicated without conclusive evidence.

PATHOLOGY AND IMMUNOPATHOGENESIS

The synovium is the primary site of inflammation. The intimal layer becomes hypertrophied (up to 10 cell layers) with increased number of both types A and B synoviocytes. The subintimal region shows features of microvascular injury with thrombosis, neovascularisation (formation of new capillaries) and hyperplasia with increased cellularity (**Figures 1 and 2**). The proliferating synovial tissue is oedematous and overgrown with villous projections protruding into the joint cavity. This structure is called *pannus*.

Lymphocytes in perivascular lymphoid aggregates are populated with CD4+/Th1 and Th-17 T-helper memory cells. The other subsets of lymphocytes are the regulatory T cells (T_{regs}) mixed with small numbers of CD8+ cytotoxic T cells mainly found at the periphery of the lymphoid aggregates and scattered in the sublining. Besides T cells, rheumatoid synovitis also shows variable number of B cells and antibody producing plasma cells that cause polyclonal increase in immunoglobulins and production of autoantibodies.

Cytokines

TNF-α, mainly produced by synovial macrophages, is the master cytokine that triggers an inflammatory cascade. The imbalance between pro- and anti-inflammatory cytokines is an important mechanism of self-perpetuating chronic inflammatory synovitis in RA (**Figures 3 and 4**).

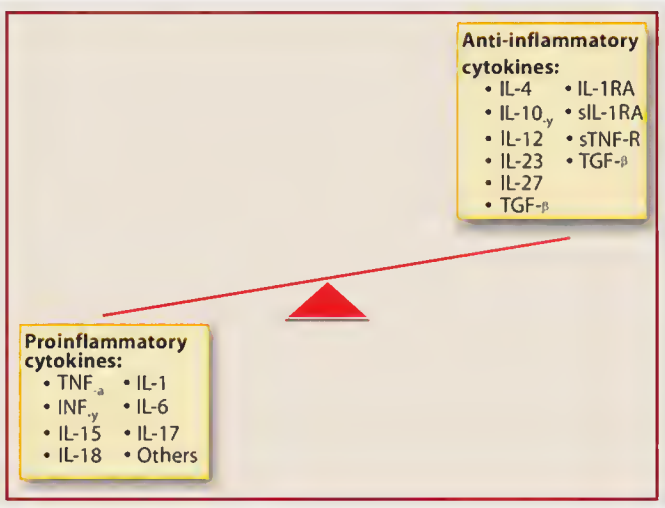


Figure 3: Cytokine imbalance in rheumatoid joint with preponderance in proinflammatory cytokines.

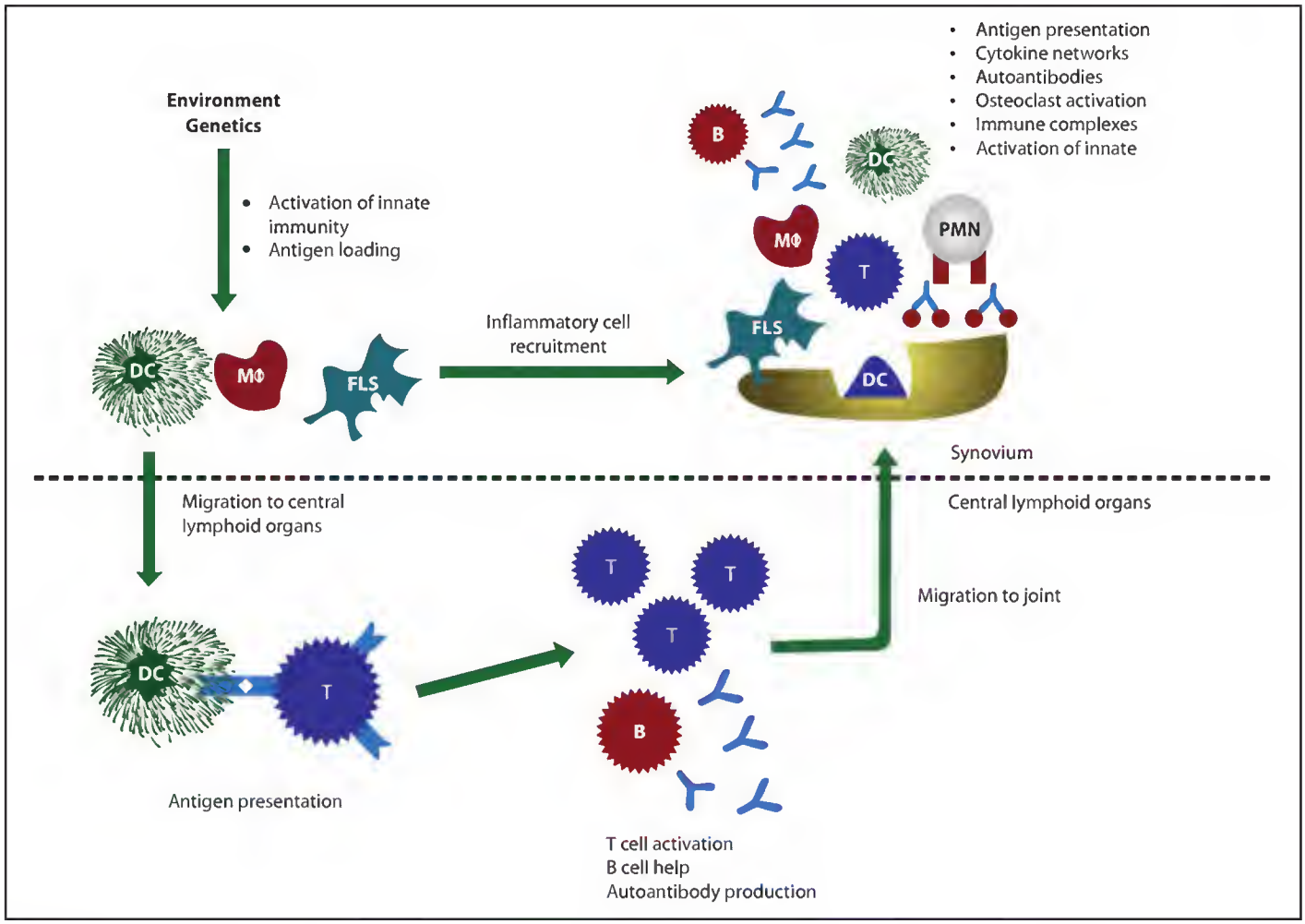


Figure 4: Immunopathogenesis of RA: Shows the current model of the immunopathogenesis of RA where both innate and adaptive immune systems co-operate and interact with each other to cause synovial inflammation in RA. The *innate immune system* is represented by antigen processing and presenting cells namely dendritic cells (DC), macrophages (MΦ), fibroblast-like synoviocytes (FLS) and polymorphonuclear leucocytes (PMN). The *adaptive immune system* is represented by T lymphocytes (T) the central cell of the adaptive immune system, B lymphocytes (B) that differentiate into antibody producing cells. Nonspecific inflammation caused by stimulation of the cells of the innate immune system, triggered by repeated exposure to environmental factors (smoking, others), and endogenous ligands, causes release of inflammatory cytokines (see Figure 3), which activate synoviocytes and macrophages to secrete chemokines and recruit T cell (of the adaptive immune system) in the joint. Locally produced autoantigens from damaged joint caused by nonspecific inflammation is processed by DC and presented in association with MHC class-II antigens, to T cells that are activated by dual signal of antigen presentation + costimulation molecule CD28. Then, activated T cells migrate out of the joint to the regional lymph nodes where they proliferate, produce a variety of cytokines, chemokines and growth factors thus recruiting and stimulating effecter T cells and B cells that migrate back to the joint. The effector T cells further amplify inflammation and provide helper signals to B cell to differentiate into antibody producing cells secreting autoantibody (rheumatoid factor [RF] and anti-citrullinated peptide antibodies [ACPA]). Autoantibodies make immune complexes activating complement cascade that further amplify inflammation. In established and late RA, local cytokine networks amplify and maintain a self-perpetuating inflammatory loop within the joint. Possibly this is aided by antigen presented by DC to T cells locally in the joints in the secondary lymphoid follicle-like structures seen in the synovial tissue at this stage. Terminal structural damage in the joint occurs through production of large amounts of proteolytic enzymes (mainly matrix metalloproteinase [MMPs], aggrecanases, collagenase, stromelysin) from pannus, PMNs and chondrocytes themselves; causing degradation of cartilage, tendon and ligaments. The invading pannus also releases cytokines namely IL-1, TNF-α that stimulate production of proteases, prostaglandins and activate osteoclasts (OC). Activated osteoclasts cause bone demineralisation (osteoporosis) and erosion. This is the end-stage joint damage of RA with erosions and irreversible structural damage leading to deformities and subluxations typical of late untreated RA. For details see text and Figures 1 to 3. (Adapted and reproduced from Waldenburger JM, Firestein GS. Rheumatoid arthritis: Epidemiology, Pathology and Pathogenesis. In: Primer on the Rheumatic Diseases, Klippel JH, Stone JH, Crofford LJ, White PH (Eds) 13th ed., Springer Science+Business Media LLC. 2008; With permission).

CLINICAL FEATURES

History

Inflammatory features include diurnal variation with symptoms, worse after a period of inactivity (e.g. early morning, after an afternoon siesta) that takes at least 30 to 60 minutes of gentle movements (e.g. taking a bath, doing daily chores) for maximal improvement, fluctuating course with disease severity varying from day-to-day, associated with constitutional symptoms of fatigue, malaise, feverish feeling (actual fever uncommon), loss of appetite and weight loss.

Pattern of Onset

Most commonly, the onset of symptoms of joint pains and swelling are insidious, evolving slowly in a fluctuating manner, over weeks to months. Much less commonly, there could be a sudden explosive onset of polyarthritis within a few days. Less common is a slow monoarticular presentation affecting larger joints such as shoulders or knees then spreading to other joints after variable periods. Still others may present with transient self-limited episodes of mono- or polyarthritis lasting days to weeks, a syndrome that is called palindromic rheumatism. Approximately 50% of such patients evolve into RA over time.

There are several uncommon modes of onset including persistent monoarthritis, abrupt acute monoarthritis of knee, shoulder or hip that may be confused with septic or crystal arthritis; persistent involvement of the joints of a single hand; inflammatory oedematous swelling on the dorsum of the hands or feet with a fluctuating course.

Joint Involvement

In early disease most commonly metacarpophalangeal (MCP) joints, interphalangeal (IP) joints of the thumbs, proximal interphalangeal (PIP) joints of fingers, wrists, mid-tarsal joints and metatarsophalangeal (MTP) joints are affected in that order (**Figure 5**). Soft swelling on the dorsum of the wrist due to tenosynovitis is an early sign. As the disease advances larger joints such as elbows, shoulders, knees and ankles are recruited. Uncommon joints to be affected in RA include hip, sternoclavicular, temporomandibular joints and joints in upper cervical spine. Rare cases have been reported with the involvement of cricoarytenoid joints in the larynx causing hoarseness of voice, interossicle joints in the middle ear causing some degrees of deafness. Typically, however, RA spares distal interphalangeal (DIP) joints and thoracolumbar spine. Thus, RA is an inflammatory joint disease characterised by symmetry, bilateralism and predilection for small joints in the hands and feet (especially in the early disease). Most of these typical clinical features of RA are incorporated in the revised 1987 American College of Rheumatology (ACR) criteria for the *classification of RA* (**Table 1**). These are not meant for making a bed-side diagnosis of RA but only for research and epidemiological studies. It is also helpful to remember that although many joints are known to get affected, the main target in RA are the 14 joint-groups namely PIP, MCP, wrist, elbow, knee, ankle and MTP. Clinical diagnosis of RA could be made if a minimum of 3 joints from these 14 joint groups are affected simultaneously for at least 6 weeks duration and show soft tissue swelling or joint effusion where at least one swollen joint is in a wrists, MCP or PIP and one of them is also present on the other side of the body (symmetrical involvement, absolute symmetry not required). The 1987 classification criteria of RA served its purpose admirably for patients with established or late disease. However, several carefully designed studies showed that it performed poorly in patients with early RA. Thus, the need for urgent revision of the old classification criteria became obvious. After more than a decade of collaborative work by rheumatologists under the aegis of the American College of Rheumatology (ACR) and European Leagues of Associations against Rheumatism (EULAR), new (2010) classification criteria for RA have been published superseding the earlier (1987) classification criteria (**Table 2**). The key points of difference from the 1987 classification criteria are as follows:

- They differ from the previous criteria in that the presence of synovitis in at least one joint is required, with no alternative diagnosis to explain the synovitis.
- Symmetric disease involvement is not required, nor is the presence of structural joint damage or rheumatoid nodules, both reflective of longstanding, established disease.

Thus, it redefines the current paradigm of RA. The other differences are:

- Their ability to utilise the diagnostic importance of antibodies to citrullinated proteins in RA (see below), advancement that was not available at the time the old classification criteria were propounded.
- Their ability to classify patients with 1-2 swollen joints and anti-citrullinated protein antibody positivity as having RA who, till recently, were labelled as having undifferentiated arthritis.
- Its ability to detect early RA that would facilitate undertaking the ideal therapeutic intervention at an early stage before the development of the final phenotype (i.e. patients with obvious joint damage); its use as a basis for initiating disease-modifying antirheumatic drug therapy at an early disease stage.

Table 1: The 1987 Revised Criteria for the Classification of RA*

Criterion	Definition
Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left proximal interphalangeal joint (PIP), metacarpophalangeal joint (MTP), wrist, elbow, knee, ankle, and metatarsophalangeal joints
Arthritis of hand joints	At least 1 joint area swollen (as defined above) in a wrist, MCP or PIP joint
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in item 2 above) both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive has been positive in < 5% of normal control subjects
Radiographic changes	Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

**Adopted from Arthritis Rheum 1988;31:315-24. With permission of John Wiley & Sons, Inc. For classificotion purpose, o potient sholl be soid to hove RA if she/he hos sotisfied ot leost 4 of these 7 criterio. Criterio 1 through 4 must hove been present for ot leost 6 weeks.*

Para-Articular Involvement

A common manifestation of RA is tenosynovitis in tendon sheaths around wrists and in the hands, a major cause of hand weakness. Carpal tunnel syndrome may also be seen.

Complications in Specific RA Joints with Associated Loss of Function

Progressive disease causes progressive structural damage leading to deformities, subluxations, and finally disintegration or ankylosis of the joints. Deformities seen in established RA include 'ulnar deviation' that occurs at the MCP joints, 'swan-neck' deformity characterised with flexion of the DIP and MCP joints with hyperextension of the PIP joint, 'Boutonnière deformity', 'Z' deformity of the thumb and subluxation of the distal radioulnar

Table 2: The 2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis*

	Score
Target population (Who should be tested?): Patients who:	
Have at least 1 joint with definite clinical synovitis (swelling)	
With the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; A Score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
Joint involvement§	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
Serology (at least 1 test result is needed for classification)††	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms§§	
< 6 weeks	0
≥ 6 weeks	1

**The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.*

†Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from, assessment. Categories of joint distributions are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

***In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g. temporomandibular acromioclavicular, sternoclavicular, etc.).*

††Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

‡‡Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§§Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g. pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

joint (**Figures 5 to 10**). More than one-third RA patients have significant foot disease like 'cock-up' toe deformity, hammer toes and 'rocker bottom' deformity (**Figures 11A to C**).



Figure 5: Typical physical findings of moderate swellings in the metacarpophalangeal and proximal interphalangeal joints in a patient with established RA.



Figure 6: The ulnar deviation (ulnar drift) of the fingers at the metacarpophalangeal joints in a patient with late RA.



Figure 7: The 'Swan-neck' deformity of the fingers in a patient with late RA.



Figure 8: The Boutonnière deformity in the finger joints; ulnar deviation (at MCP joints) is also seen.

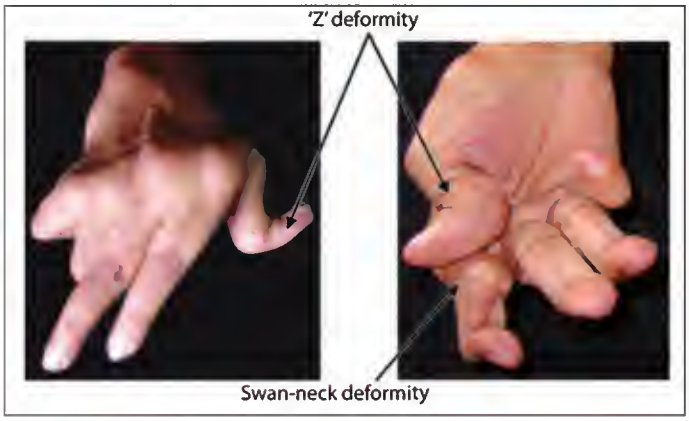
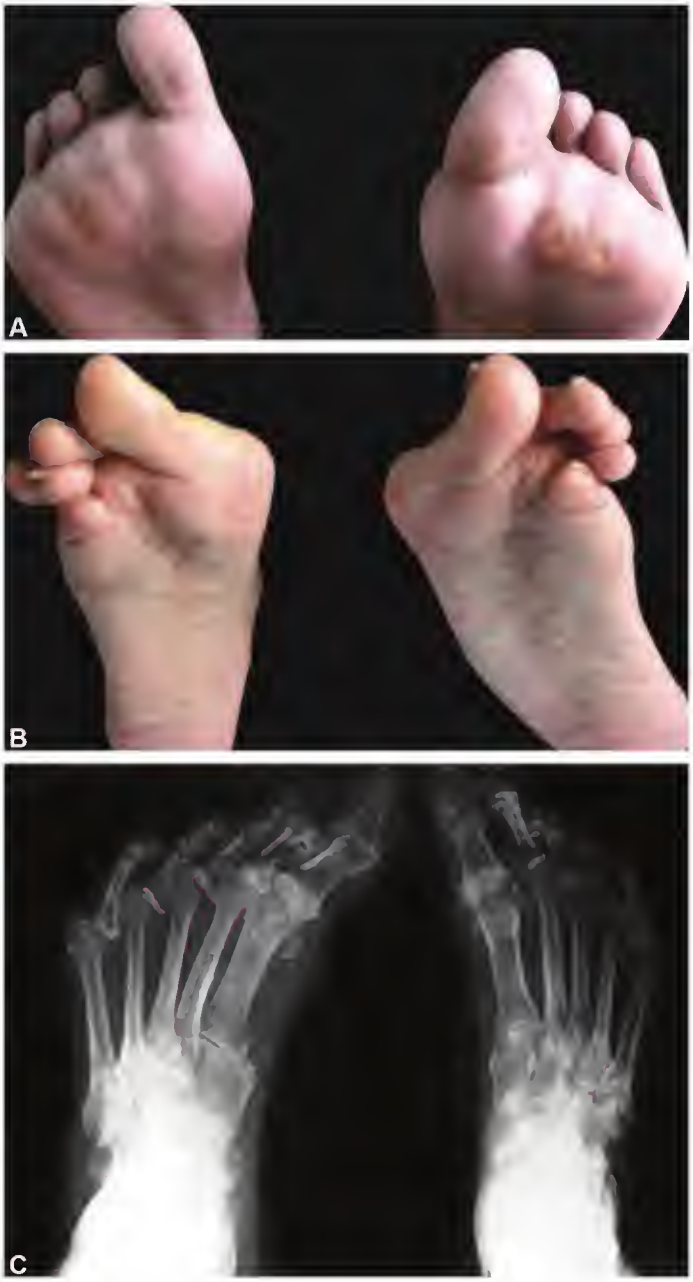


Figure 9: The 'Z' deformity in the right thumb; also note 'swan-neck' deformities in some of the fingers.



Figure 10: Late RA with advanced subluxation of the metacarpophalangeal joints with ulnar deviation and wrists with wasting of the small muscles of the hands. Note the 'squaring'-deformity of the left wrist and swan-neck deformity of the left little finger.



Figures 11A to C: Typical deformities in the forefeet in RA.

Extra-Articular Features

These include:

Rheumatoid nodules

These are firm nontender subcutaneous that tend to develop over pressure areas of the body most common being elbows and extensor surface of the proximal forearm (**Figure 12**). Other sites for rheumatoid nodules are Achilles tendon, fingers, occipital region on the scalp, and ischial tuberosities. Studies on RA from India have reported very low prevalence of rheumatoid nodules (~3%) that are very often unilateral.

Eye

Involvement of the lacrimal glands causes dryness in the eyes (keratoconjunctivitis sicca). Redness, pain, gritty feeling and excess mucous collection in epicanthus on getting up in the morning are the usual complaints. Usually there is associated parotid and minor salivary gland involvement causing dryness of mouth. Scleritis and episcleritis are the other less common

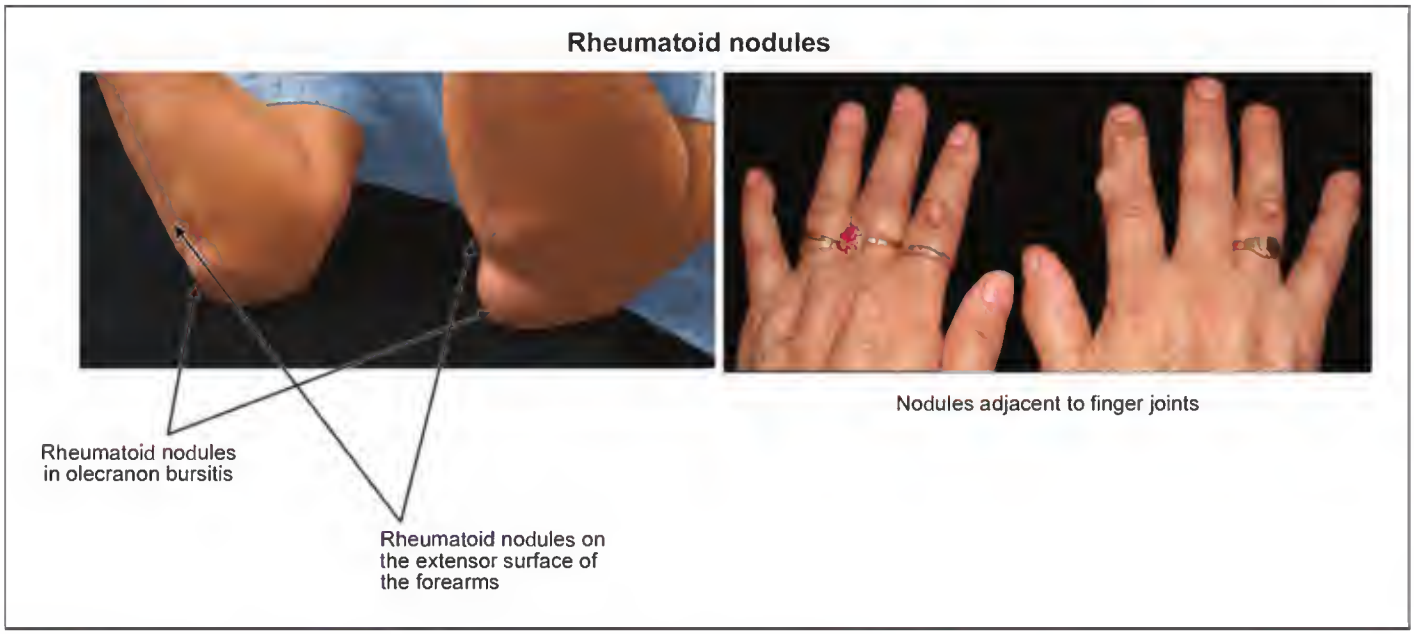


Figure 12: Rheumatoid nodules: on olecranon processes, forearms, adjacent to small finger joints.

complications of RA. In episcleritis, the eye becomes red and, in contrast to conjunctivitis, results in no discharge other than tearing in response to the gritty discomfort. Scleritis causes severe ocular pain and a dark red discolouration. No discharge is present. When severe, scleritis can cause resorption of the sclera down to the uveal layer, a complication called *scleromalacia perforans* that may cause vision loss.

Skin

There is no specific lesion of RA. The so-called 'senile' purpura resulting from skin atrophy and capillary fragility in patients inappropriately treated with long-term glucocorticoids is common. Palmer erythema and Raynaud's phenomenon may be seen. RA vasculitis usually manifests with nail fold infarcts or palpable purpura, most commonly seen on the lower leg. A severe form of vasculitis is a deep, erosive, ulcerated scarring lesion seen on the lower legs called pyoderma gangrenosum (**Figure 13**). It is indicative of severe disease that has not been well controlled. Severe systemic vasculitis, a dreaded complication of RA, is rarely seen now mainly because of early and effective treatment.

Lung

Pleuritis is the most common manifestation but in the majority it is subclinical. Interstitial pneumonia and fibrosis of non-specific class is more common in RA (as against scleroderma where the usual type interstitial lung disease is seen) (**Figure 14**). There is increasing dyspnoea associated with fine, diffuse, dry basal crepitations. Radiographs show a diffuse reticular (interstitial) or reticulonodular pattern in both lung fields often described as 'ground-glass' appearance; these can progress to a honeycomb appearance on plain radiographs and a characteristic lattice network seen on high-resolution CT scans. Less common but serious lung lesions in RA including nodules in the lung (**Figure 15**) (they may cavitate), bronchiolitis obliterans with organising pneumonia disease, arteritis with pulmonary hypertension and a rare small airways disease. Another important consideration is that methotrexate (MTX) and leflunomide (LEF), important drugs for treatment of RA, may also cause lung disease that may be difficult to distinguish from those caused by the disease itself. As a practical rule lung disease due to active RA that has been suboptimally treated is much more common than drug induced



Figure 13: Pyoderma gangrenosum on the lower leg.



Figure 14: Interstitial lung disease in RA.



Figure 15: Rheumatoid nodule in the lungs.

lung complications. Endogenous tuberculosis flare may occur after treatment with TNF-α inhibitors.

Haematological manifestations

Anaemia is common in RA. It is multifactorial and due to anaemia of chronic disease, iron deficiency due to gastrointestinal bleeding from indolent ulcers mostly caused by chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), and superimposed B12 and folate deficiency. Serum ferritin concentration is much higher in anaemia of chronic disease than is found in isolated iron deficiency. Thrombocytosis as a result of systemic inflammation is also common in RA. Similarly, there could be some degree of polymorphonuclear leucocytosis.

Other organs

Rapid wasting of muscle proximal to the affected joints with weakness is common in RA. Neurologic involvement may take the form of entrapment neuropathies (carpal and tarsal tunnel syndrome), cervical myelopathy due to cervical spine subluxation and mononeuritis multiplex due to small vessel vasculitis. Renal disease in RA is rare. But drugs used in its treatment may affect kidney, NSAIDs being the most common culprit. Secondary amyloidosis of AA variety seen in long standing RA may cause nephrotic syndrome. Subtle subclinical heart involvement is not uncommon and includes pericarditis (rarely may cause symptomatic pericardial effusion or, even tamponade), myocarditis, endocarditis, valvular disease and conduction defects. Much more important, however, is systemic inflammation-related premature atherosclerosis leading to coronary artery disease and myocardial infarction in young.

Other clinical problems

Osteopoenia and osteoporosis is common and may lead to increased fracture risk. Risk of infection is also increased by approximately 1.5 to 2 times of the matched normal controls. Cancer risk, especially haematological malignancies, is 2 to 3 times higher in RA that is not related to its treatment.

Unusual Patterns or RA Variants

These include 'elderly-onset-RA' or EORA and *arthritis robustus (details available in the web version)*.

Syndrome of Early Undifferentiated Polyarthritis

If the duration of symptoms is less than 6 weeks, RA cannot be diagnosed with certainty. 30% to 40% of such patients may go in spontaneous remission never evolving into RA. Therefore, it has been called *undifferentiated polyarthritis syndrome* (UPS). ACR defines three categories of RA disease duration: early disease (<6 months), intermediate duration (6 to 24 months), and longer duration (>24 months, late RA). Early disease has been further subdivided by disease duration of <3 months (very early RA, VERA) or 3 to 6 months (late early RA, LERA).

Prognostic Factors and Mortality

Disease duration, number of affected joints, functional status, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, degree of anaemia and presence of erosions at the time of first presentation and the presence of SE genes, correlate with severe aggressive disease. American College of Rheumatology recommends functional status (M-HAQ), presence or absence of extra-articular manifestations (rheumatoid nodules, sicca symptoms, vasculitis, lung disease); rheumatoid factor (RF) in significant titres; anti-citrullinated peptide antibody (ACPA) in significant titres; and bony erosions (on radiology) as determinants in treatment decision-making.

Life-expectancy is shortened among patients with RA than in the general population by 15% to 20% from the date of onset of illness, and lifespan is shortened by about 10 years in untreated RA. About 40% of the excess deaths were due to cardiovascular causes, other causes being infection, malignancy, and complications of the disease including increasing lung involvement, vasculitis, and other diverse causes.

Differential Diagnosis

Persistent inflammatory polyarthritis of RA pattern is seen a large number of other diseases. They are called 'mimics of RA'. The common ones include psoriatic arthritis, spondyloarthritis, reactive arthritis, systemic connective tissue diseases, systemic vasculitides, crystal-deposition arthritides, inflammatory-bowel disease related arthritis, sarcoidosis-related arthritis and several uncommon and rare conditions like Behcet's disease, relapsing polychondritis, multicentric reticulohistiocytosis, periodic syndromes, adult-onset Still's disease, relapsing seronegative symmetric synovitis with pitting oedema (RS3PE), Lyme disease, primary amyloidosis, joint symptoms related to hypothyroidism

and several other endocrinal diseases, hyperlipoproteinaemia-related joint disease. Certain noninflammatory joint diseases may be confused with RA, e.g. primary nodular osteoarthritis, joint pains in haemoglobinopathies. Psychogenic problems (e.g. fibromyalgia) may be confused with RA by inexperienced physicians.

LABORATORY INVESTIGATIONS

Routine Investigations

Routine laboratory tests at baseline are important for: (1) assessing the degree of systemic inflammation; (2) confounding factors (age, co-morbidities) requiring modification in management plan; (3) organ specific toxicities from prior drug use.

Systemic inflammation is gauged with ESR (Westergren method) and CRP levels in the blood. Systemic inflammation depresses albumin synthesis by liver causing hypoalbuminaemia. A reversal in albumin/globulin ratio is a common finding in active RA. Serum alkaline phosphatase (ALP) being an acute-phase reactant, is mild to moderately elevated in active RA.

Additional routine baseline studies should include liver enzymes, renal parameters, blood glucose and routine urine examination. These are important because certain drugs used in RA are hepatically cleared (NSAIDs, MTX, LEF). Also, drug dosages need to be modified in the presence of compromised renal status (MTX).

Autoantibodies

In addition to the above routine investigations, two antibodies should be tested in patients suspected with RA. These are RFs and ACPA. RF can belong to any immunoglobulin class (IgM, IgG or IgA). However, RF of IgM class are routinely tested in clinical immunology laboratories. Approximately 70% of patients with clinically diagnosed RA have significant titres of RF and are classified as seropositive RA while the others are classified as seronegative RA. High level of RF has approximately a sensitivity of ~ 70% and specificity of ~ 80% for the diagnosis of RA and is predictive of aggressive erosive disease with more extra-articular features and poor prognosis. Seronegative RA is usually a milder disease. It is not uncommon that the so-called seronegative RA patients turn out to have one of the mimics of RA in the follow-up; the most common being psoriatic arthritis. Thus, only a small proportion of RA patients remain truly seronegative over time. A large number of other chronic inflammatory conditions (systemic inflammatory rheumatic diseases including Sjögren's syndrome, SLE, and other connective tissue diseases, systemic vasculitides; sarcoidosis, chronic autoimmune hepatitis, primary biliary cirrhosis, others) and most chronic infections (tuberculosis, leprosy, bacterial endocarditis, hepatitis C, many others) may have RF. Like RF, significant titres of ACPA also predict aggressive, erosive disease with extra-articular features and poor prognosis. The sensitivity of significant titres of ACPA for RA is similar to RF (~ 70%) but specificity is much higher (~ 95%). ACPA is present in one-third patients who are negative RF at presentation.

It is now well established that ACPA and RF appear at least a decade before (the former appearing somewhat earlier) the onset of articular symptoms that evolve over time into RA (**Figure 2**). Antinuclear antibody (ANA) is another antibody present in approximately 20% to 30% of patients with RA, occasionally with high titres, but normal or increased serum complement levels (C3, C4) distinguish them from SLE where these are generally low. Occasionally, such patients may have true overlap of RA with SLE, often called rupus or rhupus.

Synovial fluid analysis

Examination of synovial fluid is not necessary for the diagnosis RA unless sepsis is suspected in any joint (out-of-proportion persistent swelling in an otherwise well controlled RA).

Imaging

Imaging plays an important role in the diagnosis as well as in the assessment of disease progression. Joints in the hands-wrists and, feet have smaller bones and thinner cartilage than the larger joints. Therefore, early radiographic changes are better seen in them and are recommended radiographs at the baseline and for the periodic assessment of joint disease in the follow-up. The earliest abnormality is periarticular osteopoenia, which is nonspecific and variable (**Figure 16**). With uncontrolled disease more characteristic changes of cartilage loss (joint space narrowing) and bony erosions appear by 6 to 12 months (**Figure 17**) and keep accumulating over time. Magnetic resonance imaging (MRI) and ultrasonic joint examination are more sensitive for detecting joint changes including synovial hypertrophy, joint effusion, tendon and ligament disease, erosions and rupture of joint cysts (e.g. Baker's cyst) than routine radiographs. They could be useful in early arthritis when clinical examination and standard radiographs may be unhelpful.



Figure 16: Periarticular osteopoenia (area shown with brackets).

TREATMENT AND ASSESSMENT

Approach to treatment of RA requires a team approach comprising of a physician-rheumatologist along with orthopaedic surgeon, specialist nurses, clinical assistants, physiatrists, counsellors and educators, and the supporting secretarial staff trained in the use of electronic medical records. Patient education is the key to this end. Psychosocial support to spouse and family is another important component of effective management. Socioeconomic factors need to be discussed with the patient and the family members at the outset. Health economics plays a key role in decision-making



Figure 17: Typical changes of RA on radiology with loss of joint space and erosions in most joints, and complete disorganisation of the wrist joints.

in drug treatment since most patients do not have health insurance or any kind of medical coverage in India.

Disease Assessment

Objective assessment at the baseline and at each of the follow-up visits is mandatory. The importance of objectified assessment can be better understood again with the examples of diabetes mellitus and hypertension where blood glucose/glycosylated haemoglobin levels or blood pressure measurements are needed at each follow-up visit. Similarly, joint count is mandatory for satisfactory treatment of RA.

There are well-defined domains in RA that need object assessment in the follow-up at recommended intervals. These include determination of: (i) disease (inflammatory) activity; (ii) functional status and quality of life (QOL); (iii) degree of joint damage; (iv) extra-articular problems. The assessment of disease activity is drawn from a composite of patient's perception of overall (global) pain and general health status as affected by the disease, on a visual analogue scale (VAS) of 0 to 100; the duration of morning stiffness in minutes; number of tender and swollen joints (examined and counted by the physician or any trained clinical assistant), physician's global assessment (VAS 0 to 100) after a detail clinical evaluation; and the level of inflammatory biomarkers (ESR and CRP). Using these five parameters a composite index called DAS (disease activity score) or DAS28 (if 28 joints are assessed) is calculated using a mathematical formula. The results obtained (in exact numbers on scale of 0 to 10) are then used to classify patients as having 'high', 'moderate', or 'low' disease activity or, 'remission' as determined by already established cut-off values. A simplified disease activity index (SDAI) that does not require complicated mathematical calculations has been recently devised. Simple addition of the number of tender and swollen joints, physician's and patient's global assessment (converted to 0-10 VAS) and CRP values (mg/litre) gives a number that determines the disease status based upon pre-determined cut off values. Further simplification called clinical disease activity index (CDAI), does away even with CRP values. Simple addition of the remaining four parameters gives the exact number that determines the disease status based upon pre-determined cut off values. These 'instruments' to measure disease activity, at any given point, are now being widely used in daily routine clinical practice to guide treatment decisions.

Functional status assesses all the domains of daily living (self-care, routine functions of daily living, vocational activity, avocational activities) using a self-administered health assessment questionnaire (HAQ) that provides objectified disability index (HAQ-DI). Several authenticated versions including an Indian modification (with 12 questions covering these aspects, M-HAQ-DI), are available. Radiographic damage is assessed using van der Heijde modification of the Sharp score, discussed above (see 'radiology') carried out at the baseline and at every six-month interval.

Treatment

Several overreaching principles guide the present-day treatment of RA. First and foremost is the recognition that damage and disability accrues rapidly in the first few months to two years. A delay of even as little as 3-4 months in initiating appropriate treatment makes significant difference in the outcome over long periods. The second principle is that accurate objectified assessment of disease activity used as guide for titrating treatment leads to much improved outcome both in the short as well as long-term. The third principle is based upon a notable observation that the toxicity of disease modifying anti-rheumatic drugs (DMARDs; see below), especially the newer ones led by MTX was actually less than the so-called simple painkillers NSAIDs. Based upon these principles, the modern day treatment for RA includes early diagnosis and initiation of early, aggressive, intensive, effective treatment with DMARDs to suppress inflammation continuously as ensured by periodic objectified assessment of disease activity targeting 'low-disease activity' or 'remission' all through a patient's life-time. **Table 3** gives the basic principles of modern-day treatment of RA namely, 'the tight disease control strategy'.

Table 3: Basic Principles of Modern-Day Treatment of RA: 'The Tight Disease Control Strategy' Based on Objectified Assessment of Disease Activity as a Guide for Response-Driven Targeted Treatment for Improved Outcome

Early diagnosis
The disease progresses rapidly; damage and disability accrues rapidly in the first few months to 2 years; A delay of even as little as 3-4 months in initiating appropriate treatment makes significant difference in the outcome over long periods.
Accurate objectified assessment of disease activity at base-line and at frequent intervals in the follow-up for titrating treatment.
Used as a guide for *response-driven targeted treatment* that has been shown to lead to much improved outcome both in the short as well as long term.
Aggressive treatments with DMARDs as monotherapy or in combinations, in 'step-up';'step-down' or 'saw-tooth' strategy:
Now there is proof that DMARDs are less toxic than NSAIDs, early aggressive use with MTX as the 'anchor drug'; improves both long- and short-term outcome, prevents damage and disease complications.
Judicious use of glucocorticoids.
Improved understanding of glucocorticoid actions and effective strategies for their use in RA minimising adverse effects, improves treatment outcome.

Drugs

There are three main categories of drugs used in the treatment of RA, namely NSAIDs; standard DMARDs and biological DMARDs; and glucocorticoids.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

These symptom-controlling compounds provide symptomatic relief from pain and inflammation. NSAIDs belonging to different classes are available namely; salicylates (aspirin); derivatives of acetic acid (indomethacin, etodolac), anthranilic acid (mefenamic acid), sulfonanilides (nimuselide), heteroaryl acetic acid (diclophenac), arylpropionic acid (ibuprofen, naproxen, ketoprofen), and enolic acid (piroxicam, meloxicam). These drugs belong to the standard non-selective NSAIDs group. The other category of selective COX-2 inhibitor group include the coxibs (celecoxib, etoricoxib). There is wide variability in patient preferences for these drugs and patients are allowed to choose agents of their choice, the so-called 'menu-approach'. Adverse effects of NSAIDs include gastrointestinal (abdominal pain, erosions/ulcers, bleeding and perforation in small and large bowl; nausea, anaemia), renal (salt-water retention, oedema, worsening renal function, hyperkalaemia), liver (transient rise of liver enzymes, cholestasis, acute liver injury), central nervous system (headache, dizziness, confusion, lowered seizure threshold), platelets (inhibit platelet activation, bruising, haemorrhage), cardiovascular (premature closure of ductus arteriosus, heart failure worsening, myocardial infarction, haemorrhagic stroke), and hypersensitivity (angioedema, asthma, hypotension, shock). A combination of NSAIDs should not be used as the pharmacological action of all NSAIDs/Coxibs is similar. Combinations enhance toxicity not efficacy. An important therapeutic principle of their use is to give a larger dose at bedtime that is more effective in controlling early morning symptoms, so troublesome in RA patients. Another important principle of their use is that if a patient requires their continuous use due to incomplete pain control, the cause of pain must be carefully evaluated. Persistent pain usually implies poor disease control that is definitely not an indication for continuous use of NSAIDs/Coxibs. Rather, it would require a reassessment of the choice and the dose of DMARDs (see below), the prescribed combination(s) and the patient compliance. Another reason for persistent pain despite good disease control could be mechanical in origin due to structural joint damage where a surgical intervention, if warranted, may permanently relieve the pain.

DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

Standard DMARDs (Table 4)

These are a diverse group of synthetic small molecules empirically shown to reduce the signs and symptoms of RA but, have additionally found to be effective in slowing down disease activity and halt disease progression and damage. Of a large number of these drugs, presently only four of them are widely used: MTX, sulphasalazine (SSZ), LEF, and hydroxychloroquine (HCQ). The other two, namely cyclosporine and minocycline are also used but sparingly. Older DMARDs include organic gold, D-penicillamine, and chloroquine. Other DMARDs include cytotoxic drugs, e.g. azathioprine, cyclophosphamide and others. But due to unfavourable safety profile older DMARDs and cytotoxic drugs are rarely used now.

Hydroxychloroquine (HCQ)

It belongs to the group of anti-malarial drugs. Being much less toxic than its older cousin chloroquine, HCQ is a popular drug for the treatment of RA. It is among the safest DMARDs with mild action, best suited for patients with mild disease. Approximately 40% of the patients get measurable benefit. It is also very popular as an adjunct drug for use in DMARD-combinations for patients with more aggressive disease. At the recommended dose of 400 mg daily ($\leq$ 6.5 mg/kg body weight) it has little adverse effects except darkening of the exposed skin that may be reduced with proper clothing, sun-screen lotions and avoiding direct sun exposure. Used at this dose, true retinopathy has become a rarity. However, if given for prolonged periods (>10 years) it would be prudent to get proper retinal examination done for HCQ retinal toxicity. Other reported adverse effects include abdominal discomfort, nausea, lose motions, skin rash, tinnitus, headache and myopathy. It crosses placenta, therefore, with risk of foetal abnormalities.

Sulphasalazine (SSZ)

It was the first drug to be specifically designed by Svartz (1942) for the treatment of RA. Approximately 45% of patients would have beneficial effect at the end of 6 months. It is a popular drug for mild-to-moderate early disease and, like HCQ is the most popular DMARD to be used in combination with MTX and HCQ therapy. It is generally well tolerated but, gastrointestinal disturbance and intolerance, allergic skin rash, reversible reduction in sperm count are not uncommon. Less commonly

Table 4: Disease Modifying Anti-Rheumatic Drugs (DMARDs): Standard DMARDs and Biological DMARDs

Synthetic small molecules empirically found to be effective in the treatment of RA (Standard DMARDs)			Mechanism-based molecules produced biotechnologically for targeted modification of biological response (Biological DMARDs)
DMARDs presently used widely	**DMARDs presently used sparingly**	**DMARDs not widely used now**	**Inhibitors of tumour necrosis factor-α (iTNF-α):** Infliximab, etanercept, adalimumab*, certolizumab pegol*
Low-dose methotrexate (LD-MTX)	Minocycline Cyclosporine	Organic-gold compounds D-Penicillamine	**B-cell depletion therapies** **Rituximab**
Sulphasalazine	Others: tacrolimus	Chloroquine	**Others:** Tocilizumab (inhibitor of IL-6), abatacept (co-stimulation blocker), large number of other molecules in the 'pipeline'
Hydroxychloroquine		Cytotoxic drugs: azathioprine, cyclophosphamide, chlorambucil, others	
Leflunomide			

**Not released in India at the time of writing.*

cytopoenias and liver function abnormalities may be seen. A rare manifestation is drug-induced lupus.

Methotrexate (MTX)

It was developed several decades ago as an anti-cancer drug that works as a potent inhibitor of dihydrofolate reductase (DHFR), a critical enzyme in folate metabolism. The dose of MTX required for its cytotoxic-antiproliferative action in the treatment of malignancies is, however, high; usually >1gm/m^2 (average person measures 1.73 m^2). Therefore, therapeutically, the MTX dose required to treat malignancies has been designated *'HD-MTX'*. It is of note that the rheumatologists use several folds less MTX dose than that used in oncology; mostly in the range of 7.5 to 15 mg once weekly. Only in recent days dose in the range of up to 15 mg/m^2 or 25 mg/wk (maximum of 30 mg/wk) has been recommended. The therapeutic dose of MTX used is rheumatological conditions is, therefore, called LD-MTX. It would appear that HD-MTX and LD-MTX are, for all practical purposes, two different drugs with different modes of action and different indications of use in clinical medicine (details on web version).

LD-MTX in RA

LD-MTX is now considered the 'anchor drug' among DMARDs. The beneficial effects become visible within weeks. MTX is used in RA as a monotherapy as well as the cornerstone in any DMARD combination, including those with biologicals. It has a convenient weekly dose schedule; it is inexpensive and better tolerated than most other DMARDs with high 'retention rate' over long periods of time. LD-MTX can be administered orally or by subcutaneous injections. Oral weekly dosing is convenient but, above 15 mg/week dose, a switch over to subcutaneous route improves gastrointestinal tolerability and bioavailability. Conventionally, the initial dose is 7.5 mg weekly that is escalated every two weeks to a maximum of up to 30 mg weekly dose to achieve maximum disease control. More recently, it has been recommended that in patients with no risk factors (see below) LD-MTX treatment could be initiated at the dose of 15 mg/week orally, escalating with 5 mg/month to a maximum of 25-30 mg/week with a switch to subcutaneous administration in the case of an insufficient response. However, patients with very active polyarticular disease and markers of bad prognosis will benefit from starting with parenteral administration. The dose may be successfully reduced to once in two weeks in patients with stable remission for a long-time. LD-MTX has also been shown to reduce radiological progression of disease.

Common Adverse Effects and Monitoring of LD-MTX Treatment

Toxicity monitoring is simple and inexpensive and only includes blood counts, liver enzymes (AST, ALT), and renal status (serum creatinine). Commonly seen adverse effects, albeit minimal, include gastrointestinal intolerance, stomatitis, hair loss and liver function abnormalities. At the recommended doses bone marrow suppression is rare. Folic acid or folinic acid supplementation reduces the frequency of liver function test abnormalities, stomatitis and marrow suppression. Folic acid supplementation is at the dose of 1 mg daily or 5 mg weekly on the next day of the MTX dose. Switching to subcutaneous injections is another way of offsetting GI intolerance. Mucositis can be easily controlled with folinic acid supplementation (usually 50% of the MTX dose) given 12 hours after the LD-MTX dose. MTX is teratogenic, therefore, needs to be discontinued for at least 10-12 weeks before the patient tries for pregnancy. Rare adverse effects (~1%) include interstitial pulmonary inflammation and fibrosis that would necessitate discontinuation of the drug. However, the earlier debate related to MTX-induced lung and liver fibrosis has slowly died down as this does not appear to be a great risk. Most vaccinations work well and not suppressed with LD- MTX.

Leflunomide (LEF)

It suppresses the *de novo* synthesis of pyrimidine (uridine and cytidine) nucleotides by inhibiting dihydroorotate dehydrogenase. It is given orally once a day at the dose of 10 or 20 mg. Adverse effects include diarrhoea, liver toxicity (transaminitis), leukopenia and potential to raise blood pressure. It is potentially teratogenic and normally should not be prescribed in women in reproductive age unless strict contraception is ensured.

Table 5 gives details of commonly used standard DMARDs.

Biological DMARDs

These are genetically engineered biotechnologically produced version of natural molecules that specifically target pathogenic mediators of joint inflammation and damage. There are two main categories of biologicals namely monoclonal antibodies (suffix 'mab') and, fusion proteins (suffix 'cept'). They are highly effective in controlling disease activity, and halting/reversing disease progression and damage (**Table 5**). The major drawback is cost.

Glucocorticoids (GC)

Besides their anti-inflammatory action they have been shown to retard disease progression and joint damage in RA. Unfortunately, because of serious systemic long-term adverse effects GC use in RA remains limited to only a few situations: (i) Depot-preparations for intra-articular or intra-lesional administrations to control localised disease flares such as in a single (or a few) joint(s) or para-articular lesions such as tenosynovitis, carpal tunnel syndrome others. The commonly used preparations are depot-methylprednisolone, depot-triamcinolone-acetonide and depot-triamcinolone-hexacetonide (the last one not available in South-East Asia); (ii) Depot-methylprednisolone given as intramuscular injections at weekly intervals for a few weeks at the initiation of DMARD treatment as 'bridge-therapy', to control inflammation and pain during the period it takes for slow-acting DMARDs to start their action; (iii) Large-dose intravenous bolus given on 2 or 3 consecutive days for 'debulking' of severe disease at the initiation of treatment or uncontrolled disease flare during the follow-up; (iv) As one of the drugs in a step-down combination-DMARD strategy with a moderate dose that is tapered off over the next several weeks; (v) For treating some of the more serious complications of RA, e.g. vasculitis, eye and pulmonary involvement, serositis; (vi) To prevent nausea, vomiting and gastrointestinal intolerance often seen with MTX dose of 20 mg/week or more. A small to moderate dose of GC given about 15-30 minutes before the MTX dose once-a-week may relieve this problem. Prolonged continuous daily use of GC in RA is not recommended especially in our country where metabolic syndrome is a major problem in the population. An important

Table 5: Standard and Biological DMARDs for the Treatment of RA: Dose/Route of Administration, Clinically Relevant Adverse Effects, Screening and Monitoring

Standard DMARD	Route/ Schedule	Clinically Important Adverse Effects	Screening	Monitoring
Low-dose methotrexate	Oral/subcutaneous weekly	GI intolerance, mucositis, transient transaminitis	Renal and liver status, blood counts, hepatitis B and C	Complete blood counts, liver enzymes, serum creatinine 2-3 monthly.
Hydroxychloroquine	Daily oral dose	GI intolerance, skin rash, skin hyperpigmentation Prolonged therapy with dose >6 mg/kg may rarely cause retinopathy	In patients > 50 years of age taking drug for several years, yearly eye examination for retinal toxicity	—
Sulphasalazine	Daily in divided dose	GI intolerance, skin rash, rarely granulocytopaenia	Complete blood count, liver status and G6PD deficiency	Complete blood count, liver enzymes 2-3 monthly
Leflunomide	Single daily dose	Diarrhoea, skin rash, alopecia, transaminitis, granulocytopaenia	Complete blood count, liver enzymes, renal function, hepatitis B and C	Complete blood count, liver enzymes, serum creatinine, 2-3 monthly
Biological DMARD	**Dose/route**	**Clinically important adverse effects**	**Screening**	**Monitoring**
Infliximab	IV infusion over 4-6 hours, usually 3 monthly infusions	Flare of latent tuberculosis, other infections, autoimmune phenomenon, psoriatic lesions, increased chances of malignancy?	For latent tuberculosis, infections	For tuberculosis, infections
Etanercept	50 mg weekly subcutaneous injections	Local injection reactions; infections; flare of latent tuberculosis	-do-	-do-
Rituximab	IV infusion cycles of 1 gm slow IV infusion × 2 at 15 day interval; to be repeated 6 monthly	Allergic reactions during infusions, infections, multifocal leucoencephalopathy	Infections, hepatitis B and C screening	Infections
Abatacept	1 gm as slow IV infusion every 15 days × 3; Subsequent doses 4 weekly	Infections	-do-	-do-
Tocilizumab	8 mg/kg body weight, given as slow IV infusion, every month	Infections, deterioration in lipid profile, especially blood triglyceride levels	-do-, lipid profile	-do-, lipid profile

point to remember is that, when used over prolonged periods, there is no safe dose of GC. Even at very low doses (≤7.5 mg per day) adverse effects, especially osteoporosis and cataract, do occur. Several trials in RA have shown that when given in combination with DMARDs even for a short period at the treatment initiation, the beneficial effects persist during several years in the follow-up. Therefore, the best approach is to be reasonable and use GC judiciously, always combined with effective doses of DMARDs and never prescribing it as a 'stand-alone' drug for treating RA. The most commonly used oral preparation of GC is prednisolone. Methylprednisolone oral tablets are also available but more expensive.

TREATMENT STRATEGY AND RECOMMENDATIONS

The treatment goal is to achieve rapid and lasting *low-disease activity status* or *remission*. The key step towards achieving this goal is to initiate DMARD treatment as soon as RA is diagnosed, definitely within the first 3 to 6 months. It is now the standard of care for RA. The actual treatment strategy best suited for a particular patient is then guided by the patient and the disease characteristics: (a) Disease *duration* (early <6 months, intermediate 6 to 24 months, and late >24 months); (b) Disease *severity* (low disease activity, moderate-high disease activity based on DAS28 values or CDAI, SDAI); (c) *Features of poor prognosis* (functional status as measured by M-HAQ-DI or its variations) due to large number of swollen, tender joints (usually >20 active joints); extra-articular disease (e.g. presence of rheumatoid nodules, secondary Sjögren's syndrome, RA vasculitis, Felty's syndrome, and RA lung disease); high ESR and high levels of CRP; high titres of RF and ACPA; bone oedema or erosions on imaging; and presence of certain genetic markers (HLA-DR4 SE, other single nucleotide polymorphism). Therapeutic armamentarium consists of standard and biological DMARDs,

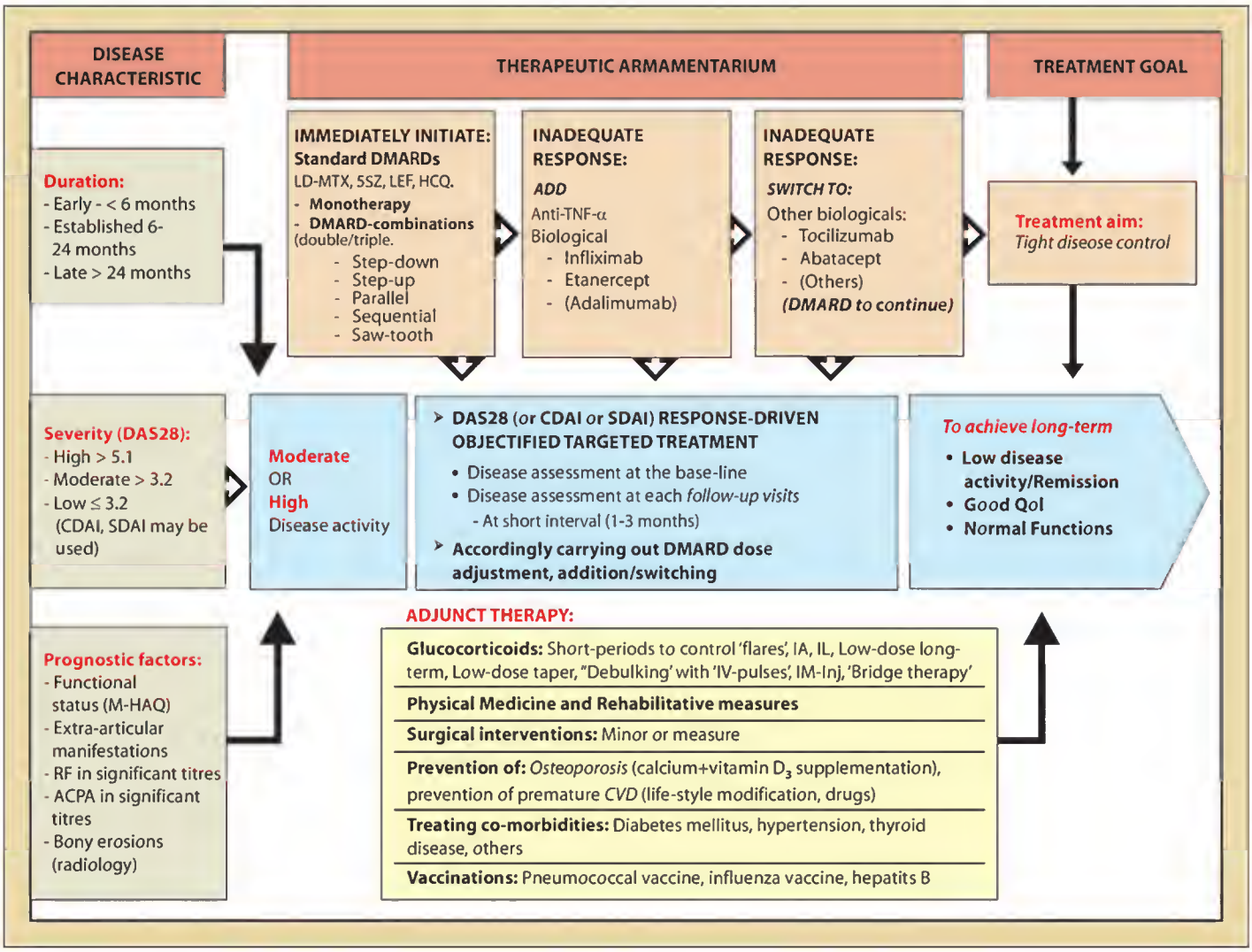


Figure 18: An overview of treatment strategy for RA.

judicious use of GC and adjunct and supportive treatment. An overview of treatment strategy for RA is given in **Figure 18.**

Use of Standard (Non-Biological) DMARDs

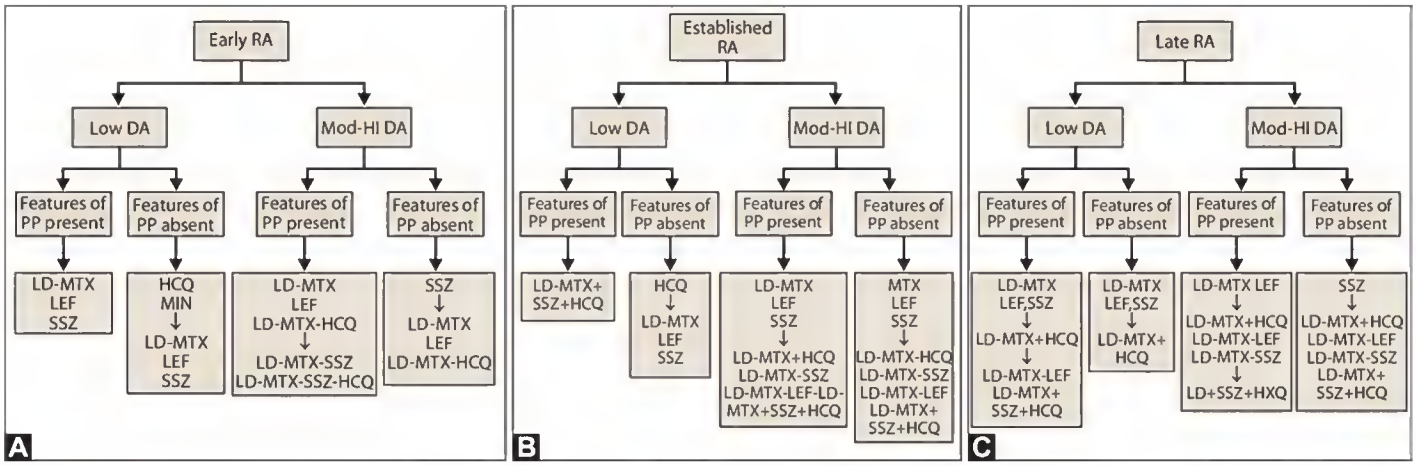
Based upon the variables mentioned above patients are treated according to the algorithm given in **Figures 19A to C.** DMARDs are used as monotherapy, as duel-DMARD combination or as triple-DMARD combination therapy. Often these are combined with systemic GC mainly at the initiation of treatment as 'bridge' therapy or for 'debulking' or during disease flares (see under 'glucocorticoids'-above). As a general rule, adequate doses of standard DMARDs should be given for adequate periods of time to achieve satisfactory response. Only if the satisfactory response is not achieved after such a trial of standard DMARDs, biologicals are considered as a therapeutic option. Traditionally 6 to 12 weeks of maximally tolerated doses are given to evaluate the efficacy of a certain DMARD/DMARD combinations. If low-disease activity state or remission is not achieved by the end of that period it could be considered an 'unsatisfactory response' and the treatment is modified accordingly.

Use of Biological DMARDs

At the time of writing the drugs approved and available in India included specific inhibitors of TNF-α namely the chimeric monoclonal antibody infliximab (fully humanised adalimumab not yet released in India) and fusion protein etanercept. Monoclonal antibody against CD20 positive B cells called rituximab, co-stimulation blocking fusion protein CTLA4-Ig called abatacept, and monoclonal antibody against IL-6 called tocilizumab are also available. Present day recommendation of these highly expensive drugs is in patients who do not achieve satisfactory disease control with standard DMARDs within a reasonable period of time. Under certain circumstances they could also be recommended in patients at a much earlier stage if several features of poor prognosis are present and the cost and insurance coverage is not a limiting factor. The algorithm for the use of biological DMARDs in RA is given in **Figures 20A to C.**

Treatment of Complications of RA and Co-Morbidities

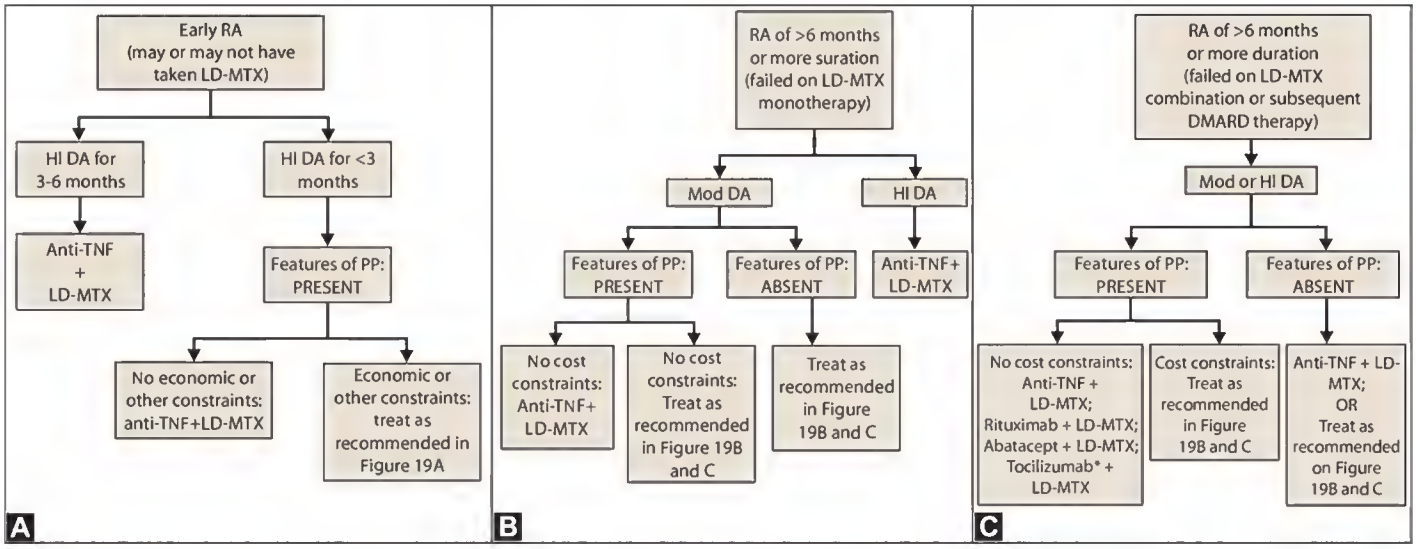
Treatment of RA requires much more than just the stringent control of disease activity. Thus, sicca features require appropriate moisturising eye drops, control of eye infections and some drugs (e.g. pilocarpine) to enhance tear production. Frequent sips of water help preventing complications in the mouth-mucosal infections, sores; stringent oral hygiene is necessary to prevent dental problems in such patients. GC and cytotoxic drugs may be required for interstitial lung. Commonly seen co-morbidities in RA include diabetes



Figures 19A to C: Algorithm for the treatment of RA with standard non-biological disease modifying drugs (DMARDs).

Early RA = RA < 6 months durotion; Low DA= low diseose octivity as defined by DAS28 volue < 3.2; Mod-HI DA = Moderote/high diseose octivity defined by DAS28 value ≥ 3.2; Feotures of PP = Feotures of poor prognosis [include functional limitotion (defined by using ony stondord measurement scoles, e.g. 'modified-Health Assessment Questionnoire' or volidoted voriotions of this scale), extro-orticulor monifestations (e.g. presence of rheumatoid nodules, secondory Sjögren's syndrome, RA vasculitis, Felty's syndrome, ond RA lung disease), rheumotoid factor positivity (in significant titres), positive onti-cyclic citrullinoted peptide antibodies (in significant titres), or bony erosions by rodiography]; LD-MTX = low-dose methotrexote (up to 30 mg/week, the dose used in rheumotology in contrast to high-dose methotrexote used in oncology proctice); LEF = leflunomide; SSZ = sulphasalozine; HCQ = hydroxychloroquine; '+' sign indicotes recommended use of these drugs in combinotion. Estoblished RA = diseose durotion of 6 to 24 months; the sign '↓' indicates 'If foilure to respond'; Late RA = diseose duration > 2 yeors.

Courtesy: Based upon recommendotions of the Americon College of Rheumotology (ACR) for the use of non-biologic ond biologic diseose-modifying ontirheumotic drugs in rheumotoid orthritis, 2008; Soog KG et ol, Arthritis Core & Research, 2008; 59(6): 762-84.



Figures 20A to C: Algorithm for the treatment of RA with biological disease modifying drugs (DMARDs).

Abbreviations used ore the some as in Figure 18; Anti-TNF = Inhibitors of tumour necrosis foctor-α.

Courtesy: Based upon recommendotions of the Americon College of Rheumotology (ACR) for the use of non-biologic ond biologic diseose-modifying ontirheumotic drugs in rheumotoid orthritis, 2008; Soog KG et ol, Arthritis Core & Research, 2008; 59(6): 762-84].

Note: Till the time of writing tocilizumab wos not opproved by Federal Drug Administrotion (FDA), USA, therefore, not mentioned in ACR recommendations, ovoiloble ond opproved for use in Indio.

mellitus, hyperlipidaemia, hypertension, cardiovascular disease and thyroid disease. These need appropriate treatment.

The Role of Physical Medicine and Surgery in the Treatment of RA

These include physical therapy exercises, use of different physical modalities for pain relief, help in maintaining muscle mass, full range of joint movements and preventing deformities. Additionally, the use of different appliances for simplifying and assisting in daily chores are available. Surgeons specialising in soft-tissue surgery and bone-and-joint surgeons play very important role in the management of RA especially in advanced disease.

RECOMMENDED READINGS

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24.7 Spondarthritides

Milind Y Nadkar

Spondarthritides or spondyloarthritides (SpA) are a family of related inflammatory diseases which include ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis and spondylitis, enteropathic arthritis and spondylitis, juvenile-onset spondyloarthritis, and undifferentiated spondyloarthritis (**Table 1**). These disorders are also referred as seronegative spondyloarthropathy (SSA) as these are negative for rheumatoid factor (RF).

Table 1: Spondyloarthropathies

Ankylosing spondylitis
Reiter's syndrome or reactive arthritis
Arthropathy of inflammatory bowel disease (Crohn's disease, ulcerative colitis)
Psoriatic arthritis
Undifferentiated spondyloarthropathies
Juvenile chronic arthritis and juvenile-onset ankylosing spondylitis

These disorders share certain clinical features and genetic associations: predilection for male sex, asymmetric lower limb large joint arthritis, sacroiliitis, enthesitis (inflammation of the ligamentous attachments to the bones), uveitis, dactylitis, absence of rheumatoid factor and a strong association with human leucocyte antigen (HLA)-B27.

The European Spondyloarthropathy Study Group (ESSG) has provided classification criterion to have uniformity among patients (**Table 2**). The sensitivity and specificity of ESSG criteria is 87%. The comparison between different members in this group is given in **Table 3**.

Table 2: European Spondyloarthropathy Study Group Classification Criteria for Spondyloarthropathies

Inflammatory spinal pain
OR
Synovitis (asymmetric, predominantly in lower limbs)
AND
Any one of the following (sensitivity, 77%; specificity, 89%)
Positive family history
Psoriasis
Inflammatory bowel disease
Alternate buttock pain
Enthesopathy
Adding sacroiliitis (sensitivity, 86%; specificity, 87%)

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is an inflammatory condition. Predominant clinical feature of AS is inflammatory backache followed by stiffness of the spine. The diagnosis of AS in most clinical trials is based on the modified New York (1984) criteria (**Table 4**). In the past radiographic sacroiliitis was an important pre-requisite to diagnose AS. However, magnetic resonance imaging (MRI) has now made it possible to make an earlier diagnosis. This has been incorporated in the newly developed Assessment of Spondylo Arthritis International Society (ASAS) SpA criteria (**Table 5**).

Table 3: Features of Spondarthritides

Characteristics	AS	ReA/ USpA	PsA	IBD-Associated Arthritis
Age of onset (years)	<40	20 to 40	30 to 55	Young and middle-age
Type of onset	Insidious	Acute	Insidious	Insidious
Male: Female	5:1	1:1	Male predominant	1:1
Sacroiliitis or spondylitis	100%	<50%	<50%	<20%
Peripheral arthritis	40%	~90%	~90%	15 to 20%
HLA-B27 (whites)	90 to 95%	~75%	~85%	~50%
Eye involvement	30%	~50%	~20%	15%
Cardiac involvement	1 to 4%	5 to 10%	Rare	Rare
Skin or nail involvement	None	< 40%	~100%	10 to 15%
Role of infectious agents as triggers	Unknown	Yes	Unknown	Unknown

AS = Ankylosing spondylitis; ReA = Reactive arthritis; USpA = Undifferentiated spondyloarthropathies; PsA = Psoriatic arthritis; IBD = Inflammatory bowel disease; HLA-B27 = Human leucocyte antigen-B27.

Table 4: Modified New York (1984) Criteria

Criteria
Low back pain of at least 3 months' duration improved by exercise and not relieved by rest
Limitation of lumbar spine in sagittal and frontal planes
Chest expansion decreased relative to normal values for age and sex
Bilateral sacroiliitis grade 2 to 4
Unilateral sacroiliitis grade 3 or 4
Definite ankylosing spondylitis
Unilateral grade 3 or 4, or bilateral grade 2 to 4 sacroiliitis and any clinical criterion

Epidemiology

AS is present in 1% to 6% of adults inheriting HLA-B27, whereas the prevalence is 10% to 30% among HLA-B27+ adult first-degree relatives. In whites, the prevalence of AS is 0.5% to 1% and male to female ratio is 5:1. The HLA-B27 is found in 90% to 95% of patients. There are no Indian data on prevalence of AS. Positivity of HLA-B27 in studies from north and south India is 94% and 83%, respectively. High concordance rate in identical twins of 65% further emphasises the genetic role.

Pathogenesis

There is a persistent inflammation at the affected synovial joints and entheseal sites with increased mononuclear cell infiltrates. Participation of both macrophages and T cells in an inflammatory

process triggered by an yet undefined antigen presented by susceptible HLA molecules is believed to be fundamental to the pathogenic process. The strong association of HLA-B27 in all ethnic groups suggests a predominant role for this class I molecule. The HLA-B27 has 29 subtypes and B2704 and B2705 are susceptible and B2706 and B2709 are non-susceptible subtypes. Certain environmental microbial factors interplay with susceptible genes to trigger off the immune-mediated synovitis. However, the link between any particular microbe with AS is weak.

Table 5: Assessment of Spondyloarthritis International Society (ASAS) Criteria for Classification of Axial SpA

Sacroiliitis on Imaging plus ≥1 SpA Feature	OR	HLA-B27 Plus ≥ 2 Other SpA Features
In patients with >3 months back pain and age at onset <45 years		
SpA Features		**Sacroiliitis on Imaging**
Inflammatory back pain Arthritis Enthesitis (heel) Uveitis Dactylitis Psoriasis Crohn's/colitis Good response to NSAIDs family history for SpA HLA-B27 Elevated CRP		Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA definite radiographic sacroiliitis according to modified New York criteria (1984)

The dramatic response of the disease to therapeutic blockade of tumour necrosis factor-α (TNF-α) indicates that this cytokine plays a central role in the immunopathogenesis of AS. The inflammed sacroiliac joint is infiltrated with CD4+ and CD8+ T-cells and macrophages and shows high levels of TNF-α.

Pathology

Common pathologic features of AS include synovitis, pannus formation, myxoid marrow, subchondral granulation tissue and marrow oedema, and enthesitis. In the spine, there is inflammatory granulation tissue at the junction of annulus fibrosus and vertebral bone. The outer annular fibres are eroded and eventually replaced by bone, which eventually forms a bony syndesmophyte, which then grows, ossifies and bridges the adjacent vertebral bodies. Ascending progression of this process leads to the typical 'bamboo spine' appearance.

Clinical Features

The average age of onset is 25 years and onset after the age of 40 to 45 years is very rare. About 15% of patients have onset of the disease in childhood. AS develops insidiously with chronic low back pain associated with early morning stiffness, which is the presenting feature in 85% of cases. The back pain is due to sacroiliitis and inflammation of the several entheseal sites where the spinal ligaments attach with the vertebral bodies. Patient complains of night pain and sleep disturbance. The inflammation of sacroiliac joint is felt as deep sacral pain, or buttock pain. Over the years inflammation progresses to ascend upwards with involvement of dorsal and cervical spine. With the involvement of dorsal spine, patient complains of chest pain and tightness of chest. The spinal inflammation results in restriction of spinal involvement, with difficulty in bending forward and looking over the shoulders, which are worse in the morning and somewhat relieved with physical activity.

Sacroiliac joint tenderness is elicited by direct palpation and compression of pelvis with patient lying on one side. Spinal restriction is tested by measuring the expansion of lumbar spine on full flexion called the Schober's test (two points one 10 cm above and 5 cm below the lumbosacral junction is marked in upright position and then the patient is asked to fully flex forward and the expansion is noted. It is considered abnormal if the expansion is less than 5 cm). Other useful measurements include finger-to-floor distance, lateral flexion of the spine, chest expansion and occiput to wall distance when patient standing erect against a wall.

Arthritis in the hips and shoulders occurs in 25% to 35% of patients, in many cases early in the disease course. If hip involvement has not occurred within 10 years of the disease onset, it is unlikely to get involved subsequently. An asymmetric arthritis of peripheral joints occurs in up to 30% of patients. Peripheral joint involvement is relatively common (up to 40%) in India.

Enthesitis is an important manifestation with pain and tenderness of tendo Achilles, plantar fascial insertion sites in the calcaneus bone, ligamentum patellae attachment at tibial spinous process, costochondral junction and tenderness over the spinous process insertion, anterior-posterior-superior iliac spine, iliac crest, etc.

In a severe untreated case with progressive spondylitis, the patient's posture undergoes characteristic changes, with obliterated lumbar lordosis, buttock atrophy, and accentuated thoracic kyphosis. A forward stoop of the neck and flexion contractures at the hips, compensated by flexion at the knees occurs.

The disease starts in adolescence and there is a mean delay of 9 to 10 years from the first symptoms to a definite diagnosis. Occasional patients, particularly in the older age group, present with predominantly constitutional symptoms. Severe spinal restriction (<3 cm of lumbar movement) occurs in up to 41% of patients and majority (81%) of these patients are severely restricted within 10 years of onset. Limitation of motion is usually out of proportion to the degree of bony ankylosis, which is due to muscle spasm secondary to pain and inflammation. Spinal progression is a function of disease duration. In patients with mild disease, life-span is comparable to that of general population. The causes of mortality are spinal fractures, cardiopulmonary involvement, complications of treatment, and accidents.

Extra-articular manifestations

The most common extra-articular manifestation is acute anterior uveitis occurring in 25% to 40% of patients. Attacks are typically unilateral, causing pain, photophobia, and increased lacrimation and tend to recur. Uveitis can occur before the onset of spondylitis.

Spinal osteoporosis frequently occurs in patients with long duration of the disease. Patients may develop atlanto-axial subluxation or *cauda equina* syndrome due to chronic adhesive arachnoiditis.

Aortitis may occur in AS leading to aortic regurgitation. Conduction disturbances may occur due to fibrosis in conduction tissues. Conduction disturbances may occur in up to 9% of patients after 30 years of the disease. Apical lung fibrosis (usually bilateral) occurs in 1% to 2% patients.

Asymptomatic enteric mucosal lesions have been detected in terminal ileum and proximal colon on colonoscopy studies in up to 60% of patients. On follow-up, 6% of these develop into inflammatory bowel disease. An increased incidence of immunoglobulin (Ig)A nephropathy has been reported in AS. Renal involvement may also be due to secondary amyloidosis.

Investigations

Mild normocytic normochromic anaemia is present in 15% of patients. Erythrocyte sedimentation rate and reactive protein are usually elevated in up to 75% of the patients with active AS. The HLA-B27 is present in approximately 90% of patients. Synovial fluid from peripheral joints in AS is non-specifically inflammatory.

The most important investigation is anterior-posterior plain radiograph of the pelvis with both hip joints (**Figures 1A and B**) and lateral view of the lumbar, dorsal and cervical spine. Bilateral sacroiliitis is the hallmark of ankylosing spondylitis. Changes in the lower-third of the joint is important and includes blurring of the joint margin, widening and narrowing, sclerosis on the ileal aspect of the joint and finally fusion. These can be graded as shown in **Table 6**. Subsequently the vertebrae are involved with shiny corners (Romanus lesion), squaring, syndesmophytes which are calcification of longitudinal ligaments which later on fuse with adjacent vertebra called as bridging syndesmophytes (**Figure 2**). In advanced cases when the entire spine is involved typical 'bamboo spine' appearance is seen (**Figure 3**). Computed tomography and MRI reveal sacroiliitis and hip arthritis (**Figures 4A and B**). On MRI, sacroiliitis can be revealed early in the course of the disease with underlying bone marrow oedema (**Figure 5**).

Table 6: Grading of Radiographic Sacroiliitis

Grade 0	=	Normal
Grade 1	=	Suspicious
Grade 2	=	Sclerosis, some erosions
Grade 3	=	Severe erosions, widening of the joint space, some ankylosis
Grade 4	=	Complete ankylosis

Differential Diagnosis

Presence of early morning stiffness and raised ESR or CRP differentiates AS from mechanical back pain. Diffuse idiopathic skeletal hyperostosis (DISH) can resemble AS both clinically and radiologically. In DISH the radiological abnormalities involve four contiguous vertebral bodies where flowing osteophytes bridge adjacent vertebrae in the absence of degenerative disc changes and sacroiliac joint changes. It is uncommon before the age of 45 years and is associated with normal ESR/CRP.

Management

Management is aimed at controlling inflammation and increasing mobility. All patients should be counselled and emphasised on exercise to mobilise the stiff spine. Back extension exercises should be encouraged. Swimming is particularly a helpful exercise that ensures adequate spinal movement.



Figures 1A and B: Radiograph of pelvis with both hips showing: (A) Bilateral sacroiliitis, pubic symphisitis and right hip joint arthritis in ankylosing spondylitis; (B) Bilateral hip joint arthritis with ankylosis of right hip joint.

Nonsteroidal anti-inflammatory drugs (NSAIDs) form the basis of treatment of this disease. It had to be emphasised that continued usage is beneficial both in maintaining functional capability to carry on with daily activities and also has disease modifying potential. Full dose indomethacin 150 mg per day in an adult will alleviate the symptoms to great extent. In those with gastrointestinal toxicity a selective COX-2 inhibitor could be used with variable efficacy. Analgesics such as paracetamol and opiates may be added for pain control. Corticosteroid injections directed to local site of musculoskeletal inflammation (enthesitis) are useful. The use of systemic corticosteroids for axial disease is not supported by evidence and should be discouraged. Sulphasalazine (SSZ) and methotrexate (MTX) have been used as DMARDs. These drugs are useful in peripheral arthritis but have little or no effect on spinal disease.

Biological agents like anti-TNF-α treatment (infliximab chimeric human/mouse anti-TNF-α monoclonal antibody), etanercept (soluble p75 TNF-α receptor-IgG fusion protein), or adalimumab (human anti-TNF-α monoclonal antibody) are currently indicated with persistent activity despite adequate NSAIDs therapy for 3 months and in case of AS with peripheral arthritis, and patients refractory to adequate trial of SSZ. Infliximab is administered at a dose of 5 mg/kg of body weight intravenously as an infusion diluted with saline over 4 hours. The recommended schedule is 0, 2 and 6 weeks followed by maintenance every 8 weekly to be given for indefinite period. Etanercept is administered at a dose of 25 mg subcutaneously



Figure 2: Radiograph of lumbar spine (lateral view) showing bridging syndesmophytes (white arrowheads) in ankylosing spondylitis joining two adjacent vertebrae.

twice a week. Both of these have been found to be equally effective in improving inflammation and functional quality of life. TNF-α inhibitors reduce the frequency of attacks of uveitis in patients with AS. However, these agents are very expensive and they may lead to reactivation of tuberculosis (TB). The risk of TB is higher with infliximab than with etanercept. It is recommended that a thorough check for TB with Mantoux test and chest radiograph should be done prior to initiation of therapy. The contraindications for starting anti-TNF-α therapy include pregnancy, lactation, previous history of TB, septic arthritis within past 12 months, persistent or recurrent chest infections.

Total hip arthroplasty should be considered in patients with refractory pain or disability and radiologic evidence of damage, independent of age. Spinal surgery, e.g. corrective osteotomy and stabilisation procedure may be of use in selected patients.

REACTIVE ARTHRITIS

Reactive arthritis (ReA) is defined as a sterile joint inflammation within a month following a gastrointestinal or genitourinary infection. Reiter's syndrome which consists of triad of urethritis, arthritis and conjunctivitis is a full blown case of ReA. The full blown cases are a rarity and in many cases the antecedent history of infection is missing yet the clinical picture resembles that of ReA when a label of undifferentiated spondyloarthropathy (uSpA) is used. Rheumatic fever and Lyme disease are forms of reactive and infection-related arthritis that are not associated with HLA-B27 and show a spectrum of clinical features different from spondyloarthritis.

Epidemiology

There are no data available on the incidence and prevalence of ReA from our country. Western data show that incidence is 30 to 40 per 100,000 population.

Pathogenesis

ReA and USpA are triggered by genitourinary infection with *Chlamydia* or gastrointestinal infections with *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter jejuni*, etc. However, the organisms are not isolated from the synovial compartment. The precise mechanisms by which the microbial agent trigger an immune mediated synovitis are not known. Finding of bacterial antigenic fragments and deoxyribonucleic acid (DNA) in some cases suggest that antigen persistence is a plausible mechanism.



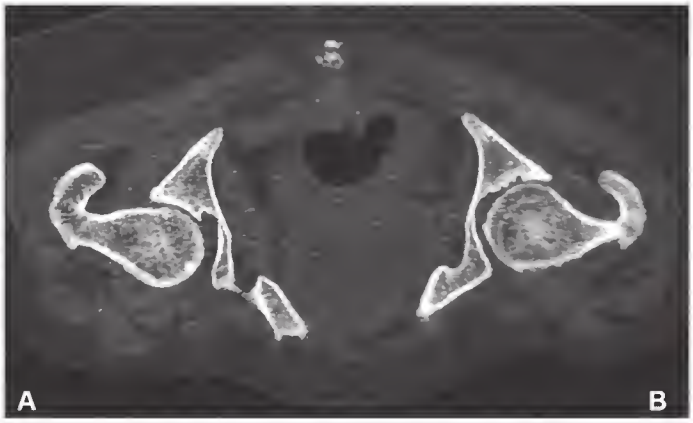
Figure 3: Radiograph of lumbar spine (post-anterior view) showing 'bamboo spine' in ankylosing spondylitis.

Clinical Features

The clinical manifestations of ReA constitute a wide spectrum that ranges from an isolated, transient monoarthritis to severe multisystem disease.

Articular features

ReA presents as an acute onset of mono/oligoarthritis associated with prominent inflammatory features. It may simulate a septic arthritis. A clear-cut history of preceding gastrointestinal or urogenital infection is found in only half of



Figures 4A and B: Computed tomography of hip joint showing bilateral hip arthritis in ankylosing spondylitis.

the patients. The usual age of onset is 20 to 40 years and both sexes are equally affected. Some patients may present with prominent systemic features like fever, fatigue and lack of appetite. In majority of the cases ReA subsides within 12 weeks, but in 30% of cases, it can lead to a chronic or recurrent arthritis. Knee, ankle, subtalar, metatarsophalangeal, and toe interphalangeal joints are involved most commonly; however, upper limb joints may also be involved. Tense joint effusions are not uncommon, especially in the knee. Chronic heel pain may be very distressing. Unilateral sacroiliitis, spondylitis and persistent hip joint disease denotes bad prognosis. HLA-B27-positive patients have shown a worse outcome. Other features include enthesitis, tenosynovitis and dactylitis (sausage digit) which is complete swelling of a digit in the hand or foot.

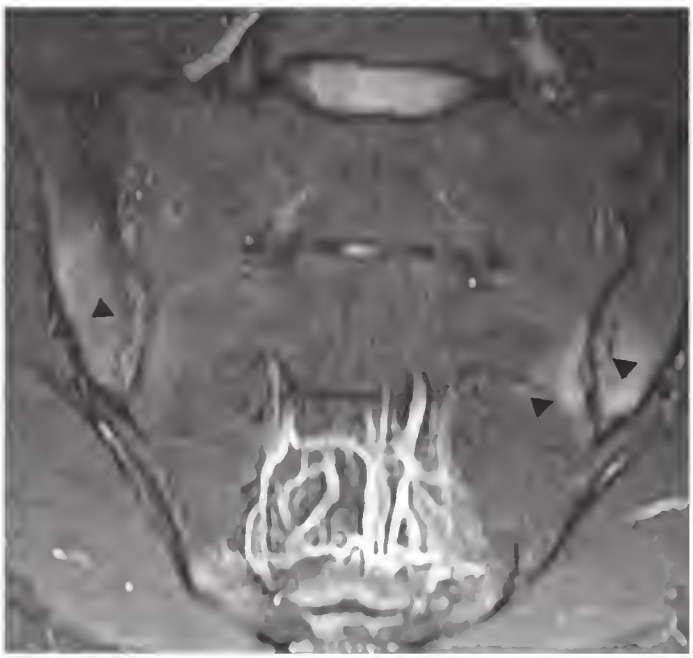


Figure 5: Magnetic resonance imaging of the lumbar spine showing bilateral sacroiliitis with underlying marrow oedema (black arrowheads).

Extra-articular features

Sterile conjunctivitis is the most common lesions; however, anterior uveitis, scleritis, keratitis or even corneal ulcer etc., may also be seen. Non-specific enteritis may be found and patient may present with abdominal pain and diarrhoea. Sterile pyuria and urethritis is quite common (present in about 50% of patients). Increased incidence of IgA nephropathy has been found.

The characteristic skin lesion is keratoderma blenorrhagicum (**Figure 6**) involving the palms and soles and it resembles psoriasis both clinically and histologically. Circinate balanitis is the lesion on the glans penis which consists of vesicles that quickly rupture to form painless superficial erosions. Nail changes are common and consist of onycholysis, distal yellowish discolouration, and/or heaped-up hyperkeratosis. Oral ulcers are usually superficial, transient and often asymptomatic.



Figure 6: Keratoderma blenorrhagicum in reactive arthritis.

Diagnosis

The diagnosis of ReA is based on the typical clinical features. Septic or crystal induced synovitis should be excluded by synovial fluid examination. Synovial fluid examination shows neutrophil leucocytosis. ESR and CRP are usually very high. Demonstration of specific antibodies to *Chlamydia*, *Yersinia* and *Salmonella* in serum by enzyme linked immunosorbent assay is of diagnostic significance in regions where the infection load in the community is less. However, in India, it is of little significance. It is advisable to test for human immunodeficiency virus in patients presenting with ReA. HLA-B27 is present in about 50% of patients with ReA. Plain radiography may show unilateral sacroiliitis and large bulky asymmetrical syndesmophytes.

Natural History

Prognosis is generally good. A typical episode lasts for about 3 to 5 months. About one-third of the patients suffer a single episode only, another one-third recurrent episodes and rest one-third chronic ReA. The presence of HLA-B27 favours development of chronic ReA.

Differential Diagnosis

The common differential diagnoses are septic arthritis (especially, gonococcal arthritis) and crystal arthropathy. Gonococcal arthritis typically presents with migratory arthritis involving both upper and lower limbs, prominent tenosynovitis, vesicular skin lesions and absence of inflammatory low backache. A positive gonococcal culture from skin lesions or urethral/cervical discharge is confirmatory.

Management

Rest to the affected joints and immobilisation till the acute inflammation subsides is advocated. Within first few weeks of the disease, the joint should not be used vigorously as even minor trauma may lead to recurrence. Indomethacin or other NSAIDs may be tried. Indomethacin is given as 75 to 150 mg

per day in divided doses till the arthritis resolves. Intra-articular injection of corticosteroids may be given when rapid control of inflammation is required. Local injection of corticosteroids may be given for tenosynovitis or enthesitis. However, there is no evidence to support that treatment with corticosteroids will prevent subsequent relapse.

Sulphasalazine, 2 to 3 g per day in divided doses, may be beneficial in patients having persistent ReA for more than 6 months. Patients with persistent disease may also respond to azathioprine (1 to 2 mg/kg per day), or to methotrexate (10 to 20 mg per week). In severe chronic cases anti-TNF-α may be useful.

Uveitis is usually treated with local administration of corticosteroid drops or injections and mydriatics.

PSORIATIC ARTHRITIS

It is defined as arthritis associated with psoriasis and usually negative for RF. The classification criteria for psoriatic arthritis (PsA) are shown in **Table 7** with a sensitivity of 91% and specificity of 98%.

Table 7: Classification Criteria for Diagnosis of Psoriatic Arthritis

A patient must have inflammatory articular disease (joint, spine or enthuses) with 3 or more points from the following five categories:
Evidence of current psoriasis, a personal, or a family history of psoriasis
Typical psoriatic nail dystrophy
A negative test result for the presence of rheumatoid factor by any method except latex
Either current dactylitis or history of dactylitis recorded by a rheumatologist
Radiographic evidence of new bone formation appearing as ill-defined ossification near joint margins

Epidemiology

Psoriasis affects ~1% of the population and arthritis affects 5% to 10% of patients with psoriasis.

Pathogenesis

PsA as well as psoriasis is a T-cell-mediated disease. There is upregulation of leucocyte-homing receptors in synovium which results in leucocyte infiltration of synovium. Cytokines are secreted by leucocytes which mediate arthritis.

Clinical Features

The mean age of onset of arthritis is 30 to 55 years. About two-thirds of the patients develop arthritis after onset of skin psoriasis, in 15% both arthritis and psoriasis occur within 12 months of each other and in the remaining arthritis precedes onset of skin lesions by more than 12 months.

Skeletal manifestations

There are five distinct patterns of joint involvement in psoriatic arthropathy. These include: distal interphalangeal (DIP) joint arthritis (15%); oligoarticular arthritis (30%); symmetrical rheumatic arthritis (RA) like arthritis (40%); spondylitis (20%); and arthritis mutilans (5%). A simpler scheme in recent use contains three patterns: oligoarthritis, polyarthritis, and axial arthritis. RA like symmetrical arthritis subset is negative for RF. There are some joints which are typically involved in PsA which include temporomandibular, manubriosternal and DIP joints (**Figures 7 and 8**). Isolated spondylitis without peripheral arthritis is very rare and found in 1% to 5% of patients with PsA. The spondylitic variety can mimic AS except that sacroiliac joints may be unilaterally involved and syndesmophytes are non-symmetrical. The DIP joint arthritis is usually associated with nail involvement. Apart from arthritis, enthesitis and dactylitis occur in one-third of patients. Poor prognostic factors are polyarticular disease (≥4 joints), presence of joint damage (erosions) and impairment of functional status. Shortening of digits because of underlying osteolysis is particularly a characteristic of PsA.



Figure 7: Hand in psoriatic arthritis showing skin psoriasis lesions, distal interphalangeal joint arthritis and nail changes.



Figure 8: Radiograph of hands showing distal interphalangeal joint involvement in psoriatic arthritis.

Skin manifestations

The evidence of typical plaque having silvery scales has to be looked for carefully particularly in hidden sites such as underneath the breast, navel, scalp, behind the ears, and extensor aspects of knees, elbows and back. The nails have to be observed for pits and onycholysis (**Figure 8**). Nail involvement is found more commonly in PsA (90%) compared to psoriasis without arthritis (40%). Patterns of nail involvement

include pitting, horizontal ridging, onycholysis, yellowish discolouration of the nail margins, dystrophic hyperkeratosis, and combinations of these findings.

Investigations

Inflammatory parameters (ESR and CRP) may be elevated. RF and antinuclear antibody are usually negative. Hyperuricaemia is seen in up to 20% of patients and is related to renal insufficiency and not to epidermal turnover as was previously thought. HLA-B27 is found in 50% to 70% of patients with axial disease, but 15% to 20% in patients with only peripheral joint involvement.

Radiologically, the distinguishing features as opposed to RA are less of juxta-articular osteopoenia, presence of periostitis, ankylosis, asymmetric involvement of peripheral joints, sacroiliitis and asymmetric bulky syndesmophytes. Pencil-in-cup deformity is characteristic of psoriasis. Erosions are seen in 35% to 50% of patients.

Management

Therapy should be directed at both the skin and joints in PsA. NSAIDs are the initial therapy for patients presenting with pain, swelling and stiffness. These are not beneficial in skin disease. DMARDs like MTX, SSZ, cyclosporine and azathioprine have variable effects on arthritis. Anti-TNF-α therapy (etanercept, infliximab) substantially improves peripheral arthritis, functional status, skin lesions and quality of life. The pyrimidine synthetase inhibitor leflunomide has been shown to be beneficial in both psoriasis and psoriatic arthritis. Other agents with efficacy in psoriasis reported to benefit PsA are retinoic acid derivatives, and psoralen plus ultraviolet light.

INFLAMMATORY BOWEL DISEASE-ASSOCIATED ARTHRITIS

Inflammatory bowel disease (IBD)-associated arthritis is defined as arthritis associated with ulcerative colitis (UC) and Crohn's disease (CD). Arthritis is the most common extra-intestinal manifestation and seen in 2% to 20% of patients with IBD. Radiographic sacroiliitis is more common. No data on incidence of arthritis in IBD is available from our country.

Clinical Features

Young and middle-aged adults are commonly affected and both sexes are equally represented.

Peripheral arthritis

Peripheral arthritis is subdivided into two groups; type 1 and type 2 arthritis. Type 1 arthritis involves less than 5 joints and are acute, self-limiting attacks often coinciding with relapse of IBD. Type 2 on the other hand are polyarticular involving 5 or more joints and are chronic which run a course independent of IBD and is associated with uveitis. Type 1 is seen in 3.6% of patients with UC and 6% patients with CD. Type 2 arthritis is found in 2.5% of patients who suffer from UC and 4% of patients with CD.

Sacroiliitis and spondylitis

Sacroiliitis and spondylitis is more common in males (ratio 3:1) and resembles AS both clinically and radiologically. These may precede bowel disease by many years. Enthesitis and dactylitis are seen as in other members of SSA.

Extra-articular features

Acute anterior uveitis is the most common ocular manifestation. It is associated with HLA-B27 and axial joint involvement. Skin rash is seen in 10% to 25% of patients and erythema nodosum is the most common skin rash and is associated with relapse of IBD. Pyoderma gangrenosum and secondary amyloidosis is infrequent.

Investigations

Common laboratory findings are iron deficiency anaemia, leucocytosis and thrombocytosis. The inflammatory parameters (like ESR, CRP) are usually elevated. Radiologically, the axial involvement of AS and IBD-associated arthritis are similar. Peripheral arthritis with erosions is seen.

Management

The treatment of IBD should be the primary aim. Managing IBD will take care of most of the peripheral arthritis. For patients presenting with pain and disability, NSAIDs are the first choice. However, they may aggravate UC. SSZ is effective in both types of IBD and MTX is useful in CD but its efficacy in associated arthritis is not known. Infliximab is now being used in treatment-resistant CD and treatment-refractory CD-associated arthritis.

JUVENILE ANKYLOSING SPONDYLITIS

Juvenile ankylosing spondylitis is a type of juvenile idiopathic arthritis (JIA). Presently it is known as JIA-ERA (enthesitis-related arthritis). It is called juvenile when the onset is before 16 years of age. The diagnostic criteria of JIA-ERA are given in **Table 8**.

Table 8: Diagnostic Criteria for JIA-ERA

Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following features:
Presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
Presence of HLA-B27 antigen
Onset of arthritis in a male over 6 years of age
Acute (symptomatic) anterior uveitis
History of AS, ERA, sacroiliitis with IBD, Reiter's syndrome or acute anterior uveitis in a first-degree relative
Psoriasis, RF and systemic-onset JIA should be excluded

Management

These are treated on the same lines as adult disease.

UNDIFFERENTIATED SPONDYLOARTHRITIS

Patients presenting with one or more features of spondyloarthritides but not fulfilling the criteria are known as undifferentiated spondyloarthritis (USpA), e.g. patients presenting with clinical feature suggestive of ReA but does not have any evidence of antecedent gastrointestinal or genitourinary tract infection are to be labelled as USpA. About 50% of such patients are HLA-B27 positive and thus HLA-B27 positivity is not useful in making or excluding a diagnosis. Over time, some of such patients may evolve into definitive arthritis.

RECOMMENDED READINGS

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24.8 Sjögren's Syndrome

Uma Kumar

Sjögren's syndrome (SS) is a chronic autoimmune exocrinopathy characterised by lymphocytic infiltration of lacrimal and salivary glands. It is a systemic disease named after the Swedish ophthalmologist, Henrik Sjögren, who introduced the term 'keratoconjunctivitis sicca' for dryness of eyes noted in patients. The SS may exist as primary SS (pSS) or secondary SS (sSS) occurring in association with other systemic autoimmune diseases, like rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, polymyositis, etc. The prevalence of pSS is 0.1% to 0.6% according to the American European Consensus criteria with female to male ratio of 9:1. It has two age peaks, with first in the twenties and the second in the fifties.

AETIOPATHOGENESIS

The pSS is a multisystem autoimmune disease with complex interaction between innate and adaptive immunity and salivary glands dysfunction. Environmental factors (viral/other intercurrent infections) are thought to trigger inflammation in a genetically predisposed individual. There is infiltration of glandular tissue by CD4+ T-lymphocytes. The glandular epithelial cells express high levels of HLA-DR which presents viral antigens or autoantigens to the CD4+ T-lymphocytes. This sets in process an inflammatory cascade with cytokine production, notably interferon-gamma (IFNγ) and (interleukin (IL)-2. CD20+ B-cell constitutes a significant component of periductal foci and patients demonstrate evidence of B-cell activation with resultant autoantibody production. In addition to the presence of antibodies to SS-A/anti-Ro and SS-B/anti-La, two-thirds of the patients also have serum antinuclear antibody (ANA) and rheumatoid factor (RF), particularly IgA-containing RF. Polyclonal hypergammaglobulinaemia is common.

CLINICAL MANIFESTATIONS

The SS has diverse clinical manifestations ranging from limited exocrinopathy to widespread autoimmune non-exocrine systemic manifestations. Non-exocrine involvement is of two types: (1) Periepithelial infiltrative processes which generally follow a benign course. It includes interstitial nephritis, liver involvement, and bronchiolitis; and (2) Extraepithelial processes which result from B-cell hyper-reactivity, hypergammaglobulinaemia, and immune complex formation. It includes palpable purpura, glomerulonephritis, and peripheral neuropathy. Systemic manifestations of pSS are given in **Table 1**.

Ocular

Patients are usually unaware of dry eyes but may complain of gritty sensation, photophobia, redness, thick mucus strands and encrusted eyelids on awakening in the morning. If untreated, the condition may result in corneal abrasion, ulcer, or infection.

Oral

Patients usually complain of difficulty in eating without the help of liquids and parched feeling in the mouth and throat. Dental caries and oral candidiasis occur frequently owing to decreased salivary flow. It is important to realise that in pSS the mouth is dry but not painful. In case of painful mouth, one must suspect fungal infection. Patients are prone to develop ductal calculi because of thick inspissated saliva in parotid ducts. A hard mass in parotid should raise suspicion of malignancy. Recurrent bilateral parotitis occurs in majority of the patients but sublingual and submandibular glands can also be affected. Approximately 40% patients also develop dryness of skin, nose and vagina.

Table 1: Systemic Features of pSS

Musculoskeletal (60%): Arthralgia, myalgia, non-erosive arthritis
Pulmonary (75%): Xerotrachea (manifest as a dry cough), interstitial lung disease, recurrent bronchitis, bronchial hyper-responsiveness, pneumonitis
Gastrointestinal: Dryness of the pharynx and oesophagus, gastroesophageal reflux, rarely pancreatitis
Cardiac: pericarditis, pulmonary hypertension
Nervous system (8% to 40%): Myelopathy, optic neuropathy, seizures, cognitive dysfunction, and encephalopathy, cranial neuropathies, mononeuritis multiplex, sensory, motor, or sensorimotor peripheral neuropathy, distal paraesthaesia
Renal: Interstitial nephritis, renal tubular acidosis, interstitial cystitis, rarely glomerulonephritis

Vascular

Vasculitis has been found in approximately 15% of pSS patients. Majority of patients present with cutaneous vasculitis ranging from hypersensitivity vasculitis to necrotising vasculitis. Palpable purpura worsening on prolonged standing is the usual presentation. One must exclude hepatitis C virus (HCV) infection if patient presents with cutaneous vasculitis, cryoglobulinemia and sicca symptoms. Raynaud's phenomenon is reported in 15% patients, rarely results in digital ulcers.

DIAGNOSIS

It is not difficult to diagnose SS in the presence of keratoconjunctivitis sicca, dryness of mouth and characteristic autoantibody profile (presence of ANA, anti SS-A and anti SS-B antibodies). However, problem arises if patient has mild symptoms and less characteristic antibody profile; anti Ro/SSA and anti-La/SSB occur in approximately 60% of the patients with pSS.

Previously, minor salivary gland biopsy was thought to be gold standard but it was realised that lymphocytic infiltrate can be modified by various factors. Only samples demonstrating foci of mononuclear cells (cluster of atleast 50 lymphocytes) should be reported as compatible with pSS. International Sjögren's syndrome research community has established classification criteria which permits diagnosis without minor salivary gland biopsy and also gives clear cut exclusion criteria. It is important to exclude secondary causes of sicca symptoms as no test is pathognomonic of pSS.

Schirmer's test, Rose-Bengal test and tear break time are all sensitive but only Rose-Bengal test is specific (>95%). Sialography seems to be as sensitive as lip biopsy but less specific. Recently, MRI has been found to be relatively more sensitive and specific for glandular involvement in pSS.

Differential Diagnosis

1. Diffuse infiltrative lymphocytosis syndrome: It commonly occurs in males with human immunodeficiency virus infection. Although 10% of these patients may have ANA and RF positive but SS-A and SS-B antibodies are absent. Immunohistochemistry of minor salivary gland helps in difficult cases.
2. Sarcoidosis: Characteristic features of sarcoidosis along with histology suggestive of non-cascating granulomas.
3. Lymphoma: It usually presents with firm painless masses in parotid gland.
4. Graft versus host disease: Significant proportions of patients have ANA and RF positivity but not SS-A and SS-B positivity. Minor salivary glands CD4+/CD8+ ratio is either low or inverse in comparison to pSS where it is more than 3.0.

Sicca symptoms can occur with ageing, amyloidosis, fibromyalgia, and certain drugs.

MANAGEMENT

Management of pSS requires collaborative effort from ophthalmologist, dental surgeon, pulmonologist, and rheumatologists.

Treatment of Dry Eyes

Adequate ophthalmic care is required to prevent corneal ulceration and its sequelae.

Preservation of tear film

Preservation of tear film can be achieved through: (1) avoiding humid environment and eye irritants, like smoke or dust; (2) avoiding activities that provoke tear film instability, e.g. prolonged hours on computers, prolonged reading hours etc.); (3) avoiding medicines causing ocular dryness (anticholinergic agents, antihistamines, diuretics, beta blockers etc.); and (4) punctual occlusion (punctal plugs, permanent occlusion by surgery or cautery) in moderate to severe cases. Goggles with specially constructed side chambers also help in reducing tear evaporation. It is better to avoid contact lenses as they may worsen dryness and predispose eye for infection.

Tear replacement

Artificial tear preferably preservative free during daytime and lubricating ointment during night is advisable. Tear substitutes must be refrigerated and discarded after single use.

Stimulation of residual lacrimation

Muscarinic receptor agonists stimulate existing lacrimal cells to increase tear production. Pilocarpine 5 mg three to four times per day or cevimeline 30 mg three times daily (currently not available in India) brings subjective and objective improvement in patients. Nausea, sweating, headache, and abdominal pain are possible side effects. Caution is required in narrow angle glaucoma, asthma, acute iritis, cardiovascular diseases and Parkinsonism. Maximal therapeutic effect may require 12 weeks of therapy in some patients. Cyclosporin A 0.05% ophthalmic emulsion in moderate to severe dry eye has shown significant improvement without any significant adverse effect. Common adverse effects have been eye irritation and conjunctival hyperaemia but soon tolerance develops. Cyclosporin decreases the conjunctival lymphocytosis and increases conjunctival goblet cells along with having antiapoptotic properties. Topical corticosteroids are of limited value in the management of dry eyes. Other drugs being tried out include rebamipide, tacrolimus and diquafosol tetrasodium.

Treatment of Dry Mouth

It includes adequate hydration and avoidance of tea, coffee and nicotine, drugs causing dryness of oral mucosa. Frequent sips of water may also help. Good oral hygiene and dental care must be emphasised. Use of fluoride (fluoride gel, toothpaste, or rinses containing 0.4% to 1.25% fluoride) is helpful. Sugar free chewing gum and lozenges may stimulate salivary flow. Oral candidiasis must be promptly treated with antifungals. Saliva substitutes (gels, mouthwashes, lozenges) may be used to improve lubrication and hydration of oral mucosa but their effect is short lasting. The muscarinic agonist, pilocarpine and cevimeline, improve salivary flow depending on residual secretory capacity of salivary glands.

Systemic Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics are the first line treatment for musculoskeletal symptoms. Hydroxychloroquine sulphate (6-7 mg/kg/day) may be used in patients having arthralgia, myalgia and fatigue. Short course of low dose corticosteroids (prednisolone 10-20 mg/day) may be given for painful debilitating joint disease. Diseases modifying anti-rheumatic drugs are usually not required for arthritis. Pilocarpine and cevimeline has been found to be of some relief in patients with skin dryness. Steroid creams may help in relieving pruritus. Mild cases of leucocytoclastic vasculitis may be treated expectantly, whereas severe cases require more aggressive immunosuppressive therapy. Persistent dry cough because of xerotrachea may respond to humidification, secretagogues and guaifenesin (1200 mg twice a day). Major organ vasculitis, interstitial lung involvement and central nervous system involvement may require high dose corticosteroids along with cyclophosphamide. Rituximab, a chimeric monoclonal antibody to CD20, leads to B-cell depletion and is emerging as a promising treatment for systemic complications of pSS.

Special Situations

1. During surgery, special precautions must be taken to avoid undue drying of eyes and mouth. Anaesthetist must be careful with the amount of anticholinergic given during intubation.
2. Presence of anti-Ro/SS-A in pSS may predispose the foetus to congenital heart block, and neonatal lupus. Close foetal monitoring is a must.
3. The pSS has approximately 40-fold increased risk of developing non-Hodgkin's lymphoma compared to age-matched controls.

RECOMMENDED READING

1. Thanou-Stavraki A, James JA. Primary Sjögren's syndrome: current and prospective therapies. *Semin Arthritis Rheum* 2008; 37: 273-92.

24.9 Systemic Lupus Erythematosus

VR Joshi

DEFINITION AND EPIDEMIOLOGY

Systemic lupus erythematosus (SLE) is a chronic immuno-inflammatory disease of unknown aetiology, that involves several organ systems and body tissues. Multiple autoantibodies are present. The disease course is variable with periods of inactivity, or low-grade activity punctuated with periods of increased disease activity (flares). The disease carries significant morbidity and mortality.

The annual incidence of SLE in the United States and Europe has been estimated to be 2 to 8 per 100,000 population and estimates of its prevalence range between 20 to 60 cases per 100,000 population. There is paucity of Indian data. In a study conducted near Delhi, the prevalence of SLE was found to be 3.2 per 100,000 population, one of the lowest in the world. More recent studies corroborate the same. The incidence of SLE is higher in American blacks, Afro-Carribeans and Indian immigrants in UK. The incidence of SLE has probably increased over the last few decades. Part of the increase may be due to increased awareness and the ready availability of diagnostic tests (apparent increase).

More than 85% of SLE patients are females. The male to female ratio tends to be equal in the very young and the old. The majority of patients are between 20 and 50 years of age.

AETIOLOGY

The exact aetiology is not known. Genetic, hormonal, and environmental factors play a role (**Table 1**). SLE is a polygenic disorder. Multiple genetic susceptibility loci have been identified. Their relative contributions and interactions are not clearly understood. Genetic factors alone do not explain the disease susceptibility. Concordance of SLE in monozygotic twins is 25% (2% in dizygotic twins). A variety of environmental factors have been incriminated. Hormonal (and possibly genetic) influence is reflected in the female preponderance. Infections most likely play a facilitatory role though no specific infective organism has been incriminated. Breastfeeding, progesterone, 1, 25(OH)D_3, omega-3 fatty acids are said to reduce SLE risk.

PATHOGENESIS

SLE is characterised by hyper-reactivity of B lymphocytes hypergammaglobulinaemia, multiple organ-specific and non-organ-specific autoantibodies, circulating immune complexes, and complement activation (low C_3, C_4, increased C_3, C_4 activation products). Antinuclear antibodies (ANA), the hallmark of SLE, can precede clinical manifestations by many years. Only 2% of ANA positive asymptomatic individuals go on to develop SLE. Cellular immunity is aberrant. There is leucopaenia, lymphopenia and monocytosis. Breakdown of tolerance to self antigens, increased apoptosis and impaired clearance of apoptotic bodies are thought to play an important role in pathogenesis. The mechanism of tissue damage is the result of immune complex deposition as well as direct cellular injury.

Table 1: Aetiological Factors in SLE*

Genetic factors
HLA B8, DR 3, DR 2
Inherited complement deficiencies (C4a-null alleles, C1q, C1r/s)
FcRλ gene polymorphism (weak binding with IgG)
Others: Ig receptors, kinases, signalling molecules, cytokines
Non-genetic factors
UV light (inflammation and tissue damage)
Physical and emotional stress (neuroendocrine changes affecting immune cell function)
Infection—EBV, CMV (molecular mimicry, disturbed immuno-regulation)
Female sex-hormones (oestrogen); (prolactin—pregnancy flare)
Diet—(production of inflammatory mediators)
Drugs—Procainamide, quinidine, hydralazine, methyldopa, chlorpromazine, isoniazid, biologicals, etc. (modify self antigens, methylation changes in promoter genes and cellular response)
Environmental factors—smoking, silica

** List not exhaustive. Not all have sufficient evidence. Genetic factors are likely to vary amongst different ethnic groups.*

Autoantibodies (Table 2)

Autoantibodies are directed against various cellular components (nuclear, cytoplasmic, cell membrane), and soluble molecules such as IgG and coagulation factors. Amongst these ANAs are most characteristic. Antibodies to dsDNA, and Sm are exclusive to SLE. Anti-dsDNA, anti-Sm, and anti-Ro antibodies are incriminated in the pathogenesis of lupus nephritis. Other associations are anti-P with neuropsychiatric lupus and hepatitis, anti-Ro with neonatal lupus, antiphospholipid with thrombosis, thrombocytopaenia and recurrent abortions and antibodies to blood cells with cytopaenias.

CLINICAL MANIFESTATIONS

The clinical features and presentations of SLE are extremely variable. SLE may present acutely with non-specific constitutional symptoms such as fever, arthralgias, rash, weight loss, lymphadenopathy or as a single organ disease, e.g. nephritis. The disease may evolve over time (sometimes over years) delaying the diagnosis, e.g. arthritis may be the only manifestation for years. The severity of the disease is variable, ranging from a benign mild disease to a severe life- or organ-threatening disorder. Arthritis, arthralgias, fever, and rash are the most common presenting manifestations. Fatigue is a prominent constitutional symptom. Other constitutional symptoms are malaise, weight loss and headache. The cumulative frequency of clinical manifestations is depicted in **Table 3**.

Table 2: Common Autoantibodies in SLE

Autoantibody	Frequency (%)	Specificity	Clinical Association
ANA	98 to 100	Not specific	Not exclusive to SLE
Anti-dsDNA	40 to 70	Most specific	Nephritis
Anti-Sm	5 to 40	Highly specific*	? Nephritis,? neuropsychiatric lupus CNS
Anti-Ribosomal P	10 to 15	Highly specific	Psychosis
Anti-Histone	40 to 80	Not specific	Drug-induced lupus
Anti-Ro (SS-A)*	15 to 40	Not specific	Subacute cutaneous lupus, photosensitivity, neonatal lupus, congenital heart-block, ANA –ve lupus, secondary Sjögren's syndrome
Anti-La (SS-B)	10 to 15	Not specific	Rarely present without anti-Ro antibodies
Anti-U-1 RNP	30 to 40	Not specific	Raynaud's phenomenon, oesophageal dysmotility, myositis (MCTD)
Anti-cardiolipin	20 to 25	Not specific	Thrombosis, foetal loss, thrombocytopaenia, secondary antiphospholipid syndrome
Anti-ssDNA	90	Not specific	—

** Higher frequency in Blacks and Indians.*

Table 3: Cumulative Frequency of Clinical Features of SLE

Feature	Indian Data (%)	Western Data (%)
Arthritis	72 to 92	86 to 94
Alopaecia	52 to 80	50
Skin rash	74 to 90	60
Photosensitivity	10 to 62	33 to 62
Malar rash	37 to 76	72 to 90
Oral ulcers	41 to 61	30
Fever	74 to 91	80
Lymphadenopathy	26 to 47	50
Neuropsychiatric	19 to 63	20 to 45
Renal	35 to 73	29 to 73
Cardiac	10 to 29	20 to 30
Pleuropulmonary	9 to 54	36 to 57

Mucocutaneous

Skin

Acute, subacute or chronic cutaneous manifestations are present in 80 to 90% of patients. Apart from the classical malar rash (seen in less than 50% of patients), rash is characteristically present in the pre-auricular, auricular, and post-auricular areas. There may be diffuse hyperpigmentation or diffuse maculopapular rash. Discoid lesions, seen in 15 to 30% of SLE patients, are not restricted to face and scalp. Livedo reticularis is typical of associated antiphospholipid syndrome (APS). Subacute cutaneous lupus (SCLE) (present in up to 25% patients) is characterised by the presence of photosensitive, superficial, non-indurated, non-scarring annular or papulosquamous psoriasis-like lesions. Anti-Ro antibodies are commonly associated with SCLE. Other cutaneous manifestations include bullous lesions, splinter haemorrhages, subcutaneous nodules, leg ulcers, and lupus profundus. Rash is often precipitated or aggravated by exposure to sunlight.

Mucous membranes and scalp

Mucous membranes of oral cavity, nose, and vagina are involved. Oral ulcers are usually small, multiple, and painless (**Figure1**). Palatal erythema at the junction of hard and soft palate indicates active disease. Though mostly painless, it may sometimes evolve into painful ulceration. Non-scarring diffuse alopaecia is common (**Figure 2**). With disease control, the hair regrow. Scarring alopecia due to discoid lesions is permanent. Scalp tenderness is sometimes present and indicates active disease.



Figure 1: Oral ulcers in SLE.

Vasculocutaneous lesions

Vasculocutaneous lesions are important markers of disease activity. The spectrum includes Raynaud's phenomenon (rarely digital gangrene), urticaria, palpable purpura, nail fold lesions, and splinter haemorrhages. Palmar vasculitic lesions resemble Osler's nodes and Janeway's lesions. Elbow is a common site of cutaneous vasculitis.



Figure 2: Alopaecia in SLE.

Musculoskeletal

Arthritis or more commonly arthralgias are one of the most frequent presenting manifestation of lupus with a cumulative frequency of >90%. Small joints of both the hands, wrists, and knees are mostly affected. Synovitis is usually less marked and the pain may seem to be out of proportion. Deformities of fingers are uncommon; when present these are typically reducible (Jacoud's arthropathy; it is due to tenosynovitis). Erosive arthritis is rare. Avascular necrosis (AVN) and infection should be suspected when a SLE patient presents with sudden onset, persistent pain and/or swelling of one or few joints. Hip, often bilateral, is the most common site of AVN. Tenosynovitis and tendon rupture can occur. Inflammatory myositis with muscle weakness is seen in a few patients. Myalgia is more frequent. CPK may not be raised. Steroid and chloroquine induced myopathy is an important exclusion. Fibromyalgia is common.

Renal

Renal involvement, present in more than 50% of patients, is an important determinant of prognosis. Clinically it may manifest as nephritis or nephrotic syndrome but can be asymptomatic (**Table 4**). Renal thrombotic angiopathy due to APS and tubulointerstitial disease are other manifestations. Unexplained hypertension should suggest renal involvement. Regular (monthly, initially) urine examination and serum creatinine estimation ensure early diagnosis. Proteinuria (dip stick 2 + or > 500 mg/24 hrs) with or without RBC casts is the most common laboratory indicator of renal involvement. Isolated haematuria (>5 RBC/HPF) or leucocyturia (>5 WBC/HPF) are uncommon presentations and need exclusion of other causes. Renal disease is usually preceded by high anti-dsDNA antibody titres and low C_3, C_4 levels. The biochemical correlates of lupus nephritis (LN) are elevated serum creatinine and low albumin. LN in Indians tends to be severe. Renal biopsy, though not essential for the diagnosis, is useful to assess severity, nature, and reversibility or otherwise of renal involvement. WHO classification of LN is being replaced by histologic classification of lupus nephritis as per the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 (**Table 5**). Diffuse proliferative glomerulonephritis (class IV) is the most common histologic type). Untreated nephritis results in chronic renal failure.

Neurological

Neuropsychiatric lupus (NSL) is the second serious manifestation of SLE, being associated with significant morbidity and mortality. Its pathogenesis is not clear. Vasculopathy, thrombosis and antibody induced cell damage or dysfunction are thought to play a role. Manifestations are diverse. Headache including migraine and subtle cognitive dysfunction are common. Other psychiatric manifestations include anxiety, acute confusional state and psychosis. Convulsions, focal motor and sensory deficits (stroke, movement disorders, cranial neuropathies, paraplegia), cerebritis, peripheral neuropathies and autonomic dysfunction are other manifestations. Myelopathy, meningitis, and chorea are rare. Primary neuropsychiatric diseases, infection, steroid psychosis, and metabolic disorders are important differential diagnoses. CSF examination, CT, MRI and PET scan are of variable diagnostic value.

Cardiovascular

Pericarditis, the most common cardiac manifestation, is often silent. Large pericardial effusion, cardiac tamponade, and constrictive pericarditis are rare. Myocarditis may present as unexplained tachycardia, heart failure, arrhythmia or heart-block. Mitral and aortic valve involvement can be clinically significant. With the availability of echocardiogram, Libman-Sacks endocarditis, the classical cardiac manifestation of SLE, is diagnosed more frequently. It is often associated with anti-phospholipid antibodies. The risk of infective endocarditis is increased. Coronary arteritis is rare. Accelerated atherosclerosis is an important late complication and a major cause of premature death. Traditional risk factors apart, SLE itself and corticosteroid use are independent risk factors for premature atherosclerosis.

Pulmonary

Pleurisy and pleural effusion are the most common pulmonary manifestations. Lupus pneumonitis, alveolar haemorrhage, and pulmonary arterial hypertension, though rare, are life-threatening manifestations. Lupus pneumonitis needs to be differentiated from infective pneumonia. Interstitial lung disease is sometimes encountered. Pulmonary tuberculosis may complicate immunosuppressive therapy. Shrinking lung syndrome is a rare manifestation. Pulmonary embolism is associated with APS.

Haematological

Anaemia of chronic inflammation is common. Concomitant iron deficiency may be present. Coombs' positive anaemia is sometimes the initial manifestation of SLE. Leucopaenia and lymphopaenia are characteristic and correlate with disease activity. Cytopaenias are most commonly due to peripheral destruction and not due to marrow suppression which is often secondary to medications. Thrombocytopaenia may be due to

Table 4: Histologic Class, Clinical Presentation, Prognosis and Treatment of Lupus Nephritis

Histologic Type	WHO Class	Frequency (%)	Proteinuria (%)	Nephrotic Syndrome (%)	Azotaemia (%)	Death (%)	Uraemic Death (%)	Treatment
Normal	I	<5	—	—	—	—	—	—
Mesangial	II	15	68	0	12	18	—	Steroids + rarely IS
Focal proliferative	III	20	100	15	18	30	11	Steroids + IS
Diffuse proliferative	IV	50	100	87	75	58	36	Steroids + IS*
Membranous	V	15	100	88	20	38	6	Steroids + IS

** and others such as plasmapheresis, biologics; IS = Immunosuppressives*

Table 5: Histological Classification of Lupus Nephritis According to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 [(ISN/RPS (2003)]

WHO Type (1995)	Description
Class 1	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy but mesangial immune deposits by immunofluorescence
Class 2	Mesangial proliferative Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
Class 3	Focal lupus nephritis Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class 4	Diffuse lupus nephritis Active or inactive diffuse, segmenal or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided to diffuse segmental (IV-S) lupus nephritis, when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class 5	Membranous lupus nephritis Global or segmental subepithelial immune deposits or their morphological sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class 5 nephritis may occur in combination with class 3 or class 4 in which case both will be diagnosed Class 5 nephritis may show advanced sclerotic lesions
Class 6	Advanced sclerotic lupus nephritis ≥90% of the glomeruli globally sclerosed without residual activity

autoimmune destruction of platelets or because of APS. Idiopathic thrombocytopaenic purpura (ITP) may antedate SLE by years. Lymphadenopathy is common. Thrombotic thrombocytopaenic purpura, bone marrow aplasia and functional hyposplenism are rarely encountered. ESR is elevated. CRP is often undetectable except in the presence of significant inflammation or infection.

Antiphospholipid syndrome (APS)

Twenty to twenty-five per cent patients of SLE test positive for antiphospholipid antibodies. The syndrome of APS is discussed separately.

Others

Abdominal pain may be due to mesenteric vasculitis, aseptic peritonitis or pancreatitis and indicates active disease. Mesenteric vasculitis may manifest with rectal bleeding. Protein-losing enteropathy is uncommon. Though parenchymal liver disease is uncommon, elevated SGOT, SGPT levels are present during active disease and/or with therapy (NSAIDs, azathioprine, methotrexate). Jaundice is uncommon. Hepatomegaly and splenomegaly are present in 25% and 10% of patients. Conjunctivitis, keratoconjunctivitis sicca, episcleritis, and retinitis are some of the ocular manifestations. Uveitis and scleritis are rare.

DIAGNOSIS

The American College of Rheumatology (ACR) has established classification criteria (**Table 6**). Though these are meant for classification and not for diagnosis, most physicians use these to diagnose SLE. A clinically diagnosed or suspected case of SLE may not satisfy the criteria, as these can evolve over time. Treatment decisions should not be delayed, till classification criteria are satisfied. Further many of the common clinical features such as alopecia, constitutional symptoms, vasculitis and rash are not included in the classification criteria. The common differential diagnoses are other autoimmune connective tissue disorders, primary vasculitides and systemic onset JIA.

INVESTIGATIONS

Following biochemical investigations are routinely carried out:

- CBC
- ESR
- Urine routine
- Serum creatinine

These are repeated periodically (monthly or at longer intervals).

Immunology investigations:

- ANA (not required to be repeated)
- Anti-dsDNA
- ENAs (Antibodies to extractable nuclear antigens) viz., Ro (SSA), La (SSB), Smith, RNP, etc.
- C3, C4
- Antiphospholipid antibodies

Others:

- X-ray chest
- Special investigations as indicated

Disease Activity Assessment

Assessment of disease activity is important as therapy depends upon severity of disease activity and the organ system involved. **Table 7** shows investigations indicated as per individual organ involvement. Periodic complete blood counts and urine analysis are mandatory. Active lupus is frequently characterised by anaemia, leucopaenia, lymphopaenia, and thrombocytopaenia (differential diagnosis being drug-induced cytopaenias). Proteinuria and active urinary sediment point to active glomerulonephritis. Rising anti-dsDNA antibody titres and falling C_3, C_4 levels predict/anticipate disease flare. Renal biopsy is useful to assess renal involvement.

Table 6: 1982 revised ACR Criteria for Classification of SLE (Updated 1997)

Criterion	Definition
Facial erythema (butterfly rash)	Fixed erythema, flat or raised over the malar eminences, tending to spare the nasolabial folds
Discoid lupus	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in the older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient's history or physician's observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterised by tenderness, swelling or effusion
Serositis	Pleuritis, convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or Pericarditis documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 gm/day or greater than 3+ if quantitation not performed or Cellular casts, may be red cell, haemoglobin, tubular or mixed
Neurologic disorders	Seizures or psychosis, other causes ruled out
Haematologic disorder	Haemolytic anaemia, leucopaenia (<4000 mm^3), lymphopaenia (<1500/mm^3), thrombocytopaenia (<100,000/mm^3)
Immunologic disorder	Anti-DNA antibody to native DNA in abnormal titre; Anti-Sm, or positive finding of antiphospholipid antibodies based on an abnormal serum level of IgG or IgM anti-cardiolipin antibody or positive test for lupus anticoagulant or false-positive serological tests for syphilis
Antinuclear antibody	A significant titre by IF method in the absence of the other causes of positive ANA

A person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

A variety of disease activity indices such as SLEDAI, SLAM, BILAG, lupus nephritis activity index are available for research and clinical applications. To assess the degree of organ damage, damage indices (SLICC/ACR damage index, lupus nephritis chronicity index) have been developed.

Table 7: Investigations Depending on Systemic Involvement

System Involved	Tests
Renal	24 hours urinary protein and creatinine; Spot urine protein creatinine ratio; C3, C4, renal biopsy
Pulmonary	PFT with DLCO, HRCT, bronchoscopy with BAL fluid examination*
Cardiac	ECG, 2D echo with colour Doppler
Haematological	Coombs test, bone marrow examination, anti-platelet antibodies, antiphospholipid antibody
CNS	CSF examination, CT/MRI, PET/SPECT scanning, antiphospholipid antibody testing

** BAL fluid should always be submitted for microbiological studies.*

TREATMENT

The severity of SLE ranges from an almost inconsequential illness to a devastating illness with renal failure and profound nervous system disturbances. Because of this variability, therapy has to be individualised and determined by the disease severity and its manifestation(s) and not based on the primary diagnosis. Following guiding principles should be followed: (i) therapy should be directed at specific, active disease manifestations; (ii) the intensity of therapy should be based on severity of disease as assessed by objective measures; (iii) the therapy should be for the shortest period possible and at the lowest effective intensity to limit toxicity and side-effects; (iv) it is usually necessary to continue low dose prednisolone along with hydroxychloroquine on a long-term basis; (v) appropriate prophylactic measures against infections, osteoporosis, atherosclerosis are necessary; and (vi) Patients with active disease should be followed-up frequently.

Patient education is important as also allaying patient's fears and anxiety. Patients and their families need to be counselled about marriage, pregnancy, breastfeeding, precautions and preventive measures. Importance of proper diet, adequate rest and exercise to maintain fitness should be stressed.

Preventive measures include: (i) Protection from sunlight; (ii) prevention of infections (chemoprophylaxis, vaccinations); (iii) anti-osteoporosis measures (calcium and Vit. D supplementation, bisphosphonates are used in patients requiring prolonged steroid treatment); and (iv) prevention of IHD (control of BP, diabetes, lipids, and abstinence from cigarette smoking).

Specific therapeutic measures

Tables 8 and 9 summarise the drug treatment of active lupus. Manifestations, like depression and convulsions are treated by standard therapy.

PROGNOSIS

Over the years, prognosis of SLE patients has improved remarkably. Five and ten-year survival rates of 90% and 80%

Table 8: Drugs Commonly Used in the Management of SLE

Drug	Dose	Important Side Effects	Monitoring
NSAIDs	Depends on the NSAID	GI intolerance, GI bleed, hypersensitivity, exacerbation of renal impairment, rarely liver toxicity, aseptic meningitis	CBC, creatinine, SGPT once in 3 to 6 months and SOS
Chloroquine/ Hydroxychloroquine	2 mg/kg/day 4 to 6 mg/kg/day	Pruritus, nausea, and maculopathy	Eye check at the start of treatment and every 3-6 months for chloroquine and every 6-12 months for hydroxychloroquine
Dapsone	50 to 100 mg/day	Pigmentation, anaemia, psychosis	Exclude G6PD deficiency
Prednisolone*	0.25 to 1 mg/kg/day, initially in divided doses, later single morning dose, tapered subsequently to the lowest effective dose	Obesity, acne, diabetes, osteoporosis, infection, ischaemic heart disease, and avascular necrosis of bone	Regular BP, ocular pressure and blood sugar monitoring, bone density assessment in those on long-term treatment
Azathioprine*	1 to 2.5 mg/kg/day oral 15 mg/kg/pulse	Cytopaenias, pancreatitis	CBC on monthly basis (initially fortnightly x 2) and at every increment; amylase and lipase levels 3 monthly
Cyclophosphamide*	1 to 2 mg/kg/day	Nausea, vomiting, cytopaenias, infections, premature menopause, haemorrhagic cystitis, bladder cancer	Ensure adequate fluid intake; CBC on the 7th and 14th day if pulse therapy is given; urine routine examination
Mycophenolate Mofetil*	1 to 2 gm/day	GI disturbances, influenza-like syndrome, infections, cytopaenias	Periodic blood counts and blood chemistry

** Immunosuppressive drugs.*

have been reported from developed countries. In India 5- and 10-year survival rates of 68% and 50% have been reported. Renal failure and infection are the two main causes of death in Indian patients. Disease severity, delay in seeking as well as lack of access to medical help, inadequate and inappropriate treatment contribute to the higher mortality. Premature atherosclerosis and coronary artery disease are important causes of premature death. Though slight, there is a definite increased risk of cancer and haematologic malignancies in SLE patients.

SPECIAL PROBLEMS

Fertility, Pregnancy, Contraception

Fertility is normal, unless the disease is very active. Patients should be advised to plan pregnancy during periods of remission (when disease is quiescent and steroid requirement is 10 mg or less for 6-12 months). With active disease, there is an increased risk of spontaneous abortion and miscarriage, still-birth, premature birth and low birth weight (independent of APS). Other risk factors are anti-Ro antibodies, anticardiolipin antibodies and/or lupus anticoagulant, history of thromboembolism and foetal loss. These patients need close monitoring by a rheumatologist and an experienced obstetrician. The disease can flare during pregnancy. Steroids, hydroxychloroquine, and azathioprine can be continued during pregnancy. Cyclophosphamide, methotrexate, and mycophenolate should be discontinued 3 to 6 months before conception. Cyclophosphamide therapy carries the risk of age-dependent ovarian failure.

Intrauterine contraceptive devices should be avoided. Oestrogen-containing contraceptives should be avoided with APS. Contraceptives and post-menopausal hormone replacement therapy with progesterone-only pills are safe. Barrier methods can be practiced safely.

Paediatric and Neonatal Lupus

The clinical manifestations of SLE in the paediatric age group are essentially similar to those of adults. There is a higher frequency of lymphadenopathy, hepatosplenomegaly, nephritis, and avascular necrosis of the bone. SLE tends to be more severe. Principles of treatment are similar to that of adult SLE.

Table 9: Choice of Therapy in SLE

Symptom	NSAIDs	Anti-malarials	Steroids	IS#	IVIgG/ Biologics
Arthritis	Yes	Yes	• Yes	No	No
Fatigue	No	Yes	• No	No	No
Malar rash	No	Yes	• Yes	No	No
Serositis	Yes	No	• Yes	No	No
Pneumonitis	No	No	•• Yes	Yes	No
Carditis	No	No	• Yes	Yes	No
Vasculitis	No	No	•• Yes	Yes	Yes*
Nephritis	No	No	•• Yes	Yes	Yes*
Cerebritis	No	No	•• Yes	?	Yes*
Haemolysis	No	No	•• Yes	Yes	Yes
Thrombo-cytopaenia	No	No	•• Yes	Yes	Yes

• *Low dose* •• *High dose ± MP pulses*

Note:

1. *Anti-coogulonts are indicoted for ontiphospholipid syndrome potients with thrombosis*
2. *Even though not specificolly indicoted for o particulor monifestation, anti-molorials should be given to oll SLE potients unless controindicoted or not toleroted since these hove multiple beneficiol effects*
3. *# Immunosuppressive theropy*
4. ** If stondord treotment foils*

Children born of mothers with SLE can develop neonatal lupus syndrome. Its manifestations include transient photosensitive discoid rash, cytopaenias, hepatosplenomegaly, myocarditis, and pericarditis. Treatment is symptomatic. Permanent features such as congenital complete heart block (CCHB), endomyocardial fibroelastosis, and other structural cardiac defects may occur. The risk of CCHB is related to anti-Ro antibodies. CCHB patients may need permanent pacemaker implantation in adulthood. Dexamethasone is given to mothers, to treat foetal CCF, pericarditis and heart block (diagnosed with foetal echocardiogram).

SLE in the Elderly

SLE in the elderly is often, but not necessarily, a milder disease. It is characterised by insidious onset, longer duration of disease at the time of presentation, and a lower incidence of renal, musculoskeletal, skin and neurological manifestations.

Infections

Patients with SLE are particularly susceptible to infections with intracellular organisms like *Candida*, Herpes, *Salmonella* and, *Mycobacteria* and capsulated organisms (*Pneumococcus, Meningococcus* and *H. influenzae*). The increased susceptibility is due to low complement levels, prednisolone (>20 mg/d), immunosuppressives (especially cyclophosphamide) and splenic hypofunction. Infection is often present along with active disease. When distinction between the two is difficult, both are treated simultaneously. Prevention of infection with chemoprophylaxis and vaccination is advised.

Drug-Induced SLE

The most commonly implicated drugs are listed in **Table 1**. Drug-induced SLE is uncommon in India. ANA, anti-histone antibodies, and LE cells are characteristic features of drug-induced SLE. The prevalence of drug-induced ANA is more common than the clinical syndrome. Clinical features are mild; renal and neurological involvement is rare. Symptoms resolve on withdrawal of the offending drug though the antibody titres may continue to remain elevated for a long time. Drugs known to induce SLE can be used to treat *de novo* SLE patients.

MCTD, Overlap Syndromes, Antiphospholipid Syndrome

These are discussed in separate chapters.

New and Experimental Therapies

Though the present therapies have significantly improved the prognosis of SLE patients, the results are far from satisfactory. Newer regimens and newer therapies are necessary. Dihydroepiandrosterone, a weak androgenic steroid, has shown moderate benefit in some studies. Newer biologic agents that target antigens, immune cells and other components of the immune response are promising newer therapies. Rituximab an anti CD 20+ (anti B cell) antibody is being used for treatment of refractory SLE. Belimumab is a totally human monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS), also known as B-cell activation factor of the TNF family (BAFF). Belimumab is indicated for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy. Recommended dosage regimens 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter by intravenous infusion. The efficacy of belimumab has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. It has been recently approved for treatment of SLE. Autologous stem-cell transplantation has met with some success.

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24.10 Antiphospholipid Syndrome

Vikas Agarwal

INTRODUCTION

The antiphospholipid syndrome (APS) is an acquired autoimmune disease characterised by thrombosis (arterial or venous) and/or pregnancy morbidity in the presence of a variety of circulating autoantibodies directed against the phospholipid-protein complexes. These autoantibodies are lupus anti-coagulant (LA), anti-cardiolipin (ACL) and antiβ2glycoprotein-1 (antiβ2GP1) antibodies. Diagnosis of APS can be relied upon in the absence of other causes of hypercoaguable state and persistent positivity for anti-phospholipid (APL) antibodies. APS may be primary (idiopathic) or secondary [in presence of disorders like systemic lupus erythematosus (SLE), rheumatoid arthritis, other connective tissue disorders]. The term 'anti-phospholipid' is misleading because the autoantibodies usually recognise complexes of proteins and phospholipids (PLs), not PLs alone.

EPIDEMIOLOGY

The exact prevalence of APS is not known; however, a female predominance has been described. About 30% of patients with LA and 30% to 50% of patients with moderate to high titres of ACL antibodies have clinical manifestations of APS. APS may account for 15% to 20% of all episodes of deep vein thrombosis, one-third of stroke below the age of 50 and 5% to 15% of recurrent foetal loss. In Indian setting, a prevalence of 27.7% has been reported in 155 females with recurrent miscarriages or late pregnancy loss from Kolkata and 40% from Tamil Nadu.

DIAGNOSIS

The revised criteria proposed in 2006 are outlined in **Table 1**. One clinical event and one laboratory abnormality are required to diagnose APS. Presence of APL antibodies is not equivalent to APS.

AETIOPATHOGENESIS

The predominant hypothesis regarding the origin of APL states that an incidental exposure to environmental agents with β2GP1-like peptides induces APL in susceptible individuals. The putative mechanisms of thrombosis include: (1) activation of endothelial cells by complexes of β2 GPI and anti-β2 GP1, (2) platelet activation after binding of the antiβ2 GPI by the activator receptor apo ER2067, (3) presence of autoantibodies against natural anti-coagulant proteins like annexin-5 and activated protein C, and (4) abnormal fibrinolysis. The mechanisms of pregnancy complications include: (1) APL binds to annexin-5 on the surface of the trophoblasts causing break in the anticoagulant shield of the placenta; and (2) an inflammatory reaction due to the activation of neutrophils, complement, and complement receptors is initiated leading to thrombosis.

Table 1: Revised Criteria for Diagnosis of Antiphospholipid Syndrome *(Miyakis et al, 2006)*

APS is present if at least one of the clinical criteria and one of the laboratory criteria are met*

Clinical Criteria

Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

Pregnancy morbidity

One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus; or

One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia, defined according to standard definitions, or (ii) recognised features of placental insufficiency; or

Three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities, excluding paternal and maternal chromosomal causes.

Laboratory Criteria**

LA present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).

ACL antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titre (i.e. >40 GPL or MPL, or >99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardised enzyme linked immunosorbent assay (ELISA).

Anti-β2 glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma (in titre >99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardised ELISA, according to recommended procedures.

**Classification of APS should be ovoided if less than 12 weeks or more than 5 years separote the positive APL test ond the clinicol manifestations.*

***Investigotors are strongly advised to classify APS patients in studies into one of the following categories: I, more thon one laboratory criterio present (ony combination); IIa, LA present alone; IIb, ACL antibody present alone; IIc, onti-β2 glycoprotein-1 antibody present olone.*

Acute thrombotic microangiopathy with minimal or no inflammation is the pathologic hallmark. The chronic changes range from hypoperfusion to atrophy and fibrosis.

CLINICAL FEATURES

Arterial or Venous Thrombosis

The major clinical manifestation of the APS is thrombosis (either arterial or venous or both) confirmed objectively by either imaging or histpathologically. Arterial thrombosis occurs predominantly in the central nervous system (CNS), but may affect any segment of the arterial tree. It may present as myocardial infarction, aseptic osteonecrosis, adrenal insufficiency, or peripheral gangrene (**Figure 1**). Arterial thrombosis in younger people or people without obvious risk factors for thrombosis should alert to the possibility of APS. Venous thrombosis commonly localises to the deep veins of the lower limbs. It may be complicated by pulmonary embolism. However, any venous segment may be involved. Superficial venous thrombosis is not included in the classification criteria.



Figure 1: Gangrene of all the fingers of bilateral hands in a female with APS.

Pregnancy Morbidity

Persistent antiphospholipids (APLs) are seen in about 15% of women with recurrent miscarriage in the first or second trimester. In these women, the foetal loss rate can be up to 90% without pharmacological treatment. It may present as unexplained foetal death after the 10th week of gestation, or unexplained consecutive spontaneous miscarriages before the 10th week of gestation, or premature birth before the 34th week of gestation because of eclampsia or severe pre-eclampsia, not pre-eclampsia alone. The risk of pregnancy morbidity is unknown in asymptomatic APL-positive patients and in patients with APS with only vascular events.

Thrombocytopaenia

Thrombocytopaenia (platelets <150,000/μL) is seen in one-third of the patients; however, platelets are rarely low enough to cause bleeding. Other causes, such as (thrombotic thrombocytopaenic purpura (TTP), disseminated intravascular coagulation (DIC), and heparin-induced thrombocytopaenia should be excluded.

Autoimmune Haemolytic Anaemia

About 10% to 20% of the patients with APS may have positive Coombs' test, however, clinically significant autoimmune haemolytic anaemia (AIHA) is uncommon. It is usually associated with cardiac valvular lesions. Rarely, AIHA and thrombocytopaenia can occur simultaneously, referred as *Evan's syndrome*.

Neurologic Manifestations

Stroke and transient ischaemic attacks are the most common presentations. Other manifestations include cognitive dysfunction, dementia, chorea, transverse myelopathy, cerebral venous thrombosis, acute ischaemic optic neuropathy, central retinal artery occlusion, amaurosis fugax, sensorineural deafness, and epilepsy.

Cardiovascular Manifestations

It can present with intracardiac thrombosis or as valvular heart lesions (non-infectious Libman-Sacks endocarditis) affecting mainly the mitral valve. It is seen in 30% to 50% of the patients on Doppler echocardiography. Valve involvement is diffuse as compared to rheumatic heart disease (localised, involve leaflet margins, associated with thickening fusion and calcification of the chordae tendinae). Presence of endocarditis warrants prophylaxis against bacterial endocarditis but rarely requires valve replacement.

Skin Manifestations

The main skin manifestation of APS is livedo reticularis, seen in 25% of patients. Other manifestations are leg ulcers (**Figure 2**), cutaneous infarcts, gangrene, necrotising purpura and nailfold infarcts.



Figure 2: Ulcers involving the dorsum of feet and the legs in a young female with APS.

Renal Manifestations

Involvement of different vessels in the kidney may lead to variable presentation like hypertension, renal infarction, haematuria, and thrombotic microangiopathy. In patients with systemic lupus erythematosus, APS worsens the renal prognosis. Histologically, thrombotic microangiopathy and/or fibrous intimal hyperplasia, focal cortical atrophy, or tubular thyroidisation may be seen.

Catastrophic Antiphospholipid Syndrome

Catastrophic APS is a rare complication with multiorgan failure secondary to widespread microvascular thrombosis. Kidneys are most commonly affected, followed by lungs, CNS and skin. Thrombocytopaenia and DIC are common laboratory findings. Catastrophic APS is initiated in 35% of the cases by a variety of infections. The mortality rate is up to 50%, due to multiorgan failure. It may mimic severe sepsis, TTP and DIC from any cause.

Two-thirds of survivors remain symptom free with anticoagulation during an average follow-up of 67.2 months. Recurrence may occur in 26% cases and a quarter of them may die.

LABORATORY DIAGNOSIS

The laboratory diagnostic criteria include ACL of IgM or IgG isotypes (moderate or high titres), LA and antiβ2GP1. LA is considered to be the best marker for the risk of thrombosis. The clinical abnormalities should be present on two or more occasions at least 12 weeks apart. The risk of thrombosis and pregnancy morbidity is higher in patients with multiple types of APL than in patients with a single APL positivity.

Antiphospholipid Assays

LA are antibodies that cause prolongation of APTT by blocking the phospholipid surfaces, (block assembly of prothrombinase, a complex of factors Xa, Va and prothrombin on a phospholipid template). This interferes with thrombin generation and slows fibrin formation. This is detected as prolongation of the clotting time in coagulation assays that include phospholipid. Moreover, this prolongation is not corrected by addition of platelet-free (i.e. no anionic phospholipids) plasma but by addition of an excess of PLs. Interpretation of the test is difficult in the presence of therapy with unfractionated heparin or with high-intensity oral anticoagulants (INR >3.5).

MANAGEMENT

Venous Thrombosis and Thromboembolism

The initial treatment of venous thrombosis is the similar to any other venous thrombosis. Treatment with intravenous unfractionated heparin or low molecular-weight heparin should be started, and vitamin K antagonist therapy should be initiated with the target INR of 2 to 3. Because of high risk of recurrence of thrombosis, lifelong anticoagulation is usually recommended. If anticoagulation is discontinued, the incidence of recurrence is highest during the first 6 months after discontinuation, and the recurrence will usually occur in the same type of vessel (venous or arterial, depending on the initial manifestation). Serial testing for APL is not useful and there is no consensus regarding discontinuation of anticoagulation in patients who have normalised APL levels.

Arterial Thrombosis

The majority of these patients will be diagnosed with a non-cardioembolic transient ischaemic attack or a stroke. Non-cardioembolic arterial thrombosis during APS should be treated with low dose aspirin. The treatment of non-cerebral arterial thrombosis is not clear; however, patients with myocardial infarction should receive long-term anticoagulation. Arterial embolism, mainly originating from the non-bacterial endocarditis, should be treated with long-term oral anticoagulation to avoid the accumulation of cerebral infarctions.

Pregnancy Complications

Women with history of pregnancy losses should be treated with subcutaneous unfractionated heparin (5000 units twice a day) plus low-dose aspirin or prophylactic doses of low-molecular-weight heparin (to reach an anti-factor Xa level of 0.1-0.3 U/mL) in combination with aspirin. Aspirin should be started at around the time of conception, and heparin as soon as the pregnancy is confirmed until the third trimester.

Catastrophic APS

It should be managed aggressively with heparin, plasmapheresis, intravenous immunoglobulin and high-dose glucocorticoids.

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24.11 Systemic Sclerosis

R Porkodi, S Rajesh

Systemic sclerosis is a chronic autoimmune disease characterised by thickening and fibrosis of the skin. Internal organs like heart, lungs, kidneys and gastrointestinal tracts are often involved. Systemic sclerosis is 3-4 times more common in women than men and occurs between 30 and 50 years of age. Localised forms of scleroderma include morphea, linear scleroderma or facial hemiatrophy (en coup de sabre).

CLASSIFICATION

The classification is based on the extent of skin involvement:

(a) *Diffuse cutaneous scleroderma:* Skin thickening present on the trunk, face, proximal and distal extremities.

(b) *Limited cutaneous scleroderma:* Skin thickening limited to sites distal to the elbows and knees, may involve face and neck. CREST syndrome, a variant seen in some patients, comprises of calcinosis, Raynaud's, oesophageal dysmotility, sclerodactyly and telangiectasia.

(c) *Sine scleroderma:* Internal organ manifestations, vascular and serologic abnormalities, without detectable skin changes.

(d) *Overlap syndrome:* Any of the above occurring concomitantly with a diagnosis of systemic lupus erythematosus, inflammatory muscle disease or rheumatoid arthritis.

The differences between limited and diffuse systemic sclerosis are outlined in **Table 1**.

Table 1: Differences between Limited and Diffuse Cutaneous Scleroderma

S. No.	Limited Scleroderma	Diffuse Scleroderma
1.	Raynaud's predates the skin by several years	Raynaud's occurs usually within one year of onset of skin changes
2.	Skin involvement over the face, neck distal to elbows and knees, calcinosis, telangiectasia	Skin involvement over the face, neck, trunk, extremities
	Slow progression	Rapid progression with oedema of hands and legs
3.	Infrequent systemic symptoms, mild arthralgia, dyspnoea	Severe arthralgia, tendon friction rubs, internal organ involvement
4.	Oesophageal dysmotility, dysphagia	Severe intestinal problems and oesophageal involvement
5.	Occasional pulmonary fibrosis	Severe pulmonary fibrosis
6.	Severe pulmonary artery hypertension (PAH)	Cardiomyopathy, arrhythmia, secondary pulmonary hypertension
7.	No renal involvement	Renal crisis
8.	Anticentromere antibodies	Anti Scl-70 (topoisomerase 1 antibodies)
		Anti RNA polymerase III

AETIOPATHOGENESIS

Genetic factors: Linkage of the disease with HLA A1, B8 and DR3 haplotype or with DR3/DR52 has been reported.

Environmental factors: Exposure to silica, polyvinyl chloride, drugs like L-5- hydroxyl tryptophan, bleomycin, pentazocine and cocaine can predispose to scleroderma.

Infectious agents: Cytomegalovirus, Epstein Barr virus infections may play a role due to molecular mimicry.

There is interplay between genetic and environmental factors and autoimmunity (**Figure 1**). Vascular and immunological changes lead to fibroblast proliferation with collagen accumulation in a genetically predisposed individual when exposed to environmental triggers.

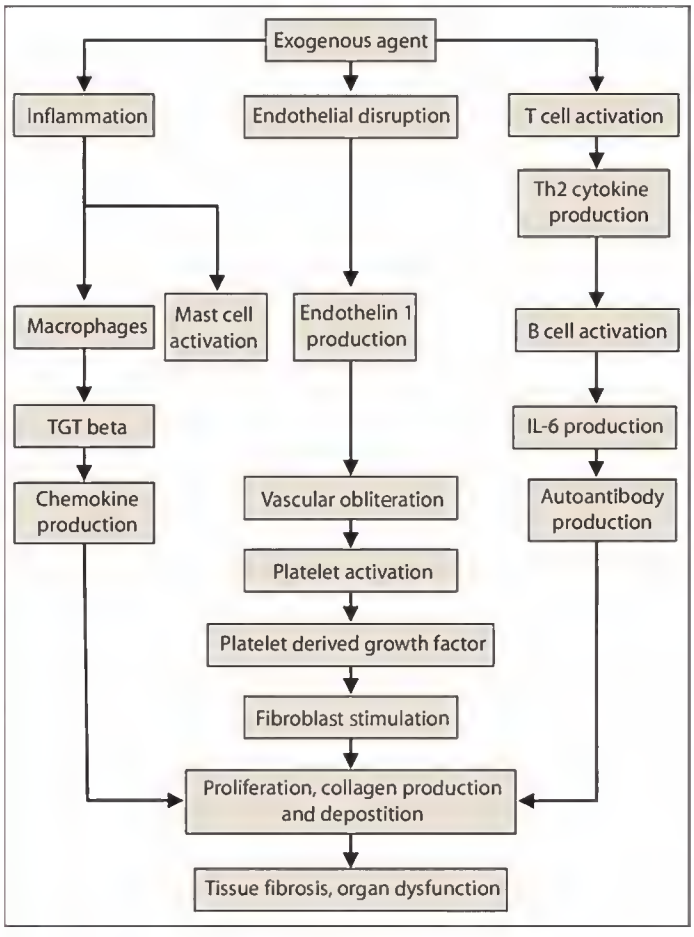


Figure 1: Pathogenesis of systemic sclerosis.

CLINICAL FEATURES

Raynaud's phenomenon is a forerunner of systemic sclerosis. Digital vessels show marked intimal hyperplasia due to collagen deposition and adventitial fibrosis. Vasoconstrictor response to cold or emotional stimuli leads to near complete occlusion of the vessel. Scleroderma renal crisis and pulmonary hypertension are the result of Raynaud's of internal organs. There is

loss of digital pulp-acro-osteolysis on radiographs (**Figure 2**) and pitting scars over the fingertips (**Figure 3**).



Figure 2: Radiograph of hands showing resorption of terminal phalanges.



Figure 3: Pitting scars over finger tips.

Skin

Pitting oedema of the fingers, dorsum of hands, face, trunk and upper arms is a characteristic feature of early scleroderma. Skin thickening of the fingers and hands (**Figure 4**) is followed by involvement of face and neck. Lips become thin and pursed, radial furrows appear around the mouth, giving a pinched appearance (**Figure 5**). Skin tightening leads to restricted mouth opening. Hair growth is sparse, salt and pepper like appearance with hypo- and hyperpigmented changes are seen (**Figure 6**).



Figure 4: Skin thickening of fingers and hands with contracture formation.



Figure 5: Pinched up facies.



Figure 6: Salt and pepper appearance.

Musculoskeletal Features

Significant arthralgia with morning stiffness is characteristic. Mild synovitis is seen in about half of these patients, erosions occur in 29%. Leathery tendon friction rubs can be palpated and auscultated with the movements of the tendons.

Muscle weakness may be secondary to disuse atrophy or there may be a mild proximal muscle weakness with mild muscle enzyme elevation and electromyographic (EMG) abnormalities like increased polyphasic potentials, decreased amplitude and duration.

Subcutaneous calcification over the fingers, olecranon and prepatellar bursae is seen in 40% of patients with limited cutaneous scleroderma.

Gastrointestinal Involvement

Oesophageal dysmotility leads to dysphagia; lax lower oesophageal sphincter causes heartburn due to reflux. 'Watermelon stomach' is characteristic due to gastric antral venous ectasia. Telangiectasia can lead to gastrointestinal (GI) bleed. Feeling of satiety, intermittent bloating, abdominal cramps, chronic diarrhoea, constipation, obstipation, pseudo-obstruction, wide mouthed diverticula, rectal prolapse and faecal incontinence are other features of GI involvement.

Pulmonary Manifestations

Pulmonary fibrosis and secondary pulmonary hypertension may be seen in diffuse variety. Pulmonary hypertension may also be present in absence of pulmonary fibrosis, especially in limited cutaneous scleroderma. Progressive exertional dyspnoea and nonproductive cough are typical features of pulmonary fibrosis. Physical findings include early inspiratory crackling rales. Usual interstitial pneumonitis (UIP), nonspecific interstitial pneumonitis (NSIP), bronchiolitis obliterans and diffuse fibrosing alveolitis are the different pathological variants. Impaired DLCO (diffusion lung capacity for carbon monoxide) and structural abnormalities on high resolution CT chest – like ground glass appearance may be seen even in asymptomatic patients (**Figures 7A and B**).

Pulmonary artery hypertension (PAH) is defined as a mean pulmonary artery pressure > 25 mmHg at rest and above 30 mmHg during exercise. PAH is a cause for the mortality and presents with exertional dyspnoea, fatigue, palpitation, chest pain, syncope and cough. Loud P2, right ventricular gallops, murmurs of pulmonary, tricuspid regurgitation, jugulovenous distension, hepatojugular reflux, leg oedema are the clinical features.

Cardiac Involvement

Patchy myocardial fibrosis leads to contraction band necrosis. This is due to ischaemia reperfusion injury. This can result in arrhythmia, cardiomyopathy with diastolic dysfunction. Pericarditis and pericardial effusion may also be seen.

Renal Involvement

Scleroderma renal crisis (SRC) occurs in 10% patients with diffuse scleroderma. Patients treated with high dose glucocorticoids are at the greatest risk. It is characterised by sudden onset of malignant hypertension, renal failure, haemolytic anaemia, proteinuria, microscopic haematuria and schistocytes on peripheral blood.

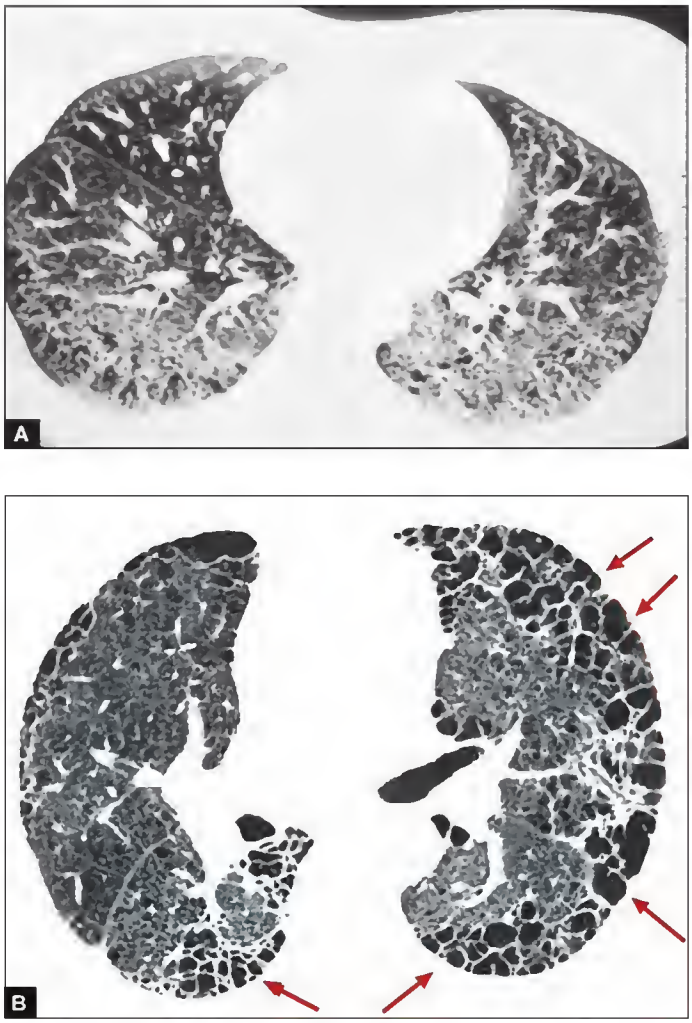
Other Symptoms

Sicca complex occurs in 20% to 30% of patients. Thyroid gland fibrosis can lead to hypothyroidism. Neuropathic pain due to trigeminal neuralgia or carpal tunnel syndrome can be present.

Pregnancy does not worsen scleroderma, though intrauterine growth retardation and low birth weight have been reported. Erectile dysfunction can occur in men.

Malignancy

Relative risk of lung cancer in scleroderma was 16.5 in one series.



Figures 7A and B: HRCT images of ground glass opacity and honeycombing of the lungs (arrows).

DIAGNOSIS

The diagnosis is clinicoserologic. Skin biopsy helps by demonstrating subcutaneous deposition of collagen, loss of hair follicles, sweat glands and inflammatory cell infiltrates in the early stages. The autoantibodies present in scleroderma are listed in **Table 2**.

Table 2: Autoantibodies in Systemic Sclerosis

Autoantibody	%	Association
ANA	90	—
Anticentromere Antibody	22 to 36	Limited cutaneous/CREST
Anti Scl 70 (topoisomerase I)	20 to 40	Diffuse cutaneous, lung fibrosis
RNA polymerase I and III	4 to 23	Diffuse cut, SRC, cardiac involvement
Antifibrillarin	6 to 8	Diffuse cut, ILD, PAH, renal crisis
Anti PM/Scl	2 to 5	Overlap with myositis
Anti Th/To	4 to 16	Limited cutaneous

Radiographs of chest for pulmonary involvement, of hands for resorption of terminal phalanges, calcinosis cutis can be done. HRCT chest, pulmonary function tests like DLCO will help in establishing early interstitial lung disease (ILD). Echocardiography will determine the pulmonary hypertension. Bronchoalveolar lavage fluid evaluation for the nature of cells—

eosinophils or neutrophils will indicate inflammation. Barium study and oesophageal gastric endoscopy will be useful. Nailfold capillaroscopy (**Figure 8**) shows dropouts and dilated capillary loops.



Figure 8: Nailfold capillaroscopy showing capillary dropout and dilated capillary loops.

DIFFERENTIAL DIAGNOSIS

Table 3: Differential Diagnosis of Systemic Sclerosis

Disorders characterised by or associated with skin thickening on the fingers and hands
Digital sclerosis of diabetes mellitus
Chronic reflex sympathetic dystrophy
Mycosis fungoides
Vinyl chloride disease
Amyloidosis
Acrodermatitis chronic atrophicans
Adult coeliac disease
Disorders characterised by or associated with generalised skin thickening, but sparing fingers and hands
Scleroderma adultorum of Buschke
Scleromyxoedema
Eosinophilic fasciitis
Eosinophilia-myalgia syndrome
Generalised subcutaneous morphoea
Porphyria cutanea tarda
Amyloidosis
Human graft versus host disease

TREATMENT

Management is based on symptoms and is organ specific. It has to be individualised.

Management of Raynaud's

Avoidance of cold temperature and keeping the hands and feet warm is helpful. Vasodilators like calcium channel blockers—Nifedipine (30 to 180 mg/d), amlodipine (5 to 20 mg/d), diltiazem, 5 HT antagonists like fluoxetine (20 mg/d), ACE inhibitors like enalapril (5 to 10 mg/d), losartan (50 mg/d) and parenteral vasodilators like iloprost (0.5 to 2 ng/kg/min) have been tried. Endothelial receptor antagonist - bosentan; phosphodiesterase inhibitors—sildenafil, tadalafil, vardenafil; anti-coagulants and surgical sympathectomy are also useful.

Pulmonary Hypertension

Drugs used in Raynaud's are also helpful in managing PAH-calcium channel blockers, bosentan (62.5 to 125 mg bid), sildenafil (50 mg bid-tid), prostanoids—epoprostenol (2 ng/kg/min), treprostinil and iloprost. Other agents used include digoxin, anti-coagulants, spironolactone and long-term low dose oxygen.

Gastrointestinal Disease

Metoclopramide (10 mg tid-qid) enhances gastrointestinal motility. Proton pump inhibitors like omeprazole are helpful in reflux oesophagitis. Frequent diarrhoea due to bacterial overgrowth is treated with antibiotics.

Interstitial Lung Disease

Corticosteroids and cyclophosphamide are widely used. Daily oral cyclophosphamide 100 mg/day or monthly intravenous cyclophosphamide (600 mg to 750 mg/m^2) are employed.

Scleroderma Renal Crisis

Prompt institution of ACE inhibitors is needed to control blood pressure. Angiotensin II receptor blocker like losartan is also beneficial.

Glucocorticoids are indicated in early oedematous phase of scleroderma, in severe arthritis, myositis, tenosynovitis, pericarditis and ILD. Steroids are used in low dose for the fear of precipitating scleroderma renal crisis.

Other Drugs

NSAIDs are used for arthritis. Methotrexate has been shown to be useful for skin involvement and arthritis. Mycophenolate mofetil has shown beneficial results for skin and ILD. A variety of other agents have been used with variable results. These include D penicillamine, cyclosporine recombinant IFN gamma, IFN alpha, halofuginone, recombinant human relaxin, minocycline, antithymocyte globulin and intravenous immunoglobulins. Immunoablation with autologous peripheral stem cell rescue and photopheresis have been tried. Other drugs under investigation include imatinib (200 mg/d), rituximab, alefacept and drugs targeting TGF-beta.

PROGNOSIS

Scleroderma is treatable, not curable. Limited cutaneous scleroderma has a good prognosis as it is a slowly progressive disease and skin thickening may improve because of atrophy. Diffuse cutaneous scleroderma may have a rapidly progressive course and median survival after the onset of significant pulmonary fibrosis, PAH or scleroderma renal crisis is usually less than five years.

RECOMMENDED READINGS

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24.12 The Vasculitides

Pradeep Bambery

INTRODUCTION

Vasculitis literally means inflammation of blood vessels. At histology, capillaries, small, medium or large vessels, of both the arterial and venous systems, demonstrate a spectrum of lesions including inflammatory cell infiltration, occlusion, granulomatous reactions and vessel necrosis (**Figure 1**). The tissues where these changes occur, display abnormalities consequent to ischaemia, haemorrhage and necrosis. Clinically, however, these translate into a large, heterogeneous, often bewildering, group of disorders with many causes, characterised by a wide diversity of symptoms, signs (**Figure 2**), extent of involvement, clinical behaviour and outcome.

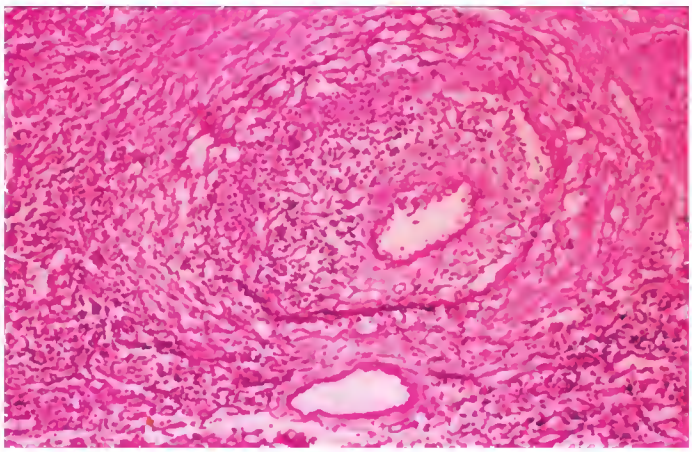


Figure 1: Vessel wall necrosis, luminal compromise, intense inflammatory cell infiltration, nuclear dusting and signs of tissue necrosis at the periphery. Classic appearance of vasculitis. Ill-formed giant cell granulomatous response is seen in the vessel wall.



Figure 2: Typical saddle nose deformity in a patient with Wegener's granulomatosis.

Clinically, however, the problem lies in thinking about vasculitis as a possible cause for the patients' problems. This is vital to force appropriate investigation leading to diagnosis and beneficial therapy. The vasculitides are uncommon disorders with largely non-specific manifestations that could mimic common, relatively benign conditions. Most patients with serious vasculitis however, give the physician clear clues and time to make a diagnosis. This is the challenge this chapter will hope to address. The possibility of successful outcome of therapy for even the most severely afflicted should go far in dispelling the perceptions of doom commonly associated with such a diagnosis.

EPIDEMIOLOGY

Reliable epidemiologic data from India is not available. Takayasu's arteritis is the commonest vasculitis described. Temporal arteritis is extremely uncommon. A significant number of patients with Wegener's granulomatosis have been reported in North India, it is relatively rare in the South. Classic polyarteritis nodosa has been well described. The incidence of systemic primary vasculitis in the Western world is around 20 per million per year. Significant geographic and ethnic variations have been noted.

CLASSIFICATION

The causes of vasculitis are listed in **Table 1**. Primary vasculitis has a presumed immune origin. If it is associated with any of the other causes, it is termed secondary (**Tables 2 and 3**). Several drugs cause vasculitis. Some of them are even anti-neutrophil cytoplasmic antibodies (ANCA) positive (**Table 4**). There are several conditions that successfully mimic vasculitis. They need to be excluded before a diagnosis is established (**Table 5**).

Table 1: Causes of Vasculitis

Immune mechanisms (idiopathic, related to recognised clinical syndromes)
Infections (bacterial, fungal, rickettsial, viral)
Drugs
Tumours
Radiation
Extremes of temperature

Classification has been a vexed, but dynamic, issue dependent on prevalent understanding of pathogenesis. Initially, it merely listed individual disease entities. It now incorporates pathology and, more recently, ANCA serology as well. The Chapel Hill Consensus Conference (CHCC) attempted to define primary vasculitides clinically as well as pathologically based entirely on vessel size (**Table 2**). As it only addressed the primary vasculitides, a sizeable part of the actual clinical spectrum was excluded. Lie attempted a wider, modified classification incorporating the entire clinical spectrum of the vasculitic disorders (**Table 2**). His classification was more flexible with

vessel size, clinically inclusive and reflected both clinical and necropsy observations. The pathologic basis of classification of primary vasculitides was further simplified by Savage (Table 3). Clearly, this remains 'work in progress'. Table 6 lists an example based on vessel size, ANCA, immune mechanisms and infectious mimics.

Table 2: Classification of the Vasculitides. Chapel Hill Classification (1993), The Current 'Gold Standard'

Chapel Hill Consensus Conference Classification 1993

Large vessel vasculitis:
- Giant cell arteritis, Takayasu disease

Medium vessel vasculitis:
- Polyarteritis nodosa (PAN), Kawasaki's disease

Small vessel vasculitis:
- Microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), Henoch-Schönlein purpura (HSP), essential mixed cryoglobulinaemia (EMC), cutaneous leucocytoclastic vasculitis

Classification of vasculitis (Lie 1994)

Primary vasculitis:
- Vasculitis of large, medium and small vessels
  - Giant cell arteritis, Takayasu disease
  - Isolated angiitis of CNS
- Vasculitis of medium and small vessels
  - PAN, CSS, WG
- Vasculitis of small vessels
  - MPA, HSP, cutaneous leucocytoclastic vasculitis
- Miscellaneous
  - Buerger's, Behcet's, Cogan's, Goodpasture's, and Kawasaki's syndromes

Secondary vasculitis:
- Infection
- Connective tissue diseases
- Drug hypersensitivity
- Essential mixed cryoglobulinaemia
- Malignancy
- Hypocomplementaemia
- Post-organ transplant

Table 3: Histopathologic Classification of Primary Vasculitis (Savage 1997)

Dominant Vessel Size	Granulomatous Pathology	Non-Granulomatous Pathology
Large	Temporal arteritis, Takayasu's arteritis	
Medium		Classic PAN, Kawasaki's disease
Small	Wegener's granulomatosis Churg-Strauss syndrome	Microscopic polyangiitis, HSP, EMC

CLINICAL MANIFESTATIONS

Although the vasculitides are truly 'multisystem' diseases, each entity has a predilection for certain organs and systems (Table 7).

General Symptomatology

Patients often have fever, weight loss, malaise, fatigue, night sweats, anaemia, generalised aches and feel unwell. Polymyalgia rheumatica, a syndrome that includes many of these symptoms is a 'red flag' suggesting vasculitis, and is frequently observed in temporal arteritis.

Table 4: Drugs Causing Vasculitis including ANCA Positive Vasculitis

Antibiotics	Macrolides, aminoglycosides, quinolones, sulphonamides, tetracyclines, penicillins, INH, rifampicin
Anti-thyroid	Propylthiouracil
Anti-convulsants	Phenytoin, carbamazepine, valproate
Anti-hypertensives	Hydralazine, methyldopa, nifedipine, atenolol, captopril, diltiazem, frusemide
Anti-arrhythmics	Quinidine, procainamide
Anti-coagulants	Heparin, warfarin, streptokinase
Vaccines	Hepatitis A, B, influenza, rubella, small pox
Interferons	Alpha, beta, gamma
Growth factors	G-CSF, GM-CSF
Leukotriene inhibitors	
Anti-metabolites	Allopurinol, colchicine, retinoids, alkylating agents, methotrexate, cytosine arabinoside
Psychoactive	Anti-depressants, cocaine, ecstasy
ANCA-positive drug-induced vasculitis	Hydralazine, propylthiouracil, leukotriene inhibitors, ciprofloxacin, minocycline, phenytoin, clozapine, sulphasalazine, allopurinol, D-penicillamine

Table 5: Conditions that Mimic Vasculitis and Need to be Excluded before Therapy is Started

Infections	Infective endocarditis, staphylococcal sepsis, nisserial sepsis tuberculosis, syphilis, invasive fungal infection, aspergillosis, mucormycosis, rickettsial infection, viral infection. HIV, CMV, VZV, parvovirus B19.
Drug-induced vasculitis	Ergot alkaloids
Cholesterol embolus disease	
Antiphospholipid syndrome	
Malignancy	Hairy cell leukaemia, carcinomas
Atrial myxoma	

The Skin

The skin is commonly involved. Many cutaneous vasculitides are, however, benign, self-limiting conditions confined to the skin and responsive to simple measures. However, the same clinical manifestations may also indicate the presence of a far more sinister, systemic necrotising vasculitis (SNV). The most common specific dermal lesion is palpable purpura. It develops most frequently near the ankle consisting of pinhead size, non-blanchable, red lesions from extravasated RBCs. Thrombocytopaenic purpura, of any causation, is, on the other hand, not palpable. Another fairly specific lesion is 'livedo reticularis', a reticulate pattern of skin vascularity delineated by small and medium vessel involvement. Other lesions include nodules and plaques that may, or may not, ulcerate, infarcts, ulcers, pyoderma gangrenosum, widespread skin necrosis and gangrene (Figure 3). Skin biopsy, from the edge of the lesion, is often very helpful in establishing a diagnosis.



Figure 3: Late in the process. Vasculitic lesions and early gangrenous changes are obvious.

Skin histology, however, is a poor predictor of clinical course. Several other skin lesions including macules, papules, vesicles, blisters and small bullae have been described in patients with vasculitis. Urticarial wheals are a feature of hypocomplimentaemic vasculitis, a benign disorder confined to the skin.

Muscles and Joints

Arthralgia, arthritis, (indistinguishable from rheumatoid arthritis) myalgia and weakness (like in polymyositis) are common non-specific complaints. Biopsy from involved muscles has a high yield for histologic confirmation of the diagnosis. Jaw claudication during mastication, is an important 'red flag' symptom in temporal arteritis.

Eyes, Ear, Nose and Throat

Scleritis, especially involving the perilimbic area (**Figure 4**), ring ulceration with corneal melt, scleromalacia, perforation of the globe, uveitis and retinal vasculitis are the usual ocular abnormalities. Recurrent otitis media often unresponsive to grommet insertion, hearing loss, perforation of the drum, recurrent, recalcitrant sinusitis, nasal septal perforation, a collapsed bridge of the nose, and severe oral ulceration are other manifestations.



Figure 4: Severe scleritis in a patient with vasculitis. Limbal ulceration is also seen in the picture.

Airways and Lungs

Trachea and bronchi are characteristically involved in Wegener's granulomatosis (WG) leading to stenosis, stridor and ventilatory compromise. Stridor is a 'red flag' symptom. Lung lesions include

Table 6: Aetiopathogenic Classification of the Vasculitides Incorporating the Modified CHCC Classification by Lie, Pathogenic Mechanisms and Infections

Dominant Vessel	Primary Vasculitis	Pathogenesis	Secondary Vasculitis	Pathogenesis	Infections
Large arteries	Giant cell arteritis Takayasu's arteritis	T-cell mediated	Aortitis of RA		*Staphylococcus*, *Salmonella*, Syphilis, *Aspergillus*, Mucor, Coccidiomycosis
Medium arteries	Classical polyarteritis nodosa	Immune complex related	Hepatitis B virus related PAN	Immune complex disease	*Streptococcus*, *Mycobacterium tuberculosis*, HBV, HCV, HIV, parvovirus B19
	Kawasaki's disease	Antibody-mediated hypersensitivity			
Small and medium vessel arteritis	Wegener's granulomatosis	Antibody-mediated (ANCA)	Vasculitis of RA, SLE, Sjögren's syndrome	Immune complex disease	*Streptococcus*, *Staphylococcus*, *Mycobacterium tuberculosis*, *Aspergillus*, Mucor, HBV, HCV, HIV, CMV
	Churg-Strauss syndrome	Atopic, hypersensitivity (ANCA)	Drug-induced		
	Microscopic polyangiitis	Antibody-mediated (ANCA)			
Small vessel vasculitis (leucocytoclastic)	Henoch-Schönlein purpura	Immune complex-mediated	Drug-induced		*Staphylococcus*, *Streptococcus*, *Salmonella*, *Mycobacterium*, *Yersinia*, *Nisseria*, *Rickettesial*, HIV, CMV, VZV, parvovirus B19
	Essential mixed cryoglobulinaemia	Immune complex-mediated			
	Cutaneous leucocytoclastic vasculitis				

Table 7: Clinical Features of the Major Vasculitides Encountered Clinically with Relative Frequency of each Area of Involvement

	Henoch-Schönlein Purpura	Microscopic Polyangiitis	Wegener's Granulomatosis	Churg-Strauss Syndrome	Classic Polyarteritis Nodosa
Purpura	4+	3+	1+	2+	Rare
Peripheral nerves	1+	2+	2+	2+	2+
CNS	1+	1+	1+	2+	1+
Glomerulonephritis	2+	4+	4+	2+	*
Alveolar haemorrhage	1+	2+	2+	1+	*
Pulmonary cavities infiltrates	1+	2+	4+	4+	*
Upper airways	Rare	1+	4+	2+	1+
Ears	1+	1+	3+	Rare	Rare
Eyes	Rare	2+	3+	2+	1+
Coronary arteries	Rare	1+	1+	3+	2+
GI tract	3+	2+	1+	2+	2+
Joints	3+	3+	3+	2+	2+

*1+ reported (< 10%), 2+ common (10-40%), 3+ very common (50-70%), 4+ almost invariable (> 70%); * not possible as per Chapel Hill definition.*

infiltrates, nodules, cavities, mass lesions, 'abscesses', areas of consolidation and haemorrhage. Clinical features comprise of cough, chest pain, expectoration, haemoptysis and respiratory failure. Large pleural effusions are uncommon. Cavitating nodules are highly suggestive of vasculitis. Metastases and disseminated infection need to be excluded.

Heart

Pericardial and myocardial involvement is commonly seen at necropsy but is rarely of great clinical significance. Coronary arteritis leading to significant ischaemic injury is associated with Kawasaki's disease and classic polyarteritis nodosa.

Gastrointestinal Tract

Gastrointestinal manifestations are caused by bowel ischaemia. Symptoms range from mild abdominal angina to those of perforation and peritonitis. The later carry a grave prognosis. In a patient with established vasculitis and in those with an obscure multisystem disease, abdominal pain, emesis, intestinal obstruction and bleeding are important 'red flags' that warrant immediate investigation and treatment.

Haemobilia and hepatic infarction especially in polyarteritis nodosa (PAN), splenic infarcts, pancreatitis, and a syndrome resembling inflammatory bowel disease have been reported.

Kidneys

Renal lesions due to vasculitis are diverse. Large vessel disease results in ischaemia and renovascular hypertension. Medium vessel involvement leads to infarction and haematomas within and around the kidney while small vessel disease is associated with glomerulonephritis. This can vary from mild, focal or segmental disease to rapidly progressive, crescentic involvement leading to significant, often life-threatening, renal failure. Glomerular lesions may show immune complex deposition or could be pauci-immune as in the ANCA associated vasculitides. In patients with suspected vasculitis, proteinuria, microscopic haematuria and active urinary sediment, in the absence of infection, should start alarm bells ringing for urgent management.

Reproductive Organs

Testicular infarction, presenting like torsion, is common in medium vessel vasculitis like PAN. Penile ulcers on the glans and shaft are uncommon but reported. These, and scrotal ulcers are, however, frequently seen in Behçet's syndrome.

Nervous System

Mononeuritis multiplex and polyneuritis cranialis are the most important 'red flags' suggesting a vasculitic process. Diffuse brain dysfunction is possible consequent to metabolic disturbances like renal and respiratory failure or sepsis.

CLINICAL SUSPICION

Acute progressive palpable purpura, ulcerating nodules and plaques, skin infarction or necrosis, and impending gangrene of unidentifiable cause, all suggest systemic vasculitis which must be investigated (**Tables 8 and 9**) and treated expeditiously (**Table 10**). These lesions are an important warning to physicians at the onset and relapse of SNV.

In patients without skin involvement, diagnosing SNV can be difficult. A high index of suspicion is essential to link apparently unrelated, seemingly unimportant and unexplained manifestations together. Chronic unresolving sinusitis, obstinate otitis media, recurrent or poorly responsive scleritis, severe constitutional symptoms without specific laboratory abnormalities, pulmonary 'tubercular' infiltrates unresponsive to adequate antitubercular drug therapy, non-resolving pneumonia despite adequate antibiotic therapy, abdominal angina in a young person, unexplained gastrointestinal bleeding, failure to recover from a 'successful' appendectomy, testicular 'torsion' in a young hypertensive, unexplained haematuria, and all the 'red flags' mentioned above should prompt the question 'Could this be a systemic vasculitis?' (**Table 11**).

If more than one system is involved, (e.g. otitis media in a patient with 'pulmonary TB', abdominal pain and mononeuritis multiplex in a young hypertensive) it is easy to answer in the affirmative. However, even when only one system is involved, a less than optimal response to standard therapy should be enough to start investigating along these lines. In desperately ill patients with an unexplained, rapidly progressive, systemic disease, it is justifiable to initiate life-saving treatment after eliminating sepsis.

INVESTIGATION

Investigations are listed in Table 8.

Table 8: Essential Investigation for Patients with Suspected Systemic Vasculitis

Haematology	Hb, TLC, DLC, platelet count, ESR (preferably Westergren method)
Biochemistry	Renal and hepatic function, serum albumin, globulin, alk. Phosphatase, CRP (quantitative) or other acute phase reactants*
Urine	Protein, microscopy and culture
Microbial	Blood culture, cultures for fungi*
Serology	ANCA, RF, ANA, hepatitis B and C, cryoglobulins, GBM*
Imaging	Chest radiograph, CT of head, chest and abdomen*, angiogram*, echocardiogram
Histology	Biopsy from involved area essential to confirm diagnosis

**Denotes tests that may be indicted in some, but not for all, patients.*

Routine

Systemic inflammation, the hallmark of SNV, can be established by an elevated ESR, leucocytosis, thrombocytosis, normocytic, normochromic anaemia, hypoalbuminaemia, hyperglobulinaemia and elevated acute phase reactants like CRP. Urine analysis and microscopy help establishing renal involvement. Appropriate culture to exclude infection must be done.

Serology

Serologic tests help in distinguishing between primary and secondary vasculitis. Rheumatoid factor (RF) is frequently positive in patients with vasculitis. High titres are, however, a hallmark of systemic rheumatoid vasculitis.

Anti-nuclear antibodies (ANA) are present in high titres in patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SS) and other overlap syndromes. When these conditions are responsible for vasculitis, a positive ANA, contributes significantly to the correct diagnosis. Positive tests for Hepatitis B and Hepatitis C virus help in the diagnosis of classic polyarteritis nodosa (cPAN) and cryoglobulinaemic vasculitis due to essential mixed cryoglobulinaemia (EMC). Anti-glomerular basement membrane (GBM) antibodies, in patients with the pulmonary renal syndrome, indicate Goodpasture's syndrome.

ANCA

Anti-neutrophil cytoplasmic antibodies (ANCA) have added a new dimension to the study, understanding and classification of the vasculitides (Table 9). Serum with ANCA produce three basic patterns at indirect immunofluorescence (IIF). The classic cytoplasmic, or C-ANCA, shows central, coarse, dense, granular fluorescence. Perinuclear, or P-ANCA, shows perinuclear fluorescence and atypical ANCA shows a mixed pattern. The antibody specificities and clinical correlation of each pattern are listed in Table 9.

ANCA testing, using IIF and ELISA, is essential in the investigation of all patients with presumed vasculitis. While ANCA is positive in high titres during the acute phase of the ANCA associated vasculitides, there is poor correlation between titres and clinical disease activity.

Table 9: Anti-neutrophil Cytoplasmic Antibodies (ANCA). Indications, Methods, Patterns, Antigens, Associations and Interpretation

Indications for testing

- Suspected systemic necrotising vasculitis
- Pulmonary renal syndromes
- Sub-glottic stenosis and tracheobronchial pathology
- Retro-orbital, nasal, paranasal sinus related mass/destruction
- Scleritis, scleromalacia, limbal inflammation, recurrent/unresponsive

Methods used

- Indirect immunofluorescence (IIF) using unstimulated, ethanol fixed human neutrophils for pattern
- ELISA for antibody specificity

Patterns and antigens

- C-ANCA coarse granular central fluorescence linked to anti-serine proteinase 3(PR3).
- P-ANCA perinuclear linked to anti-myeloperoxidase (MPO), lactoferrin, cathepsin G, elastase, defensins, azurocidin, BPI (bactericidal permeability increasing protein), lysozyme, etc. All neutophilic granular proteins with antimicrobial functions.

Associations

- C-ANCA (anti-PR3), WG (> 90% in active disease), MPA (about 10% in active disease), CSS (50-60% in active disease)
- P-ANCA, (anti-MPO), MPA (70-90% in active disease), WG (< 10% in active disease)
- P-ANCA and indeterminate staining ANCA, (non-MPO), inflammatory rheumatic diseases, RA, Felty's syndrome, SLE, juvenile arthritis, systemic sclerosis, inflammatory bowel disease, autoimmune hepatitis, crescentic glomerulonephritis, sepsis, infective endocarditis, malaria, tuberculosis, Hansen's disease, onchocercosis, bronchiectasis, cystic fibrosis, drug-induced vasculitis, lung cancer and other neoplasia

Interpretation

- C-ANCA with anti-PR3 in the clinical setting of WG is highly suggestive of WG
- C-ANCA with anti-PR3 is positive in only the rare patient with MPA
- P-ANCA with anti-MPO in the clinical setting of MPA is highly suggestive of MPA
- P-ANCA, non-MPO, is not diagnostic of any condition
- P-ANCA, anti-lactoferrin and anti-elastase in the appropriate setting support drug-induced vasculitis
- P-ANCA anti-cathepsin G and anti-lactoferrin in the appropriate setting support inflammatory bowel disease

Imaging

Clinical diversity precludes the development of a radiologic protocol suitable for all patients. A chest radiograph is essential and may show a variety of lesions. Nodular cavitating infiltrates are characteristic of WG. On serial examinations, they may also migrate. Unresolving or rapidly progressive consolidation during adequate antitubercular or antibiotic therapy, also suggests a vasculitis. Pulmonary haemorrhage (WG, MPA) manifests as a rapidly enlarging parenchymal lesion. Angiography, CT, MRI and PET scans help with diagnosis, delineation of disease extent, identification of a biopsy site and monitoring response to therapy.

Patients with large vessel vasculitis like Takayasu's need angiography to define the extent of disease, classify it and identify areas for intervention like angioplasty and stent insertion. Angiography may show the pathognomonic visceral aneurysms in PAN.

Histology

Histologic proof of vasculitis remains the gold standard. Every possible attempt should be made to identify and biopsy the involved tissue (**Figure 1**). Skin lesions are an obvious first choice. However, it must be emphasised that the same histologic findings may be observed in patients with benign cutaneous vasculitis and SNV.

If the kidneys are involved, renal biopsy is often helpful. While it is usually not possible to distinguish between WG and MPA based on renal glomerular histology alone, granulomatous inflammation, is present, supports WG.

In the presence of mononeuritis multiplex, a sural nerve biopsy may reveal vasculitis of the vasa nervosum. Similarly, mucosa of the sinuses and nose may be sampled if the area is involved. Biopsy from these sites is limited by the size of the sample that can be safely taken and many pieces may be needed to establish the diagnosis. Vasculitis is often a patchy process and may be completely missed in a small biopsy. Open lung biopsy is a safe and highly rewarding procedure in patients with obscure lung shadows. As relatively large samples can be taken, they provide excellent material for diagnosis.

Differential Diagnosis

The vasculitides have many mimics (**Table 5**). Their treatment is different hence, they need to be excluded.

Decision to Treat

While patients with benign cutaneous or a slowly progressive disease allow time for histologic confirmation, seriously ill patients do not. As these patients carry a high mortality risk, institution of therapy is of paramount importance. The five factor clinical score is an excellent simple objective measure of the gravity of the clinical situation. In patients with SNV, the presence of renal failure, proteinuria more than 1 gm/24 hours, gastrointestinal involvement, CNS manifestations or cardiomyopathy are each accorded a score of one. Over 2 years, patients with a total score of 0 had a mortality of 12%, those with 1, 26% and those with 2, 46%. Clearly, patients with visceral disease should receive prompt and aggressive treatment, frequently on empirical grounds. Infections are also common in such patients, before, during and after immunosuppressive therapy. Frequently, the two are inseparable and need to be treated simultaneously. The vasculitides and their mimics are frequent among patients presenting to the emergency departments. Diagnosis is delayed at survival peril. **Table 10** lists the problems that must raise the question of a possible vasculitis in this group.

TREATMENT (TABLE 11)

Vasculitis caused by infection should be treated with the appropriate antimicrobial agents and surgical intervention. Results are good if instituted early.

Benign cutaneous vasculitic conditions generally respond well to low dose steroids, antihistaminics to suppress itching, dapsone and exposure of ulcerated areas to ultraviolet light. The occasional unresponsive patient may be helped with azathioprine or methotrexate. It is very unusual for isolated cutaneous vasculitis to require aggressive immunosuppressive therapy.

Patients with SNV mandate the use of high dose corticosteroids, cytotoxic and other immunosuppressive agents (**Table 10**). The NIH protocol, the first successful treatment plan for these conditions, commenced with oral prednisolone (1 mg/kg/day) and cyclophosphamide (CYC) (2-3 mg/kg/day). Steroids were tapered off and stopped within 6 months, but CYC continued in the same dose for a year after remission was attained. Thereafter, it was tapered gradually. This treatment revolutionised the management of these conditions. Before its development, 5-year survival for SNV like WG was less than 5% to 7%. With treatment, it increased to 75% to 85%. Problems related to treatment, like haemorrhagic cystitis and bladder cancer due to CYC, marrow toxicity, a high relapse rate after withdrawal, and infection gradually emerged. The search for an ideal regimen has, thus, continued.

Table 10: Emergency Medicine, Presentations to the Emergency Department, Symptoms and Signs

Presentation	Organ/System Involved	Manifestations
Very acute	Lungs	Pulmonary haemorrhage, respiratory failure, anaemia, increased DLCO, bronchopneumonia
	Airways	Stridor due to tracheomalacia
	Kidneys	Acute, rapidly progressive renal failure, haematuria, infarction, accelerated hypertension
	Urinary/genital tract	Haematoma, ureteric obstruction, bladder neck obstruction, testicular infarction
	Nervous system	Mononeuritis multiplex, polyneuritis cranialis, infarction, stroke, retinal ischaemia
	GI Tract	Perforation and peritonitis, intestinal ischaemia, occasionally bleeding
	Heart	Acute coronary syndrome
	Liver and biliary tract	Infarction, haemobilia, pancreatitis
Acute	Lungs	Pulmonary nodules and infiltrates, consolidation, compromised airway
	Kidneys	Loin pain, haematuria, worsening renal function, proteinuria with active sediment
	Urinary/genital tract	Testicular pain, hydronephrosis, perirenal haematoma
	Nervous system	Focal neurologic defect
	GI Tract	Abdominal angina
Indolent with acute exacerbation	The patient	With polymyalgia rheumatica, red eye, chronic sinusitis, worsening or miraculously improved asthma, oral ulceration, new onset hypertension, fever, arthralgia, non-specific skin rash, with recent onset palpable purpura and other systemic features in permutations and combinations beg the question, 'Is this a vasculitis?'

Table 11: Management of Vasculitis with Risk and Extent Stratification (* = very rarely used)

Distribution	Progression	Involvement	Investigation	Eliminate	Initiate Therapy With	Therapy for Poor Response
Cutaneous	Slow	Skin alone	All listed + biopsy	All mimics	Steroids	Azathioprine, Methotrexate, Dapsone, Cyclophosphamide
Systemic	Slow	Skin, joints, polymyalgia ENT	All listed + biopsy	All mimics especially chronic infections	Steroids + Methotrexate	Azathioprine, Cyclophosphamide, Mycophenolate mofetil
Systemic	Slow initially, with acceleration	Above + Kidney, CNS GI tract, heart, lungs liver, spleen	All listed + biopsy if possible	All mimics especially Infections and tumours	There is a place for empirical therapy Steroids + Cyclophospha-mide ± Plasmapheresis	Azathioprine, Mycophenolate mofetil, Cyclosporin, biologic therapy
Systemic	Rapid	As above + Lung haemorrhage, rapidly progressive renal failure, focal CNS defect, Multiple organ/ system involvement, GI perforation	As much as possible	Infection	Empirical high dose IV methyl-prednisolone + IV Cyclophospha-mide ± Plasmapheresis and Antibiotics (if infection not clearly eliminated), ventilation, dialysis, ICU measures with monitoring of fluid therapy, electrolytes and organ/ system support Surgery (as indicated)	Addition of another drug like azathioprine may help some. Anti TNF therapy may be helpful. Rituximab has helped (Other useful agents are listed in text)

Currently, the use of intermittent 'pulse' CYC (750 mg/m^2) has gained ground. It is used every 2 to 3 weeks initially for 2 to 3 doses and then every 4 weeks till six 'pulses' have been administered. With steroids, this treatment is very successful in inducing a remission. This form of therapy also results in lower infection rates and a far lower cumulative dose of CYC to achieve remission. This should lead to reduced rates of secondary malignancy. Once remission is achieved, recent trials have established that they can be maintained using azathioprine or methotrexate.

Some forms of vasculitis have been shown to respond very well to specific interventions. Temporal arteritis is very responsive to corticosteroids. Infusions of immunoglobulins are very useful for Kawasaki's disease, while Behçet's disease responds to colchicine, azathioprine, cyclosporine and thalidomide. Patients with cryoglobulinaemia and hepatitis B related classic PAN respond well to plasmapheresis to achieve initial control and subsequently to antiviral drugs.

Several patients, however, do not respond to conventional therapy described above. Alternate regimens incorporating mycophenolate mofetil, deoxyspergualine, and several monoclonal antibodies have been tried with variable success. Patients with vasculitis, on treatment, need to be carefully monitored for side effects and complications of these toxic regimes. Those on CYC should be encouraged to drink plenty of water to avoid cystitis, and possibly cancer.

Further treatment depends on the demonstration of relapse. All patients with vasculitis and specially those with the life-threatening SNV need to be closely followed, preferably with objective systems of record keeping. The Birmingham Vasculitis Activity score is one such instrument that permits, on a single page, a comprehensive record of each clinic visit with a numerical expression of both improvement and deterioration.

IMPORTANT INDIVIDUAL VASCULITIDES

Large Vessel Vasculitis

Takayasu's arteritis

Takayasu's arteritis (TA) is relatively common in India while temporal arteritis is extremely rare. TA affects young people who present with symptoms and signs of ischaemia involving the ocular, cerebral, renovascular, cardiopulmonary, limb, and splanchnic circulation in various permutations and combinations. The disease is classified according to the angiographic pattern of aortic involvement. Very few patients present with acute vascular inflammation. Most of them present with established stenotic or rarely, aneurysmal lesions. The common clinical findings are absent pulses, asymmetric blood pressure measurements and vascular bruits. If present, tenderness over the involved vessels, specially the carotids (carotidynia) is an important sign of active disease. Treatment with immunosuppressive regimens suppresses active inflammation but has only marginal effect on vessel patency. Patients with critical stenosis require angioplasty with stent insertion or surgical revascularisation for relief from ischaemia.

Temporal arteritis

Giant cell arteritis (GCA) is a disease of older people characterised by headache, polymyalgia rheumatica, and a distended, tortuous, thickened and sometimes tender temporal artery. Jaw claudication is an important symptom and blinding serious retinal ischaemia develops in several patients. The ESR is often over 100 mm and ultrasonography of the artery is helpful in identifying areas of involvement. The disease usually responds very well to corticosteroids alone.

Medium and Small Vessel Vasculitis

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a disease of protean manifestation with involvement of several organ systems. There is a close association between hepatitis B virus infection and PAN, and it was also the first vasculitis which was successfully treated with antiviral drug therapy. Patients usually have a nondescript febrile illness with loss of weight and other constitutional symptoms. However, most patients develop additional features like hypertension, mono or polyneuropathy, testicular pain, myalgia, and muscle weakness and renal insufficiency. Some patients will develop signs and symptoms of intestinal obstruction/perforation, renal, hepatic and splenic infarction. Investigations are usually not very specific but angiography may demonstrate the almost pathognomonic micro-aneurysms. Only an occasional patient is ANCA positive. Treatment has made a great difference to the outcome. When no effective treatment was offered, the median survival was three months. Today, with the appropriate use of steroids and cytotoxic drugs, five years survival has increased to over 80%. Classic PAN is often a 'one shot' illness and relapses are less frequently observed than in other SNVs.

Churg-Strauss syndrome

This entity is also called allergic angiitis and granulomatosis. The dominant feature is asthma and eosinophilia. The asthma may be long standing or of relatively recent origin. At the start of the vasculitic phase, most patients complain of severe worsening and unresponsiveness of previously controlled asthma. However, in some patients asthma may almost vanish at the time vasculitis develops. Cardiac and skin involvement is common in this disorder. Histology reveals vasculitis and an extravascular eosinophilic granuloma. Significant renal involvement is rare compared to other systemic vasculitides. Most patients respond adequately to corticosteroids but a few may require cytotoxic drug therapy.

Wegener's granulomatosis

This entity shows very wide clinical variations. It is compatible with several years of survival at one end of its clinical spectrum and death within days at the other. The upper airways, lungs and kidneys are the most commonly involved areas; however, no organ system is consistently spared.

Patients may present with severe ocular inflammation including scleritis, uveitis, corneal ulceration, dacryocystitis, lid ulcers and proptosis. Ear involvement includes severe unresponsive otitis media, perforation of the drum, bleeding and deafness. Nasal manifestations include extensive crusting, discharge, bleeding, perforation of the septum and a saddle nose deformity. Pulmonary manifestations include cough, sputum production, haemoptysis and pulmonary haemorrhage. The chest radiograph may show infiltrates, nodules, cavities or consolidation. Renal involvement is in the form of pauci-immune focal, segmental or crescentic glomerulonephritis with or without renal failure.

In many patients, WG starts as an indolent, locally confined, inflammatory disease. This, 'granulomatous' phase may last from weeks to several years before the aggressive 'vasculitic' phase supervenes. In patients from northern European origin, a prolonged indolent phase enables the diagnosis to be made while the disease is confined to a single area. In India, however, it appears that this phase is abbreviated. Well over half of our patients presented with established widespread systemic involvement.

The clinical similarity with pulmonary tuberculosis has often delayed consideration of WG. A very large number of the patients with WG in India had, and continued to receive anti-tubercular drug therapy in spite of continued clinical deterioration. There are a few pointers that may help to distinguish between these two. Ocular, ear, paranasal sinus, and nose involvement as well as vasculitic skin involvement and renal insufficiency are very uncommon in patients with tuberculosis. The presence of any of these features should raise suspicion and a diagnosis of WG should be considered. Radiologically, the infiltrates in TB are usually apical and the cavities are in the upper zone. However, in WG, infiltrates and cavities are more in the middle and lower zones of the lung. The demonstration of C-ANCA is useful however, rare patients with TB are P-ANCA positive so, the testing must be done carefully.

WG is treated with a combination of steroid and cytotoxic drugs for variable duration depending upon the response. Given the possible complications of the disease and its treatment, such patients should be treated in a specialised unit with adequate experience. Untreated WG had a mean survival of a few months. Renal failure, apart from pulmonary haemorrhage and widespread vasculitis are the usual causes of death in the first year. Later, destructive pulmonary disease and respiratory failure become more important. With adequate therapy more than 90% of patients should achieve a clinical remission.

Systemic rheumatoid vasculitis

This complication develops in patients with longstanding seropositive rheumatoid arthritis and carries a poor prognosis. The usual manifestations include new or worsened constitutional symptoms, cutaneous leucocytoclastic vasculitis and mononeuritis multiplex. Treatment should include steroids and cytotoxic drugs.

Small Vessel Vasculitis

Microscopic polyangiitis

This disorder was initially considered to be a variant of PAN. It has now come to be recognised as an independent entity with closer similarity to WG. While its renal manifestations and alveolar haemorrhage are very similar to WG, its other manifestations, including involvement of the skin, the nerves, and GI tract resemble PAN. Serologically, 90% of patients are P-ANCA positive. There are no granulomata seen at histology.

The dominant clinical features are due to a pauci-immune glomerulonephritis. Other features include pulmonary haemorrhage, cutaneous vasculitis, mononeuritis, joint pains, hypertension, GI tract involvement and occasionally CNS involvement. The disease responds to immunosuppressive treatment protocols useful for WG.

Henoch-Schönlein purpura

This condition predominantly affects children and young adults. The typical presentation includes palpable purpuric skin lesions, GI tract involvement with bleeding, arthralgia and glomerulonephritis. In most instances, it is a self-limiting condition and does not require treatment. However, the presence of severe bowel involvement and other atypical features like focal neurologic deficit, pulmonary haemorrhage and rapidly progressive renal failure warrant steroid and/or cytotoxic drug therapy even though their efficacy has not yet been established in a clinical trial. These complications are more frequently observed in adult patients.

Cutaneous leucocytoclastic vasculitis

Vasculitis confined to the skin producing infarcts, nodules, ulcers and very occasionally, gangrene is common. These patients should be investigated for the presence of systemic disease and if found negative can be treated with low doses of steroids and immunomodulating agents like dapsone.

Behçet's syndrome

This vasculitic disease entity has a pronounced geographical distribution, from Turkey to Japan *via* Iran and also the northern part of India. It affects young people and is more virulent in males. The dominant clinical manifestations are of painful oral and genital ulcers, a variety of skin lesions, severe, vision threatening ocular inflammation, arthralgia, focal CNS dysfunction, aseptic meningitis, colonic ulceration, aneurysms and venous thrombosis. There is a strong association with HLA B51 and it is the leading cause of blindness in Japan. The course is relapsing and remitting. However, the intensity wanes with advancing age. A variety of agents have been found to be useful including steroids, cytotoxic drugs, cyclosporine, thalidomide, colchicine, antibiotics and anti-TNF therapy.

Kawasaki's disease

This, predominantly childhood, vasculitis has a strong affinity for the coronary arteries. Most patients are under 5 years of age. Fever, conjunctival congestion, inflamed oral mucosa, cervical non-suppurative lymphadenopathy and cutaneous manifestations are the major features. Immunoglobulins have been found to be very effective in treating this condition. Follow-up echocardiograms may reveal the development of coronary aneurysms.

Cogan's syndrome

Is a rare disease of young adults characterised by non-syphilitic interstitial keratitis, recurrent symptoms like Meniere's disease and large vessel vasculitis, frequently involving the aorta and its major branches. Other features include joint pain, fever, abdominal pain, intestinal bleeding, hepatosplenomegaly and lymphadenopathy. While ocular involvement may respond to topical steroids, ear involvement requires systemic treatment. Vasculitis requires aggressive immunosuppressive therapy as outlined above.

Primary angiitis of the central nervous system

It is a rare disorder characterised by focal, or occasionally diffuse, neurologic involvement, MRI abnormalities and characteristic angiographic appearances without any other systemic features. Biopsy reveals a granulomatous angiitis in many patients. Treatment with steroids and cyclophosphamide is successful if the diagnosis is made early.

THE CHALLENGE

Thinking that a vasculitis could be responsible for the patient's problems is the biggest hurdle we need to cross. Treatment is very rewarding but entails hard work. Due to the multi-system nature of these disorders, the development of a multi-disciplinary team greatly facilitates patient management.

RECOMMENDED READING

1. The Vasculitides, Section 11 in Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH (editors), Rheumatology; 3rd Ed. Mosby; 2003: pp 1583-715.

24.13 Mixed Connective Tissue Disease and Overlap Syndromes

G Narsimulu, Vara Prasad IR

DEFINITION

Mixed connective tissue disease (MCTD) is a disease characterised by combination of clinical features of systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis (PM), and rheumatoid arthritis (RA). MCTD is considered as a distinct clinical entity because of the presence of very high anti-U1RNP antibody. A few authorities consider MCTD as a subset of SLE or scleroderma.

EPIDEMIOLOGY

The prevalence is four times less than that of SLE indicating an overall prevalence of 10/100,000. The peak onset of the disease is in the second and third decade, but it can occur in children and elderly also. The female to male ratio is 9:1.

IMMUNOPATHOLOGY

U1nRNP is a subunit of spliceosomes. Spliceosomes are complex nuclear particles involved in the processing of premessenger RNA into mature spliced RNA. Two subunits of spliceosomes are antigenic targets in autoimmunity. These are:

1. Small nuclear ribonucleoprotein particles (snRNPs).
2. Heterogenous nuclear RNP (hnRNP).

The snRNP contains small RNAs that are complexed with proteins. These RNAs contain a high content of uridine and are, therefore, called U RNAs. Five different types of URNAs are defined on the basis of immunoprecipitation (U1, U2, U4, U5, and U6). Autoantibodies to these complexes are mainly directed to the protein components. Antibodies directed exclusively against U1 subunit are known as antiU1RNP antibodies. They precipitate three proteins with molecular weight of 68000, 33000, and 22000. The clinical correlates of MCTD appear to be most closely associated with antibodies to the 68 kD and the 33000 proteins of the U1 RNP complex. A proposed model of RNP self antigen-driven autoimmunity is shown in **Figure 1**.

The characteristic lesions in the involved organs are intensive obliterative proliferative vascular lesions in large, medium and small vessels with less inflammatory infiltrates. There is increased synthesis of type III collagen leading to abnormal type I to type III ratio, unlike scleroderma where the ratio is maintained.

CLINICAL FEATURES

The various features of the connective tissue disorders making up MCTD develop over many months or years. The presenting symptoms are Raynaud's phenomenon, puffy hands, arthralgia, myalgia and fatigue. The fingers as well as the entire hand may become puffy.

SKIN AND MUCOUS MEMBRANE

Skin manifestations include Raynaud's phenomenon, sclerodactyly, skin tightening, photosensitivity, malar rash, and the rash of dermatomyositis and panniculitis. Sclerodermal changes are usually limited to the distal extremities and sometimes the face but spare the trunk. Telangiectasia and calcinosis may also occur. Other lesions include oral uclerations, sicca symptoms, orogenital ulceration, livedo vasculitis, and nasal septal perforation.

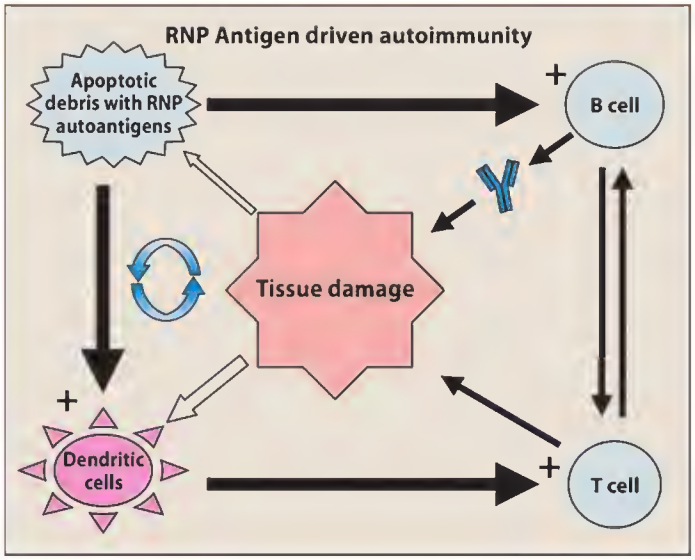


Figure 1: Model of RNP self antigen-driven autoimmunity. Self antigen (including 68kD and U1-RNP) triggers both the innate and adaptive arms of the immune system and breaks immunologic tolerance. Activation of B cells and dendritic cells leads to autoantibody production and also activate T cells leading to tissue damage.

Joints

Joint pains, stiffness and non-erosive peripheral arthritis are common. Joint involvement in MCTD is more common and more severe than seen in SLE. Deformities can occur but joint erosions are uncommon.

Muscle

Myalgia is a common symptom. Myositis also occurs frequently, but most often without significant demonstrable weakness, electromyographic changes or muscle enzyme elevation. Sometimes, it may present as inflammatory myositis with anti-U1RNP antibody without other features of MCTD.

Lung

About 85% of patients have pulmonary involvement, which is often asymptomatic. Low diffusion capacity for carbon monoxide may be the only abnormality. Pleurisy commonly occurs, but is seldom associated with large pleural effusion. Interstitial lung disease (ILD) also is well described in MCTD. HRCT is a sensitive tool to determine the presence of ILD in MCTD. Pulmonary hypertension is the most common cause of death in MCTD. Pulmonary arterial hypertension (PAH) is usually caused by a bland intimal proliferation and medial hypertrophy of pulmonary arterioles. PAH may also be due to coexistent antiphospholipid (APL) antibodies.

Heart

All three layers of heart can be involved in MCTD. Pericarditis may occur in 10% to 30% of cases. Myocardial involvement also is described. ECG changes are seen in 20% cases. Arrhythmias, conduction disturbances and mitral valve prolapse also can occur.

Gastrointestinal System

Gastrointestinal involvement is seen in about 70% patients. The most common manifestations are oesophageal dysmotility, lower oesophageal sphincter laxity, and gastro-oesophageal reflux. Abdominal pain, malabsorption syndrome, and chronic active hepatitis also are described. Pseudodiverticula along the antimesenteric border of colon can occur like in scleroderma.

Kidney

Approximately 25% of patients develop renal disease. Membranous glomerulonephritis is the most common. It is usually mild, but can cause nephrotic syndrome. Diffuse proliferative glomerulonephritis (DPGN) is unusual in MCTD. This is believed to be due to the protective role played by the high titers of anti-U1RNP. Renal crisis secondary to malignant renovascular hypertension is seen in a few patients.

Central Nervous System

Central nervous system (CNS) involvement is rare in MCTD. Trigeminal neuropathy is the most common problem encountered. Vascular headache, aseptic meningitis, peripheral neuropathy, transverse myelitis and sensorineural hearing loss also are described.

Fever

Fever may be prominent feature, can present as pyrexia of unknown origin. Fever may be traced to co-existent myositis, aseptic meningitis, serositis, lymphadenopathy or intercurrent infection.

Haematology

Anaemia of chronic inflammation is seen in 75% of patients. Other abnormalities noted are positive Coombs' test, leucopaenia, thrombocytopaenia, thrombotic thrombocytopaenic purpura and red cell aplasia.

LABORATORY FINDINGS

The diagnosis of MCTD depends on the demonstration of antiU1RNP antibody in high titres. Antinuclear antibody positivity is seen in 100% of patients in high titre with coarse speckled pattern. This finding should prompt the measurement of antibodies to U1RNP, Sm, Ro and La. Anti U1RNP antibodies by haemagglutination test titre > 1:1600 is characteristic feature of MCTD. The absence of anti-Sm antibodies and anti-DNA antibodies in a patient seropositive for anti U1RNP is an important finding discriminating MCTD from SLE.

Other investigations show features common to connective tissue diseases in general. The most frequent haematological findings are leucopaenia, thrombocytopaenia and a high ESR. Serum immunoglobulins may be extremely high, with IgG concentrations reaching more than 40 g/l in some patients. In contrast to SLE, in MCTD the complement concentrations are usually normal or high. Rheumatoid factors are increased in approximately 70% of patients.

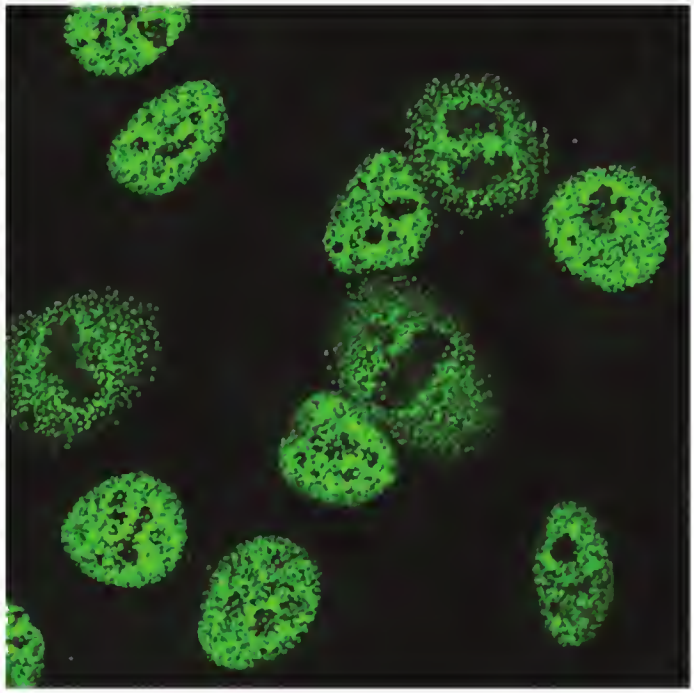


Figure 2: Indirect immunofluorescence on Hep-2 cells with a patient's serum containing anti-U1-RNP antibody. This shows speckled nuclear staining, with characteristic sparing of the nucleoli and negative staining of the chromosomes of the cell in early metaphase.

DIAGNOSIS

The diagnosis of MCTD is clinicoserologic. The two diagnostic criteria for MCTD that are widely employed are Alarcon-Segovia's Criteria and Kahn's Criteria.

Alarcon-Segovia's Criteria

(a) Serologic criteria: High titre anti RNP

(b) Clinical Criteria: Swollen hands, synovitis, myositis, raynaud's phenomenon, acrosclerosis

MCTD present if criteria A accompanied by 3 or more clinical criteria, one of which should be synovitis/myositis.

Kahn's Criteria

(a) Serologic criteria: High titre antiRNP >1:1600 with speckled ANA

(b) Clinical criteria: Swollen fingers, Synovitis, Myositis, Raynaud's phenomenon

MCTD present if criteria A is accompanied by Raynaud's phenomenon and two or more of the three remaining clinical criteria.

When myalagia replaces myositis in diagnostic criteria sensitivity increased to 81.3% from 62.5% with no change in specificity.

PROGNOSIS

The course of MCTD is unpredictable. In most of the patients it has a benign course. It is the major organ involvement that dictates the morbidity and mortality in an individual case.

MANAGEMENT

There is no specific treatment for MCTD. The treatment depends on the pattern of clinical involvement (**Table 1**).

Pulmonary hypertension being the most common cause of death, patients should be evaluated at regular intervals for its development. It should be suspected in patients with increasing breathlessness. Echocardiogram is the most useful screening test. A definitive diagnosis requires cardiac catheterisation showing a mean resting pulmonary arterial pressure more than 25 mmHg at rest.

Table 1: Guidelines for Managing MCTD

Problem	Treatment
Raynaud's phenomenon	Use gloves, keep warm, prevent finger trauma, stop smoking, avoid beta blockers
	Drugs: Nifedipine, Prazosin, bosentan
Arthralgia/Arthritis	NSAID's, hydroxychloroquine, methotrexate
Myositis	Acute severe: high dose Prednisone 60 to 100 mg/day
	Chronic, low grade: low dose Prednisone 10 to 30 mg/day methotrexate or IVIG
Pleurisy/Pericarditis	NSAIDs, low dose Prednisone 10 to 30 mg/day
Myocarditis	Steroids + monthly cyclophosphamide, avoiddigoxin
Nephrotic syndrome	Steroids + monthly IV cyclophosphamide/ daily/oral cyclophosphamide + ACE inhibitors + low dose aspirin and Dipyridamole to prevent thrombotic complications
Aseptic meningitis	High dose steroids
Dysphagia	Proton pump inhibitors and prokinetic drugs (mosapride, domperidone)
Digital gangrene	Anticoagulation, local chemical sympathectomy, endothelin receptor antagonist therapy

Analgesics and nonsteroidal anti-inflammatory drugs alone may be needed in one-third cases. Manifestations like aseptic meningitis, myositis, pleurisy, pericarditis and myocarditis usually respond to corticosteroids. Gloves and calcium channel blockers are useful in Raynaud's phenomenon. Arthritis and cutaneous manifestations respond well to antimalarial agents such as hydroxychloroquine. High dose steroids are indicated for the treatment of severe systemic disease such as vasculitis myositis, or interstitial lung disease. IV gammaglobulin or danazol can be tried in patients with steroid-resistant thrombocytopaenia, refractory myositis and haemolytic anaemia. Unless contraindicated, all patients should take supplementary calcium and vitamin D. Immunosuppressive drugs may be useful for induction of remission or for their corticosteroid sparing effects. The commonly used agents are azathioprine, cyclophosphamide and methotrexate.

OVERLAP SYNDROMES

Overlap syndromes occur when patients meet criteria for the diagnosis of more than one connective tissue disease. Raynaud's phenomenon, arthritis, and sclerodactyly are usually found in most of the overlap syndromes. For example, a patient with SLE who develops erosive arthritis in a distribution similar to RA, is labelled an overlap of RA and SLE. Usually one syndrome gradually takes on the features of another. Sometimes, the features of both diseases may occur concurrently. Sjögren's syndrome commonly overlaps with RA, SLE, Systemic sclerosis, PM, primary biliary cirrhosis, etc. MCTD is a serologic subset of overlap syndrome characterised by the presence of antibodies to U1RNP. Other overlap syndromes include SLE with polymyositis in 4% to 16% of cases, SLE with RA (positive rheumatoid factor, nodules and erosive arthritis) known as '*rhupus*'. Scleroderma can be associated with myositis and limited scleroderma with primary biliary cirrhosis (Raynold's Syndrome). The management of overlap syndromes is dictated by individual organ involvement and not by diagnostic labels. For example, the arthritis of SLE, RA or scleroderma is treated in a more or less similar fashion.

24.14 Inflammatory Muscle Diseases

Alakendu Ghosh, Pradyot Sinhamahapatra

INTRODUCTION

The idiopathic inflammatory myopathies (IIM) are a heterogenous group of acquired muscle disorders, presenting with muscle weakness, increased serum muscle enzymes, abnormal myogram and inflammatory changes in muscle histology. The three major entities in IIM are: polymyositis (PM), dermatomyositis (DM) and inclusion-body myositis. In all age groups, DM is the most common and PM is the least common. Inclusion-body myositis is the most common myopathy above the age of 50.

CLASSIFICATION

The classification is summarised in **Table 1**.

Table 1: Classification of Idiopathic Inflammatory Myopathies (IIM)

1. Primary idiopathic polymyositis
2. Primary idiopathic dermatomyositis
3. Polymyositis or dermatomyositis with malignancy
4. Juvenile dermatomyositis (or polymyositis)
5. Polymyositis or dermatomyositis associated with other connective tissue diseases
6. Inclusion body myositis
7. Rare forms of idiopathic myositis: Granulomatous myositis, eosinophilic myositis, focal myositis, orbital myositis, etc.

CLINICAL MANIFESTATIONS

PM is a subacute myopathy that evolves over weeks to months and presents with proximal muscle weakness. It affects adults, but rarely also children.

The patient presents with painless weakness of the proximal muscles of limbs, trunk and neck flexors over few months (55%), and sometime acute or subacute painful proximal weakness (30%). There may be some constitutional features. Uncommonly, the patient may present with a more indolent course over years, myalgia alone, or a rash alone in DM. Facial and bulbar weakness are rare and ocular weakness is not a feature of idiopathic PM. However, dysphagia due to oropharyngeal weakness occurs in one-third, and signifies poor prognosis.

DM is associated with characteristic cutaneous rash that accompanies muscle weakness (**Figure 1**). These skin manifestations include: (i) typical 'heliotrope' rash, which is a violaceous discolouration around the eyelids, may be oedematous, accompanied by an erythematous rash on the face (ii) Gottron's papules, which are erythematous scaly lesions on the hands, over bony prominences like the knuckles at the metacarpophalangeal and interphalangeal joints; (iii) the erythematous rash on the face, neck, and anterior chest (in many patients in a 'V' sign) or back and shoulders (Shawl sign), lateral



Figure 1: Dermatomyositis with skin rash.

thighs (Holster' sign); and (iv) dilated capillary loops at the base of the finger nails. DM affects both children and adults and women more than men. Juvenile DM may present with calcification. Calcinosis is associated with increased morbidity (**Figure 2**).

Inclusion body myositis (IBM) occurs over the age of 50 years and is more common in men. It usually affects proximal as well as distal muscles and can be asymmetric. Muscle atrophy and swallowing difficulty are prominent in IBM.

Facial and extraocular muscles are never affected. Neck extensor muscles may be involved causing head drop. Myalgia is uncommon occurring in 30% of patients.

IIM may be associated with a number of extramuscular clinical manifestations like fatigue, malaise, weight loss and low-grade fever. Pulmonary involvement in IIM is due to weakness of the thoracic muscles or interstitial lung disease (ILD) (around 40%) or aspiration pneumonia due to pharyngeal weakness. Cardiac involvement in IIM may include atrioventricular conduction disturbances and myocarditis/pericarditis. Joint contractures occur mostly in dermatomyositis. The patients can have dysphagia, or reflux. Gastrointestinal ulcerations due to vasculitis and infection are common in children with dermatomyositis.

Inflammatory myopathies can have association with malignancies in some organs like ovaries, gastrointestinal tract, nasopharyngeal, lung, breast, non-Hodgkin's lymphoma (NHL) specially in elderly people. The malignancy may be during antecedent, or subsequent to myositis onset.



Figure 2: Juvenile dermatomyositis (JDM) with calcinosis.

DIAGNOSIS

The clinical diagnosis of PM and DM is confirmed by three laboratory investigations: (i) serum muscle enzyme concentration, (ii) typical electromyography, and (iii) muscle biopsy histology. In addition, magnetic resonance imaging (MRI), MR spectroscopy can help localisation of extent and autoantibody testing helps in the evaluation.

Autoantibodies like antisynthetase or anti-SRP (signal recognition particles) are found in 20% of patients. Jo-1 antibodies predicted the persistent use of drugs. Antinuclear antibodies (ANA) may be positive in 50% to 80% and rheumatoid factor in 20% of patients (**Table 2**).

Age appropriate screening for malignancy (thorough clinical examination, colonoscopy, mammography, chest computed tomography (CT), abdominal with pelvic CT, stool occult blood, prostate specfic antigens (PSA), serum CA125, CA19-9) is recommended, especially in elderly patients with dermatomyositis, high erythrocyte sedimentation rate (ESR), and/or in presence of cutaneous necrosis on the trunk, cutaneous leucocytoclastic vasculitis, evidence of capillary damage in muscle biopsy.

The most sensitive muscle enzyme assay is creatinine kinase (CK), which is increased up to 50 times the normal upper limit in active disease. CK increases before clinical weakness and falls before clinical improvement. However, CK can be normal in some patients with active DM and late stages of polymyositis. CK levels are normal in corticosteroid induced myopathy. CK may be increased in a number of conditions (**Table 3**).

PM/DM may be associated with other connective disease usually termed as overlap syndrome. DM develops in up to 12% of patients with systemic sclerosis, PM in 5% to 8% of lupus patients.

Table 2: Clinical Profiles of IIM Based on Autoantibodies

Myositis specific antibodies		**Clinical features**
1.	Antisynthetase	PM/DM features, with acute onset muscle weakness; associated with fever, Raynaud's phenomenon, 'mechanic's' hand, interstitial lung disease (Antisynthetase syndrome) (Jo-1 with mainly PM features and other antibodies with mainly DM features)
2.	Anti-signal recognition particle (SRP)	PM features, with very acute onset and severe muscle weakness; cardiac involvement; poor response to treatment; high mortality
3.	Anti-Mi 2	DM features, with acute onset; associated with 'V' sign and 'shawl' design, cuticular overgrowth at fingers; good response to treatment
4.	Anti-MAS	PM features; acute onset; association with alcoholic rhabdomyolysis; good response to treatment
Myositis associated antibodies		**Clinical features**
5.	Anti-Ku and anti-PM-Scl	Associated with a PM and scleroderma overlap clinical picture
6.	Anti-KJ	Associated with PM features, Raynaud's phenomenon and interstitial lung disease
7.	Anti-U1-RNP	Associated with PM/DM overlap syndrome
8.	Anti-Ro/SSA and anti-La/SSB	Associated with DM/PM features and an overlap clinical situation with SLE or Sjögren's syndrome.

Needle electromyography can be helpful for detecting an active myopathic process, recognising that the process is consistent with IIM and excluding other neuropathies and some myopathies. The most common findings are low amplitude, short duration, polyphasic potentials. However, the

Table 3: Causes of Elevated CK Levels other than IIM

Following strenuous and/ or prolonged exercise:	**Muscle trauma:**	**Muscle diseases (other than IIM):**	**Drugs:**	**Endocrine/ Metabolic:**	**Others:**
An important, but often forgotten cause of an isolated elevation of CK	Injury Following EMG Needle stick Surgery	Infections: Viral, bacterial, protozoal or fungal Idiopathic: associated with other connective tissue disorders Dystrophies Metabolic Myocardial infarction Rhabdomyolysis	Toxic myopathy Causing myositis: D penicillamine Direct elevation by reducing the excretion of CK: barbiturates, morphine, diazepam	Hypothyroid Hypokalaemia Ketoacidosis or hyperosmolar state Renal failure Diabetic nephritic syndrome	CNS disease; cerebral ischaemia, head injury, psychosis, delirium tremens Tumours: gastrointestinal, bronchial Pneumococcal sepsis

characteristic triad is: (a) myopathic potentials, (b) fibrillations, positive sharp waves, increased insertional activity, and (c) complex repetitive discharges. Typical electromyographic features may not be present in 10% of patients.

The muscle biopsy is the gold standard and can provide definitive evidence for diagnosing IIM, but at the same time, most common cause of misdiagnosis due to erroneous interpretations. Biopsy should be performed on the side opposite to the electromyogram (EMG) study to avoid needle artifact. MRI might help localising the extent of muscle involvement. In PM multifocal endomysial CD8+ lymphocytic infiltration in histologically healthy muscle fibre is found. In DM, the inflammation is predominantly perimysial and perivascular infiltration by CD4+ lymphocytes.

Skin biopsy findings are not specific for DM, and are not routinely required, but exclude other skin conditions that can have similar clinical appearances.

Differential Diagnosis

Other causes of proximal muscle pain and weakness must be excluded. These are endocrine (hypothyroidism, hyperthyroidism, osteomalacia, Cushing's syndrome—usually steroid induced, Addison's disease) and metabolic causes (hypokalaemia) plus rare causes like muscle enzyme defects. Infectious myositis (viral- HIV, picornavirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), rubella, influenza; bacterial- pyomyositis, Lyme, tuberculosis, parasitic- Toxoplasma, Trichinella, etc.) needs exclusion. Drugs like statins, fibrates, zidovudine, penicillamine, colchicine, hydroxychloroquine, cyclosporine and alcohol, cocaine are also important causes of muscle pain and weakness.

It is important to note: (i) to exclude PM in suspected muscular dystrophy where the history is short – CK, EMG, and muscle biopsy would help; (ii) to diagnose overlap of PM with another disease like rheumatoid, lupus where assessment of muscle power is difficult because of pain – CK, muscle biopsy helps; (iii) to exclude polymyalgia rheumatica in cases with significant pain, especially in elderly with high ESR; (iv) patients with muscle pain and weakness due to endocrine and metabolic myopathies—clinical suspicion is a must. A summary of diagnosis is given in **Table 4**.

Table 4: Summary of Diagnosis of PM/DM

Symmetrical proximal muscle weakness developing over weeks/ months
Elevated serum muscle enzymes: Creatine kinase (CK), aldolase
Abnormal electromyography: Myopathic potentials (short duration, low amplitude, polyphasic), fibrillation, positive sharp waves, insertional activity, complex repetitive discharges
Abnormal muscle biopsy: Multifocal endomysial mononuclear cell infiltration, degeneration and regeneration
Skin manifestations of dermatomyositis: Gottron's papules, Gottron's sign, Heliotrope rash

TREATMENT

Very few controlled trials are available. The goals of therapy are to improve the ability to carry out activities of daily living by increasing muscle strength and control the extramuscular manifestations of IIM. Improvement in muscle strength rather than a reduction of CK levels should be the clinical parameter that denotes response to therapy (**Figure 3**).

Prednisolone is the first line drug. The initial dose of prednisolone is 1 to 2 mg/kg/d (60-100 mg/day) for 4 to 8 weeks (variable) and then tapered gradually as muscle strength

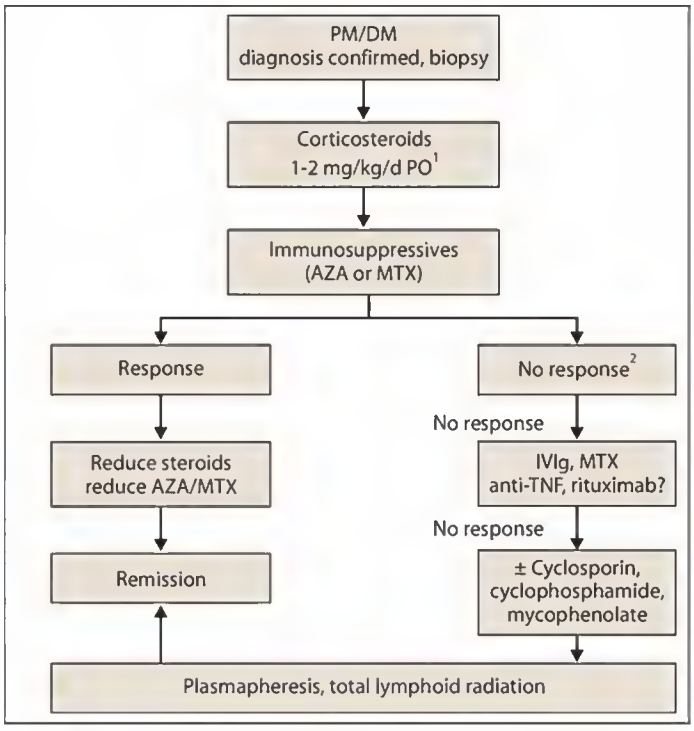


Figure 3: Treatment algorithm for PM/DM.

Notes:
Physical therapy to maintain muscle strength is important at all stages
MTX = Methotrexate; AZA = Azathioprine
1. IV Pulse if ther is alveolitis, dysphagia or myocarditis
2. Is severe disease, IVIg may be added at this stage

improves (reduce dose by 10% every two weeks) over 2 to 3 months, to a maintenance dose of around 0.25 to 0.5 mg/kg per day. Pulsed intravenous methyl prednosolone (15 mg/kg/d, max 1g) is used in severe cases especially with alveolitis, severe dysphagia, or myocarditis. Prevention and monitoring for steroid induced side effects is mandatory. Calcium and bisphosphonate supplementation should be given as necessary.

Most patients will respond to this therapy, but some will require additional immunosuppressive drugs. Increasingly, immunosuppressives are being used along with corticosteroids from begining. Selection of an immu-nosuppressive drug remains empirical and depends on personal experience of treating physician. Azathioprine is given orally in a dose of 2 to 3 mg/kg/day tapered to 1 mg per kg per day once steroid is tapered to 15 mg per day. It can take 4 to 6 months to work. The maintenance dosage is 50 mg per day. Methotrexate is given orally in a dose of 7.5 to 25 mg weekly. This usually acts more rapidly. As dosage increases, taper off steroid dose. Concomitant folic acid minimises side effects of methotrexate. Patients need to be monitored regularly with blood counts, serum creatinine and alanine aminotransferase (ALT). Cyclosporine has also been found to be beneficial and is used in a dose of 3 to 5 mg/kg/day. *Mycophenolate mofetil* is emerging as a promising and well-tolerated drug and is used in a dose of 2 gm/day. Cyclo-phosphamide, given intravenously every 3 to 4 weeks has shown mixed results, but may be of particular benefit for patients with active ILD. Rituximab has been tried in refractory cases. Antimalarials are used for skin lesions in DM. Intravenous immunoglobulin (IVIg) has been shown to be beneficial in improving muscle strength acutely. It is used as a single intravenous infusion of 2 gm/kg. Plasmapheresis was not found to be helpful in a double blind placebo-controlled study.

Lack of improvement of muscle power may be due to relapse or activity (accompanied by rise in CK) or steroid myopathy (CK normal). Neck flexor strength would be unchanged in patients developing steroid myopathy. Muscle power may not recover fully in all subjects. If other features suggest inactive disease, drugs may be reduced.

COURSE AND PROGNOSIS

Disease related death occurred in at least 10% of patients, 20% remained in remission and were off drugs whereas 80% had polycyclic course. DM infrequently relapses, but usually respond to therapy. PM patients have frequent relapses, but recover with less strength after each bout. Patients with IBM and polymyositis with anti-SRP antibody have the poorest prognosis. Older patients, and those with associated malignancy, delayed treatment, and cardiorespiratory complications have poor survival.

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2. Dalakas MC. Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol* 2010; 6: 129-37.
3. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet* 2003; 362: 971-82.

Web Resources

1. International Myositis Assessment and Clinical Studies Group https://dir-apps.niehs.nih.gov/imacs/index.cfm
2. The Myositis Association http://www.myositis.org

24.15 Rheumatic Manifestations of Systemic Diseases

Debashish Danda

INTRODUCTION

Forty per cent of all human beings suffer from some musculoskeletal symptoms during their life time and one-third have a true musculoskeletal disorder. However, at times musculoskeletal symptoms and signs are manifestations of non-rheumatic systemic diseases. Lack of awareness can lead to erroneous or delayed diagnosis of primary illness. Hereditary, inflammatory, infective, neoplastic, metabolic, nutritional, drug-related and psychogenic diseases can present with rheumatic complaints (**Table 1**). Some of the common systemic conditions with rheumatic manifestations are discussed below.

DIABETES MELLITUS

It can cause rheumatic manifestations as direct, indirect or associated features.

Calcaneal Osteolysis

One of the most common rheumatic symptoms in diabetics is foot pain due to calcaneal osteolysis.

Neuropathic Joint (Charcot Joint)

Unlike syphilis in the past, diabetes is now the most common cause of neuropathic joint, the most damaged and deranged joint, one can imagine. It can affect any weight-bearing joint like knees and ankles, but small joints can also be affected. Clinical clues include significant sensory deficit and pain which is far less than what one might expect from the degree of radiologic damage. Osteomyelitis is an important differential diagnosis.

Rotator Cuff Disease

Restricted abduction of shoulders due to degenerative process causing supraspinatus tendonitis, bicipital tendonitis, and subacromial bursitis is fairly common in diabetics, often loosely termed as 'periarthritis'.

Diffuse Idiopathic Skeletal Hyperostosis (DISH)

Also called as Forestier's disease, it is seen in elderly women with diabetes mellitus with back pain. Radiographs reveal exuberant, bridging osteophytosis in spine which superficially resembles ankylosing spondylitis (AS). However, there is no sacroiliitis in DISH in contrast to AS where sacroiliitis is the characteristic feature. DISH is a degenerative condition. It is not specific for diabetes and may be seen even in absence of diabetes mellitus.

Crystal Arthritis

Both gout and pseudogout are found with higher prevalence in diabetics, when compared to non-diabetics. Gout typically afflicts the big toe while pseudogout usually affects large joints with intermittent inflammatory arthritis, mimicking a septic arthritis but without leaving much residual damage. Radiographs in pseudogout may show chondrocalcinosis at various places: triangular ligament calcification of hands or calcifications of intervertebral space, pubic symphysis or knee joint cartilage. Synovial fluid examination under polarising microscope can clinch the diagnosis. Gouty fluid is likely to show needle-shaped intracellular negatively birefringent crystals of monosodium urate (MSU), whereas calcium pyrophosphate dihydrate (CPPD) crystals of pseudogout are blunt, rhomboid-shaped and positively birefringent.

Septic Arthritis

Diabetes is one of the most common conditions associated with septic arthritis and septic bursitis. Joint aspiration and synovial fluid examination by Gram stain and culture are important. *Staphylococcus aureus* and Gram-negative organisms are the usual causative agents. Septic arthritis requires prolonged and aggressive antibiotic treatment with joint lavage. Delay can lead to joint destruction and contractures.

Diabetic Cheiroarthropathy (Prayer Sign or Namaste Sign)

Myxomatous deposition around small joints of hands, tendons and ligaments leads to this complication causing limited joint mobility (LJM). In one series, LJM was diagnosed in 42.9% of type 1 and 37.3% of type 2 diabetic patients. Abnormally thick skin was detected in 31.4% of type 1 and 33.7% of type 2 diabetic patients. Skin abnormalities were observed mainly in patients with LJM. There was a high prevalence of hand flexor tendon abnormalities (18.6%). Decreased range of shoulder and hip mobility and flexor tendon abnormalities were significantly more common in patients with LJM.

Other Musculoskeletal Features in Diabetes

Complex regional pain syndrome (CRPS) or shoulder-hand syndrome or reflex sympathetic dystrophy is often found in diabetics. Other musculoskeletal features include carpal tunnel syndrome, Dupuytren's contracture, sclerodactyly and scleroderma-like skin changes, tendency for early osteoporosis with tendency to fracture vertebra or neck of femur.

HAEMATOLOGICAL MALIGNANCIES

Haematological malignancies can cause arthropathy by direct infiltration, immune complex-mediated inflammatory arthropathy, haemarthrosis due to low platelets and altered clotting mechanisms, septic arthritis or hyperuricaemia-related gouty type arthritis. They are, therefore, notorious masqueraders leading to delayed diagnosis, especially in children. The clue is pain and tenderness out of proportion to findings in the joints, associated low haemoglobin, low platelets, and at times, abnormal white cell counts (high or low) or morphology. Bone marrow examination can be confirmatory. Metaphyseal radiolucent bars in radiographs are a clue for leukaemic arthropathy. Multiple myeloma (predominantly kappa light chain) and primary amyloidosis (lambda light chain predominant myeloma) can present with features exactly like rheumatoid arthritis including subcutaneous nodules, arthritis and carpal-tunnel syndrome. 'Shoulder pad' sign, macroglossia or lytic lesions on radiographs should arouse suspicion of multiple myeloma.

Table 1: Rheumatic Manifestations of Systemic Diseases

Hereditary diseases with rheumatic manifestations
- Heritable collagen diseases, e.g. benign hypermobile joint syndrome, osteogenesis imperfecta, Ehlers-Danlos syndrome, Marfan's syndrome, pseudoxanthoma elasticum, cutis laxa, Stickler's syndrome, spondyloepiphyseal dysplasia, Alport's syndrome, etc.
- Inborn errors of metabolism, e.g. homocysteinuria, alkaptonuria, Menke's kinky hair syndrome, mucopolysaccharidoses, Fabry's disease
- Storage diseases, e.g. Haemochromatosis, Wilson's disease
- Primary immunodeficiency diseases, e.g. DiGeorge's syndrome, Brutton's agammaglobulinaemia, IgA deficiency, common variable immunodeficiency, hyper IgM syndrome, complement deficiency disorders
- Bone and joint dysplasia, e.g. osteochondrodysplasia, spondyloepiphyseal dysplasia, hypophosphatasia

Inflammatory disorders with rheumatic manifestations*
- RA
- Primary Sjögren's syndrome
- SLE
- Overlap syndromes
- Vasculitic disorders

Infective conditions with rheumatic manifestations
- Viral : Hepatitis B, hepatitis C, HIV, parvovirus, Epstein-Barr virus, cytomegalovirus, rubella, coxsackie, echovirus, O'nyong-nyong, chikungunya and dengue
- Bacterial : Septic arthritis, infective endocarditis, melioidosis, brucellosis, Mycobacterial TB, atypical mycobacteria, leprosy
- Parasitic : Guinea worm arthritis, trichinosis causing myositis, filariasis, schistosomiasis, and amoebiasis causing arthralgia
- Fungal : Sporotrichosis

Neoplastic diseases with rheumatic manifestations
- Haematological : Leukaemias, lymphomas, myelomas
- Solid tumours : Renal cell carcinoma, pancreatic carcinoma
- Metastatic process
- Primary amyloidosis

Metabolic diseases with rheumatic manifestations
- Diabetes mellitus
- Hypothyroidism
- Hyperthyroidism
- Hypoparathyroidism
- Hyperparathyroidism
- Acromegaly
- Cushing's syndrome
- Renal tubular acidosis
- Paget's disease

Nutritional diseases with rheumatic manifestations
- Osteomalacia
- Rickets

Drug or treatment related
- Serum sickness like process following vaccination, drugs
- Drug-induced lupus (INH, phenytoin, D-penicillamine, biological agents like TNF-blockers)
- Drug-induced vasculitis (propylthiouracil and leukotriene inhibitors monteleukast/zafirleukast-induced Churg-Strauss syndrome)
- Hyperuricaemia with drugs (Pyrazinamide)
- Myositis/myopathy (statins, zidovudine, penicillamine, steroid)
- Haemodialysis

Psychogenic diseases with rheumatic manifestations
- Chronic pain syndromes (controversial)

**The diagnosis can often be made without difficulty because joint pains are frequently the presenting feature. Other diseases where musculoskeletal involvement is evident include sarcoidosis, inflammatory bowel disease, coeliac disease and psoriasis.*

The classical triad comprises of bone pain, anaemia and renal failure. Bone marrow examination, electrophoresis for 'M' band and serum immunoglobulin levels confirm the diagnosis. There may be higher levels of the pathogenic isotype of immunoglobulins and suppression of the other isotypes, e.g. in IgA meloma, IgA will be high and IgG, IgM and other isotypes may be low in quantity.

Hairy cell leukaemia can present with polyarteritis nodosa-like vasculitis. Some lymphomas can produce dermatomyositis-like presentations, as paraneoplastic manifestation. Other presentations include erythromelalgia in myeloproliferative diseases presenting as red, swollen, warm, stout, and puffy fingers and toes; and cryoglobulinaemic vasculitis in plasma cell dyscrasias, etc. Rheumatic associations of myelodysplastic syndromes include polyarteritis nodosa type systemic vasculitis and polymyalgia rheumatica.

SOLID MALIGNANCIES

Lung cancers causing hypertrophic osteoarthropathy (triad of clubbing, polyarthritis or polyarthralgia and widening of wrists and ankles), panniculitis in pancreatic carcinoma, dermatomyositis/polymyositis in carcinoma of stomach, ovary and several adenocarcinomas are well known entities. Jaccoud's arthritis is described in lung malignancies while scleroderma-like process

may be seen in adenocarcinomas and carcinoid tumours. Solid tumours and tumours of mesenchymal origin can also give rise to oncogenic osteomalacia presenting as out of proportion bony pain and tenderness. Renal cell carcinoma is another malignancy which causes myriad of rheumatological manifestations including arthritis, vasculitis, etc. due to production of pro-inflammatory cytokines by this tumour. Carcinomatous polyarthritis is a special entity mostly associated with explosive onset, asymmetric, large joint polyarthritis often sparing the upper limbs. This can occur even with haematological malignancies, not necessarily with carcinomas alone.

Rheumatic manifestations suggesting a hidden cancer include rapid onset of an unusual inflammatory arthritis, clubbing or diffuse bone pains in a patient 50 years of age or older, chronic unexplained vasculitis, refractory fasciitis, Raynaud's phenomena unresponsive to vasodilator therapy, rapidly progressive digital gangrene or Lambert-Eaton myasthenic syndrome.

Paraneoplastic rheumatological syndromes may coincide, follow or antedate the diagnosis of cancer, or herald its recurrence. The clinical course generally parallels that of the primary tumour, and treatment of the underlying malignancy often results in regression of the rheumatic disorder. Awareness that cancer can cause certain non-metastatic symptoms is important for early diagnosis and treatment of an occult neoplasm. Management consists of control of the underlying cancer and symptomatic treatment of the rheumatic syndrome with nonsteroidal anti-inflammatory drugs.

CHIKUNGUNYA ARTHRITIS

Chikungunya fever is associated with severe arthralgias, myalgias and skin rash. The fever usually lasts a few days. However, the rheumatic complaints can be crippling. The viral polyarthropathy frequently involves the small joints of the hand, wrist and ankles and may also involve other larger joints such as knees and shoulders. The pain may be severe enough to immobilise the patient and interfere with activities of daily living. Rheumatological manifestations are less severe in children in this infection. The arthralgias can persist for weeks to months. Treatment is mainly symptomatic.

MYCOBACTERIAL INFECTIONS

Tuberculosis (TB) usually presents as chronic inflammatory monoarthritis of large joints. Atypical mycobacteria and at times tuberculosis can present with polyarticular large and small joint disease with significant tenosynovitis, associated bursitis and discharging sinuses, similar to fungal arthropathies.

Mycobacteria-related rheumatic manifestations are often classified into four different categories:

1. Direct musculoskeletal involvement of *M. tuberculosis*, including spondylitis, osteomyelitis, septic arthritis, and tenosynovitis.
2. *M. tuberculosis* infection complicating rheumatologic diseases such as rheumatoid arthritis after therapy with tumour necrosis factor-alpha inhibitors.
3. Anti-mycobacterial drug-induced rheumatologic syndromes such as pyrazinamide and ethambutol-induced hyperuricaemia, quinolone-induced tendinopathy, drug-induced lupus with INH.
4. Reactive immunologic phenomena in mycobacterial infection, such as Poncet's arthritis, erythema nodosum, etc.

Poncet's arthritis is a form of reactive arthritis in tuberculosis. It is a sterile arthritis of large or small joints, usually short lasting and non-deforming, thought to be due to hypersensitivity to mycobacterial antigens. It was originally seen after intravesical instillation of BCG vaccine for bladder malignancies. It is more common with extrapulmonary TB, rather than in pulmonary TB. Usually, symptomatic treatment with NSAIDs suffices most of the time. Erythema nodosum seen in the setting of TB can be confused with sarcoidosis. Mantoux test in such a case may be helpful.

LEPROSY AND LEPRA REACTION

Striking rheumatological manifestations can be seen in leprosy and lepra reactions. Type 2 lepra reaction is a type 3 immune response, i.e. immune complex- mediated process similar to SLE. Therefore, it is not surprising to find lupus-like presentations in these patients. They may even present with dermatomyositis, overlap connective tissue disease and medium vessel vasculitis-polyarteritis nodosa-like process. Infiltration of ear lobule and infiltrated appearance of face, depressed bridge of nose, nerve thickening and madarosis can be the clues in a suspected case. In a case of mononeuritis multiplex presenting as foot drop, wrist drop, cranial nerve palsy, one must suspect leprosy if diabetes is ruled out. The other differential diagnosis includes classic polyarteritis nodosa. Seven quadrant slit-skin smear is a good test; the other test is nerve biopsy with appropriate acid-fast staining for *M. leprae*.

HIV

Table 2 shows rheumatic manifestations of HIV. A host of autoantibodies are also described in HIV infection namely: anticardiolipin, anti-beta-2 GPI, anti-DNA, anti-small nuclear ribonucleoproteins (snRNP), anti-thyroglobulin, anti-thyroid peroxidase, anti-myosin and anti-erythropoietin antibodies. The clinical correlation of autoantibodies in HIV-infected patients with clinical autoimmune disease is yet to be established. With the upsurge of HAART (highly active anti-retroviral treatment), the incidence of autoimmune diseases in HIV-infected patients is increasing, especially after immune reconstitution syndrome.

Table 2: Rheumatic Manifestations of HIV

Increased incidence of reactive arthritis due to possible several gastrointestinal infections
Aggressive psoriatic arthritis
Sjögren's-like disease called diffuse interstitial lymphocytosis syndrome (DILS)*
Septic arthritis
Pyomyositis and polymyositis
Systemic lupus erythematosus
Anti-phospholipid syndrome
Vasculitis

**Presents as prominent parotid and lacrimal gland enlargements. This differs from Sjögren's by the presence of CD8-positive lymphocytes infiltration rather than CD4 cells seen in Sjögren's syndrome.*

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2. Schon L, Easley MC. Charcot neuroarthropathies of the foot and ankle. *Clin Orthop* 1998; 349: 116-31.

24.16 Miscellaneous Rheumatic Disorders

Binoy J Paul

This chapter deals with a group of unrelated disorders like heritable connective tissue disorders, relapsing polychondritis, Charcot's arthropathy, hypertrophic osteoarthropathy and pigmented villonodular synovitis.

HERITABLE CONNECTIVE TISSUE DISORDERS

Heritable diseases of connective tissues are a diverse group of disorders characterised by abnormalities in the musculoskeletal tissues including cartilage, bone, tendon, ligament, muscles and skin. They are further classified into disorders primarily affecting the cartilage and bone (skeletal dysplasias) and diffuse disorders that have a more profound effect on the connective tissues like Ehler-Danlos syndrome (EDS), Marfan's syndrome and other disorders manifested by abnormal extracellular matrix molecules.

Skeletal Dysplasias (Osteochondrodysplasias)

These are a group of developmental disorders of the chondral and osseous tissues that are often accompanied by short stature. They include defects of tubular and flat bones or of the axial skeleton, disorganised development of cartilaginous and fibrous component and idiopathic osteolysis.

The most important varieties of skeletal dysplasias are osteogenesis imperfecta, chondrodystrophies like achondroplasia and spondyloepiphyseal dysplasias (**Table 1**).

Table 1: Heritable Diseases of Connective Tissues

Skeletal dysplasias
- Osteogenesis imperfecta
- Chondrodystrophies, e.g. Achondroplasia
- Spondyloepiphyseal dysplasias
- Kniest dysplasia
- Morquio's disease
- Hereditary multiple exostoses
- Diastrophic dysplasia
- Idiopathic osteolysis

Diffuse heritable diseases
- Ehler-Danlos syndrome
- Marfan's syndrome
- Pseudoxanthoma elasticum
- William's syndrome
- Benign joint hypermobility syndrome

Osteogenesis imperfecta (OI)

It is a genetic syndrome of abnormal bone matrix with secondary osteoporosis. OI is one of the most common heritable disorder of connective tissue. It is inherited as autosomal recessive or autosomal dominant manner depending on the disease subtype. It is associated with abnormalities of structure or synthesis of Type I collagen (**Table 2**).

The severity of the disease ranges from a slight increase in susceptibility to bone fractures to forms that are lethal *in utero*. In addition to fracture susceptibility there is marked osteoporosis secondary to osseous matrix abnormality. The skeletal abnormalities varies with the type (**Table 2**).

OI is associated with variable non-osseous features like blue sclera, dentinogenesis imperfecta, deafness, pectoral deformities, mitral valve prolapse and growth retardation. The diagnosis of OI can be usually made clearly on clinical and radiological basis.

Treatment with bisphosphonates or calcitonin may be beneficial to prevent vertebral compression than long bone fractures and to delay the development of scoliosis. These drugs also reduce the bone pain. Long-term management requires expert physical therapy or orthopaedic surgery.

Table 2: Classification of Osteogenesis Imperfecta

Type	Inheritance	Sclera	Deafness	Skeletal abnormalities
I	Autosomal dominant	Blue	50%	Mild to moderate bone fragility No deformities Mild to moderate short stature
II	Autosomal dominant or recessive	Blue	No	Extreme fragility of connective tissue Congenital fractures Soft large cranium Micromelia, Beaded ribs Lethal in the perinatal period
III	Autosomal dominant or recessive	Variable	Common	Progressive deformity of bone Very short stature Relative microcephaly Triangular facies Dentinogenesis imperfecta
IV	Autosomal dominant	Normal	Uncommon	Variable short stature Mild to moderate bone deformities Dentinogenesis imperfecta Moderate joint hyperextensibility

Chondrodystrophies

Chondrodystrophies are a large and strikingly heterogenous group of heritable skeletal dysplasias with abnormal proportion of limbs, trunk and/or skull and often associated with short stature.

Some chondrodystrophies are associated with an abnormality of Type II collagen. However, in most chondrodystrophies the abnormality of extracellular matrix is unknown.

Achondroplasia

Achondroplasia is the most common skeletal dysplasia, which is due to mutation in the gene expressing the fibroblast growth factor receptor 3 (FGFR3). The distinguishing features are present at birth, although the diagnosis is seldom made at that time. The head is large with frontal bossing, midface hypoplasia and prognathism. There is rhizomelic shortening of arms and legs, increased lumbar lordosis, bowing of the legs, overgrowth of fibula and a trident shaped hand with short broad phalanges.

Radiographs show a very small sacrosciatic notch of pelvis, changes in the epiphysis of distal femur and constriction at the base of the skull. Adult life may be shortened if there is spinal canal stenosis causing spinal cord compression. Otherwise most of these persons live a healthy productive and independent life. Limb lengthening involving bilateral femoral and tibial distraction osteotomies may add up to 12 inches to the adult height. The procedures are best done in the second decade.

Spondyloepiphyseal dysplasias

Spondyloepiphyseal dysplasias (SEDs) constitute a group of closely related disorders characterised by short stature and a disproportionately short trunk. Infants with the most severe forms of SEDs are obviously dwarfed at birth. Many other less severely affected patients may not present until later in life and their symptoms can be easily confused with those of osteoarthritis. They present with short stature and symmetric joint pain caused by epiphyseal changes. There are two types of spondyloepiphyseal dysplasias Congenita and Tarda (**Table 3**). Radiographic features include flattening and/or sclerosis of epiphyses of long bones. There will be flattening of the vertebral bodies also.

Table 3: Spondyloepiphyseal Dysplasias

Type	Onset	Inheritance	Associated features
Congenita	Birth	Autosomal Dominant	Short limbs Equino varus feet Myopia, retinal detachment
Tarda	Late childhood	X-linked recessive	Moderately short stature Platyspondyly Onset of pain in the hip and back at the age of about 10 yrs Progressive joint deformities

DIFFUSE HERITABLE CONNECTIVE TISSUE DISORDERS

Ehler-Danlos Syndrome (EDS)

EDS is a genetic syndrome affecting primarily joints, skin and blood vessel all. It consists of a heterogenous group of generalised connective tissue disorders associated with multiple modes of inheritance and associated with abnormalities of types I, III, V collagen or fibronectin, enzyme deficiencies or abnormalities of copper metabolism.

There are around 10 types of EDS. The genetic inheritance and incidence varies with the type.

1. Type 1 EDS is the gravis form. Patients have velvety and hyperextensible skin, marked joint extensibility, cigarette paper scars and easy bruising.
2. Type II EDS (mitis) has a less severe presentation of type I with associated premature degenerative arthritis.
3. In Type III EDS joints are hypermobile with repeated joint dislocations and degenerative arthritis.
4. Type IV (Vascular EDS) is the severest form associated with lethal complications like rupture of arterial wall, colon or pregnant uterus. There is a characteristic facies with large eyes and thin nose and lips. Patients have marked bruisability, an aged skin appearance on hands and feet and joint hypermobility limited to the small joints of hands. Type I to IV are having autosomal dominant inheritance.
5. Type V EDS is clinicaly similar to Type II but the mode of inheritance is X-linked.
6. Type VI EDS is having autosomal recessive inheritance with soft extensible skin, scoliosis, ocular fragility and hypermobile joints.
7. Type VII EDS presents predominantly with joint symptoms beginning with congenital dislocation of hips usually bilateral and continuing with striking joint laxity and multiple dislocations. There may be moderate short stature and mild skin bruising and extensibility.
8. Type VIII EDS is associated with generalised periodontitis in addition to skin and joint hyperlaxity.
9. Type IX EDS has bladder diverticula and rupture, soft lax skin associated with bony occipital horns.
10. Type X EDS is associated with abnormal platelet aggregation in addition to mild joint hypermobility and easy bruising.

Management of EDS is mainly conservative. Joint hypermobility generally decreases with age. Sports that hyperextend and otherwise stress the joints should be discouraged in childhood. Joint surgery may be performed for pain, instability or poor range of motion. Skin fragility in EDS necessitates particular attention to closure in even minor surgical procedures. Sutures should be more closely spaced and left in place for a longer period than normal. In Type IV EDS, patient should be asked to report to the physician for all appropriate vascular and visceral symptoms for prompt evaluation. If pregnancy is attempted, elective caesarean section through lower uterine segment is essential to prevent uterine rupture or vaginal tears.

Marfan's Syndrome (MS)

Marfan's syndrome was the first heritable connective tissue disorder to be described which has an autosomal dominant inheritance. There is no racial or geographic influence on incidence with an approximate prevalence of one per 20,000.

Aetiopathogenesis

Classic Marfan's syndrome is caused by mutation in fibrillin-1 (FBN-1) gene. Fibrillin is a glycoprotein abundant in aortic tunica media, ciliary zonules, skin and periosteum.

Clinical features

Musculoskeletal features include stature greater than 95 percentile and limbs disproportionately long for trunk size (arachnodactyly), scoliosis, pectus excavatum or carinatum, high arched palate, flat feet and marked laxity of joints. Ocular features include non progressive upward subluxation of lens and myopia. Cardiovascular manifestations include mitral valve prolapse and dilatation of ascending aorta which lead to mitral or aortic regurgitation. Ghent nosology (Table 4) helps in the diagnosis of Marfan's syndrome.

Table 4: Ghent Nosology of Marfan's Syndrome

Skeletal system (four or more of)	Ocular system
Pectus carinatum	Ocular system
Pectus excavatum	Ectopia lentis
Span to height >1.05	Cardiovascular
Wrist and thumb sign	Dilatation of ascending aorta involving at least sinuses of Valsalva
Scoliosis >20°	
Elbow extension <170°	Dissection of aorta
Pes planus	Family/Genetic history
Protrusio acetabulae	First degree relative with Marfan's syndrome
Lumbosacral dural ectasia by CT/MRI	Presence of FBN-1 mutation

For index case: Diagnosis requires major criterio in at least two different organ systems and involvement of a third organ.

For a relative of index case: Major criterion in one organ system and involvement of a second organ system.

Management

Management of Marfan's syndrome is multidisciplinary including periodic ophthalmology, orthopaedics, cardiovascular and rheumatology evaluation. Surgical intervention may be needed when scoliosis exceeds 45°. Cardiovascular care includes periodic ECG and echocardiographic evaluation for aortic root dilatation. Treatment with β-blockers decreases the rate of aortic root dilation and increases survival. Aortic surgeries for aneurysms, valve regurgitation using composite graft to replace both ascending aorta and aortic valve has markedly increased the survival in these patients. Pregnancy is better avoided in women with Marfan's syndrome having moderate aortic dilatation.

Benign Joint Hypermobility Syndrome

Benign joint hypermobility syndrome (BJHS) is a common disorder which is strongly heritable. It is characterised by the development of symptoms in otherwise healthy individuals with hypermobile joints. Some of the workers regard it as being the same as Ehler-Danlos syndrome Type III (EDS-Hypermobility type). It is three times more common in females and exhibits a dominant inheritance with variable penetrance.

Clinical features

Trivial strain or injury to the joints, ligaments, tendons or enthesis can cause pain, swelling in these patients. Recurrent joint instability or subluxation could be the initial symptoms in some patients. Secondary osteoarthritic/spondylotic changes in the peripheral or spinal joints can occur later in life.

Extra-articular features include soft silky skin, hiatus hernia, rectal prolapse, uterine prolapse and varicose veins which can occur in some of these patients. Mitral valve prolapse and spontaneous pneumothorax are rare manifestations. BJHS patients also display Marfanoid habitus increased skin stretchiness and other manifestations overlapping with other heritable diffuse connective tissue diseases. Brighton's criteria will help to make a diagnosis of hypermobility syndrome (Tables 5 and 6).

Table 5: Brighton Hypermobility Score – Nine Points

No.	The ability to	Right	Left
1.	Passively dorsiflex the 5th metacarpophalangeal joint to ≥90°	1	1
2.	Oppose the thumb to volar aspect of the ipsilateral forearm	1	1
3.	Hyperextend the elbow to ≥10°	1	1
4.	Hyperextend the knee to ≥10°	1	1
5.	Place the hands flat on the floor without bending the knee	1	
	Total	**9**	

Table 6: The 1998 Brighton Revised Diagnostic Criteria for the Benign Joint Hypermobility Syndrome (BJHS)

Major criteria

A Brighton score of 4/9 or greater (either currently or historically)

Arthralgia for longer than 3 months in 4 or more joints

Minor criteria

A Brighton score of 1, 2 or 3 out of 9 (0,1, 2 or 3 if aged 50+)

Arthralgia in one to three joints or back pain or spondylosis; spondylolysis or spondylolisthesis

Dislocation in more than one joint or in one joint on more than one occasion

Three or more soft tissue lesions

Marfanoid habitus

Skin striae, hyperextensibility, thin skin or abnormal scarring

Eye signs, drooping eye lids, myopia or antimongoloid slant

Varicose vein, hernia, uterine/rectal prolapse

BJHS is diagnosed in the presence of two major criterio or one major and two minor criterio or four minor criterio. Two minor criterio will suffice if there is an affected 1st degree relative. Major criterio one and two are mutually exclusive.

Management

Simple analgesics or anti-inflammatory drugs are useful in pain and soft tissue injuries. The widespread chronic pain can be treated with serotonergic and noradrenergic agents. Physiotherapeutic approaches include building up of muscles responsible for joint and core stability, avoiding harmful postures and mobilising techniques to restore the normal tensile strength of lax tissues.

Relapsing Polychondritis

Relapsing polychondritis (RP) is a rare autoimmune disease of unknown aetiology with episodic but potentially progressive inflammatory manifestations, primarily involving cartilaginous structures of the ear, nose, eyes, airways and joints. It affects people of 40–60 years age group with equal frequency in both sexes. Over 30% of the cases are associated with an existing autoimmune or haematological disease (Table 7).

Table 7: Conditions Associated with Relapsing Polychondritis

Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Sjörgen's syndrome
Seronegative spondyloarthritis
Wegner's granulomatosis
Polyarteritis nodosa
Churg-Strauss vasculitis
Behçet's disease
Myelodysplastic syndromes
Lymphoma
Inflammatory bowel disease
Primary biliary cirrhosis

Pathogenesis

Autoimmune reaction of unknown aetiology stimulates the release of degenerative enzymes causing cartilage destruction. The cartilage matrix is initially infiltrated with mainly mononuclear and occasionally plasma cells and later leads to fibrosis and calcification.

Clinical features

Auricular chondritis is the key manifestation and is rarely absent in the course of the disease. Acute episodes manifest with pain, tenderness, swelling, warmth and marked redness affecting helix, antihelix or tragus sparing the soft lobule which lacks cartilage. Attacks resolve spontaneously within days but relapses invariably, leading to induration of pinna, drooping or cauliflower ear. Nasal conduits are far less obvious resulting in nasal pain tenderness mild swelling or redness and can cause saddle nose deformity. Laryngeal, tracheal and bronchial conduits can lead to hoarseness of voice, stridor, cough or expiratory dyspnoea. Costal chondritis provokes localised parietal pain and rarely results in depression of anterior chest wall.

Joint manifestations vary from arthralgia to oligo or polyarthritis which can be acute and migratory or chronic non-erosive and non-deforming variety. Peripheral arthropathy is usually asymmetric and mainly affects the wrists, metacarpophalangeal and proximal interphalangeal joints, elbows, knees and ankles.

Vestibular dysfunction, hearing impairment, conjunctivitis, uveitis, keratitis, episcleritis, ascending aortic aneurysm, glomerulonephritis, cutaneous or CNS vasculitis can also occur.

Diagnosis

Although the diagnosis of RP is relatively easy many conditions can mimic the initial changes or the associated disease may confuse the clinical picture. An empirical diagnostic criterion has been evolved (**Table 8**).

Investigations

Elevation of acute phase reactants occur during acute flares, tests for rheumatoid factor or ANA can be positive. Histological examination of the affected cartilage is suggestive of the diagnosis when it shows the association of degenerative changes with the presence of inflammatory cell infiltrates especially CD4+ lymphocytes, macrophages and polymorphonuclear cells. Loss of basophilic staining of the matrix is also seen reflecting the proteoglycan depletion.

Table 8: Diagnostic Criteria for Relapsing Polychondritis

Major Criteria

- Proven inflammatory episode involving auricular cartilage
- Proven inflammatory episode involving nasal cartilage
- Proven inflammatory episode involving laryngo tracheal cartilage

Minor Criteria

- Ocular inflammation (Conjunctivitis, keratitis, episcleritis, uveitis)
- Hearing loss
- Vestibular dysfunction
- Seronegative inflammatory arthritis.

When two major criterio or one mojor and two minor criterio ore present diognosis is confirmed.

Treatment

Systemic treatment is empirical and should depend on the clinical manifestation, disease activity and severity. In mild auricular or nasal chondritis and arthritis nonsteroidal anti-inflammatory drugs (NSAIDS), colchicine, dapsone or low dose prednisolone can be used. Methylprednisolone 'pulses' (1gm/day for 3 days) are useful in frank respiratory flares, recent sensory neural deafness or systemic vasculitis. Immunosuppression with methotrexate (0.3mg/kg/week) or cyclophosphamide (50-150 mg/day) in addition to steroids is used in severe resistant cases. Local steroids (eye drops, intra articular injections or inhaled steroids) are useful in ophthalmic articular or airway diseases. Airway obstruction or stenosis may need tracheostomy or stents.

Neuropathic Arthropathy (Charcot's Joint)

Neuropathic joint disease (Charcot's joint) is a progressive destructive joint disease associated with sensory loss. The common causes are diabetes mellitus, leprosy, tabes dorsalis, syringomyelia, hereditary sensory neuropathies, amyloidosis and spinal cord trauma.

Clinical features

The distribution of the joint involvement depends on the underlying neuropathy as shown in **Table 9**. The onset of neuropathic arthropathy is usually gradual. The joint will be swollen and warm. Because, there is relatively little pain, patient often do not seek medical consultation until progressive deterioration has occurred. Arthralgia is well documented in 50% of patients though the symptoms are usually less than expected from the degree of joint destruction.

Table 9: Joint Involvement in Neuropathic Arthropathy

Disease	Site of involvement
Diabetes mellitus	Metatarsophalangeal, tarsometatarsal, intertarsal joints
Leprosy	Tarsal, tarsometatarsal joints
Syringomyelia	Shoulder, elbow, wrist
Hereditary sensory neuropathy	Knee, ankle, intertarsal Metatarsophalangeal joint
Tabes dorsalis	Knee, hip, ankle
Amyloidosis	Knee, ankle

Investigations

Plain radiography in early stages shows joint effusion periosteal calcification or minimal subluxation. Subsequently

fragmentation of articular surface occurs leading to complete joint disorganisation. This is associated with prominent periosteal new bone formation. Osteocartilaginous bodies of synovial origin and fragments from articular surface lead to a great deal of osseous debris inside the joint. Osteosclerosis and osteophytosis are very prominent radiological features. Synovial fluid may be serous, sero-sanguinous and lipid crystals secondary to subchondral bone lesions may be seen.

Treatment

The management of Charcot's joint consists of joint immobilisation and rest for stabilisation of the joint. Weight bearing may be avoided and orthotic devices like plaster cast crutches stabilising splints or braces are used as required to permit limited mobilisation. The treatment of basic neurological disease usually does not prove beneficent to the joint. Recently bisphosphonates like pamidronate have been used successfully to halt the underlying bone resorption in neuropathic arthropathy.

Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy (HOA) is a syndrome characterised by abnormal proliferation of the skin and osseous tissues at the distal part of extremities, clinically manifesting as clubbing, periostosis of tubular bones and synovial effusions. HOA is classified as primary or secondary and the latter having very diverse aetiologies as shown in **Table 10**. There is now evidence to sustain the belief that clubbing and HOA represent different stages of same disease process. In majority of cases the finger deformity is the first manifestation and as the syndrome progresses periostosis becomes evident.

Table 10: Classification of Hypertrophic Osteoarthropathy

Primary (Patchy dermoperiostosis)	
Secondary	
Pulmonary	
	Bronchogenic carcinoma, lung abscess, emphysema, Bronchiectasis
	Pulmonary fibrosis, Mesothelioma of pleura, arteriovenous fistula
Cardiovascular	
	Congenital cyanotic heart disease, bacterial endocarditis, Aortic aneurysm, Eisenmenger's syndrome
Hepatic	
	Cirrhosis, hepatoma
Intestinal	
	Inflammatory bowel diseases, oesopharyngeal or colonic carcinoma
Miscellaneous	
	Graves' disease, thymoma, thalassemia, connective tissue diseases

Clinical features

Primary HOA (Patchy dermoperiostosis) is an autosomal dominant condition characterised by insidious development of clubbing with cylindrical thickening of forearm and legs. Recurrent mildly symptomatic joint effusions may be accompanied. Facial features may be thickened and furrowed with nasolabial fold and a corrugated scalp known as 'Leonine' facies. Skin may show excessive sweating and a 'greasy' feel. Other features include gynaecomastia, acne vulgaris, striae and cranial suture defects.

Investigations

ESR may be elevated with increase in serum alkaline phosphatase (due to considerable new bone formation). Synovial fluid is characteristically non-inflammatory.

Radiological examination shows periosteal new bone formation often seen in the tibia, radius, ulna, fibula and femur. The coarse layered appearance is most evident along the diaphysis. Radionucleotide bone scan and MRI are more sensitive in detecting periosteal reaction earlier than plain radiography.

Treatment

For patients with painful osteoarthropathy, NSAIDs are effective in alleviating pain. Treatment of the underlying disease results in dramatic regression of all features of secondary HOA. Vagal block and vagotomy are also helpful in symptomatic relief.

Pigmented Villonodular Synovitis

Pigmented villonodular synovitis (PVNS) is a benign proliferation of the synovial tissue that usually presents as an indolent progressive monoarthritis or tenosynovitis. The disease usually affects young adults. The synovium has a brownish colour and has numerous large fingers like villi. The proliferated synovium grows into the subsynovial tissue and invades the adjacent cartilage and bone.

Patients often present with insidious onset of pain and swelling of the affected joint, most often the knee rarely hip or ankle. Radiographs show joint space reduction, erosions and subchondral cysts. Joint fluid can be brown or black in colour. Treatment consists of total synovectomy followed by irradiation of the joint.

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24.17 Emergencies in Rheumatology

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INTRODUCTION

Rheumatological emergencies do occur in a considerable number of patients. The first presentation itself can be an emergency. Presentation may vary depending on the underlying disease process. If the underlying disease is already known, approach towards diagnosis is easier as compared to cases presenting for the first time.

EMERGENCIES IN RHEUMATOID ARTHRITIS (RA)

Septic Arthritis

Septic arthritis is caused by pyogenic bacteria. The infection spreads through the bloodstream, or through surgery, an injection, or injury. The causative organism is usually *Staphylococcus* or *Streptococcus*. In adults, gonococci and mycobacteria may be the causative agent. Intravenous drug users and immunocompromised are more likely to have septic arthritis caused by gram-negative bacteria. Symptoms are, severe pain and swelling in the affected joint (**Figure 1**). Chills and fever are also common. Septic arthritis in the hip may be experienced as pain in the groin area that becomes much worse if the patient tries to walk. Synovial fluid should be tested for TLC, which is usually high, and for bacteria and other organisms. A culture of blood and synovial fluid should also be done and radiographs obtained to assess any joint damage. Antibiotics should be started and should be continued for at least six weeks. Draining the fluid from the infected joints may be required. Surgical drainage is reserved for septic arthritis of the hip, as that site is inaccessible for repeated fluid removal. Splinting can relieve pain. After a period of rest, gentle exercise to prevent stiffness should be started. Recovery is usually good, although many patients will develop osteoarthritis or deformity.

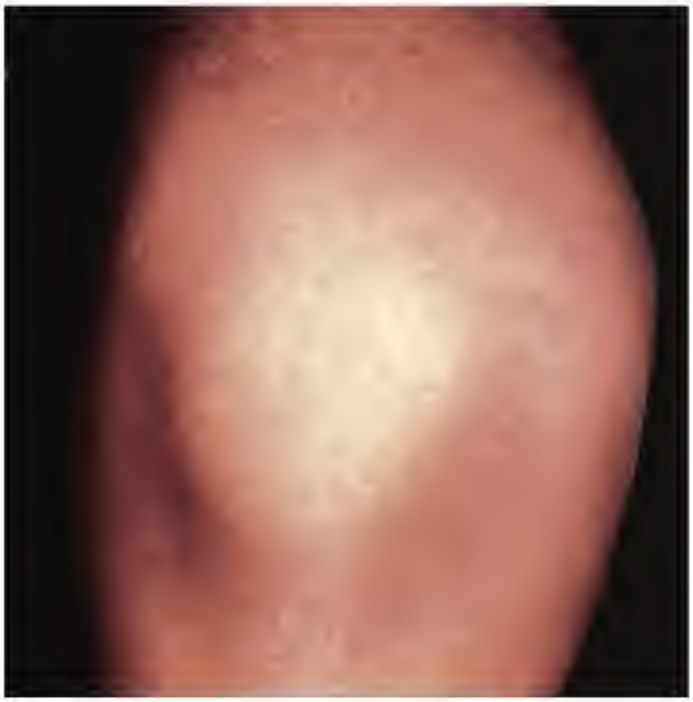


Figure 1: Septic arthritis of the knee joint.

Atlantoaxial Dislocation

Atlantoaxial subluxation is a well-recognised complication of RA. Anterior subluxation is most common, but vertical subluxation of the dens may also occur. Symptoms include paraesthesia, numbness, and muscular weakness. In severe cases this can result in spastic paralysis, paraplegia, tetraplegia, sensory loss and also loss of bladder control, faecal incontinence, and syncope. Physical examination may reveal upper motor-neuron weakness, hyper reflexia, and a positive Babinski's sign. Immediate immobilisation should be done. Magnetic resonance imaging (MRI) is valuable for the assessment of spinal cord damage. A single horizontal or vertical spinal dislocation without significant neurologic features requires no surgical intervention. A neck collar may suffice and, if necessary, non-steroidal anti-inflammatory drugs (NSAIDs) and simple neck traction. Neurologic symptoms and signs of cord compression is a strong indication for neurosurgery. Different surgical techniques are now being developed which allow removal of the odontoid peg and/or fusion without the need for long periods of immobilisation.

Rheumatoid Heart Disease

Pericarditis and rheumatoid valve involvement occurs in seropositive patients with subcutaneous nodules. This usually involves the mitral and aortic valve. Rheumatoid aortic valve disease may be haemodynamically significant and it can be rapidly progressive simulating aortic cusp rupture. Pericarditis occurs in 30% to 50% of patients. Rapidly progressive effusive pericarditis is associated with high morbidity. Pericarditis resolves as the rheumatoid disease is controlled. Symptomatic patients generally respond to NSAIDs. Occasionally, gluco-corticoids are required if the symptoms are severe. Heart failure will require diuretics and inotropic agents. Cardiac tamponade will require therapeutic aspiration. Valve replacement may be indicated in patients with severe or progressive valvular stenosis or regurgitation.

Acute Upper Airway Obstruction

Cricoarytenoid arthritis can occur in RA. Rheumatoid nodules can develop within the larynx and trachea and can erode through local structures. If large, the nodules can cause dyspnoea, due to obstruction of the larynx, especially during acute infections. Symptoms may range from dysphonia to frank aspiration and even acute airway compromise. Indirect laryngoscopy in the acute phase reveals erythema and swelling of the arytenoid mucosa. Operative direct laryngoscopy is the standard for definitive diagnosis of cricoarytenoid joint fixation. High resolution computed tomography (HRCT) is the investigation of choice in assessing cricoarytenoid involvement.

Management consists of tracheostomy for an acute obstruction. Medical treatment includes corticosteroids at the earliest. Periarticular local steroid injections have helped in ameliorating acute joint dysfunction.

EMERGENCIES IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Acute Transverse Myelitis

It presents as a rapidly progressive motor, sensory and autonomic dysfunction. The risk increases in the presence of antiphospholipid antibodies (APLA) syndrome. The pathogenesis of acute transverse myelitis may be related to a vascular thrombosis, or to a direct interaction between antiphospholipid antibodies and membrane phospholipids at the spinal cord level. Clinical presentation is with sudden onset of leg weakness or sensory loss and/or bowel or bladder dysfunction. Evolution of the neurodeficit is complete by 1 to 2 days. Thoracic spinal cord is most commonly involved followed by lumbar and cervical.

Cerebrovascular Accident

Vasculitis, local thrombosis or artery-to-artery emboli sometimes manifests with clinical stroke syndromes (**Figure 2**). Emboli can occur as a result of Libman-Sacks endocarditis which produces sterile vegetations on the heart valves. Strokes may be secondary to treatment of SLE, as steroids can cause atherosclerotic changes. Evidence of disease activity in other organs is helpful. Important is to evaluate cerebrospinal fluid (CSF) to rule out infection. CSF abnormalities, such as elevated cell count, elevated protein, or reduced glucose, may be present in one-third of the patients. Low levels of C4 and other complement components have also been detected in the CSF. MRI appears to be superior to conventional computed tomography (CT). Nuclear magnetic resonance (NMR) spectroscopy may provide better demonstration of brain lesions.

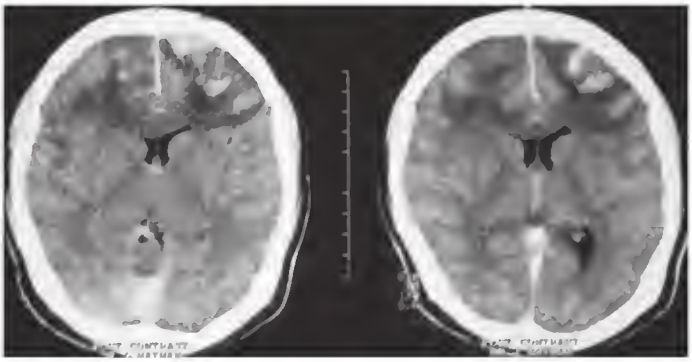


Figure 2: MRI showing venous infarcts in SLE.

Corticosteroids are the most important class of drugs available. Methylprednisolone (0.5 to 1g per day) intravenously for 3 to 5 days followed by oral prednisolone 1 mg/kg should be employed. Intravenous cyclophosphamide (0.5 to 1 g) has also been reported to be effective in serious forms of central nervous system manifestations. With APLA, anticoagulation is necessary. For progressive unresponsive disease, plasmapheresis or intravenous immunoglobulin may be considered. Usual therapies for seizures should also be employed.

EMERGENCIES IN SPONDYLOARTHROPATHIES

Uveitis

Uveitis is the most common extra-articular manifestation in ankylosing spondylitis. The incidence is higher in individuals who are HLA-B27 positive. Uveitis may also be seen in other spondyloarthropathies including reactive arthritis, undifferentiated spondyloarthropathy and psoriatic arthritis. Presentation is usually acute and unilateral, with a painful red eye, photophobia, increased lacrimation, and blurred vision. The involvement is usually anterior, rarely involving posterior elements. The iris is oedematous and discoloured. Pupil may become irregular if posterior synechiae form. There is copious exudate in the anterior chamber of the eye, which can be seen on slit-lamp examination. In most cases topical therapy with corticosteroid eye drops and mydriatics is all that is required. The eye may need to be protected from the light to ensure comfort during the period of pupillary dilatation. Administration of steroids orally, intravenously or by intraocular injection is required when local treatment fails to relieve the inflammation. Inadequate treatment may lead to adhesions and secondary glaucoma.

EMERGENCIES IN VASCULITIDES

Alveolar Haemorrhage and Pulmonary Renal Syndrome (PRS)

Alveolar haemorrhage is a medical emergency and occasionally is the initial presenting manifestation. Pulmonary-renal syndrome is diffuse alveolar haemorrhage and glomerulonephritis occurring simultaneously. Haemoptysis is the most classic finding in combination with peripheral oedema and haematuria or other signs of glomerulonephritis. Bleeding is from low-pressure vessels but it is rarely massive. Haemoglobin levels can drop dramatically. Pulmonary infiltrates may be diffuse or patchy, and usually are perihilar, sparing the apices (**Figure 3**). The renal pathology is small-vessel vasculitis resulting in a form of focal proliferative glomerulonephritis. Goodpasture's syndrome is the prototype cause, but Wegener's granulomatosis, microscopic polyangiitis, and, less commonly, other vasculitides can also cause pulmonary renal syndrome.



Figure 3: X-ray chest of a patient with pulmonary haemorrhage in *Polyarteritis nodosa*.

Initial testing includes urinalysis for evidence of haematuria and red cell casts (suggesting glomerulonephritis). Diffusion

capacity of carbon monoxide (DLCO) may be increased. Bronchoscopy is important to exclude infection and to document the presence of blood when there is no haemoptysis. Hemosiderin-laden macrophages provide proof that bleeding has occurred within the lung. Serum antibody testing may help distinguish some causes, such as antiglomerular basement membrane antibodies in Goodpasture's syndrome, antinuclear antibodies (ANA), and anti-deoxyribonucleic acid antibodies in SLE, anti-neutrophil cytoplasmic antibodies (ANCA) directed against proteinase-3 (PR3-ANCA) in Wegener's granulomatosis, perinuclear ANCA (p-ANCA) in microscopic polyangiitis. Definitive diagnosis requires lung biopsy and/or renal biopsy.

Standard therapy includes pulse intravenous methylprednisolone (500 to 1000 mg once a day for 3 to 5 days). Mechanical ventilation with high positive end expiratory pressure may be required. As life-threatening features subside, the dose can then be reduced to 1 mg/kg, prednisone tapered gradually over the next 12 weeks. Cyclophosphamide should be added at a dose of 0.5 to 1 g/m^2 administered intravenously as a monthly pulse or 1 to 2 mg/kg per day orally. Maintenance therapy includes low-dose corticosteroids coupled with cytotoxic agents.

Visual Impairment in Giant Cell Arteritis (GCA)

Permanent visual loss is one of the most dreaded manifestations of GCA. Visual disturbances have been described in 25% to 50% of cases, although the incidence of visual loss is much lower, about 6% to 10% in most series. Blindness might be partial or complete. Other visual symptoms include transient or permanent diplopia or ptosis. Loss of vision in GCA is caused by inflammation in the arteries supplying the optic nerve head or retina. Involvement of the second eye can occur. On early fundoscopy, the optic disc is pale and swollen whereas the retina appears almost normal. Within 4 to 6 weeks, the optic disc becomes atrophic, with a chalky appearance. The retina will appear greyish, swollen and a contrasting red zone, 'cherry red spot', can be seen in the macula.

Acute phase reactants like erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) are commonly elevated. Often there is normocytic normochromic anaemia. Colour doppler ultrasonography may show a dark 'halo' around the lumen of temporal arteries, stenoses or occlusion may also be found. Temporal artery biopsy, however, remains the gold standard.

Oral steroids are commonly used but intravenous methylprednisolone can be used for severe cases. The treatment is initiated at 1 mg/kg per day of prednisolone for 4 to 6 weeks followed by taper of 5 mg every 1 to 2 weeks while monitoring clinical symptoms and ESR or CRP. Azathioprine has been shown to exert a modest corticosteroid-sparing effect. There has been a value of methotrexate in corticosteroid-resistant cases.

Acute Mesenteric Vasculitis

Abdominal pain caused by bowel ischaemia secondary to mesenteric vasculitis is an uncommon complication of systemic vasculitis. Bowel ischaemia can lead to perforation and haemorrhage, and has a high mortality. The onset may be acute and severe (e.g. mesenteric infarction) or chronic due to mesenteric ischaemia. Chronic mesenteric ischaemia may be manifested by a variety of symptoms including abdominal pain after eating ('intestinal angina'), weight loss, nausea, vomiting and diarrhoea. Ultrasonography demonstrates oedematous bowel loops. Gastroscopy and colonoscopy can show signs of ischaemia and ulceration. Common CT findings include dilated bowel, focal or diffuse bowel-wall thickening, abnormal bowel-wall enhancement, mesenteric oedema, engorgement of mesenteric vessels and ascites. Vascular thromboembolism and aneurysms that involve fairly large vessels can also be demonstrated by conventional or CT angiography (**Figure 4**).

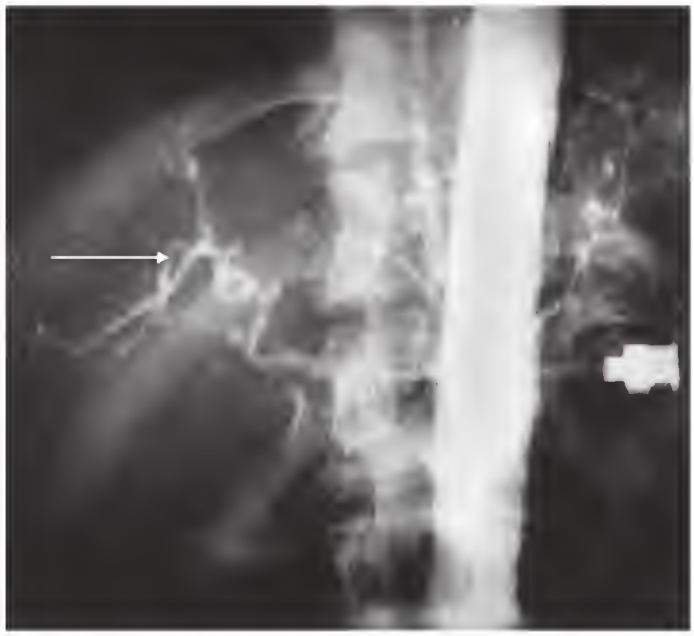


Figure 4: Coeliac angiography with superior mesenteric artery cannulation revealing aneurysm at porta hepatis in a patient with *Polyarteritis nodosa*.

Aggressive anti-inflammatory immunosuppressive treatment should be initiated. The treatment of choice is high-dose intravenous infusions of methylprednisolone or an equivalent agent. Use of heparin is a double edged sword and its use is to be decided on individual basis. In non responding patients and with severe haemodynamic compromise, surgical management is required.

Mononeuritis Multiplex

The onset may be sudden, with pain and paresthesias radiating in the distribution of a peripheral nerve, followed in hours or days by a motor deficit of the same peripheral nerve. This may progress asymmetrically to involve other peripheral nerves and produce a mononeuritis multiplex or a multiple mono-neuropathy. All sensory modalities and motor functions may be affected. Nerve conduction studies should be done at the earliest. Confirmation is by nerve biopsy. Small arteries in the epineurium are affected. Changes include fibrinoid necrosis in acute lesions to intimal proliferation and perivascular fibrosis in more chronic lesions. Methylprednisolone 500 to 1000 mg intravenously for 3 to 5 days should be used to obtain a rapid response followed by oral corticosteroids. Other immunosuppressives like cyclophosphamide, azathioprine, methotrexate, cyclosporine and *Mycophenolate mofetil* can also be used. Plasmapheresis and IVIG are reserved for fulminant cases.

EMERGENCIES IN SYSTEMIC SCLEROSIS

Scleroderma Renal Crisis

Scleroderma renal crisis is characterised by sudden onset of accelerated hypertension, rapidly progressive renal

insufficiency, microangiopathic haemolysis, and consumptive thrombocytopaenia. Markedly elevated plasma renin activity and dramatically rising creatinine is found in most cases. Renal crisis must be considered in any patient with scleroderma whose blood pressure rises even mildly above previous recordings.

Vasospasm occurring on pre-existing renal arteriolar disease is thought to cause excessive renin release. The subsequent effects of angiotensin II induce further renal cortical ischaemia and fixed loss of cortical blood flow and necrosis. Vascular injury in the form of intimal disruption, fibrin deposition and micro-angiopathic haemolysis is the sequel. Corticosteroid therapy has been postulated as an associated factor. Anaemia and thrombocytopaenia occurs, blood smears demonstrating fragmented red cells, followed by increase of fibrin degradation products and reticulocytosis. Urine analysis typically reveals protein and red cells.

Aggressive treatment improves outcome. Angiotensin converting enzyme (ACE) inhibitors should be used. When maximum doses of ACE inhibitors do not control the blood pressure, calcium channel blockers or vasodilators can be used, as needed. Dialysis may be necessary. ACE inhibitors should be continued since there may be delayed recovery of renal function. Renal transplantation can be done successfully.

EMERGENCIES IN INFLAMMATORY MYOPATHIES

Respiratory Muscle Weakness

Significant respiratory muscle weakness may develop in patients with polymyositis or dermatomyositis. Both inspiratory and expiratory muscles may be affected, including the diaphragm. Bulbar weakness results in hoarseness or dysphonia, dysphagia with regurgitation of liquids. Pharyngeal and tongue involvement increases the risk of aspiration. Muscle biopsy should be performed in all cases to confirm the diagnosis. Arterial blood gases will show hypoxia with carbon dioxide retention. Chest radiograph should be done to exclude infection. A simple bedside investigation includes periodic single breath count. Increasing hypoxia, neck muscle weakness (**Figure 5**), falling single breath count, paradoxical breathing is an indication of impending respiratory failure and need for mechanical ventilation. Patient should be started on intravenous Methylprednisolone (1g per day) for 3 to 5 days followed by oral prednisolone 1mg/kg per day. IVIG or plasmapheresis has been successfully used for severe non-responding disease. Biological agents like rituximab have been showed to be useful in a few case reports. Outcome is usually good with most patients regaining power to normal.

Cardiac Disease

Signs of cardiac involvement in PM and DM may be found in more than 70% cases. It is commonly asymptomatic, but can contribute to mortality. The activity of the cardiac disease may be independent of the myositis. The major manifestations include conduction disturbances, arrhythmias, and myocarditis. Less common is congestive heart failure due to myocarditis or fibrous replacement of the myocardium. Symptomatic pericarditis is rare. Although electrocardiographic abnormalities are frequent, most are minor non-specific ST-T wave changes. The MB fraction of creatine kinase is frequently elevated. Treatment includes diuretics for cardiac failure. Dopamine or dobutamine should be added as per clinical requirement. ACE inhibitors should be used as these agents are known to prevent maladaptive remodelling.



Figure 5: Neck muscle weakness in a patient with polymyositis.

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Catastrophic antiphospholipid syndrome is a life-threatening complication where multiple thromboses of medium and small arteries in three or more organs can occur over a few days. This is discussed elsewhere.

CONCLUSION

Spectrum of emergencies varies from patient to patient. Superimposed infections, disease flares and adverse reaction to drugs can contribute to morbidity and mortality. A thorough knowledge, appropriate investigations and rapid, accurate treatment of rheumatological emergencies should favourably influence morbidity and outcome.

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Section 25

Nutrition

Section Editor: S.V. Madhu

25.1 Nutrition—Basic Considerations **1896**
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25.2 Assessment of Nutritional Status **1900**
Prema Ramachandran

25.3 Protein Energy Malnutrition **1904**
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25.4 Water Soluble Vitamins **1909**
Milind Y. Nadkar

25.5 Fat Soluble Vitamins **1913**
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25.7 Food Allergy and Food Intolerance **1922**
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25.8 Eating Disorders **1924**
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25.9 Enteral and Parenteral Nutrition **1927**
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25.1 Nutrition—Basic Considerations

SV Madhu

INTRODUCTION

The word nutrition comes from the Latin word *nutrire,* to suckle or feed—the primary act of suckling so characteristic of the process of nutrition. Nutrition by definition is the process of nourishment while nutrient is the substance that provides nourishment. Humans not only need nutrients for their nourishment but they also need it in sufficient amount. Nutrients are classified as macronutrient or micronutrient based on daily requirement. Macronutrients include carbohydrates, proteins, fats and minerals like calcium, phosphorus, sodium, chloride, potassium, sulphur and magnesium. Vitamins and minerals that are required in amount less than 100 mg per day constitute micronutrients. Nutrients that cannot be synthesised in body are called essential. While carbohydrates, fats and proteins mainly provide energy and help in tissue building and maintenance, vitamins and minerals mainly support metabolism. Hence, a person must consume a balanced diet to provide all the nutrients in proper measure, known as requirements. A requirement is defined as the lowest continuing intake of a nutrient that will maintain a defined level of nutrition in an individual.

GENERAL PRINCIPLES OF DIETARY RECOMMENDATIONS

Dietary standards are basically the average daily amounts of essential nutrients required to meet the physiological needs of practically all healthy persons in a group with specified characteristics. It is estimated on the basis of available scientific knowledge. These standard values are together called dietary reference intake (DRI). These include estimated average requirement (EAR), recommended daily allowance (RDA), adequate intake (AI) and tolerable upper intake level (UL). A nutrient has either EAR and an RDA, or an AI. When an EAR for the nutrient cannot be determined (and therefore, neither can the RDA), then an AI is set for the nutrient.

Dietary Reference Intakes

Estimated average requirement (EAR): Average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group.

Recommended dietary allowance (RDA): Average daily nutrient intake level sufficient to meet the nutrient requirement of nearly all (97% to 98%) healthy individuals in a particular life stage and gender group.

Adequate intake (AI): A recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate, used when an RDA cannot be determined.

Tolerable upper intake level: Highest average of daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the upper intake level, the potential risk of adverse effects increases.

RDA AND ITS IMPORTANCE

RDA is estimated by first evaluating the EAR for an absorbed nutrient by healthy individual's representative of a sex and age group. An amount is then added as a safety factor which is to compensate for the individual variation and bioavailability of nutrients in commonly consumed foods. When the standard deviation (SD) of the EAR is available and the requirement of the nutrient follows Gaussian distribution, the RDA is calculated as:

$$RDA = EAR + 2SD_{EAR}$$

In cases where SD is not available, a coefficient of variation of 12.5% is assumed and RDA is 25% (+ 2SD) higher than the mean requirement.

Adult men and women differ in their nutrient requirements to a small degree but requirement in the latter group alters significantly during pregnancy and lactation. RDA should be such that it allows maximal rate of growth, prevents biochemical and clinical abnormalities, allows for saturation of enzymes and co-factors, accounts for obligatory losses and builds up the stores. They meet the requirements only when all other nutrients are also provided in optimal amounts. For example, giving fat soluble vitamins according to RDA in the presence of very low fat content food will lead to vitamin deficiency despite being given at RDA levels. However, it must be recognised that RDA is not meant to be used as standard to determine whether or not a given individual requirement has been met, since it is a level above the requirement of most individuals in a given population.

RDA for Indians

The first attempt towards defining the dietary allowances for Indians was made by the Nutrition Advisory Committee of the Indian Research Fund Association [now Indian Council of Medical Research (ICMR)] in 1944. The ICMR constituted an Expert Group in 2008 to revise and update the nutrient requirements and dietary allowances for the Indian population. This is the Sixth Expert Group constituted by the ICMR. The last Group was constituted in 1988. The committee was guided by the newer developments that are published in FAO/World Health Organisation (WHO)/UNU reports and background information generated by research and surveys in India.

Since RDA is the average daily dietary intakes sufficient to meet the nutrient requirement of nearly all healthy individuals, it is necessary to take into account the factors that influence the metabolism of food nutrients. These are: (i) the bioavailability, and (ii) the individual variability.

ENERGY REQUIREMENT

The energy requirement of an individual has been defined by WHO in 1985 as "the level of energy intake from food that balances energy expenditure when the individual has a body size and composition and level of physical activity, consistent with long-term good health, also allowing for maintenance of economically essential and socially desirable activity. In children, and pregnant and lactating women, it includes the energy needs to be associated with the deposition of tissues or secretion of milk at rates consistent with good health".

The energy expended includes the expenditure at rest (basal metabolic rate), physical activity and thermogenesis (specific dynamic action of foods).

Pregnancy and Lactation

Extra energy is required during pregnancy and lactation for the growing foetus and infant, respectively. According to the recent ICMR recommendations, the additional intake of energy is changed to 350 Kcal/day during second and third trimesters of pregnancy, 600 Kcal/day for the first 6 months of lactation and 520 Kcal/day in next 6 months.

DIETARY SOURCES OF ENERGY

Carbohydrates, fats and proteins constitute the sources of energy. Each gram of carbohydrate and protein gives 4 Kcal each while a gram of fat gives 9 Kcal of energy. These three energy sources are to be balanced such that the person receives enough protein for tissue building and maintenance, and sufficient carbohydrate and fat to fulfil the energy requirement.

Carbohydrates

Carbohydrates account for the major part of energy requirement. They are basically made of either simple sugars or complex sugars. Recent scientific evidence considers the unhealthy role of simple sugars. Hence, it is recommended that simple sugars should not account for more than 10% of total energy. A wide range of carbohydrate (55% to 75%) intake should be from whole grains and legumes, vegetables and fruits.

Proteins

The dietary proteins are essential to provide amino acids for the synthesis of body proteins, both structural proteins and biologically active enzymes and other biologically important nitrogenous compounds in the body. Adequate dietary protein is essential during growth in children. In the adult, it is essential for the synthesis of new proteins to replace those, which are being broken down. Additional proteins are also required during pregnancy and lactation for the growing foetus and infant.

There are eight essential amino acids (EAA) that are considered essential as they cannot be synthesised in the body. They need to be provided in proper proportions and in adequate quantities to synthesise tissue proteins in the body. In a diet, proteins are to be provided in proper quantity as well as proper quality. The quality of protein depends on its ability to supply the required amounts of essential amino acids. Animal proteins are generally considered to be of better quality. Egg protein is used as a reference against which the other proteins are compared. Vegetable proteins lack one or the other EAA, such as lysine or methionine. Lysine is the limiting amino acid in most cereals while methionine in the pulses. The biological quality of a mixture of vegetable proteins based on cereals and pulses is only 65% as compared to 100% of egg protein. The safe level of intake in terms of dietary protein is 1.0 g/kg body weight per day. Additional protein requirements of 15 g per day during pregnancy and 25 g per day during 0-6 months of lactation have been recommended.

Fats

Fats being concentrated forms of energy, both optimum and safe intakes need to be mentioned while recommending fats. Source of the fat in diet can be from visible sources or from invisible sources. Visible sources include vegetable oils or animal. A substantial amount of fat is present in cereals, pulses and vegetables which form the invisible fat.

Like amino acids, there are fatty acids that are essential for body and are called essential fatty acids (EFAs). Generally referred as polyunsaturated fatty acids (PUFAs), they include linolic and alpha-linolenic acid.

The minimum amount of fat that should be taken by average Indian adult is 20% of total energy (TE); 10% from visible sources and 10% from invisible sources. However, the fat intake should not exceed 30% of TE. Of these saturated fatty acids should not exceed 10% of TE. 10% of TE should be from PUFA. The remainder should be from monounsaturated fatty acid (MUFA).

Dietary Fibre

Dietary fibre which forms an indigestible and important component of plant foods were never considered as source of energy. Some dietary fibres undergo fermentation in the colon and yield short chain fatty acids. These are used as source of energy by the colonic cells and by the liver. Up to 2.6 Kcal of energy is derived from a gram of fermentable foods and no energy from non-fermentable fibre. Normally, 70% of fibres are fermentable. Hence, energy conversion factor for fibre is taken as 2.0 kcal/g. The intake of 40 g/2000 kcal may be rationalised in different groups based on recommended energy intake.

MALNUTRITION

A decade ago, in India, malnutrition meant mostly undernutrition. But India now being a country in developmental transition, has come to face the other burden of malnutrition, namely overnutrition. With 10% rural adults and 20% urban adults suffering from overnutrition, India is in nutritional transition as well. Pre-transition undernutrition and post-transition overnutrition are together leading to an emerging double burden of malnutrition.

Undernutrition

Undernutrition has improved compared to post-independence time substantially but the improvement has slowed down with very little improvement in last few years. Though severe clinical forms of protein-energy malnutrition (PEM) and other nutrient deficiencies are reduced to major extent, there are still sub-clinical forms of deficiencies that are persisting. Around 36% of women and 34% of men are still having body mass index (BMI) below normal. More than 50% women (particularly pregnant women) and children suffer from iron deficiency anaemia (IDA). The fight against undernutrition is becoming more and more difficult because for every frank case of nutrition deficiency,

there are dozens of others suffering from subclinical malnutrition who are missed.

Factors causing undernutrition

It is necessary to look into the factors that are responsible for undernutrition in order to fight against it. Factors like Illiteracy and low socioeconomic status were responsible for undernutrition in post-independence India, the same factors are still playing the main role 60 years after independence. Women, especially pregnant women and children are the vulnerable risk groups. Rural areas have more percentage compared to urban, almost double in case of adults according to National Family Health Survey-3 (NFHS-3). In case of children, higher birth order and the nutritional status of mother are also important risk factors. Over that, the never ending cycle of undernutrition leading to infections, which in turn leads to undernutrition, makes the problem more complicated.

Protein Energy Malnutrition (PEM)

Despite various government schemes undernutrition is still a major problem in our country. Among children less than 3 years, there are 45% who are stunted, 23% who are underweight and 40% who are wasted. The problem is more in rural, uneducated and low socioeconomic households. Despite the efforts of various organisations, the problem still persists because of lack of awareness and motivation. Even among adults 36% of women and 34% of men are underweight. With the problem involving well more than one-third of Indian population it will have negative impact on the health and development of the country.

Macromineral Deficiency

Among the macrominerals calcium (Ca^{2+}) deficiency has been the main concern. Other macrominerals are sufficient in the diet and do not cause any deficiency. Although intakes according to previous ICMR (1988) survey have been successful to reduce fracture rates, it has resulted in compromises in stature and restriction in the function of the skeletal system. Human body has the ability to adapt to different levels of intakes of Ca^{2+} and maintain a positive Ca^{2+} balance even at 400 mg per day. This prompted earlier committee to fix 400 mg per day as RDA. Despite more than 50% of the adult population obtaining the RDA level of 400 mg per day, there is evidence of widespread Ca^{2+} depletion as indicated by bone density measurements, particularly in women after repeated pregnancies and lactation. These observations lead to new RDA of 600 mg per day.

Micronutrient Deficiency

Even though micronutrients are required in small amounts, they are essential in various body functions. Hence, even slight deficiency can present profoundly. Moreover, many of these are present in lesser amounts in diet and are easily altered by various cooking practices.

Among minerals iodine and iron deficiencies are important public health problems. Iodine deficiency is the single greatest cause of mental retardation both worldwide and in India. Also iodine deficiency disorders (IDDs) are one of the most important micronutrient deficiency disorders of public health significance in India. Environmental factors and goitrogens in food are the two main factors responsible for deficiency. A study conducted by National Institute of Nutrition (NIN) and Director-General of Health Services (DGHS) in 2003, in 40 districts, revealed that the overall prevalence of total goitre registered a significant decline from 14% to 69% during 1984-94 to 2% to 40% in 2003, especially in the Northeastern regions after universal iodisation. But with focus now on whole spectrum of IDD, 263 out of 324 districts surveyed by DGHS have been labeled as endemic. Iodine deficiency has ceased to be a disease of high altitudes. Also living on the sea coast does not guarantee iodine sufficiency, as significant pockets of iodine deficiency have been reported from the coastal regions too. According to NFHS-3 only half of the children below 5 years live in household using iodised salt, same as reported during NFHS-2. A lack of iodine in the diet can lead to IDD, which can cause miscarriages, stillbirths, brain disorders, and retarded psychomotor development, speech and hearing impairments, and depleted levels of energy in children. Iodised salt effectively will account for only half of RDA and so the food practises should be altered to avoid goitrogens in the food. Hopefully the ban on un-iodised salt by the Government of India (in 2006) will improve the scenario in coming years.

Iron is the other micromineral that poses a public health burden. Around 70% of children, 55% of women and 24% of men are anaemic according to NFHS-3. In a study conducted in slum children, 75% of anaemia responded to iron and 22% to vitamin B_{12}. The situation has actually worsened in children and women compared to NFHS-2 despite various government schemes.

Widespread zinc (Zn) deficiency has been thought as a possible cause for growth failure and morbidity in children according to some available data. But lack of supportive evidence of lowered blood Zn levels and other causes that can manifest as the symptoms assumed to be due to Zn deficiency makes it difficult to attribute them to Zn deficiency specifically.

Vitamin deficiencies are also significant. Although there has been a significant reduction in severe clinical forms of vitamin-A deficiency, it is still a public health problem with 40% to 60% children in developing countries showing inadequate biochemical status of vitamin A. Only 25% of below 3 years children received vitamin A supplementation in last 6 months. Very low intakes, poor bioavailability of pro-vitamin A from the predominantly vegetarian diet and recurrent infections are thought to be the main reasons for widespread prevalence of vitamin A deficiency. While the severe forms of bone disease are no longer prevalent in children now, growing urbanisation, reduced physical activity and low exposure to sunlight has contributed to a spurt of vitamin D deficiency (VDD) as evidenced from low circulating vitamin D levels.

Among water soluble vitamins thiamine, riboflavin, folic acid and B_{12} deficiencies are important concern. According to National Nutrition Monitoring Bureau (NNMB), 40% households meet RDA of thiamine and only 13% do so for riboflavin. According to various studies, it is estimated that the B_{12} deficiency involve up to 30% to 40% of Indian population.

OVERNUTRITION

With increased usage of unhealthy processed foods, decreased usage of time tested traditional diets and increased sedentary lifestyles; India is fast approaching other developing countries

which are becoming more obese. According to NFHS-3, around 9% of adult men and 13% of adult women are overweight. Even rural areas are not behind with 10% of adult population of rural area being overweight. Obesity is becoming a substantial problem among several groups of women in India, particularly women living in urban areas, who are well educated, and those from households with a high standard of living. Approximately 25% in each of these groups have a BMI of 25 or more. Indians already being at risk for obesity and diabetes due to their ethnicity, the rising trend of over nourishment might put more burden compared to what it could do in other developing or developed countries.

Though clear-cut nationwide data are not available on childhood obesity, it is estimated that around 25% of urban children are obese. This is to be taken seriously as these children carry a significant risk of developing diabetes, hypertension, metabolic syndrome and coronary heart disease (CHD) in the future as they grow into adulthood. The percentage of adults, who are malnourished, i.e. both under-nourished and over-nourished, does not vary too much across various states or in urban and rural population. The reason being, as the percentage of under-nourished are decreasing, there is an increase in number of adults who are overweight.

Hence, the planning to correct undernutrition has to consider even the possible problem of overnutrition in future. Unless correct measures are taken regarding proper balanced diet, India might become obesity capital as well apart from already being diabetes mellitus capital.

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25.2 Assessment of Nutritional Status

Prema Ramachandran

INTRODUCTION

It is well known that nutritional status is an important determinant of health and modifier of course and outcome of diseases. Nutritional status is normal when the food and nutrient intake of the person is sufficient to meet the requirements for normal physical activity, and physiological requirements for growth and development. Balanced diet and adequate physical activity promote normal nutritional and health status and protect against illnesses due to lack or excess of nutrient intake. Appropriate nutritional care during illness can reduce the severity, shorten the duration of illness, hospitalisation and convalescence. Therefore, assessment of nutritional status of the individual seeking health care should be incorporated as a part of promoting good health as well as clinical management of illness.

Health care seekers are becoming increasingly aware of the importance of nutrition and collect information from individuals about: (i) nutritional status; (ii) appropriate and sustainable diets and lifestyle that will prevent illnesses and protect and promote health; and (iii) dietary management during illness that will provide symptomatic relief and promote rapid recovery.

Undergraduates and postgraduates should have the necessary knowledge and skills for assessment of nutritional status and providing appropriate nutrition advise to the individuals, families and communities for prevention and management of under- and overnutrition and nutrition care during illness and convalescence.

PARAMETERS FOR ASSESSMENT OF NUTRITIONAL STATUS

Major parameters used for assessment of nutritional status are:

- Dietary intake
  - Food frequency method
  - 24-hour recall
- Physical activity pattern
- Clinical assessment of nutritional deficiency signs
- Anthropometric assessment of nutritional status
- Body composition studies using various techniques
- Biochemical assessment.

Assessment of Dietary Intake

Dietary intake of individuals, families and communities vary depending upon their socioeconomic status, dietary habits and customs. Information of nutrient intake will help in identifying factors responsible for under- and overnutrition and micronutrient deficiencies which could have contributed to illness. Illness may modify the dietary intake and aggravate nutritional deficiencies.

Food frequency questionnaire provides a relatively rapid and easy method of assessing food consumption of the individual, including meal and dietary patterns, specific foods avoided or preferred. Food frequency questionnaire will not give any idea about the quantities in which the food stuffs are consumed which is an important determinant of deficiency or excess.

Diet history using 24-hour recall is an excellent tool to obtain information on the family cooking patterns, intra-family distribution of food and individual's dietary intake. Diet survey using 24-hour dietary recall should not be done on the day following holidays or festival or fast days because dietary intake on these days will not be representative. Single day 24-hour dietary recall cannot be taken as accurate representation of dietary intake of the individual but if repeated over time may provide useful information whether nutrition counselling has resulted in on dietary modifications of the individual.

Available data from diet surveys in India indicate that Indian diets remain predominantly cereal-pulse based. Dietary intake in poor segments especially in children and adolescents are below the requirement; as a result undernutrition rates are high. Low intake of vegetables and fruits, poor bioavailability of iron, and lack of universal use of iodised salts are responsible for micronutrient deficiencies being major public health problems even today. Even segments of population with no economic constraints, do not consume diversified balanced diets with adequate intakes of fruits and vegetables, animal/dairy products. In some urban affluent segments there is an increase in consumption of junk food, rich in carbohydrates and fat, resulting in rapid increase in obesity in these groups. Assessment of dietary intake and appropriate advise is important for maintenance of optimal health and combating over- and undernutrition.

Physical Activity Pattern

Physical activity pattern is emerging as an important determinant of nutritional status both in urban and rural areas. Earlier majority of men and women in rural and urban areas were moderately active. However, increasing access to mechanised transport, access to water and fuel in the vicinity of the house hold and increasing mechanisation of the occupational activities have resulted in a steep decline in physical activity. This in turn has resulted in substantial reduction in energy requirements of the individual. Steep reduction in physical activity and relatively unchanged energy intake have been identified as the major factors responsible for rising obesity rates in urban and rural populations. In some urban affluent groups, increased intake of energy dense junk food and sedentary lifestyle are emerging as major factors associated with overnutrition.

Nutrition surveys carried-out by the National Nutrition Monitoring Bureau (NNMB) has shown that by mid nineties there had been a steep reduction in physical activity not only in urban but also in rural areas (**Table 1**). Health education

about exercise to become a part of daily routine to promote muscle and bone health and prevent development of adiposity in all age groups is critical for prevention of overnutrition and associated health hazards. As and when any person seeks health care, the opportunity should be utilised to assess nutritional status and physical activity and advise appropriate lifestyle modifications.

Table 1: Physical Activity Pattern in Rural Adults Based Upon NNMB Survey 1994-95

Activity status	Men		Women		Total	
	No.	%	No.	%	No.	%
Sedentary	1349	33.3	2765	62.7	4114	48.6
Moderate	2650	65.5	1632	37.0	4282	50.6
Heavy	48	1.2	14	0.3	62	0.8
Pooled	4047	100.0	4411	100.0	8458	100.0

NNMB = National Nutrition Monitoring Bureau.

Clinical Assessment of Nutritional Status

In the last century, clinical assessment of nutritional deficiency signs was a very important component of assessment of nutritional status. However, with improvement in dietary intake and better access to health care, there has been a steep decline in the prevalence of clinical signs of deficiencies. Pellagra, scurvy, keratomalacia are no longer seen. Even in tertiary hospitals, kwashiorkor, and marasmus are rarely seen. Glossitis, angular stomatitis (suggestive of vitamin B complex deficiency), Bitot's spots (vitamin A deficiency) are seen in less than 1% of children and adults. There has been a steep decline in goitre even in the erstwhile goitre belt. Even though clinical forms of macro- and micronutrient deficiencies have become uncommon, sub-clinical biochemical deficiencies continue to be common.

It is a matter of concern that unlike all other nutritional deficiencies, there has not been any change in the prevalence of anaemia. Clinical signs of anaemia are non-specific (easy fatiguability, pallor, oedema feet) and do not revert soon after therapy, e.g. spoon shaped nails. It is not possible to clinically assess severity of anaemia and response to iron therapy; so estimation of of haemoglobin by cyanmethaemoglobin method is the best method for diagnosis of anaemia and assessing response to therapy. Majority of Indians irrespective of age, sex and socioeconomic status are iron deficient and anaemic; in view of this whenever any person seeks health care for any reason, they should be screened for anaemia and appropriate treatment provided for all anaemic persons.

Anthropometric Assessment

Anthropometric assessment is one of the most widely used methods for assessment of nutritional status both at the community level and for the individuals because of the relative ease and reproducibility of measurements, availability of standards based on normal population for comparison and demonstrated association between abnormal measurements and clinical illnesses. In the past when undernutrition was the major problem, weight and height were the most widely used measurements for the assessment of nutritional status. Height is the index that reflects the cumulative impact of past undernutrition. Weight is the index that reflects partly the cumulative impact of past undernutrition (because stunting is associated with lower body weight) and partly current nutritional status [low body mass index (BMI) for the current height is associated with lower body weight]. With the emergence of dual nutrition burden, BMI (weight in kg/height in m^2) has been increasingly used for the detection of both under- and overnutrition, especially in developing countries where stunting is common. In children BMI varies with age; World Health Organisation (WHO) has published the standards for BMI for age from 0 to 5 years in 2006 and 5+ to 18 years in 2007 and recommended that BMI for age which takes current height, weight and age into account and assesses current energy deficit or excess, should be used for the assessment of nutritional status, detection of both under- and overnutrition in children. India has accepted the WHO standards (2006 and 2007) for height, weight and BMI for age for assessment of under- and overnutrition in infants, children and adolescents. For adults, BMI has long been used as an indicator for both over- and undernutrition.

Measurement of length/height

In infants and children who cannot stand erect recumbent length is measured using either a stadiometer or an infantometer (**Figure 1**). In the past, height was measured using anthropometry rod or stadiometer. In recent years when almost all health care institutions have a vertical wall and good cement flooring, there is a greater tendency to use simple wall mounted tape instruments to measure height in children and adults in hospital settings. The instrument is hung on the wall exactly two meters from the floor. To measure height accurately, the person is made to stand erect with back of heels, knees, buttocks, shoulder and head touching the wall. The head is to be positioned in Frankfurt plane (lower margin of the orbital fossa in the horizontal line with the external auditory meatus) and the horizontal limb of the instrument is brought down, so that it lies on the top of the head. The reading at the horizontal red mark on the tape is the height of the person.



Figure 1: Measuring length in infants.

Height is an excellent indicator of cumulative past undernutrition; serial height measurements in children can indicate whether they are growing according to their trajectory or deviating from it. Data from national surveys of India indicate that average height in men and women are about 160 cm and 150 cm, respectively and about 11% of women have height below 145 cm. Low birth length, stunting in childhood (nearly half of the pre-school children are stunted) and adolescence are major factors responsible for the low adult height in Indians.

Measurement of weight

During the last century accurate beam balances were used for measurement of weight in clinical settings. These balances were heavy and could not be shifted readily from one place to another. With the advent of electronic balances, it has became possible to measure weight with 100 g accuracy using a battery operated, relatively inexpensive, light and readily portable balances (**Figure 2**). In the past when undernutrition was the most common nutritional problem in the country, weight was the most widely used measurement for assessment of nutritional status in adults and children because it provided some insight into past and current energy deficiency. Underweight individuals are more prone for infections and infections can result in further deterioration in body weight. Nutritional support during illness and convalescence can limit and reverse the weight loss associated with illnesses. Data from national surveys indicate that mean weight in men and women are 45 and 53 kg, respectively. It is estimated that about half the children and a third of adult men and women are underweight in Indian population.



Figure 2: Measuring weight on an electronic weighing machine.

Computation of BMI

With the emergence of dual nutrition burden it has become essential to assess current energy deficiency and excess; BMI which provides this information has been increasingly used for assessment of nutritional status. Low BMI is associated with increased susceptibility to infections; high BMI is associated with increased risk of cardiovascular diseases. Earlier the computation of BMI was considered difficult in clinical settings; however, with the ready availability of calculators (even in mobile phones), it has become very easy to compute BMI. In adults, cut-off points used are less than 18.5 for undernutrition and more than 25 for overnutrition. In children BMI varies with age; WHO's BMI for age chart can be used to assess whether the child is undernourished or over-nourished.

Data from NFHS-3 indicate that if BMI is used as the indictor for the assessment of nutritional status, about 17% of pre-school children and a third of men and women are under-nourished; about 2% of pre-school children and 9% of men and 13% of women are overnourished (**Figure 3**). India has entered the dual nutrition burden era; all practising physicians should assess the current nutritional status using BMI and provide appropriate advise regarding dietary intake and physical activity to all persons seeking health care.

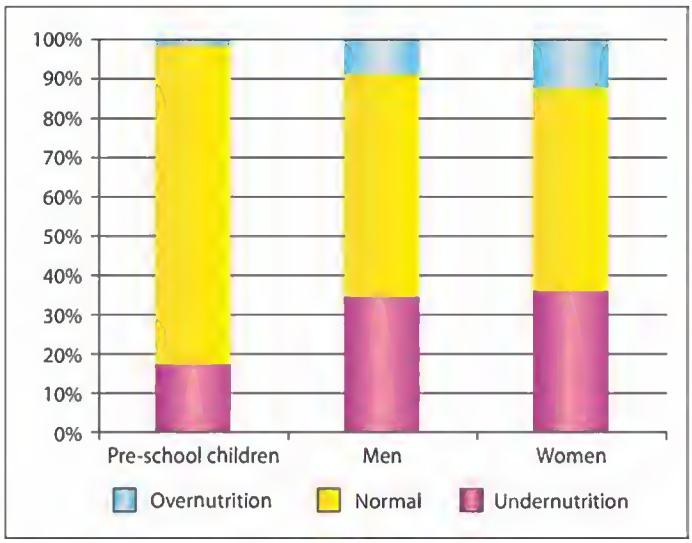


Figure 3: Nutritional status of children and adults-NFHS 3.

Waist circumference

With the emergence of non-communicable diseases as an important cause of morbidity in our country, it has become very important to measure waist circumference as an index of central adiposity. This correlates very well with insulin resistance and is a good indicator of the risk of diabetes and cardiovascular diseases. It is measured as the smallest circumference mid way between iliac crest and lower end of rib cage in standing position and at end of expiration. Waist measurements of 90 cm or above in males and 80 cm and above in females indicate central obesity in Asian Indians.

Assessment of Body Composition

The Indians have higher body fat for a given BMI as compared to Caucasians; higher adiposity in Indians begins in infancy and childhood. Both amount and distribution of the adipose tissue have been shown to influence the risk of cardiovascular diseases; therefore, increasing attention being paid to fat mass and its distribution. Earlier circumferential measurements (mid arm circumference, waist and hip circumferences and waist/hip ratio) and measurement of fat fold thickness (triceps, biceps, supra-iliac and subscapular fat folds measured using Harpenden's calipers) were commonly used for the assessment of fat mass and its distribution. Fat fold measurement requires a trained and skilled person; this has come in the way of widespread use of this relatively simple technique. In recent years, bioelectrical impendence measurement has been widely used in clinical settings for the assessment of total fat. Fat mass estimation by bioelectrical impedance assessment (BIA) when combined with the measurement of mid arm, waist and hip circumference can be used to differentiate overall, truncal and abdominal obesity. Epidemiological studies have explored the relative risk of diabetes and cardiovascular diseases with overall adiposity, truncal adiposity and abdominal adiposity, and also as between subcutaneous, intraperitoneal and retroperitonal fat accumulation in abdominal adiposity. Available data suggest

that abdominal adiposity is a part of metabolic syndrome which is associated with increased risk of both type 2 diabetes and cardiovascular disease risk.

Biochemical Assessment of Nutritional Status

Ideal biochemical test should be non-invasive, easy to carryout, specific, sensitive and preferably inexpensive. Such ideal tests are very few. In the development of any disease associated with deficiency or excess of nutrients, it is logical to expect that biochemical changes precede clinical manifestations. Biochemical tests can, therefore, expected to provide early warning of impending clinical problems. Biochemical tests in blood and urine can help diagnosis of the deficiency at the sub-clinical stage and confirm the clinical diagnosis. It has been reported that biochemical evidence of many vitamins and minerals have been seen in nearly half the apparently normal children and adults. It may not always be possible to get good correlations between biochemical tests, dietary intake and clinical parameters because of the wide range of normal biochemical values, varied rates of change of biochemical parameters, clinical deficiency and functional impairment. Inspite of these inherent limitations, biochemical tests have been widely used for the assessment of subclinical macro- and micronutrient deficiencies and excesses and risk of or confirmation of clinical problems. While isolated single biochemical estimation may not be of much use in the assessment of nutritional status, well chosen tests combined with dietary history, physical activity patterns and clinical examination findings provide complete information on nutritional status of the individual. Commonly used biochemical tests for the assessment of nutritional status and associated disease risks are dealt with in the respective chapters.

CONCLUSION

India is currently in the midst of socioeconomic, demographic, lifestyle, nutritional and health transition. Undernutrition continues to affect large segments of the population and is associated with increased risk of morbidity due to infections; simultaneously obesity and associated risk of non-communicable diseases are emerging as important public health problems, especially, among affluent segments of the society. Data from India also indicate that undernutrition in early life, followed by increased energy intake and sedentary lifestyle predispose to overnutrition and risk of non-communicable diseases during adult life. Physicians and programme managers have to play a critical role in combating the dual nutrition and disease burden and enable the country to achieve rapid improvement in health and nutritional status of the population through: (i) assessment of nutritional status of the community through appropriate screening; (ii) appropriate nutrition and lifestyle counselling for health promotion and health protection; and (iii) promoting synergy between health and nutrition services.

Assessment of nutritional status is an important component of both public health interventions and care of individuals seeking health care. Ideally nutritional assessment should be carried out periodically in all individuals and more often during vulnerable segments of population such as children, adolescents, pregnant and lactating women and elderly citizens. Our population and the health systems is still not geared to such routine periodic assessment and appropriate counselling for health promotion and early detection and effective management of nutritional deficiencies and excesses before clinical problems arise. In view of this, assessment of nutritional status should be carried out as and when there is an opportunity—as a part of community based nutrition surveys—and when any person seeks health care. Once assessment is done appropriate advice should be given depending upon their nutritional status.

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25.3 Protein Energy Malnutrition

Piyush Gupta

INTRODUCTION

Adequate food and nutritions are essential for proper growth and physical development to ensure optimal work capacity, normal reproductive performance, adequate immune mechanism, and resistance to infections. Inadequate diet may produce several forms of malnutrition in children, the most important being the protein-energy malnutrition (PEM).

Acute undernutrition results in wasting and occurs when food consumption is suddenly and severely reduced. *Chronic undernutrition* occurs when long-term food consumption is insufficient to meet the energy requirements on a daily basis for daily energy expenditure. It is usually assessed in terms of body measurements: in adults – thinness; in children – stunting.

More than one-fourth of children under five years of age worldwide (about 150 million) are underweight while about one-third (182 million) are stunted. Geographically, more than 70% of PEM children live in Asia, 26% in Africa and 4% in Latin America and the Caribbean. The prevalence of stunting has fallen in developing countries from 47% in 1980 to 30% in 2006-07, although progress has been uneven according to regions. One key target of the United Nations Millennium Development Goals is to reduce the prevalence of underweight among children younger than 5 years by half between 1990 and 2015. However, worldwide, underweight prevalence is projected to decline from 27% in 1990 to 18% in 2015. The Asian data on overall prevalence of PEM is shown in **Table 1**.

Table 1: Prevalence of Childhood Malnutrition

Country	Per cent of infants born with low birth weight	Per cent of children under five years suffering from malnutrition			
		Underweight			
		Moderate	Severe	Wasting	Stunted growth
Afghanistan	–	39	12	7	54
Bangladesh	22	46	–	16	36
Bhutan	15	19	3	3	40
China	2	7	–	–	11
India	28	46	–	19	38
Maldives	22	30	7	13	25
Myanmar	15	35	8	9	34
Nepal	21	45	10	12	43
Pakistan	19	38	13	13	37
Sri Lanka	22	29	–	14	14
World	14	25	–	11	28

Source: UNICEF, State of the World's Children 2009, data not available for the space left.

According to National Family Health Survey-3 (NFHS-3) (2005-06) report, 43% of children under five years of age were underweight, and almost half (48%) were stunted (**Figure 1**).

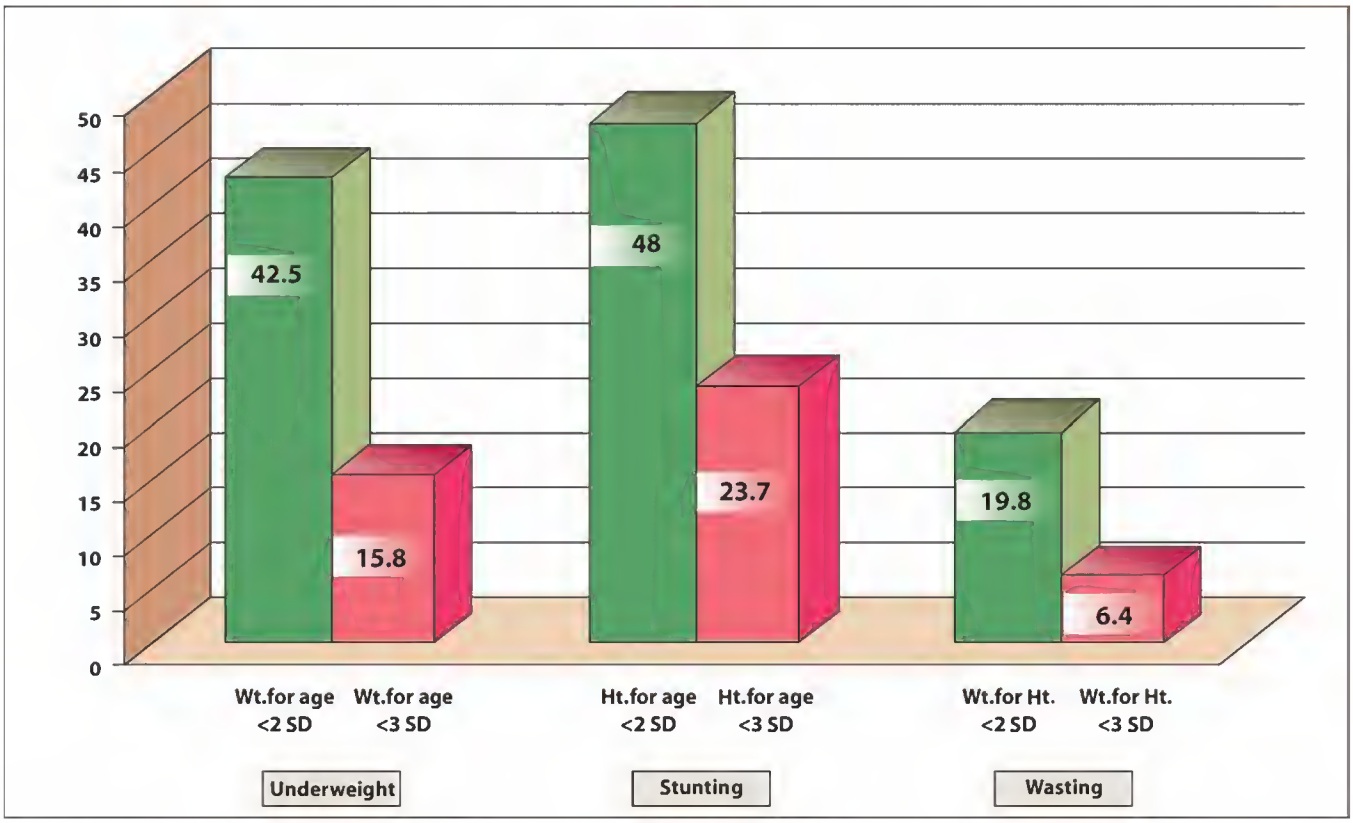


Figure 1: Nutritional status of children under five years of age in India according to National Family Health Survey-3.

Wasting (weight- for height <80% or <2SD of expected) was less prevalent, affecting 20% of children under five years of age.

Nutritional Status of Adults

Data on nutritional status of adults are determined by body mass index (BMI), which is expressed as follows:

$$BMI = Weight\ (Kg)/Height\ (m^2)$$

A cut-off point of BMI of 18.5 is used to define thinness or acute undernutrition and a BMI of 25 or above indicates overweight or obesity. However, there is a strong justification for using BMI cut-offs of 23 for defining overweight in Indian population. At any given BMI, Asians have higher body fat percentage as compared to other ethnic groups. **Table 2** presents the nutritional indicators of adults in India. More than one-third (36%) of women have a BMI below 18.5, indicating a high prevalence of malnutrition.

Table 2: Nutritional Status of Indian Adults (15-49 Years of Age)*

Nutritional status	BMI	Per cent females	Prevalence males
Obese	>30	2.8	1.3
Overweight	25–29.9	9.8	8.0
Normal	18.5–24.9	51.8	56.5
Mildly thin	17–18.4	19.7	20.4
Moderately/severely thin	<17	15.8	13.8

**Source: National Family Health Survey.*
BMI = Body mass index

EPIDEMIOLOGY OF PROTEIN-ENERGY MALNUTRITION

The proportion of children who are stunted or underweight increases rapidly with the child's age through age 20 to 23 months. Overall, girls and boys are about equally undernourished. Undernutrition is generally lower for first births than for subsequent births and consistently increases with increasing birth order for all measures of nutritional status (**Table 3**).

Table 3: Factors in Causation of Protein-energy Malnutrition

Short birth interval
Mother's education
Underweight mothers, especially BMI of less than 18.5
Lack of breastfeeding in initial 6 months after birth
Bottle feeding with unclean bottle and nipples
Dietary practices and taboos in families and society
Poverty
Recurrent infections diarrhoea, pneumonia

BMI = Body mass index.

These factors not only precipitate PEM but also decrease the immunity resulting in repeated infections and vicious cycle of malnutrition.

CLASSIFICATION OF PROTEIN-ENERGY MALNUTRITION

PEM may be classified according to the severity, course and the relative contributions of energy or protein deficits. Severity classifications based on anthropometric measurements, mainly weight and height are suggested.

Weight for Age Classifications

Gomez's is an international classification that considers a weight of more than 90% of what was expected for that age (median or 50th percentile) as normal. Weight for age groups between 76% to 90%, 61% to 75% and less than or equal to 60% are classified as grades I, II and III malnutrition, respectively. Indian Academy of Pediatrics (IAP) considers a weight of more than 80% of median for that age as normal. Grades of malnutrition are grade I (71% to 80%), II (61% to 70%), III (51% to 60%) and IV (<50%). The disadvantage of weight-based classifications is that these do not take in account the child's height. The weight is also dependent on height, besides the build; thus, children who are short statured (not necessarily because of nutritional deprivation) are also misclassified as PEM by these classifications.

Current Nomenclature

The above classifications measure undernutrition and are based on weight for age alone. However, it is important to distinguish undernutrition from *wasting* (deficits in weight-for-height) and *stunting* (height-for-age).

1. *Wasting* indicates a deficit in tissue and fat mass and may result either from failure to gain weight or from actual weight loss. It usually signifies acute onset of malnutrition.
2. *Stunting* signifies accumulated consequences of retarded growth over some years and generally points towards a chronic course of malnutrition. It may also be a residue of past malnutrition or could be due to non-nutritional disorders, like genetic short stature or endocrinal disorders.
3. *Wasting and stunting* are frequently coexistent and a greater and disproportionate reduction in weight as compared to reduction in height indicates *acute on chronic PEM.*

World Health Organisation (WHO) classification of undernutrition is based on this nomenclature. This classification is used for assessing the magnitude of malnutrition amongst children under five years of age in national health programmes (**Table 4**).

Table 4: WHO Classification for Undernutrition

	Moderate undernutrition	Severe undernutrition
Symmetrical oedema	No	Yes[a] Oedematous malnutrition
Weight for height (measure of wasting)	SD score[b] -2 to -3 (70-79% of expected[c]) Wasting	SD score < -3 (< 70% of expected) Severe wasting
Height for age (measure of stunting)	SD score[b] -2 to -3 (85-89% of expected[c]) Stunting	SD score < -3 (<85% of expected) Severe stunting

a = This includes kwashiorkor and marasmic kwashiorkor.

$$b = SD\ score = \frac{observed\ value - expected\ value}{Standard\ deviation\ of\ reference\ population}$$

c = Median (50th percentile of NCHS standards).
WHO = World Health Organisation; SD = Standard deviation; NCHS = National Child Health Survey.

CLINICAL FEATURES

Clinical features of malnutrition depend on the severity and duration of nutritional deprivation, the age of the undernourished subject, and the presence or absence of associated

infections. Severely malnourished subjects form only tip of the iceberg. A much larger number of subjects suffer from mild-to-moderate nutritional deficit. Key features of kwashiorkor and marasmus are listed in Table 5.

Table 5: Characteristic Clinical Features of Protein-energy Malnutrition

	Essential Features	Other Features
Kwashiorkor	Growth retardation Oedema Psychomotor changes	Infections Hair and skin changes Hepatomegaly
Marasmus	Wasting	Infections, irritability

Marasmus

A marasmic child is markedly wasted with body weight less than 60% of the expected weight for the age. The child appears disproportionate with long body, thin limbs and unduly large head. Buttocks are flattened with wrinkling of skin over the front of thighs. The scapulae look winged. Abdomen appears distended. The fat in the adipose tissues is severely depleted because it is used up for providing energy. The contour of atrophic muscles is evident under the thin and wrinkled skin. Loose folds of skin are prominent over the glutei and the inner side of thigh. The buccal pad of fat is preserved till the malnutrition becomes extreme. The skin appears dry and inelastic. The hair is hypopigmented. Child appears all bones and skin and the bony points appear unduly prominent (Figure 2). The child usually appears alert.

Kwashiorkor

Marked growth retardation, psychomotor changes, and oedema of dependent parts are three essential clinical features of Kwashiorkor (Figure 3). The face appears moon-shaped and puffy. The trunk is affected to a lesser extent. In a previously malnourished child, oedema may be precipitated by debilitating illnesses, such as measles or diarrhoea. The child becomes lethargic, listless and apathetic. He takes little interest in the environment and does not play with toys. Appetite is impaired and it is difficult to give oral feeds. The hair becomes thin, dry, brittle and hypopigmented. The liver is enlarged due to fatty infiltration. Skin becomes erythematous, hyperpigmented, and hyper-keratotic. The epidermis peels off in large scales, exposing tender raw area underneath. It appears like old paint flaking off a wooden surface. Petechiae and purpura appear in severe cases.



Figure 3: Children showing various features of Kwashiorkar.



Figure 2: Child showing features of Marasmus.

Kwashiorkor results from an imbalance between the production of free radicals and their safe disposal. Various *noxae* to which these children are exposed produce an oxidative toxic stress which leads to excess of free radical, peroxide and carbonyl formation. These toxic products cause damage as the mechanisms for their disposal are also compromised. The free radical damage is much more in kwashiorkor than marasmus. Red cell glutathione, serum ferritin, and proportion of red cell NADP in oxidised form are therefore markedly different in 2 conditions. Free radicals cause cell membrane damage that leads to increased permeability and hence oedema of kwashiorkor. The free radical theory (Michael Golden) may explain the whole range of manifestations of kwashiorkor whereas the protein deficiency theory just accounts for oedema.

Associated Nutritional Deficiencies

PEM is usually associated with multiple nutritional deficiencies. Anaemia may occur due to iron, protein, vitamin B_{12} or folate deficiency. Ariboflavinosis is common. Vitamin A deficiency is almost universal in children with severe PEM. Vitamin C deficiency manifests as bleeding gums, or subperiosteal haemorrhage. Despite underlying vitamin D deficiency, clinical manifestations of rickets may not be overt, since rickets is a disease of growing bones.

CHANGES IN BODY COMPOSITION

In a severely malnourished child, muscle mass is severely compromised, reducing by up to 70%. Body fat may be reduced

by up to 95%. Total bone mass is reduced with osteoporosis and delayed ossification. Total body water in malnourished children is increased to 70% to 80% of body weight.

Metabolic Alterations

Basal metabolic rate (BMR) is reduced by 30% and energy expenditure due to activity is very low. Heat generation and heat losses are affected so that the child may behave like a poikilotherm. These factors predispose to hypothermia. Cardiac output and stroke volume are reduced. Blood pressure is low and renal perfusion is compromised. Glomerular filtration rate and renal plasma flow are reduced. Insulin levels are reduced and the child has glucose intolerance. Cortisol and growth hormone levels are increased.

PRINCIPLES OF PROTEIN-ENERGY MALNUTRITION MANAGEMENT

The patient is evaluated for the severity of PEM, presence or absence of systemic infections, other nutritional deficits, such as vitamin deficiencies or anaemia, and fluid and electrolyte disturbances.

Moderate Malnutrition

These children are best treated in their own home surroundings, because domiciliary treatment of malnourished children by their mother has an inbuilt advantage of practical health education. The parents are advised to increase the food intake of the child by all available means. The child should receive adequate calories and proteins in the diet, which should be prepared from the locally available and inexpensive food.

Recurrence of malnutrition is infrequent among children treated in their own homes. After the initial treatment, these children should be kept undernutritional surveillance to detect and prevent deterioration in their nutritional status, and as early as possible to promote their nutrition and health by prompt remedial measures.

Severe Protein-Energy Malnutrition

Severely malnourished children should be treated in the hospital. Vigorous and prompt treatment is necessary to save them from death or irreversible functional handicaps. With appropriate treatment (as per WHO guidelines), the usual case fatality rate of 30% to 50% can be reduced to less than 5%. The 10 steps for the management of severe malnutrition are listed in **Figure 4**. These steps are accomplished in two phases: an initial stabilisation phase where the acute medical conditions are managed; and a longer rehabilitation phase. Sequential management of severe PEM is also depicted.

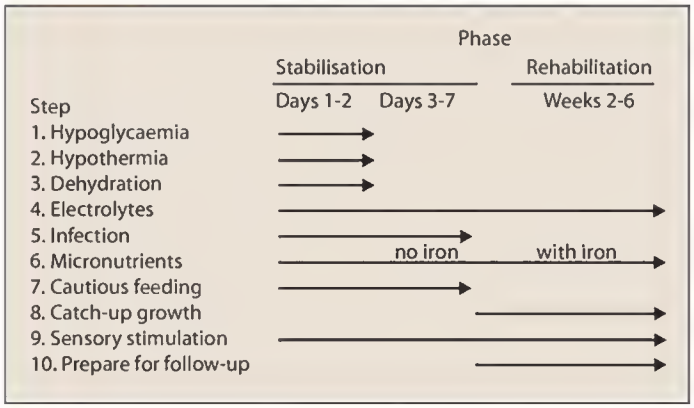


Figure 4: Sequential approach to management of severe PEM.

The ten steps to treat severe PEM

Step 1. Treat/prevent hypoglycaemia: By supplementing with oral glucose. Formula feeds are started after this.

Step 2. Treat/prevent hypothermia: Marasmic infants are prone to become hypothermic and require rewarming by warm blanket or other means (Kangaroo technique).

Step 3. Treat/prevent dehydration: It is difficult to evaluate dehydration in children with severe malnutrition. Thus all children with severe PEM and diarrhoea should be presumed to have some dehydration and given low osmolarity ORS. Intravenous therapy should only be given for shock.

Step 4. Correct electrolyte imbalance: All severely malnourished children have excess body sodium even though plasma sodium may be low. Therefore, only low osmolarity ORS should be given when rehydrating. Food should be prepared without salt. The child needs to be given extra potassium (3-4 mmol/kg per day) and magnesium (0.4-0.6 mmol/kg) for at least 2 weeks.

Step 5. Treat/prevent infection: The child should be clinically examined for the presence of infections and adequately treated. Antibiotics should be given routinely.

Step 6. Correct micronutrient deficiencies: All severely malnourished children should receive: vitamin A orally on Day 1 (200,000 IU for age >12 months; 100,000 IU for 6-12 months and 50,000 IU for 0-5 months) unless there is definite evidence that a dose has been given in the last month. The following micronutrients should be given on daily basis for at least 2 weeks: (i) multivitamin supplement; (ii) folic acid 1 mg per day (give 5 mg on Day 1); (iii) zinc 2 mg/kg per day; and (iv) copper 0.3 mg/kg per day.

Blood transfusion is required if haemoglobin is less than 4 g/dL and/or if there is respiratory distress with a haemoglobin of 4 to 6 g/dL. In mild or moderate anaemia, oral iron should be given after controlling the infection.

Step 7. Start cautious feeding: In the stabilisation phase a cautious approach is required because of the child's fragile physiological state and reduced homeostatic capacity. Feeding in the stabilisation phase should be started as small, frequent feeds of low osmolarity and low lactose. These can be given as oral or nasogastric (NG) feeds. One should start with 100 kcal/kg per day of calories and 1-1.5 g/kg per day of proteins, in the beginning. The fluid intake should be restricted to 130 mL/kg per day of fluid (100 mL/kg per day if the child has oedema). Calculations are made on the basal recorded weight and this can lead to both initial weight gain or weight loss.

Breastfeeding should be continued; in addition, rational food supplement formula is to be added.

Step 8. Achieve catch-up growth: The rehabilitation phase starts after a week and requires a vigorous approach to feeding to achieve rapid weight gain of >10 g/kg per day. At this time gradually switch from one formula to other richer formula diet. Modified family foods can be used provided they have comparable energy and protein concentrations.

Step 9. Provide sensory stimulation: Provide tender loving care; a cheerful, stimulating environment and maternal involvement.

Step 10. Prepare for follow-up after recovery: Return of appetite, gain in body weight with loss of oedema, disappearance of hepatomegaly and rising serum albumin are the early signs of recovery. A child who has achieved 90% weight-for-length is considered to have recovered. The child is still likely to have a low weight-for-age because of stunting. Good feeding practices and sensory stimulation should be continued at home. Educate parents about feeding and maintain a close follow-up plan.

Treatment of associated conditions

Associated conditions may require appropriate treatment with vitamin A, zinc supplementation, mebendazole or anti-tuberculosis treatment wherever required.

PREVENTION OF PROTEIN-ENERGY MALNUTRITION

Improvement of nutrition of people is an essential component of primary health care. It is necessary to keep the community under nutritional surveillance, to take appropriate decision to prevent malnutrition and promote health and nutrition in people. The nutrition can be improved by adopting two major strategies, *viz. nutritional planning*, and *direct nutrition and health interventions*. Both strategies need to be carried out concurrently, since the former results in long-term permanent benefits, and the latter provides immediate relief to those who need help. Concurrent nutritional surveillance is essential to monitor the impact of planning and intervention, and to introduce nutritional supplementation to bring about an immediate change in the nutritional status of the community.

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25.4 Water Soluble Vitamins

Milind Y Nadkar

INTRODUCTION

Water soluble vitamins include vitamin B complex and vitamin C. They act as co-enzymes for various biochemical reactions. Vitamins present in food are absorbed into the portal vein and transported to the liver. Excess amounts are excreted in urine. There is little storage of these vitamins and they need to be constantly supplied in the diet. Excess intake is generally well tolerated because of excretion in urine, except for toxicity reported with large doses of niacin, pyridoxine, and vitamin C.

THIAMINE (VITAMIN B_1)

Thiamine was the first B vitamin to be identified; hence termed as vitamin B_1. The active form is thiamine pyrophosphate (TPP). It acts as a co-enzyme in decarboxylation and transketolation reactions involved in carbohydrate metabolism and synthesis of adenosine triphosphate (ATP). It is also believed to play a part in nerve conduction.

Dietary sources include whole grains, nuts, meat, and legumes. Milled and polished rice is deficient in thiamine. Recommended daily allowance (RDA) for adults is 1.2 mg per day.

Aetiology—Thiamine Deficiency

The most common cause of thiamine deficiency is poor dietary intake due to poor socioeconomic conditions or alcoholism. Consumption of polished rice or other highly refined foods such as sugar and wheat flour as staple diet leads to thiamine deficiency. Part of thiamine is also lost by faulty cooking habits. High carbohydrate intake increases need for thiamine for its metabolism. Vitamin/energy ratio of 0.5 mg/1000 cal should be maintained in the diet. Carbohydrate repletion without adequate thiamine can precipitate acute thiamine deficiency and causes Wernicke-Korsakoff syndrome. Chronic illnesses like cancer and chronic dialysis are associated with thiamine deficiency.

Clinical Features

Mild deficiency in early stages produces non-specific symptoms like irritability and anorexia.

The clinical syndrome of prolonged thiamine deficiency is beriberi. It is classified as dry beriberi and wet beriberi, although there is considerable overlap. Wet beriberi is characterised by high output cardiac failure due to impaired myocardial energy metabolism. Patient presents with oedema, dyspnoea, palpitations, tachycardia, wide pulse pressure, pulmonary crepitations, hepatomegaly and ascites. Dry beriberi presents as symmetric, motor and sensory peripheral neuropathy. Legs are more severely affected than hands. Symptoms include pain, paraesthesias, numbness of extremities and difficulty in rising from squatting position. On examination, there is glove and stocking type of anaesthesia, motor weakness and diminished reflexes.

Wernicke's encephalopathy is seen in alcoholic patients with thiamine deficiency. The classic clinical triad is ophthalmoplegia, ataxia and confusion. Horizontal nystagmus is also present. The chronic state is characterised by anterograde amnesia and confabulations. It is called Korsakoff's psychosis.

Laboratory diagnosis of thiamine deficiency is made by the assay of erythrocyte transketolase activity or by thiamine concentration in serum or urine.

Treatment

In severe deficiency, with cardiovascular and/or neurological impairment, 100 mg of thiamine is given per day parenterally, for seven days, followed by 10 mg per day until recovery. Cardiovascular improvement occurs in 12 hours; ocular palsies improve within 24 hours. Ataxia improves slowly. Psychosis may persist for several months or may be permanent.

Glucose infusion can precipitate Wernicke's encephalopathy in alcoholic patients. Hence, thiamine should be administered to all alcoholic patients prior to parenteral glucose.

Toxicity

Anaphylaxis has been reported after high doses of thiamine given parenterally. No adverse effects have been recorded from high doses of thiamine in food supplements.

RIBOFLAVIN (VITAMIN B_2)

Riboflavin is essential for the metabolism of carbohydrates, fats, and proteins. The active forms of riboflavin are flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The FMN and FAD serve as prosthetic groups of several oxidoreductase enzymes, known as flavoproteins.

Dietary sources are milk and milk products, legumes, meat, fish and eggs. The RDA is 1.1 to 1.3 mg per day.

Aetiology—Riboflavin Deficiency

It is usually seen in conjunction with deficiencies of other B vitamins. It is widely prevalent in populations of lower socioeconomic group due to poor intake of vitamins. Children, pregnant and lactating women are susceptible to riboflavin deficiency due to increased demands. Chronic illnesses like tuberculosis (TB), cancer and alcoholism also lead to riboflavin deficiency. Chlorpromazine inhibits conversion of riboflavin to active form.

Clinical Features

Clinical manifestations of riboflavin deficiency are non-specific and not life-threatening. Mucocutaneous lesions include angular stomatitis, glossitis, cheilosis and magenta-red tongue or bald tongue. Seborrhoeic dermatitis of facial and scrotal skin characterised by fine, greasy scaling and desquamation is a common feature. Photophobia, lacrimation, burning of eyes is

also found and is believed to be due to corneal vascularisation. Personality changes have been reported rarely.

Laboratory diagnosis of riboflavin activity can be made by measurement of erythrocyte glutathione reductase activity with or without added FAD.

Treatment

Riboflavin supplementation in a dose of 5 to 10 mg per day is adequate along with improvement in the diet.

Toxicity of this vitamin has not been reported.

NIACIN (VITAMIN B_3)

Niacin refers to nicotinic acid and nicotinamide. These are converted in the body to nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), which are co-enzymes for many oxidoreductases. Therefore, these are key components of many metabolic pathways.

Dietary sources include beans, milk, meat and eggs. The RDA is 16 mg per day. The amino acid tryptophan can be converted to NAD^+ for every 60 mg of tryptophan, 1 mg equivalent of niacin is produced.

Niacin Deficiency

A diet which is poor in both niacin and tryptophan leads to niacin deficiency, e.g. diet based on maize (corn). High leucine content of *Sorghum* inhibits conversion of tryptophan to niacin. Pyridoxal phosphate acts as co-factor in synthesis of niacin from tryptophan. Thus, vitamin B_6 deficiency potentiates niacin deficiency. Alcoholism and isoniazid therapy for TB are common causes of niacin deficiency. Rare causes are carcinoid syndrome and Hartnup disease.

Clinical Features

Syndrome of niacin deficiency is known as pellagra. The manifestations include 4D's: 'dermatitis, diarrhoea, dementia and death'. The initial symptoms are irritability, loss of appetite, vomiting, abdominal pain and glossitis. The dermatitis manifests as hyperpigmented patches with scaling in sun-exposed areas. The skin rash around the neck is termed as 'Casal's necklace'. Diarrhoea occurs due to proctocolitis as well as malabsorption syndrome. Dementia, which is associated with depression and seizures, can ultimately lead to death.

Investigations done are measurement of urinary excretion of metabolites of niacin.

Treatment

Nicotinic acid or nicotinamide is given 100 to 200 mg orally three times a day for 5 days.

Other uses of nicotinic acid include treatment of dyslipidaemia where higher doses are required (>1.5 g per day).

Toxicity

The most frequent side-effect is cutaneous flushing. It improves with continuous administration or can be prevented with pre-treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). The most serious adverse effect is hepatotoxicity. Few cases of fulminant hepatitis have been reported with high doses of niacin (3-6 g per day).

Niacin potentiates the action of warfarin. Other toxic effects are glucose intolerance, gastro-oesophageal reflux, and macular oedema.

PANTOTHENIC ACID

It is formed by combination of pantoic acid and alanine. It is a component of co-enzyme A (CoA). It is essential for synthesis and oxidation of fatty acids, synthesis of cholesterol, steroids and vitamins A and D. CoA is also required for formation of various amino acids and delta-ALA. Deficiency of pantothenic acid is rare because it is widely distributed in foods. Liver, egg yolk, vegetables, whole grain cereals and legumes are good sources of pantothenic acid. The RDA is 5 mg per day.

Deficiency has been reported after feeding semi-synthetic diets or by using specific antagonist of the vitamin in the diet. Symptoms are fatigue, depression, vomiting, abdominal pain, muscle cramps and paraesthesias. The burning feet syndrome, in prisoners of war during World War II, was found to be due to pantothenic acid deficiency. This syndrome is also known as Gopalan's syndrome and responds to parenteral calcium pantothenate. No toxicity of this vitamin has been reported.

PYRIDOXINE (VITAMIN B_6)

Vitamin B_6 consists of 3 closely related compounds: pyridoxine, pyridoxal and pyridoxamine, along with their corresponding phosphates. They can be interconverted in the body. Pyridoxal phosphate acts as a co-factor in amino acid metabolism and glycogenolysis. Vitamin B_6 is essential for the synthesis of haem, neurotransmitters, and synthesis of niacin from tryptophan.

Dietary sources include meat, legumes, nuts, wheat bran and eggs. The RDA is 1.5 mg per day.

Pyridoxine Deficiency

Dietary deficiency occurs along with deficiency of other B vitamins. Alcoholism, malabsorption and dialysis can cause deficiency of pyridoxine. Drugs like isoniazid, cycloserine, and penicillamine inhibit metabolism of vitamin B_6. Pregnant and lactating mothers manifest vitamin B_6 deficiency due to increased requirement.

Clinical Features

Angular stomatitis, glossitis and cheilosis are seen with deficiency of vitamin B_6. Dermatitis associated with pellagra can respond to this vitamin. Neurological defects include peripheral neuropathy, personality changes, depression, confusion and abnormal electroencephalogram (EEG). Seizures in infants are attributed to pyridoxine deficiency. Haematological manifestations include microcytic hypochromic anaemia due to diminished haemoglobin synthesis. Sideroblastic anaemia responds to pyridoxine therapy. In sideroblastic anaemia, there is failure of incorporation of iron into haem. The excess iron accumulates in the mitochondria of erythroblasts, which are called sideroblasts.

Since pyridoxine is required for metabolism of homocysteine, deficiency of pyridoxine leads to hyperhomocysteinaemia. It is believed to accelerate atherosclerosis and it is an independent risk factor for cardiovascular diseases.

Increased ratio of AST (SGOT): ALT (SGPT) found in chronic alcoholics is due to deficiency of pyridoxal phosphate, which is required for synthesis of ALT.

Treatment

Pyridoxine, given at dose of 10 to 20 mg per day, is effective for oral lesions and peripheral neuropathy. Haematological manifestations require higher doses of 50 to 200 mg per day. Also pyridoxine is used to treat Isoniazid psychosis.

Pyridoxine is given to suppress vomiting in pregnancy with 20 mg per day. Pyridoxine is also used for breast milk suppression. In hyperhomocysteinaemia pyridoxine is given along with folate and vitamin B_{12}.

Toxicity

Toxicity of pyridoxine occurs with long-term use at high doses (100-200 mg per day). It manifests as severe sensory neuropathy. Rarely, photosensitivity and dermatitis are seen.

BIOTIN

Biotin is an imidazole derivative, which acts as co-enzyme for the carboxylases. Carboxylase enzymes are involved in carbohydrate and lipid metabolism. Food sources of biotin include liver, soy, beans, yeast and egg yolk. The RDA is 30 µg per day. A large portion of the human requirement of biotin is met by intestinal bacterial synthesis. Deficiency of biotin is rare. It can be caused by ingestion of diet with large quantities of raw egg-white which contains a heat labile protein, avidin. Avidin tightly binds with biotin in gastrointestinal treat and prevents its absorption. Consumption of boiled eggs does not lead to biotin deficiency. Other causes are biotin-free total parenteral nutrition and malabsorption syndrome. Symptoms include depression, hallucination, paraesthesias, myalgia, anorexia and vomiting. Scaling, seborrhoeic, and erythematous rash may be seen on face and extremities. Infants present with hypotonia, apathy, lethargy, alopaecia and skin rash. Treatment consists of biotin supplements in doses up to 10 mg per day. No toxicity of this vitamin has been reported.

FOLIC ACID

Folic acid or folate consists of pteridine attached to PABA and glutamic acid. The active form of this vitamin is tetrahydrofolate. It is a carrier for activated one-carbon units in various metabolic reactions. Folate is required for synthesis of nucleotides, which are the building blocks of deoxyribonucleic acid (DNA), and for synthesis of methionine from homocysteine.

Green leafy vegetables and fruits are the primary sources of folate in the diet. The RDA is 0.5 mg per day. Requirements are increased in pregnancy, infants, malignancy and exfoliative skin diseases, i.e. the states with high cell turnover and increased DNA synthesis.

Aetiology—Folic Acid Deficiency

The major cause of folic acid deficiency are inadequate dietary intake, alcoholism, states of increased folate requirement, malabsorption, e.g. tropical sprue, intake of phenytoin, barbiturates. Drugs like methotrexate, trimethoprim, pyrimethamine and pentamidine impair folate metabolism.

VITAMIN B_{12}

It is an organometallic compound with corrin ring and cobalt atom at the centre. It is stored in the liver in the form of methylcobalamin and adenosylcobalamin. The commercial preparation is cyanocobalamin. Methylcobalamin is a co-enzyme in the conversion of homocysteine to methionine and of methyl-tetrahydrofolate to tetrahydrofolate. Thus, deficiency of vitamin B_{12} results in deficiency of tetrahydrofolate; which is being trapped as methyl-tetrahydrofolate. This is known as folate trap. Adenosylcobalamin is necessary for the conversion of methyl-malonyl CoA to succinyl CoA.

Animal products are the only dietary sources, i.e. meat and dairy products. It is totally absent in plant products. The RDA is 2.5 µg per day.

Aetiology—Vitamin B_{12} Deficiency

Inadequate intake occurs in vegans, i.e. strict vegetarians who do not even consume milk and milk products. Poor absorption occurs due to achlorhydria, gastrectomy, pernicious anaemia, malabsorption syndromes, ileocaecal TB, blind loop syndrome and fish tapeworm (*D. latum*) infestation.

Clinical Features of Vitamin B_{12} and Folic Acid Deficiency

Haematological effects are characterised by megaloblastic anaemia, which may be associated with leucopaenia and thrombocytopaenia. Patient presents with pallor, other features of anaemia, hyperpigmentation of skin and sometimes with icteric tinge. Peripheral smear shows macrocytes and hypersegmented neutrophils.

Neurological manifestations occur due to vitamin B_{12} deficiency. There is demyelination of peripheral nerves, posterior and lateral columns of spinal cord and brain. Patient presents with paraesthesia and numbness of extremities, weakness and sensory ataxia. Sphincter disturbances may be present. This condition is called subacute combined degeneration of spinal cord. Involvement of brain results in irritability, dementia or frank psychosis. Neurological disease may occur without haematological manifestations. Folate supplementation alone unmasks the neurological presentation of vitamin B_{12} deficiency.

Folic acid deficiency in pregnancy is responsible for neural tube defects in the foetus. Hence, folic acid supplementation is advocated in pregnant women. Plasma homocysteine levels are elevated in both folate and vitamin B_{12} deficiency. It is a risk factor for arterial and venous thrombosis. However, it is not yet clear whether folate and vitamin B_{12} supplements have favourable effects on the occurrence of cardiovascular events.

Investigations

Serum levels of vitamin B_{12} and folate are measured by radioimmunoassay. Serum methylmalonic acid and homocysteine are elevated in vitamin B_{12} deficiency and homocysteine is also elevated in folate deficiency. The pathogenesis of vitamin B_{12} deficiency can be delineated by Schilling's test.

Treatment

Oral cobalamin 1 to 2 mg per day is sufficient in patients with poor intake of the vitamin. In patients with poor absorption, cyanocobalamin is given intramuscularly at dose of 1 mg per week for 8 weeks, followed by 1 mg per month for the rest of the life. Toxicity of this vitamin has not been reported.

Folic acid is replaced at doses of 1 to 5 mg per day orally. Folate in large doses can correct the megaloblastic anaemia of

vitamin B_{12} deficiency; but neurological manifestations may be aggravated. Hence, combination therapy is preferred. Haematological abnormalities respond to therapy rapidly. The response of neurological abnormalities is slow, and may not be complete.

VITAMIN C

Ascorbic acid and dehydroascorbic acid have vitamin C activity in the body. Ascorbic acid acts as a donor of reducing equivalents, and thus, serves as a biological antioxidant. Vitamin C is essential in a multitude of biological reactions like oxidation of tyrosine in formation of norepinephrine and hydroxylation of proline in collagen synthesis. It acts as an antioxidant and prevents conversion of nitrites and amines to carcinogenic nitrosamines. Presence of vitamin C in the gastrointestinal tract significantly enhances the absorption of iron.

Dietary sources include citrus fruits, tomatoes and green vegetables. *Amla* and guava are the richest sources of vitamin C. The RDA is 60 mg per day.

Aetiology—Vitamin C Deficiency

Poor dietary intake usually occurs in the elderly and alcoholics. Smoking, haemodialysis and stress (infection, trauma) increase requirement of vitamin C.

Clinical Features

Scurvy is the classical syndrome of vitamin C deficiency. The basic defect is in the formation of mature connective tissue resulting in capillary fragility. There is bleeding into skin (petechiae, ecchymoses and perifollicular haemorrhages), inflamed and bleeding gums. There may be internal bleeding into joints, in peritoneal cavity, pericardium, adrenal glands. Wound healing is delayed and susceptibility to infections may be observed.

In children, there is impaired bone growth. The characteristic signs are tenderness of bones and follicular hyperkeratosis. Scorbutic rosary is seen due to enlargement of costochondral junctions. Typical radiological changes are detected, particularly around the knee joint.

Treatment

Administration of vitamin C 200 mg per day improves the symptoms over several days.

High doses of vitamin C (1-2 g per day) are given to shorten the duration and symptoms of upper respiratory tract infection. Diets rich in vitamin C have been claimed to reduce the incidence of oesophageal and gastric cancers. Vitamin C supplements are useful in osteogenesis imperfecta and Chediak-Higashi syndrome.

Toxicity

Very high doses of vitamin C (>2-3 g per day) can cause abdominal pain, diarrhoea, nausea and elevated ALT. It can also lead to haemolysis in G6PD deficient people, oxaluria and renal calculi. There is a risk of iron overload in the patients receiving iron supplements. Sudden withdrawal after chronic ingestion of high doses of vitamin C can lead to 'rebound scurvy'. Vitamin C interferes with laboratory tests for detection of occult blood in stool (guaiac reaction).

CONCLUSION

Water soluble vitamins are essential micronutrients. Their deficiency results in various biochemical alterations in the body which lead to the typical clinical syndromes. It is important for a clinician to recognise these, as these are easily correctable with vitamin supplements. However, considering the toxicity of some of these vitamins, the routine use of supplements in all the patients is not advisable. A balanced diet is the key to the prevention of vitamin deficiency states.

25.5 Fat Soluble Vitamins

Ghan Shyam Pangtey

INTRODUCTION

Vitamin is coined from the word vital plus amine but later it was found that amino acid is not common in most vitamins. Vitamins are mainly divided into two groups: water soluble (vitamins B-complex and C) and fat-soluble (A, D, E and K). Unlike water-soluble vitamins that need regular replacement in the body, fat-soluble vitamins can be stored for long periods in the human body in liver and fatty tissues and are eliminated much more slowly than water-soluble vitamins. The differences between the water soluble and fat soluble vitamins are summarised in **Table 1**.

Table 1: Differences between Fat Soluble Vitamin and Water Soluble Vitamin

Properties	Fat soluble vitamins	Water soluble vitamins
Major vitamin	A, D, E, K	Vitamin B complex and C
Solubility	Fat soluble	Water soluble
Absorption	Along with lipids, requires bile secretion	Simple absorption
Storage	Mainly liver and sometime fatty tissue (large amount)	Usually no storage
Excretion	Not excreted	Excreted
Deficiency	Late manifestation	Early manifestation
Toxicity	Present	Unlikely
Treatment of deficiency	Single dose may be effective	Regular dietary supplementation is required

When consumed in excess, fat-soluble vitamins can cause toxicity as they are stored for long periods, this is not true for the water soluble vitamins, as these water soluble vitamins can easily get excreted from body and thus unlikely to have high concentration leading to adverse effects. Eating a normal, well-balanced diet will not lead to toxicity in otherwise healthy individuals. However, taking vitamin supplements that contain mega doses of vitamins A, D, E and K may lead to toxicity as the body only needs small amounts of these vitamins. The recommended dietary allowance (RDA) of Indian populations has been made and revised by Indian Council of Medical Research (ICMR) in 1988 and are available for some vitamins but it is infrequently used. **Table 2** presents the United States RDA of fat soluble vitamins according to different age groups.

VITAMIN A

Vitamin A (retinol) is an essential nutrient, needed in small amounts by humans for the normal functioning of the visual system; growth and development; and maintenance of epithelial cellular integrity, immune function, and reproduction. Three different forms of vitamin A are active in the body: retinol (alcohol form), retinal (aldehyde form) and retinoic acid (acid form) which are collectively called retinoids. The retinal is the active component of vitamin A associated with visual function. The vitamin A deficiency is one of the major causes of severe visual impairment/blindness, in a recent study from India, 7.5% to 25% of blindness was reported to be due to vitamin A deficiency.

Table 2: Recommended Dietary Allowances (RDAs)/Adequate Intake of Fat Soluble Vitamins for Individuals

Life stage	Vitamin A (RAE*)	Vitamin D** (µg/d)	Vitamin E (µg/d)	Vitamin K (µg/d)
Infants	400-500	5	4-5	2-2.5
Children (1-13 yr)	300-600	5	6-11	30-60
Males (>14 yr)	900	5-15	15	75-120
Females (>14 yr)	600-700	5-15	11-15	75-90
Pregnancy	750-770	5	15	75-90
Lactation	1200-1300	5	19	75-90

*Nate: *as retinal acid equivalent. 1RAE = 1 µg retinal, 12 µg β carotene; ** As calciferol. 1 µg calciferol = 40 IU vitamin D.*

Source: Adapted fram Faad and Nutritian Baard, Institute af Medicine-Natianal Academy af Sciences: Dietary Reference Intake, 2002. National Academy Press, Washington, DC.

Vitamin A Metabolism

Food derived from animals provide compound (retinyl esters) that are easily converted in intestine to retinol. Food derived from plants provides carotenoids, some of which may have vitamin A activity. There are more than 600 carotenoids in nature; β carotene is the most prevalent carotenoid with vitamin A activity, which can be split into intestine and liver to retinol. The β carotene absorption and conversion is less efficient than retinoids. The 12 µg of β carotene is equivalent to 1 µg of retinol.

The retinol binding protein (RBP) is the special transport protein which binds to retinol in blood and transports it to the appropriate cells that have specific protein receptors for their binding.

Vitamin A Biological Role

The major role of vitamin A in body includes:

- Supporting growth and reproduction
- Promoting vision
- Maintenance and growth of epithelial cells of skin and mucous membrane
- Antioxidant.

The vitamin A retinol has the major role in transport of vitamin A and in supporting growth and reproduction. In men retinol participates in sperm development and in women it supports normal foetal development. Retinol also has major role in the normal growth and remodelling of bones. The retinal plays two major roles in normal vision. Firstly, it is required for maintenance of crystal clarity of cornea and secondly it participates in the conversion of light energy into nerve impulse in the retina. The rhodopsin pigment present in retina

is composed of a molecule of retinal and a protein opsin. When light strikes the retina the rhodopsin pigment gets bleached and retinal shifts from *cis* to *trans* configuration. This *trans* retinal cannot bind to opsin leading to change in membrane potential of opsin and activation of electrical impulse, which transmits it to nerve cell and later to brain. Much of *trans* retinal is converted back to active *cis* form but small amount of it gets converted to irreversible retinoic acid which has to be replaced with dietary intake.

Retinoic acid-vitamin A has important role in promotion of cell differentiation and protein synthesis leading to normal development of epithelial cells of skin and mucous membrane integrity.

Sources of Vitamin A

The vitamin A recommendations are expressed in retinol activity equivalent (RAE). One RAE equals to1 µg of retinol; 12 µg of β carotene; 3.33 IU of vitamin A. Previously the vitamin A recommendations were used to be given in international units (IUs) but it is now expressed in µg and the same will be used in this chapter. **Table 2** summarises the estimated mean requirements for vitamin A and the recommended safe intakes, taking into account the age and sex differences in mean body weights.

Preformed vitamin A is found almost exclusively in animal products, such as human milk, glandular meats, liver and fish liver oils, egg yolk, whole milk, and other dairy products. Preformed vitamin A is also used to fortify processed foods, which may include sugar, cereals, condiments, fats and oils. Provitamin A carotenoids are found in green leafy vegetables (e.g. spinach, amaranth and young leaves from various sources), yellow vegetables (e.g. pumpkins, squash, and carrots), and yellow and orange non-citrus fruits (e.g. mangoes, papayas).

Foods containing pro-vitamin A carotenoids tend to have less biologically available vitamin A but are more affordable than animal products. It is mainly for this reason that carotenoids provide most of the vitamin A activity in the diets of economically deprived populations.

Vitamin A Deficiency (VAD)

Vitamin A deficiency is a major health problem of developing countries. World Health Organisation (WHO) estimates that more than 100 million children's have some degree of deficiency. In a recent study from India, the prevalence of Bitot's spots and night blindness in schoolchildren was found to be around 5%, while prevalence of night blindness in pregnant females was found to be as high as 20% in few centres. The ocular manifestation due to VAD is known as xerophthalmia. The night blindness is the earliest manifestation of the VAD in which there is lack of vitamin A in back of eye (retina), in later stages of xerophthalmia there may be total blindness due to involvement of front of eye (cornea). The corneal involvement starts with dryness and hardening (xerosis) and later followed by softening, ulceration and necrosis (keratomalacia).

The normal range of serum vitamin A (retinol) is between 30-100 µg/dL. The other methods used to diagnose normal levels are blood spot retinol, tests for dark adaptation and liver biopsy to estimate the vitamin A reservoir. The serum level below 20 µg/dL is regarded as VAD. The clinical and subclinical infections can lower serum levels of vitamin A, on an average by as much as 25%, independently of vitamin A intake.

Management of Vitamin A Deficiency

Any stage of xerophthalmia should be treated with three 60 mg of vitamin A soft gel capsule given on day 0, day 1 and day 14. The dose should be half (30 µg) for the children's in the age group of 6 to 11 months. Pregnant mothers with deficiency should be a treated with 7.5 mg per week for 3 months. Patients with malabsorption should be treated with 15 mg per day of water soluble vitamin A and this should be followed by maintenance dose according to serum retinol levels.

Prophylactic vitamin A dose of 60 mg every 6 months is recommended in high-risk individuals and similarly children's suffering from measles should be given two capsules of 60 mg for two consecutive days.

Vitamin A Toxicity

Routine consumption of large amounts of vitamin A over a period of time can result in toxic symptoms, including liver damage, bone abnormalities and joint pain, alopecia, headaches, vomiting and skin desquamation. Hypervitaminosis A appears to be due to abnormal transport and distribution of vitamin A and retinoids caused by overloading of the plasma transport mechanisms. Very high single dose can also cause transient acute toxic symptoms that may include bulging fontanelles in infants; headaches in older children and adults; and vomiting, diarrhoea, loss of appetite and irritability in all age groups.

VITAMIN D

Vitamin D (calciferol) is the only vitamin which can be synthesised in human body. It is required to maintain normal blood levels of calcium and phosphate, which are in turn needed for the normal mineralisation of bone, muscle contraction, nerve conduction, and general cellular function in all cells of the body. Vitamin D achieves this after its conversion to the active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], or calcitriol. This active form regulates the transcription of a number of vitamin D-dependent genes which code for calcium-transporting proteins and bone matrix proteins.

Metabolism of Vitamin D

Vitamin D, a seco-steroid, can either be made in the skin from the cholesterol like precursor (7-dehydrocholesterol) by exposure to sunlight or can be provided pre-formed in the diet. The version made in the skin is referred to as vitamin D_3 or cholecalciferol whereas the dietary form known as vitamin D_2 or ergocalciferol (**Figure 1**). The vitamin D is also known as a prohormone because it can be synthesised in human body and acts like a hormone at distant target cells.

The vitamin D_3 is metabolised first in the liver to 25-hydroxyvitamin D (calcidiol) and subsequently in the kidneys to1,25$(OH)_2$D (calcitriol) to produce a biologically active hormone. The calcitriol and other vitamin D metabolites are complexed to vitamin D-binding protein (globulin) in the blood. Calcitriol is believed to act on intracellular receptors similar to steroid hormones.

Recently there has been rising interest in the discovery of vitamin D receptors in more than 20 different cells of the body

which includes brain, bone marrow cells, skin, lymphocytes, etc. The exact role of these receptors is still unknown but it is speculated that this may have some important functions of immunomodulation and cell differentiation.

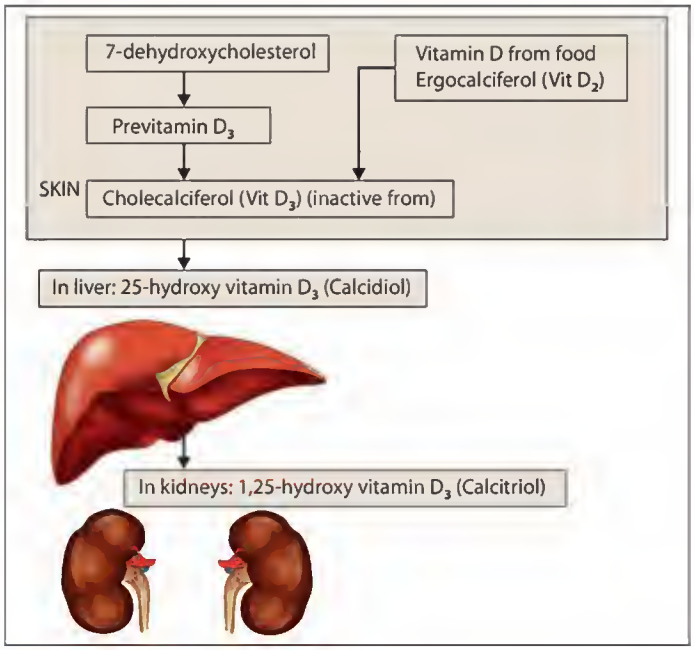


Figure 1: Synthesis of vitamin D in humans.

Sources of Vitamin D

The most efficient and physiologically relevant endogenous synthesis of vitamin D is from the skin. This is maximum in the world, in a broad band around the equator. Approximately 30 minutes of adequate exposure of arms and face to sunlight can provide the daily adequate requirement of an individual. However, skin synthesis of vitamin D is negatively influenced by the following factors: latitudes >42° N or >42° S, winter months, thinned skin of elderly, dark pigmented skin (Asian and Africans), clothing and sunscreens use. It is reported that in winter months, persons living in latitudes higher than 42° have zero vitamin D synthesis.

Vitamin D recommendation is usually given in international unit (IU) and the conversion used is 1IU = 0.025 µg cholecalciferol. The RDA for vitamin D is given in Table 2. The food sources rich in vitamin D are fortified dairy products, fortified margarine, fish oils and egg yolk.

Vitamin D Deficiency

Vitamin D deficiencies is widely prevalent in India and in recent studies up to 90% of Indians are found to be having hypovitaminosis D, which may be due to dark skin complexion, poor sun exposure, vegetarian food habits and lack of vitamin D in food fortification programme. The vitamin D acts on intestinal cells to increase calcium absorption from gut, therefore, in its deficiency serum ionised calcium level decreases leading to rickets in children's and osteomalacia in adults. Optimal vitamin D level of 25(OH) D is >25 ng/mL (37 nmoL/L) but the level at which the parathyroid hormone (PTH) increases and bone density decreases is <15 ng/mL of vitamin D.

Management of Vitamin D Deficiency

Recommended daily intake of 800 IU of vitamin D is associated with decrease in risk of hip fracture in elderly. The cause of vitamin D deficiency should be investigated and treated first before vitamin D and calcium correction. In patient with chronic renal insufficiency or 1α-hydroxylation defect the treatment should be with 0.25-0.5 µg/day of calcitriol [1, $25(OH)_2D_3$]. Patients with intact vitamin D hydroxylation should be treated with 60,000 IU of cholecalciferol sachet/week for 4 to 12 weeks followed by maintenance therapy of once monthly sachet or 800 IU daily. In patients with fat malabsorption intramuscular vitamin D should be used in the dose of 2.4 lac IU/6 months.

Vitamin D Toxicity

The safety margin of vitamin D is very large and the toxicity is only seen at very large doses in the range of 40,000 IU/day. It may lead to hypercalcaemia and hypercalciuria, leading to nephrolithiasis if urinary calcium rises >250 mg/24 hour.

VITAMIN E

Vitamin E consists of family of eight naturally occurring isomers of tocopherol and tocotrienols that are synthesised by plant homogentisic acid. It is the major lipid-soluble antioxidant in the cell antioxidant defence system and is exclusively obtained from the diet. The major biological role of vitamin E is to protect polyunsaturated fatty acids (PUFAs) and other components of cell membranes and low-density lipoprotein (LDL) from oxidation by free radicals. The recent studies do not document the beneficial role of vitamin E as antioxidant to prevent heart disease and cancer as previously thought.

Vitamin E Metabolism

Absorption of vitamin E from the intestine depends on adequate pancreatic function, biliary secretion and micelle formation. Conditions for absorption are like those for dietary lipid, that is, efficient emulsification, solubilisation within mixed bile salt micelles, uptake by enterocytes, and secretion into the circulation via the lymphatic system. After absorption of tocopherol (vitamin E), it is incorporated into the chylomicrons in the enterocyte and secreted into the lymphatic's and blood stream. The chylomicrons carry tocopherols to the liver parenchymal cells as well as in systemic circulations where they are acted upon by lipoprotein lipase and get incorporated inside the very low-density lipoprotein (VLDL) and LDL. The tocopherol is mainly delivered to the peripheral tissue by the LDL through LDL receptor mechanism.

Dietary Sources of Vitamin E

Vitamin E is naturally present in plant based diets and animal products. The vegetable oils and their products are the major source (60%) of vitamin E in human diet. The other important sources of vitamin E are animal fats, vegetables, meats, fruits, nuts, cereals and dairy products. Small amount of vitamin E is also present in eggs, fish, and pulses. The RDA for vitamin A is 15 mg per day for all adults.

Vitamin E Deficiency

The dietary deficiency of vitamin E usually does not exist. This suggests that diets contain sufficient vitamin E to cover nutritional needs. The deficiency in humans is usually seen in infants and adults with fat-malabsorption syndromes or liver disease, in individuals with genetic anomalies in transport or binding proteins (e.g. abetalipoproteinaemia), and possibly in premature infants. The deficiency may precipitate in the

community at times of ecological disaster and famine. Disorders provoked with low vitamin E status include cardiac or skeletal myopathies, neuropathies, and liver necrosis. The blood levels of α tocopherol <5 μg/mL is suggestive of vitamin E deficiency.

Management of Vitamin E Deficiency

In deficient states vitamin E is required to be given in doses of 800-1200 mg per day. In patients with abetalipoproteinaemia the dose recommended is 5000-7000 mg per day of α tocopherol. In children with fat malabsorption the vitamin E deficiency should be treated with water soluble form of α tocopherol as well as by intramuscular injections.

Vitamin E Toxicity

Vitamin E appears to have very low toxicity potential, evidence of pro-oxidant damage has been associated with the feeding of supplements but usually only at very high-doses of >1000 mg per day. High-doses can also interfere with platelet aggregation and vitamin K metabolism leading to bleeding tendency. Other common symptoms of toxicity include nausea, vomiting and flatulence.

VITAMIN K

Vitamin K has essential role in maintenance of normal blood coagulation in the human body by acting as a cofactor in post-translational modification of vitamin K dependent proteins or G1a proteins. The vitamin K dependent coagulation proteins are synthesised in the liver and comprises of factors II, VII, IX, and X, which have a haemostatic role and protein C and S, which have an anticoagulant role. Nutritional deficiency of vitamin K leads to bleeding tendency.

Vitamin K Biological Role

There are two types of naturally occurring vitamin K, the phylloquinone (vitamin K_1) is synthesised by plants and menaquinone (vitamin K_2) is synthesised by bacteria. Vitamin K_1 can be converted to Vitamin K_2 in some specific organs.

The biological role of vitamin K is to act as a co-factor for a specific carboxylation reaction that transforms selective glutamate (Glu) residues to α-carboxyglutamate (Gla) residues.

Apart from the coagulation proteins, several other vitamin K-dependent proteins have been isolated from bone, cartilage, kidney, lungs, and other tissues. Only two, osteocalcin and matrix Gla protein (MGP), have been well characterised. Both are found in bone but MGP also occurs in cartilage, blood vessel walls, and other soft tissues. Evidence of a possible association of a suboptimal vitamin K status with increased fracture risk remains to be confirmed.

Sources of Vitamin K

The highest values of phylloquinone (normally in the range 400-700 mg/100 g) are found in green leafy vegetables (turnip greens, spinach, cauliflower, cabbage and broccoli, etc.). The next best sources are certain vegetable oils (e.g. soyabean, rapeseed, and olive), which contain 50-200 mg/100 g. The animal food is generally poor source of vitamin K. The average daily requirement in adult is 100 μg per day.

Animals and humans obtain a significant fraction of their vitamin K requirement from direct absorption of menaquinones produced by bacterial microflora present in the gut.

Vitamin K Deficiency

Infants up to around age of six months are prone to vitamin K deficiency due to low levels of vitamin K in breast milk, low fat store, gut sterility, liver immaturity and poor placental transfer of vitamin K. The deficiency syndrome has been termed vitamin K deficiency bleeding (VKDB) disorder.

In adults, primary vitamin K-deficient states that manifest as bleeding are almost unknown except when the absorption of the vitamin K is impaired as a result of an underlying chronic small intestinal disease (e.g. coeliac sprue) or intestinal resections.

Diagnosis of vitamin K deficiency can be made by direct measurement or by prolonged prothrombin time.

Management of Vitamin K Deficiency

Vitamin K deficiency should be treated with 10 mg of parentral dose. In chronic malabsorption states the vitamin K dose required is 1-2 mg per day orally or 1-2 mg per week parentrally.

Vitamin K Toxicity

When taken orally, natural K vitamins seem free of toxic side-effects. However, synthetic preparations of menadione or its salts may be associated with neonatal haemolysis and liver damage. High-doses of vitamin K can impair the actions of oral anticoagulants.

RECOMMENDED READINGS

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25.6 Minerals, Trace Elements and Antioxidants

M Raghunath, D Sreeramulu

MINERALS

Although minerals constitute small proportion of the human body, they perform several vital functions which are absolutely essential for normal metabolism. Most of the minerals are provided by the diet one consumes. Minerals are classified as major elements and trace elements according to the quantities present in the body and required by humans. If more than 100 milligrams (mg) of an element is needed per day, it is classified as major mineral and the minerals which are present and needed in amounts less than 100 mg per day are classified as trace elements. They are subdivided as follows in Table 1.

Table 1: Minerals and Trace Elements

Major Minerals	Trace Elements		
	Essential	**Possibly essential**	**Non-essential (to date)**
Calcium (Ca)	Iron (Fe)	Cadmium (Cd)	Aluminum (Al)
Phosphorus (P)	Iodine (I)	Barium (Ba)	Bismuth (Bi)
Sodium (Na)	Zinc (Zn)	Nickel (Ni)	Boron (B)
Potassium (K)	Selenium (Se)	Vanadium (V)	Lead (Pb)
Magnesium (Mg)	Copper (Cu)	—	Mercury (Hg)
Chloride (Cl)	Fluorine (F)	—	Silver (Ag)
Sulphur (S)	Molybdenum (Mo)	—	—
—	Chromium (Cr)	—	—

Calcium

Among different minerals calcium occurs in the highest amounts in the human body. About 99% of the calcium in the body is found in bones and teeth, while 1% is found in the blood and soft tissue. Calcium levels in blood and fluid surrounding the cells (extracellular fluid) must be maintained within a very narrow concentration range 9 to 11 mg/dL for normal physiological functions. Oxalic acid, also known as oxalate, is the most potent inhibitor of calcium absorption and is found in high concentrations in spinach and in lower concentrations in sweet potatoes and dried beans.

Metabolic functions of calcium

1. Calcium is essential for the formation of bones and teeth. The mineral component of bone consists mainly of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] crystals, which contain large amounts of calcium and phosphate.
2. Calcium plays a role in mediating the constriction and relaxation of blood vessels (vasoconstriction and vasodilatation), nerve impulse transmission, muscle contraction and secretion of hormones like insulin.
3. Calcium is essential for clotting of blood. It acts as a cofactor for enzymes and proteins.

Parathyroid hormone regulates calcium levels in blood and calcium metabolism in the bone. Causes of abnormal low blood calcium levels include chronic kidney failure, vitamin D deficiency and low blood magnesium levels that occur mainly in cases of severe alcoholism in addition to low dietary Ca intake.

Phosphorus

About 80% of phosphorus present in the body is in bone and teeth and 10% in muscles. Phosphate is mainly an intracellular ion and is present in all cells. Requirement of phosphorus is about 500 mg/day. Serum phosphorus levels range from 3 to 4 mg/dL in normal adults and 5 to 6 mg/dL in children and they are regulated through urinary excretion. Serum phosphorus levels are decreased in hyperparathyroidism and rickets.

Metabolic functions of phosphorus

1. Phosphorus is necessary for the formation of bone and teeth.
2. It is needed for the synthesis of nucleoside co-enzymes such as NAD and NADP, high energy phosphate compounds such as ATP, CTP, GTP, creatine phosphate and for DNA and RNA synthesis.
3. It is essential for carbohydrate and lipid metabolism, e.g. formation of phosphate esters such as glucose 6-phosphate and phospholipids.
4. Activation/inactivation of enzymes occur by phosphorylation/dephosphorylation.
5. To maintain the phosphate buffer system in blood, the ratio of Na_2HPO_4: NaH_2PO_4 required in blood is 4:1 and this responsible to maintain pH of blood at 7.4.

Sodium

About 50% of sodium present in the body is in bones, 40% in extracellular fluid (ECF) and about 10% in soft tissues. Normal plasma sodium levels range from 136 to 145 mEq/L. It is a major cation which regulates extracellular fluid volume. Sodium pump operates in all cells to maintain sodium extracellular in an ATP dependent mechanism.

Metabolic functions of sodium

1. The Na^+-K^+ ATPase pump moves three sodium ions out of the cell in exchange for two potassium ions moving into the cell during which process ATP is hydrolysed to ADP.
2. Sodium ions play a special role in originating and maintaining the heartbeat and transmission of nerve impulse.

Potassium

About 75% of body potassium is present in skeletal muscle. Normal levels of plasma potassium ranges from 3.5-5 mEq/L. It is one of the major intracellular cation, and it helps to maintain the intracellular osmotic pressure.

Metabolic functions of potassium

1. Potassium helps to maintain intracellular pH and osmotic pressure.

2. Required for contraction of heart and transmission of nerve impulses.

Magnesium

Magnesium plays an important role in the structure and function of the human body. The adult human body contains about 25 grams of magnesium. Over 60% of all the magnesium in the body is found in the skeleton, about 27% in muscle, 6% to 7% in other cells and less than 1% is found outside the cells. Because magnesium is a part of chlorophyll, the green pigment in plants, green leafy vegetables are rich in magnesium. Magnesium is involved in more than 300 essential metabolic reactions.

Metabolic functions of magnesium

1. The metabolism of carbohydrates and fats to produce energy requires numerous magnesium-dependent chemical reactions; such as the adenosine triphosphate (ATP).
2. Magnesium plays a structural role in bone, cell membranes and chromosomes. It is necessary for proper calcium and vitamin D metabolism.
3. Magnesium affects the conduction of nerve impulses, muscle contraction and normal heart rhythm through the active transport of ions like potassium and calcium across cell membranes.
4. Mg is required in cell signalling for the phosphorylation of proteins and formation of cyclic adenosine monophosphate (cAMP). It is also involved in cell migration and helps in wound healing.

Magnesium deficiency is quite rare in healthy individuals who consume balanced diet since magnesium is abundant in both plant and animal foods. However, in some disease conditions like gastrointestinal, renal disorders and chronic alcoholism, etc. the risk of magnesium deficiency is increased. Mg deficiency leads to hypertension, cardiovascular disease, endothelial dysfunction, diabetes mellitus, osteoporosis and asthma.

Chloride

Chloride concentrations in plasma range from 96 to 106 mEq/L. The homeostasis of Na, K and Cl are interrelated. Chloride is important in the formation of hydrochloric acid in gastric juice. Chloride is excreted through urine and sweat. Renal threshold is about 110 mEq/L. Daily excretion of Cl^- is about 5 to 8 g per day.

Metabolic functions of chloride

Chloride is the major extracellular anion. It is involved in maintaining osmolality, blood volume, and electric neutrality.

Sulphur

Sulphur present in the body in the form of sulphur-containing amino acids cysteine and methionine in the body proteins. Hence, the source of sulphur is mainly from the amino acids: cysteine and methionine. Proteins contains about 1% sulphur by weight. Inorganic sulphates of Na^+, K^+ and Mg^{++} though available in food are not utilised by the body. All sulphur groups are ultimately oxidised in liver to sulphate (sulphuric acid) group and excreted in urine. The total quantity of sulphur in urine is about 1 g per day.

Metabolic functions of sulphur

1. Sulphur containing amino acids are important constituents of body proteins. The di-sulphide bridges keep polypeptide units together, e.g. insulin, immunoglobulin's, etc.
2. Keratin, rich in sulphur, is present in hair and nails.
3. Sulphates play an important role in detoxification mechanisms.

The major food sources of the minerals, their deficiency, symptoms and recommended daily allowances (RDAs) are given in **Table 2**.

TRACE ELEMENTS

Iron

Iron has the longest and best described history among all the micronutrients. It is a key element in the metabolism of almost all living organisms. In humans, iron is an essential component of hundreds of proteins and enzymes. Most of the body iron exists in complex forms bound to protein either as porphyrin or haemcompounds or as ferritin and transferrin. Iron is required for the formation of haemoglobin in RBC and is involved in oxygen transport and storage. Copper is essential for utilisation of iron for haemoglobin formation. Iron depletion leads to iron deficiency anaemia. About 50% to 60% of Indian population suffers from iron deficiency anaemia. Iron is absorbed only in the ferrous form. The dietary iron absorption in normal individuals is only around 10% of intake.

Table 2: Summary of Major Minerals (Food Sources, Effect of Deficiency and RDA)

S. No.	Mineral	Major Food Source	Deficiency Symptoms	RDA
1.	Calcium	Milk, milk products, GLVs, dried small fish	Decreased growth, osteoporosis and hyperplasia	300 to 500 mg
2.	Phosphorus	Milk, egg, meat and fish	Hyperthyroidism and rickets	500 mg
3.	Sodium	Milk and pulses	Heat cramps and headache	200 to 500 mg
4.	Potassium	Banana, oranges, apple, pineapple and tender coconut water	Weakness, muscular paralysis	3 to 4 g
5.	Magnesium	Cereals, pulses, coffee, tea	Neuromuscular hyperirritability cardiac arrhythmias and symptoms are similar to calcium deficiency	200 to 300 mg
6.	Chloride	Egg, pulses, whole and skim milk	Excess sweating and vomiting, Addison's disease	300 to 750 mg
7.	Sulphur	Amino acid cysteine and methionine	Obstructive jaundice, amino-aciduriase Taurocholic acid in urine	850 mg

Metabolic role of iron

1. Haemoglobin is the primary protein in red blood cells and represents about two thirds of the body iron.
2. Iron participates in electron transport and energy metabolism and DNA synthesis and plays a role in antioxidant functions.

Iodine

Iodine is a constituent of thyroxin, the active principle of the thyroid gland. It is a non-metallic trace element, required for the synthesis of thyroid hormone in humans. Iodine deficiency is an important health problem throughout much of the world. Iodine deficiency is now accepted as the most common cause of preventable brain damage in the world. According to the World Health Organisation (WHO), iodine deficiency disorders (IDD) affect 740 millions people throughout the world and nearly 50 millions people suffer from some degree of IDD. The spectrum of IDD includes mental retardation, hypothyroidism, goitre and varying degrees of other growth and developmental abnormalities. Thyroid enlargement or goitre is one of the earliest and most visible signs of iodine deficiency. The thyroid enlarges in response to persistent stimulation by TSH. In mild iodine deficiency, this adaptive response may be enough to provide the body with sufficient thyroid hormone. However, more severe cases of iodine deficiency result in hypothyroidism. Adequate iodine intakes reduce the size of goitres, but the reversibility of the effects of hypothyroidism depends on an individual's stage of development. Iodine deficiency has adverse effects in all stages of development but is most damaging to the developing brain. Thyroid hormones regulate a number of physiological processes including growth, development, metabolism and reproductive function.

Zinc

Zinc is an essential trace element for all forms of life. Zinc plays important roles in growth, development, immune response, neurological functions and reproduction. Approximately 300 different enzymes depend on zinc for their ability to catalyse vital chemical reactions. Zinc-dependent enzymes can be found in all known classes of enzymes. Zinc plays an important role in the structure of proteins and cell membranes. Loss of zinc from biological membranes increases their susceptibility to oxidative damage and impairs their function.

Clinical zinc deficiency in humans was first described in 1961, when the consumption of diets with low zinc bioavailability due to high phytic acid content was associated with 'adolescent nutritional dwarfism' in the Middle East. Zinc bioavailability is relatively high in meat, eggs and seafood because of the absence of compounds that inhibit zinc absorption and presence of certain amino acids (cysteine and methionine) that improve zinc absorption.

Severe zinc deficiency results in the slowing or cessation of growth and development, delayed sexual maturation, characteristic skin rashes, chronic and severe diarrhoea, immune system deficiencies, impaired wound healing, diminished appetite, impaired taste sensation, night blindness, swelling and clouding of the corneas and behavioural disturbances.

Selenium

Selenium is a component of several enzymes. It protects cell membranes, prevents free radical generation and functions as an antioxidant. There by it decreases the risk of CVDs and few cancers. Selenium is required for normal function of several selenium-dependent enzymes, also known as selenoproteins, e.g. glutathione peroxidases. It is also needed for normal maturation of spermatozoa.

Role of selenium

1. Some of the selenoproteins that are involved in the metabolism are glutathione peroxidases, thioredoxin reductase, iodothyronine deiodinases.
2. It functions as an antioxidant that protects endothelial cells from damage.
3. It is necessary for normal development of spermatozoa.

Copper

Copper (Cu) is an essential trace element for the formation of haemoglobin in the body. Copper shifts between the cuprous (Cu^{1+}) and cupric (Cu^{2+}) forms, though the majority of the body's copper is in the Cu^{2+} form. The ability of copper to easily accept and donate electrons explains its important role in oxidation-reduction (redox) reactions and in scavenging free radicals.

Role of copper

1. Copper is a critical functional component of a number of essential enzymes known as cuproenzymes. These enzymes play important roles in cellular energy production, cross-linking of collagen and elastin, iron transport and in the function of the brain and nervous system.
2. The copper-dependent enzyme, cytochrome *c* oxidase, plays a critical role in cellular energy production.

Copper deficiency may result in abnormally low numbers of white blood cells known as neutrophils (neutropaenia), a condition that may be accompanied by increased susceptibility to infections. Osteoporosis and other abnormalities of bone development are related to copper deficiency and are most common in copper-deficient low-birth weight infants and young children. Less common features of copper deficiency may include loss of pigmentation, neurological symptoms and impaired growth.

Fluorine

Fluorine occurs naturally as the negatively charged ion, fluoride (F^-). Fluoride is considered a trace element because only small amounts are present in the body and because the daily requirement for maintaining dental health is only 1 to 2 ppm. About 95% of the total body fluoride is found in bones and teeth. Although its role in the prevention of dental caries (tooth decay) is well established, fluoride is not generally considered an essential trace element because excess fluorine content in water (>2 ppm) is a major public health problem than the fluoride deficiency. About 25 million Indians spread in 15 states of India are suffering from flurosis. Among them Nalgonda, Nellore and Prakasam districts of Andhra Pradesh and Patiala district of Punjab are badly affected.

In humans, the only clear effect of inadequate fluoride intake is an increased risk of dental caries (tooth decay) for individuals of all ages. The incidence of dental caries in children is observed to be high in areas where the fluoride content of drinking water is less than 0.5 ppm. Fluoride toxicity is

observed where the drinking water contains excessive amounts of fluoride (>3 ppm). This leads to osteoporosis and osteosclerosis with brittle bones, the condition being called fluorosis, which is more dangerous than dental caries. In these cases hypercalcification of the bone of the spine, pelvis and limbs occurs. In addition, the ligaments of spine become calcified, producing a 'poker back'. Neurological disturbances were observed secondary to changes in the vertebral column. Such persons are crippled and cannot perform simple daily tasks, such as bending, squatting, etc. as the joints become stiff. Fluoride toxicity can be prevented only by removing fluorides from drinking water supplies by treatment with activated carbon or by some other suitable adsorbents.

Molybdenum

Molybdenum is one of the essential trace elements.

Molybdenum functions as co-factor for some enzymes in humans, any disturbance of molybdenum co-factor metabolism can disrupt the function of all molybdoenzymes. These disorders result from recessive traits, for those individuals who inherit two copies of the abnormal gene (one from each parent) develop the disease. The symptoms of isolated sulfite oxidase deficiency and molybdenum co-factor deficiency are identical and usually include severe brain damage, which appears due to the loss of sulfite oxidase activity. Normally the average diets provide adequate amounts of molybdenum to humans and deficiency is rare.

The major food sources of the trace elements, their deficiency symptoms and recommended daily allowances are given in **Table 3**.

Table 3: Summary of Trace Elements (Food Sources, Effect of Deficiency and RDA)

S. No.	Trace element	Major food source	Deficiency symptoms	RDA
1.	Iron	Green leafy vegetables, pulses, jaggery, poultry, fish and egg yolks	Iron deficiency anaemia, impairment of learning in children and in adults impairment of work capacity	20 to 40 mg
2.	Iodine	Shell fish, sea weeds and sea fish	Goitre, Mental retardation	150 to 200 µg
3.	Zinc	Whole grains and sea food	Growth retardation, Delayed genital maturation	10 to 15 mg
4.	Selenium	Whole grains	Muscle weakness and fatigue	50 to 100 µg
5.	Copper	Shell fish, nuts and legumes	High blood pressure fragile bones	1 to 1.4 mg
6.	Molybdenum	Legumes, grains and nuts	Amino acid intolerance and reduced fertility	75 to 250 µg
7.	Fluoride	Water, sea foods and tea	Dental caries, skeletal fluorosis	1 ppm
8.	Cobalt	Curd/milk, Dietary Source of vit B_{12}	Wasting disease observed in animals	*No RDA necessary*

ANTIOXIDANTS FREE RADICALS

Production and Physiological Relevance

Electrons are normally present in pairs. In the course of metabolism several atoms or groups of atoms are generated in the body, which have unpaired electrons, which are called free radicals. They usually seek electrons from other atoms to become paired electrons and thus stabilise their structure. Free radicals can react with proteins, nucleic acids, lipids and other molecules and alter their structure. In turn they attack other molecules due to their powerful oxidative nature and results in tissue damage. An imbalance between free radical generation and radical scavenging systems in the living organism causes oxidative stress which ends up in generation of reactive oxygen species (ROS) and RNS. It has been implicated in tissue damage, damage of lipids, proteins and DNA resulting in cell injury. Excess free radical production underlies the pathogenesis of diseases like atherosclerosis, carcinogenesis, diabetes, cataract and accelerated ageing.

Types of Free Radicals

Superoxide	O_2^-
Hydrogen peroxide	H_2O_2
Hydroxy radical	HO
Nitric oxide	NO
Lipid radicals	L
Lipidperoxyl radicals	LO2
Thiyl radicals	RS
Protein radicals	P

Sources of Free Radical

Oxidative damage can be brought about by free radicals generated from endogenous as well as exogenous sources. Some common endogenous sources are: 1. Mitochondria, 2. Electron transport, 3. Defense-phagocytes, 4. Membrane oxidases, and 5. Catecholamines.

The exogenous sources of free radicals are: 1. Alcohol, 2. Chemicals, carcinogens, 3. Pollutants, 4. Radiation, 5. Smoking (tobacco), and 6. Stress.

$$3H_2O \xrightarrow{\text{Radiation}} H_2 + H^+ + OH^- + H_2O_2$$

Physiological Relevance of Free Radicals

If the free radical production in our body is specially uncontrolled as happens under the conditions of alcoholism, over eating and smoking, the ROS/free radicals damage many of our biological systems.

Age related diseases are believed mainly to be the after effects of free radicals. In aged people the defects in secretary glands, eye sight and memory are partly due to the onslaught of free radicals and partly due to metabolic defects/nutrition, etc.

ANTIOXIDANTS

To defend against damage from free radicals and ROS, humans and other living organisms have developed powerful and complex antioxidant system. Antioxidants are diverse group of molecules that protect key biological sites from oxidative damage. They are either produced in the body (endogenous) or derived from the diet (exogenous). The endogenous antioxidant defense systems of the body are essentially of two types: enzymatic and non-enzymatic.

Different Types of Antioxidant Systems

The living organisms are endowed with a battery of antioxidant systems which defend the organism against oxidative stress due to various endogenous and exogenous sources. The balance between oxidative stress/antioxidant defense systems of the body, determine to a great extent the susceptibility of the organism to free radical/ROS induced tissue damage and associated diseases. Biological antioxidant is 'any substance that when present at low concentrations compared to those of an oxidisable substrate significantly delays or prevents the oxidation of that substrate'.

The following are the various defense systems *in vivo* against oxidative damage.

Enzymatic antioxidants

Superoxide dismutase (CuZnSOD present in Cytosol, Mn SOD in mitochondria and SOD in extracellular space), Catalase, Glutathione peroxidase (GSHPx), Glutathione reductase, etc. are the common antioxidant enzymes in the body. These are preventive antioxidants which suppress free radical formation as follows:

1. Non-radical decomposition of hydroperoxides and H_2O_2

S. No.	Antioxidant	Mechanism
i.	Catalase	Decomposition of H_2O_2
ii.	Glutathione peroxidase (cellular)	Decomposition of H_2O_2 and Free fatty acid hydroperoxides
iii.	Glutathione peroxidase (Plasma)	Decomposition of H_2O_2 and phospholipid hydroperoxides
iv.	Phospholipid hydroperoxides Glutathione peroxidase	Decomposition of phospholipids and hydroperoxides
v.	Peroxidase	Decomposition of H_2O_2 and lipid peroxides
vi.	Glutathione S transferase	Decomposes lipid hydroperoxides

2. Antioxidants that sequester metals by chelation

S.No.	Metal Chelaters	Mechanism
i.	Transferrin, Lactoferrin	Sequestration of iron
ii.	Heptoglobin	Sequestration of haemoglobin
iii.	Hemopexin	Stabilisation of haem
iv.	Ceruloplasmin, albumin	Stabilisation of copper

3. Antioxidants that quench active oxygen species: Superoxide dismutase-dismutates superoxides where as carotenoids, vitamin E, etc. Quenches singlet oxygen.
4. *De novo* enzymes: These enzymes repair the damage and reconstitute membranes, e.g. Lipase, protease, DNA repair enzymes and transferases.
5. Adaptation enzymes: These enzymes are generated at appropriate antioxidant enzymes and transfer them to the right site at the right time in right concentration.

Non-enzymatic antioxidants

Ascorbic acid, β-carotene, α-tocopherol, glutathione, selenium, lycopene, uric acid, bilirubin, flavonoids and other chemical antioxidants, etc. constitute some of the non-enzymatic antioxidants. These are radical scavenging antioxidants which scavenge radicals to inhibit chain initiation and break chain propagation, e.g. Hydrophilic ones among them are vitamin C, Uric acid, bilirubin and albumin, etc. whereas vitamin E, Ubiquinol, carotenoids and flovonoids constitute lipophylic antioxidants.

Phenolic antioxidants

These are another group of antioxidants commonly present in plant foods. A large number of phytochemicals exert antioxidant activity and are known as non-nutritional antioxidants. These natural antioxidants are present mostly in plant foods as polyphenolic compounds (Phenolic compounds made up of multiple phenol rings). These phenols, especially those with multiple phenolic groups, are found to be better antioxidants than the well-known antioxidant vitamins. There are more than 5,000 individual phenolic compounds (flavonoids, monophenols and polyphenols) identified till date and more are expected to exist in nature. Major classes of phytochemicals are given in **Table 4**.

Table 4: Major Classes of Phytochemicals with Antioxidant Activity

S. No.	Major Classes of Phytochemicals	Compounds
1.	Carotenoids	Lycopene, lutein, astaxanthin
2.	Bioflavonoids	Genistein, diadzein, quercetin
3.	Phytosterols	Sitosterol, Stigmasterol, oryzanol
4.	Tannins	Catechins and other polyphenol compounds
5.	Chlorophylls	Chlorophyll A and chlorophyllin
6.	Terpenoids	limonin and limonene
7.	Allylic Compounds	Diallyl sulfide and disulfide
8.	Indoles	Indele-3-carbinol

Recent evidence strongly suggests that eating plenty of antioxidant – rich plant foods may reduce the risk of chronic diseases. It is hypothesised that phytochemicals present in plant foods exert beneficial effects by combating oxidative stress in the body through maintaining a balance between oxidants and antioxidants. Polyphenols can act chemically as antioxidants due to their extensive conjugated π-electron system, which allows ready donation of electrons or hydrogen atoms from the hydroxyl moieties to free radicals, which causes antioxidant activity.

Polyphenols are low molecular weight compounds found in commonly consumed plant foods, e.g. fruits, green leafy vegetables (GLVs), vegetables, nuts and oil seeds, etc. They are important to plants wherein they acts as antioxidants, enzyme regulators and precursors of toxic substances. Since different antioxidants work in different ways and in different places in the body, it is important to eat a variety of foods to get various antioxidants.

Judicious selection and consumption of plant foods rich in polyphenoilc antioxidants could therefore be of great help in modulating the oxidative stress and associated diseases in the population.

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25.7 Food Allergy and Food Intolerance

UV Mani

The importance of food comprising of macro, micro and other health promoting nutrients required for the growth and development of human life from conception to senescence is well known since the time immemorial. Extensive studies on the physicochemical and nutritional aspects of foods have also brought out various deleterious effects of some foods and food components in causing various health problems.

Allergy is one of the side-effects of immunity develops under some conditions. There are several different types of allergies, some of which can occur in any person, and others that occur only in persons who have a specific allergic tendency.

FOOD ALLERGY

Food allergy is recognised as a common worldwide problem and, like other atopic disorders, its incidence seems to be increasing. Any abnormal clinical response associated with ingestion of a food or food additive is generally termed as food allergy. These adverse reactions can be further classified as food allergy and food intolerance depending on the type of mechanism involved. Food allergy refers to an abnormal immunologic response to a food that occurs in a susceptible host. Food allergy can be IgE-mediated, mixed IgE and cell-mediated.

Epidemiology

The prevalence of food allergy is highest in infants and toddlers. Cow's milk allergy is experienced by 2.5% of infants and up to 8% of children less than three years of age. The prevalence of food allergy decreases slightly with age, affecting almost 4% of the general population.

Aetiology

The diverse clinical manifestations of food allergy result in part from different immune mechanisms, target organ responses, and characteristics of triggering proteins. Conceptually, it is useful to categorise the immune mechanisms according to three general types—IgE antibody-dependent diseases (triggered by multiple foods, raw fruits and vegetables), cell-mediated disorders without detectable IgE antibodies (triggered by egg, milk, wheat and soy) and disorders with mixed IgE and non-IgE mechanisms (triggered by wheat, lactose, fructose and some food additives). The development of allergy frequently starts in early childhood with initial eczema, followed by the subsequent sequential development of food allergy, allergic rhinitis, and asthma—the so-called 'atopic march'. Allergic diseases are also an example of gene-environment interactions.

Clinical Features

Allergic reactions to foods generally occur within a few minutes to one hour after eating the offending food which range from mild discomfort to severe life-threatening reactions. Symptoms can last for days or even weeks. The specific symptoms and severity of an allergic reaction are affected by the amount of the allergen consumed and the sensitivity of the allergic person.

Diagnosis

The evaluation of a patient with a possible allergic food reaction begins through clinical history and a complete physical examination to consider a potentially broad differential diagnosis between food-induced allergic clinical disorders and other gastrointestinal diseases, such as food intolerance (toxic and pharmacological effects or metabolic disorders), infections (viral, bacterial and parasitic), coeliac disease, inflammatory bowel diseases, bowel ischaemia, gall bladder disease, pancreatic insufficiency, and gastrointestinal neoplasms.

Management

Once a food allergy is diagnosed, strict elimination of the offending food allergen from the diet and avoidance of any contact with the food by ingestion, skin contact, inhalation, or injection is necessary. Thus, the primary therapy for food allergy is to avoid the causal food. Clinical tolerance develops to most food allergens over time, except for peanuts, nuts and seafood. Periodic re-introduction of food allergens under physician supervision is warranted to determine whether clinical tolerance has developed or not. There is a relationship between the decrease in serum food-specific IgE concentrations and the likelihood of developing tolerance. A greater decrease in serum food specific IgE levels over a shorter period of time might be indicative of a greater likelihood of developing tolerance.

Prevention

Approaches to delay or prevent allergy through dietary manipulation have been considered. Some studies suggest a beneficial role for exclusive breastfeeding of infants at high-risk for atopic diseases in the first 3 to 12 months of life and avoidance of supplementation with cow's milk or soy formulas in favour of hypoallergenic formulas if breastfeeding is not possible. Maternally ingested food can pass in immunologically intact form into breast milk and might induce reactions in infants. No conclusive studies indicate that manipulation of mother's diet during pregnancy or breastfeeding or the restriction of allergenic food from the infant's diet will prevent the development of food allergy whereas the introduction of solid can be delayed until 6 months of age and major allergens, such as peanuts, nuts and seafood, be introduced after 3 years of age till the child develops its own immunity.

Supplementation of antioxidant vitamins and minerals showed some good results in prevention of food allergy. It is postulated that an allergic response to antigen challenge, including inflammatory cell infiltration, results in the generation and release of reactive oxygen species. These oxygen free radicals lead to bronchoconstriction, increased mucus secretion and microvascular leakage.

Thus, by carefully analysing the causes and further by eliminating those causative agents, it is possible to overcome and control this disorder.

FOOD INTOLERANCE

Food intolerance (FI) reactions comprises of metabolic, pharmacologic, and gastrointestinal responses to foods or food compounds. It is a negative reaction, often delayed to a food, beverage, food additives or compounds present in the foods which produce symptoms in one or more organs and systems. In most cases, food intolerance is not associated with the production of IgE antibodies whereas food allergy does. Therefore, food intolerance is generally not life-threatening.

Aetiology

The various organic chemicals present in a wide variety of foods, both of animal and vegetable origin, food additives, (colouring and flavouring agents) preservatives, (monosodium glutamate) and many food chemicals have been identified as the causative agents.

A deficiency in digestive enzymes can also cause some types of food intolerance. Lactose intolerance is a result of the body not producing sufficient lactase to digest the lactose in milk, dairy foods, such as cheese. Another carbohydrate intolerance caused by enzyme deficiency is hereditary fructose intolerance.

Coeliac disease is an autoimmune disorder caused by an immune response to the protein gluten found in many foods (wheat, rye, barley and to some extent oat) which results in gluten intolerance and can lead to temporary lactose intolerance also.

The most widely distributed naturally occurring food chemical capable of provoking reactions is salicylate although tartrazine and benzoic acid are well recognised in susceptible individuals. Benzoate and salicylate occur naturally in many different foods, including fruits, vegetables, spices, herbs, nuts, tea, wines, and coffee, besides salicylates being present in pharmacological source such as aspirin and nonsteroidal anti-inflammatory drugs.

Other chemicals which commonly cause reaction and cross-reactivity include amines (banana, chocolate, cheese, tomato, etc.) nitrates and sulphites (in processed food) and some chemicals involved in aroma and flavour. Since the threshold levels vary in individuals, the consumption of large quantity of a single causative factor or many causative factors in a small quantity will result in FI of different degrees. FI can also occur as a secondary manifestation to an in-born error of metabolism (phenylketonuria and favism). Food intolerance can also be psychological in origin if the symptoms are triggered by emotional responses to the food in question.

Clinical Features

Symptoms of food intolerance vary greatly and can be similar to the symptoms of food allergy. Food intolerance symptoms usually begin within half an hour after consuming the food in question, but sometimes the symptoms may appear even after 48 hours. Food intolerance can present with symptoms affecting the skin, respiratory tract, gastrointestinal tract (GIT) either individually or in combination. On the skin, there may be skin rashes, urticaria (hives), angioedema, dermatitis and eczema. Respiratory tract symptoms can include nasal congestion, sinusitis, pharyngeal irritation, asthma and an unproductive cough. GIT symptoms include mouth ulcers, abdominal cramp, nausea, gas, intermittent diarrhoea, constipation and irritable bowel syndrome. Estimates of prevalence of food intolerance vary widely from 2% to over 20% of the population.

Diagnosis and Management

The easiest test for food intolerance is to remove the food from the diet and see if symptoms improve and disappear. If the symptoms appear on re-introduction of the food, presence of FI is confirmed.

Lactose intolerance can be tested more thoroughly using a lactose intolerance test, a hydrogen breath test and stool acidity test.

Food intolerance can be managed simply by eliminating the causal food from the diet. It is also useful to avoid foods with additives which may cause FI. If the sensitive food chemicals are identified, an appropriate diet can be prescribed excluding those food chemicals with the help of a dietician. The treatment involves consumption of gluten free diet. Among the cereals, only rice, corn and possibly oats can be used. It is not advisable to eat pasta, salad dressing and some margarine because they contain wheat or wheat extractsand also drinking beer should be avoided.

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25.8 Eating Disorders

Anupam Prakash

INTRODUCTION AND EPIDEMIOLOGY

Eating disorders are characterised by a severe and persistent disturbance in eating behaviour that causes psychosocial and sometimes, physical impairment.

Anorexia nervosa (AN) and bulimia nervosa (BN), the two distinct forms of eating disorders, are 10 times common in females and the prevalence of the two disorders among females is respectively, 0.5% to 1% and 1% to 3%. The onset of the AN is observed in mid-adolescence and for the latter BN in late adolescence to early adulthood. Eating disorder 'not otherwise specified' (NOS) is observed usually in middle-aged, and the female sex predilection is absent and is observed in obese individuals. Eating disorder NOS is the most common eating disorder encountered in clinical settings constituting about half of adult outpatient eating-disordered population, with patients of bulimia nervosa constituting about a third, and the rest being cases of anorexia nervosa. In inpatient settings, the great majority of cases are either underweight forms of eating disorder NOS or anorexia nervosa.

Since eating disorders were originally identified, the relationship between obsession with food and that with body weight has been consistently debated. It is also important to understand the particular way in which people with eating disorders perceive their bodies in the presence of other people.

Two notions are fundamentally important: 'body-self' and 'body-for-others'. The 'body self' is understood as the basis of self consciousness and inter subjectivity. 'Body-for-others' means how one experiences one's own body when someone else is looking at it and the subject body thus becomes conscious of being a body-object for others. Apart from a combination of psychological, biological and cultural risk factors; genetic factors also contribute to the risk of development of eating disorders. The exact aetiology hitherto remains unknown.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Psychiatric diagnosis are categorised by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM IV). Eating disorders are an extremely heterogenous diagnostic category. DSM IV recognises two eating disorders in adults, AN and BN; and a residual category-eating disorder not otherwise specified (EDNOS).

Two subtypes each for AN and BN have been identified, depending upon the method adopted by the patients to control their weight: restricting type (AN-r) and binge-/purging (AN-p) for AN and purging/non-purging type for BN.

The diagnosis of AN is made in the presence of the following features:

1. The over evaluation of body shape and weight; that is, judging self worth largely, or even exclusively, in terms of shape and weight. This has been described in different ways and is often expressed as strong desire to be thin combined with an intense fear of weight gain and fatness.
2. The active maintenance of an unduly low body weight; this is commonly defined as maintaining a body weight less than 85% of that expected or a body mass index (BMI) of 17.5 or less.
3. Amenorrhoea, in post-pubertal females not on oral contraceptive; this criterion is proposed to be removed in DSM V.

For a diagnosis of BN, the following three features need to be present:

1. Over evaluation of body shape and weight, as in AN.
2. Recurrent binge eating: A 'binge' is an episode of eating during which an objectively large amount of food is eaten for the circumstances and there is an accompanying sense of loss of control.
3. Extreme weight-control behaviour, such as recurrent self-induced vomiting, regular laxative misuse, or marked dietary restriction.

In addition, the diagnostic criteria for AN should not be met. This ensures that the two diagnosis are mutually exclusive. Hence, the BMI becomes a distinguishing feature between the two.

There are no positive criteria for the diagnosis of eating disorder NOS. Instead, this diagnosis is reserved for eating disorders of clinical severity that do not meet the diagnostic criteria of AN or BN. However, under the rubric of eating disorder NOS, DSM IV lists 'binge eating disorder' (BED). It is proposed that BED should be recognised as a specific eating disorder in DSM V.

CLINICAL FEATURES

Eating disorders share a common psychopathology, the over evaluation of the importance of body shape and weight, and their control. For people with eating disorders, self worth is dependent largely, or even exclusively, on their shape and weight and their ability to control them. The salient features of various eating disorders are outlined in **Table 1**.

Anorexia Nervosa (AN)

Patients become underweight, either because of persistent and severe restriction of both the amount and the type of food that they eat, or because of adopting a driven form of exercising. Anorexia nervosa patients typically value the sense of control that they derive from undereating. A subgroup of anorexia nervosa patients practice self-induced vomiting, laxative and/or diuretic misuse, especially those who experience episodes of loss of control over eating. Interestingly, the amount of food

eaten during these 'binges' is often not objectively large; hence, they are described as 'subjective binges'. Many other psychopathological features tend to be present and include depressed and labile mood, anxiety features, irritability, impaired concentration, loss of libido, obsessions to a varied extent and social withdrawal.

A hierarchical relationship in order of severity has been proposed:

(a) AN and behaviourally similar disorders — most severe
(b) BN and behaviourally similar disorders
(c) BED and behaviourally similar disorders
(d) Eating disorder NOS — least severe

Table 1: Salient Clinical Features of Eating Disorders

	Anorexia Nervosa	Bulimia Nervosa	Binge-Eating Disorder	Eating Disorder NOS
Age of onset	13 to 25 years	16 to 35 years	25 to 50 years	25 to 50 years
Sex predilection	Female (10:1)	Female (10:1)	None	None
BMI (kg/m^2)	<17.5	18.5 to 25	>25	Normal to high
Menstruation	Amenorrhoea	Normal	Normal	Normal
Restrictive eating	Criterion for diagnosis	Absent	—	—
Binge-eating	May be seen in 25% to 50%	Criterion for diagnosis	Intermittent, absent compensatory behaviour	Variable
Suicidal ideation	Yes	Rare	—	—
Mortality	Approx. 5% per decade	Low to nil	—	—
Physical characteristics	Physical overactivity, lanugo hair on trunk and limbs, oedema, azotaemia, anaemia, leucopaenia, sialadenosis, delayed gastric emptying, constipation, hypoglycaemia hypokalaemia, hypomagnesaemia, metabolic alkalosis, osteopaenia, hypotension, bradycardia, acrocyanosis	Less common. Hypokalaemia, hyponatraemia, hypomagnesaemia, metabolic alkalosis, dental caries, enamel erosion, sialadenosis, azotaemia, arrhythmias	Complications related to obesity, limited ability to lose weight	—

Bulimia Nervosa

It resembles BN, both in terms of eating habits and methods of weight control, but the distinguishing feature is that attempts to restrict food intake are regularly disrupted by episodes of (objective) binge eating. These episodes are often followed by compensatory self-induced vomiting or laxative misuse, although there is also a subgroup of patients who do not purge (non-purging BN). Due to this combination of under eating and over eating, the weight of most patients with BN tends to be unremarkable and is within the healthy range (BMI = 20–25 Kg/m^2). Features of depression and anxiety are prominent in these patients. Rarely, these patients can engage in self harm and/or substance and alcohol abuse. Physical complaints are much less common, although electrolyte disturbance may occur in those who vomit or take laxatives or diuretics frequently.

Binge-Eating Disorder (BED)

This disorder refers to a clinical picture characterised by recurrent binge eating in the absence of the extreme weight-control behaviour seen in AN and BN. In fact, BED is rather different from AN and BN, and from the many presentations relegated to eating disorder NOS. Those affected tend to be middle-aged rather than adolescents or young adults, the marked preponderance of females is absent, and the state commonly co-occurs with obesity. Patients of BED invariably have a BMI >25 Kg/H^2 (are overweight or obese). Furthermore, in marked contrast to AN and BN, BED tends to be intermittent rather than continuous with many individuals reporting sustained periods when they are free from binge-eating.

MANAGEMENT

Anorexia Nervosa (AN)

The primary management is restoration of weight to at least 90% of the normal. However, this is greatly resisted by the patients and consequently is accompanied by frustration. Therefore, counselling of the patient is imperative. Patients with suicidal ideations and with serious medical complications need to be admitted. Otherwise outpatient counselling sessions providing behavioural therapy and interpersonal psychotherapy along with requisite nutritional advice can be provided. Family-based therapy can be used for adolescents. Behaviour therapy focuses on gaining control and changing unwanted behaviours. Drug therapy, including psychotropic drugs, is not found to be useful in AN. However, selective serotonergic reuptake inhibitors may be useful for treating comorbid anxiety or depression. The prognosis is good in the short-term, but long-term outlook is variable. One-fifth make a full recovery and one-fifth remain chronically ill, while the remaining have recurrent episodes of anorexia. Mortality from suicide or physical complications is reported at the rate of 5% per decade.

Bulimia Nervosa (BN)

Cognitive behavioural therapy is the treatment of choice. Cognitive behavioural therapy is a short-term, i.e. 4 to 6 months psychological treatment and produces symptomatic remission in 25% to 50% of patients. Interpersonal therapy is also beneficial. Fluoxetine or other selective serotonergic reuptake inhibitors can be used for bulimia symptoms and the latter can

also benefit co-morbid symptoms. BN patients can be treated on outpatient basis and usually do not require admission. The prognosis is far better than AN patients and mortality is unusual.

Eating Disorder Not Otherwise Specified and Binge-Eating Disorder

Group or individual cognitive behavioural therapy has been found to be beneficial. Sibutramine or orlistat was being used for weight loss and selective serotonergic reuptake inhibitors for co-morbid depression or anxiety. Sibutramine has been banned and recent reports of orlistat causing hepatotoxicity have made its use controversial at the moment.

CONCLUSION

Eating disorders are severe psychological illnesses and are associated with significant physical and psychological disturbances in turn compromising the quality of life. It is important to realise that eating disorders form a spectrum of disorders across different age groups and varying body proportions. It is imperative to be aware of these disorders to make an early diagnosis and provide multidisciplinary therapy for restoration of health in these patients.

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25.9 Enteral and Parenteral Nutrition

Varsha

INTRODUCTION

Clinical nutrition can significantly improve patient care in hospitals. Until antibiotics were developed the combination of poor nutrition and infection contributed to the significantly high morbidity and mortality associated with many hospital admissions, particularly for patients needing surgical operations. Since infections can be largely overcome, the dangers of poor nutrition to malnourished patients, with serious illnesses remains highlighted. So much more needs to be done and must be done both in the assessment and management of sub-optimal nutrition in hospitals.

"Sick patients do not oblige their doctors by separating 'metabolic' from 'tissue pathology' states. The whole problem must be solved together, not in sections" (Francis D Moore, 1959). Definition of 'Critical illness', in itself indicates the depth and magnitude of what the Francis Moore statement wishes to convey – its primarily a metabolic response to injury, and is secondary to a wide range of conditions, such as trauma, burns, systemic infection (sepsis), severe head injury, sterile inflammatory processes, etc. Needless to state the macronutrients and the micronutrients permutations and combinations would work out an astronomical figure when one begins fitting the puzzle of a perfect prescription for a sick individual. There are no shortcuts and the vista is yet unchartered for evidence-based documentation on the formulations that would work well not only in just prolonging life, but also to support healing with resultant good quality of life. If this were the basis for formulating nutrition support, it should work well. It is on this that Nutritional Support (NS) was started and has grown in popularity and it is now a multibillion dollar-a-year industry. This growth was and is still spurred by the assumption that such an intervention would improve patient outcome. The reasons of this multinational support are outlined in **Table 1**.

Table 1: The Basis of this Wide Acceptance of NS (Parenteral NS ENS – PNS) Rests on 5 Lines of 'Reasoning'

1. Any living organism, when deprived of nutrient intake for a long enough period, will die.
2. An individual with a given disease who is also malnourished has a poorer prognosis than does one with the same disease but who is not malnourished (Studley's observation).
3. NS improves measured parameters of malnutrition (especially such things as body weight or nitrogen balance).
4. Retrospective or prospective (with or without nonrandomised control groups) reports allegedly demonstrate therapeutic efficacy.
5. Doing something is better than doing nothing.

Translating knowledge into practice is always difficult clinical exercise. It seems appropriate that every hospital will have organised and effective clinical nutrition service, since there is a quantum leap in the concept that has not kept pace with the formulations of products. The original concept was "The Classic Approach to Nutrition Support" that centered on maintenance of Body Cell Mass (BCM) and Nitrogen Balance (NB) and its measurements to assess the effectiveness of NS. It must if not totally, be replaced to accommodate the more advanced concept of The Contemporary Approach to Nutritional Support that *recognises the multi-factorial nature of illness*: such as alteration of the stress response, administration of tissue-specific nutrients [arginine, glutamine, etc.]; stimulation or administration of growth factors is the GOALS of NS. Hence, the immediate translation of this new concept in understanding the importance of nutrition to critically ill patients (**Table 2**), would mean maintenance of organ function and immune status and improvement in clinical outcome more important than maintenance of BCM or NB. NS is currently in a dynamic phase fostered by knowledge from molecular biology, and it equates to 'improves the efficiency and effectiveness of NS'.

Table 2: Importance of Nutrition to Critically Ill Patients

Goals for nutrition support – *to meet the demands of accelerated energy and nitrogen flux as progressive protein-energy malnutrition (PEM) appears to increase morbidity and mortality*

1. Early detection and correction of pre-existing malnutrition
2. Prevention of progressive PEM
3. Optimisation of the patient's metabolic state (including provision of fluid and electrolytes)
4. Reduction of morbidity, and
5. Reduction of subsequent duration of recovery.

Prospective randomised and double blind studies on the efficacy on NS in malnourished patients with curable or reversible disorders are unethical given the present state of knowledge and experience. NS is indicated in the following patients:

1. A previously well-nourished patient with actual or expected complications or with 'stress', e.g. infections, polytrauma.
2. A previously well-nourished patient who has not consumed sufficient oral nutrition for 5 to 7 days prior to admission.
3. A patient found to be malnourished on admission.

The information is pertaining to the existing scenario and one must begin by looking at the learning objectives that govern nutritional support's two arms: enteral nutrition (EN) and parenteral nutrition (PN) and their access devices, formulations, implementation, complications and management.

The introduction of chemically defined foods led on to the development of parenteral feeding, which has such life-saving potential for many seriously ill patients. However, EN is physiological and is superior to PN in terms of cost, reduced complications, ease of maintenance, efficacy of nutritional repletion, and maintenance of organ function. Providing even 'token' EN diminishes gut mucosal atrophy and maintains gut integrity thereby preventing translocation of bacteria and toxins from the gut into the circulation. It is this translocation that results

in the 'Stress Syndrome'. Peristalsis is NOT necessary for absorption of nutrients from the ileum. If access into jejunum is achieved, nutrients can be infused in the absence of bowel sounds, immediately after laparotomy and with 'ileus' Nasogastric suction (as in the management of stress-induced gastritis, gastric atony, etc.) is not a contraindication for distal feeding into the jejunum.

INDICATIONS FOR NUTRITIONAL SUPPORT

The key biochemical concept to remember in critical care is that stressed starvation is not the same as simple starvation. In the former, hypermetabolism (increase in resting energy expenditure) and hypercatabolism (loss of lean tissue, negative nitrogen balance) occur due to hormonal changes. Counter regulatory (or 'anti-insulin' hormones) such as catecholamines cortisol and glucagons are all elevated. While circulating insulin levels are also elevated as there is a relative insulin-resistance. Unless an attempt is made to decrease this 'autocannibalism', loss of protein results in death.

Guidelines for protein, carbohydrate, and fat are the same for EN and PN. Besides this, the *route of delivery* is equally an important integral factor in outcome. An algorithm delineated (**Table 3**) with respect to determining the appropriate route of delivery.

ENTERAL NUTRITION

Access

Oral, nasogastric, nasojejunal, gastrostomy or Jejunostomy (needle catheter or tube).

Enteral Infusates/Formulations

Commonly classified as elemental or non-elemental. The elemental diets are said to be better tolerated. However, the human gut is capable of absorbing complex moieties just as well. A disadvantage of elemental diets is their high carbohydrate content. Modular changes in EN (i.e. specific addition of protein, fat or carbohydrate as needed to standard commercially available formulae) are required for optimal National Status (NS). Formulae enriched with glutamine (to preserve gut integrity), fibre (to improve tolerance and to stimulate gut mucosa by virtue of degradation to short chain fatty acids) and omega-3 fatty acids with RNA (to stimulate immunity) are commercially available but their superiority in nutritional repletion has not been convincingly proven.

Appropriate formula selection is important and an integral component of successful enteral tube feeding. First modern enteral formulas were homemade from blenderized foods diluted enough to pass through a feeding tube. The inherent problems were: difficulty with consistency and lack of nutrient standardisation.

Modern enteral formulas have evolved over these years (**Table 4**) and designed to meet patient nutrient requirements in a specified volume of formula. The basis of this evolution, however, has been the understanding of the patient's digestive and absorptive capacity that influences the selection of formula composition, e.g. one must be aware of the following facts:

1. Gastric atony associated with sepsis may limit the use of direct intragastric feedings.
2. Limiting enteral feeding is advised in haemodynamically unstable patients because of reduced splanchnic blood flow.
3. Gastric feeding should be carefully monitored to avoid high gastric residuals and pulmonary aspiration.

The different categories of enteral formulations are given in **Table 4**.

Table 3: Determining Route of Nutrition Support

TPN
Yes ↓
TPN

Intestinal obstruction - bowel use X?
No ↓
Paralytic ileus?
Yes ↓ TPN
No ↓
Pancreatitis?
Yes ↓
Pancreatitis severe?
– Pancreatic pseudocyst
– Pancreatic ascites
– Pancreatic haemorrhage
– Pancreatic infection
– Pancreatic phlegmon
– Severe pain?
Yes ↓ TPN
No ↓ EN
No ↓
Intractable vomiting?
Yes ↓ TPN
No ↓
Diarrhoea?
Stool output > 1 litre?
Yes ↓ TPN
No ↓ EN
Enterocutaneous fistula?
Yes ↓
- Oesophagus
- Stomach
- Duodenum
- Proximal jejunum? Or 150 cm ileum?
Yes ↓ EN distal to fistula
No ↓ TPN
No ↓
Severe short bowel syndrome < 100 cm jejunum
Yes ↓ TPN
No ↓ EN

Table 4: Enteral Formulations: Categories

Type	Comment
Polymeric diets	Whole protein nitrogen source, for use in patients with normal or near normal GI function
Monomeric diets	Predigested nutrients; most have a low fat content or a high percentage of medium chain triglycerides for use in patients with severely impaired GI function
Fibre containing	Polymeric diets containing source of fibre; diets reportedly beneficial for prevention/ treatment of altered bowel function in enterally fed patients
Disease specific	Formulas designed for feeding patients with specific disease states – now available for patients with respiratory disease, diabetes, renal failure, hepatic failure, and immune compromise, well-designed clinical trials may or may not be available

Mode of Infusions: Bolus, Cyclic, Continuous

With respect to bolus mode, though there are disadvantages it is physiological mode of feeding. Continuous feeding is unphysiological as glucose stimulates release of insulin, which in turn decreases lipid mobilisation. In cyclic feeding, either the infusion is interrupted for 4 to 6 hours each day or a glucose-free solution with decreased amount of intracellular ions (K, Mg, and P) is infused. Better nutritional repletion and a decrease in liver-enzyme elevation occurs. However, managing fluid balance and glucohomeostasis in an ICU patient is difficult with cyclic feeding.

Developing Enteral Formulary

Criteria used for selecting EN products included on the enteral formulary are depicted in **Tables 5A to D** and **Table 6**.

Table 5A: Carbohydrate (CHO) Source and Quality

Generally provided using combination of:
- Hydrolysed cornstarch
- Maltodextrins
- Corn syrup solids, and/or
- Sucrose

Form of carbohydrate (CHO)
- Influences osmolality, sweetness and digestibility of the enteral product – Monosaccharides; Oligosaccharides 2-8 units; Polysaccharides >8 units
- Most CHO except Lactose, easily digested, absorbed by the small bowel
- CHO content of formulas ranges from approx. 40% to 90% of total caloric content
- Symptoms of CHO intolerance range from abdominal discomfort to flatulence and diarrhoea

Table 5B: Protein Source and Quality

Amount ranges from 4% to 32% of total calories
- Low protein (<10%) – when restriction – renal failure
- Standard protein (11% to 15%) – when no increased requirements
- Intermediate protein (16% to 20%)
- High protein (>20%) – in increased nitrogen requirements – e.g. trauma, burns, etc.

Commercial formulas
- Intact protein
- Protein hydrolysates
- Crystalline amino acids

Table 5D: Electrolyte, Mineral Content, and Vitamin Content (Volume Necessary to Supply RDA)

Most enteral products meet 100% of RDA at a given volume of formula (excluding renal and hepatic formulas)

However, RDAs do not reflect needs during critical illness or severe hypermetabolism – hence manufacturers adopt different reference standards

Of current interest – relationship between β-carotene and immune function - β-carotene may increase cytotoxicity of natural killer cells, enhance immune response, and increase levels of T-helper cells

Presently six enteral products contain β-carotene

Developing Enteral Formulary: Conclusions

I. Appropriate formula selection requires knowledge about
   - The nutrient requirements of specific patient populations
   - Awareness about the potential effects of formulas on gastrointestinal, metabolic and immunologic functions.

II. Critical evaluation of formula composition to ensure efficacy and safety of product use: Formulas developed for particular disease states or clinical conditions – supported by well-designed clinical trials.

III. Enteral nutrition products: Market significant >80 products.

IV. Choices include:
   - Formulas with peptides, fibre and β-carotene
   - Formulas, disease specific
   - Formulas designed to improve immune function

V. Can current standard formulations be improved?
   1. Are specific nutrients being given in excessive amounts, i.e. chromium and manganese?
   2. Is there still too much contamination with toxic minerals, i.e. aluminum?
   3. Are there nutrients and non-nutritional factors present in foods that will be beneficial if added to purified formulas?

Table 5C: Fat Source and Quality

FAT: Essential fatty acids (EFAs)

Fat provides an isotonic, concentrated energy source

Fat content of ENF ranges from <10% to >50% of total calories

Fat sources in enteral products – soy, corn – more frequently used, safflower and sunflower oils; canola oil, beef fat, refined marine fish oil – less frequently used, medium-chain triglycerides (MCT's), and structured lipids

Many products contain fats that do not provide adequate quantities of both linoleic (w-6 – 1-2% total calories) and linolenic (w-3 – 0.2-0.3% total calories) acid

FAT: Medium chain triglyceride (MCT)

Quickly hydrolysed intraluminally, increased levels of intake may increase the luminal osmotic concentration and cause abdominal distension and diarrhoea

Metabolised in the liver – ingestion of high levels contraindicated in cirrhosis – may induce a situation similar to hepatic encephalopathy

MCTs ketogenic – not be given to hyperosmolar diabetic syndrome patients

Table 6: Physical Characteristics of Enteral Formulations (EFs)

Osmolality

Enteral products range in osmolality from 270 mOsm/kg to approximately 700 mOsm/kg - as a general rule, do not worry about diets whose osmolalities are 350-450 mOsm/kg water or less, *except* when fed directly into the duodenum or jejunum

Osmolality may affect patient tolerance to a particular formula – hypo- and hyperosmolar feedings delay gastric emptying

Hyperosmolar formulas may increase intraluminal osmotic concentration and create GI intolerance - the importance of hypertonicity in causing diarrhoea has probably been overestimated

If the osmotic load relative to free water exceeds the ability of the kidney to concentrate, an osmotic diuresis results, leading to dehydration

Nutrient Density (ND)

1. Calorie-Nutrient Density – may affect tolerance of tube feeding by its effect on gastric emptying
   a. The greater the ND (kcal/mL) the slower the emptying rate into the duodenum
   b. Tolerance of a particular formula – fat, most powerful inhibitors of gastric motility – high intakes or rapid infusion into the duodenum – a significant delay in gastric emptying
   c. A consideration when initiating enteral feedings, especially in GI tract compromised patients – not used for an extended period or have mucosal disease/damage
2. Introduce nutrients gradually in a diluted or low-calorie formula – not to exceed the capability of the intestinal enzymes to hydrolyze the nutrients

Approximate water content of EFs based on caloric density

Caloric density (kcal/mL formula)	Water content (kcal/H20/1000 mL formula)	Water content (%)
1.0 -1.2	800-860	80-86
1.5	760-780	76-78
2.0	690-710	69-71

pH

Solutions with a pH of less than 3.5 reduce gastric motility

Not a major concern with most commercial formulas

Residue

1. Many formulas contain little or no residue
2. May be advantageous in the management of specific gastrointestinal disorders (e.g. bowel fistula or enteritis)
3. Low-residue diets may cause constipation in some patients

Complications

1. Aspiration pneumonitis.
2. Diarrhoea (due to hypoalbuminaemia, antibiotics, organisms). The use of intravenous albumin to improve tolerance to EN is controversial.

PARENTERAL NUTRITION (PN)

Access

Peripheral IV cannulae or central (single or multiluminal) catheters. Catheter insertion and care should follow established protocols.

PN Formulation Components

1. Energy substrates – carbohydrate and lipids
2. Protein
3. Electrolytes
4. Vitamins
5. Trace elements
6. Water

Various combinations of these components are incorporated into the regimen for IV administration based on the patient's individual needs and clinical limitations. Parenteral feeding imposes increased risks, major expense, and a serious handicap. Current clinical data on commercially available parenteral nutrition solutions – not embraced the new approaches (**Tables 7A to F**).

Several amino acid solutions with varying concentrations with or without added electrolytes and major minerals are available. Dextrose solutions vary in concentration from 10% to 70%. A trained pharmacist usually does mixing. Fat emulsions are available as 10% or 20% solutions. The convenience and safety of 3-in-1 admixtures have made this popular. All components of PN are mixed in one high-volume bag and provided to the patient. While there are theoretical reasons to provide branched-chain amino acid-enriched infusates to stressed patients; the cost-effectiveness of its routine use has not been demonstrated.

PN Formulation Conclusions

1. Parenteral feeding imposes increased risks, major expense, and a serious handicap.
2. Current clinical data on commercially available parenteral nutrition solutions – not embraced the new approaches.

Table 7A: Energy Substrates – Protein

Crystalline amino acids – 4.0 kcal/g

Amino acids: Standard – provide EAA and Non-EAA

Standard amino acid (STD AA) formulations, based on egg protein – the workhorse for providing nutrients during the formative years of parenteral nutrition – this approach sought to provide nutrients for total-body nitrogen utilisation

Table 7B: Energy Substrates – Carbohydrate

Dextrose – hydrated – 3.4 kcal/g – multiple concentrations range from 2.5% to 70%

Dextrose – acidic – pH range 3.5 to 6.5 – osmolarity vary depending on concentration

Higher concentrations of dextrose (>10%) reserved for administration via a central vein due to propensity to cause thrombophlebitis in peripheral veins

Sugar alcohol glycerol – less frequently used – 4.3 kcal/g – protein sparing – ?induces less insulin response than dextrose-based regimens

Dextrose solutions

70% = 2.38 kcal/mL
50% = 1.70 kcal/mL
40% = 1.36 kcal/mL
30% = 1.02 kcal/mL

Table 7C: Energy Substrates – Lipid – Emulsion – Energy and EFA

10% - 1.1 kcal/mL

20% - 2.0 kcal/mL

30% - 3.0 kcal/mL – not for direct administration

Soyabean oil or 50:50 mix of safflower and soyabean – other components of lipid emulsions – egg yolk phospholipid (emulsifier) – glycerin (to render formulation isotonic) – vitamin K and sodium hydroxide to adjust the final pH (range 6.0-9.0)

Metabolic fate of lipid emulsions – issue of concern – lipids are not completely oxidised – during stress increased re-esterification of FFA into triglycerides and deposition into storage tissues and large amounts of lipid emulsion at rapid infusion rates result in compromised function of granulocytes, leucocytes, neutrophils, and phagocytes and decreased T-helper: T-suppressor cell ratios

Hence, accepted method for Tx – provide 500 ml of a 10% IV fat emulsion 2 to 3 times weekly

The practice of providing fat in 3-in-1 solutions (i.e. fat-CHO-protein) or total nutrient admixtures (TNAs) standard

Long-chain IV fat emulsions – for Tx of EFAD and as parenteral caloric source, provides a dense caloric source with minimal fluid volume to the patient

For clinical situations requiring 4 to 7 kcals/kg/d fat emulsions be prescribed and administered

A baseline serum triglyceride level should be obtained and triglycerides monitored biweekly

Table 7D: Vitamins

Single entity products and combinations of both fat-soluble and water-soluble vitamins

Multivitamin for adults – typically include vitamins A, D, E, C (ascorbic acid), B_1 (thiamin), B_2 (riboflavin), niacin, folic acid, B_6 (pyridoxine), pantothenic acid, biotin, B_{12} (cyanocobalamin).

Vitamin K (if ordered) – added to the PN formulation separately or administered subcutaneously

Pediatric formulations – pediatric doses of the same as listed above + vitamin K

Vitamins marketed as single entry injectible products include all of the above except biotin, pantothenic acid, riboflavin, vitamin A and vitamin E

Carnitine necessary for proper transport and metabolism of fatty acids – IV form of L-carnitine available

Complications

1. Catheter malfunction and sepsis; 2. Electrolyte and mineral deficiency; and 3. Glucose intolerance. Warning: Do Not Overfeed! hypophosphataemia and hypokalaemia can occur with lethal results during the 'refeeding syndrome'.

Developments in PN

1. Medium-chain triglycerides (MCT) containing formulas since it is carnitine-independent for transportation into mitochondria.
2. Glutamine-enriched formulas, as glutamine is vital for gut environment.
3. Carnitine and RNA enriched formulas, as these are implicated in enhancement of immune function.
4. Hormones supplementation (e.g. human growth hormone) that promote positive nutritional status.

Table 7E: Electrolytes

Standard daily ranges include:

Sodium (Na) and Potassium (K)	: 1-2 mEq/kg + replacement of losses
Calcium (Ca)	: 10-15 mEq
Magnesium (Mg)	: 8-20 mEq
Phosphate (P)	: 20-40 mmoL

Acetate and chloride – no specific ranges for intake – adjusted as needed to maintain acid-base balance

Electrolytes available in salt forms

- Na and K – chloride, acetate, and phosphate
- Ca – chloride, gluconate, glycepatate
- Mg – sulphate, chloride
- Generally gluconate salt of Ca and sulphate salt of Mg preferred forms of cations – less likely to produce physicochemical incompatibilities

Trace Elements

- Adults, paediatrics, neonates – with or without electrolytes commonly used in PN
  - Zinc (Zn), Copper (Cu), Chromium (Cr), Manganese (Mn), Selenium (Se)
  - Other Trace Elements (TE)? may be included
    - Molybdenum (Mo), Iodine (I), Iron (Fe – available only as a single-entity product)

Table 7F: Volume Aspects

Sterile water for injection – used to provide necessary fluid and volume to the PN feeding formulations

Critically ill patient presents a challenge in fluid management

TPN + other IV fluids given for concurrent medical problems – i.e. antibiotic, cardiac and pulmonary therapy.

To minimise fluid overload, considerations be given to using concentrated solutions to provide nonprotein kilocalories and protein

MONITORING OF NUTRITIONAL SUPPORT

Nutritional Monitoring

Weight gain, serum total protein and albumin levels, and nitrogen balance, total lymphocyte count.

Fluid Status Monitoring

A negative balance during repletion is common due to mobilisation of intracellular water. In EN, the amount of free water in infusions is only 75% to 85% of the total volume.

Biochemical Monitoring

1. Acid-base and electrolyte status, 2. Glucose levels, 3. Renal functions (BUN, Creatinine), 4. Liver functions (Bilirubin, enzymes) 5. Major mineral status (Calcium, Phosphorus, Magnesium) and 6. Serum triglycerides.

Haematologic Monitoring

Complete blood count, coagulation functions (prothrombin time).

Functional Monitoring

Sensorium, improvement in ventilatory muscle function.

Frequency of Monitoring

Each of the monitoring parameters listed above could be on a frequency that is hourly, daily or weekly basis on the degree and level of stability to be attained.

MISCELLANEOUS

Highly-Related Issues

Ethics

Philosophies about NS in seriously ill patients should be discussed with the patient's family. Ethics committees help to protect and guide the intensivist. Prolonging useful life is different from delaying death.

Team approach

For optimal, safe and cost-effective PN and EN, a well-trained team is necessary.

CURRENT STATUS AND PROBLEMS

Currently those involved in providing special oral, enteral (tube) and/or parenteral nutrition can have a good degree of satisfaction in achievements in nutrition support. However, this satisfaction be tempered by the recognition that particularly with regard to not only parenteral nutrition but also in some respects to enteral feeding, there are unresolved issues of varying degrees of clinical importance. Good survival outcomes, e.g.:

- In pregnant women who are dependent on long-term parenteral nutrition, there is improved outcome of the very low-birth infant.
- Improved nutritional status of patients with a variety of serious malabsorption states including long-term survival and a good quality of life for those with severe short-bowel syndromes.
- Improved survival and outcome of acutely ill patients with severe trauma, burns, and infections.

Providing NS to ICU patients, when indicated, is as important as haemodynamic, respiratory, and pharmacologic support. Delay in initiating and maintaining effective NS is lethal. No patient is 'too sick' to receive NS! However, appropriate protective randomised controlled trials (PRCTs) to evaluate the role of NS in the ICU is needed. Some NS (i.e. PNS) may actually have established harm. "Thy food shall be thy remedy" Hippocrates (400 BC) – May Be Wrong. It is what we think we know already that often prevents us from learning. Claude Bernard ...Miles to go before?! Success.

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Section 26

Poisoning and Toxicology

Section Editor: N.P. Singh

26.1 Poisoning—Basic Considerations and Epidemiology **1934**
N.P. Singh, Gurleen Kaur

26.2 Aluminium Phosphide Poisoning **1936**
S.N. Chugh

26.3 Organophosphorous Poisoning **1939**
Surjit Singh

26.4 Corrosive Poisoning **1941**
Rakesh Kochhar

26.5 Alcohol Poisoning **1944**
Pritam Gupta, Ankur Gupta

26.6 Plant Poisoning **1947**
D.K.S. Subrahmanyam

26.7 Drug Overdose **1950**
Nusrat Shafiq

26.8 Snake Bite Poisoning **1955**
H.S. Bawaskar

26.9 Scorpion Sting **1960**
H.S. Bawaskar

26.10 Fluorosis **1965**
D. Raja Reddy

26.11 Lathyrism **1970**
U.K. Misra, J. Kalita

26.12 Epidemic Dropsy **1972**
Navneet Sharma

26.13 Heavy Metal Poisoning **1974**
Praveen Aggarwal

26.14 Miscellaneous Poisoning **1983**
Subhash Varma, Vikas Suri

26.1 Poisoning—Basic Considerations and Epidemiology

NP Singh, Gurleen Kaur

INTRODUCTION

The past 3 to 4 decades have seen a remarkable change in incidence and type of poisoning. A number of new compounds have been added to the list of potentially poisonous materials. Poisoning is the fourth most common cause of mortality in rural India, with childhood poisoning constituting 2.1% of total paediatric admissions and 1.2% of total deaths in this population. Acute poisonings are on the rise in many countries and similar trends have been observed in India as well. In spite of the fact that acute poisoning cases are second only to road traffic accidents in numbers, this is often a neglected health problem compounded with the problem of difficult diagnosis in poisoning cases. It is important to realise that poisonings are largely preventable and majority of poisoning cases die within 1 to 6 hours of exposure to poison. Therefore, it is imperative to have a sound knowledge in the subject of poisoning. In simple terms, a 'poison' is any substance that produces toxic effects to the human body. Hence, even drug overdose will be treated as poisoning.

EPIDEMIOLOGY

The exact incidence of poisoning in India remains uncertain but 1 to 1.5 million cases occur every year, of which 50,000 succumb to it. There is an increasing trend of poisoning with increase in age up to the third decade following which it declines, peak incidence being in 20 to 30 years of age group and rare cases occurring after 65 years of age. Half of the poisonings in India are suicidal, followed by accidental poisonings which are about one-fourth in proportion and homicidal poisonings contribute much less. Both suicidal and homicidal cases of poisoning are more common in India than in the Western countries, because of the ease with which poisons can be obtained from any market. Males are affected more than the females and most victims are recorded from the medium to low socioeconomic group primarily from rural areas. Most cases are literate and married people outnumber unmarried cases. Aluminium phosphide is the commonest poisoning agent reported from rural areas while organophosphorous agents are the commonest reported from other areas. Therapeutic drugs are responsible for only a minor proportion followed by food poisoning cases. Among the paediatric population, nonmedicinal compounds are the largest contributors, of which kerosene alone is responsible for the majority of cases.

APPROACH

While dealing with a case of poisoning, it is important to consider the following important facts:

1. Identification of the poison
   a. From the history/circumstantial evidence
   b. Signs and symptoms of the case
2. Entertain alternative differential diagnosis
   a. Differentiate from illnesses which can mimic poisonings
3. Identify comorbidities
4. Offer treatment
   a. Stabilise patient's vitals
   b. Removal of unabsorbed poison
   c. Use of antidote
   d. Enhance removal of poison from body
   e. Supportive management
5. Offer psychiatric counselling, especially for suicidal cases

HISTORY AND EXAMINATION

A proper history may be elusive because these patients may not be conscious or cooperative. However, an attempt should be made to ascertain the nature of poison, the quantity consumed, mode of exposure, the time of exposure and if there was any vomiting subsequently, which resulted in spontaneous expulsion of the ingested poison. A clinician should always suspect poisoning if there is any sudden unexplained unpredictable illness in a preceding healthy individual, specially if he/she is young or in transit (at railway stations or bus stations, drugging of innocent passengers with stupefying agents is common). A history of recent consumption of an unknown drink/food item from an unverified source, depression or acute stress, presence of insecticide box or pill box near the patient; are suggestive of poisoning.

In cases of poisonings, medical management needs to be provided promptly, resuscitative measures may need to be instituted in comatose or unconscious patients (see chapter on Cardiopulmonary Resuscitation). The first assessment of the patient's clinical condition is very important since it provides the baseline which can be used for subsequent assessments and also outlines the need for instituting emergency measures. After assessment of sensorium and vital signs and need for their management, a quick but thorough physical examination is essential. Absence of any focal deficits and just depression of sensorium without any parasympathetic or sympathetic symptoms could result from a cerebral depressant/sedative. Pupillary signs and signs of cholinergic or anticholinergic stimulation may help aid the diagnosis and in the institution of proper management. Miosis is observed in poisonings with organophosphates/carbamates, narcotics, barbiturates, phenothiazines, clonidine, phencyclidine; while mydriasis is seen with atropine, LSD, MAO inhibitors, nicotine, amphetamines, anti-histamines, tricyclic antidepressants. Skin colour can also be helpful at times – a cherry-red colour seen in carbon monoxide poisoning and cyanosis in absence of hypoxia indicates methaemoglobinaemia. Perioral corrosive burns and intraoral ulcerations and congestion suggest attempts at corrosive ingestion.

Odour of the poison may be evident from the clothes or skin, and breath odour can be helpful in cases of ethanol or aluminium phosphide poisoning. Colour of the urine can indicate jaundice resulting from hepatic toxicity or black colour may result from intravascular haemolytic reactions.

MANAGEMENT

Apart from the routine investigations vomitus, urine, gastric lavage samples and suspected skin scrapings should be preserved for toxicological screening.

Removal of Unabsorbed Poison

It is important that whatever poison has not yet gained entry into the human body should be immediately removed. Clothes need to be removed in cases of organophosphorous poisonings, wherein the poison might have spilled on the clothes since these poisons can gain entry though the skin as well. In cases of poisoning with gas (carbonmonoxide poisoning), patient should be removed from the room and brought to fresh air. Skin and eyes should be thoroughly washed in cases of corrosive burns. Gastric lavage is one of the most effective methods to remove the unabsorbed ingested poison, if performed within 2 to 5 hours of ingestion, but is contraindicated in corrosive and kerosene poisonings. Induction of emesis is not advocated as it is not an effective method and, moreover, it can result in aspiration, induce convulsions and there exists a danger of the poison being pushed in to the small bowel from the stomach and getting easily absorbed.

Use of Antidotes

By definition, antidotes are agents which counteract the effects of poisons. Specific antidotes to all poisons are not known and hence nonspecific antidotes along with supportive therapy are provided in most cases. Activated charcoal acts mechanically by absorbing and retaining within its pores organic and also, to a less degree, mineral poisons. Activated charcoal 50 gm per dose can be repeated 4-hourly and can be given with a cathartic agent like sorbitol. Potassium permanganate, because of its oxidising properties, is a nonspecific chemical antidote and a dilute solution of 1:2000 is commonly used for gastric lavage in opium poisoning. Specific antidotes like atropine is a physiological antidote for organophosphorous insecticide poisoning, naloxone for morphine poisoning, BAL (Dimercaprol) for chelating arsenic or mercury, calcium sodium edentate for lead poisoning, Desferrioxamine for iron poisoning, D-penicillamine for other heavy metal poisonings (lead, gold, mercury and copper).

Enhance Removal of Poison from Body

Adequate hydration is one of the foremost steps since most toxins/poisons are excreted by the kidneys. Adequate hydration helps maintain the blood pressure which in turn maintains proper perfusion of the kidneys and also aids renal excretion of the poison. Overhydration should be avoided if patient has underlying heart disease, severe anaemia, incipient heart failure or pre-existing renal failure. Forced diuresis can be employed by using frusemide and/or mannitol infusions. Forced acid diuresis is useful for amphetamine poisoning, while alkaline diuresis is beneficial for aspirin and barbiturate poisoning. Urinary alkalinisation is done by administration of IV sodium bicarbonate (1 litre of a 1.26% solution over 3 hours). Intravenous potassium supplementation is necessary to ensure the production of an alkaline urine. Urinary acidification is achieved by giving ammonium chloride 4 gm every 2 hours through Ryle's tube.

Dialysis Support

Small molecules that are free in the plasma (i.e. not protein bound) are removed by haemodialysis by diffusion down a concentration gradient from the plasma to the dialysate. This way, toxins of molecular mass up to 2000 D can pass unhindered through all dialysis membranes; the cut-off for high-flux membranes is above 10,000 D. Clearance is enhanced by increasing the blood flow rate and also the ultrafiltration rate. Haemodialysis is, however, ineffective if the poisons or toxins are lipid-soluble or significantly protein-bound. Haemodialysis can be employed for several poisons like barbiturates, theophylline, lithium, bromides, salicylates, digitalis and methanol. Haemofiltration generates convective transport of solute through the membrane and allows high flux up to a molecular mass of 40,000 D. Since most poisons have molecular weights of less than 1,000 D, haemofiltration usually does not offer any particular advantage over haemodialysis but is occasionally required for large molecules like metal chelating complexes (desferrioxamine and sodium ethylenediamine tetraacetic acid) and aminoglycosides. Haemoperfusion is more suitable in scenarios of poisonings vis-a-vis haemodialysis since it does not depend upon the ability of poison to cross a selectively permeable membrane. Peritoneal dialysis is relatively inefficient compared to haemodialysis or haemofiltration as it achieves low mass transfer of solute and at a slower pace. However, it can be employed when haemodialysis is not rapidly available or is contraindicated.

Exchange transfusion also has a role for poisoning cases complicated by massive haemolysis, as in sodium chlorate poisoning, wherein it will remove not only the poison but also red cell fragments and free haemoglobin. It can also be employed for hydrogen sulphide poisoning which is complicated by methaemoglobinaemia and sulphaemoglobinaemia.

Supportive Management

In many cases of poisonings, the agent may not be discernible and often a specific antidote does not exist. In these circumstances, the mainstay of management is supportive care supplanted by prevention and prompt treatment of complications. Common complications which may need to be managed include pain, arrhythmias, hypotension, electrolyte disturbances, seizures, coma, respiratory failure, hepatic failure, and acute renal failure.

CONCLUSION

Poisoning is a major problem in India. It can be suicidal, homicidal or accidental. Early, aggressive and planned approach is important. Try to identify, detoxify (removal of unabsorbed poison, use of antidotes or by haemofiltration/haemodialysis) maintain vitals, provide effective CPR required and once improved psychological assessment and support is a must, specially in suicidal poisoning. Legal aspects must, be kept in mind.

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26.2 Aluminium Phosphide Poisoning

SN Chugh

INTRODUCTION

Aluminium phosphide (AIP), a solid fumigant pesticide is widely used in India for grain preservation at homes and in warehouses. It protects the stored grain from pests, insects and rodents by liberating toxic phosphine (PH_3) gas after coming in contact with moisture. It is available in the form tablets, each weighing 3 g and packets, each weighing 10 g, packed in containers (**Figures 1A to C**). Each tablet/packet contains 56% of AIP and 44% of ammonium carbonate [$(NH_4)_2CO_3$] as active ingredients; is able to liberate PH_3 by one-third of its weight. Phosphine, being a gas, diffuses uniformly throughout the grains and the residues such as phosphite and hypophosphite of aluminium are left in the packet/grains which are nontoxic.

The poisoning is generally suicidal, rarely homicidal and occasionally accidental (children) and is common in younger age groups.



Figures 1A to C: Available packagings of celphos. (A) Tube containing tablets of celphos; (B) Small pack containing 10 packets of celphos weighing 10 g each, and (C) Large container having 50 packets of celphos weighing 10 g each.

MODE OF ACTION OF PHOSPHINE

Its toxic effects are due to the liberation of PH_3 in the stomach after ingestion of AIP. Inhalation toxicity (inhalation of PH_3) is uncommon and primarily involves lungs. The other gases liberated in addition to PH_3 include ammonia and CO_2 which provide an inert media for PH_3 to act:

$$AlP + 3HCl \rightarrow AlCl_3 + PH_3\uparrow$$
$$AlP + 3H_2O \text{ (moisture)} \rightarrow Al(OH)_3 + PH_3\uparrow$$
$$(NH_4)_2CO_3 + H_2O \rightarrow 2NH_3\uparrow + CO_2\uparrow + 2H_2O$$

The exact mode of action of PH_3 is not known. It has been claimed to inhibit cytochrome c oxidase, a respiratory chain enzyme, similar to cyanide. Some workers have claimed inhibition of mitochondrial catalase enzyme, extra-mitochondrial release of hydrogen peroxide (H_2O_2) and generation of oxygen free radicals by phosphine (PH_3). Free radicals seem to play a role in the initiation and propagation of cell damage, in addition to the direct toxic effects of phosphine.

CLINICAL TOXICITY

The toxic dose of oral AIP compound is 500 mg/70 kg in humans. Toxicity occurs either due to suicidal ingestion of AIP or inhalation of liberated PH_3 from fumigated grains. Phosphine is widely absorbed and distributed in the tissues. It is also known that AIP is absorbed as such and possibly deposited in liver leading to slow release of PH_3 which may be responsible for extended poisoning in humans.

The signs and symptoms of acute, moderate-to-severe ingestional poisoning appear within 45 minutes to one hour. The organs involved include gastrointestinal tract, heart, lungs, liver, kidneys and the brain. The clinical manifestations are depicted in **Table 1**.

Inhalational toxicity is invariably accidental; occurs in persons sleeping in warehouses where stored grains are fumigated with AIP. An exposure to high PH_3 concentration leads to shock or cardiovascular collapse but a lower concentration produces pulmonary oedema. However, the lower concentration (7.5 mg/m^3) may cause cough, dyspnoea and mild respiratory failure.

Table 1: Symptoms and Signs of Moderate-to-severe Aluminium Phosphide Poisoning

System	Common	Uncommon/Rare
Gastrointestinal tract	Nausea, vomiting, epigastric discomfort, retrosternal burning	Diarrhoea
Cardiovascular	Hypotension or shock tachycardia myocarditis arrhythmias	Bradycardia pericarditis congestive heart failure
Respiratory	Cough, dyspnoea, rhonchi, crackles, foul breath	Type 1 and type 2 respiratory failure
Hepatobiliary	—	Jaundice, hepatomegaly, raised transaminases, hepatic failure
Renal	—	Acute renal failure
Central nervous system	Anxiety, apprehension, irritability, disturbances in consciousness	Drowsiness and coma

INVESTIGATIONS

1. Complete haemogram
2. Blood biochemistry, e.g. urea, sugar, creatinine, transaminases, bilirubin, electrolytes, etc.
3. Electrocardiogram (ECG) for arrhythmias, myocarditis and conduction defects.
4. Chest radiograph (posteroanterior view) for acute respiratory distress syndrome (ARDS), aspiration pneumonia, etc.

5. Blood gas analysis for hypoxia and acidosis
6. Serum magnesium levels
7. Toxicologic screening, e.g. blood phosphine levels.

DIAGNOSIS

The clinical diagnosis of acute moderate-to-severe poisoning can be made from:

1. History of intake of fresh AIP compound
2. Decaying fish or garlic-like odour in breath
3. Evident clinical manifestations, cardiac arrhythmias and metabolic acidosis
4. The confirmation of diagnosis is done by positive qualitative silver nitrate test with gastric fluid or with breath (**Figure 2**) or blood phosphine levels.

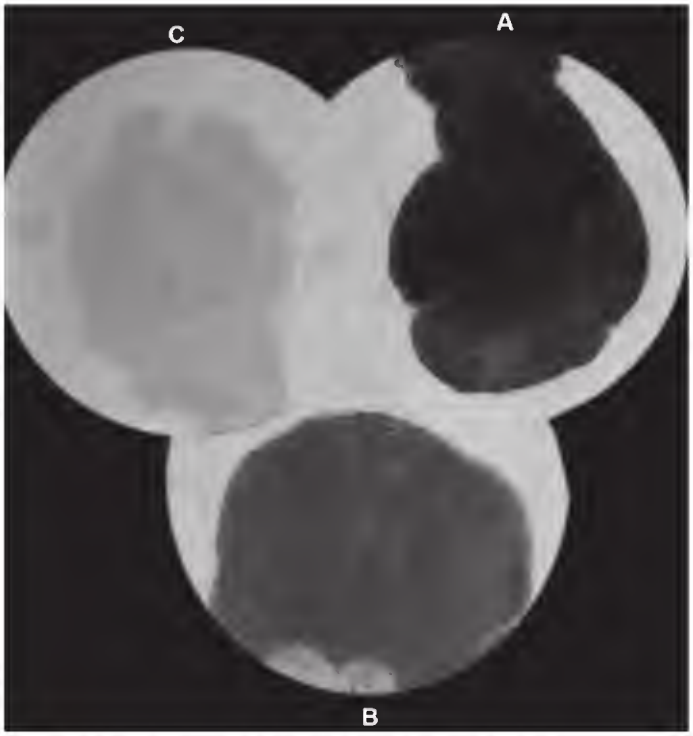


Figure 2: Qualitative silver nitrate ($AgNO_3$) impregnated (0.1 N) paper test in aluminium phosphide poisoning. Blackening indicates positivity; (A) positive with gastric lavage fluid; (B) positive with breath; and (C) a control for detection of H_2S.

Nil toxicity means ingestion of exposed compound (tablets kept out of containers or powder in open packets) which does not produce any systemic manifestation except local symptoms such as nausea, vomiting or retrosternal burning. Prognosis is excellent.

Mild ingestional toxicity is diagnosed by the history of taking a small dose of partially exposed compound (broken tablet/exposed packet/non-smelling tablet). There is a slight drop in blood pressure with nausea, vomiting, retrosternal burning or pain. Arrhythmias are occasional and metabolic acidosis is rare. $AgNO_3$ test is negative. Most of these patients survive.

All types of cardiac arrhythmias (brady- or tachy-arrhythmias) have been observed either alone or in combination with other ECG changes in 40% to 80% patients with moderate-to-severe poisoning. The ST segment elevation/depression due to acute myocarditis (**Figure 3**) is also observed commonly (30%). The conduction disturbances (sinoatrial, atrio-ventricular, bundle branch blocks, intra-ventricular conduction delay, etc) are least common, occurring in 5% to 10% patients.

There may be hypoxaemia (PaO_2 <60 mmHg) and metabolic acidosis (pH <7.1) in 75% to 80% cases. Magnesium levels have been found to be low or normal. Hypokalaemia or hypoglycaemia has been observed.

Sometimes, patients may not divulge the history of AIP ingestion. In such a situation, a high degree of suspicion combined with sudden onset of unexplained shock or cardiac arrhythmias and blood samples, if appear too dark to explain, form important clues to the diagnosis of this poisoning in younger patients.

MANAGEMENT

The early recognition and management is essential to reduce mortality. The main goal of therapy is to sustain life till PH_3 gets excreted.

Steps to Remove as well as to Retard PH_3 Absorption

Gastric lavage with $KMnO_4$ (1:10,000) or magnesium sulphate to inactivate or oxidise the unabsorbed poison. Slurry of activated charcoal (100 g) may be given to absorb PH_3.

Judicious use of antacids (60 mL/hour) to reduce gastric symptoms and to reduce PH_3 absorption. In addition, if needed H_2-blockers may be given as intravenous infusions.

Steps to Reduce Tissue Toxicity

There is no specific antidote to phosphine. Magnesium sulphate possesses membrane stablising properties and has been used in several studies from India. The effective dose schedule is to start with 1 g IV, then 1 g IV after one hour for 3 consecutive hours, then 1 g IV infusion after 4 to 6 hours for 3 to 5 days. It can reverse some arrhythmias and mortality is reduced.

Phosphine is a stable, partially water soluble gas and is excreted to some extent in the urine but is mainly excreted through breath; hence, adequate hydration and renal perfusion by IV fluids and low-dose dopamine 2 to 4 µg/kg/min must be maintained to allow its renal excretion. Diuretics are not useful in the presence of shock. Patients with severe poisoning are haemodynamically unstable but maintain a good urine output, hence, dialysis is usually not done. If acute renal failure develops and patient is haemodynamically stable, then dialysis may be useful.

Supportive Measures

The various supportive measures to manage complications are shown in **Table 2**.

MORTALITY

Mortality is highly variable (37% to 100%) depending on the factors such as dose of the fresh pesticide consumed, early vomiting, duration and severity of poisoning, severity of shock and its response to resuscitative measures, etc. The most common cause of death is acute cardiovascular collapse followed by the development of ARDS. Early vomiting is the single factor that improves mortality.

POSTMORTEM FINDINGS

Postmortem findings include the viscerae to be heavy, oedematous and emitting foul smell. The lungs show desquamated epithelium with alveoli thickened by haemolysed red blood cells and leucocytic infiltration around bronchioles.

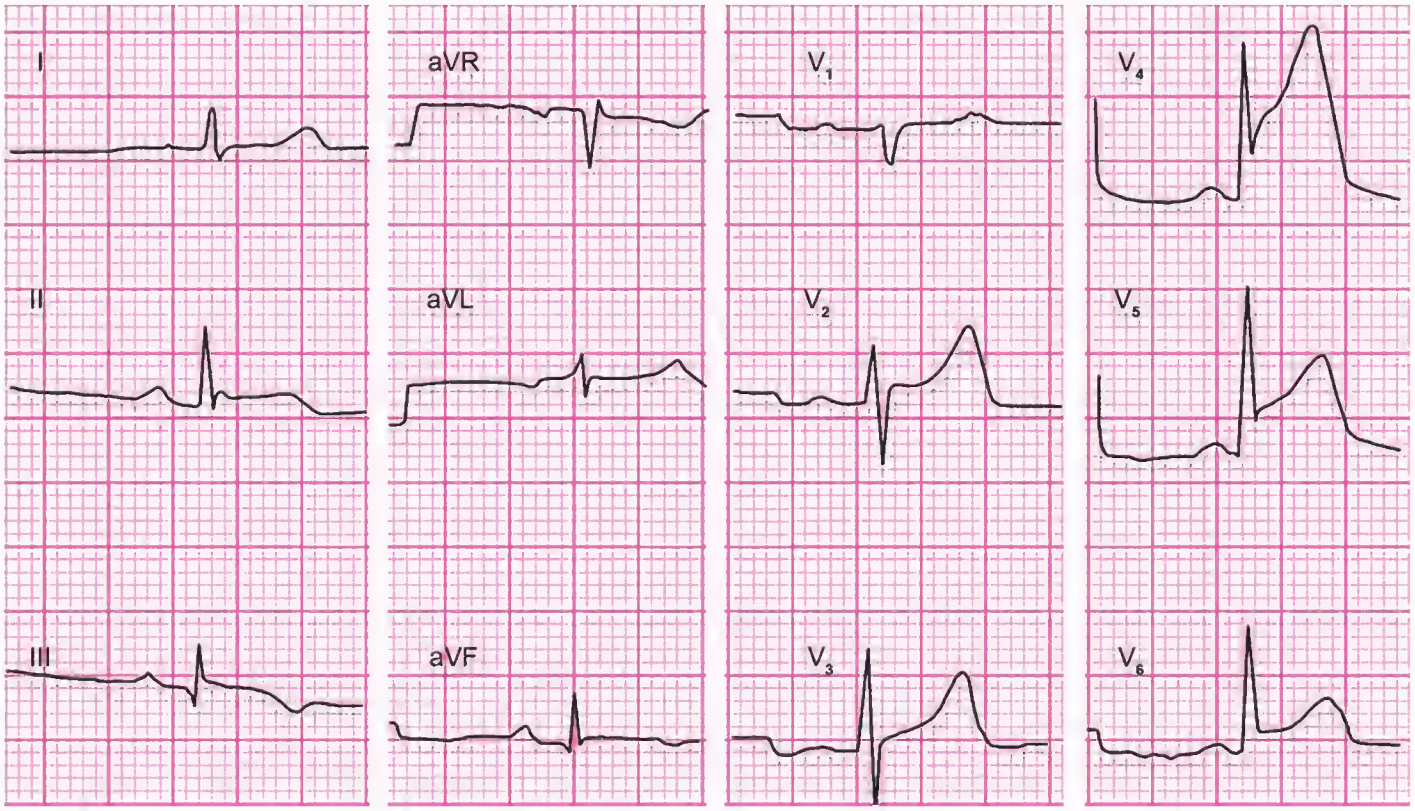


Figure 3: Myocarditis: The ECG shows: (i) Low voltage of QRS complexes in standard leads (I, II, III, aVR, aVL, aVF); (ii) Slight prolongation of QT (QTc) interval; and (iii) Elevation of ST segment with concavity upwards in leads II, III, aVF and V_1-V_6. Reciprocal ST depression in aVR is also seen.

Table 2: Treatment of Complications

Hypoxia	O_2 inhalation, patent airway (endotracheal intubation and assisted ventilation, if necessary). Monitor blood gases.
Shock	Intravenous (IV) fluids (2 to 3 litres, out of which 50% should be saline) to be given during first 3 to 6 hours guided by central venous pressure or pulmonary capillary wedge pressure. Monitor electrolytes. Blood pressures should be monitored and kept above 80 mm Hg. Low-dose of dopamine (2 to 4 µg/kg/min) and dobutamine (2.5 to 5 µg/kg/min) may be used in combination to maintain renal perfusion. IV hydrocortisone (200 to 400 mg) every 4 to 6 hours has been used to restore sensitivity to endogenous catecholamines.
Arrhythmias	Conventional antiarrhythmic drugs such as digoxin and xylocaine are ineffective. Others drugs being myocardial depressants are avoided but amiodarone has been used to combat fatal arrhythmias. Atropine has been found ineffective in bradyarrhythmias. $MgSO_4$ has also been found effective as a potent antiarrhythmic drug in the presence of hypoxia (anti-hypoxic effect), has been extensively used and found to be effective in certain arrhythmias.
Metabolic acidosis	IV sodium bicarbonate to keep the HCO_3^- levels around 18 to 20 mmol/L and pH >7.1. Dialysis is to be done if metabolic acidosis persists and patient is haemodynamically stable.
Acute respiratory distress syndrome (ARDS)/noncardiogenic pulmonary oedema	Remove the patient to open air and loosen the clothes around the neck. To achieve PaO_2 around 60% with lowest inspired fraction of O_2 (FiO_2), oxygen is delivered by simple face mask or face mask fitted with inspiratory reservoir bags at moderate flow rates (5 to 10 L/min of 100% O_2). Mechanical support is indicated if above measures fail. Positive end expiratory pressure therapy may be tried to lower FiO_2 below 0.6 provided patient is haemodynamically stable. Swan-Ganz catheter may be inserted for monitoring arterial and pulmonary wedge pressure, to measure cardiac output, fluid therapy, to monitor blood gas analysis and to guide diuretic therapy.
Hypoglycaemia	IV dextrose to combat hypoglycaemia which is reversible.

The liver shows congestion, oedema, areas of centrizonal necrosis and mild-to-moderate fatty infiltration. The heart shows congestion, oedema, fragmented fibres, focal areas of myocardial necrosis and leucocytic infiltration. The kidneys show congestion, oedema, necrosis and degenerative and regenerative activity of the tubules. The stomach and the intestines also show congestion, oedema and leucocytic infiltration with sloughing of mucosa.

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26.3 Organophosphorous Poisoning

Surjit Singh

Organophosphorous (OP) compounds are a diverse group of chemicals comprising of either esters, amides or thiol derivatives of phosphoric acid principally used as insecticides in agriculture. They can be classified into low volatile compounds, e.g. chlorpyriphos, dimethoate, dichlorvos, methyl parathion, etc. used for agricultural purposes as insecticides or highly volatile nerve gases, e.g. sarin, tabun, etc. mainly used for chemical warfare. Acute OPs poisoning occurs mainly following ingestion with suicidal intent and less commonly following accidental exposure during agricultural spray.

PATHOPHYSIOLOGY

Organophosphates inhibit both plasma cholinesterase (PChE) and acetylcholinesterase (AChE), the later being present in red blood cells and tissues. The significance of inhibition of PChE is not clear. AChE is found at neuronal synapses in central nervous system (CNS) and peripheral nervous system and its main function is to hydrolyse acetylcholine (ACh). The bond between organophosphates and AChE changes with time and becomes irreversible when one of the alkyl radicals gets separated from OPs, the process being called as ageing. The time course of ageing depends on the molecular structure of the OP compounds. It is shorter for methoxy than ethoxy compounds. Once AChE has been inactivated, its inhibition leads to accumulation of ACh throughout the autonomic nervous system, somatic nervous system and the brain, resulting in overstimulation of the muscarinic and nicotinic receptors.

CLINICAL FEATURES

Following organophosphate poisoning (OPP), 3 well-defined neurological syndromes are recognised. These are cholinergic crisis, intermediate syndrome and delayed polyneuropathy. In addition, there are effects on other physiological systems such as CNS, cardiovascular system (CVS), pancreas, etc. which are also important.

CHOLINERGIC CRISIS

The initial cholinergic crisis is a medical emergency which may require intensive treatment. The crisis occurs as a result of accumulation of ACh at muscarinic and nicotinic sites. The excess ACh at these receptors leads to their initial stimulation and then eventual exhaustion. The accumulation of ACh at muscarinic sites leads to increased secretions leading to bronchorrhoea, salivation, sweating and tearing. There also occurs bronchospasm, vomiting, diarrhoea, the latter being due to increased gastrointestinal (GI) motility (**Table 1**). In eyes, miosis and blurred vision results. The accumulation at nicotinic sites results in muscle fasciculation's and flaccid paralysis. The accumulation in CNS leads to headache, giddiness, drowsiness and in severe poisoning coma. Death can occur as a result of respiratory failure which may be central, peripheral or both or following fatal cardiac arrhythmias. The cholinergic crisis can last from 24 to 72 hours.

Table 1: Clinical Features of Cholinergic Crisis

Muscarinic effects	
Broncho-pulmonary	Bronchospasm, bronchorrhoea, noncardiogenic pulmonary oedema
Gastrointestinal tract	Nausea, vomiting, diarrhoea, abdominal pain
Sweat glands	Excessive sweating
Salivary glands	Excessive salivation
Eyes	Miosis, blurred vision, lacrimation
Cardiovascular system effects	Bradycardia, occasionally tachycardia, arrhythmias, QT prolongation, hypotension, hypertension (rare)
Nicotinic effects	Fasciculation, muscle weakness
Central nervous system effects	Headache, giddiness, drowsiness, coma seizures

INTERMEDIATE SYNDROME

It was first termed as type II paralysis and subsequently renamed as intermediate syndrome (IMS). It occurs between the cholinergic syndrome and late onset peripheral neuropathy. It develops 12 to 96 hours after exposure and reflects a prolonged action of ACh on nicotinic receptors. The clinical features are muscular weakness in the ocular, neck, bulbar, proximal limb and respiratory muscles with occasional dystonic posturing (**Table 2**). The risk of mortality is due to respiratory depression as a result of muscle paralysis. IMS has been found to be associated more with certain OPC's, like diazinon, dimethoate, methyl parathion, methamidaphos, monocrotophos, fenthion and ethylparathion.

Table 2: Clinical Features of Type II Paralysis (Intermediate Syndrome) in Organophosphate Poisoning in 101 Patients in a Study by Wadia *et al.*

Inability to lift neck	87
Inability to sit up	99
Ophthalmoparesis	27
Slow eye movements	39
Facial weakness	52
Swallowing difficulty	14
Limb weakness (proximal >distal)	86
Areflexia	52
Respiratory failure	37
Death	33

DELAYED NEUROPATHY

Some organophosphates, particularly triorthocresyl phosphate (TOCP) and tricresyl phosphate (TCP) produce what is called delayed neuropathy. On ingestion, they do not produce significant cholinergic crisis but 7 to 20 days later lead to a pure motor axonal neuropathy with wrist and foot drop. It is probably due to depression of a different type of esterase (neuropathy target esterase) in the nervous system. This form of toxicity has

been seen occasionally in small epidemics in India due to adulteration of cooking oil with TOCP. However, with presently used organophosphates such as chlorpyriphos, it is uncommon.

LABORATORY DIAGNOSIS

The diagnosis can be made from history of ingestion or muco-cutaneus exposure, clinical features and laboratory evaluation of plasma cholinesterase (PChE) and red cell acetyl cholinesterase (Red Cell AchE) activity inhibition. The depressed cholinesterase activity confirms the diagnosis of OP poisoning and it continues to remain depressed for 4 to 7 weeks. Though red cell AChE is more specific, PChE assay is easy and more widely available.

Prolonged QTc interval, elevated ST segment, inverted T waves and prolonged PR interval are often observed electro-cardiographic (ECG) findings. *Torsade de pointes* and complete heart block have also been reported.

MANAGEMENT

The initial management involves maintaining a clear airway and intubation might be necessary in case of respiratory distress. Assessment of vitals should be done and undertake resuscitation if necessary. The rest of management includes removal of OPCs from skin and gastrointestinal tract, administration of activated charcoal, atropine or glycopyrrolate, oximes and some newer compounds in addition to ventilatory support which they may require.

Washing the skin with soap and water after removal of clothing is essential if there has been an accidental exposure, e.g. during agricultural spray. Care should be taken by health workers to protect themselves by using gloves, aprons, eye protection, etc., as they run the risk of getting poisoned by contact. In case of ingestion, emesis should not be induced as it can lead to complications like aspiration pneumonia, diarrhoea, paralytic ileus. There is no evidence at present that it helps in outcome and can lead to complications like lung aspiration, laryngeal spasm, oesophageal perforation and hypoxia. In India, as suicide is still an offence, gastric lavage is being carried-out routinely for medicolegal reasons to collect lavage sample. As it becomes necessary in our country, due to legal reasons, it should preferably be carried-out using wide bore nasogastric tube and smaller aliquots of water or normal saline with airway protection in obtunded patients. Both single dose and multiple dose activated charcoal have been administered after lavage. However, its benefit is not clear and complications include aspiration pneumonia, vomiting, diarrhoea, constipation, ileus, etc. A recent study suggests that if administered within one hour of ingestion, it may improve outcome. However, if patient needs resuscitation, removal should not be given priority and patient should be resuscitated first.

Atropine acts as physiological antidote as it antagonises the muscarinic receptor mediated actions of excessive acetyl choline. However, it has little effect at nicotinic sites. It blocks excessive tracheobronchial secretions, bronchoconstriction, salivation and bradycardia. Unlike glycopyrrolate which cannot cross blood brain barrier, it counteracts the effects of ACh in CNS. It has also been shown to enhance neuromuscular transmission and transmitter release possibly by acting on muscarinic presynaptic inhibitory receptors which are involved in the feed back mechanism of transmitter release. Though optimum dose is not known, the first doses are generally given as boluses followed by infusion if dose requirement is large. The initial dose is 2 mg intravenously repeated every 5 to 10 minutes until signs of atropinisation appear, i.e. pulse rate >80 beats/min, pupillary dilatation, drying of axillae and clear chest. After this it can be given as boluses or as infusion to maintain the atropinisation (0.02 to 0.08 mg/kg/min), the later being considered better with dose being titrated by clinical response.

Glycopyrronium bromide has been used in place of atropine. Its effects are similar to atropine but there is less CNS toxicity as compared to atropine as it does not cross blood brain barrier.

The use of oximes is controversial. Oximes reactivate the AChE by removing the phosphoryl group from inactivated enzymes. As ageing takes longer with diethyl compounds than with dimethyl compounds, it is likely that oximes may lead to better reactivation in the former. Pralidoxime is the oxime used worldwide. It occurs in two forms, i.e. pralidoxime chloride and mesylate, the latter being less effective. Its major effect is on the peripheral nervous system as it does not cross the blood brain barrier easily. Its main action is to effect recovery of neuromuscular transmission at nicotinic synapses. Complications of oximes include hypertension, cardiac dysrhythmias, headache, blurred vision, dizziness, etc. Obidoxime can lead to hepatic failure. A recent double-blind, randomised study from Sri Lanka has shown a higher mortality in the group treated with high-dose pralidoxime though in some previous studies a better outcome in patients given high-dose pralidoxime was observed. Thus, role of oximes is still controversial.

Diazepam is the standard treatment for organophosphorous induced seizures.

Mortality in OP Poisoning

The mortality in most large series is between 7% to 12%. Death is usually a result of respiratory paralysis. The other complications which can lead to fatality are asphyxia as a result of increased bronchial secretions and bronchoconstriction and rarely pulmonary oedema. Occasionally serious cardiac arrhythmias can lead to fatality. The mortality can be greatly reduced if patients are provided atropine and respiratory assistance in time.

NERVE GAS POISONING

Nerve gases used in warfare are organophosphates (soman, sarin, etc.). They are powerful irreversible inhibitors of ChE. In addition they phosphorylate other proteins and part of their toxicity may be due to this. The usual oximes are not effective in nerve agent poisoning.

CARBAMATES

Carbamate poisoning, e.g. Baygon poisoning (Propoxyfur) is increasingly being seen in urban areas in India. They are commonly used in households to kill cockroaches. They produce toxicity similar to that of OP poisoning. The management is similar except that oximes are contraindicated.

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26.4 Corrosive Poisoning

Rakesh Kochhar

The term corrosive poison encompasses alkaline and acidic agents which cause tissue destruction when they come in contact with mucous membranes. While Lye is the commonest ingested corrosive in the West, acidic agents are more often ingested in the developing world. Corrosive poisoning is often accidental in children, but in adults suicidal ingestion is common. Suicidal acid ingestion in the form of toilet cleaning agents has been one of the commonest form of corrosive poisoning for the last 3 decades.

CORROSIVE AGENTS (Table 1)

Caustic injury is usually produced by strong alkaline or acidic agents. Acid ingestion is common in India where hydrochloric acid and sulphuric acid are easily available as toilet cleaners. Commercially available liquid alkali, sodium hydroxide (e.g. Harpic) is the commonly ingested alkali in India. Laboratory workers (hydrochloric acid, nitric acid, sulphuric acid) and goldsmiths (aqua regia) ingest acids accidently. In recent years, button-cell battery ingestion in children is also being increasingly recognised.

Table 1: Common Corrosive Agents

Acidic Corrosives		
Total cleaners	:	Hydrochloric acid, Sulphuric acid
Antirust compounds	:	Hydrochloric acid, Oxalic acid
Soldering fluxes	:	Hydrochloric acid
Automobile battery fluid	:	Sulphuric acid
Slate cleaner	:	Hydrochloric acid
Alkaline Corrosives		
Drain cleaners	:	Sodium hydroxide
Surface cleaners	:	Ammonia, Phosphates
Laundry and dishwasher	:	Phosphates, Carbonates
Clinitest tablets	:	Sodium hydroxide
Industrial strength bleach	:	Sodium hydroxide, Calcium hypochlorite

The extent of injury following corrosive ingestion depends upon the nature of the corrosive agent ingested, its physical state, amount and concentration and the duration of contact with the mucosa. Acid solutions cause immediate pain which causes the person to spit the corrosive out. However, if the ingestion is intentional the corrosive is swallowed before the protective reflexes can be evoked. Severity of injury is also influenced by the physical state of the corrosive (solid or liquid). Soild crystalline agents (e.g. sodium hydroxide crystals, potassium permanganate crystals) tend to adhere to glossopharyngeal, palatal and upper oesophageal mucosa producing deep burns limited to the corresponding area. Liquid alkalis and acids, because of their easy deglutition and high specific gravity, pass rapidly through the oesophagus. Injury pattern also depends upon the postprandial state of the patients. If the stomach is full the agent is rapidly diluted and gastric mucosa is spared. When the stomach is full, the corrosive bolus flows rapidly from the gastro-oesophageal sphincter along the lesser curvature to the pyloric antrum where maximum damage occurs. It was earlier believed that alkalis bite the oesophagus due to liquefaction necrosis of the squamous epithelium, and lick the stomach due to dilution by its acidic contents. Acids were believed to spare the oesophagus and damage the stomach. However, we have shown that concentrated alkalis and acids, both cause similar damage to oesophagus as well as the stomach. Solid corrosives in powder form, like caustic soda, more often cause oropharyngeal burns while liquid corrosives damage the oesophagus and the stomach.

PATHOPHYSIOLOGY

Concentrated acids produce coagulative necrosis with a protective eschar. This coagulum tends to limit the penetration into deeper muscular coats. But sloughing and expulsion of large areas of the surface lining of the stomach and oesophagus with secondary infection and perforation may pose problems. In severe cases associated with perforation, the resulting peritonitis or mediastinitis can lead septicaemia and its sequelae. Apart from oesophageal injury causing strictures because of antral pooling of the caustic agent, some patients may develop pyloric obstruction or antral stenosis or hourglass deformity. These can develop within weeks to months after ingestion of the agent.

Alkaline caustic agents rapidly penetrate into tissues and produce injury by liquefaction necrosis with intense inflammation and saponification of mucous membrane, submucosa and muscularis mucosa within 2 to 3 days of contact. Mucosal sloughing occurs 4 to 7 days after injury. Stricture formation starts by 3rd week, although it can occur for the first time several years later.

CLINICAL PRESENTATION

Acute Phase (1 to 10 days)

This is characterised by acute symptoms like pain, dysphagia, haematemesis, etc. Laryngeal oedema can cause hoarseness of voice and stridor. Aspiration of the caustic agents into airways can cause chemical bronchitis. Full thickness necrosis can produce perforation leading to mediastinitis, pleural effusion, empyema or peritonitis. Septicaemic shock is a common cause of death in acute phase.

Subacute Phase (11 to 16 days)

There is transient decrease in above mentioned symptoms.

Chronic Phase (28 days to months)

Characterised by oesophageal strictures causing dysphagia, and gastric stenosis causing gastric outlet obstruction.

ENDOSCOPIC FINDINGS AND CORRELATION WITH OUTCOME

Symptoms and signs are poor indicators of degree and extent of damage to the gastrointestinal tract. Radiological studies are also not sensitive. The best method to stratify patients with

acute corrosive ingestion is upper gastroduodenal endoscopy whose safety has been well established. Flexible endoscopy can be performed safely at any time from 6 to 96 hours of ingestion, provided the patient is stable and there is no evidence of perforation. However, it should be avoided in the sub-acute phase (5 to 15 days) after corrosive intake when the tissues slough and there is increased danger of perforation. On the basis of endoscopic findings, corrosive burns have been classified into grades 0, 1, 2 and 3 (**Table 2**). Most perforations and fatalities in the acute phase occur in patients with grade 3b injury, while strictures develop in patients with grade 2b or worse injury. Therefore, such patients need to be kept under close supervision.

Table 2: Endoscopic Classification of Corrosive Burns

Grade 0	Normal examination
Grade 1	Oedema, hyperaemia of the mucosa
Grade 2a	Friability, haemorrhage, erosions, blisters, whitish membrane exudate and superficial ulceration
Grade 2b	Grade 2a + deep discrete or circumferential ulceration
Grade 3a	Multiple ulcerations and small, scattered, nonconfluent areas of necrosis (area of brown-black or greyish discolouration)
Grade 3b	Extensive necrosis, confluent necrosis

MANAGEMENT

Acute Injury

The management of acute corrosive injury consists of recognition and treatment of acute complications and treatment of sequelae. Early treatment includes maintaining the patient nil per orally, intravenous fluids, airway maintenance and supportive treatment. After resuscitation, acute complications like perforation and peritonitis should be ruled out by radiograph chest, radiograph abdomen and a radiological soluble contrast study, if indicated. Upper gastrointestinal endoscopy should be done to evaluate the severity of burn. Airway management may require tracheostomy. Treatment of infections is an essential part of early management.

There is sufficient evidence that gastric lavage, use of emetics, or purging agents are contraindicated, since these cause more harm than any good. Neutralisation of the corrosive agents with weak acid or alkali used to be done in the past. But its efficacy could never be proved probably due to the rapid action of acids or alkalies. Dilution with water is also not useful as it may cause more harm by liberation of heat. Hence, neutralisation is contraindicated.

Antibiotics are given only when patients have symptoms and signs of secondary infection. Steroids have no role in prevention of late sequelae. The only indication of using steroids could be laryngeal oedema. Parenteral steroids may lead to systemic infection in a bed-ridden patient. Indications for surgery include perforation of oesophagus or stomach, massive upper gastrointestinal bleed and full thickness burns of oesophagus or stomach with charring.

Patients are unable to have normal diet in the first few weeks after acute corrosive ingestion due to mucosal oedema and ulceration. Later development of cicatrisation in the oesophagus and stomach precludes normal feeding. Hence for 6 to 8 weeks, patients require nutritional support with total parenteral nutrition or feeding jejunostomy. The latter is preferred in India. Recently, endoscopically placed naso-jejunal tubes are being used for maintaining enteral nutrition in these patients.

Chronic Phase

Late sequelae include oesophageal and/or gastric cicatrisation. It is essential to do a barium study to assess the site, extent and nature of oesophageal and gastric stenosis (**Figures 1 to 4**). Generally, endoscopic treatment is offered 6 to 8 weeks later, once re-epithelialisation has taken place.

1. Oesophageal strictures are often long, tortuous, multiple and very tight (**Figures 1 and 2**). They require repeated dilatation endoscopically with bougies or balloons and recurrences are frequent. Corrosive oesophageal strictures



Figure 1: Barium swallow showing a long stricture involving middle and lower thirds of oesophagus in a patient with sulphuric acid ingestion (Anteroposterior view, left; left oblique view, right).



Figure 2: Barium swallow showing a single short mid-oesophageal stricture in a patient with toilet cleaner ingestion.

are difficult to dilate but over three-fourths of them respond to endoscopic dilatation. It has been shown that combining intralesional steroid injections with dilatation is very rewarding in difficult strictures. Recently, self expanding plastic stents have also been used in such patients with good results. Patients who cannot be dilated or have frequent recurrences are subjected to esophageal bypass using a jejunal or colonic loop or gastric pull up.

2. Gastric cicatrisation leads to pyloric and/or antral stenosis (**Figures 3 and 4**), clinically presenting as recurrent vomiting. Such patients often require surgery with antrectomy or partial gastrectomy. Some patients have linitus-plastica like deformity involving a large part of the stomach requiring subtotal or total gastrectomy. Recently, endoscopic balloon dilatation has been used successfully to treat pyloric stenosis due to corrosive injury.
3. Oesophageal carcinoma: Risk is estimated to be 1,000-3,000-folds and it usually occurs 20 to 30 years after an acute injury.



Figure 3: Barium meal study showing a dilated stomach with total obstruction at pylorus in a patient with hydrochloric acid ingestion.



Figure 4: Barium meal study showing two strictures, one at body-antrum junction and another at pylorus in a patient with sodium hydroxide ingestion.

SUMMARY

In India, acid ingestion is more common than alkali ingestion. Strong acids and alkalis cause equal injury to oesophagus and stomach. Management of acute injury involves resuscitation, maintenance of airways and supportive care. At 6 to 8 weeks barium studies are done to assess for chronic sequelae. Endoscopic dilatation of oesophageal strictures and localised pyloric stenosis form the first line of treatment. Surgical treatment is indicated for long oesophageal strictures, in patients who fail to respond to dilatation and those with long segment of gastric stenosis.

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26.5 Alcohol Poisoning

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The most commonly used alcohol is ethyl alcohol (ethanol). Unlike ethanol, methyl alcohol (methanol) is extremely toxic. Two other alcohols commonly used (though not as much as methanol and ethanol) are propyl alcohol and butyl alcohol. Prompt recognition and treatment of patients intoxicated with these substances can reduce the morbidity and mortality associated with these alcohols.

ACUTE ALCOHOL POISONING

The term alcohol in common use refers to ethyl alcohol. At low doses, alcohol can have some beneficial effects such as decreased rate of myocardial infarction, stroke, gallstones and possibly vascular and Alzheimer's disease. However, if taken in large amounts, it can be toxic as well as fatal. The characteristic flavour of alcoholic beverages is due to organic compounds called congeners, such as propyl alcohol, octyl alcohol, glycerine, aldehyde, esters and certain acids. The total content of congeners rarely exceeds half per cent.

Metabolism

Twenty per cent of alcohol is absorbed from oral cavity, oesophagus, stomach and the rest from small intestine. About 60% of diluted alcohol is absorbed within half an hour if taken on an empty stomach. The rate of absorption is increased by rapid gastric emptying, absence of fats and proteins, optimal dilution of 20% by volume and carbonation. Five per cent of alcohol is excreted in breath and another 5% through urine. The peculiar odour of alcohol is due to excretion of alcohol from skin glands. Ninety per cent of alcohol is metabolised in the liver. Alcohol is oxidised into acetaldehyde by alcohol dehydrogenase (ADH). Acetaldehyde in turn gets converted to acetate and fatty acids by aldehyde dehydrogenase and acetyl-CoA. Finally, acetate enters the general pool and oxidises into carbon dioxide (CO_2) and water (H_2O) through the Kreb's cycle pathway.

Clinical Manifestations

Ethanol depresses primarily the reticular activating system. In lower concentrations, it causes depression of more specialised and sensitive cells of the cerebral cortex (centers regulating conduct, judgement and self-criticism), with release of their inhibitory tone and leads to unrestrained behaviour. Increasing concentration progressively depresses brain function. Finally, the vital centres in the midbrain and medulla are depressed, which may cause cardiorespiratory failure and death. It also causes generalised vasodilatation, especially in the skin. It is hypnotic and diaphoretic. The toxic effects of alcohol depend upon its concentration in the blood (**Table 1**). The clinical manifestations can be classified in 3 stages:

1. Stage of excitement
2. Stage of incoordination
3. Stage of narcosis

Table 1: Systemic Effects of Alcohol

Blood Alcohol Concentration	Effects
0% to 50 mg%	No significant effect or mild euphoria
50% to 100 mg%	Decreased inhibitions and attention span, increased self confidence, slurring, alteration of judgement, nystagmus
100% to 150 mg%	Mental confusion, emotional instability, ataxia, impaired memory, sleepiness, slowed reaction time
150% to 300 mg%	Loss of coordination, drowsiness, exaggeration of emotions, dizziness, disorientation, thickened speech
300% to 400 mg%	Stupor, marked decrease in response to stimuli, marked incoordination, possibly coma
400 mg% and above	Anaesthesia, depression of responses, respiratory failure, deep coma, death

Cause of Death

In alcohol intoxication, death may be due to the depressive effects on brainstem respiratory centre or due to aspiration of vomitus. Deaths due to acute overdose of alcohol are not as common as due to the chronic effects of alcohol.

Differential Diagnosis

The differential diagnosis of acute alcohol intoxication includes all causes of depressed levels of consciousness such as infections of brain, head injury, intracerebral haemorrhage, brain tumours and other metabolic conditions affecting the brain like hypoglycaemia, hyponatraemia, hepatic encephalopathy, uraemia or drug overdoses.

Management of Acute Alcohol Intoxication

Unabsorbed ethanol may be removed by gastric lavage. Adequate ventilation with maintenance of airway is important in a comatose patient. Sodium bicarbonate may be administered to alkalinise the urine. Hypoglycaemia is common and should be corrected with dextrose infusion along with simultaneous administration of 100 mg of thiamine parenterally. In a life-threatening emergency haemodialysis may be done to lower ethanol levels rapidly.

METHYL ALCOHOL POISONING

Methanol is a common ingredient in antifreeze, paints and solvents. It is also used in photocopying fluid, shellacs, and windshield-washing fluids. Poisoning usually follows ingestion of contaminated alcohol beverages or 'methylated spirits'. Intoxication in industrial settings follows absorption across the skin or lung.

Methanol is primarily metabolised in the liver via alcohol dehydrogenase into formaldehyde which is subsequently

metabolised via aldehyde dehydrogenase into formic acid, which is detoxified ultimately to folic acid, folinic acid, CO_2 and H_2O. Formic acid is responsible for the majority of the toxicity associated with methanol. Without competition for alcohol dehydrogenase, methanol undergoes zero-order metabolism. Once methanol experiences competitive inhibition from ethanol or fomepizole, the metabolism changes to first-order. In this latter scenario, the excretion half-life ranges from 22 to 87 hours.

Clinical Picture

It causes early temporary central nervous system (CNS) depression followed by a latent period lasting 6 to 24 hours before the development of metabolic acidosis and visual symptoms. Significant ingestion causes nausea, vomiting and abdominal pain. Its effects on the CNS resemble those of ethyl alcohol, although in low doses it does not have a euphoric effect. Visual symptoms present as falling visual acuity and photophobia. Specifically, vision is often described as a 'snow field', though a variety of visual complaints including blindness may be verbalised. Early signs include optic disc hyperaemia and decreased pupillary light reflex. Ingestion of only 10 mL can cause blindness and 30 mL can be fatal. Arterial pH seems to correlate best with formate levels and pH (< 7.2 is a severe intoxication).

Up to two-thirds of patients have raised serum amylase levels. Autopsy reveals haemorrhagic pancreatitis. Seizures are seen in severe intoxication. Computed tomography usually shows cerebral oedema or even necrosis in the basal ganglia (a Parkinsonian-like state is sometimes seen with recovery).

Serum methanol levels should be obtained when this diagnosis is suspected. Both the osmolal and anion gap should be obtained in addition to liver function tests, renal function tests and plasma glucose levels.

Management

Ipecac/gastric lavage is useful only if patient presents within 2 hours of ingestion. Activated charcoal is not indicated. Seizures should be best treated with phenytoin since this will have less of a CNS depressant effect than diazepam. Folinic acid should be administered at a dose of 1 mg/kg, with a maximal dose of 50 mg. It should be repeated every 4 hours. If folinic acid is not immediately available, folic acid can be substituted at the same dose. Metabolic acidosis should be treated with sodium bicarbonate.

Specific antidotes—ethanol or fomepizole should be used to prevent formation of formic acid (**Table 2**). Haemodialysis should be considered in certain situations (**Table 3**). The guidelines for the use of ethanol and fomepizole have been summarised in **Tables 4 and 5**, respectively.

Table 2: Indications for Treatment of Ethylene Glycol or Methanol Poisoning with Ethanol or Fomepizole

Documented plasma levels >20 mg/dL or
Recent history of ingestion and osmolal gap >10 mmol/kg
Strong clinical suspicion and at least 2 of the following:
pH <7.3
HCO_3^- <20 mmol/L
Osmolal gap >10 mmol/kg
Urinary oxalate crystals (in case of ethylene glycol) or visual signs/symptoms (in case of methanol)

Table 3: Indications for Haemodialysis in Ethylene Glycol or Methanol Poisoning

pH <7.3
Acute renal failure
Visual signs/symptoms
Deteriorating vitals despite intensive supportive care
Documented plasma levels >50 mg/dL

ETHYLENE GLYCOL

Ethylene glycol is an odourless, colourless, sweet-tasting liquid, which is used in many manufacturing processes. It is probably most commonly used as an antifreeze. It is absorbed rapidly from the gastrointestinal tract. Ethylene glycol itself is nontoxic, but it does get metabolised into toxic compounds. Ethylene glycol is oxidised via alcohol dehydrogenase into glycoaldehyde which subsequently undergoes metabolism via aldehyde dehydrogenase into glycolic acid. The conversion of glycolic acid to glyoxylic acid is slower and is the rate-limiting step in the metabolism of ethylene glycol. Glyoxylic acid is subsequently metabolised into several different products, including oxalic acid (oxalate), glycine, and alpha-hydroxy-beta-ketoadipate.

The majority of the metabolic acidosis occurs from glycolic acid. One form of morbidity occurs when oxalate combines with calcium to form calcium oxalate crystals, which accumulates in the proximal renal tubules, thereby inducing renal failure. Hypocalcaemia can ensue and cause coma, seizures, and dysrhythmias. Autopsy studies have confirmed that calcium oxalate crystals are deposited not only in the kidneys, but in many organs, including the brain, heart, and lungs.

Clinical Picture

Clinical presentation can be described in the following four stages:

1. The first stage, called the *neurologic phase*, can occur in less than 1 hour after ingestion and lasts up to 12 hours. During this stage, the patient appears inebriated. The patient may not have any other significant findings during this stage. Occasionally, hypocalcaemia can occur at this point and induce muscle spasms and abnormal reflexes.
2. The second stage, which occurs between 12 and 24 hours after ingestion, is referred to as the *cardiopulmonary stage*. During this stage, the patient frequently develops mild tachycardia and hypertension. Acute respiratory distress syndrome (ARDS) can also occur. These findings are believed to result from calcium oxalate crystal deposition in the lung parenchyma and myocardium. Significant hypocalcaemia can occur at this stage, with QT prolongation and associated arrhythmias. Hyperventilation may occur as metabolic acidosis progresses.
3. The third stage, also called the *renal stage*, typically starts after 24 hours. During this stage, flank pain and acute renal failure can occur.
4. The fourth stage is characterised by delayed neurological sequelae that occur 6 to 15 days after the original insult. Patients present with hyper-reflexia, ataxia, facial nerve palsy and other cranial nerve abnormalities.

Management

If presenting within a few hours of ingestion, gastric lavage is indicated. Commercial 'anti-freeze' often contains fluorescein which is easily detected with a UV light source (also detectable in urine). Microscopic evaluation of a fresh urine sample looking for the needle-shaped crystals of calcium oxalate monohydrate is pathognomonic.

Ethanol and fomepizole are specific antidotes and should be used as indicated in **Tables 2, 4 and 5**. Haemodialysis may be required in certain circumstances (**Table 3**).

Table 4: Guidelines for the Use of Ethanol in the Treatment of Ethylene Glycol or Methanol Poisoning

Loading dose: 0.6 g/kg IV 10% ethanol in 5% dextrose water or 43% of oral solution

Maintenance dose

- In alcoholic patients—154 mg/kg per hour
- In nonalcoholic patients—66 mg/kg per hour
- Double the dose during haemodialysis
- Double the dose if given orally with charcoal

Continue until ethylene glycol or methanol concentrations are <20 mg/dL and patient is asymptomatic with a normal pH

Table 5: Guidelines for the Use of Fomepizole in the Treatment of Ethylene Glycol or Methanol Poisoning

Loading dose: 15 mg/kg IV in 100 mL 0.9% saline over 1 hour

Maintenance dose: 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours.

Continue until ethylene glycol or methanol concentrations are <20 mg/dL and patient is asymptomatic with a normal pH

SOME MEDICOLEGAL PITFALLS

1. Patients with alcohol intoxication should be evaluated for coexisting injuries. A common error is to assume that a patient with altered mental status is simply intoxicated without adequate consideration of other possible causes of an altered mental status.
2. Hypoglycaemia should always be sought, particularly in the setting of an altered mental status because it can occur both as a result of intoxication with alcohol and as a result of treatment with ethanol after toxic alcohol ingestion. At-risk populations include children, chronic alcoholics, and others whose glycogen stores are depleted such as malnourished patients.
3. Additional pitfalls include assuming that intoxication is due to simply ethanol without adequate consideration of the possible presence of a toxic alcohol, either exclusively or as a coingestant.
4. Patients who have accidentally ingested a mouthful of methanol or ethylene glycol can ingest enough to be at risk of developing significant toxicity.
5. Another pitfall is to assume that the absence of an anion gap rules out the possibility of toxic alcohol poisoning. This is especially true early in the course when a patient appears inebriated without other symptoms and before significant metabolism has occurred so that an anion gap has not yet developed.
6. Not considering the use of haemodialysis, particularly in the presence of metabolic abnormalities, is another potential pitfall. Consultation with a Nephrologist and/or Toxicologist may be of assistance.
7. Failure to initiate treatment while awaiting laboratory tests to confirm the presence of a toxic alcohol is another common source of medical error.

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26.6 Plant Poisoning

DKS Subrahmanyam

INTRODUCTION

Plant poisoning in humans is a well known phenomenon, especially in semi-urban and rural India. It occurs following ingestion of any of the various parts of the plant, viz. fruits, seeds, flowers, leaves, stem and root, as in most situations all parts of the plant can be poisonous. The nature of the plant poisoning is influenced by regional practices, and hence, varies to some extent in various parts of our country, though oleander and abrus poisoning are seen all over. There appears to be a seasonal influence on the severity of the poisoning besides quantity and mode of ingestion. Plant poisoning can occur from contact, ingestion and rarely by inhalation. Most of the cases in adults are suicidal, less commonly accidental or homicidal. The following are the commonly encountered acute and at times fatal plant poisoning (in adults) in our country.

- Yellow oleander
- *Abrus precatorius*
- *Datura*
- Castor seed
- Aconite
- *Cleistanthus collinus*
- Indian hemp
- *Cerbera odollam*
- Nux vomica

SALIENT FEATURES

1. All parts of most plants are usually poisonous, though specific parts are used
2. Life-threatening poisoning occurs by ingestion
3. The severity of the toxicity is influenced by the time of the year (season effect)
4. The toxic dose is very unpredictable
5. Antidote is not available
6. Stomach wash and activated charcoal is indicated for all
7. There is an increased tendency to accidental poisoning, though in most, it is suicidal
8. Mortality is low
9. Good supportive care is the sheet anchor for treatment

CLASSIFICATION

Poisonous plants can be classified based on the chemical nature of the toxin, the mechanism of action of the toxin or the predominant system of the body involved. To the healthcare provider and recipient, classification based on the body system involvement is most useful and is as follows:

1. Gastrointestinal: *Abrus precatorius*, *Ricinus communis*, *Jatropha curcas*
2. Cardiovascular: Yellow oleander, white oleander, *Cerbera odollam*, aconite
3. Central nervous system (CNS): *Datura, Atropa belladonna*, *Strychnos nux-vomica*, Indian hemp (kidney)
4. Nephrotoxic: Aloe
5. Haemotoxic: *Gingko biloba*, fava beans
6. Hepatotoxic: Liquorice
7. Dermatological/contact poisons: Poison ivy, capsicum
8. Miscellaneous: *Cleistanthus collinus*, neem

Commonly encountered plant poisoning limited to their acute presentation following oral ingestion are described below.

YELLOW OLEANDER POISONING

Cerbera thevetia, commonly known as yellow oleander, is a shrub with green long lanceolate leaves, bell-shaped yellow flowers and a green fruit with two pale yellow seeds (**Figure 1**). Poisoning occurs following ingestion of the seeds or the crushed/chewed fruit. The number of seeds needed to cause significant poisoning is very variable. The active principles are thevetin, thevetoxin, cerebrin and nerifolin. These are all digitalis-like glycosides. As is with digitalis, toxicity occurs due to inhibition of Na^+/K^+ ATPase on cell membranes.

Patients may be asymptomatic even after ingestion of a large number of seeds. Symptomatic patients present most commonly with various cardiac arrhythmias including sinus bradycardia, various sino-atrial (SA) nodal disturbances (sinus pause, sinus arrest), atrio-ventricular (AV) nodal disturbances (first, second and third degree blocks), combined SA and AV nodal disturbances and ectopic rhythms. Tachyarrhythmia is uncommon. Other symptoms include nausea, vomiting, diarrhoea, pain abdomen and less commonly dry throat, oral paraesthesias, refractory hypotension and altered sensorium/delirium.

Blood biochemistry study may uncommonly show hyperkalaemia (because of shift from intracellular compartment)



Figure 1: Yellow oleander poisoning.

otherwise it is unremarkable. Electrocardiogram is essential to demonstrate the various arrhythmias for the management.

Management includes stomach wash using a wide bore tube. Activated charcoal 50 g is used as single dose and repeated if required. Cardiac arrhythmias of the SA nodal and AV nodal disturbances are best managed by temporary venous pacing. Sinus bradycardia can be managed with atropine injections at regular intervals or isoprenaline but with close monitoring. Tachyarrhythmias are treated with intravenous lidocaine. The role of intravenous magnesium in such situations is not well-defined. Hypotension is poorly responsive to routine measures. Serious poisoning can be treated with digoxin specific antibody fragments (Fab digoxin) 1,200 mg single intravenous dose. Hyperkalaemia rarely requires treatment and is best managed, if necessary, with intravenous dextrose and insulin. Intravenous calcium is to be avoided. Mortality in yellow oleander poisoning is 3% to 4%.

ABRUS PRECATORIUS POISONING

Abrus precatorius is a climbing plant with seeds that are scarlet red in colour with a black spot at one end. It is also called rosary pea, jequirity bean, rati, etc. Poisoning results from consumption of the seeds either crushed or chewed or made into a paste but not when consumed as a whole intact seed and rarely by inhalation when the active moiety is used as chemical warfare agent. It is usually ingested with suicidal intent. The toxic principle is abrin which is a toxalbumin or toxic protein with two chains namely A and B. The A chain has 256 residues and is the toxic component. It binds to 60S rRNA and inactivates it thereby preventing protein synthesis and causing cell damage. The B chain has 268 residues and is bound to the A chain by a disulphide bond at position cys 8 with cys 247 of A chain. The B chain binds to the cell surface receptor and facilitates the entry of the molecule into the cytoplasm. Abrin is a highly toxic chemical, only 0.1 to 1 mg/kg being sufficient to cause death.

Clinical manifestations are commonly of gastrointestinal origin and include nausea, vomiting, pain abdomen, diarrhoea which later turns bloody. Patient may later develop hypotension and shock. Acute renal failure, hepatotoxicity, intravascular haemolysis, altered sensorium and seizures can also occur. The toxin because of its nature of action can cause tissue oedema and vascular leakage/capillary leak syndrome.

Laboratory abnormalities include leucocytosis and other blood biochemical changes depending on the organ involvement.

Management includes gastric lavage, activated charcoal (50 g), and supportive care. Specific antidote is not available. There are reports of using intravenous methylprednisolone and mannitol for CNS toxicity. Seizures are controlled with diazepam, initial 10 to 20 mg (5 mg/min) followed by 3 mg/min continuous infusion over 24 hours. Alternatively phenytoin can also be used.

CASTOR SEED POISONING

Ricinus communis (castor) is so called as it resembles the common tick. This, like abrus, is an ornamental bean. The active principle is ricin, a glycoprotein also called RIP2 (ribosomal inhibitory protein 2), like abrin as it contains two chains A and B unlike RIP1 which is ubiquitous in the plant kingdom and which contains only the A chain. The mechanism of action, clinical features and treatment is the same as abrus. Mortality with castor seed poisoning is around 8%.

DATURA POISONING

The plant (*Datura fastuosa*) grows widely all over India. The flowers are bell-shaped, white or black/deep purple in colour. The fruit is green with spiny surface and contains capsicum (chilly) like seeds. Poisoning commonly results from ingestion of the seeds or the fruit (chewed/crushed). The active principles are hyoscine and hyoscyamine which have anticholinergic action.

A commonly and oft quoted rhyme to describe the clinical features of *datura* poisoning is: *'dry as bone, hot as a hare, red as beet, blind as a bat and mad as a hen'.*

Clinical features include bitter taste, vomiting, dry mouth and throat (dry as bone) with intense thirst and at the same time difficulty in swallowing and burning pain in the abdomen. On examination, patient feels hot/febrile with dry skin and rapid pulse. Body temperature may be as high as 40°C to 42 °C (hot as a hare). Face is flushed with suffused conjunctivae (red as beet). Neurological features include giddiness, dilated pupils with photophobia, diplopia loss of accommodation for near vision and near blindness (blind as bat). Unsteadiness with inability to stand/walk, confusion, agitative, violent, noisy, restlessness with tendency to runaway (mad as a hen) or silent muttering delirium, visual and auditory hallucinations with tendency to grasp imaginary objects or picking up bed clothes or pulling imaginary threads from finger tips (carphologia), spontaneous laughing/crying. This delirium phase lasts a few hours after which deep sleep supervenes following which he awakens with headache, vomiting, blurred vision, vertigo. This may last a few days followed by complete recovery. In fatal cases, patients pass into deep coma with hypotension/shock, respiratory depression, convulsions and death.

Management includes stomach wash (avoid in unconscious or violent individual), activated charcoal (50 g) with magnesium sulphate 30 g as cathartic every 4 to 6 hours till stools turn black. Supportive care includes intravenous diazepam for seizures, tepid sponging for hyperthermia, cool, calm and dark room if patient is agitated and intravenous physostigmine 0.5 to 2.0 mg in extreme situations.

ACONITE POISONING

Popularly known as 'monk's hood', its botanical name is *Aconitum napellus*. All parts of the plant are poisonous but the root is mainly used. It is more common in Eastern India. Poisoning results from ingestion either accidentally (mistaken for other edible roots) or taken in drink or food with homicidal or suicidal intent. The active principles are aconitine, mesaconitine, picraconitine, napelline, aconine, hypaconitine and other alkaloids. It acts on the voltage gated sodium channels keeping them in a persistent open state. These channels are predominantly in the heart, nerves and muscles which explains the symptomatology. In the heart it causes increased triggered activity and arrhythmogenicity, in the nerves it blocks neuromuscular transmission, in the CNS it acts on the ventromedial nucleus of the hypothalamus and causes hypotension and bradycardia. It also causes vigorous contractions of the ileum through increased release of acetylcholine from postganglionic cholinergic nerves.

Clinical features relate to the gastrointestinal, cardiovascular and neurological systems. Following ingestion patient complains of severe burning and tingling sensation in the lips, tongue, mouth,

throat and later numbness and anaesthesia of these parts. Nausea, vomiting, pain abdomen and less commonly diarrhoea ensue. Tingling and formication (sensation of ants crawling under the skin) all over the body, motor weakness, alternate dilatation and constriction of pupils (hippus) with visual impairment and vertigo are the neurological features. The cardiovascular features include chest pain, bradycardia or tachycardia, arrhythmias like ventricular ectopics, ventricular tachycardia and fibrillation, hypotension and shock. Death is mainly due to the refractory ventricular arrhythmias. Consciousness is usually retained till the end.

Treatment includes stomach wash, activated charcoal and supportive therapy. Supportive therapy includes inotropic therapy for hypotension, amiodarone, flecainide or even cardiopulmonary bypass for the arrhythmias. However response to these medications is poor. Mortality is 5.5% in aconite poisoning.

CLEISTANTHUS COLLINUS

More commonly known as 'oduvanthazhai' (Tamil = leaves of the 'oduvan' plant). It is a plant poison seen mainly in South India, especially in Tamil Nadu and Puducherry regions. All parts of the plant are poisonous though it is the leaves that are consumed. It is most fatal when a decoction is made from the leaves. It is used mainly for suicidal purposes and is more common in women. The active principles are the glycosides cleistanthin A, cleistanthin B, collinusin and diphyllin. Their mechanism of action is not known.

Clinical features include pain abdomen, occasionally nausea and vomiting, giddiness and visual disturbances, initially. Later they may develop fever, tachycardia followed by bradycardia, tachypnoea followed by bradypnoea, refractory hypotension and muscle weakness. Sensorium is clear till the end. A few may also develop nonoliguric renal failure.

Laboratory features include leucocytosis, hypokalaemia, mild metabolic acidosis, blood gases show acute respiratory distress syndrome (ARDS) like picture, hyponatraemia and azotaemia in some. Hypokalaemia too is a prominent feature.

Treatment includes gastric lavage and supportive therapy. Hypokalaemia requires potassium supplementation both by oral and intravenous route. Most fatal poisonings will require ventilatory and inotropic support. Death results from respiratory failure or refractory hypotension or both.

Mortality is 100% in those who have respiratory failure or hypotension. Overall mortality is 20% in *Cleistanthus collinus* poisoning.

STRYCHNOS NUX-VOMICA

Nux-vomica seeds are round disc like seeds, one side being convex while the other concave. They are about 2 cm in size, grey to light brown in colour. Poisoning results only when the seeds are crushed and not when swallowed as a whole. The active principles are the alkaloids strychnine and brucine, the latter being more abundant in the bark of the tree. They act at the spinal anterior horn cells where they inhibit the post-synaptic inhibitor glycine by competitive antagonism. The result is uncontrolled contraction of all muscle groups.

Clinical features of poisoning set in rapidly within minutes to an hour and include a bitter taste in the mouth, choking sensation in the throat, difficulty in swallowing saliva with drooling, restlessness, apprehension, convulsions, intermittent spasms causing opisthotonos (backward bending) or emprosthotonos (forward bending) or pleurosthotonos (lateral bending), spasm of the facial muscles can cause *Risus sardonicus* (grin/smile on face). Spasm of the masseters with lockjaw is a late feature. In between spasms, the muscles are relaxed. The spasms and convulsions can cause asphyxia and cyanosis with sudden death. The increased muscle activity can be initiated by slight noise or movement of the patient or even flash of light. Rhabdomyolysis and acute renal failure can ensue. The whole episode lasts for 4 to 6 hours with complete recovery, if patient survives.

Treatment of the patient in a quiet darkroom is preferable. The muscle activity is controlled with anticonvulsants and in extreme cases, muscle paralysis with relaxants and ventilation. Adequate intravenous fluids are to be administered to prevent renal failure. Recovery is usual.

ODOLLAM POISONING

Cerbera odollam (manghas) is a common form of poisoning seen almost only in Kerala. It is the green fruit of the plant which is poisonous. It looks like a mango, the South Indian term for which is manghas. It is used mainly for suicidal purpose, less commonly for homicide or accident ingestion. When used for suicide, the kernel is mashed with jaggery or sugar and when used for homicide, it is mashed with spicy food to coverup the bitter taste. The active principle is cerberin, a glycoside. It acts similar to yellow oleander toxins.

The majority of the victims are women. Following ingestion they develop nausea, severe vomiting and pain abdomen. The main toxicity is on the heart where like oleander it causes various arrhythmias and hypotension. Hyperkalaemia is more common than in oleander poisoning and demands redressal.

Treatment is the same as oleander poisoning.

INDIAN HEMP POISONING

This is also known as *Cannabis sativa* or *indica*. It is used in various forms, viz. *ganja*, *charas*, majun and *bhang* or *sidhi*. Ganja and charas are smoked, *bhang* is a liquid intoxicant and majun is a confection. The active principle is delta 9 tetrahydro-cannabinol. Serious poisoning is rare and is mostly accidental and rarely homicidal. It is used to stupefy mainly rail passengers to relieve them of their belongings. It acts on the cannabinoid receptors (CB1, CB2) in the central nervous system (cerebral cortex, basal ganglia, hippocampus and spinal cord).

Clinical features consist initially of excitement with talkativeness, laughter, euphoria, excessive hunger especially for sweets, motor restlessness, bloodshot eyes and tachycardia. Later giddiness, unsteadiness, generalised paraesthesias and weakness, visual hallucinations and delirium develops. Finally patient goes into deep slumber. Death is rare but may occur, especially in individuals with diseased heart. However, during the stage of excitement they can cause damage to property and injure other persons fatally. The whole episode lasts for a few hours.

Treatment is supportive.

RECOMMENDED READINGS

1. Rajapakse S. Management of yellow oleander poisoning. *Clin Toxicol* 2009; 47 (3):206-12.
2. Shankar V, Jose VM, Bangdiwala SI, Thomas K, Epidemiology of Cleistanthus Collinus (Oduvani) Poisoning: Clinical features and risk factors for mortality. *Int J Inj Contr Saf Promot* 2009; 16(4): 223-30.

26.7 Drug Overdose

Nusrat Shafiq

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

– Paracelsus, 1567.

DRUG OVERDOSE

Drug overdose may be defined as the ingestion or application of a drug or other substance in quantities greater than what is recommended or generally practiced. It may be intentional (suicide, homicide) or accidental (error) intake or administration (parenteral, oral, inhalational or contact on skin/mucous membranes) of a drug or medicine. In the present chapter some commonly used drugs with therapeutic potential will be discussed.

Although the concept of Paracelsus about dose determining toxicity holds true till date, pharmacogenomics studies have demonstrated an individual variability of response to a drug. For instance, we now know that some individuals may be more sensitive to a particular drug and may experience toxicity when 'normal' doses are used. For example, individuals with either of the CYP2C9*2 and CYP2C9*3 variants metabolise coumarins slowly and usual doses of warfarin may cause toxicity.

GENERAL PRINCIPLES OF DEALING WITH A CASE OF DRUG OVERDOSE

Most of the symptoms produced are due to exaggeration of pharmacological actions of the drug.

In overdosage the pharmacokinetics of the drug may be altered and, in general, the drug effects appear sooner, peak later and last longer in overdosage. However, some drugs or sustained release preparations are absorbed slowly, distributed slowly or require metabolic activation ('toxic time bombs').

General examination of patient should be done with a view of a pattern of recognition. The conglomeration of signs and symptoms is called toxidrome and can broadly be categorised as excitatory or depressed.

Plasma concentrations may only serve as a guide and the patient, not the drug concentrations, need to be treated. Moreover, the facility for drug level estimation is not available everywhere and reports take time.

Chemical antidotes are not always available. Supportive measures are key to recovery. Physiological antidotes are very useful.

Decontamination of the gut is important for preventing further absorption. Activated charcoal, gastric lavage using saline, whole bowel irrigation, ipecac are the available alternatives. They should be used judiciously on a case-to-case basis.

Enhanced elimination has a limited role but may be important in some poisonings. Alkalinisation of urine to a pH of 8.0 by administering bicarbonate with normal saline and potassium replacement is useful in salicylate poisoning; gut dialysis using repeat-dose activated charcoal 0.5 gm/kg PO or NG every 4 hours may be useful for some drugs like theophylline, carbamazepine and phenobarbital. Haemodialysis may be needed in some cases (salicylates, methanol, ethylene glycol, lithium).

Discussed briefly herein is the management of overdosage of some commonly used drugs:

Acetaminophen (Paracetamol)

The reactive metabolite of acetaminophen, N-acetyl-p-benzoquinoneimine (NAPQ) combines with cell structures causing hepato-cellular damage following acetaminophen overdose. Glutathione (conjugates NAPQ, removing it) stores are overwhelmed when this reactive metabolite is produced in excess.

Presentation

The signs and symptoms vary depending on the time after ingestion a patient presents (**Table 1**).

Table 1: Signs and Symptoms of Drug Overdose

Time since Ingestion	Signs and Symptoms
Phase I (0-24 h)	Anorexia, nausea, vomiting
Phase II (24-72 h)	Right upper quadrant pain, elevated liver enzymes, PT and INR may be elevated
Phase III (72-96 h)	Vomiting, symptoms of liver failure, renal failure and pancreatitis may occur
Phase IV (>4 days)	Resolution of symptoms or progression to fatality

Management

A normogram (**Figure 1**) based on plasma acetaminophen concentrations, drawn no less than 4 hours after ingestion, serves as a guide for management. *Importantly, in most of the Indian centres, facilities for the estimation of serum acetaminophen concentrations are not available.*

N-acetylcysteine is the treatment of choice. It is a sulfhydryl compound that serves as a substitute of glutathione. Both oral (140 mg/kg, followed 4 hours later by 70 mg/kg every four hours for 17 doses) and intravenous routes (150 mg/kg in 200 mL of D5W infused over 1 hour, followed by 50 mg/kg in 500 mL of D5 W over 4 hours and then 100 mg/kg in 1000 mL of D5W over 16 hours) may be used. Possibility of anaphylactoid reaction with N-acetylcysteine may necessitate the use of antihistamine and/or epinephrine.

Benzodiazepines (BDZ)

Benzodiazepines are generally, considered safe and their overdose alone is seldom fatal though they have a habit-forming potential. Exaggerated action at the inhibitory GABA receptor is the cause of central nervous system (CNS) depression.

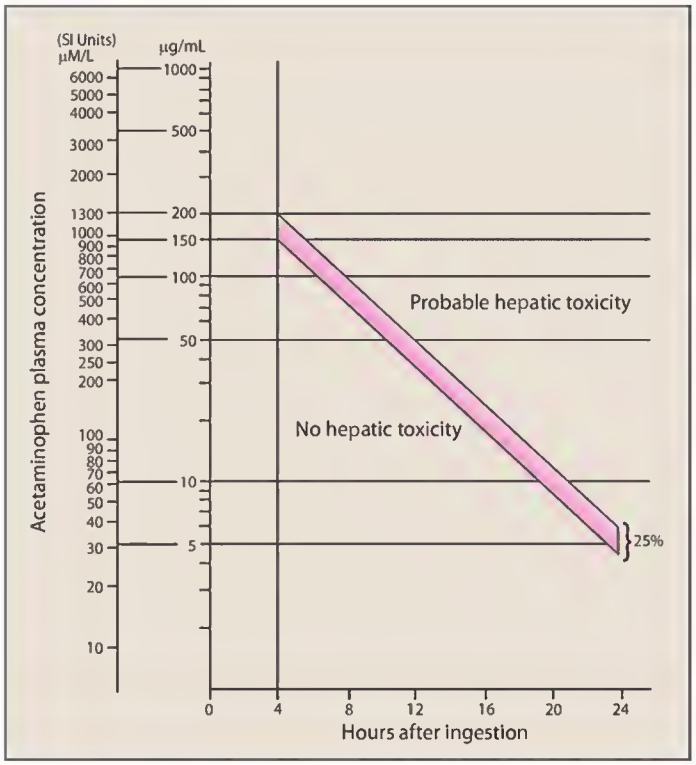


Figure 1: Semi-logarithmic plot of plasma acetaminophen levels vs time. *Source: Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 1975; 55 (6): 871-6.*

Presentation

Reversible impairment of consciousness, nystagmus, reduced cognition, slurred speech occurs, very rarely deep coma and respiratory depression may occur. Respiratory depression is usually not profound. Anxiety, insomnia and sometimes convulsions may be precipitated on recovery from overdosage.

Management

Flumazenil is a competitive antagonist of benzodiazepine at GABA receptor and usually reverses the symptoms rapidly. It is given as 0.1 to 0.2 mg IV doses, repeated every 1 minute to a total dose of 1 mg at one time or 3 mg in 1 hour; or as 0.1 mg/min infusion. Inadequate response to a dose of 5 mg of flumazenil should make one suspect of an alternative diagnosis. Flumazenil itself may precipitate seizures especially if barbiturates or tricyclic antidepressants were also taken simultaneously.

Antidepressants

Antidepressants were the seventh leading cause of toxic exposures in 2008, according to the US National Poison Data System Annual report and led to 80 deaths. Out of the three groups of drugs are generally used as antidepressants – the tricyclic amines (TCAs), selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOI), overdosage due to TCAs is common.

Presentation

In case of overdosage with TCA onset of symptoms typically occurs within 2 hours of ingestion and deterioration occurs rapidly. Lethargy, dry mouth, mydriasis, urinary retention, tachycardia and hypotension (may be refractory), prolongation of QT interval progressing to fatal ventricular arrhythmias are the key presenting features. Coma, delirium, seizures, and hyperthermia may also occur.

Rather than overdosage, drug-drug interaction in case of SSRIs may acutely raise the serotonin levels leading to a neuro-autonomic syndrome, serotonin syndrome. The presentation includes confusion, agitation, hyperthermias, diaphoresis, tachycardia, hypertension, myoclonus, rigidity, tremor, ataxia, and nystagmus. The condition usually resolves within 1 to 3 days.

Management

For overdosage with TCAs, activated charcoal may help since delayed gastric emptying caused by anticholinergic effect occurs commonly. Serum alkalinisation with intravenous sodium bicarbonate has been the mainstay of therapy in TCA-induced cardiovascular toxicity, particularly QRS prolongation (>160 ms). For ventricular tachycardia, overdrive pacing or lidocaine may be used. Hypotension should be treated with intravascular fluids, norepinephrine or dopamine. Benzodiazepines are used to suppress seizures. Animal studies have shown hypertonic saline to be effective in reversing TCA toxicity but human data are lacking. Physostigmine, should not be used in treating TCA toxicity because of the reported cases of physostigmine-induced seizures and asystole.

Salicylates

Salicylate overdose often occurs in children and can be fatal. The morbidity and mortality associated with an acute overdose are 1% and 16%, respectively, and with chronic intoxication is 30% and 25%, respectively. Fatal dose cannot be defined and death has been reported with 10 to 30 g of sodium salicylate ingestion. Plasma salicylate concentrations (**Table 2**) are often measurable at most centres. However, it should not be considered as indispensible for patient management.

Table 2: Categories for Assessing the Potential Severity and Morbidity of an Acute, Single Event, Nonenteric-coated, Salicylate Ingeston

Less than 150 mg/kg – No toxicity to mild toxicity
From 150 to 300 mg/kg – Mild-to-moderate toxicity
From 301 to 500 mg/kg – Serious toxicity
Greater than 500 mg/kg – Potentially lethal toxicity

Presentation

Salicylism refers to mild chronic intoxication characterised by headache, dizziness, tinnitus, difficulty in hearing, diminished vision, mental confusion, lassitude, drowsiness, sweating, hyperventilation, nausea, vomiting.

In acute overdosage, besides the above, CNS effects including confusion, convulsions and coma, hyperthermia and stimulation of respiratory system occurs. The latter is due to direct (stimulation of respiratory centre) and indirect (uncoupling of oxidative phosphorylation leading to accumulation of carbon dioxide) effects. Respiratory alkalosis with renal acidosis, dehydration with hypernatraemia ensues. Aerobic metabolism of glucose is impaired and hence hypoglycaemia may be dangerous. Petechiae due to impaired platelet function also may occur. Respiratory failure is the cause of death in these patients.

Management

Activated charcoal may be particularly helpful if enteric coated preparations have been ingested. Volume replenishment, restoration of acid-base and electrolyte balance, administration

of glucose and sodium bicarbonate (with the aim of maintaining a pH between 7.5 and 7.55 and achieving alkaline diuresis) is needed. Haemodialysis may be needed if all the above measures do not lead to improvement and/or plasma salicylate concentration is more than 1000 µg/mL.

Beta-Blockers

Over 9,000 cases of overdosage with beta-blockers have been reported with propranolol being the commonest agent implicated. A physiological depressant state is a common finding.

Presentation

Atrioventricular block (sotalol may cause tachyarrhythmias), hypoglycaemia and hyperkalaemia are the important features of beta-blocker poisoning. Although the half-life of these compounds is usually short (2 to 12 hour), their effects in overdose patients may be prolonged (>72 hour) because of decreased metabolism (a depressed cardiac output, reduced blood flow to the liver and kidneys), formation of active metabolites, saturation kinetics prolong elimination at the high plasma concentrations that typically occur with overdose, and more common use of long-acting preparations.

Management

Restoration of heart rate can be achieved by atropine, isoprenaline, amrinone, dopamine, dobutamine, epinephrine or norepinephrine. For managing hyperkalaemia and hypoglycaemia, glucose with insulin may be instituted. Because glucagon is both diagnostic and therapeutic, it can be administered empirically in a dose of 2 to 10 mg and response checked. It is considered drug of choice by many toxicologists and it acts by stimulating cAMP production through nonadrenergic pathways resulting in enhanced myocardial contractility, heart rate, and AV conduction. Benzodiazepines are the drugs of choice if seizures occur.

Calcium Channel Blockers (CCBs)

The three types of CCBs may all produce a physiologically depressed toxidrome. In 2008, the US National Poison Data System reported 10,398 exposures to CCBs, resulting in 12 deaths (0.11%) and 63 major outcomes (0.6%).

Presentation

Hypotension and bradycardia are typical presentations but reflex tachycardia after exposure to dihydropyridines can also occur. Pulmonary oedema, nausea, vomiting, hyperglycaemia are commonly present. Severe hypotension may lead to mesenteric ischaemia and colonic infarction. Paralytic ileus may be present. Since sustained release preparations are commonly used, presentations may be delayed. Even a single tablet of a CCB can be fatal in children.

Management

Restoration of cardiovascular parameters as for beta-blockers should be instituted. In severe cases a bolus dose of calcium chloride (10 to 20 mg/kg up to 1 to 3 g) is the preferred therapy. Bolus infusion of glucagon (0.05 to 0.20 mg/kg, over 1 to 2 minutes) is useful. For refractory cases, intravenous bolus of regular insulin with 50% dextrose may have some benefit.

PHENYTOIN

Symptoms of toxicity appear above plasma concentration of 20 µg/mL. However, there is a large inter-individual variation. Presentation of toxicity depends on the route of administration of phenytoin. Data from the United States of America suggest moderate morbidity rates of 22%, major morbidity in 1.88%, and fatality in 0.17% of phenytoin overdose cases.

Presentation

In an emergency setting when fosphenytoin intravenously is administered, toxicity symptoms (cardiac arrhythmias with hypotension and/or CNS depression) may appear if given at a fast rate (more than 150 mg of phenytoin sodium equivalents per minute).

Toxicity due to acute oral overdosage leads to cerebellar or vestibular symptoms. Chronic oral toxicity presentations include behavioural changes, increased frequency of seizures, gastrointestinal symptoms, gingival hyperplasia, and osteomalacia.

Management

GI decontamination to limit the systemic burden with multiple dose activated charcoal and control of seizures, if any, with benzodiazepines are the mainstay of treatment.

Digoxin

Various studies suggest that approximately 1.1% of outpatients on digoxin, and 2% to 18% of inpatients on digoxin have manifestations of toxicity. The incidence has declined due to increased awareness about drug interactions, decreased use of digoxin to treat heart failure and arrhythmias, and the availability of accurate rapid radioimmunoassays to monitor drug levels. Toxicity usually appears at a concentration > 2 ng/mL and is more likely to occur in those with impaired renal function, hypokalaemia, hypercalcaemia and hypomagnesaemia.

Presentation

Cardiac arrhythmias range from ventricular arrhythmias to atrioventricular blocks to sinus bradycardia. Non-cardiac symptoms include anorexia, nausea, vomiting, abdominal pain, halos, photophobia, fatigue, dizziness, delirium, and psychosis.

Management

Further doses of digoxin should be stopped. Conduction delays and blocks should be treated with atropine. Intravenous potassium may help in junctional or ventricular automaticity, lidocaine or phenytoin for ventricular tachyarrhythmias. Antidigoxin antibody is indicated for dysrhythmias associated with haemodynamic instability, altered mental status, K^+ >5 mEq/L, serum digoxin level >10 ng/mL in adults at steady state and ingestion of >10 mg in adults or >0.3 mg/kg in children. The dose is calculated as either (mg ingested) x 0.8/0.6 or [serum level (ng/mL) x 5.6 x body weight (kg)/1000]/0.6.

Methylxanthines

As is the case of digoxin, the number of reported cases of theophylline toxicity is decreasing for similar reasons. The toxicity may occur in two settings – in an emergency setting when aminophylline may be used, or chronic toxicity due to repeated oral administration.

Presentation

Rapid administration of aminophylline may even lead to sudden death. At concentrations more than 20 µg/mL, headache,

palpitation, nausea, hypotension, precordial pain, restlessness and agitation occur. Tachycardia, arrhythmias and seizures are important causes of concern.

With chronic toxicity, the concern is that of seizures which may be refractory to treatment.

Management

Decontamination with charcoal, especially if sustained release preparations are used, propranolol for the management of tachyarrhythmias with hypertension, any beta-blocker if hypertension is not present, diazepam, phenytoin or barbiturates for seizure control are the mainstay of treatment. Haemoperfusion or haemodialysis are indicated for unstable vital signs, seizures and plasma concentration of theophylline more than 80 to 100 µg/mL for acute overdose and 40 to 60 µg/mL for chronic exposure. Metoclopramide or ondansetron may be used for vomiting, and IV fluids/pressor agents for hypotension.

Iron

Iron overdose is one of the leading causes of fatality from toxicological agents due to non-intentional ingestion in children although the incidence has decreased considerably. Ingestion of 40 mg/kg or more of elemental iron is associated with serious toxicity. Generation of oxidative free radicals is the main mechanism of injury. Iron tablets can be visualised on abdominal radiograph if taken within 2 hours of ingestion.

Presentation

Iron poisoning may be classified into 5 distinct stages (**Table 3**). It is important to know them because the second recovery stage may lure the treating doctor into a false sense of security and lead to pre-mature discharge from the hospital.

Table 3: Stages of Iron Poisoning

Stage 1: Gastrointestinal
Usually occurs within 6 hours after exposure
Nausea and diarrhoea, often with excessive fluid and blood loss

Stage 2: Latent
This deceptive stage is characterised by resolution of GI symptoms
Usually occurs 6 to 12 hours after ingestion and may last for 24 hours

Stage 3: Metabolic/Cardiovascular
Metabolic acidosis and cardiovascular symptoms
Stupor and coma
Most patients die during this phase
It can start very early (6 to 8 hours), depending on severity of exposure, and it can last up to 2 days

Stage 4: Hepatic
Elevated liver enzymes and bilirubin levels with coagulopathy
Hypoglycaemia

Stage 5: Delayed
Scarring of the healing GI tract. The stomach and/or intestines may be affected, resulting in gastric outlet or intestinal obstruction
Experienced weeks after a severe poisoning

Management

Polyethylene glycol is the preferred agent for gut decontamination. Intravenous fluids and sodium bicarbonate may be needed for fluid and electrolyte balance. Patients with systemic symptoms should be given intravenous desferrioxamine. An initial dose of 1 g is given, either intravenously at a maximum rate of 15 mg/kg per hour, or by intramuscular injection; subsequent doses of 500 mg may be given, by infusion over 4 to 12 hours or intramuscularly at intervals of 4 to 12 hours, to a maximum of 6 g in 24 hours. Deferiprone is an orally active iron chelator used in the treatment of iron overload in patients with thalassaemia for whom desferrioxamine is unsuitable or ineffective. It may be given by mouthing doses of 25 mg/kg three times daily. Doses above 100 mg/kg daily are not recommended.

Warfarin

Warfarin overdose presents as excessive anti-coagulation reflected in elevated levels of Internationalised Normalised Ratio (INR) (**Table 4**).

Table 4: Excessive Anticoagulation Shown by Increased INR

INR Value	Management
0.5-6	Reduction in dose or withdrawn
6-8 (No bleeding/ Minor bleeding)	Stop warfarin
>8	Vitamin K1 (0.5 mg IV or 2.5 mg of IV dose given IV)
Major bleeding	Stop warfarin, Vitamin K (5 to 10 mg by slow intravenous infusion, concentrate of II, VII, IX, X) and fresh frozen plasma

Antipsychotics

Typical antipsychotics have by and large a wide therapeutic index.

Presentation

Overdosage may result in neuroleptic malignant syndrome characterised by extreme hyperthermia, 'lead pipe' skeletal muscle rigidity causing dyspnoea, dysphagia, and rhabdomyolysis, autonomic instability, fluctuating consciousness, leucocytosis, and elevated creatine phosphokinase.

The newer antipsychotic agents were evaluated for their effects in overdosage in a study in UK. Symptoms were most marked with clozapine, with a majority of patients experiencing agitation, dystonia, central nervous system (CNS) depression and tachycardia. Olanzapine and sulpiride produced a range of different symptoms, including cardiac arrhythmias with sulpiride and most patients who had taken risperidone were asymptomatic.

Management

The treatment of malignant syndrome includes immediate withdrawal of neuroleptic drugs, intravenous infusion of dantrolene, and oral administration of bromocriptine; or the combination of levodopa-carbidopa. Other measures include the use of benztropine, lorazepam if catatonic symptoms persist, or electroconvulsive therapy (ECT) if psychotic symptoms persist.

PROMETHAZINE

Promethazine, a first generation antihistaminic is commonly used for management of vomiting and cough.

Presentation

The important feature of promethazine overdose is delirium. Central nervous system (CNS) depression and anti-cholinergic

effects, including delirium, agitation and hallucinations are important features. Delirium may be masked by CNS depression. Dystonic reactions, psychosis in the absence of other anti-cholinergic symptoms or signs and neuroleptic malignant syndrome (NMS) may also occur.

Management

Dystonic reactions respond well to benztropine or diphenhydramine. Early administration of charcoal may reduce the occurrence of delirium.

Isoniazid

Acute ingestion of 1.5 g of INH can cause mild toxicity, 6 to 10 g causes severe toxicity and 15 g is usually fatal.

Presentation

Signs and symptoms of overdosage include slurred speech, hallucinations, metabolic acidosis, hyperglycaemia, respiratory distress or tachypnoea, convulsions and coma; fatalities may also occur.

Management

In adults an initial intravenous dose of pyridoxine hydrochloride equivalent to the estimated amount of isoniazid ingested (or, if the amount ingested is unknown, pyridoxine hydrochloride 5 g) has been recommended by the UK National Poisons Information Service for the management of convulsions; diazepam should also be given. For children the recommended dose of pyridoxine hydrochloride is 70 mg/kg (to a maximum of 5 g). If convulsions continue or recur, this dose may be repeated. Oral activated charcoal (50 g for adults and 10 to 15 g in children) may be considered if this is given within 1 hour of ingestion of isoniazid.

Lithium

Lithium is a narrow therapeutic index drug. Moreover it is subject to clinically significant drug interactions. Toxicity manifests more in those with renal failure, dehydration, hyponatraemia or those on diuretics.

Presentation

Acute intoxication is characterised by vomiting, diarrhoea, tremors, ataxia, coma, and convulsions. The more serious effects involve the nervous system and include mental confusion, hyper-reflexia, gross tremors, dysarthria, seizures, and cranial nerve and focal neurological signs, progressing to coma cardiac arrhythmias, hypotension, albuminuria, and death.

Management

There is no specific antidote for Li^+ intoxication, and treatment is supportive. Electrolyte and fluid balance is important. Dialysis is indicated for patients exhibiting symptoms of toxicity or patients with serum Li^+ concentrations greater than 4 mEq/L in acute overdoses or greater than 1.5 mEq/L in chronic overdoses.

Phenobarbitone

The plasma concentration of 10 to 35 microgram/mL is usually associated with attainment of therapeutic response.

Presentation

At high doses nystagmus and ataxia may occur and the typical barbiturate-induced respiratory depression may become severe. Overdosage can prove fatal; toxic effects include coma, severe respiratory and cardiovascular depression, with hypotension and shock leading to renal failure. Hypothermia may occur, with associated pyrexia during recovery. Skin blisters (bullae) occur in about 6% of patients with barbiturate overdose.

Management

Gastric lavage, multiple doses of activated charcoal (MDAC), airway protection, oxygenation, mechanical ventilation, IV fluids and vasopressors are the mainstay of treatment. The urinary elimination of phenobarbital (pKa of 7.2) may be enhanced with alkalinisation of the urine by sodium bicarbonate with the aim of maintaining urinary pH between 7.5 and 8. Haemodialysis or haemoperfusion are indicated for phenobarbital poisoning in the presence of renal failure and shock with ileus.

CONCLUSION

Drug overdosage is an important problem with significant morbidity and mortality. Though the ideal management would occur at poisoning and toxicology centres, more often than not these cases need to be managed at primary or secondary care centres. Supportive management is the mainstay of treatment and antidotes are helpful in very few poisonings. Limited dispensation policies, purchase on prescription could help bring down the incidence of suicidal overdosage.

26.8 Snake Bite Poisoning

HS Bawaskar

INTRODUCTION

Snake bite envenomation is a common acute life-threatening medical emergency. More than 200,000 snake bites are reported in the country and an estimated 35,000 to 50,000 people die each year. Majority of snake bite deaths go unreported as many victims go to traditional healers and many deaths occur before reaching hospital.

AETIOLOGY

There are about 216 species of snakes identifiable in India, of which 52 are poisonous. The major families of poisonous snakes in India are Elapidae which includes common cobra (*Naja naja*, **Figure 1A**), king cobra and common krait (*Bungarus caeruleus*, **Figure 1B**), Viperidae includes Russell's viper (**Figure 1C**), *Echis carinatus* (saw scaled or carpet viper, **Figure 1D**) and pit viper and hydrophiidae (sea snakes). Snake venom is not a substance evolved to attack man or big vertebrates, but is intended to paralyse the prey before swallowing. Venom secretion in all venomous snakes appears to vary in seasons. In warmer months its output is more than in the cold season. Similarly, darker the snake, more is the venom it secretes. Most snakes inject 10% of available venom in a single strike except Russell's viper which injects 75% of stored venom in one bite and is responsible for high morbidity and mortality in India.



Figure 1A: Common cobra (*Naja naja*).



Figure 1B: Common krait (*Bungarus caeruleus*).



Figure 1C: Russell's viper (*Vipera russellii*).



Figure 1D: Saw-scaled viper (*Echis carinatus*).

PATHOPHYSIOLOGY

Snake venoms are not single toxins but a cocktail of many components: enzymes, polynucleotide toxins, nontoxin proteins, carbohydrates, metals, lipids, free amino acids, nucleotides and biogenic amines. The content and potency of venom in any snake varies with size, age, diet, climate, and time of year. Moreover, a small snake's immature venom may not respond to routine anti-snake venom.

Procoagulant enzymes are the major factor in viper venom, which stimulates blood clotting and consumption of fibrinogen, causing disseminated intravascular coagulation (DIC). Russell's viper venom contains several different procoagulants which activate various steps of the clotting cascade. Fibrinolytic activity of the viper venom is so fast that sometimes within 30 minutes of the bite, the coagulation factors are so depleted that blood does not clot. Haemorrhagins are zinc metalloproteinases, which damage the endothelial lining of the blood vessels causing spurting of red blood cells and spontaneous systemic bleeding. Cytolytic or necrotic toxins damage the cell membranes and stimulate apoptosis. These digestive hydrolases, polypeptide toxins and other factors increase permeability resulting in local swelling and nonhealing ulcers and gangrene of the bitten part. Haemolytic and myolytic phospholipases A2 (PLA2) damage cell membranes, endothelium, skeletal muscle, nerve and red blood cells. Presynaptic neurotoxins are phospholipids A2 that damage nerve endings, initially releasing acetylcholine transmitter, then interfere with its release. Postsynaptic neurotoxins are

polypeptides which compete with acetylcholine for receptors in the neuromuscular junction and lead to curare-like paralysis (cobra venom).

The amount of venom injected at the time of bite depends on the species and size of the snake and the mechanical efficiency of the bites. At times snake may be able to control whether or not venom is to be injected at the time of bite. This is the reason why irrespective of bite by poisonous snake, sometimes there is no systemic sign of envenomation, i.e. dry bite.

ECHIS CARINATUS OR SAW-SCALED VIPER OR CARPET VIPER

It is 1 to 3 feet long, head is sub-ovate with short rounded snout, body is cylindrical, short and covered with rough, serrated flank scales, neck is distinctly constricted. It is pale brown or tawny with dark brown. A cruciform or trident or arrow type or just like the bird foot print shaped mark is seen on head. It flourishes in hot and humid climate in the coastal regions of India. It is alert, diurnal in habit and capable of quick movement when necessary. It hibernates in the winter. Readiness with which it bites on smallest provocation with extremely rapid strike makes it one of the more dangerous snakes. It forms a double coil in the form of figure of 8 with its head in the centre a striking position. It is viviparous producing 3 to 15 young at a time. It injects 0.0046 gram venom at the time of bite. Farmers, hunters, labourers, and persons walking barefoot in jungles and rocky areas are often bitten by this snake.

Clinical Manifestations

Local manifestations

Within an hour of the bite, swelling develops over the bitten part. Fang marks or abrasions with clotted blood are seen (**Figure 2**). Venom is of big molecular size and is circulated through the lymphatics, hence within 60 to 120 minutes the victim experiences a painful lymphadenopathy of the drainage area of the bitten part. Ecchymoses are seen over the bitten part or may spread over lymphatic drainage areas. Acute bleeding in the form of gum bleeds (**Figure 3**) or bleeding from abrasions on any other part of body or from vene-puncture sites is seen within 90 to 120 minutes of a bite. Occasionally, in untreated patients, bleeding can persist for 1 to 2 weeks in the form of blood-stained sputum, haematuria and then disappears of its own. Such patients are markedly anaemic and report to hospital for weakness or nonhealing bleeding cellulitis. Natural immunity against the *Echis carinatus* venom develops in cases of repeated bites by the same species in endemic areas as reported in Jammu region. Renal failure due to *Echis carinatus* has been reported from Puducherry and Jammu areas, but not from Maharashtra.



Figure 2: Two fang marks with bleeding spot at fang marks over the second toe due to *Echis* bite.



Figure 3: Acute bleeding from gums and oral cavity due to *Echis* bite.

RUSSELL'S VIPER OR *DABOIA* OR *VIPERA RUSSELLII SIAMENSIS*

It inhabits ten south Asian countries and ranks amongst one of the topmost important causes of snake bite mortality. While protecting the paddy and wheat from the rodent (rats) population, it kills many farmers unlucky enough to tread on it.

It is a 3 to 5 feet long snake; the head is covered with small scales and without shields. The body is massive and cylindrical, narrowing at both ends; the head is flat, triangular with short snout, large gold flecked eyes with vertical pupils and large open nostrils. Its belly is round with constricted neck. Typical rows of oval arranged in two rows is characteristic of Russell's viper. Its natural prey includes mice, rats, frogs, lizards, snakes, and birds. The young snakes are cannibalistic. The females produce 20 to 60 young usually around the month of June or July. Length of fangs in an adult snake is 16 mm and curved. The amount of venom injected at the time of bite is 63 ± 7 mg.

Clinical Manifestations

Local manifestations

The victim experiences severe local pain at the site of the bite, active bleeding from fangs marks within a few minutes, rapid swelling progressing to the whole limb within six to eight hours (**Figure 4**). Ecchymoses and blebs occur over the bitten part. Because of oedema of muscle and bleeding there is development of compartment syndrome characterised by swelling, painful passive movement, and loss of sensation over the nerve areas passing through the compartment. Subsequently, wet gangrene or nonhealing ulcers develop. Lymph nodes proximal to the bite become enlarged and tender.



Figure 4: Extensive swelling with ecchymosis due to Russell's viper bite and recovery after 8 days.

Systemic manifestations

Hypotension and shock are due to sudden liberation of bradykinin into the circulation, bleeding and loss of fluid in swollen part, bleeding in the adrenal glands, or peritoneal or massive blood loss by haematemesis or haemoptysis.

Haemostatic failure: Pro-coagulant content of venom initiates rapid thrombosis, hypofibrinogenaemia and consumptive coagulopathy. In human victims of Russell's viper bite, the injected dose of venom is insufficient to cause massive fatal intra-vascular coagulation within a minute of the bite, unlike in animals. Once the patient's blood has become defibrinated and incoagulable, spontaneous systemic bleeding ensues. Haematuria, bleeding in the skin, and pituitary haemorrhage can occur. Russell's snake bite victims can subsequently develop amenorrhoea, Sheehan's syndrome, loss of libido due to hypopituitarism, as reported from southern India. Enhanced capillary permeability is seen in the form of pleural and pericardial effusion, ascites, and conjunctival congestion/haemorrhage. High fatality is due to hypotension and resistant shock syndrome due to capillary leaks.

Renal failure: 20% to 40% cases subsequently develop anuria, oliguria and acute renal failure. Renal angle tenderness is the most important clinical sign for early diagnosis of renal failure. There is serial rise in blood urea and serum creatinine with acidosis and hyperkalaemia. Tubular damage by venom itself, interstitial nephritis, haemoglobinuria, hypotension, and microthrombi in the kidney contribute to acute tubular necrosis. Renal failure is the commonest cause of death.

Neurological effects: Ptosis, bulbar palsy, inter-nuclear ophthalmoplegia and respiratory paralysis due to presynaptic neuromuscular block in a Russell's viper bite has been reported from Kerala and Sri Lanka.

Green pit viper and bamboo pit snake bite cases, reported from Kerala, are characterised by local oedema and rarely a systemic bleeding disorder. Coagulopathy and renal failure has been reported due to Hump-nosed pit viper snake bite.

ELAPIDAE POISONING

Common Indian Krait (*Bungarus caeruleus*); local names: kala gandait, kala taro, kandar, manyar, chitti, kattu viriyan, valla pamboo.

Krait is the most poisonous snake, its venom being 10 times more poisonous than cobra venom. It is 1 to 4 feet long, with enlarged hexagonal vertebral scales, uniform white or red belly and narrow white crossbars on the back, more or less distinctly in pairs, the crossbars are typically absent near the head and neck region. The common krait resides in the vicinity of human habitation, near the wattle and daub, mud and small hut dwellings. Krait is a nocturnal, terrestrial snake that enters human dwellings in search of prey such as rats, mice, and lizards. It eats even the small snakes (cannibalism). The common krait is regarded as the most dangerous species of venomous snake in the Indian subcontinent. Most bites occur during the cooler months of June to December when snakes may, during the course of their hunting activity, linger in a person's bedding to take advantage of the warmth therein.

Clinical Manifestations

Majority of the cases of snake bite are reported between 11 pm to 5 am, usually when the person is asleep and the reflexes are greatly diminished; and the krait, having sharp small fangs, injects maximum venom in such a person. The victim might experience mild pain at the site of bite, paraesthesiae or numbness, without any local marks or swelling or bleed, hence the bite is neglected and falsely initially attributed to an ant or rat. Venom is small molecular size hence directly absorbed in the circulation. The venom stimulates the autonomic nervous system thus within 20 to 30 minutes of the bite, victims experience a transient abdominal colicky pain, bradycardia, sweating, vomiting, raised blood pressure. Subsequently, within 30 minutes to 18 hours the venom attacks presynaptic acetylcholine receptors resulting in ptosis (**Figures 5A to C**), pooling of saliva, dysphagia, dyspnoea, inter-nuclear opthalmoplegia, weakness of neck muscles, respiratory muscles and lastly the diaphragm. Patient complains of blurred vision,



Figures 5A to C: Manifestations of krait bite: (A) ptosis with bulbar palsy; (B) after recovery; and (C) fang marks over the ear lobules.

diplopia and lands in respiratory paralysis, coma and anoxic cardiac arrest. Venom induced paralysis of pupillary muscle causes non-reacting pupils. After recovery, a few patients had signs and symptoms of peripheral neuropathy. Many a times, patients succumb to iatrogenic respiratory infection or adult respiratory distress syndrome.

Cobra bite

Cobra bite tends to occur during the day time, when the transportation is more readily available. Moreover, because of its known severity, victims report to hospital early.

Cobra venom is a cardiotoxic, neurotoxic, haematotoxic and cytotoxic. The fangs of a cobra are small and sharp. Its venom is small molecular size hence rapidly absorbed into the circulation.

Soon after a bite, the victim experiences severe pain at the site of bite with fang marks covered with blood clots. Rapid development of swelling over the bitten part, ecchymoses, blebs, and massive damage of skin and subcutaneous tissue due to myocytolysis can occur. If the victim saw the biting hooded cobra, massive liberation of endogenous catecholamine into the circulation due to fear of death can actually result in lethal cardiac arrhythmias or cardiogenic shock due to massive myocardial infarction. Sinus bradycardia, A-V block and hypotension are due to cardio-depressant action of the venom. Sudden respiratory arrest without any other neurological manifestations can occur resulting in anoxic cardiac arrest. Rapid ptosis and bulbar palsy accompanied with respiratory depression can occur. Rarely, haematotoxic effects are seen. Blurring of vision and loss of accommodation are the earliest neurological signs of envenomation.

Locked-in syndrome

This may be seen in few cases, but such victims recover totally within 3 to 4 days if treated properly by maintaining oxygen saturation with proper ventilator support, maintaining electrolytes and nutrition and prevent iatrogenic infection. This phenomenon is due to blocked post-synaptic acetylcholine receptors including pupillary muscle which are rich in acetylcholine receptors.

Sea snakes

Sea snakes are seen all over the coastal region. Sea snake is accidentally handled by fishermen during fishing. Its venom is neurotoxic, myotoxic and haematotoxic. Soon after a bite, the victim experiences severe muscle pain, marked tenderness all over the muscles, trismus, muscular paralysis, respiratory arrest, without local manifestations at the site of bite. Myotoxic effects of venom causes hyperkalemia and myoglobinuria causing acute tubular necrosis.

Management

Figure 6 outlines the management of snake bite envenomation. Reassurance is important to allay anxiety and fear of death. Local incision, tight tourniquet or suction, and electric shock are to be discouraged. Patient should be shifted to the nearest equipped medical facility. Immobilisation of the bitten part by a splint, keeping the bitten part below heart level is preferred. It is worthy to apply crepe bandage (with a pressure enough that one can easily introduce the finger between skin and bandage) to krait bite case if victim took more than 30 minutes but less than 2 to 3 hours to reach the hospital. This helps to delay the absorption of venom and moreover, may prevent rapid development of respiratory paralysis.

Treatment with anti-snake venom (ASV)

History of snake bite or evidence of fang marks are not an indication for administration of ASV. There should be signs and symptoms suggestive of envenomation.

Initially, 100 mL ASV is to be added to 200 mL of crystalloid solution and administered over 60 minutes by intravenous route in a victim of krait, cobra and Russell's viper envenomation. It

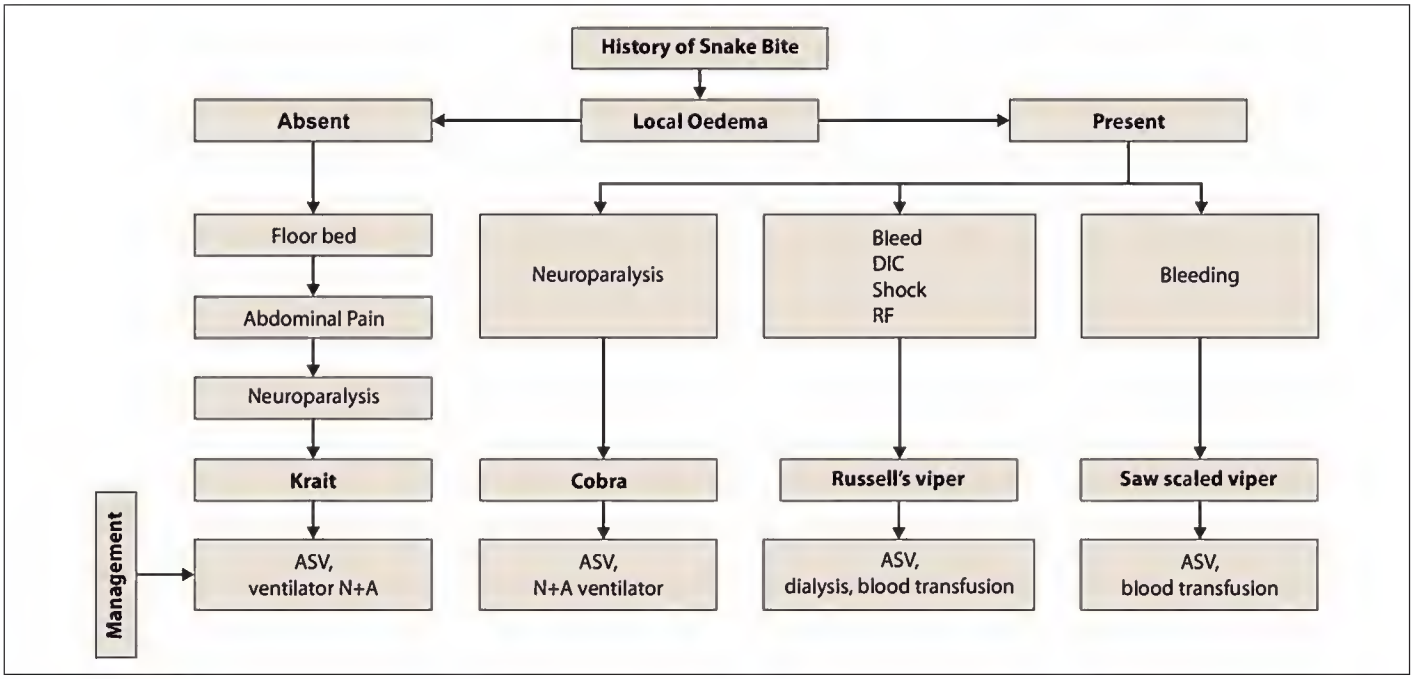


Figure 6: Flow chart for management of venomous snake bite.

ASV = Anti-snake venom; N = Neostigmine; A = Atropine; RF = Renal failure; DIC = Disseminated intravascular coagulation

neutralises the circulating venom. While the venom is absorbed slowly from the site of the bite, which acts as a depot, can be neutralised by 20 to 30 mL of ASV at 6-hourly intervals.

In case of elapidae envenomation, 50 mL of ASV can be administered if there is no improvement within 30 to 60 minutes after the initial dose; while the total initial dose required for *Echis carinatus* envenomation is 20 to 40 mL over one hour and 20 mL over the next 24 hours.

ASV may be administered even after 12 to 14 days after viper bite if systemic toxicity is present. After the initial dose of ASV, if active bleeding such as haematemesis, haematuria, bleeds from the wound do not disappear within 20 to 30 minutes, particularly in viper bite, one can repeat 20 to 50 mL ASV as an extra bolus.

Twenty minute whole blood clotting test (20WBCT) is the gold standard bedside test and can be performed by unskilled staff. Before injecting ASV, from same venepuncture 2 to 3 mL of blood is withdrawn and added to a dry glass tube (not washed with detergent), and then kept standing for 20 minutes. If the tip of the blood did not clot, hypofibrinogenaemia is confirmed. This test should not be repeated earlier than 6 hours after administration of ASV, as the liver takes six hours for synthesis of coagulant factors. 20WBCT test decides further requirement of ASV. This test is important for diagnosis and also indicates the improvement.

Once the venom gets attached to the target organs (receptors) such as neuromuscular receptors, red blood cells, platelets, renal tubules, and myocardium, then any amount of ASV will not be able to reverse the effects.

Elapidae venom blocks the acetylcholine receptors, this action of venom can be reversed by neostigmine in the dose of 25 microgram per kg per hour preceded by atropine. Post-synaptic receptors blocked by cobra venom can be totally reversed by choline-esterase inhibitor, while in krait bite venom which blocks both pre- and post-synaptic receptors, neostigmine may help to delay the respiratory depression in early stage. Need for artificial ventilation is indicated by grade 3 power, pulling of saliva, or tidal volume below 200 mL.

Hypotension, bradycardia are to be treated with dopamine drip and atropine. Complete heart block in cobra bite needs isoprenaline drip, ASV and temporary pacemaker.

Renal failure: Early administration of ASV, mannitol, diuretic and acetylcysteine may help to prevent the renal failure in Russell's viper bite. Close monitoring of urine output is important to detect early renal failure in Russell's viper bite. Early renal failure is treated by intravenous frusemide 200 to 500 mg or torsemide by continuous intravenous drip and dopamine drip with fluid restriction. Haemodialysis or peritoneal dialysis may also need to be offered in established renal failure cases.

Profuse bleeding can be treated by blood transfusion. Shock due to accumulation of fluid in compartment syndrome or muscle damage can be prevented by surgical decompression, but the following criteria should be fulfilled before any surgical procedure: (1) marked tenderness over muscles, (2) pain during passive movement of muscles, and (3) loss of sensation or hypo-aesthesia in the supply of a nerve passing through the compartment.

Hyperkalaemia is managed on standard lines – intravenous calcium gluconate, diuretics, insulin-glucose drip, salbutamol nebulisation and if required, dialysis.

Anaphylaxis can result from ASV, but test dose of ASV is not essential. Recently, it is reported that adrenaline can be used as prophylaxis before starting ASV. Earliest symptom of anaphylaxis is vomiting sensation, warm sensation in ears or head, itching behind ears, urticaria, itching all over body, hypotension, tachycardia, bronchospasm, dysphagia, swelling of tongue and lip, feeling of obstruction in throat. ASV should not be given by rapid intravenous bolus as it may activate complement and result in a severe reaction. One should keep watch for appearance of anaphylaxis for 10 to 180 minutes after administration of ASV. While diluting ASV if there is a precipitate, it should be discarded as such precipitated proteins are more likely to cause severe anaphylaxis.

Intra-muscular injection should be avoided if the patient's blood fails to clot.

Total requirement of ASV dose can be reduced by preparing mono-specific ASV or purified F(ab)2 ASV.

ELISA kit for detection of venom antigen helps a treating doctor know the exact species of snake and even help to monitor the circulating venom antigen, thus the dose of ASV.

Prevention

Firewood, dry cow dung, cattle shed and rubble should be kept away from residential areas. Old storage rubble, particularly in old house, should be handled in full sunlight. Rubble in the attic should not be handled blindly. Barefoot walking in darkness for open toilet in grown grass should be avoided, or one should go out with a torch and a heavy stick so as to vibrate the place before stepping. Proper care of rats, mice and lizards must be taken. No attempt should be made to catch the snake or to kill it. Killed snake should not be handled. Thick electric rubber gloves with rubber shoes should be worn at the time of handling the crops husk. A bamboo cot with scrupulous use of a mosquito net prevents scorpion sting, krait and mosquito bite alike. The victim should report as early as possible to the nearby primary health centre where enough storage of ASV is kept ready.

Training in appropriate use of antivenom and protocol of indications for its use should be arranged at general hospital level to ease the crisis of supply of ASV. It is important to note that already applied tourniquet to the part at site of venomous snake bite should not be released until full dose of snake antivenom is administered.

RECOMMENDED READINGS

1. Bawaskar HS, Bawaskar PH. Envenoming by the common Krait (Bungarus caeruleus) and Asian Cobra *(Naja naja)*: clinical manifestations and their management in a rural setting. *Wilderness and Environmental Medicine* 2004; 15: 257-66.
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26.9 Scorpion Sting

HS Bawaskar

Scorpion envenomation is a major public health problem in tropical and sub-tropical countries, especially in Africa, Middle-East, Latin America and India. At times it poses a significant life-threatening acute time limiting cardiovascular emergency. Irrespective of different species of scorpion, similar cardiovascular effects are reported. Irrespective of the understanding of the pathophysiology and management, the morbidity and fatality remains high in rural areas due to nonexistent medical facilities and the delay in hospitalisation due to superstitions and faith in village healers. Scorpion envenoming has been underestimated as this problem is faced by majority of underdeveloped and developing countries. Since the advent of prazosin therapy the fatality has dropped from 29% to less than 1%.

The Indian red scorpion *Mesobuthus tamulus* (**Figure 1**) is the most lethal amongst all the poisonous species of scorpions.



Figure 1: Photograph showing an Indian red scorpion (*Mesobuthus tamulus*).

The scorpion envenomation has been frequently reported from Puducherry, Karnataka, Tamil Nadu, Andhra Pradesh, Saurashtra, Uttar Pradesh, Bihar and Marathwada and Western Maharashtra. Thousands of scorpion stings are reported annually from India and 15% to 20% of these stings manifest with systemic symptoms. Farmers are more prone to get stung by scorpion during handling debris and paddy husk in the months of April to early June and September to October as due to sudden rise in environmental temperature, scorpions come out of their hides. The sting during these months is more potent and prone to serious envenomation. Scorpion is nocturnal in habit and people walking bare foot become their victim more commonly.

SCORPION

Nearly 1,000 species of scorpion are known worldwide, which belongs to six families. However, only the scorpion belonging to the family *Buthidae*, secretes neurotoxic venom that is toxic to human; around 86 species of this family are found in India. *M. tamulus*, an Indian red scorpion, is venomous and its envenomation is fatal if not treated in time. Its claws are red coloured, but tail, legs and body is covered with *khaki* coloured cuticles. It is 2.5 to 4 inches in length. The tail consists of stout segments with terminal bulb containing pair of telson venom secreting salivary glands. It actively secretes venom at the time of sting by a sharp semi-curved stinger. The stinger is 2 to 4 mm in size and human skin thickness is 1.5 to 4 mm. Scorpion venom is rich in neurotoxin.

The black scorpion *Palmaneus gravimanus* is less poisonous (**Figure 2**). It is seen in Kerala, Vidharbha and Marathwada region of India. It is bigger in size as compared to red scorpion. It inflicts severe and excruciating painful sting. Its claws are broad and thick and strong while tail consists of thin segments.



Figure 2: Photograph showing a black scorpion (*Palmaneus gravimanus*).

Scorpion Venom

All scorpion species secrete venom. Venom is a mixture of various active substances; of these neurotoxins are the most important. Neurotoxins consist of different small sized proteins with sodium and potassium cations, which interfere with the neurotransmission. Venom action on neurotransmitter is rapid and fast. It contains peptide neurotoxin that opens the sodium channels (beta-toxin). The scorpion venom depolarises the cell membrane; in addition it also inhibits the deactivation of sodium channels (alpha-toxin). There is massive release of endogenous catecholamines in to the circulation due to delayed activation of sodium neuronal channel by the venom. The venom of the *M. tamulus* (Indian red scorpion), *Buthus martensii* (Chinese scorpion) and *Leiurus quinquestriatus* (yellow scorpion) causes autonomic storm by stimulating autonomic nervous system (ANS). Charybdotoxin another component of the venom inhibits the calcium dependent potassium channels; similarly iberiotoxin isolated from *M. tamulus* has similar action on potassium channels. Scorpion venom also contains serotonin, which may cause local pain at the site of the sting. The venom of Tityus species has a kallikrein inhibitor causing raised bradykinin levels. Venom of *Tityus serrulatus* from Trinidad is pancreotoxic, responsible for the development of acute pancreatitis.

CLINICAL MANIFESTATIONS

Clinical effects of the envenoming depend upon the species of scorpion and dose of venom injected at the time of sting. The severity of envenoming is related to age, size of scorpion and the season of the sting. High fatality rate is seen in children. The early or pre-monitory clinical manifestations characterised by vomiting, profuse sweating all over the body (**Figure 3**), priapism (**Figure 4**), cold extremities and mild tolerable pain. This pain becomes severe and excruciating when extremities become warm, a sign of recovery.

Clinical presentations can be divided into following two grades:

1. Local manifestations—severe local pain without systemic involvement
2. Systemic manifestations.



Figure 4: Priapism.

Local Manifestations

Local pain or severe excruciating pain is the only clinical manifestation seen in 35% of cases in a recent series. In 57%, 33% and 11% cases; lower extremities, upper extremities and the other part of the body are the sites of sting, respectively. Severe pain radiates along the corresponding dermatomes. Local oedema, urticaria, fasciculation and spasm of underlying muscles are seen at the site of sting due to persistent stimulation of pain conducting receptors and the liberated serotonin. Due to pain there is transient bradycardia, transient rise in blood pressure and mild sweating with warm extremities. Sudden tap at the site of sting induces severe pain and sudden withdrawal of the part called 'tap sign'. Patient continuously moves the stung part of body or holds it firmly to find a comfortable position.

Systemic Manifestations

Soon after scorpion sting the victim suffers from the autonomic storm and shows all pre-monitory signs and symptoms. The red scorpion venom is potent sodium channel activator and stimulates the ANS resulting in sudden pouring of catecholamines in the circulation. Both sympathetic and parasympathetic twigs are stimulated leading to 'autonomic storm', characterised by initial parasympathetic stimulation clinically detected in form of vomiting once or twice, profuse sweating all over the body (4 to 12 hours), ropy salivation (**Figure 5**), priapism (6 to 8 hours), mydriasis, bradycardia, hypotension, transient premature



Figure 3: Profuse sweating.



Figure 5: Ropy salivation.

ventricular beats. Sympathetic stimulation is characterised by propped eyes, puffy and anxious facies, oculogyric crisis, chest discomfort, perioral paraesthesias, at times tingling and numbness all over body and cool extremities. Skin over hands, feet, palm and sole look like a washer-man hands as they appears finely wrinkled and cold. Clinical manifestations at times are apparently diverse irrespective of similar pathology. In some patients there is minimal local pain on arrival but as the peripheral circulation improves with time and warming, they start experiencing excruciating pain. Severe transient muscle spasm may occur due to the loss of electrolytes.

Clinical manifestations depends upon the time elapsed between sting and hospitalisation and the treatment received at periphery. The major manifestation includes hypertensive crisis and pulmonary oedema (PE) which may be fatal if not treated timely.

Hypertension

Upto 45% of victims with systemic involvement were found to have hypertension when reported within 15 minutes to 11 hours after the sting. Children may present with agitated look, confusion, generalised convulsion, transient hemiplegia, oculogyric crisis, bilateral extensor plantar response, propped up eyes and a puffy face suggestive of hypertensive crisis. It may be difficult to measure accurate blood pressure in such children. Majority of these cases complained of headache, chest discomfort, suffocation, giddiness and paraesthesia.

Transient initial hypotension is due to hypovolaemia secondary to acetylcholine excess, it is further aggravated by hot climatic conditions in summer months of the tropics.

Pulmonary oedema

PE occurs in upto 30% severe scorpion sting cases with respiratory failure. PE develops within 30 minutes to maximum 36 hours. In up to 8% cases massive PE may be life-threatening. Clinically PE can be suspected when respiratory rate is >24 per minute, orthopnoea, intractable cough, low volume fast thready pulse, narrow pulse pressure, summation gallops, systolic murmur and moist basal rales, central cyanosis. Intractable cough with massive expectoration of blood mixed froth from the mouth and nostril with central cyanosis, hypo- or hyper-tension and loud death rattle sound heard are suggestive of massive PE.

Alpha receptors stimulation plays an important role in the pathogenesis of PE. Disseminated intravascular coagulation, coma, convulsion, miosis, mydriasis and hemiplegia, aphasia, cerebral infarction, transient bilateral cerebellar syndrome and subdural hematoma have been reported during pre-prazosin era. Acute renal failure due to scorpion sting is rare. However, ill-treated, delayed reporting of a case may result in death due to multi-system organ failure and acute respiratory distress syndrome.

After 20 to 30 hours of recovery from autonomic storm, the victim develops asymptomatic warm extremities, accompanied with bradycardia, hypotension with prolonged QTc interval (0.50 to 0.65 sec) on electrocardiogram (ECG). He may look exhausted. The depletion of tissue catecholamines following autonomic storm is the cause and patient usually recovers within 72 to 96 hours without any intervention. This phenomenon does not occur if victim receives scorpion antivenom and prazosin simultaneously.

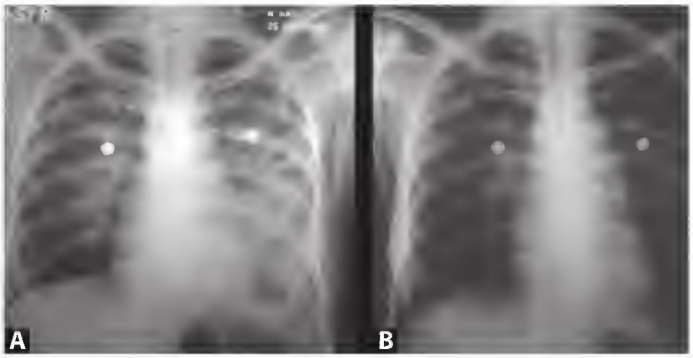
Fatality

Victim can die suddenly due to ventricular arrhythmias which usually occur within 15 to 30 minutes of sting. Many victims die from severe PE, brain haemorrhage and multi-system organ failure, if not treated properly and in time.

INVESTIGATIONS

Total leucocyte counts are raised to 11,000 to 26,000 due to venom induced interleukin-6 and tumour necrosis factor-α release. Cardiac CPK MB is raised. Reduction in serum amylase and serum calcium levels may be observed. There is raised serum glucose, potassium and reduction in insulin level.

Chest radiograph may reveal unilateral or bilateral batwing or patchy PE (**Figures 6A and B**). At times secondary respiratory infection in the form of consolidation is seen in a hospitalised patient recovering from PE. Mild cardiomegaly may be present. In author's series of cases of PE due to scorpion sting, the follow-up of more than 15 years did not show any cardiovascular abnormality.



Figures 6A and B: Chest radiographs showings (A) pulmonary oedema in a patient and (B) after recovery.

Electrocardiogram

ECG is one of the most important diagnostic and easily available investigation. Not a single victim with systemic involvement has normal ECG. Sinus bradycardia seen in early hypertensive cases with a heart rate of 42 to 60 per minute, ussually persisted for 3 to 4 hours. The other common findings are ventricular premature contraction, couplets, transient nonsustained ventricular tachycardia and rarely fatal ventricular arrhythmias (**Figure 7**). The sinus tachycardia, injury to conducting system in the form of left anterior hemiblock, bundle branch block, complete heart block and marked tented T waves may be the other common findings. The tall T waves may mimic acute myocardial infarction (AMI). Elevated ST segment with small Q wave is also often seen in lead 1 and AVL. Severe PE cases showed low voltage pattern with PQRST alterans with ST segment depression. Recovering victim's ECG showed large T wave with wide base and round top suggestive of delayed depolarisation with prolonged QTc, accompanied with asymptomatic bradycardia and hypotension. The severity of ECG changes did not correlate with clinical condition.

Echocardiography

Echocardiography shows poor global contractility 12 to 15 hours after sting with low ejection fraction, decreased systolic ventricular performance and mitral incompetence. Abnormal diastolic filling persisted for five days to four weeks. There is

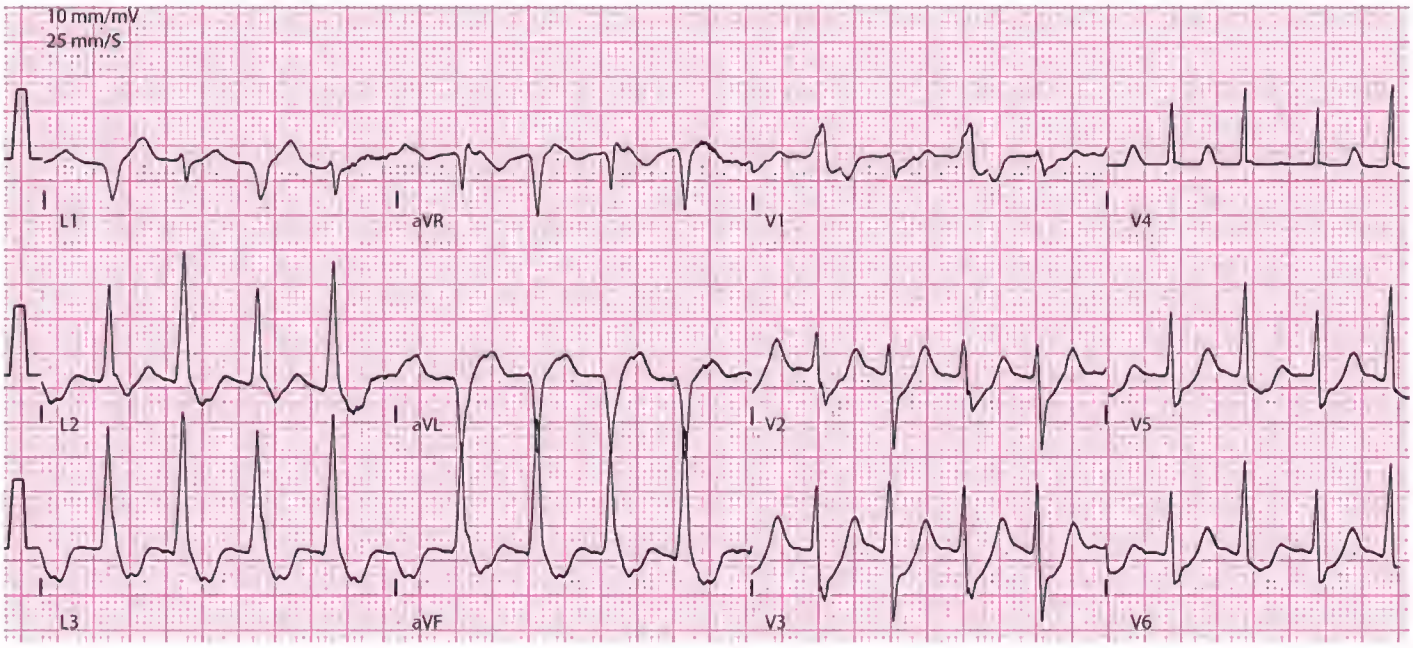


Figure 7: Electrocardiogram of a patient showing ventricular ectopics.

good echocardiographic correlation between clinical improvement and return of left ventricular function.

Mild envenomation causes severe vasoconstriction and hypertension; while predominant left ventricular dysfunction with normal systemic vascular resistance with PE is seen in severe scorpion sting. However, severe hypotension depends upon the fluid balance, while hypotension and shock with warm extremities occurs in terminal stage due to biventricular dysfunction and terminal vasodilation (warm shock).

MANAGEMENT

No scorpion sting should be taken as benign unless observed for 24 hours, irrespective of species involved. On the basis of pathophysiology, therapeutic effort should be directed against venom, the clinical manifestations of the over stimulated ANS and after effects of excessive catecholamine and correction of hypovolaemia. The incision at the sting site or tourniquet is not advisable and patients who come for medical care after 4 hours of sting and do not show signs of systemic envenomation can be treated symptomatically without prazosin or scorpion antivenom.

Local Envenomation

Mild pain can be abolished by application of ice packs over the site of sting. Severe excruciating pain can be transiently relieved by local anaesthesia (lignocaine without adrenaline). However, oral diazepam and nonsteroidal anti-inflammatory drugs (NSAIDs) with first initial dose of lignocaine can give prolonged relief from pain. At times, severe intolerable pain patient tossing in bed without signs of autonomic storm injectable opoid (pentazocin).

Systemic Envenomation

Dehydration leading to hypovolaemia is due to vomiting, excessive salivation and profuse sweating. It should be corrected by oral rehydration. Intravenous crystalloids or hydration by nasogastric tube may be necessary in a confused and agitated victim. Fluid deficit must be corrected since hypovolaemia is one of the proposed mechanisms of shock syndrome in scorpion sting. Electrolyte imbalance should also be corrected.

Prazosin

An α-1 adrenergic receptor blocker reduces preload, left ventricular impedance without causing tachycardia. It reverses the metabolic syndrome evoked due to excessive catecholamines release. Prazosin is a pharmacological and physiological antidote to scorpion venom actions. It also inhibits sympathetic outflow in CNS. It inhibits phosphodiesterase, thereby enhancing a cGMP level which is one of the mediators of nitric oxide synthesis. It enhances insulin secretion which is inhibited by venom. Thus, its pharmacological properties can antagonise the haemodynamic, hormonal and metabolic effects of scorpion venom (**Figure 8**). It can be administered orally in a dose of 250 to 500 µg/Kg in children and 500 to 1000 µg/kg

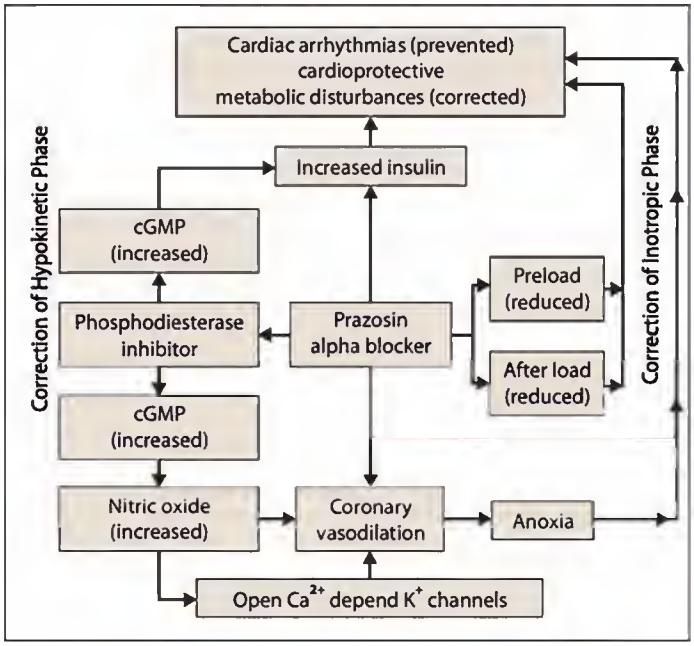


Figure 8: Flow chart showing effects of prazosin (venom antidote).

in adults and should be repeated every 3 hourly until the signs of clinical improvement appear or till dry and cool extremities persist. If the initial dose has been vomited, it should be repeated. Due care should be taken to avoid postural fall in blood pressure which is a known side-effect of prazosin (first dose phenomenon). Postural hypotension should be treated by lowered head position and intravenous fluids. Since the advent of prazosin the fatality due to severe scorpion sting has reduced to less than 1%. Prazosin is poor man's scorpion antivenom.

Scorpion antivenom

It is available for clinical use. Venom causes transient parasympathetic and prolonged sympathetic stimulation. Ongoing cholinergic phenomenon is suggestive of free circulating scorpion venom, which can be neutralised by antivenom, while sympathetic stimulation suggests after effects and fatality is due to sympathetic over activity. Scorpion antivenom is more effective if a victim is brought in a stage of acetylcholine excess that is early stages of scorpion sting. Early use of scorpion antivenom in addition to prazosin hastens the recovery. Total dose of antivenom required is 30 to 100 ml. However, scorpion antivenom is expensive and always in short supply. No test dose is required as there are high circulating catecholamines and anaphylaxis is very rare.

Supportive Management

PE is the most important cause of mortality and should be treated with propped up position, nasal oxygen, intravenous loop diuretics, oral prazosin. Massive PE may also require immediate oral nitroglycerin (NTG) spray to reduce the pulmonary congestion and intravenous NTG drip or if available sodium nitroprusside 4 to 5 µg/kg/minute. Blood pressure should be closely monitored and maintained at the level of systolic 80 to 90 mm Hg. Inotropic support with dopamine and dobutamine 5 to 15 mg/kg/minute is advocated for 36 to 48 hours in warm hypotensive shock patients. Unconscious patients with cardio-respiratory failure may also require invasive or non-invasive mechanical ventilatory support. A step-wise management of scorpion sting is shown in **Figure 9**.

Cardiac arrhythmias are many times self-limiting. Intravenous amiodarone should be used with caution as it may precipitate massive PE, marked bradycardia and cardiac arrest. Captopril, glucose insulin potassium drip and L-carnitine have also been tried to alleviate the venom effects on the heart but does not approved indication.

Atropine, steroids, antihistamines, beta-blockers, calcium channel blockers, excessive diuretics, adrenalines and narcotics are to be avoided as these do more harm than good in scorpion envenoming.

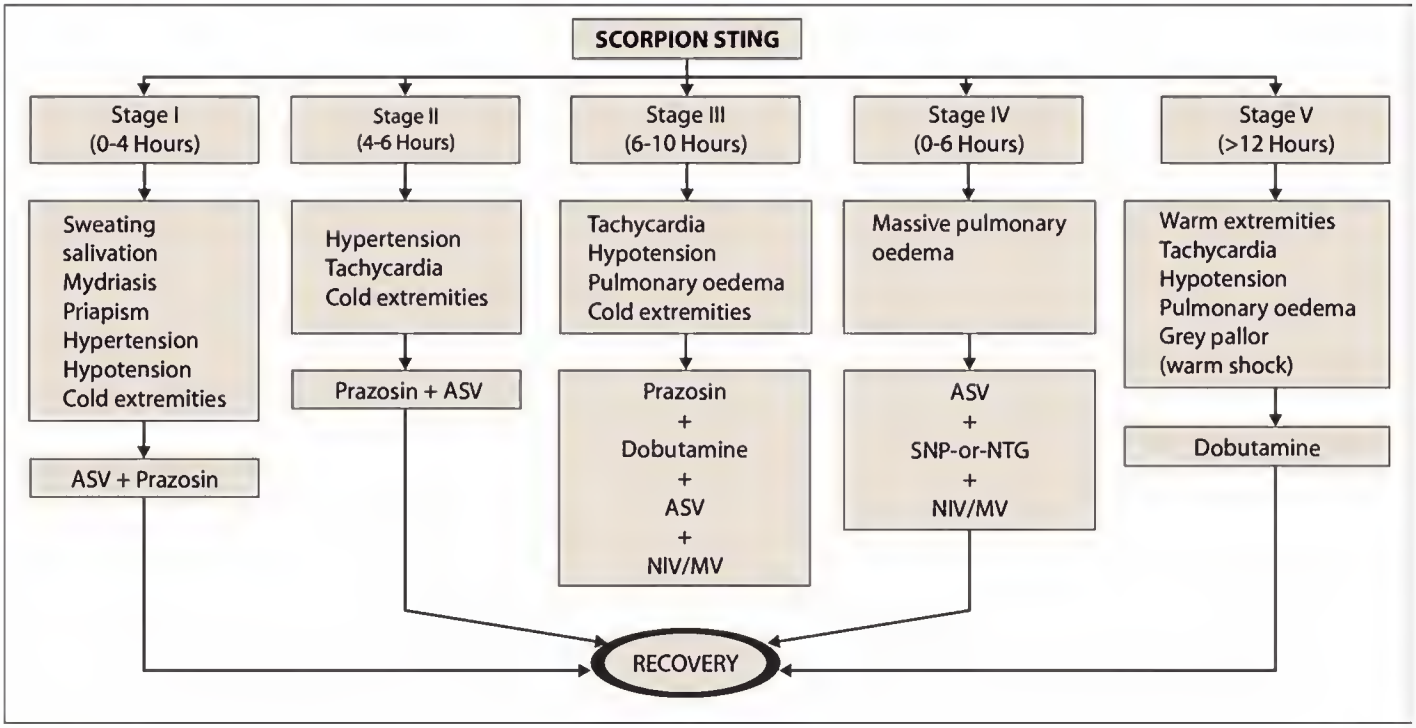


Figure 9: Management of scorpion sting.

ASV = Anti-scorpion venom; SNP = Sodium nitroprusside; NTG = Nitroglycerin; NIV = Non-invasive ventilation; MV = Mechanical ventilation

PREVENTION

Scorpions are killed by organophosphorous pesticides. A false ceiling of plastic sheet should be put under the roof of hut to prevent scorpions falling in bed from loose tiles of roof. Shoes and clothes should be checked before wearing. Shoes should be packed with paper or cloth so as to prevent the entry of scorpion in night. Hand gloves made of thick rubber should be worn while harvesting fire wood, dry cow dung, lifting paddy, *jowar* (sorghum) and sugar cane husk. Children should not be allowed to go outside in early darkness without shoes. Simple sandal or slipper did not prevent the sting. One should not put hand blindly in crevices, doors or old storage material during night hours and bedding or cot should kept at distance from mud house wall and one should not backrest on mud wall.

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26.10 Fluorosis

D Raja Reddy

INTRODUCTION

Fluorine being electronegative and reactive of all elements does not occur in free form in the nature. This element combines directly with most elements and indirectly with few to form fluorides, which are the 13th commonest element in earth's crust. Fluorides being ubiquitous in nature are present in nearly all foods and natural waters. The relationship between optimum fluoride intake and decreased incidence of dental caries and osteoporosis has been recognised. Endemic skeletal fluorosis is a disease caused by excessive ingestion of fluorides through water, food or both. The upper limit of optimum fluoride level in drinking water for a tropical country like India is 0.5 ppm. The upper limit of safe total intake of fluoride from food and water per day for an adult is 6 mg. Biological effects of fluoride intoxication are related to the total amount of fluoride ingested whatever the source be it food, water, beverages or all.

INCIDENCE

First ever cases of endemic skeletal fluorosis in the world and its neurological manifestations were recorded from Podili, Darsi and Kanigiri areas of Prakasam district in Andhra Pradesh in 1937. Subsequently, the cases of fluorosis were reported from other regions of Andhra Pradesh and also from other parts of India and the world. It is now estimated that 66 million people are living in endemic areas of fluorosis, which are spread over 275 districts out of 619 in the country and these are located in 20 states and union territories, such as Andhra Pradesh, Assam, Bihar, Chhattisgarh, Delhi, Gujarat, Haryana, Jharkhand, Karnataka, Kerala, Jammu and Kashmir, Madhya Pradesh, Maharashtra, Orissa, Punjab, Rajasthan, Uttar Pradesh, Uttarakhand, Tamil Nadu and West Bengal. The populations in endemic areas are at risk of developing skeletal fluorosis and 6 million people are crippled because of it. Hence, skeletal fluorosis is a major public health problem not only in India but also in 25 odd countries.

EPIDEMIOLOGICAL STUDIES

Ten million of people living around the world are affected by fluorosis, and hence, factors governing the development of chronic fluoride intoxication need to be understood so that effective measures can be instituted to contain it. The factors which govern the causation of fluorosis are the following:

1. High levels of fluoride in drinking water supplies and foodstuffs in the endemic areas. Fluoride levels in natural waters in India vary from 0.2 ppm to 42.5 ppm. Fluorosis is predominantly a rural problem because 90% of rural water sources are ground water whereas all major cities get their water from perennial rivers, which have optimum levels of fluoride. Fifty per cent of ground water sources in our country have excess fluoride and the crops cultivated by water having high amounts of fluoride leads to high content of fluoride in cereals and vegetables in these areas. Hence, significant amounts of fluorides also come from food in endemic regions. The total daily intake of fluorides from water and food in three villages of high endemic areas of Nalgonda varied from 54.66 mg to 75.76 mg.
2. Tropical weather and hard manual labour activity increases the intake of water and fluoride.
3. Diets deficient in calcium, magnesium and vitamin C aggravate fluoride toxicity. Optimum intake of calcium in the diet reduces the amount of fluoride absorbed from the gut. Magnesium has a peculiar relationship with fluoride and its optimum intake helps in elimination of fluoride from the body. Vitamin C is beneficial in some way in reducing fluoride toxicity. Diets deficient in calories and calcium intake increases the incidence of skeletal fluorosis in endemic areas. The National Nutrition Monitoring Bureau and National Family Health survey reports from India reveal gross malnutrition of rural population and also their lower intake of calcium especially among growing children, which may explain the high incidence of fluorosis in rural areas of our country.
4. Renal disease aggravates the incidence of fluorosis by the increased deposition of fluoride in the bones since diseased kidneys cannot handle fluoride excretion from the body. This may explain the severe forms of fluorosis in Prakasam district even though drinking water contains mostly 1 ppm to 3 ppm of fluoride and it rarely exceeds 6 ppm and the majority of cases investigated had kidney disease.
5. Presence of abnormal amounts of certain trace elements, such as strontium, arsenic, silica, uranium, chromium, etc. in drinking water supplies and foodstuffs also affect fluoride metabolism. Ninety-four drinking water samples from endemic areas in Andhra Pradesh were investigated for their content of fluoride and strontium. Fluoride levels ranged between 0.1 ppm and 9.5 ppm with a mean fluoride content of 2.1 ppm whereas strontium levels varied between 4.9 ppb and 9931.7 ppb with a mean of 1591.2 ppb. Strontium is a bone seeking element akin to calcium and fluoride which causes osteogenesis and bone changes similar to fluoride and now is the preferred drug for the treatment of post-menopausal osteoporosis. Arsenic is known to aggravate fluoride toxicity in experimental studies and this element may play a role in fluorosis in eastern parts of our country where arsenic is a known hazard. Silica, uranium and chromium are nephrotoxic if taken in abnormal amounts through water and these elements may be responsible for the high incidence of kidney disease in some endemic areas of India such as Prakasam.

AETIOPATHOGENESIS

In fluorosis, there is an overall increase in bone mass and calcification and ossification of ligaments and inter-osseous

fasciae along with periosteal new bone formation and development of exostoses on long bones and osteophytes on the spine. These changes in skeleton underlie the clinical manifestations of fluorosis.

CLINICAL FEATURES

Chronic fluoride intoxication presents an extraordinary degree of uniformity in its clinical manifestations. It occurs in humans as dental and skeletal fluorosis, since 96% to 99% of fluoride retained in the body combines with mineralised bones because of its affinity to calcium phosphate moiety, and hence, skeleton suffers. Dental and skeletal stages are separated by a prolonged, relatively symptom-free interval during which the skeleton does not stop accumulating fluoride. In its advanced stages, skeletal fluorosis causes crippling deformities and neurological complications.

Dental Fluorosis

Dental fluorosis mainly involves enamel but severe intoxication may affect dentine as well as pulp. Enamel fluorosis occurs when fluoride concentrations in or in the vicinity of the forming enamel are excessive during its pre-eruptive development. Mottling of teeth is one of the earliest and most easily recognisable features noticed in the first decade of life (**Figure 1**). Both sexes are equally affected. It is the permanent teeth that are affected and they lose their normal creamy white translucent colour and become rough, opaque and chalky white. Pitting and chipping are other marks of fluorosis. Brown, yellow or black pigment gets deposited on the defective enamel and once established tends to remain there permanently. Incidence of dental fluorosis in endemic areas exhibits a linear relationship to the fluoride content of water but it may also vary with other factors. Dental fluorosis does not obviously occur, when there has been no exposure to excess fluoride in the first decade of life.



Figure 1: Characteristic mottling of the teeth in dental fluorosis. Mottling is most conspicuous on the upper incisor teeth.

Pre-Skeletal Stage

The duration of this stage may vary with the amount of daily fluoride ingested. Reportedly, it ranges from 10 years to 30 years or even longer in endemic areas. It is usually free of any signs or symptoms in its early stages in endemic regions. However, various reports from Europe and America suggest that there would be symptoms corresponding to gastro-intestinal, musculoskeletal, respiratory and visceral systems during this stage. The majority of these visceral symptoms may be due to allergy to fluoride in susceptible individuals or the effect of fluoride on the various target organs and these are nonspecific.

Skeletal Fluorosis

Early in the development of fluorotic changes in the skeleton, the patients often complain of a vague discomfort and paraesthesia in the limbs and the trunk. Pain and stiffness in the back appear next, especially in the lumbar region, followed by dorsal and cervical spines. Restriction of the spine movements is the earliest clinical sign of skeletal fluorosis. The stiffness increases steadily until the entire spine becomes one continuous column of bone manifesting a condition referred to as 'poker back' (**Figure 2**). When the condition becomes severe and chronic, pathology spreads from axial skeleton to various joints in the limbs owing to the involvement of the joint capsules, the related ligaments, tendinous attachments to the bones and interosseous membranes. The involvement of the ribs gradually reduces the movement of the chest during breathing, which finally leads to restrictive lung disease. With the increasing immobilisation of the joints due to contractions, flexion deformities may develop at hips, knees and other joints, which make the patient bed-ridden (**Figure 3**).

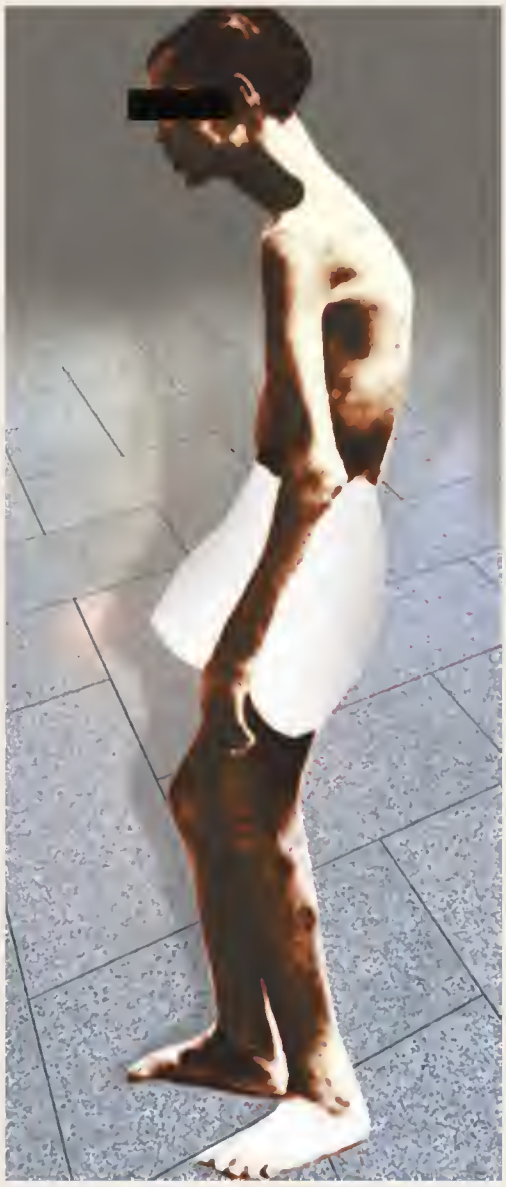


Figure 2: Skeletal fluorosis manifesting with restriction of spine movements, which ultimately leads to 'poker back'.



Figure 3: Crippling stage of skeletal fluorosis manifesting with neurological deficits and joint changes.

The stage at which skeletal fluorosis becomes crippling usually occurs between 30 and 50 years of age in the endemic regions. Newcomers to a hyperendemic region may sometimes develop symptoms of skeletal involvement within 4 years of their arrival. Men suffer more than women from severe affects of the disease presumably because their work usually more strenuous than that of women. In regions with very high fluoride content, the disease may affect younger age groups including children. The longer the exposure to fluoride higher will be its incidence.

Endemic Genu Valgum

Deformities occur most notably in weight-bearing lower limbs in children poorly nourished with low calcium intake in endemic areas. There is increased calcium turnover in the cases of endemic skeletal fluorosis. Diets poor in calcium provoke secondary hyperparathyroidism. This, in turn, leads to osteoporosis and deformities of weight-bearing lower limb bones (**Figure 4**).

Neurological Manifestations of Skeletal Fluorosis

The neurological sequelae in skeletal fluorosis manifesting usually as radiculomyelopathy arise principally because of the mechanical compression of the spinal cord and nerve roots brought about by osteophytosis and sclerosis of the vertebral column. But the neural toxicity attributable to fluorides is yet to be established.

Neurological complications arise at a late stage of the disease in about a tenth of the total number of skeletal fluorosis cases.



Figure 4: Gross deformities of lower limbs in the residents of Yellareddyguda of Nalgonda, India, which is high endemic village for fluorosis.

But there have been few reports of fluorosis with neurological complications from countries other than India.

The patients suffering from neurological manifestations varied in age from 20 to 70 years and, in the case of younger age groups, these complications may be traced to higher levels of daily fluoride ingestion. The men were reported to have been affected more frequently than the women. Similar findings were reported by other investigators from India, except for one lone report from Rajasthan where females slightly predominated over males and also developed fluorosis earlier than men.

It is the cervical cord rather than the dorsal cord that is commonly affected by fluorosis although, lumbar spine is usually the first to exhibit skeletal changes caused by fluorosis, compression of *cauda equina* rarely occurs because its roots are so easily accommodated that by the time these are pressed upon, other parts of the spinal cord would have been affected. Although the disease develops slowly but relentlessly, the neurological deficits may sometimes be precipitated by a minor trauma. Such cases present a wide spectrum of neurological deficits, which may be found manifesting either the lower motor neuron or the upper motor neuron defects or both, which is much more common. These may be found along with those caused by skeletal fluorosis resulting in restriction of spine movements. It is to be noted that in fluorosis abnormalities of higher functions of cerebrum or cranial nerve palsies except eighth nerve are rarely encountered.

Peripheral Neuropathies

Exostoses, which mainly develop around the knee, elbow and ankle, may press upon the median, ulnar or lateral popliteal nerves. Even meralgia paresthetica has been reported to occur in fluorosis. Fluorotic patients may also manifest entrapment syndromes involving other peripheral nerves.

DIAGNOSIS

Urinary, Serum and Bone Fluoride Estimations

Urinary fluoride levels are the best indicators of fluoride intake. Since fluoride excretion is not constant throughout the day, 24-hour samples of urine are more reliable than random or morning samples. There is a linear relationship between urinary fluoride levels and fluoride intake. The urinary and serum levels of fluoride in normal and fluorotic cases are listed in **Table 1** below.

Table 1: Serum and Urine Fluoride Levels in Healthy Adults and Patients of Fluorosis

Group	Number	Range	Mean
Serum fluoride levels		**mg/L/ppm**	**mg/L/ppm**
Healthy adults	500	0.03 to 0.13	0.08
Patients of fluorosis	17	0.04 to 0.28	0.16
Urine fluoride levels		**24-hr/mg/ppm**	**mg/L/ppm**
Healthy adults	60	0.38 to 1.82	0.88
Patients of fluorosis	17	0.68 to 7.80	3.28

Bone fluoride content measures the extent of bone fluoride retention and is a useful complement of bone histological studies for the diagnosis of skeletal fluorosis. In skeletal fluorosis, fluoride content varies between 6000 and 8400 ppm in bone ash, normal fluoride content ranges between 500 and 1000 ppm or mg/kg.

Radionuclide Bone Scan

Technetium labelled methylene diphosphonate (99mTc-MDP) bone scanning measures skeletal metabolism and in skeletal fluorosis shows mostly a super scan appearance and in some cases joints abnormalities (**Figure 5**).

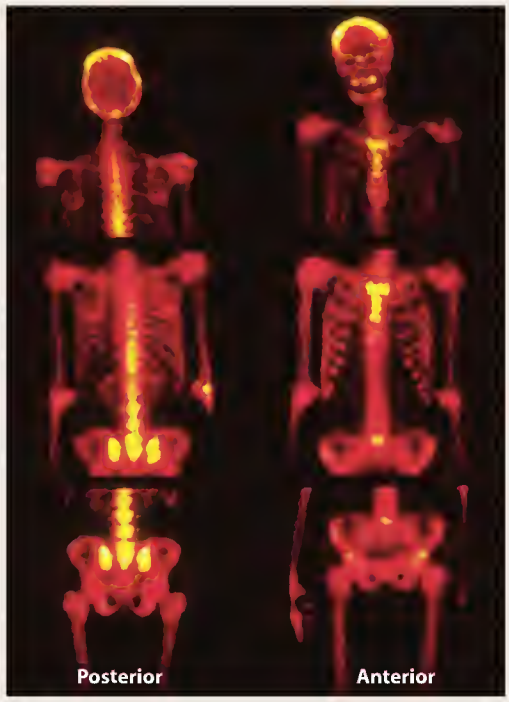


Figure 5: Technetium-99m scans of skeleton in an individual with skeletal fluorosis suggesting an appearance of 'super scan'. There is high bone turnover in endemic skeletal fluorosis with increased tracer uptake in axial and appendicular skeleton. There is reduced soft tissue uptake, absent renal images and 'tie sign' in the sternum. Increased metabolic turnover of bone, impaired collagen synthesis and increased avidity for calcium are the features of fluoride toxicity.

Radiology

In fluorosis, radiological findings closely parallel the pathological changes. In adults, the radiological findings can be categorised into three stages:

Stage I

Findings mainly confined to the axial skeleton, trabeculae appear rough and bone appears ground glass.

Stage II

Thick primary trabeculae merge with sclerotic secondary trabeculae to make bone homogenously dense, bone contours become uneven, calcification of paraspinous, sacrospinous and sacrotuberous ligaments.

Stage III

Axial skeletal bones demonstrate the typical radiological features. Calcification is marked at the insertion of muscles and tendons. Ossification of interosseous membranes of forearm bones is diagnostic sign of fluorosis (**Figure 6**).



Figure 6: Radiograph of forearm bones of a patient with fluorosis. The forearm bones are dense with calcification of a portion of interosseous membrane. Prominent bony tuberosities and musculotendinous attachments are noteworthy.

Osteosclerosis is well known effect of chronic fluoride intoxication, which can also manifest with osteoporosis and osteomalacia in endemic areas with poor nutrition. Hence, the radiological changes are varied and these seem to be dependent upon calcium intake by the individuals.

Imaging

Computed tomography (CT) is the best imaging modality for visualisation of bone pathology and provides more details than plain radiographs. The CT is better to visualise the direction of the osteophytes, a finding which may help in surgical planning. Spinal canal and root canal stenosis are also better appreciated with CT. The calcified ligaments are visualised with much more clarity and earlier than by plain radiograph, so are the indentations of the epidural space and the alterations in the spinal canal. By reconstruction, CT provides exact dimensions of the ossified intra-spinal ligaments, such as posterior longitudinal ligament and yellow ligaments.

Magnetic resonance imaging (MRI) being non-invasive obviates the difficulties in performing myelography and also delineates soft tissue structures and changes in the spinal cord. It is worthwhile to image the entire spine that may demonstrate

incidental pathological lesions peculiar to fluorosis. Fluorotic vertebrae are hypointense in both T1- and T2-weighted images and these are diagnostic (**Figure 7**).



Figure 7: Magnetic resonance imaging of dorsal spine. T1 (left) and T2 (right) weighted images demonstrating hypointense signal of the vertebral bodies suggestive of sclerosis in skeletal fluorosis, which is diagnostic. Note the cord compression at multiple levels from calcified ligamentum flavum.

DIFFERENTIAL DIAGNOSIS

In endemic areas, the diagnosis of dental and skeletal fluorosis does not present much of a problem. In industries, where fluoride toxicity is a known hazard, skeletal fluorosis marked by restriction of spine movements can easily be diagnosed. In early stages of skeletal fluorosis patients complain of arthritic symptoms, which have to be differentiated from other types of arthritis. Diseases that are associated with osteosclerosis also need to be considered in the differential diagnosis. In children and young adults, genu valgum and other deformities have to be distinguished from those associated with rickets and sometimes with osteodystrophies. When sclerosis of the vertebral column is not marked, calcification of the interosseous membrane of forearm, a radiographic sign of fluorosis, should suggest the diagnosis of fluorosis.

Endemic Fluorosis

In India over 50% of ground water sources have excess of fluoride and affect more than 150,000 villages. Potable water supply with permissible levels of fluoride though desirable cannot obviously be made available to the vast number of people neither can they be shifted from their area of domicile. Thus, there is a rationale to press into service water-purifying or defluoridation plants in those areas. Defluoridation plants are based on *Nalgonda method* of lime and alum and domestic units were based on filtration of fluoride-rich water with PAC granules, which are activated alumina. Aluminum has been incriminated in the causation of two neuro-degenerative diseases, namely Parkinsonism and amyotrophic lateral sclerosis. Defluoridation methods are expensive and difficult to maintain and they also increase aluminum levels of filtered water. Hence, these methods are not preferred. Nutrition appears to play a crucial role in the incidence and severity of fluorosis and hence a balanced diet having adequate calcium, magnesium and vitamin C should be promoted to reduce the toxicity of fluoride.

MEDICAL TREATMENT

Patients with skeletal fluorosis, when kept off fluoride intake, register a negative fluoride balance while continuing to excrete large amounts of fluorides for years. It is obvious that excretion of fluorides mobilised from the skeleton through urine and faeces is a very slow and prolonged process lasting for many months to even years. Hence, this method is not practicable.

Studies, both *in vitro* and *in vivo*, have been done to study the effect of various drugs on the binding of fluoride and also on the excretion of fluoride. Serpentine was used to increase fluoride excretion in human fluorosis with some success. Serpentine, a naturally occurring mineral, is chemically a magnesium meta silicate and has enormous capacity to absorb fluoride at a wide range of pH. There is a need to do long-term studies to see the effectiveness of these various agents in human fluorosis.

SURGERY IN SKELETAL FLUOROSIS

Neurological manifestations of fluorosis are mainly mechanical in nature. However, surgery is obviously of little help in the alleviation of neurological deficits in view of the extensive prevalence of the disease. Surgical decompression is only possible in such of those early cases in which the compression is confined to a limited segment of the vertebral column, but managing even these patients bristles with problems because of rigidity of spine and restrictive lung disease. However, in recent years with accurate localisation of the compression, its extent in both vertical and axial planes by imaging, fiberoptic intubation, better illumination and instrumentation during surgery for drilling and removal hard fluorotic bone and postoperative ventilatory support made surgery safe and effective in alleviation of mechanical compression in fluorosis. The results of surgery are better in the case of cervical and lumbar areas and poor in the case of dorsal cord compressions. It is also not known what happens to all those patients after surgery, when they go back to their endemic areas and again start to consume high-fluoride-containing water and food.

PREVENTION OF FLUOROSIS

The best approach to tackle this public health menace will be prevention since no cure is possible once the disease sets in.

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26.11 Lathyrism

UK Misra, J Kalita

Lathyrism is a neurodegenerative disease characterised by spastic paraplegia following excessive consumption of the legume *Lathyrus sativus*. *Lathyrus sativus* forms the staple food of poor villagers, especially during the period of food scarcity following a flood or famine. Lathyrism has been reported from Asia, Africa and Europe. However, in recent years, it has only been reported from developing countries such as Bangladesh, Ethiopia, India and Nepal. In India, epidemics have been reported from Maharashtra, Madhya Pradesh (Satna and Rewa), Bihar, West Bengal and Uttar Pradesh (Unnao) with an incidence between 0.3% and 2.5%.

CURRENT STATUS OF LATHYRISM IN INDIA

Currently, lathyrism is not a major health problem in India, and hardly any patient have been reported after the last epidemic of lathyrism in Unnao (UP) in 1984. This is because of the ban on the trade of *L. sativus* seeds in India.

PATHOPHYSIOLOGY

L. sativus is known to contain a number of toxic amino acids. Intraperitoneal injection of an alcoholic extract of *L. sativus* produces opisthotonus and leg weakness in chicks. Two free amino acids, β-N-oxalylamino-L alanine (BOAA) and β diaminopropionic acid have been found to be toxic in animal models, such as rats, mice and monkeys. *L. sativus* treated monkeys also had prolongation of central motor conduction time. These results suggest pyramidal tract dysfunction following *L. sativus* or BOAA intoxication. The only autopsy report including the brain is of a patient who developed lathyrism 31 years prior to death. On brain histology, loss of giant Betz cells and shrinkage of pyramidal neurons in the pre-central gyrus were observed. The other studies reported spinal cord autopsy findings which include distal and symmetrical degeneration of lateral and central corticospinal tracts associated with degeneration of spinocerebellar tracts and tractus gracilis. In another patient, who developed lathyrism 31 years ago, some changes in anterior horn cells with swelling, Hirano bodies and dispersion of Nissl bodies were seen. In the absence of precise neuropathological studies including motor areas, it is not clear whether lathyrism primarily originates in the neurons or is a central distal axonopathy involving the pyramidal tracts. BOAA excitotoxic hypothesis suggests that molecular pathology of lathyrism could start at the neuronal level in motor cortex with secondary degeneration of pyramidal fibres in spinal cord. BOAA also produces seizures in experimental animals because it is a potent glutamate agonist. Glutamate also results in neuronal death when post-synaptic glutamate receptors are over stimulated for a long period. The concentration of BOAA in lathyrus plants varies from 0.1% to 1%. It has been suggested that BOAA could selectively inhibit the brain mitochondrial enzyme NADH dehydrogenase. In monkeys, pyramidal tract dysfunction has been produced by feeding *L. sativus* for 3 to 10 months or BOAA for 3 months. The affected monkeys develop tremors, myoclonic jerks and increased tone in the legs. Another non-protein amino acid of *L. sativus*, β-isoxazoline alanine (BIA) is also neurotoxic to neurons in culture, but to a lesser extent than BOAA. BOAA toxicity is more pronounced in younger animals compared to the older ones. Brain lesions are mainly observed in areas where blood brain barrier is normally absent.

CLINICAL FEATURES

Lathyrism affects adolescents and young adults who are otherwise healthy. Females, however, are less commonly affected. Lathyrism can present in 3 ways.

Sudden onset of leg weakness on getting up from sleep is the most common presentation; subacute onset of walking difficulty occurs in some patients or insidious progression of spastic paraplegia occurs rarely.

Majority of patients complain of leg stiffness, weakness and heaviness prior to the onset of paraparesis. Some patients may also complain of cramps and calf pain, unsteadiness, leg paraesthesia and urgency of micturition. On neurological examination, the patients have spastic paraplegia, scissoring gait, exaggerated knee and ankle reflexes and extensor plantar response. Crossed adductor reflex and patellar and ankle clonus may also be present. Cranial nerves, cerebellar functions and sensations are normal. Upper limbs are also normal. Associated peripheral neuropathy has been reported from Bangladesh and lower motor neuron signs from Israel, but these are not found in our experience.

The disability in lathyrism is graded according to the need for help for walking. Most patients walk slowly without the need of a stick (no stick stage), while others need one or two sticks (one or two stick stage) and those crawling on hands and knees (Crawler stage) (**Figure 1**).

Non-invasive transcranial motor stimulation studies have been employed to evaluate the conduction in motor pathways. Central motor conduction time to lower limbs in lathyrism reveals mild to moderate slowing in majority of patients. Occasionally, central motor conduction time may be normal or even markedly prolonged. These results are consistent with the wide spectrum of involvement of motor pathways. Somatosensory evoked potentials are normal which is consistent with normal sensations in lathyrism.

DIAGNOSIS

The diagnosis of lathyrism is based on the typical clinical findings and history of consumption of *L. sativus*. There are no specific laboratory tests. The patients of lathyrism should



Figure 1: Different stages of clinical severity of lathyrism.

be differentiated from primary lateral sclerosis, hereditary spastic paraplegia, nutritional myelopathy, early spinal cord compression, HTLV myelopathy and multiple sclerosis, especially in an endemic area.

TREATMENT

Treatment includes elimination of *L. sativus* from the diet in all cases. This may result in improvement in some patients, but in majority, the spasticity persists. Symptomatic relief may be obtained by antispasticity drugs such as baclofen, tizanidine and diazepam. Physiotherapy may also help. Botulinum toxin has been tried, but cost limits its use.

For preventing lathyrism, cultivation and trade of *L. sativus* should be discouraged and alternative cultivation such as rice and wheat should be encouraged. Giving food aid of grains and pulses will stop the people from consuming *L. sativus*. The toxicity of *L. sativus* can be reduced by soaking it for 24 hours and repeated changing of the soaking water.

RECOMMENDED READINGS

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26.12 Epidemic Dropsy

Navneet Sharma

DEFINITION AND EPIDEMIOLOGY

Dropsy (from Hydropsy) is the description referring to a collection of serous fluid in all or any of the body's cavities or in the meshes of its tissue. Epidemic dropsy is the condition characterised by extensive progressive oedema of the legs caused by the ingestion of mustard oil (cooking media) derived from mustard seeds (*Sinapis albae*) contaminated with seeds of the plant *Argemone mexicana*. *Argemone mexicana* normally grows as a weed in many parts of India, the seeds of which resemble brown mustard seeds that contaminate the mustard oil with toxic alkaloids of the benzophenanthridine group.

The first record of epidemic dropsy was from the state of Calcutta in the year 1877 and since then numerous outbreaks of this condition have occurred in different parts of India. In the latest Delhi epidemic in 1999, there were 60 casualties and 3,000 victims had to be hospitalised. In 2002, another outbreak of epidemic dropsy occurred in Uttar Pradesh affecting 21 individuals.

AETIOPATHOGENESIS AND CLINICAL FEATURES

For clinical features of epidemic dropsy to develop, the estimated level of contamination of edible mustard oil with *Argemone* oil is ~0.5% to 1%. The route of exposure, aetiopathogenesis and clinical features are shown in **Figure 1**. The toxic alkaloids in *Argemone* oil cause an increase in permeability of blood vessels in different organs, i.e. heart, skin, liver, lungs, kidneys and eyes. Ocular manifestations occur in 12% cases and gastrointestinal symptoms in 52% to 84% of cases. Death has been reported due to cardiac and respiratory failure in 5% of cases. In 25% cases, oedema persists beyond 2 months and in 10% beyond 5 months.

LABORATORY ABNORMALITIES

Anaemia, leucopaenia and thrombocytopaenia have been reported. Anaemia is often normocytic normochromic. Mild impairment of renal and hepatic functions is present. Hypoalbuminaemia is a universal finding and combined respiratory alkalosis and metabolic acidosis is also present along with restrictive pulmonary ventilation defects. The chest radiograph may reveal pleural effusion, pulmonary oedema or pneumonia. Echocardiography is characteristically normal suggesting noncardiogenic pulmonary oedema as the cause for breathlessness.

DIAGNOSIS

It is usually straightforward when a history of contaminated oil use is forthcoming. In sporadic cases, a high index of suspicion is necessary for the diagnosis. The nitric acid test can be done easily at bedside on oil samples to detect contamination, but quantitative demonstration of alkaloids requires HPLC (detects 0.001% contamination by *Argemone* oil).

TREATMENT

Patients can present to the emergency department with pulmonary oedema. General measures recommended are: bed

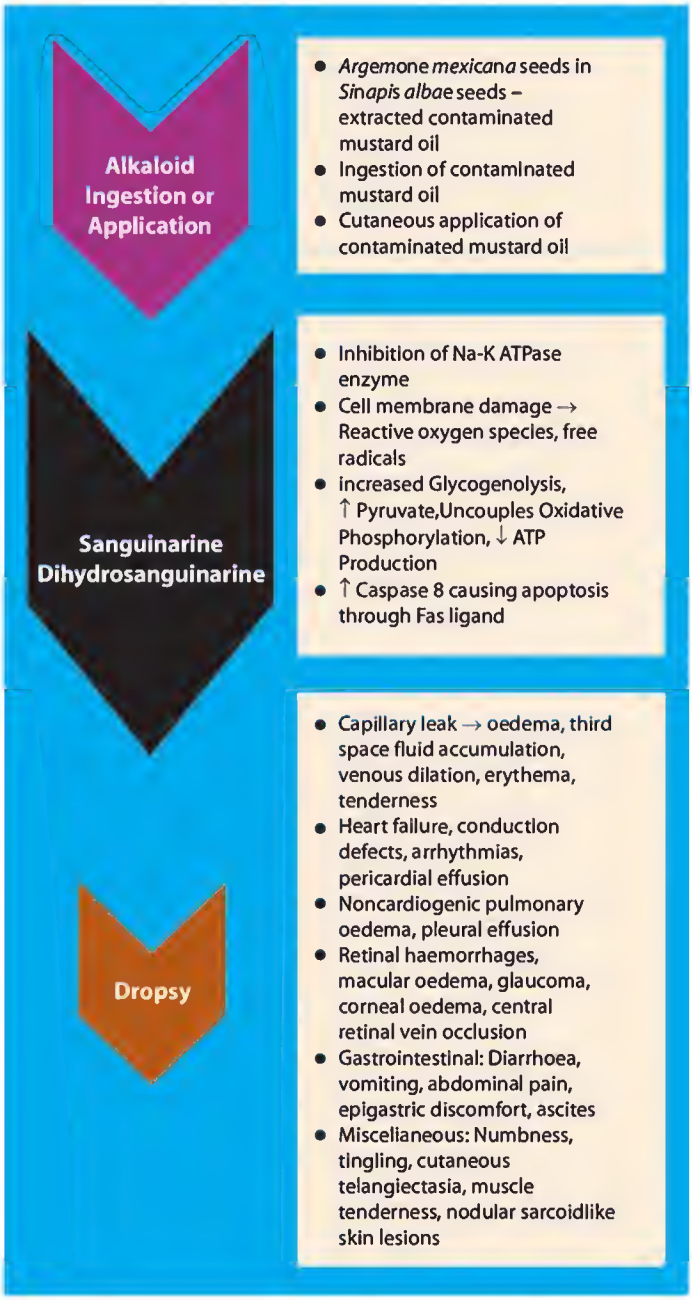


Figure 1: The aetiopathogenesis and clinical features of epidemic dropsy.

rest, oxygen inhalation, salt and fluid restriction, inotropic agents for hypotension and diuretics. For type 1 respiratory failure, non-invasive ventilation (NIV) is a promising treatment modality. Antioxidants like vitamin E and C and vitamin B complex although used have little evidence to support their use. Although, ACE-inhibitors, ARB's and aldosterone antagonists can be used for managing congestive heart failure (CHF), yet, their use has not been validated. Glaucoma is managed medically, but may need surgical intervention and follow-up with opthalmological services.

PREVENTIVE MEASURES

Mustard oil that is marketed should be subjected to rigid quality control measures to detect contamination and if found so, withdrawl from the markets.

RECOMMENDED READINGS

1. Khilnani GC, Trikha I, Malhotra OP, Prabhakaran D, Pande JN. Pulmonary Functions in patients with epidemic dropsy. *Indian J Chest Dis Allied Sci* 2003; 45: 25-9.
2. Rangan C, Barceloux DG. Food contamination. *Dis Month* 2009; 55: 263-91.

26.13 Heavy Metal Poisoning

Praveen Aggarwal

INTRODUCTION

Patients with heavy metal poisoning generally present with multi-system involvement producing gastrointestinal, cardiovascular, neurologic and renal effects. The most common heavy metals and their compounds producing poisoning are mercury, lead, arsenic, antimony, cadmium, bismuth and thallium. Of these, poisoning with mercury, lead, arsenic, copper and thallium are of great concern to the general public and the medical community. The present Chapter will deal with the toxicology of these heavy metals.

ARSENIC

Arsenic is widespread geologically and exists in elemental, organic and inorganic (trivalent and pentavalent) forms with each of them having different toxicities. Arsine gas is the most toxic, followed by trivalent arsenic compounds (e.g. sodium arsenite, arsenic trioxide, potassium arsenite). Pentavalent inorganic arsenicals (e.g. lead arsenate, arsenic acid, calcium arsenate) are less soluble and less toxic. Elemental arsenic is considered to be nontoxic. Most of the organic arsenic compounds (melarsoprol, arsanilic acid) are less toxic than inorganic arsenic salts. Seafood contains arsenic in the form of organoarsenicals (e.g. arsenocholine and arsenobetaine), which are nontoxic.

Sources of Exposure

Arsenic is used in the manufacture of pesticides and rodenticides in the agricultural industry. It is widely used in timber preservatives, termicides, herbicides, glass production, specialised alloys and pigments. In many parts of the world, arsenic is a natural contaminant of ground waters. Sodium arsenate is used as an ant-killer. Fowler's solution, which was used in the treatment of psoriasis, contains 1% potassium arsenate. Melarsoprol is used to treat trypanosomiasis. Arsenic trioxide is occasionally used in the treatment of relapsed acute promyelocytic leukaemia. Arsenic toxicity can occur when arsenic-containing solutions are exposed to acids.

Arsenic Poisoning in India

A number of cases of chronic arsenic poisoning due to drinking of contaminated underground water have been reported from West Bengal. The maximum permissible limit recommended in the absence of an alternative source of potable water in the affected areas by the World Health Organization (WHO) in groundwater is 10 µg/L. However, in India, the accepted level is below 50 µg/L. The levels are higher than 50 µg/L in several districts of West Bengal. More than 40 million people live in the arsenic-affected region of the state. It is suspected that about 5 million people drink arsenic-contaminated water in West Bengal. Recent reports indicate the propensity of arsenicosis affecting other states in the Ganga/Brahmaputra plains too. Northeastern states; Bihar, Jharkhand, Uttar Pradesh, Andhra Pradesh and Chhattisgarh are also reported to be in the grip of this deadly disease. This makes it one of the world's worst calamities in recent times.

Mechanism of Toxicity

Both inorganic and organic arsenic salts may be absorbed after oral ingestion. However, because of low solubility, many pentavalent arsenic compounds are excreted in the stool before dissolution. Arsine gas is very rapidly absorbed from lungs. Trivalent arsenic compounds inhibit pyruvate dehydrogenase complex via inhibition of sulfhydryl group-containing cellular enzymes, which results in reduced citric acid cycle activity and reduced gluconeogenesis. Pentavalent arsenic produces toxicity by converting into trivalent arsenic. In addition, pentavalent arsenic produces toxicity by uncoupling oxidative phosphorylation resulting in ineffective generation of adenosine triphosphate. Arsine becomes localised in the red blood cell, which results in rapid and often severe haemolysis.

Another postulated mechanism for toxicity produced by various heavy metals, including arsenic, lead and mercury, is generation of reactive free radicals, which produce cellular damage, depletion of enzyme activities, damage to lipid bilayer and DNA.

Clinical Features

Although as little as 1 mg of arsenious oxide can produce acute toxicity, doses in the range of 20 mg of arsenic in adults are often associated with severe symptoms. The lethal dose has been estimated at 200 mg to 300 mg. Exposure to large doses produces acute toxicity while exposure to substantially lower amounts over a period of time will result in chronic toxicity.

Arsine gas poisoning

Initial symptoms of acute arsine poisoning are generally vague and include headache, weakness, nausea, vomiting and abdominal pain. Within a few hours, the patient develops intravascular haemolysis leading to jaundice, haemoglobinuria and acute renal failure.

Acute arsenic poisoning

The symptoms of acute intoxication may be evident within minutes of arsenic ingestion or may be delayed for several hours if food is present in the stomach. Acute exposure leads to vomiting, watery (may have 'rice water' appearance), and later bloody stools and severe abdominal pain. This can result in electrolyte imbalance, hypotension and shock. Cardiotoxicity manifests as altered myocardial function, electrocardiogram (ECG) changes (prolongation of QT interval and abnormal T-waves) and arrhythmias. Acute encephalopathy can develop and progress over several days and results in delirium, coma and convulsions. Occasionally, peripheral neuropathy with a glove and stocking distribution may occur acutely. Other features include acute respiratory distress syndrome, hepatitis,

haemolytic anaemia and rhabdomyolysis. Acute renal failure may develop due to fluid loss, myoglobinuria, haemoglobinuria or direct renal toxicity. Fever may develop in a few patients. A garlic-like odour of breath may help in diagnosing arsenic poisoning. Fatalities occur within one to four days due to cardiovascular collapse.

Patients who have been poisoned acutely with lower amounts of arsenic develop less severe manifestations, which include gastroenteritis that may continue for several days.

Following acute intoxication, patients often develop additional features. Peripheral sensorimotor neuropathy typically develops in 1 to 3 weeks. This may mimic Guillain-Barré syndrome. Encephalopathic features include headache, drowsiness, reduced memory, hallucinations and seizures. A few patients develop haemoptysis and patchy infiltrates in the lungs. Skin manifestations are alopaecia, oral lesions and macular rash. Mees' lines [transverse white bands (1 to 2 mm wide) on the nails] may develop but are uncommon. Similar lines have also been described in thallium, lead poisoning, Hodgkin's disease and renal failure.

Chronic arsenic poisoning

Arsenicosis has been defined by the WHO working group as a chronic health condition arising from prolonged ingestion (not less than 6 months) of arsenic above a safe dose, usually manifested by characteristic skin lesions, with or without involvement of internal organs.

Chronic exposure to arsenic produces muscle weakness, myalgias, abdominal pain, and excessive salivation and lacrimation. Typical manifestations of chronic arsenic poisoning include pruritus, hyperpigmentation or less commonly, hypopigmentation of skin with a 'raindrop' pattern and thickening (hyperkeratosis) of palms and soles, which sometimes may show nodularity (**Figure 1**). Sometimes, macular areas of depigmentation may appear on normal skin or hyperpigmented background producing the distinctive appearance of 'leucomelanosis'.

Symmetrical peripheral neuropathy, involving both sensory and motor neurons, is common and the patient presents with paraesthesias, numbness, pain and muscular weakness of the extremities. The neuropathy is generally axonal and preferentially affects the large fibres.

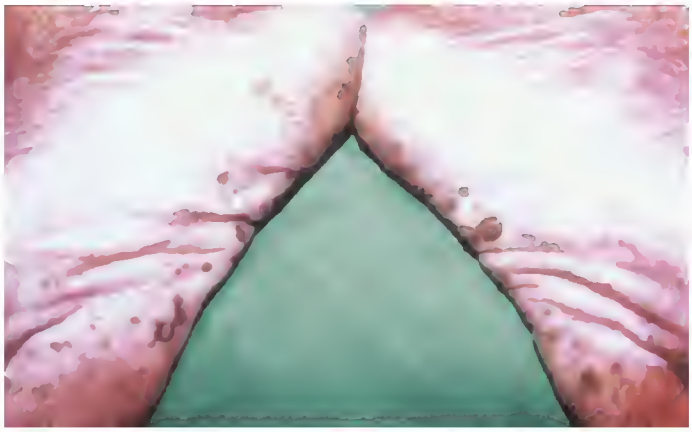


Figure 1: Photograph showing nodular hyperkeratosis of soles in a patient with chronic arsenic poisoning.
Courtesy: Dr M Romom, All Indio Institute of Medicol Sciences, New Delhi.

Haematological abnormalities include varying degrees of anaemia, leucopenia and thrombocytopaenia. Anaemia is most commonly normocytic and normochromic. Basophilic stippling may be seen.

Cardiovascular features include conduction abnormalities and prolongation of QT interval. Acrocyanosis and Raynaud's phenomenon occur occasionally and may progress to endarteritis and frank gangrene of the extremities (black-foot disease).

Chronic exposure to arsenic may lead to hepatomegaly and non-cirrhotic portal hypertension. Other uncommon features include development of diabetes mellitus and restrictive lung disease. Arsenic has been classified as a carcinogen and the patients may develop Bowen's disease, squamous and basal cell carcinomas of skin and lung and bladder carcinomas. Arsenic poisoning has also been shown to cause immunosuppression.

Table 1 lists some of the common clinical features of chronic arsenic poisoning.

Table 1: Clinical Features of Chronic Arsenic Poisoning

Cutaneous	Melanosis: Fine freckled or spotted pigmentation (raindrop pigmentation); diffuse hyperpigmentation; guttate hypopigmentation on normal or hyperpigmented background (leucomelanosis) Hyperkeratosis: Keratotic papules with thickening of palms and soles Malignant/Pre-malignant lesions: Bowen's disease, squamous cell carcinoma, basal cell carcinoma
Neurological	Peripheral neuropathy: Predominantly sensory
Peripheral vascular disease	Raynaud's phenomenon, claudication, gangrene (black-foot disease)
Respiratory	Chronic bronchitis, pulmonary fibrosis, bronchiectasis
Hepatic	Non-cirrhotic portal fibrosis, cirrhosis of liver, portal hypertension
Gastrointestinal	Anorexia, nausea, chronic diarrhoea
Haematological	Anaemia, leucopaenia, thrombocytopaenia

Diagnosis

Arsenic is radio-opaque and an abdominal radiograph may reveal a radio-opaque substance in the gut. However, it is rapidly absorbed from the gastrointestinal tract and radiographs taken in cases of known arsenic ingestions are usually negative.

Blood levels of arsenic are not of much use in diagnosing poisoning. Urinary arsenic levels are required to make a definitive diagnosis of arsenic exposure. Excretion of arsenic of more than 100 µg in 24 hours or 50 µg/L is abnormal. The urine specimen should be collected in a metal-free container. Since most laboratories measure total urinary arsenic, patients should be told to avoid seafood for at least 3 days prior to urine collection. Arsenic levels in hair and nails are also useful in diagnosis of chronic poisoning (normal arsenic levels in hair and nails are below 0.5 mg/kg and 1 mg/kg, respectively). A single dose of arsenic can be detected at the distal tip of the nails about 100 days after the exposure.

Treatment

Treatment of acute arsenic poisoning should include decontamination, chelation and supportive care. Since profuse vomiting is a common early symptom, gastric lavage may not

be necessary, but should be considered in every case. Whole bowel irrigation is another option for decontamination. Since activated charcoal does not adsorb arsenic, its role is limited to unknown ingestions. Intravenous fluids are frequently necessary to assure adequate intravascular volume. Electrolytes must be monitored and imbalances corrected when necessary. Glucose levels and glycogen stores should be maintained by parenteral administration of dextrose. Treatment of cardiotoxicity may require vasopressors. Haemodialysis may be indicated for renal failure; however, it does not remove significant amount of arsenic and is not indicated if renal function is normal.

The chelation therapy in acute arsenic toxicity consists of dimercaprol (British anti-Lewisite) and should be started immediately in suspected acute poisoning before laboratory confirmation. However, there is some evidence that BAL may increase arsenic transport into brain. It is available in vials containing 3 ml solution with 100 mg BAL/ml. It should be administered by deep intramuscular injection. Dimercaptosuccinic acid (DMSA) and dimercapto-1-propane sulphonate (DMPS) appear to be better alternatives than BAL in most patients who are not critically ill. The DMPS is administered in a dose of 5 mg/kg intravenously every 4 hours till the patient can be able to tolerate the medication orally. The oral dose in adults is 400 mg every 4 hours for a week. The recommended dose of DMSA is 10 mg/kg every 8 hours for 5 days and then 10 mg/kg every 12 hourly. D-penicillamine has not been shown to be efficacious in patients with arsenic poisoning.

Chelating agents have frequently been considered for treatment of chronic arsenic toxicity and arsine toxicity; however, their usefulness is yet to be established. The only treatment presently available for arsine poisoning is exchange transfusion or haemodialysis if renal failure develops.

LEAD

Lead is ubiquitous in the environment but has no physiologic role in our biological systems. It exits in elemental form (e.g. bullets), as well as in inorganic and organic forms. Inorganic lead compounds include lead oxide, lead chromate, calcium plumbate and lead sulphide. Tetraethyl lead, the anti-knock compound added to gasoline, is an organic lead compound.

Sources of Exposure

Lead is a persistent metal that is present in the environment (in water, soil and dust). **Table 2** gives common sources of lead exposure.

Table 2: Common Sources of Lead

Paint (lead-based)
Household dust
Lead water pipes
Soil around the home
Herbal and traditional remedies
Food-storage articles: Lead-glazed ceramic ware, lead crystals and lead-soldered cans
Paint on children's toys
Industrial: Smelting, soldering, battery making, ship building, glass manufacture

The most common sources of inorganic lead exposure include paints and lead-contaminated soil. Lead-based paints are still widely used in developing countries. Lead pigments (usually lead carbonate) account for as much as 50% of many white household paints and a thumbnail-sized chip of this paint may contain as high as 200 mg of lead. Lead-based paints have also been used in toys. Studies from India have reported lead levels within permissible limits as well below 600 ppm in latex paints but the levels have been found to be high (upto 1,40,000 ppm) in most samples of enamel paints. Among the enamel paints, white paints have been found to have the lowest concentration of lead while yellow and orange with the highest concentration. More than 30% samples of floor dust in Delhi homes have been shown to contain excessive lead.

Drinking water is also a major source of lead exposure as leaded plumbing components continue to be used in water pipes. Food storage articles like lead-glazed ceramic ware, lead crystals and lead-soldered cans may contain significant amount of lead.

Industries classically associated with lead exposure include smelting, battery making, ship building and glass manufacture. Automotive and industrial emissions are the major contributors to lead in air. Use of lead-free petrol has reduced lead toxicity produced by automotive emission to a large extent and has resulted in marked reduction in lead levels among children in developed nations as well as in India. Chronic sniffing of petrol may produce lead poisoning. Recycling of automobile batteries is another source of lead exposure.

Surma (kohl, kajal) has also been reported to produce lead encephalopathy in children. Many samples of *surma* contain as much as 88% of lead sulphide. *Sindoor* contains a high amount of lead (roughly 57% by weight) and may produce lead toxicity if used as food-colouring agent. Many herbal preparations may contain significant amounts of heavy metals with lead content ranging from 5 µg/g to 37,000 µg/g.

Another source of lead is the consumption of illicit liquor which is contaminated by lead (moon shine). Swallowing foreign bodies containing lead and retained lead bullets in joints have been linked to chronic poisoning.

Mechanism of Toxicity

The amount of inorganic lead absorbed through gut is about 10% to 15% of the ingested quantity; for pregnant women and young children, the amount can increase upto 50%. The absorption of lead is enhanced if the diet is deficient in iron, calcium and zinc. Approximately 30% to 40% of inhaled lead is absorbed into the blood-stream. Inorganic lead is minimally absorbed through the skin, but tetraethyl lead (leaded gasoline) is well absorbed through skin.

Once absorbed, 99% of circulating lead is bound to erythrocytes for approximately 30 to 35 days and is dispersed into the soft tissues over the following 4 to 6 weeks. Lead is stored in bones for up to 30 years. When bone metabolism increases (e.g. during pregnancy and lactation, fracture healing and chelation therapy), stored lead leaves the bone and re-enters the circulation and can increase the risk of lead toxicity. It can also expose the foetus to lead if mother had lead exposure previously.

Lead poisoning is also known as *saturnism* or *plumbism*. Lead forms complexes with sulphur, nitrogen and oxygen, and exerts its toxic effects by combining with sulfhydryl groups in proteins,

thus inhibiting sulfhydryl-dependent enzymes. It may act as an inhibitor or agonist of calcium-dependent processes. Lead inhibits several steps in haeme synthesis. It inhibits D-aminolevulinic acid dehydratase, producing increased levels of delta-aminolevulinic acid (ALA) in blood and urine. Several studies have shown that accumulation of ALA induces reactive oxygen species generation, which produces oxidative damage. Lead also inhibits coproporphyrinogen oxidase and ferrochelatase causing increased urinary coproporphyrin III and erythrocyte protoporphyrin concentrations, respectively.

Lead also interferes with excitatory neurotransmission by glutamate, which is the transmitter at more than half the synapses in the brain and is critical for learning. N-methyl-D-aspartate receptor is blocked selectively by lead. This compromises permanent retention of newly learned information. It is thought that lead affects the renin-angiotensin system, causing hypertension.

Clinical Features

Acute lead poisoning

The symptoms of lead toxicity are often vague and may arise acutely, even though the poisoning is usually chronic. Acute lead poisoning is uncommon. It can result from inhalation of large quantities of lead. In children, ingestion of large oral dose from various sources can produce acute poisoning. It can also occur in children with pica. Characteristics of acute poisoning are abdominal colic, constipation, fatigue, anaemia, renal failure, peripheral neuropathy, renal insufficiency, and in severe cases, encephalopathy (coma, convulsions, papilloedema). Vomiting is common in children. Neuropathy is generally of pure motor type resulting in foot and wrist drop.

Chronic lead poisoning

The important clinical symptoms and signs of chronic lead poisoning are given in **Table 3**.

Chronic lead poisoning in children

Chronic lead toxicity is more common, and in children, presents with pallor, underweight, short stature, loss of appetite, intermittent vomiting, constipation, headache and neuropsychological disturbances (irritability, nervousness, tremors, intermittent lethargy). Features compatible with lead encephalopathy include drowsiness, irritability, seizures, gait disturbances, evidence of increased intracranial tension and coma and can occur if exposure to lead continues. The probability of developing encephalopathy increases with rising lead levels and becomes significant when the levels exceed 70 µg/dL. Clinically important colic, peripheral neuropathy and chronic renal disease are uncommon in children as compared to adults.

Chronic lead poisoning in adults

Adults often present with abdominal colics, anaemia, hypertension and peripheral motor neuropathy. Renal toxicity has been well documented in occupationally exposed workers and it manifests as proximal tubular damage, glomerular sclerosis and interstitial fibrosis. Presentation may include proteinuria, impaired transport of glucose and organic anions and tubulointerstitial nephritis with or without renal failure. It can also precipitate gout (lead-induced gout or saturnine gout). Encephalopathy is rare in adults but neuropsychiatric features may develop. Occasionally, patients may develop lead line or Burton's line, which is a grayish-black line, at the junction of teeth and gums. It develops due to deposition of lead sulphide pigment formed by the lead molecules reacting with hydrogen sulphide in the oral cavity. There is an association between elevated blood lead levels and higher risk of amyotrophic lateral sclerosis.

Table 3: Clinical Features of Lead Poisoning

Apparently asymptomatic (lowest exposure; blood lead levels may be below 10 µg/dL)
Reduced learning and memory
Lowered IQ
Impaired speech
Hyperactivity
Low exposure
Myalgia
Paraesthesia
Fatigue/lethargy
Irritability
Mild abdominal discomfort
Change in taste
Moderate exposure (additional features)
Arthralgias
Inability to concentrate
Short-term memory loss
Tremor
Headache
Diffuse abdominal pain
Vomiting
Constipation
Hypertension
High exposure
Abdominal colic
Paresis or paralysis (wrist and foot drop)
Papilloedema
Somnolence, coma
Seizures
Lead line on gingival tissue (Burton's line)

Chronic petrol sniffing

Tetraethyl lead and its metabolites are highly neurotoxic. The clinical features vary from nonspecific symptoms, such as loss of appetite, lethargy and irritability, to altered mental status, psychosis, tremors, ataxia, myoclonus, chorea and seizures. Some of these features may be related to the associated toxic aromatic hydrocarbons contained in petrol. In the case of severe exposure, death may occur within a few hours or may be delayed for several weeks. Anaemia is uncommon with organic lead exposure.

Elevated lead levels in pregnancy

Elevated blood lead levels during pregnancy are associated with an increased risk of preterm births and can increase the risk of spontaneous abortion. The first pregnancy carries the greatest risk of lead toxicity. Blood lead levels may actually increase in women during pregnancy as a result of increased mobilisation of lead from bones into the blood. Lead freely crosses the placenta, and there is a strong correlation between maternal and umbilical cord blood lead levels. Because of incomplete blood-brain barrier, the effect of lead on the foetus's central nervous system is greater during gestation and in the first 3 years of life than in later life. The effects of lead exposure on the

foetus during gestation may be manifested after birth by low performance on cognitive tests. However, it is still unclear if lead is a teratogen.

Subclinical effects

Recent studies evaluating the relationship between blood lead levels and neurobehavioural performance have shown the evidence of effect at levels below 10 µg/dL – the current level considered excessive for children. At low-level exposure to lead, subclinical effects on central nervous system are the most common effects seen in children. As blood lead concentration increases by 10 µg/dL, the intelligence quotient decreases by 2 to 3 points. The child may become inattentive, hyperactive and disorganised. Delinquency is seen as the child grows. There is no evidence that chelation will reverse cognitive impairment.

Diagnosis

Measurement of blood lead levels is the standard screening test for lead toxicity. There is no toxic threshold for lead, i.e. there is no measurable level of lead in the body below which no harm occurs. For diagnostic purpose, blood lead levels above 10 µg/dL are considered abnormal although some neurological damage may occur even at lower levels. Blood lead level is only a reflection of recent or continued lead exposure and does not adequately reflect past exposure or accumulated bone lead levels.

In case of acute ingestion, abdominal radiograph may show radio-opaque lead chips. A normocytic anaemia with basophilic stippling of the red blood cells and abnormal liver function results are characteristics of lead poisoning. However, basophilic stippling and anaemia only occur after significant levels of exposure; at blood lead levels over 50 µg/dL in adults and 25 to 40 µg/dL in children. The urine may show protein and glucose.

Lead lines are dense transverse bands at the metaphyses of long bones. These lines generally develop after months of exposure. Since laboratory analysis of lead levels cannot be readily performed, children with unexplained encephalopathy should undergo radiography of the knees to look for dense metaphyseal band.

Measurement of erythrocyte protoporphyrin (EP) was used as an inexpensive screening test during 1970s. However, it is no longer recommended as it usually does not rise unless blood lead levels are above 25 to 35 µg/dL. Further, it may be elevated in iron deficiency states, porphyria, cirrhosis of liver and alcoholism. The EP assays may still be used if facilities to estimate blood lead levels are unavailable. The threshold for EP is 30 µg/dL. Similarly, calcium disodium edetate mobilisation test, which was used to assess lead excretion after a single dose of edetate, is not recommended at present.

Cortical bone lead measured by radiographic fluoroscopy, is considered a sensitive biomarker for cumulative lead exposure and correlates well with historical rather than current blood lead level measurements.

Treatment

Treatment of lead toxicity involves prevention of further exposure, decontamination, supportive care and chelation. Lavage should be used for recent ingestions. Whole bowel irrigation is recommended for ingestion of lead-containing foreign bodies. It is generally not indicated for lead paint chips. Activated charcoal does not bind lead. Seizures from lead encephalopathy may be resistant to benzodiazepines and phenobarbital; in such cases, measures to reduce intracranial pressure (mannitol, steroids, hyperventilation) are recommended. The options for symptomatic treatment of abdominal cramps are limited because these symptoms do not respond well to relaxants or analgesics. In patients with pronounced anaemia, transfusion may become necessary.

Dietary advice includes adequate intake of iron, calcium and vitamin C. Adequate iron and calcium stores may decrease lead absorption and vitamin C may increase renal excretion. The current recommendations for the management of children and adults with high lead levels are given in **Tables 4 and 5**.

Table 4: Treatment of Lead Poisoning in Children

Blood Level	Treatment
<10 µg/dL	No intervention
10 to 14 µg/dL	Lead education (dietary, environmental) Monitor lead levels every 3 to 6 months Correct iron deficiency, if any
15 to 19 µg/dL	Lead education (dietary, environmental) Monitor lead levels every 3 to 6 months Proceed according to actions for next category, if: Blood lead level increases or Blood level remains in this range in follow-up sample
20 to 44 µg/dL	Lead education (dietary, environmental) Monitor lead levels every 1 month Complete history and examination Laboratory work-up Haemoglobulin Iron status Correct iron deficiency, if exists Environmental investigation Abdominal radiograph if lead ingestion suspected
45 to 69 µg/dL	Same actions as listed above Administer chelation therapy with DMSA or $CaNa_2EDTA$
≥70 µg/dL	Hospitalise and start therapy with BAL and $CaNa_2EDTA$ Proceed according to actions for 45 to 69 µg/dL

Table 5: Treatment of Lead Poisoning in Adults

Blood Level	Treatment
<30 µg/dL	No treatment required
30 to 40 µg/dL	Monitor lead levels every 6 months Remove the source of exposure Screen for iron deficiency; administer iron if required
41 to 60 µg/dL	Monitor lead levels every 2 months until two consecutive levels are below 40 µg/dL Remove the source of exposure
>60 µg/dL	If symptomatic, administer $CaNa_2EDTA$ or DMSA If encephalopathy present, give BAL and $CaNa_2EDTA$ If asymptomatic, remove from source of exposure and monitor lead levels every month
>80 µg/dL	Start treatment with $CaNa_2EDTA$ or DMSA If encephalopathy present, give BAL and $CaNa_2EDTA$

Chelation therapy

The current recommendation is to use a combination of intramuscular BAL and intravenous calcium disodium edetate ($CaNa_2EDTA$) if blood lead levels are above 70 μg/dL in children or 100 μg/dL in adults. Unlike EDTA, BAL chelates lead from the brain also. An initial dose 50 mg/m² of BAL is given by deep intramuscular injection and 4 hours later, $CaNa_2EDTA$ 1000 mg/m²/day is begun via continuous intravenous infusion. The BAL is then continued simultaneously at a dose of 300 mg/m²/day in divided doses for every 4 hours. If encephalopathy is present, the daily doses of BAL and $CaNa_2EDTA$ are 450 mg/m² and 1500 mg/m², respectively. The treatment is given for 5 days. Courses of $CaNa_2EDTA$ can be repeated every 2 to 5 days.

Dimercaptosuccinic acid (DMSA) or succimer is effective in both children and adults. It is recommended if blood lead levels are 45 to 69 μg/dL in children or 70 to 100 μg/dL in adults, provided serious features including encephalopathy are not present. In contrast to BAL, DMSA is a more specific chelator of lead, arsenic and mercury while sparing essential metals such as zinc, calcium, copper, magnesium and iron. It is administered in a dose of 10 mg/kg every 8 hours for five days followed by 10 mg/kg every 12 hours for another 14 to 21 days. An alternative is to give repeated courses of 10 mg/kg every 8 hours for 5 days with a gap of 1 to 2 weeks between the courses. The length of course may be tailored to individual patient's response as indicated by the assessment of blood lead concentration.

Oral DMSA and parenteral $CaNa_2EDTA$ are both effective chelators of lead. There is currently insufficient data, however, to conclude that either antidote is superior in enhancing lead excretion. Both antidotes resolve the symptoms of moderate and severe lead toxicity rapidly. In tetraethyl lead, chelator therapy is almost completely ineffective.

D-penicillamine has also been used for lead poisoning. The usual dose is 25 to 40 mg/kg in four divided doses a day for 1 to 6 months. The adult dose is 1 to 1.5 g/day. The drug should be taken on an empty stomach. It may be useful in mild lead poisoning or when unacceptable adverse effects to both edetate and DMSA have occurred.

Various chelating agents useful in heavy metal poisoning are given in **Table 6**.

Antioxidants

Antioxidant molecules are thought to play a crucial role in counteracting free radical induced damage to macromolecules and have been found to heel the free radical mediated cell damage. Antioxidants like vitamin E, vitamin C, β-carotene and α-lipoic acid have been shown to be beneficial in studies conducted on animals with heavy metal poisoning.

MERCURY

Mercury occurs geologically in its elemental state and as inorganic salts (e.g. mercuric chloride, mercuric iodide, mercuric oxide, mercuric sulphide, mercurous chloride) and organic salts (e.g. ethylmercury, methylmercury, merbromin, phenylmercurial salts). Elemental mercury readily volatises at standard temperature (0°C) and its presence in an open container can result in significant air concentrations in unventilated or poorly ventilated spaces.

Sources of Exposure

Mercury is used in the manufacture of batteries, latex paint, urethane, polyvinyl chloride, scientific instruments and fungicides. It is also used in gold mining and refining and electrical industry. Organic salts such as merbromin and nitromersol are still used widely as topical antiseptics. Organomercurials have been used in human and veterinary medicines as an antiseptic, but the widest use has been in agricultural fungicides. Calomel (mercurous chloride) was used extensively in medicines. It is still being used in some creams and laxatives. Thiomersal, a long-chain alkyl mercury compound is widely used as a preservative in pharmaceutical industry. Some of the herbal medicines also contain inorganic mercury. Mercury-containing disc batteries may lead to mercury toxicity when ingested.

Industrial discharge into rivers and streams has been a major source of mercury pollution. The major dietary contribution comes from seafood. There is accumulation of potentially toxic

Table 6: Chelating Agents in Heavy Metal Poisoning

Chelating Agent	Dose	Precautions/Side Effects
Dimercaprol (BAL, British anti-lewisite)	300 to 450 mg/m²/d in 6 divided doses for 3 to 5 days deep intramuscularly	First dose precedes $CaNa_2EDTA$ by 4 hours Do not administer iron concurrently May produce hypertension, tachycardia, a constricting feeling in the chest, burning sensation in throat, lacrimation, urticaria, haemolysis (in G-6PD deficient patients)
$CaNa_2EDTA$ (edetate)	1000 to 1500 mg/m²/d for 5 days intravenously as infusion	Monitor renal functions Ensure adequate urine flow May produce fever, myalgia, tremors, headache, hypotension, vomiting, mild increase in liver enzymes, hypercalcaemia
DMSA (succimer)	10 mg/kg every 8 hourly for 5 days, then 10 mg/kg every 12 hourly orally	Monitor liver functions, blood counts May produce vomiting, diarrhoea, metallic taste, elevated liver enzymes, drowsiness, neuropathy, skin rash, nasal congestion, cardiac arrhythmia
DMPS (dimercapto-1-propane sulphonate)	5 mg/kg every 4 to 6 hourly orally or intravenously	Can be administered orally as well as parenterally
D-penicillamine	25 to 40 mg/d orally in 2 to 4 divided doses (maximum 1 g/day) orally	To be given empty stomach Monitor total leucocyte counts, platelets, haemoglobin, liver and renal functions Contraindicated in patients with penicillin allergy May produce rashes, arthralgia, lymphadenopathy, urticaria, vomiting, diarrhoea, bone marrow depression, nephrotic syndrome, neuropathy

quantities of mercury in freshwater fish in some lakes with acid water. Acidification increases bacterial formation of methylmercury, which then enters the food chain. *Minamata disease* was the first outbreak of methylmercury poisoning caused by consumption of methylmercury-containing seafood from the Minamata Bay in Japan in 1953. Later, another mass methylmercury poisoning was reported from Iraq where it was caused by contaminated bread.

Mechanism of Toxicity

After the inhalation of elemental mercury, approximately 80% is absorbed from the lungs and can cross the blood-brain barrier. The absorbed mercury is also rapidly oxidised to inorganic mercury in the red cells and tissues, which does not cross the blood-brain barrier effectively. After oral ingestion, elemental mercury is essentially unabsorbed. Inorganic mercury and phenylmercury are absorbed 7% to 15% after oral ingestion. These mercury compounds cross the blood-brain barrier poorly. Methylmercury is readily absorbed in the gastrointestinal tract. Mercurials bind to sulfhydryl groups present on the cell membranes and enzymes and cause their toxicities. Mercuric ions also accumulate in the kidneys, causing acute renal failure due to the necrosis of the proximal tubular epithelium, usually within 24 hours.

Clinical Features

Toxicity of mercurials depends on the form of mercury and on whether the exposure is acute or chronic.

Acute elemental mercury poisoning

Acute inhalation of elemental mercury results initially in pulmonary toxicity causing cough, haemoptysis, tachycardia, pulmonary oedema, cyanosis and death. Gastrointestinal features include vomiting, diarrhoea, metallic taste, dysphagia and salivation. If the patient survives, headache, blurred vision and encephalopathy can occur. Some patients develop cardiac arrhythmias, tremors, renal dysfunction and gingivostomatitis. Survivors of acute inhalation may develop interstitial lung fibrosis.

Oral ingestion of elemental mercury is associated with low risk of toxicity due to its limited absorption. Features of mercury toxicity may develop if there is inordinate delay of mercury passage through the gastrointestinal tract. In addition, mercury lodging in the appendix can cause appendicitis or a ruptured appendix.

Systemic features of mercury poisoning are usually absent after parenteral administration. Local features after parenteral administration include abscess formation with discharge of mercury granules, thrombophlebitis and granuloma formation. Embolisation of mercury may result in the presence of multiple, tiny spherules of mercury in various organs, including lungs, which are visible on a plain chest radiograph. Occasionally, intravenous injection of elemental mercury can cause severe pneumonitis and embolisation of the pulmonary vasculature, which can subsequently lead to hypoxia.

Acute inorganic mercury poisoning

Acute exposure to inorganic mercury salts results initially in gastrointestinal toxicity manifesting as abdominal pain, nausea, vomiting and in severe cases, bloody diarrhoea. This may result in vascular collapse. In high doses, renal necrosis and acute renal failure may occur and this is related to both hypovolaemia and direct renal toxicity.

Acute organic mercury poisoning

Acute exposure to phenylmercury and related organic mercury compounds other than methylmercury causes toxicity similar to that of inorganic mercury poisoning. Acute exposure to methylmercury causes similar effects that occur after its chronic exposure, but the onset of symptoms may be as early as 15 days after its ingestion.

Chronic mercury poisoning

Chronic exposure to elemental mercury vapour, inorganic mercury and phenylmercury produce similar toxic features. These include dermatitis, loosening of teeth, gingivitis, salivation, stomatitis, intention tremor and a neuropsychiatric syndrome called *'erethism'*. The features of erethism include loss of appetite, insomnia, emotional lability, loss of self-control and memory loss. Another syndrome, *'acrodynia'* or *'pink disease'* is characterised by painful, erythematous extremities, sweating, photophobia, tachycardia, hypertension, insomnia and irritability. It is probably a hypersensitivity reaction which occurs only in children and does not occur in newborns or adults. Renal dysfunction, ranging from proteinuria to immune-complex-mediated nephritis especially membranous nephropathy may occur.

Chronic methylmercury poisoning

Chronic exposure to methylmercury causes neurotoxicity with onset one to two months after initial exposure. Clinical features include cerebellar ataxia, dysarthria, constriction of visual field, hearing impairment, sensory disturbances in the distal parts of the extremities, and emotional and cognitive defects. Foetal exposure to methylmercury may cause cerebral palsy, microcephaly, mental retardation and developmental delay.

Dental amalgams

Dental amalgam, used to restore carious lesions in teeth, is approximately 50% metallic mercury. Small amounts of mercury vapour liberated by chewing may be inhaled and may result in measurable levels of mercury in the body. However, at present, there is no evidence that exposure to mercury from dental amalgams is associated with adverse psychosocial outcomes or other clinical features of chronic mercury poisoning.

Mercury in vaccines

Thiomersal, which contains approximately 50% ethylmercury, has been widely used as a preservative in multiuse vials of vaccines. In the United States, it has been removed from most childhood vaccines by 2001 as a precautionary measure. At present, there is no data to support that thiomersal may account for adverse neurodevelopmental outcomes in children.

Diagnosis

Diagnosis of mercury poisoning is aided by the determination of mercury levels in whole blood, 24-hour urine samples and hairs. For elemental mercury and mercury salts, whole blood mercury levels reflect only very recent exposure while urinary mercury is a better marker for chronic exposure. In contrast, since methylmercury (an organomercurial compound) is mainly excreted in bile, urinary level is a poor measure of exposure.

Blood mercury levels are the best indicator of acute exposure to methylmercury, while hairs may be the best specimen for the evaluation of chronic exposure. Normal levels of mercury in whole blood and urine are below 10 µg/L and 50 µg/L, respectively.

Abdominal radiographs can be used to document the presence of ingested mercury and to evaluate the potential benefit of gastric lavage. If the respiratory tract is involved, a chest radiograph may be helpful.

Treatment

Acute mercury poisoning is best managed by discontinuing the exposure, providing supportive care and removal of metal from the body. Patients with pneumonitis from acute elemental mercury inhalation require oxygen, close monitoring of respiratory status and if required, assisted ventilation. Although ingestion of elemental mercury is often nontoxic, some patients may require surgical removal of metal that is entrapped in the intestines or appendix. In case of subcutaneous injection of mercury, surgical removal of mercury and surrounding granulated tissue is important. Radiographs and blood, urine and hair assays for mercury are aids for instituting treatment with chelators.

Ingestion of inorganic mercury requires supportive treatment with aggressive fluid replacement and if required, haemodialysis. Patients should also be started on chelation therapy. Gastric lavage has been recommended for acute organic salt ingestions, especially if mercury is visualised on abdominal radiographs. Lavage may be done with protein-containing solutions, such as milk or egg white, as mercury may be bound to the administered sulfhydryl-containing proteins.

Whenever mercury poisoning is suspected in critically ill patients, chelation therapy should be started regardless of the suspected form of mercury; however, chelation may be ineffective at reversing toxicity from chronic organic and chronic elemental mercury exposure. Dimercaprol has been extensively used for inorganic mercury poisoning. However, it is contraindicated in methylmercury poisoning.

The DMSA and 2,3-dimercaptopropane-1-sulphonate (DMPS) are useful for both inorganic and elemental mercury poisoning. The DMSA is administered in a dose of 30 mg/kg per day. The duration of treatment is adapted to the evolution of clinical manifestations and urinary mercury levels. D-penicillamine is also useful in mercury poisoning although its efficacy is only about 30% of that with DMSA. It is administered in a dose of 250 mg 6 hourly along with pyridoxine (40 mg/day). This is continued till the urinary mercury levels fall below 500 µg/L after which the dose is reduced to 250 mg thrice daily. The DMPS has also been used with N-acetylcysteine (NAC) and haemodialysis as a part of a successful regimen for acute methylmercury poisoning. The NAC has also been used as a single agent in the treatment of acute elemental mercury poisoning. Oral DMPS may also be useful in mercury inhalational poisoning.

COPPER

Copper is an ingredient of several vital enzymes. It exits as elemental copper or as salts. Elemental copper is not toxic, but many of its salts are poisonous. Common salts include cupric acetoarsenite (Paris or Vienna green), cupric arsenite (Scheele green), cupric oxide, and copper or cupric sulphate (*'neela thotha'*). Most of the salts of copper are greenish in colour except for copper sulphate, which is blue in colour. Copper compounds are used as insecticides and fungicides and also as pigments. Acute or chronic copper poisoning can occur when copper ions are leached from copper pipes. Storage of acidic substances, such as orange juice in copper containers, may cause poisoning. Copper sulphate poisoning, one of the most common poisonings in 1960s and 70s in India, has reduced significantly over the past four decades.

Mechanism of Toxicity

In an acute intoxication, a high fraction of copper is bound to serum albumin and is biologically active. It is actively involved in oxidation-reduction reactions in the body, which is responsible for its toxicity. It inhibits several enzymes including mitochondrial electron transport chain and also disrupts lipid membranes. It also inhibits sulfhydryl groups on enzymes, including glucose-6-phosphate dehydrogenase and glutathione reductase, which may be responsible for haemolysis.

Clinical Features

Acute poisoning

The average fatal dose of copper sulphate is 10 to 20 g. Initial features of acute poisoning include myalgia, retrosternal pain, abdominal pain, vomiting (greenish or bluish) and diarrhoea. Gastric perforation or haemorrhage can occur due to ulceration. Acute intravascular haemolysis occurs within 24 hours and can lead to anaemia, jaundice and renal failure. Jaundice may also occur due to liver injury. Some patients may develop methaemoglobinaemia due to oxidation of haeme and this may precede haemolysis. The central nervous system effects include agitation, convulsions and coma and are usually related to hepatic failure. Hypotension and cardiovascular collapse occur due to fluid loss from gastrointestinal tract; direct effects of copper on heart and vascular tree may also contribute to shock.

Chronic poisoning

Chronic exogenous copper poisoning is uncommon. Chronic inhalation of copper sulphate spray used as an insecticide can produce interstitial lung disease, the latter having histiocytic granulomas containing copper on biopsy. In children, consumption of copper-containing supplements over long periods may produce liver damage and cirrhosis. Other features include malaise, weakness, headache, dizziness, tightness in the chest, and leg and back pain.

Diagnosis

Following acute copper poisoning, liver function tests and haemogram may reveal evidence of haemolysis and liver damage. Blood copper level more than 1.5 mg/dL indicates serious copper toxicity. Elevated copper levels are also seen in patients with inflammatory conditions. Urinary copper levels are also elevated (normal urinary copper value < 25 µg/day).

Treatment

Aggressive supportive care is the mainstay of management of patients with acute copper poisoning. The fluid and electrolyte balance must be ensured. Gastrointestinal decontamination is usually not required as the patient vomits within minutes of ingesting a copper salt. When the patient presents early after ingestion, administration of milk may help, as albumin present

in milk combines with copper. Haemodialysis is of little use in enhancing excretion of copper. Since methaemoglobin produced by copper is released into plasma due to intravascular haemolysis, methylene blue is not useful for its treatment.

Chelation therapy is indicated when haematological or hepatic manifestations are present even though the efficacy of chelators is not well studied. Most commonly recommended chelator initially is BAL as the patient has vomiting, and therefore, oral D-penicillamine cannot be given. When tolerated, D-penicillamine should be started. The DMSA may be used in patients with mild symptoms. Use of DMPS may worsen haemolysis and therefore, is not recommended in copper poisoning.

THALLIUM

Thallium metal is nontoxic, but its salts are highly toxic. Thallium salts are tasteless, colourless and odourless. Thallium sulphate and nitrate were used as rodenticides. Some thallium salts are occasionally used as cockroach poison. It is still used in some homeopathic medicines. Thallium is widely used in industry. It is used in imitation jewellery, which sparkles rather like diamonds. It is also used as an alloy, a catalyst, and for making low-temperature thermometers and semiconductors. Thallium isotopes are used in nuclear medicine.

Mechanism of Toxicity

Thallium salts can be absorbed from the skin as well as by inhalation and ingestion. After absorption, thallium distributes throughout the vascular space in the first few hours. After several hours to days, it enters the nervous system and other tissues of the body. Thallium associates with the Na^+/K^+ ATPase channel with 10 times the affinity of potassium. Once intracellular stores of thallium accumulate, thallium interferes with the function of a number of enzymes by binding sulfhydryl groups and ultimately inhibiting cellular respiration, disrupting calcium homeostasis, and interacting with riboflavin and riboflavin-derived cofactors. Secondary riboflavin deficiency can then result in dermatitis, alopaecia, Mees' lines and neuropathy. The fatal dose of thallium is estimated to be 10 to 15 mg/kg.

Clinical Features

The initial clinical features of thallium intoxication are nonspecific and usually develop after several hours of exposure. The gastrointestinal symptoms are usually not severe and include nausea, vomiting, abdominal pain and diarrhoea or constipation. Within 2 to 5 days, the patient may develop paraesthesia, burning pain in feet and hands, motor weakness, respiratory depression, nystagmus, optic atrophy, cranial nerve palsies, delirium, convulsions and coma. The picture may resemble Guillain-Barré syndrome superficially, but sensory neuropathy and preservation of reflexes exclude this syndrome. Tachycardia and hypertension frequently develop during the first or second week of intoxication. Within 2 to 3 weeks, skin lesions (acne, palmar erythema, dry skin and occasionally a 'butterfly' rash on the face) and alopaecia develop. The hair is lost in large tufts and within three weeks, the whole of head is bare. Mees' lines on the nails may be seen in 2 to 4 weeks. Cardiac arrhythmias may occur up to 2 months after exposure.

Diagnosis

Abdominal radiographs may demonstrate radio-opaque material in the gut when patient presents early. Microscopic examination of hair root shows deep black pigmentation in more than 95% cases. The definitive diagnosis can be made by blood and urine thallium levels. Normal urine thallium levels are less than 5 µg/L.

Treatment

The initial treatment is supportive and includes gastric decontamination if the patient presents shortly after ingestion. Activated charcoal is useful in adsorbing substantial amount of thallium salts.

Administration of potassium increases the excretion of thallium in the urine by 2 to 3 times. However, it can potentially increase neurologic toxicity due to mobilisation of thallium from its stores, and is therefore, not recommended. Administration of B-complex vitamin may be useful. Haemodialysis and haemoperfusion have been used with some success.

Traditional chelators are of little use in thallium poisoning. Prussian blue (potassium ferric hexacyanoferrate) can be used as a chelator. Oral Prussian blue binds with thallium in the gut and also interferes with enterohepatic circulation. It reduces half-life of thallium by 50% in animal models. The dose is 250 mg/kg/day in 2 to 4 divided doses.

CONCLUSION

Heavy metal poisonings with lead, mercury, arsenic, copper and thallium are infrequently encountered; however, early recognition of these poisonings is required for efficacious treatment and a favourable outcome. A thorough history (including occupational) and physical examination are essential for the accurate diagnosis.

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26.14 Miscellaneous Poisoning

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CARBON MONOXIDE POISONING

Carbon monoxide (CO) is a colourless, tasteless and odourless (lavender odour at extremely high concentrations) gas with a density of 0.97 that of air.

Sources of Carbon Monoxide

Sources of CO from combustion include fuel, engine exhaust and gas/coal-heater emissions, smoke from accidental fires and fumes from cupolas of steel foundries, pulp paper mills and formaldehyde-producing plants. Indoor burning of charcoal or animal dung produces a disproportionate level of accidental CO intoxication. CO poisoning can also result from inhaling methylene chloride or volatile liquids found in degreasers, solvents and paint removers.

Mechanism of CO Toxicity

Since CO has 200 to 250 times greater affinity for haemoglobin than oxygen, it displaces oxygen from oxyhaemoglobin (HbO_2) and converts it into carboxyhaemoglobin (COHb) causing decreased oxygen delivery to tissues. It also shifts the oxygen dissociation curve to left and reduces oxygen availability to the tissues further. It also acts as cellular poison as it competes with oxygen for other haemoproteins such as myoglobin, peroxidase, catalase and cytochromes. High-oxygen-extracting organs such as the brain and the heart easily become dysfunctional from CO intoxication.

Activation of inflammatory processes and resultant lipid peroxidation play a role in the development of neurological damage. They contribute to the development of systemic inflammatory response syndrome (SIRS) and delayed neurological sequelae (DNS).

Clinical Features

Signs and the symptoms of CO poisoning are related to effects of hypoxaemia predominantly on the heart and brain. Concentrations of CO, duration of exposure as well as level of activity of the victim at the time of exposure have a bearing on clinical picture.

Acute Poisoning

Headache is the earliest symptom of mild to moderate toxicity. Subsequently dizziness, nausea, dyspnoea and loss of muscle control develop. Severe CO intoxicated patients have cherry pink colour of the skin, nails and mucosa. Ophthalmoscopy may show retinal discolouration with bright red retinal veins, flame-shaped retinal haemorrhages or papilloedema. In severe cases hypotension, bradycardia, bradypnoea and noncardiogenic pulmonary oedema may develop.

Neurologic symptoms and signs include fatigue, malaise or flu-like symptoms, nausea, vomiting, dizziness, weakness, lethargy, difficulty in thinking, concentration and memory, emotional lability, paraesthesia, somnolence, stroke, coma, seizure, and respiratory arrest.

Cardiovascular symptoms and signs include chest pain from myocardial ischaemia, palpitations from arrhythmia, mildly to severely mottled skin from diminished circulation, poor capillary refill, hypotension, and cardiac arrest.

The symptoms and signs of CO toxicity are exacerbated by circumstances that increase neurologic and myocardial oxygen demand.

Subacute Poisoning

Secondary injury from ischaemia due to CO poisoning can manifest within a few days of exposure as peripheral neuropathy, skin lesions (bullae and purpuric spots), rhabdomyolysis, renal failure, circulatory shock, noncardiogenic pulmonary oedema, disseminated intravascular coagulation and multi-organ failure. Glycosuria and albuminuria are often present.

Delayed Neurologic Sequalae (DNS)

DNS can arise 3 to 240 days after apparent recovery in approximately 40% of patients with significant CO exposure. These include headache, weakness, dizziness, nausea, aphasia, apraxia, apathy, disorientation, hallucinations, rigidity, gait disturbances and faecal and urinary incontinence. DNS generally occurs within 20 days of CO poisoning but deficits may persist for a year or longer. DNS correlates poorly with COHb levels. However, loss of consciousness, advancing age and neurological signs during acute intoxication may increase the risk.

Chronic Exposure

Long-term, low level exposure may result in light-headedness, persistent headaches, confusion, memory loss, nausea, vomiting and depression that tend to get better on cessation of exposure. Long-term exposure to CO can promote the development of atherosclerosis and polycythaemia.

Diagnosis

Acute CO poisoning is suspected on a suggestive history but the diagnosis of chronic CO intoxication is extremely difficult. Standard pulse oximetry does not differentiate COHb from HbO_2 and is a poor indicator of CO exposure. Eight-wavelength pulse oximeters capable of measuring COHb and methaemoglobin are being developed but need further validation. COHb is estimated by spectrophotometry. It may be tested on bedside by adding 10 mL of distilled water and 1 mL of 5% sodium hydroxide (NaOH) to 1 mL of patient's blood. The solution turns straw yellow when COHb concentration is < 20% and stays pink when it is > 20%. Non-invasive pulse co-oximeters capable of photo-spectroscopic measurements of COHb are in development stage.

On-site CO-oximetry determination of COHb levels correlate reasonably well with the signs and symptoms of CO injury.

However, the predictive values of COHb levels falls considerably by the time, the patient gets to the emergency department after breathing air as well as prehospital oxygen administration but a rough correlation can be made with various clinical manifestations (Table 1).

Table 1: Symptoms of Acute CO Poisoning Based on Blood Carboxyhaemoglobin Levels

Carboxyhaemoglobin Level	Clinical Features
<10%	Very few, mainly headache
10% to 20%	Dyspnoea on exertion, lethargy, nausea, chest pain, tightness around forehead
20% to 30%	Headache, irritability, fatigue, nausea, vomiting, disturbed judgement, vision and vertigo
40% to 50%	Severe headache, confusion and collapse
50% to 60%	Same as above + syncope, Cheyne-stroke breathing, fits
60% to 70%	Coma, seizures, weak thready pulse and slow breathing, respiratory failures and death
80%	Rapidly fatal

Other investigations include complete blood counts (CBC), renal functions, metabolic profile, urinalysis, creatine kinase, ECG, cardiac enzymes and coagulation profile. Imaging studies like chest radiography, CT and MRI scans may be done to assess organ damage.

Treatment

Prehospital care

The ABCs (airway, breathing, and circulation) of resuscitation apply to the seriously ill or injured victims with presumed CO intoxication. The patient must be removed promptly from the source of CO exposure.

Hospital care

Patients with only mild symptoms (nausea, headache, weakness, or flu-like malaise) should receive 100% normobaric oxygen (NBO) for a period of about 4 hours with periodic re-assessment. The ability of oxygen treatment to eliminate CO from the body has often been estimated using the half-life of COHb with different treatment regimens which is 3 to 4 hours while breathing room air, 60 minutes with 100% NBO and 15 to 23 minutes with 100% hyperbaric oxygen (HBO) at 2.5 to 2.8 atmospheric pressure. A patient with mild symptoms will require oxygen for 4 to 6 hours or until COHb level is <5%. HBO treatment has been used in patients with major symptoms (any history of loss of consciousness, profound dip in blood pressure, amnesia, or myocardial ischaemia) with dramatic improvement. However, its superiority over NBO with regard to short- and long-term outcomes is controversial since HBO use is associated with barotrauma, ear pain and oxygen toxicity.

OZONE (O_3) POISONING

Ozone (O_3) is widely used by cleaning services for use in indoor building environments to deodorise, disinfect, 'kill' mould and for 'general health' and generating equipment companies. It is formed as an atmospheric pollutant by the action of sunlight on air having hydrocarbons and nitrogen oxide. Ozone toxicity is due to its oxidative potential and most commonly reacts with amino acids, peptides and other proteins as well as unsaturated fatty acids in the fluid layer of lung lining and epithelial cell membrane making lungs most commonly affected organ. The ozonisation of the fatty acids leads to the release of pro-inflammatory mediators in the lung resulting in inflammatory damage.

Clinical Features

Ozone at a concentration of 0.25 to 0.75 ppm (parts per million) causes shallow rapid breathing, cough, tightness in the chest and dryness of throat. It also increases the sensitivity of the lungs to allergens, histamine and acetylcholine.

Prevention

Ozone toxicity can be prevented by vitamin C, alpha tocopherol and sulfhydryl compounds in laboratory animals. Glutathione depletion affects the cellular sensitivity towards ozone. Alpha tocopherol has significant scavenging action.

CYANIDE POISONING

Cyanide is a potent cellular toxin and one of the most rapidly acting poisons. Common sources of exposure include: (a) occupational settings: electroplating plants, photographic development, plastic production, (b) inadvertent, suicidal, or homicidal ingestions, (c) patients on infusions of sodium nitroprusside, and (d) inhalation of smoke from burning plastics in closed-space fires. The natural source of cyanide includes bitter almond, apricot, peach, plums, apple, raw papaya, pear seeds and *Sorghum* grass (African cereal).

Pathophysiology

The avidity with which cyanide binds to metal-containing enzymes accounts for its serious cellular toxicity. By binding to iron of mitochondrial cytochrome C, it inhibits cellular respiration that results in anaerobic metabolism with increased lactic acid production and cell death.

Clinical Features

The time course and severity of the clinical effects of cyanide are a function of the nature of the cyanide-containing compound, the route of exposure, and the concentration of cyanide to which the patient is exposed. When inhaled, rapidly progressive and potentially fatal symptoms are evident within seconds. Concentration of < 50 ppm causes restlessness, anxiety, palpitations, dyspnoea, and headache. Higher levels of hydrogen cyanide (HCN) gas cause severe dyspnoea, loss of consciousness, seizures and cardiac arrhythmias, and cardiovascular collapse. Still higher levels are fatal and median lethal dose (LD50) for humans is estimated to be 200 ppm for a 30-minute exposure and 600 to 700 ppm for a 5-minute exposure.

On examination, patient may be anxious with a breath smelling like bitter almonds or garlic. The skin may appear cherry red and those with smoke inhalation may have soot over skin, mouth and nose. Other manifestations include tachycardia, hypotension and shock, irregular acidotic breathing, cyanosis, alteration in sensorium, confusion, ataxia, tonic and clonic seizures, paralysis and coma. Fundoscopy shows bright red retinal arteries and veins with dilated reactive pupils.

Investigations

Direct measurement of blood cyanide levels is not generally available. Plasma lactate level > 8 mmol/L is highly suggestive. Severe metabolic acidosis is a consistent accompaniment and its absence virtually excludes the diagnosis of cyanide toxicity. COHb levels are undertaken to rule out associated CO exposure.

Decreased cellular extraction of oxygen is reflected by an increased oxygenation of venous blood and decreased normal arterio-venous oxygen [(a-v) O_2] difference. Electrolytes are measured for anionic gap. Other causes of anion gap and metabolic acidosis need to be excluded. Imaging is not needed for acute poisoning but MRI may be required in case late neurological effects appear.

Treatment

Though severely poisoned patients may survive with supportive care (100% oxygen, intravenous fluids), use of antidote in massive exposure improves survival. Gastric decontamination should never take priority over resuscitation of the symptomatic patient. Crystalloids, vasopressors and sodium bicarbonate are used as per clinical indications.

Antidote therapy

Nitrites: Nitrites result in production of methaemoglobin which binds avidly to cyanide, frees cytochrome and restores aerobic cellular respiration. Ten millilitres of 3% solution of sodium nitrite is administered by slow intravenous infusion. It should be avoided in victims of smoke inhalation unless the COHb levels are <10%. Sodium nitrite is followed by administration of sodium thiosulphate (adult dose 50 ml of 25% of solution - 12.5 gm) at 5 ml per minute over 10 minutes. Sodium thiosulphate enhances the activity of the enzyme rhodanese. Twenty-five millilitres of 25% solution is repeated after 30 minutes. It is desirable to keep methaemoglobin levels below 30%. Significant side-effects include hypotension and excessive methaemoglobinaemia. Cyanide antidote kit (CAK) contains amyl nitrite pearls, sodium nitrite and sodium thiosulphate.

Hydroxocobalamin: It directly chelates cyanide and restores cytochrome oxidase aerobic respiration. Hydroxocobalamin (adult dose 50 mg/kg or 4 gm intravenous over 30 minutes) is used in combination with sodium thiosulphate.

METHAEMOGLOBINAEMIA

Methaemoglobinaemia results from conversion of ferrous ion on haem to ferric ions. Methaemoglobin has high affinity to oxygen and impairs oxygen delivery to the tissues. It may be congenital (deficiency of NADH methaemoglobin reductase) or acquired secondary to several drugs or chemicals that cause oxidative stress (**Table 2**). Concomitant oxidation of haemoglobin protein may cause its precipitation and a haemolytic anaemia.

Clinical Features

Clinical features are dependent upon not only the level of methaemoglobin (**Table 3**) but also on its rate of formation and associated toxicity of the responsible toxin.

Laboratory Diagnosis

Blood appears chocolate brown in colour. For a bed-side test when one to two drops of patient's blood are put on white filter paper a chocolate brown colour, which does not change with time, is observed. PaO_2 as well as calculated saturation is relatively the normal but measured arterial oxygen saturation (SaO_2) is reduced. This oxygen saturation gap, i.e. the difference between the calculated and the measured oxygen saturation, is >5% in normal circumstances.

Estimation of methaemoglobin in the blood is needed to confirm the diagnosis. Normal methaemoglobin levels are <1%. This widely available test requires only a venous specimen, although arterial blood may be used if arterial puncture is indicated for another reason.

Table 2: Chemicals Inducing Methaemoglobinaemia

Amyl nitrite	Naphthalene
Aminophenol	Nitrobenzene
Aniline dye and its derivatives	Nitroglycerine
Chlorates	Nitroprusside
Chloroquine and primaquine	Oxides of nitrogen
Copper sulphate	Paraquat
Lidocaine, benzocaine	Phenacetin
Local anaesthetic agent	Phenazopyridine
Metoclopramide	Sulphonamides, Dapsone

Table 3: Clinical Features of Methaemoglobinaemia

Methaemoglobin Concentration	Clinical Features
0% to 3%	Asymptomatic
3% to 15%	Usually no features
15% to 20%	Cyanosis with grey-brown hue, unresponsive to oxygen
20% to 50%	Dyspnoea, headache fatigue, syncope, weakness, dizziness, tachycardia
50% to 70%	Tachypnoea, hypoxia, metabolic acidosis, seizure, arrhythmia, central nervous system (CNS) depression, bradycardia
>70%	Haemolytic anaemia, renal failure, coma and death

Treatment

The toxin if recently ingested should be removed by gastro-intestinal decontamination. Mild methaemoglobinaemia with levels ≤20% can be treated with oxygen supplementation. Antidotal therapy with methylene blue is reserved for patients with severe methaemoglobinaemia. Methylene blue indirectly accelerates the enzymatic reduction of methaemoglobin by NADPH-methaemoglobin reductase. It is administered intravenously in a dose of 1 to 2 mg/kg body weight as a 1% solution slowly over 5 minutes. If significant improvement does not occur in an hour, it can be repeated. It results in bluish discolouration of skin and urine that may make clinical assessment of true cyanosis difficult. Side effects include precordial chest pain, dyspnoea, restlessness, apprehension and tremor. Highly unstable patients may additionally benefit from exchange transfusion through immediate enhancement of oxygen delivery. Exchange transfusion may also be used in G6PD deficiency where methylene blue is contraindicated. Inappropriate response to methylene blue may be seen following dapsone intake and sulphaemoglobinaemia. Vitamin C, a slow acting drug for methaemoglobinaemia, may be tried if methylene blue is not available. Dialysis may be useful.

HYDROGEN SULPHIDE

Hydrogen sulphide is a colourless irritant gas that is heavier than air with an odour of rotten eggs. It is formed in sewers and cesspools. It causes cellular asphyxia through the inhibition of the mitochondrial cytochrome a3.

When inhaled in pure form, it is almost immediately fatal, causing coma and respiratory failure. It causes irritation of eyes, nose, throat and respiratory passages at low concentration whereas higher concentrations would cause dizziness, headache, vomiting, abdominal pain, cyanosis, dilated pupils, laboured breathing, irregular pulse, seizures, delirium, stupor, coma and death. Pulmonary oedema and adult respiratory distress syndrome may occur. Pharyngeal and conjunctival erythema and corneal abrasions are observed on clinical examination.

Treatment

The victim must be removed from the source of exposure and resuscitated at site. Hospital management consists of control of hypoxia, seizures, pulmonary oedema and acidosis. Hyperbaric oxygen therapy has been found to be useful. If not available, patients should receive 100% oxygen. Inducing methaemoglobinaemia using amyl nitrite and sodium nitrite has been found to be useful as methaemoglobin has higher affinity to hydrogen sulphide than to cytochrome oxidase. Sodium thiosulphate use is not beneficial.

COPPER SULPHATE

(CUPRIC SULPHATE, BLUE VITROL, BLUE STONE, *NILA THOTHA*)

Copper sulphate, a blue, crystalline irritant, is used chiefly in agriculture as a pesticide, herbicide or fungicide. It is also used in leather industry and was in the past used as a precipitator in heavy metal poisoning as well as in the treatment of gastric and topical exposure to phosphorous. It has a nauseous and metallic taste. Solutions are acid to litmus. Fatal dose is 15 to 30 g.

Clinical Features

Copper sulphate is absorbed from the skin as well as gastrointestinal tract. Skin exposure results in burning pain and itching. Eye contact causes redness and corneal injury. Oral ingestion results in a metallic taste, salivation, thirst, nausea, abdominal pain and recurrent vomiting within 15 to 30 minutes. The vomitus is blue or green that turns deep blue on addition of ammonium hydroxide. Painful diarrhoea may occur. Systemic copper toxicity affects first erythrocytes and then the liver and kidneys. Intravascular hemolysis appears 12 to 24 hours following its ingestion either due to direct red cell membrane damage or secondary to the inactivation of enzymes (including glutathione reductase) that protect against oxidative stress. It is followed by jaundice, oliguria and renal failure. Cramps in the legs, spasm or convulsion can occur. Large dose produces frontal headache and circulatory collapse. Severe neurological symptoms include paralysis of the limbs, drowsiness and coma. Fatalities are known in severe poisoning.

Treatment

Treatment is mainly symptomatic and supportive. Ovalbumin or 1% potassium ferrocyanide should be used for gastric lavage. Patients with renal failure need dialysis.

HOUSEHOLD POISONS

Kerosene Oil

Kerosene oil, a petroleum product, is a mixture of hydrocarbons contaminated with organic sulphur. Petrol, gasoline, vaseline and paraffin are other related hydrocarbons. Besides household cooking and burning, kerosene is used as paint thinner. Lethal dose of kerosene oil is 30 to 100 mL.

Clinical features

Kerosene is toxic both through inhalational and oral routes. Inhalation results in dizziness, nausea, vomiting, burning sensation in chest, dry cough, headache and ataxia. Severe poisoning produces pulmonary oedema, haemoptysis, mental confusion, hallucinations, stupor, cyanosis, convulsion and coma. Death is mainly due to ventricular fibrillation and respiratory failure. Ingestion of kerosene oil produces burning pain in the mouth, throat, dry irritating cough, nausea, vomiting, colicky abdominal pain and diarrhoea. Large quantity of oil can produce neurological dysfunction similar to the one described for inhalational toxicity. The pupils are initially constricted and later dilated. Aspiration of as little as 0.2 mL of kerosene oil can produce chemical pneumonia and pulmonary oedema. The breath, vomitus and urine gives off the peculiar smell of kerosene. The chest radiograph may reveal perihilar densities, basal pneumonia, and atelectasis.

Treatment

In case of inhalational toxicity, remove the victim to open air, ensure patent airway, keep the body warm and on hospitalisation administer oxygen. Follwing ingestion, induction of vomiting or gastric lavage is contraindicated due to increased risk of aspiration. Activated charcoal is not useful. Antibiotic and steroids are not indicated. Victims with severe respiratory symptoms and abnormal radiography should be observed for complications and managed appropriately for at least 2 to 3 days.

Hair Dye

Hair dyes are classified as oxidative dyes (permanent), direct dyes (semi-permanent or temporary), metal salts and natural salts. Most of the modern commercially available oxidative dyes consist of two components that are mixed prior to use and generate the dye on/in the hair by oxidative chemical reaction. They contain several ingredients which includes primary intermediates (para-phenylenediamine [PPD], para-toluenediamine [PTD], substituted para-diamines, ortho- or para-aminophenols), couplers or modifiers (m-phenylene-diamines, m-aminophenols, resorcinol), oxidants and alkalinising agents. PPD is an aromatic amine $C_6N_4(NH_2)_2$ in which at least one hydrogen of the cycle has been replaced by an amine substitute. For dyeing purposes, PPD is added with hydrogen peroxide resulting in the formation of Bandrowski's base, which is highly allergic and toxic. The principal adverse effect of high oral doses of PPD in man and higher mammals is angioneurotic oedema leading to acute respiratory distress. It may cause acute renal failure secondary to rhabdomyolysis, hypovolaemia, intravascular haemolysis or direct toxic effects of PPD or its metabolites on the kidneys. Other less commonly reported features of PPD poisoning are liver failure, drowsiness, altered sensorium and convulsions, gastrointestinal symptoms, exophthalmos and chronic renal failure.

Treatment of systemic PPD poisoning is mainly supportive as there is no specific antidote. Early clinical diagnosis and therapeutic interventions in the form of tracheostomy, intravenous fluids and haemodialysis leads to full recovery.

Household and Toilet Cleaners

Cleaners that are usually toxic when ingested include dishwasher, toilet bowl, and oven cleaners. They can pose a significant risk, especially in children and elderly, but majority of the affected individuals have minimal or no side-effects.

Detergents

These are products that contain anionic surfactants and detergent builders, such as sodium phosphates, sodium carbonate and sodium aluminosilicates, which are highly alkaline. Detergents fall into three main categories—nonionic, anionic, and cationic. Nonionic and anionic detergents are of low toxicity. Cationic detergents, such as benzalkonium chloride and cetrimide, are less frequently encountered in domestic cleaners and produce corrosive effects if a concentrated solution is consumed. The route of exposure is almost always oral ingestion but inhalational, ocular and dermal exposures and even intravenous route have been reported. Corrosive injury to the gastrointestinal, respiratory and corneal mucosa (depending on route of exposure), cardiac dysfunction, acute renal failure with rhabdomyolysis, ARDS (early and late onset), haemolysis, frequent ventricular tachycardia and coagulation abnormalities have been reported secondary to exposure to household detergents. There is no standardized treatment protocol for detergent poisoning. Endotracheal intubation and supportive ventilation are required frequently. Syrup of ipecac is not advised due to the risk of aspiration and further caustic injury to the oesophagus.

Toilet Rim Block

Disinfectant used in flush toilets is made from anionic surfactants. It may be of two types, in cistern or rim blocks. The composition can vary, but they contain borax, troclosene sodium, sodium percarbonate, sodium carbonate (washing soda). Systemic toxicity is low but local corrosive action predominates if ingested.

Bleaches

These household solutions contain approximately 3% to 10% sodium hypochlorite or less commonly 3% hydrogen peroxide. These are extremely unpalatable and unlikely to cause serious damage. Symptoms are same as that of caustic ingestion but respiratory symptoms may result when bleach is mixed with ammonia (producing chloramine gas) or with toilet cleaners, (forming chlorine gas).

Treatment

Removing the patient from the source and minimising the period of contact between the corrosive and the tissue will prevent tissue damage. Irrigation with copious amount of water is paramount as prompt dilution reduces the exposure. Patients with respiratory distress may have significant oral, pharyngeal, and/or laryngotracheal injury necessitating emergency airway management. Prior to intubation, extent of airway injury should be assessed by fiberoptic endoscopy. Early endoscopy is indicated in patients with corrosive ingestion for prognostication and should be done as soon as the patient is haemodynamically stable. Before endoscopy, perforation should be ruled out. Endoscopy can also be used to place a naso-jejunal tube across the lesion so as to facilitate early initiation of enteral feeding.

Rodenticides/Insect Repellent

Rodenticides usually contain hydroxycoumarin anticoagulant. Second-generation superwarfarins and the indandione derivatives were introduced when rodent resistance to warfarin began to appear. Others contain bromethalin, cholecalciferol, alpha chloralose strychnine and zinc phosphide. Alphachloralose causes central nervous system (CNS) depression. Most one-time warfarin ingestions are insignificant accidental poisonings and do not cause any bleeding problems. Toxicity requires large amounts in a single exposure or a repetitive exposure over several days. Therapy is not necessary for ingestion of a single mouthful of warfarin. The superwarfarins have a longer biologic half-life; a single ingestion may result in marked anticoagulation effects for weeks to months. Acute intentional or repeated ingestions can cause severe bleeding. For potentially toxic ingestion, therapy consists of activated charcoal and a cathartic, with a baseline International normalisation ratio (INR) determination and repeated in 12 to 24 hours. If the INR is greater than twice the normal, vitamin K (phytonadione) administration is indicated.

Boric Acid
(Boracic Acid, Acidum Boricum, H_3BO_3)

Boric acid, an odourless white powder, is used as an antiseptic, effective agent against cockroach infestation as well as in leather industry and the production of glaze and enamel. The usual fatal dose of boric acid is 15 to 20 g for adults and 5 g for children.

Clinical features

The victim presents with anorexia, nausea, vomiting and epigastric pain. Skin involvement occurs within 1 to 3 days of ingestion. Skin turns erythematous with bullae and blisters initially over the hands that become generalised. Severe intoxication results in acute kidney injury and renal failure. Bloody diarrhoea with severe colicky abdominal pain and jaundice can occur. Other symptoms include malaise, lethargy, headache, restlessness, hyperpyrexia, muscle twitchings, tremors, seizures followed by coma and Cheyne-Stoke respiration. Chronic poisoning may lead to diffuse alopecia, raw tongue anorexia and renal damage.

Management

It includes gastric lavage and activated charcoal to remove the toxin, administration of intravenous crystalloids with alkaline solutions and glucose to ensure adequate urine output. Boric acid is dialyzable. Renal failure is managed like any other acute renal injury. Oxygen and artificial ventilatory support are required for respiratory failure.

Essential Oils

These are volatile mixtures of esters, alcohols and ketones. Some substances, e.g. camphor, an active ingredient of common OTC products such as Vicks Vapo Rub are very toxic. Mucosal irritation, vomiting, epigastric pain may be followed by

secondary hepatic and renal failure in severe toxicity. Clinical observation and supportive treatment is needed.

Nail Care/Nail Varnish Removers

These contain acetone or ethyl acetate. Irritation of mucous membranes, vomiting, CNS depression, ketosis, acidosis and hyperglycaemia are commonly observed. Presence of other solvents may lead to different complications like caustic injury (methanol/methacrylic acid), methaemoglobinaemia (nitroethane) and cyanide poisoning (acetonitrile). Hospital admission is needed in symptomatic individuals. Nitroethane and acetonitrile ingestions require referral to the emergency.

Naphthalene

It is a hydrocarbon contained in the middle oil distillation of coal tar. It is chiefly used in the manufacturing of certain azo dyes, moth repellent, wood preservative and deodorant. Ingestion of naphthalene produces nausea, vomiting, loose motions, headache, gait disturbances, drowsiness, muscle twitching, cyanosis and profuse perspiration. Severe toxicity produces jaundice, haemolytic anaemia in G6PD deficient individuals, albuminuria, haematuria and acute renal failure. CNS manifestations include encephalopathy, seizures, coma and death. There is no specific antidote; hence the treatment consists of gastric lavage, saline purgative, intravenous fluids, sodium bicarbonate, blood transfusion and diuretics as supportive therapy.

PHOSPHORUS

Of the two varieties, yellow or white is more toxic than the red phosphorus. White phosphorous on exposure to light slowly oxidises and emits white fumes of phosphorus trioxide that has garlic-like odour and is luminous in dark. Red phosphorus is tasteless, odourless, not luminous and nonpoisonous substance that is used in the manufacturing of safety matches.

Clinical Features

It acts rapidly when, for example, ends of lucifer matches are swallowed, through mistake or malice. The fatal dose of yellow phosphorus is 10 to 100 mg. Symptoms develop after a latent period of 1 to 6 hours. Large dose produces severe vomiting, retrosternal and epigastric burning associated with unquenchable thirst. The vomitus is luminous in the dark and may be associated with haematemesis. Large offensive smelling diarrhoea indicates severe toxicity. These symptoms are relieved temporarily after 24 to 48 hours. Subsequently, features of hepatic failure and renal failure may develop after 1 to 6 days. Liver injury is characterised by jaundice with severe pruritis that is associated with pain in stomach, vomiting with haematemesis and bleeding from various sites. Renal involvement leads to oliguria and renal failure. Urine is high coloured with albuminuria, bile pigments, casts and occasionally leucine, tyrosine and cystine crystals. Electrolyte disturbances, hypoglycaemia and hypoprothrombinaemia are often present. CNS symptoms in severe intoxication include severe frontal headache, hallucinations, restlessness, insomnia, tinnitus, tremors, deafness, drowsiness, convulsions and coma. Cardiac toxicity may lead to severe depression of cardiac function leading to circulatory failure and arrhythmia. Priapism, severe delirium and convulsions with peripheral circulatory failure precede death.

Chronic poisoning with yellow phosphorus produces necrosis of mandible, cachexia and anaemia.

Treatment

There is no specific antidote for phosphorus. The treatment is mainly supportive.

CHLORATES

Sodium potassium chlorates, used as weed killers, in matches and mouthwashes, are strong oxidising agents. These cause damage to the liver, kidneys and the circulating cells. Liver injury and disseminated intravascular coagulation are common features of intoxication. Death during early phase of intoxication is due to dineminated intravascular coagulation (DIC) or hypoxia caused by methaemoglobinaemia and haemolysis and renal failure in late stages. The treatment is mainly supportive. Sodium thiosulphate inactivates chlorates and hence, it can be used as lavage fluid. Use of vitamin C and methylene blue is ineffective in converting methaemoglobin into haemoglobin. Exchange transfusion, peritoneal dialysis and haemodialysis have been found to be effective in some cases.

HYDROGEN PEROXIDE

Hydrogen peroxide is available as 3% solution for use as an antiseptic. However, industrial grade solution is 35%. Ingestion of 3% solution is generally nontoxic as it is converted into water and oxygen in the stomach. Since the volume of oxygen liberated is 10 mL per millilitre of hydrogen peroxide solution, ingestion of large amount of dilute solution may produce gastric distension. If large amount of solution containing higher concentration (>10%) of hydrogen peroxide is ingested, the patient may develop coma, cyanosis, hypotension, heart block, metabolic acidosis and seizures.

Treatment

If there is gastric dilatation due to oxygen, a Ryle's tube should be inserted to decompress it. Otherwise, the management is symptomatic.

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Section 27

Environmental Medicine

Section Editor: Randeep Guleria

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27.1 Basic Considerations of Environmental and Occupational Diseases

Randeep Guleria

INTRODUCTION

Environmental and occupational health is emerging as an important discipline in medicine due to the change that is occurring in climate due to industrialisation and urbanisation. It is being increasingly recognised that environmental factors have an important link with many chronic and infectious diseases. Deaths from heart disease and respiratory illness increase during heat waves and many diseases such as malaria, dengue, chikungunya and cholera are sensitive to changes in the climate.

According to the World Health Organization (WHO), 'In its broadest sense, environmental health comprises those aspects of human health, disease and injuries that are determined or influenced by factors in the environment. This includes the study of both the direct pathological effects of various chemical, physical and biological agents, as well as the effects on health of the broad physical and social environment, which include housing, urban development, land use and transportation, industry and agriculture'. The WHO estimates that 24% of the global diseases burden and 23% of all deaths can be attributed to environmental factors. Also, environmental factors have a much bigger impact in developing countries than developed ones and this effect is seen much more in the vulnerable population like children and elderly.

Environmental medicine encompasses human illness or dysfunction that may occur due to environmental factors. Many diseases are affected by environmental factors. These include diarrhoea, lower respiratory tract infections, injuries, malaria, perinatal conditions, chronic obstructive pulmonary disease, coronary artery disease, lead toxicity and drowning. Illnesses that occur due to workplace environmental factors are termed as occupational diseases.

In a developing country like India, the burden of various diseases increases due to environmental factors. It is estimated that 94% diarrhoeal disease burden can be attributed to environmental factors like unsafe food, unsafe drinking water and poor sanitation and hygiene. Similarly, there is strong evidence in our country linking lower respiratory tract infection to indoor air pollution caused by the use of solid fields in household. Almost 42% of acute lower respiratory tract infections in developing countries are attributable to environmental factors. Besides this the close link between vector borne diseases and environmental conditions is well established. Also, factors like deforestation, increasing vehicular traffic, migration from rural to urban areas, decreasing water resources and inadequate drainage system are important environmental factors that contribute to infectious diseases.

Occupational diseases also form an important but often neglected part of human health. It is estimated that in India about 45,000 fatal injuries and 17 million non-fatal injuries occur due to occupational factors. It has been estimated that in India prevalence of silicosis is 6.2% to 34% in mica minors, 4.1% in manganese miners, 30.4% in lead and zinc miners, 9.3% in coal miners, 27.2% in iron foundry workers and 55% in state pencil workers. Also asbestosis occurs in about 3% of asbestosis miners and 21% of mill workers in India. Also, it is estimated that about 28% to 47% of textile workers are exposed to dust and suffer from byssinosis.

Broadly, environmental diseases could be caused by exposure to harmful and toxic agents through air, water, soil and food. Environmental exposure can cause or aggravate a number of diseases like asthma, dermatitis, etc. In many cases these disease do not have a unique presentation and can present to different specialties. Environmental diseases occurring through air pollution are a major cause of concern and their prevalence is increasing. The important environmental pollution consists of air pollution, water pollution and the recent emergence of E-waste which may be the crux of environmental diseases.

AIR POLLUTION

Air pollutants affect the human body through the inhalational route. There are more than hundred substances which pollute the air we breathe and that can harm human health. Pollutants are generally classified as primary or secondary pollutants. Chemicals which are directly emitted from a source are known as primary pollutants. These include sulphur dioxide, nitrogen oxides, carbon monoxide, volatile organic compounds, etc. Also particulate matter emitted due to combustion from a source such as automobile exhaust, heating, cooking and from industrial sources are primary pollutants. Secondary pollutants are those pollutants that are formed from a chemical or photochemical reaction in the atmosphere. On exposure to sunlight volatile organic compounds and nitrogen oxides reacts photochemically and after a complex series of chemical reactions produces pollutants which are harmful. Ozone is an important secondary pollutant and can produce significant adverse effects on human health. Other secondary pollutants include formaldehyde, nitric acid, and different aldehydes.

Sulphur Dioxide

Sulphur dioxide is produced mainly by burning of coal and by the combustion of fossil fuels in power plants. Sulphur dioxide is mainly absorbed in the upper airways as it is water soluble. Some of it reaches the lower airways and causes bronchoconstriction. It can therefore worsen asthma.

Nitrogen Dioxide

Nitrogen dioxide is emitted from automobiles. Nitrogen oxides play an important role in the reaction which occurs in the atmosphere and leads to the formation of ozone. They also form nitrate particles and acid aerosols. Exposure to nitrogen dioxide for a short term leads to changes in airway responsiveness

and deterioration in pulmonary function in individuals with underlying lung disease. Long term exposure may lead to increased chance of recurrent respiratory tract infections and alter lung mechanics.

Carbon Monoxide

Carbon monoxide is produced mainly due to motor vehicle emission. In urban areas more than 80% of carbon monoxide emission may be due to motor vehicles. Besides this, the combustion of coal, oil and gas also leads to carbon monoxide production. Carbon monoxide quickly enters the blood stream and forms carboxyhaemoglobin which causes more systemic effects. It reduces oxygen delivery to the tissues and may have a serious health threat to those with underlying heart disease.

Lead

The atmospheric levels of lead have decreased due to the use of unleaded fuel. However, lead toxicity continues to be a problem due to the exposure occurring in drinking water. Lead exposure leads to adverse effect on the central nervous system, kidney and liver. Lead toxicity can lead to lower intelligence, learning deficits and behavioural disturbances.

Ozone

Ozone is produced as a secondary pollutant and is a component of photochemical smog. Ozone is a pulmonary irritant and an oxidant. Exposure to ozone causes cough, chest tightness and wheezing. It also leads to a decline in lung function. Ozone also affects mucous membrane and causes pulmonary inflammation and has both a local and systemic effect on immune system. Patients with underlying respiratory illness like asthma and chronic obstructive airway disease are more prone to the harmful effect of ozone. High ozone concentrations have been linked with increased hospital admissions for pneumonia, COPD and asthma.

Particulate Matter

Particulate matter consists of liquid or solid mass contained in an aerosol. It is a mixture of numerous different chemicals with varying properties. Particulate matter was initially expressed as total suspended particulates (TSP). Subsequently the term PM_{10}, i.e. suspended particulates with a mean aerodynamic diameter of 10 microns or less was used. It was later realised that still finer particulate matter can be harmful and the term $PM_{2.5}$, i.e. particulate matter with a mean aerodynamic diameter of 2.5 or less was used. Broadly particulate matters from 2.5 microns to 10 microns in diameter are coarse particulate matter. Coarse particulate matter consists of mainly of airborne soil dust and elements such as silicon and aluminium. Fine particles are those with a diameter of less than 2.5 microns. They are formed mainly from combustion or from photochemical reactions and are composed mainly of sulphate and organic material. Particles of more than 10 microns are mainly filtered in the upper airways and do not reach the lower airways. Smaller particles between 2.5 microns to 10 microns reach the lower airway and are deposited there. Particles less than 2.5 microns go deeper and reach the alveolar region and cause damage in this area.

Indoor Air Pollution

Indoor air pollution has a significant effect on human health globally. This effect is more pronounced in developing countries. It is estimated that more than 60% of households in India use biomass fuels as energy source. Wood, roots, crop residue, cattle dung are amongst the biomass substances used for energy source. Biomass cooking converts 6% to 20% of the fuel carbon to toxic substances due to poor combustion. The harmful air pollutants that are emitted by using biomass fuel include carbon monoxide, particulate matter, hydrocarbons, oxygenated organics and chlorinated organic compounds. There is now a strong evidence linking indoor air pollution exposure to a number of illnesses especially lung diseases. Indoor air pollution is linked to acute lower respiratory tract infection. In adults there is a strong association of indoor air pollution and chronic obstructive lung disease especially in women who start cooking in rural areas at an early age. Also, there is evidence to suggest that biomass exposure in pregnant women may lead to an increase in low birth weight neonates and increased chance of still births. There is also some epidemiological evidence linking exposure to indoor air pollution to lung cancer and tuberculosis although the association is not that strong. Biomass exposure also significantly contributes to fine particulate matter exposure, i.e. $PM_{2.5}$. Exposure to $PM_{2.5}$ may lead to a higher chance of lower respiratory tract illness and still births in pregnant women.

WATER POLLUTION

Water is essential for human survival. Water pollution constitutes another serious risk to health. Water pollution occurs when energy and substances are released and that degrades the quality of water for other users. Anything that is added to water that is more than its capacity to break it down constitutes water pollution. Chemical pollution of surface water causes major health problems as it can be used directly for drinking or it may contaminate shallow wells which are used for drinking. Usually, it is human action which is responsible for water pollution, although it may occur naturally as happens when water flows through soil with high acidity. Ground water, which is much deeper, has very few pathogens as it gets filtered when it passes through many underground layers. It can be polluted by toxic chemicals like fluoride and arsenic which may be present in the soil or the rock layers. Similarly, pollution of coastal water can cause contamination of sea food. The global effect of water pollution has not been studied in detail, and is limited to mainly outbreaks of waterborne infections or certain chemical toxins in limited areas, i.e. arsenic in drinking water in Bangladesh, mercury poisoning in the United States, etc. Acute exposure to contaminated drinking water can cause inflammation to the eyes, skin and the gastrointestinal tract. Chronic exposure to contaminated water can cause significant health effects and can lead to liver and kidney damage. This occurs due to chronic exposure to copper, cadmium, arsenic, mercury, chromium and chlorobenzene. Endocrine effects have been reported and problems relating to reproduction, development and behaviour have also been observed.

ELECTRONIC WASTE (E-WASTE)

Pollution due to electronic and electrical waste has rapidly grown over the last decade. Waste which is generated from used electronic devices and household appliances constitutes E-waste. This waste comprises of a wide range of equipments and devices such as computers, mobile phones, refrigerators, washing machines, air conditioners, etc. E-waste may contain many toxic substances which may be harmful to the environment and human health. This can have a significant

economic and social impact on society. The E-waste obsolescence rate in India for 2005 was estimated to be 1,46,180 tonnes, and it is estimated that this will exceed 8,00,000 tonnes by the year 2012. A large number of hazardous substances can be found in E-waste. These include lead, cadmium, chromium, mercury and plastics. Uncontrolled burning, disposal and dismantling of E-waste can cause a number of problems including air pollution and water pollution. There is a lack of an environmentally effective recycling infrastructure for E-waste and this leads to pollution of the environment. There is, therefore, a need to increase public awareness about the harmful effects of E-waste and develop an effective recycling and disposal plan to prevent or minimise air and water pollution.

CONCLUSION

It is important to understand that environmental and occupational health problems will have a number of acute and chronic effects on human health. This can be both for infectious and non-infectious illnesses. A holistic view is needed to address the problem of environmental health where agriculture, animal husbandry, public health, water safety and air pollution need to be looked at in a combined manner for education, planning and resource allocation. A close team work between scientists, public health professionals and administrators is needed for integrated vertical and horizontal planning.

For clinicians an awareness about the health effects of pollution is important as this will help in the prevention and proper management of many diseases associated with both air and water pollution.

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27.2 Climate Change—Health and Disease

Anil Gurtoo

INTRODUCTION

Our planet, Earth, which is some 4.5 billion years old, has been through at least 5-mass extinctions. The first extinction is known as Ordovician (439 million years back) and this was followed by Devonian (354 million years), Permian-Triassic (252 million years), Cretaceous-Tertiary (65 million years) and Paleocene-Eocene Thermal Maximum (PETM) 55 million years ago. All these species extinctions are thought to be triggered by global climate change. The worst happened during the Permian-Triassic extinction event, which is also known as 'the great dying', when some 90% of marine and 70% of land species were wiped out, consequent to a large scale build up of green house gases (GHGs) and a temperature rise of more than 8°C caused probably by a large scale volcanic eruption over Siberia. The most recent is the PETM, occurred some 55 million years ago as a result of sudden release of vast quantum of GHGs that triggered a surge in global temperatures of about 5°C to 8°C over a span of a few thousand years and lasted 100,000 years. The source of GHGs is speculated to have arisen from the destabilisation of beds of frozen methane hydrate sequestered at the ocean's bottom. The release of frozen sea bed methane was probably triggered by an anomaly in the thermo haline circulation (THC) that pushed down warm waters leading to the release of sea bed methane (a green house gas with a warming potential 25 times of carbon dioxide).

ANTHROPOGENIC CLIMATE CHANGE

In the landmark study of temperature change, *Charles Keeling* in 1958 began recording monthly carbondioxide (CO_2) levels at Mauna Loa observatory, atop a 3,970 m high extinct volcano in Hawaii. Measurements taken over the past 50 years reveal two superimposed trends.

(i) A progressive rise in CO_2 levels from 275 ppm in 1958 to 385 ppm at present, and

(ii) Superimposed upon the rising CO_2 curve, a sharp annual rise and fall in CO_2 by about 50 ppm. This see-saw corresponds to the thickening and thinning of the photosynthesising green cover on account of seasonal shedding (winters) and gaining (summers) of green leaves in the Northern Hemisphere.

This gave rise to the famous Keeling's Curve: The annual see-saw atop a steadily rising CO_2 concentrations. In parallel to the rising CO_2 the average surface global temperature has already increased by 0.76°C above the pre-industrial levels and the sea-level by 4 cm (is rising at 3 mm/year). The Intergovernmental Panel on Climate Change (IPCC) was formed in 1988, it states that the evidence for global warming is unequivocal and is due to human activity (anthropogenic).

The Green House Effect

If our Earth lacked its gaseous atmosphere, all the incoming solar energy would be radiated back in to the space and the average surface temperature would plunge to –18°C. However, on account of the heat trapping effects of atmosphere, the Earth's surface temperature averages at 14.4°C. This is called the 'green house effect'. Out of the total sunlight that reaches earth:

1. About 30% gets reflected back to the outer space by reflectivity of bright surfaces such as low level clouds, dust, snow and ice. This reflective property of bright/white surface is called 'Albedo' and is a factor in cooling. Conversely, darker surfaces like ice-cleared sea absorb the incoming solar energy and are a factor in warming (low albedo).
2. More than 20% of sunrays are absorbed by the atmosphere mainly by water vapour.
3. The remaining 50% is absorbed by the Earth's surface – land, forests and oceans. Of this 50% is absorbed by the Earth, a third or so is re-radiated back as infrared waves (heat waves). Most of this radiated infrared is absorbed by the green house gases (GHGs) present in the atmosphere, which then radiate some of it to the outer space and some back to the Earth, thus keeping the mean surface temperature warm at 14.4°C.

The Green House Gases

The main GHGs are CO_2, methane, water vapour, ozone, nitrous oxide (N_2O) and chlorofluorocarbons.

Carbondioxide

CO_2 forms some 0.04% of the atmosphere and is the main green house gas. Its present concentrations are the highest ever recorded at 384 ppm, and rising by 1 ppm to 2 ppm per year as a consequence of human activities. Historical data from the 650,000 year old ice-core samples from Vostok, Antarctica reveal that atmospheric CO_2 levels have always held constant between 180 ppm (during ice-ages) and 280 ppm for most of our Earth's geological past. While the natural CO_2 is produced by the decomposition of dead organic matter and exhalations of humans and animals, the anthropogenic CO_2 is generated mainly by the combustion of fossil fuels (coal, oils and gas) and land clearing for agriculture. Of the total CO_2 thus released to atmosphere, nearly 50% is absorbed back by the natural sinks: the oceans and the land (chiefly by plant photosynthesis) in an equal measure of 25% each. The remainder stays up in the air as a green house gas for nearly 100 years.

Methane (CH_4)

It is a far more potent GHG with a warming potential 25 times that of CO_2. But its residence time is only 10 years and its atmospheric concentration has stayed low at 2 ppm. In nature it is produced from the livestock (aerodigestive processes), decaying organic matter, and the anthropogenic component is generated by: untreated sewage, industrial actions, rice cultivation, livestock rearing and land fills.

Water vapour

Though a weak GHG, it acts mainly as a force multiplier through a positive feedback effect wherein, as the temperatures rise, more and more of vapour gets released due to enhanced evapotranspiration, this extra-vapour in turn further enhances the warming, which in turn further increases the amount of vapour. Such a spiralling signal enhancement (temperature rise) is termed as positive feedback effect.

Ozone (O_3)

Ground level (harmful) ozone is produced when sunlight acts upon the aerosols present in the stagnant air masses and smog. It is this ground-level ozone that causes the excess cardio-respiratory mortality. Its concentration has stayed fixed at 0.03 ppm and has a residence time of only a few days. Quite the contrary, the high level (stratospheric) of ozone acts as a shield to the harmful UV light. It is here that its decrease (ozone hole) due to anthropogenic CFCs, leading to an increased influx of UV radiation.

Nitrous oxide (N_2O)

It is present in concentrations of 3 ppm, but with a warming potential 300 times of CO_2 and a residence-time of 300 years. In nature, it is produced mainly by lightening thunders and soil bacteria, whereas, its anthropogenic sources lie in diesel based combustion and fertiliser use.

Chlorofluorocarbons

Produced as a result of human actions (refrigeration, aerosol products), these are extremely potent with warming potentials 124 to 14,800 times of CO_2 (hydrofluorocarbons); 7,400 to 12,200 times of CO_2 (perfluorocarbons); and 22,800 times of CO_2 (sulphur hexafluoride). They form around 1 ppm of the air but are extremely long lived. They have been responsible for the causation of ozone hole.

HEALTH EFFECTS OF CLIMATE CHANGE

The health impacts resulting from climate change can be framed in terms of an integrated model centred on the 'epidemiological triangle' is conceptualised in **Figures 1 and 2**. The key variables are displayed in **Figure 1**, while **Figure 2** displays the 'upstream domains' which stress the epidemiological triad and destabilise it. The 'downstream domains' depict the health outcomes and their socioethical implications.

Tipping Points

A term that refers to a critical threshold, beyond which even a minor perturbation can lead to the emergence of a new state.

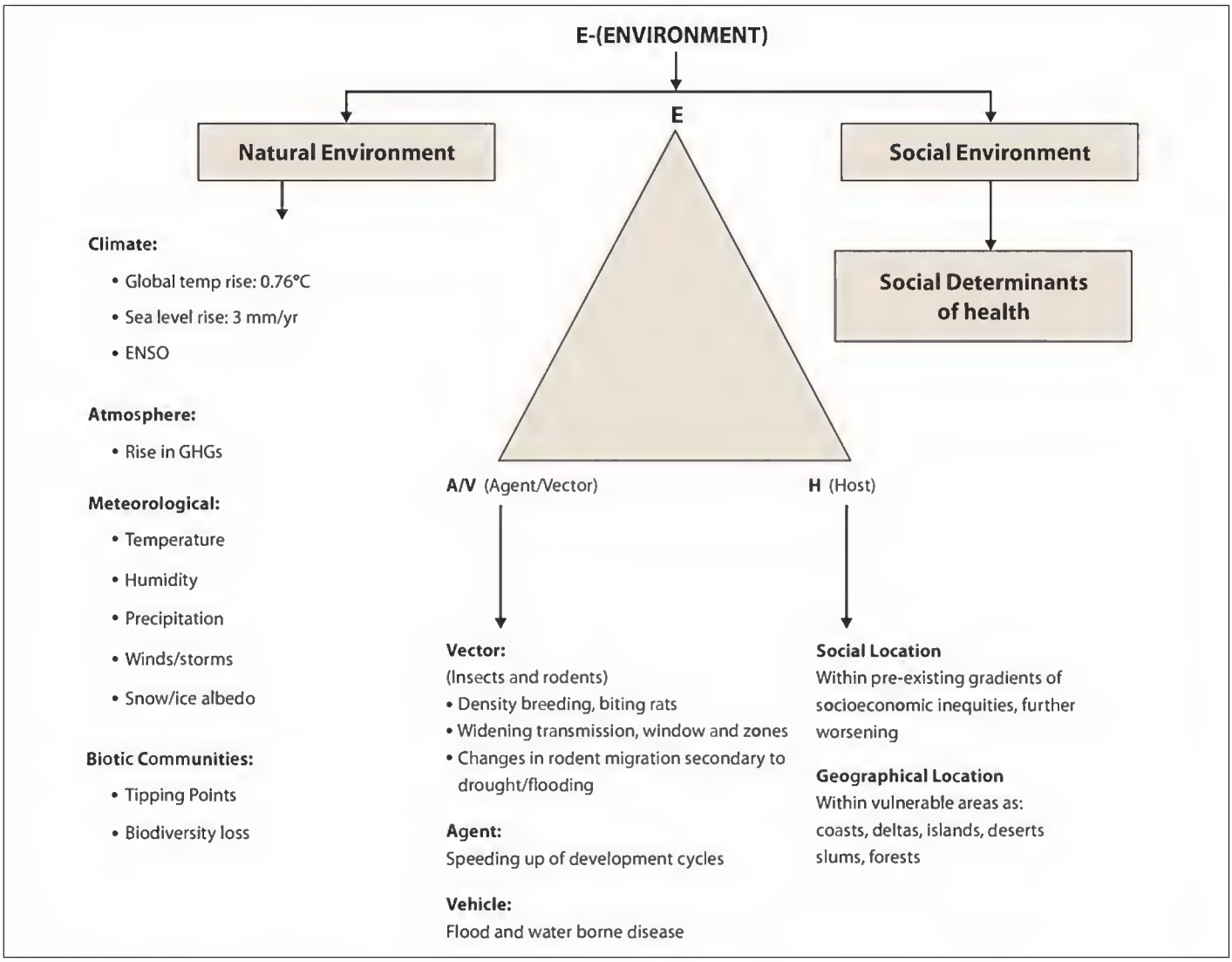


Figure 1: The epidemiological triangle of climate change and its health effects.

ENSO = EL-Nino Southern Oscillation; GHGs = Green House Gases.

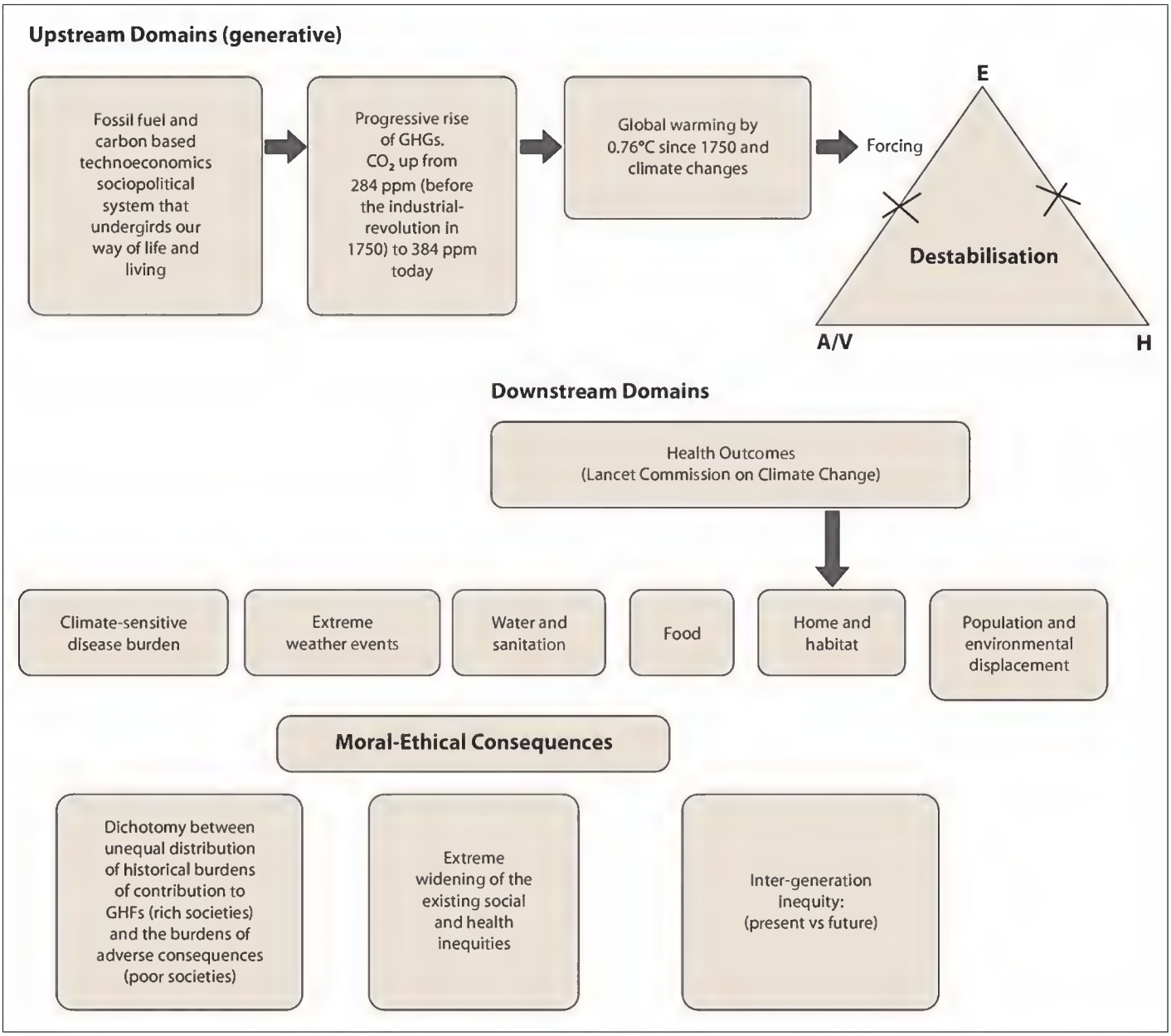


Figure 2: Upstream and downstream domains responsible for destabilisation of epidemiologic triangle.

Once a tipping event is triggered after the crossing of the tipping point or threshold, there is no turning back, even if all the GHG emissions were to end.

Lenton *et al* have identified several sectors of Earth's ecological systems that might cross the tipping points leading to non-linear outcomes including several orders of magnitude larger than predicted by current models (**Table 1**).

Table 1: Important Tipping Points in the Climate Change and their Consequences

S. No.	Tipping Event	Consequences
1.	Loss of Arctic Summer Sea ice	Higher average global temperatures
2.	Greenland ice sheet meltdown	Global sea level rise up to 7 m
3.	Collapse of West-Antarctic ice shelf	Global sea level rise up to 5 m
4.	Increased frequency and intensity of El-Nino events	Increased droughts in South Asia and Africa
5.	Amazon rain forest die-back	Massive species extinctions, decreased rainfall, massive loss of carbon-sinks
6.	Changes in Indian Monsoon System (Strengthening El-Nino will weaken monsoons)	Widespread drought
7.	Collapse of thermo haline circulation	Extremes of winters and summers over Europe
8.	Thawing of Tundra's permafrost	Meltdown and release of frozen methane hydrates

PATTERNS OF CLIMATE SENSITIVE DISEASES

The added burden of climate change sensitive diseases will further worsen the already existing health inequities creating enormous challenges to public health. Though complex and interdependent, for clarity's sake, one could divide the resultant health outcomes as: (1) direct; and/or (2) indirect impacts of climate change.

Direct Health Impacts

Results from extreme weather events such as heat waves, sudden flooding, storms and cyclones, droughts and inundation due to

sea level rise. All of these events are set to increase in both amplitude and frequency as a consequence of climate change. A partial glimpse of some recent extreme events is given in Table 2.

Table 2: Recent Extreme Events of the World

Place	Event/Consequence
Andhra Pradesh heat wave, 2003	Killed 1,421 people
Orissa heat waves, 1998 & June 2005	June 2005, Bhuvaneshwar recorded a high of 46.3°C. In year 1998, the heat wave claimed >1,000 lives
Mumbai, India, July 2005	Heaviest rainfall ever recorded in a single day in the last 100 years: 944 mm.
Pan-India monsoon deficit induced droughts	Recurring Monsoon deficit-induced serious droughts: 2000-2002, 2009.
Cherrapunji, Meghalaya, 2005	The world's wettest place went through a rain deficit-induced drought
European heat wave, 2003	Caused 70,000 deaths

Scanning through the European heat mortality data, a question begins to form; how could a simple heat spell of 35°C to 40°C end up killing 70,000 people? Clearly, the heat wave need not have to be extreme in order to kill. This phenomenon of multiplier effect (disproportionately wider and stronger health impact) may well hold true for most other climate sensitive diseases.

In the Europe of 2003, it was a combination of a sequence of hot days coupled with unusually hot and humid nights, cityscapes built for a cooler weather and a population culturally and physiologically un-acclimatised to heat that contributed to the multiplier effect. Indeed, most of the heat mortality seems to be a function of higher night time minimum temperature, duration of heat wave, pre-existing background vulnerabilities (extremes of age, cardio-respiratory disease and poverty), amount of ozone and PM-10 in the near ground stagnant air pollution, and heat island effect. More than the day time maximum, it is the night time minimum which determines the degree of heat stress. According to IPCC, the 12 warmest years in the past 150 years have been during the last 13 years with 1998 being the warmest, followed by 2005, 2002, 2003 and 2004.

Defining heat wave as a stretch of at least 5 days with highs of 5°C above average, IPCC estimates that the heat waves are likely to become more frequent and longer across most of the planet, especially towards the middle and upper-middle latitudes involving the central and southern Europe, the Western USA and Eastern Asia.

Indirect Effects on Health

Climate-sensitive diseases share some epidemiologic commons.

1. They display indirect transmissions employing either a vector (mosquitoes, ticks, fleas, flies), or a vehicle (water or food borne).
2. Insects being cold-blooded, a minor change in temperature can amplify into a large biologic effect on disease transmission. Therefore, climate change can act as a force multiplier and alter the incidence, seasonal transmission windows and the geographic range of diseases such as malaria, dengue, chikungunya, yellow fever, filaria caused by mosquitoes and leishmaniasis by sand fly.
3. Their distribution is determined by ecological synergies between a set of variables such as temperatures, rainfall, humidity, flooding or drought, sea level rise, phytoplankton and algal blooms on sea surface, EL-Nino Southern Oscillation (ENSO) and changes in water salinity. Rodent migratory behaviour is often dictated by changes in food sources, cropping patterns, grain storage, flood or drought induced displacements.
4. The extrinsic incubation period of an infective agent within its vector is sensitive to changes in temperature and humidity.
5. If both the agent (Plasmodium) and the vector (Anopheles) are competent and robust in the newly warmed and humid climate, then both will multiply and spread very rapidly giving rise to sudden emergence of explosive epidemics.
6. Like the climate itself, malaria incidence too displays a non-linear threshold—tipping point response in reaction to minor temperature changes.
7. The growth of mosquito and parasite population densities in response to warming can be several orders-of-magnitude larger than what the unit change in temperature would suggest.
8. Some scientist has demonstrated that, just half-a-degree centigrade increase in temperature can amplify into a 30% to 100% increase in mosquito population.
9. Likewise, the Lancet-UCL Climate Change Commission believes that a small increment in the risk for climate-sensitive diseases such as diarrhoea, malnutrition, dengue, etc. could snowball into disproportionately large increases in total disease burden.
10. As regards to the possible epidemiologic behaviour of malaria in India, WHO estimates that: (a) 10% more states may offer breeding-favourable climatic conditions throughout the year with respect to base year 2000; (b) transmission windows for malaria are likely to increase in the North and North-Western areas from the present 4 – 6 months to 7 – 9 months; and that (c) by the year 2080, malaria may move up in altitude up to elevations of 1,800 m.
11. Dying or drying rivers often fragment into a series of stagnant pools that serve to increase mosquito breeding rates.
12. Counter intuitively, a drought or drying may actually trigger mosquito-based epidemics. Drought and water shortages often trigger social behaviours that lead to increased water storage in household containers that increases the density of peri-domestic dengue transmitting Aedes mosquito. In fact, the chikungunya outbreak of 2004 that began in drought-affected Lamu in coastal Kenya and spread to India via the islands of Indian Ocean, also displayed climate-sensitivity.
13. Climate phenomena such as: EL-Nino events and the resultant sea surface warming are also linked with the emergence of cholera epidemics. *Vibrio cholerae* thrives in warm, saline sea waters in association with the floating

blooms of zooplankton and phytoplankton (which themselves proliferate with the warming seas). In Bangladesh, seasonal plankton blooms in the Bay of Bengal are correlated with sea-surface warming and the emergence of cholera outbreaks. Few scientists reported a strong correlation of inter-annual variability of cholera with (1) sea surface temperatures in Bay of Bengal; (2) EL-Nino Southern Oscillation (ESNO); (3) the extent of flooding in Bangladesh over short periods of <7 years; and (4) monsoon rains and Brahamputra river discharge over longer periods of >7 years. Similar finding was also reported from Lima, Peru where EL-Nino induced winter time warming of 5°C during 1997-98, was correlated to >200% daily admissions for diarrhoea as compared with the baseline. In fact, they observed that with every 1°C rise in air temperature above normal, there was an 8% increase in hospital admission rates for childhood diarrhoea.

CLIMATE-SENSITIVE HEALTH BURDENS

WHO believes that climate change has been responsible for 5.5 million disability adjusted life years (DALYS) lost in 2000 on account of diarrhoea, malaria, malnutrition and accidents due to extreme weather events.

Heat Stress

The IPCC in 2007 made projections that superimposed upon the global rise in mean surface temperature and there will be trend of extreme variability leading to frequent and intense heat waves. While the phenomenon of excess mortality resulting from heat waves is well recognised, warmer than average temperatures *per se* are also associated with higher mortality rates. Most of this vulnerability will be located in cohorts with poor adaptive capacities such as: the older age and the very young, the urban poor, those with chronic medical conditions (particularly, cardiovascular and respiratory diseases), and in the socially isolated. Infact Curiero and Mc Michael *et al* have characterised the relationship between temperature and mortality as a: 'J-shaped curve', such that the mortality increases with both colder and warmer temperatures beyond a certain optimal temperature at which it is the lowest. During the 2003 European heat wave, IPCC (2007) estimates that while France experienced 15,000 excess deaths, the total for Europe was estimated to be 35,000 excess deaths. Also IPCC expects a rise in frequency and intensity of global warming triggered extreme weather events (cyclones, flash floods and droughts) which will adversely impact public health through a combination of direct and indirect effects.

Changes in Climate-Sensitive Infectious Disease Burden

Climate change is not likely to result in the emergence of new or unforeseen diseases but an exacerbation of the existing disease burdens engendered through a redistribution of the classic determinants of health such as air, water, food, shelter, temperature and humidity. Of particular concern are the vector borne diseases which are bound to expand across geographical range due to climate change-induced alterations.

Malaria and Climate Change

Climate change increases malaria transmission by amplifying growth enabling factors such as the optimum temperature windows between 15°C and 39°C for the favourable development of both the vector (mosquito) and the parasite (plasmodium). Global warming will ensure that the transmission windows for malaria will remain open for 10 to 12 months in much of the central, coastal and north-eastern India from the present duration of 6 to 7 months.

Ambient Air Pollution

Tropospheric (ground level) ozone production is forecast to increase as a function of rising average temperatures (IPCC, 2007). Ozone is formed via sunlight driven photo-chemical reactions involving nitrogen oxides and hydrocarbon precursor aerosols. Warmer temperatures are known to amplify these ground level ozone generating reactions. Fossil fuel burning also worsens the particulate air pollution. Both ozone and particulate matter air pollution have been associated with increased risks of mortality and morbidity resulting from the respiratory and cardiovascular events (WHO, 2006).

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27.3 Environmental Pollution

Ashok A Mahashur

Industrialisation and urbanisation have resulted in the deterioration of urban air quality. Amongst the environmental pollution, air pollution is most deleterious to the respiratory system as the pollutants are inhaled directly into the respiratory tract. The sources of air pollution are vehicular emissions and indoor industrial smoke.

'Air pollution' comprises of a diverse nature of chemical emissions including gaseous combustion products, volatile chemicals and aerosols (particulates). The most common pollutants are ozone, carbon monoxide, sulphur dioxide and nitrogen dioxide.

OZONE

Ozone gas is a very strong oxidant, reacting with biomolecules to form ozonides and free radicals. The ozone-induced inflammation is mediated from prostaglandins (PGE_2, PGF_2, TXB_2), neutrophils, fibronectin, interleukin-6, cytokines, etc. These lead to increased airway permeability, macrophage function impairment leading to increased susceptibility to bacterial infection.

Ozone has different health implications in stratosphere and troposphere. In the stratosphere (ozone layer) 10 to 15 km above the earth, ozone presents a critical barrier to solar ultraviolet radiation and prevention from skin cancers, cataracts, etc.

Symptoms

Ozone-induced illnesses include conjunctival irritation; lower respiratory tract irritation, cough and shortness of breath, wheezing, reduced tidal volume, nausea, malaise and headache. It also causes a peculiar type of pain which is substernal, mainly tearing or burning in character which is more severe during inspiration. Asthmatic children playing outdoors are roughly 20% to 40% more likely to suffer from asthmatic exacerbation. Ozone leads to impairment of pulmonary function and increased hyper-reactivity of airways. Persons at risk include asthmatics, chronic obstructive lung disease (COLD) and those who are active outdoors for prolonged periods like athletes, policemen, labourers, construction workers, etc.

PARTICULATES

More than 70% of the population in the world lives in areas with high particulate levels. The particulate air pollution is a heterogeneous classification of liquid and solid aerosols which include emissions from fuel combustion (coal, oil, and biomass), transportation and high temperature industrial processes. The large particles above 10 microns get deposited in the nasal and tracheobronchial regions and smaller particles less than 10 microns penetrate directly into the lungs.

Symptoms

Acute signs and symptoms include restricted activity, respiratory illnesses and exacerbation of asthma and chronic obstructive pulmonary disease (COPD). The group at large-risk includes the elderly and persons with chronic heart and lung diseases. There is reduced pulmonary function leading to increased morbidity due to respiratory illnesses and cardiac illnesses.

CARBON MONOXIDE

Carbon monoxide (CO) exposure is usually high due to local accumulation of CO in heavy traffic. Indoor levels are generally low in the absence of strong indoor sources.

Sources of CO exposure include inside passenger car, proximity to busy roads, constructions site parking areas and traffic tunnels. Their important contributors include traffic volume, traffic speed, and winter season.

Health Effects

Health effects are due to decrease in oxygen carrying capacity of blood and disruption of cytochrome function. The symptoms usually consist of headache, fatigue and flu-like symptoms. Risk groups include smokers and those with coronary artery disease (CAD), peripheral vascular disease and COPD. Adverse cardiac effects include decreased exercise capacity, arrhythmias, etc.

SULPHUR DIOXIDE

Sulphur dioxide (SO_2) gas is formed during combustion of sulphur containing fuel (coal and oil). The major health effects are breathing difficulty, respiratory illnesses, alteration in pulmonary defences and aggravation of existing cardiovascular disease. Children, elderly persons and persons with asthma, cardiovascular disease and chronic lung disease are more susceptible to adverse health effects associated with SO_2. The SO_2 reacts in the atmosphere to create sulphuric acid (H_2SO_4) and form acid aerosol (acid rain).

NITROGEN DIOXIDE

Nitrogen dioxide (NO_2) is released from fossil-fuel combustion. It reacts in the presence of sunlight and VOCs to form ozone gas and contributes atmospheric reaction to the formation of nitrous and nitric acid aerosols.

Health Effects

It is absorbed in both large and small airways. Their high concentration (more than 200 ppm) is very dangerous causing lung injury, fatal pulmonary oedema and bronchopneumonia. Lower concentration causes impaired mucociliary clearance, particle transport, macrophage function and local immunity.

AIR TOXICS

Toxic air pollutants is a term applied to certain volatile chemicals, pesticides, herbicides, metals and radio nucleotides, released in atmosphere by various industrial processes. They reach the general population by direct pulmonary assimilation.

Diagnosis

Diagnosis of respiratory illness related to ozone, NO_2 particulates, SO_2, diesel, and air toxics is clinical and presumptive, based on a history of elevated community pol-lutant levels, especially in combination with prolonged exposure outdoors with elevated workloads. The soft clues include an association with typical symptoms (ocular and upper respiratory irritation, chest pain, shortness of breath, cough, wheezing, nausea, malaise, headache), and signs (conjunctival and upper respiratory inflammation, pulmonary inflammation or infection, wheezing, prolonged expiratory phase). The chest pain associated with ozone exposure is characteristically exacerbated during inspiration and relieved during expiration, resulting in a decreased tidal volume. Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and diffusion lung capacity for carbon monoxide (DLCO) may be reduced and methacholine responsiveness may be increased.

Differentiation from other common causes of respiratory illnesses is not well defined, and several aetiologies may contribute to an individual's illness. Similarly, atmospheric concentrations of multiple pollutants often fluctuate simultaneously, making precise aetiologic differentiation rarely practical.

INCINERATORS POLLUTION

Particulate and gaseous emissions from municipal solid waste incineration depend on the waste stream composition and incinerator engineering and operation, but typically include heavy metals (Hg, Pb, As, Cd, Cr, Mn, Ni, Sb, Se, Zn, V), polychlorinated dibenzodioxins, dibenzofurans, and polycyclic aromatic hydrocarbons, in addition to acid gases and oxides of nitrogen, sulphur and carbon. Batteries, fluorescent light bulbs, magazine dyes, papers, plastics are sources of metals; lead and cadmium are emitted mostly in the particulate fraction, while mercury is more in gaseous form. Incinerator ashes contain high concentrations of metals. Chlorine and fluorine are emitted as acid gases, and contribute to halogenated aromatic organic compound formation. Proximity to incinerators has been associated with local lead soil distribution; the association of dioxin exposure with incinerators is less consistent. The major route of dioxin ingestion is in animal fat foods (milk, eggs, animal flesh), although plant deposition and inhalation contribute small amounts. Dioxins have also contaminated herbicides which are widely sprayed along highways and rail-road right-of-ways. Nonetheless, cow's milk may be more contaminated with dioxins near municipal solid waste incinerators. A recent ecological study found stomach and lung cancers to be elevated in communities near municipal solid waste incinerators in Great Britain. This preliminary and unconfirmed finding is an outcome of concern in light of parallel cancer elevations in a study of MSW workers. Increasing attention is being paid to dioxin and mercury emissions from medical waste incinerators.

DIESEL AND AUTOMOBILE EXHAUST/HEALTH EFFECTS

Diesel exhaust contributes to ambient sulphur oxides, ozone precursors, and aerosols, seems to contribute to chronic respiratory morbidity and mortality and probably contributes to the cancer risk of urban air pollution. Mutagenic and carcinogenic compounds (such as PAHs) are adsorbed to diesel soot.

In humans, occupational case control and cohort studies have found a small but generally consistent association of prolonged exposure to high diesel concentrations, when adjusted for cigarette smoking, with a relative risk (RR) of lung cancer incidence of 1.4 to 1.7 in the best studies. While most studies have problems with exposure assessment, wide confidence intervals and low effect magnitude. A recent meta-analysis of over 20 studies examining occupational exposure to diesel exhaust, confirmed a statistically significant RR of 1.33 for lung cancer, with adjustment for cigarette smoking.

Heavy exposure to diesel is clearly associated with pulmonary inflammation, with some evidence of increased incidence of respiratory symptoms (cough, phlegm, and wheezing) and small work shift pulmonary function decrements; heavily exposed cohorts may have elevated risks of mortality from chronic lung disease (COPD and respiratory infection).

Acute Respiratory Effects

Four acute respiratory effects of air pollution are well established; asthmatic attacks, hyper-reactive airways, respiratory infections, and reversible changes in lung functions.

Asthma is a condition in which the airways suddenly narrow, obstructing the flow of air through the lungs. The narrowing is caused by spasms of the small muscles that encircle the airways and by the release of thick, excessive mucus that plugs them. Air pollution can bring on asthmatic attacks. Attacks have also been associated with ozone and particulate pollution. In areas surrounding power plants and smelters, SO_2 and sulphate particulates cause bronchospasm. It is not known whether air pollution can actually cause asthma or whether it only triggers asthmatic attacks.

Hyper-reactive airways are those that constrict much more readily than average in response to foreign matter. Unlike asthma, some constriction of the airways is a normal defence mechanism to prevent inhaling noxious substances in persons with hyper-reactive airways. The airways respond to levels that do not bother most people. The symptoms are similar to asthma—shortness of breath, coughing, and wheezing. SO_2 particulates, ozone, and NO are known to stimulate airway reactivity.

The incidence of respiratory infections, particularly in children, is increased by air pollution. Upper respiratory infections, such as cold, influenza and sore throat are associated with sulphate, sulphur dioxide, and particulates in outdoor air. NO_2 released indoors by cooking gas stoves, is associated with more frequent cold in children under the age of 10 compared with children who live in homes equipped with electric appliances. Animal studies show that concentrations of ozone and NO_2 typical of peak pollution episodes lower the resistance to bacterial infections such as pneumonia and acute bronchitis. Air pollutants disable the clearance mechanisms that remove viruses and bacteria from the respiratory tract and incapacitate the cells that fight the infections.

Short-term, reversible changes in lung function are also caused by air pollutants. For example, the maximum amount of air that can be inhaled or exhaled in one second is reduced in both children and healthy adults when exposed to elevated pollutant concentrations, but this returns to normal when exposure ceases. Whether such changes indicate that long-term damage is being done is not known at present.

Chronic Respiratory Effects

The two chain effects of long-term exposure to air pollutants, aside from lung cancer, are COPD and changes in the development and ageing of the lungs. COPD is actually a group of diseases that share the common symptoms of breathlessness. Because a clear-cut diagnosis is often impossible until after death, the conditions are grouped together. The group includes chronic bronchitis, emphysema, and small airways disease. Chronic bronchitis involves the persistent secretion of excessive amounts of mucus into the airways; its leading symptom is a lasting phlegmatic cough. Emphysema is a destruction of the wall of the air sacs (alveoli) and is indicated by breathlessness without cough. Small airway disease involves inflammation and narrowing of the smallest airways (bronchioles) and is the earliest sign of smoking-induced COPD. These diseases can appear separately or together. The long-term survival is influenced strongly by how susceptible the individual is to respiratory infections such as influenza and pneumonia. About 10 million people in the United States of America are afflicted with COPD.

The main causes of COPD are smoking, occupational exposures to such substances as coal and cotton dusts, high concentration of SO_2, and particulates and genetic factors. Air pollution plays a role in several ways. Some evidence suggests that a history of respiratory infections during childhood may contribute to pulmonary disease in old age, and as previously mentioned, air pollution increases childhood infections. Air pollution has been linked to COPD in recent studies of Mormons, a group with a very low rate of smoking. The longer and greater the exposure to outdoor levels of SO_2 and sulphate particulates, the more prevalent and severe the disease symptoms. Studies in laboratory animals have shown that long-term exposure to NO_2 and ozone causes destruction of alveolar walls, similar to emphysema.

Lung growth is also affected by air pollution. The lungs typically grow until the age of 20, and then slowly decline in their ability to hold air with age. Slowed rates of lung growth have been observed in children aged 6 through 12 exposed to certain indoor air pollutants. The changes are greatest in homes with smokers. A smaller adult lung size means less reserve against the inevitable shrinkage of the lungs with old age and against the onset of obstructive pulmonary disease, which occurs more commonly at older ages.

Lung Cancer

Cancer of the lung is the leading fatal cancer among both men and women, responsible for over one-fourth of all cancer deaths. Smoking is the major cause of lung cancer. Air pollution causes some fraction of lung cancers, but exactly how much is in dispute. Some experts contend that air pollution causes only a small percent of all cases, while others argue that it is 20% or more. It is clear that carcinogenic compounds are present in indoor air and polluted outdoor urban air. Chemical analysis of air show the presence of cancer-causing by-products of burning such as benzo-[a]-pyrene and dioxins, fibres such as asbestos, and metals such as arsenic and cadmium. Toxicological studies show that extracts of polluted air can produce lung tumours in mice, rats, and hamsters and cause injury to the genetic material deoxyribonucleic acid. Studies in human populations have found increased cancer rates around smelters and factories, in cities compared to rural areas, and with duration of exposure to pollution.

The major question has been to what extent these materials alone have caused cancer compared with tobacco smoke. Tobacco smoke interacts synergistically with other carcinogens, including radon, asbestos, arsenic, and alcohol, to increase the underlying cancer risk. Many people who have never smoked are exposed passively to tobacco smoke either at work or at home. These and other problems blur the role of air pollutants in producing lung cancers. Nevertheless, there are estimates that between 5,000 and 20,000 cases of lung cancer per year are caused by radon, with most cases occurring among smokers.

Non-Respiratory Effects

Air pollution affects organs in the body other than the lungs. Once inhaled, pollutants can be absorbed into the blood stream and can reach all areas of the body. Air-borne lead has caused nervous disorders in children, including learning disabilities and hyper-activity, kidney damage leading to high blood pressure in both children and adults and outright poisoning. Lead levels have dropped dramatically in the last 15 years as leaded gasoline has been phased out, but deposits on the ground from earlier years are a lingering source of exposure.

Benzene is a cause of leukaemia in rubber and chemical workers and is present in the air from refinery operations and gasoline combustion. Benzene in outdoor air has been attributed to cause cancer. Various other organic solvents are associated with nervous system disorders in workers, but again, concentrations are so low that it is difficult to ascribe any particular cases to such exposures.

CO may play a part in the development of ischaemic heart disease, in which the heart muscle does not get enough oxygen over long periods and its tissues slowly die. Similarly, the added strain on the heart and lungs caused by a lack of oxygen during peak CO episodes when smoking cigarettes or when stuck in rush hour traffic may trigger heart attacks. While evidence of CO playing a widespread role in heart diseases is not conclusive at the moment, most experts think it is possible.

27.4 Air-Borne Pollutants and Smoke-Related Hazards

Rajeev Gupta

INTRODUCTION

Environmental toxins are major risk factors for disease. The Global Burden of Diseases Study has reported that unsafe water, sanitation and hygiene, indoor smoke from solid fuels and smoking tobacco use are the leading risk factors for mortality and disease burden, especially in low income developing countries such as India (**Table 1**). Urban outdoor air pollution, lead, global climate change, risk factors for injury, industrial carcinogens, air-borne particulates, ergonomic stressors and noise are other important environmental and occupational risk factors. In this chapter, we shall focus on some of these factors—outdoor air pollution, indoor air pollution from solid fuels, environmental tobacco smoke, occupational particulate matter and common industrial toxins.

Table 1: Risk Factors for Mortality and Burden of Disease Globally and in Developing Countries (Global Burden of Diseases Study)

Rank	Global		Developing Countries, e.g. India	
	Mortality	**Burden of disease**	**Mortality**	**Burden of disease**
1.	High blood pressure	Childhood and maternal underweight	Childhood and maternal underweight	Childhood and maternal underweight
2.	Smoking and tobacco use	Unsafe sex	Unsafe sex	Unsafe sex
3.	High cholesterol	High blood pressure	High blood pressure	*Unsafe water, poor sanitation and hygiene*
4.	Childhood and maternal underweight	Smoking and tobacco use	*Unsafe water, poor sanitation and hygiene*	*Indoor smoke from solid fuels*
5.	Unsafe sex	Alcohol	High cholesterol	Zinc deficiency
6.	Low fruit and vegetable intake	*Unsafe water, poor sanitation and hygiene*	*Smoking and tobacco use*	Iron deficiency anaemia
7.	High BMI	High cholesterol	*Indoor smoke from solid fuels*	Vitamin A deficiency
8.	Physical inactivity	*Indoor smoke from solid fuels*	Low fruits and vegetable consumption	High blood pressure
9.	Alcohol	Iron deficiency	Iron deficiency anaemia	*Smoking and tobacco use*
10.	*Unsafe water, poor sanitation and hygiene*	High BMI	Vitamin A deficiency	High cholesterol

BMI = Body mass index.

OUTDOOR AIR POLLUTION

Air pollution is an important determinant of population health. The World Health Organization (WHO) estimates that, at the global level, 1.4% of all deaths and 0.8% of disability-adjusted life years are the result of particulate air pollution. The short-term health effects of particulate and gaseous air pollutants have been well documented. A combined analysis of data from 124 large cities in Europe and North America reported an estimated increase in rate of deaths from any cause ranging from 0.2% to 0.6% for an increase in ambient small particle ($PM_{2.5}$) concentrations of 10 microgram per cubic metre. The long-term effects of exposure to major air pollutants (particulate matter, ozone, sulphates, sulphur dioxide, nitrous oxides, and carbon monoxide) have been well-documented in large cohort studies, and the second American Cancer Society Prevention Study reported an increase of 3% to 6% in mortality for every 10% change in air-pollution levels in USA.

Pollutants are generated from power plants, industrial complexes, automobiles and other vehicles and none of the pollutants occur in isolation. Pollutants change by chemical reactions after being emitted. Sulphur oxide can convert to acid sulphates and oxides of nitrogen and oxidants from automobiles react with sunlight to produce ozone. The symptoms and disease associated with air pollution are the same as conditions associated with smoking. Respiratory infections in children are associated with chronic exposure to traffic-related gases and respirable particles. Studies in urban locations in developed countries have reported higher cardiopulmonry hospitalisations and mortality. Pubic health measures such as stricter ambient air quality standards, publicising pollution alerts and avoidance of polluted areas have been useful to prevent and control the ill-effects of outdoor pollution.

INDOOR AIR POLLUTION

Indoor air pollution is due to widespread use of unprocessed solid fuels (biomass and coal) for cooking and space heating in India and other developing countries, often in unventilated situations. The 1991 Indian Census, for the first time, asked a question about the primary household fuel used and reported that at a national level 81% of households primarily used biomass fuel (dung, crop-residues and wood).

High pollutant concentrations result from emission factors from such fuels in simple small scale combustion devices and frequently result in high indoor air particulate concentrations that could lead to PM_{10} concentrations of more than 2,000 µg/m^3 in some households. It has been estimated that 400,000 to 550,000 premature deaths can be attributed annually to the use of such biomass fuels and indoor air pollution in India, mainly due to acute respiratory infections, chronic obstructive pulmonary disease (COPD), lung cancers, pulmonary tuberculosis, asthma and coronary artery disease (CAD) (**Figure 1**). This pollution also leads to frequent upper airways infections in subjects with and without underlying COPD and is a leading cause of disability-adjusted life years (DALYs) and high person sick-days in India. The pollution levels are more in urban than rural locations but can be very high in individual households. Exposure is not only the number of people involved, but also a function of frequency and duration of contact-person hours of exposure.

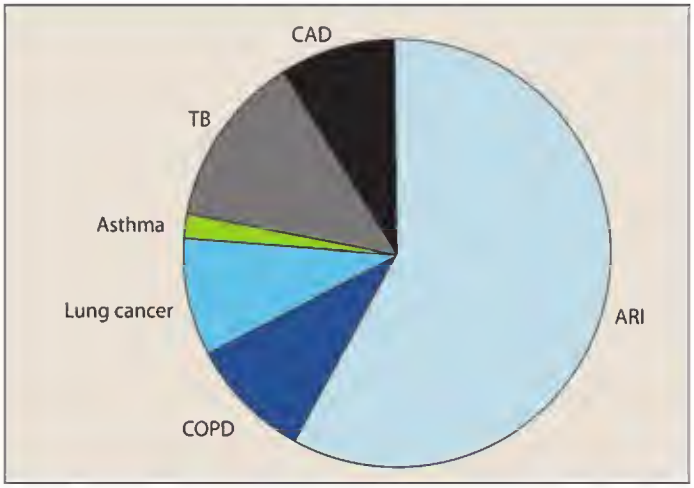


Figure 1: Estimated distribution of causes of annual death burden of 400-550 thousand due to indoor air pollution in India.

ARI = Acute respiratory infections; COPD = Chronic obstructive pulmonory disease; TB = Tuberculosis; CAD = Coronory artery diseose.

Salient features of indoor pollution in India and many developing countries as compared to developed countries are: (i) the biomass fuels produce relatively more organic compounds (e.g. benzene, formaldehyde, 1, 3-butadiene, polyaromatic hydrocarbons) and fossil fuels produce more sulphur oxides; (ii) chemical characteristics of the particles produced by biomass combustion are different; (iii) indoor pollutant concentrations are more during the day (because of household cooking) and place women and young children at greater risk; (iv) exposure levels in poorly ventilated biomass fuel areas are 10 to 50 times greater than urban outdoors in developed countries; (v) people exposed to indoor pollution in India are the poorest, most stressed and youngest as compared to other countries; (vi) implications on long-term health are unclear; (vii) misclassification of outcomes due to confounding by smoking exists; (viii) the attributable risk of indoor pollution on health outcome is difficult to quantify; (ix) there are no large scale data on the level of indoor air pollution in India using systematic sampling strategies; and (x) the estimates of mortality and DALYs are not well-defined. Therefore, it is essential that larger studies be conducted in India and other developing countries to better assess the role of indoor pollution.

At the global level, India seems to have some 30% of all household solid-fuel stoves, although the estimates are generally much less reliable than in India where fuel use is determined in the national census. On that basis, the total world health impact on women and children would be roughly three times larger than the Indian estimates. The alarming scale of toxicity of indoor air pollution argues for additional efforts to understand and ameliorate the conditions that lead to such severe pollution levels in the village and urban slum homes of India and elsewhere in the Third World. At the very least, they call for a serious effort to conduct the medical and abatement research that would pin down more accurately the impact of pollution and effective ways to reduce it.

ENVIRONMENTAL TOBACCO SMOKE

Smoking is rampant among Indian men and environmental tobacco smoke (ETS) should be an important health issue (**Figure 2**). The health hazards due to exposure to ETS are increasingly being established. ETS contains thousands of chemicals including 43 known carcinogens. Known health effects of ETS exposure are lung cancer in non-smokers, childhood disorders such as bronchitis, and perhaps, heart disease. Workplace exposure to ETS is widespread and is influenced strongly by the type of smoking policy in the workplace. To decrease ETS exposure, efforts to restrict public smoking have proliferated over the past decades. These restrictions have emanated from government as well as voluntary measures by various private industries. Ban on public smoking are effective in reducing non-smokers' exposure to ETS. Workplace smoking bans also influence the intensity of smoking among employees and may increase quit smoking rates. In addition to the health benefits from smoke-free workplaces, there are likely cost savings to employers who implement such policies.

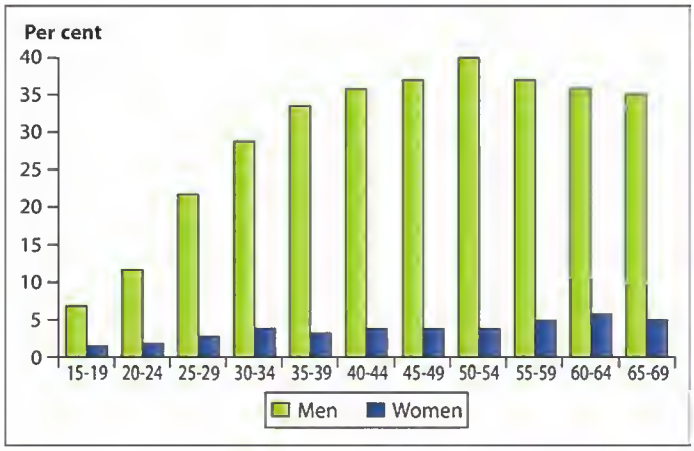


Figure 2: Age-specific prevalence of smoking among men and women in India *(Nationol Fomily Health Survey-2).*

ETS is also an indoor pollutant. Increases in prevalence of respiratory illnesses and reduced level of pulmonary function, measured by simple spirometry, are found in children of smoking parents. Recent meta-analyses for lung cancer and cardiopulmonary diseases, combining data from the best of ETS exposure studies suggest a 25% increase in relative risk.

OCCUPATIONAL INORGANIC AND ORGANIC DUSTS

Table 2 shows the broad categories of chemical and biological substances that are related to occupations and can lead to

Table 2: Occupational Exposure to Inorganic and Organic Dusts and Pulmonary Disease

Occupational Exposures	Respiratory Diseases
Inorganic dusts	
Asbestos: Mining and processing	Asbestos related fibrosis, pleural disease, cancer, mesothelioma
Silica: Mining, stone cutting, sandblasting, quarrying	Fibrosis (silicosis), progressive massive fibrosis, cancer, silicotuberculosis, COPD
Coal: Mining	Fibrosis (coal workers pneumoconiosis), progressive massive fibrosis, COPD
Beryllium: Processing alloys	Acute pneumonitis, chronic granulomatous disease, cancer
Other metals: Aluminium, chromium, cobalt, nickel, titanium, tungsten	Acute pneumonitis, lung cancer, asthma, etc.
Organic dusts	
Cotton dust: Milling, processing	Byssinosis, chronic bronchitis, COPD
Grain dust: Farmers, milling, bakers	Asthma, chronic bronchitis, COPD
Other agricultural dusts: Fungal spores, vegetable products, insect fragments, animal dander, bird and rodent faeces, endotoxins, microorganisms, pollens	Hypersensitivity pneumonitis, asthma, chronic bronchitis
Wide variety of industrial chemicals and toxins	Bronchitis, emphysema, etc.

pulmonary disease. Multiple agents are responsible for such occupational lung diseases but in India only a few toxins such as asbestos, silica, coal-dust, cotton-dust, grain dust and other toxic chemicals are important.

Asbestosis

One important pulmonary disease is due to asbestos and several different mineral silicates including chrysolite, amosite, and anthophyllite. In addition to workers involved in mining, milling and manufacturing of asbestos, those involved in construction trades are also exposed. Community exposure can result from use of asbestos containing mine or mill-tillings such as landfills, road surface or playground material. In India, asbestos has been used extensively since mid-1900s and it is only recently that it is being replaced by synthetic mineral fibres such as fibreglass or slag wool. The major health effects from exposure to asbestos are pleural and pulmonary fibrosis and cancers of the respiratory tract, pleura and, rarely, peritoneum. Asbestosis is diffuse interstitial fibrosis that is directly related to intensity and duration of exposure. Usually moderate to severe exposure of more than 10 years is required for disease to become manifest and can occur following exposure to any asbestiform fibres. The disease resembles other forms of diffuse interstitial fibrosis with decrease in lung volumes and diffusing capacity. Chest radiographs can be used to detect a number of manifestations of exposure such as parietal pleural plaques. Interstitial disease causes linear opacities in lower lung fields, which then spread to middle and upper zones. High resolution CT scan of lungs shows distinct changes of subpleural curvilinear opacities 5 mm to 10 mm parallel to pleural surface. There is no specific therapy and supportive care is similar to other interstitial lung diseases.

Lung cancer (of all histological types) is the most frequent cancer associated with asbestos exposure. A minimum latency of 15 to 19 years is reported between first exposure and the disease. Use of CT scan for screening high risk individuals is being evaluated. Mesotheliomas are also associated with asbestos exposure. Relatively short asbestos exposures for $\leq$1 to 2 years, occurring up to 40 years in the past, have been associated with development of mesotheliomas. These tumours are generally locally invasive and death usually occurs from local extension. There is no effective therapy.

Silicosis

Free silica or crystalline quartz (SiO_2) is still a major occupational hazard. Main occupational exposures include mining, stone cutting, employment in abrasive industries (stone, clay, glass and cement manufacturing), foundry work, packing of silica flour and quarrying especially granite. The pulmonary fibrosis due to silica often follows a dose-response curve after many years of exposure. Workers heavily exposed through sandblasting in confined spaces may develop acute silicosis in less than one year of exposure. The chest radiograph shows profuse miliary infiltration or consolidation and the characteristic CT scan pattern of crazy-paving is at times observed. The disease may be quite severe and progressive despite discontinuation of exposure. Whole-lung lavage may slow progression. Long-term low-intensity exposure results in small rounded opacities in the upper lobes after 15 to 20 years of exposure. Calcification of hilar nodes may occur and lead to characteristic egg-shell pattern. Less hazardous silicates include kaolin, Fuller's earth, mica, silica gel, soapstone, carbonate dusts and cement dusts. Patients with silicosis are at greater risk of acquiring bacterial infections because silica is toxic to macrophages. Infections with *Mycobacterium tuberculosis*, atypical mycobacteria and fungi are common. Another potential complication is autoimmune connective tissue disorders such as rheumatoid arthritis and scleroderma. It is also a potential lung carcinogen.

Coal-Worker's Pneumoconiosis

In India, coal mining is an important industry and coal-worker's pneumoconiosis is a disease with tremendous social, economic and medical significance. Simple radiographic disease is observed in about 10% of coal miners and in as many as 50% of anthracite miners with more than 20 years work on coal face. The prevalence of disease is lower in bituminous coal workers. With prolonged exposure (15 to 20 years) small rounded radiological opacities develop but are not associated with pulmonary impairment. Much of the symptomatology occurs due to development of chronic bronchitis and COPD and the effects of smoking are additive. Complicated disease manifests

as the appearance of nodules on chest radiograph and can involve the entire lobe. This condition can lead to progressive massive fibrosis and premature mortality. Caplan's syndrome includes seropositive rheumatoid arthritis with characteristic pneumoconiotic nodules.

Byssinosis and Organic Dusts

Some of the specific diseases associated with organic dusts are listed in **Tables 2 and 3**. Often the temporal relationship of exposure to symptoms furnishes the best evidence for the diagnosis. Some diseases common to India include those due to cotton dust (byssinosis), grain dust and moldy hay (Farmers' lung). Byssinosis is due to occupational exposure to cotton, flax or hemp. Exposure occurs throughout the manufacturing process, but is most during blowing, mixing and carding of the fibres. Risk is associated with fibre and endotoxin levels and can be substantially reduced by dust control using cotton hoods, increased ventilation and wetting procedures. It is characterised clinically by chest tightness on the first day of the work-week (Monday chest tightness) which becomes less over the week. In 10% to 25% of workers the disease may be progressive, with chest tightness persisting the whole week. After >10 years of exposure persons with recurrent symptoms develop obstructive lung disease.

Grain dust exposure is common in India, but the exact data of illnesses due to this exposure are not available. The presence of obstructive airways disease in grain dust workers is similar to smokers with persistent cough, dyspnoea and wheeze. Farmer's lung is due to exposure to moldy hay containing spores of thermophilic actinomycetes. In UK, the disease occurs in 10 to 50 per 1000 farmers; reliable data are not available in India. Acute Farmer's lung presents as fever, chills, malaise, cough and dyspnoea without wheezing, 4 to 8 hours after exposure and is diagnosed by history of exposure. In chronic disease, there is history of repeated attacks after exposure and patchy fibrosis can occur in lungs. For those patients who present with hypersensitivity pneumonitis, a careful inquiry about occupation, hobbies or other home environmental exposures is necessary to uncover the source of aetiological agent.

OCCUPATION-RELATED HYPERSENSITIVITY PNEUMONITIS

These conditions are also known as extrinsic allergic alveolitis and are due to inflammation of alveoli and terminal airways in susceptible hosts by repeated inhalation of a variety of organic agents (**Table 3**). Causes of hypersensitivity pneumonitides are typically designated by colourful names denoting occupational risk associated with the disease. The frequency of these conditions varies with the environmental exposure and the specific antigen involved. The diseases are immune-complex mediated reaction and cell-mediated hypersensitivity is important. The early reaction is characterised by infiltration of polymorphs in alveoli and small airways and T-cell mediated mononuclear cell infiltration leading to granuloma formation occurring later. The clinical picture is that of an interstitial pneumonitis which varies from patient to patient. The presentation can be acute, subacute or chronic and at times the diagnosis may be difficult. These conditions need to be differentiated from collagen vascular diseases, drug-induced lung diseases and sarcoidosis.

Table 3: Examples of Occupational Exposure-Related Hypersensitivity Pneumonitis

Disease and Occupational Exposures	Antigen and Source
Bagassosis	Thermophilic actinomycetes; sugarcane
Bird fancier's lung	Parakeet, pigeon, chicken, turkey proteins; avian droppings or feathers
Cephalosporium pneumonitis	Contaminated sewage; *Cephalosporium*
Cheese washers' lung	*Penicillium casei;* moldy cheese
Chemical workers' lung	Isocyanates; polyurethane foam, varnishes, lacquer
Compost lung	Aspergillus; compost
Detergent workers' lung	*Bacillus subtilis* enzymes; detergent
Farmers' lung	Thermophilic actinomycetes; moldy hay, grain, silage
Furriers' lung	Animal fur dust; animal pelts
Humidifier or air-conditioner's lung (ventilation pneumonitis)	*Aureobasidium pullulans*, *Candida albicans*, Thermophilic actinomycetes, mycobacterium spp, etc. Contaminated water in humidification or air-conditioning systems
Malt workers' lung	*Aspergillus fumigatus* or *A. clavatus;* moldy barley
Miller's lung	*Sitophilus granarius;* infested wheat flour
Miscellaneous medications	Amiodarone, bleomycin, efavirenz, gemcitabine, hydralazine, hydroxyurea, isoniazid, methotrexate, paclitaxel, penicillin, procarbazine, propranolol, riluzole, sirolimus, sulphasalazine
Mushroom workers' lung	Thermophilic actinomycetes; mushroom compost
Potato riddlers' lung	Thermophilic actinomycetes; moldy hay around potatoes
Streptomyces albus lung	*Streptomyces albus;* contaminated fertiliser
Suberosis	*Penicilium gabratum*; cork dust
Thatched roof disease	*Saccharomonospora viridis;* dried grasses and leaves
Tobacco workers' disease	Aspergillus spp; mold on tobacco
Winegrower's lung	*Botrytis cinerea;* mold on grapes
Woodworker's lung	Wood dust, Alternaria; oak, cedar, pine and mahogany dusts

CLINICAL FEATURES

The exact magnitude of the problem is unknown but there is no question that large numbers of individuals are at risk for developing serious respiratory disease as a result of environmental and occupational exposures. For example, for populations over age 15, 15% to 20% of the burden of asthma and COPD is estimated to be due to occupational factors in USA. In India, the burden may be greater given the high level of exposure. The patient's history is of paramount importance in assessment. Detailed inquiry into specific work practices is required and temporal association of exposure at work and symptoms provides clues to occupation-related diseases.

History provides of exposure to potentially toxic agents at home, hobbies, exposure to second hand smoke, and proximity to traffic and industrial facilities should be obtained. The physical examination of patients with suspected environmental lung diseases may help to differentiate the nature and severity of the pulmonary condition. Unfortunately, these findings do not point to the specific causative agent and other information must be used to arrive at the aetiological diagnosis. The investigations include pulmonary function testing and chest imaging. Measurement of exposure is included if reliable environmental data are available.

Many mineral dusts produce characteristic alterations in the mechanics of breathing and lung volumes that indicate a restrictive pattern. Exposure to organic dusts or chemical agents may result in occupational asthma or COPD. Measurement of FEV_1 before and after a working shift can be used to detect a bronchoconstrictive or acute inflammatory response.

Chest radiograph is useful for detecting and monitoring the response to mineral dusts, certain metals and organic dusts which are capable of inducing hypersensitivity response. The International Labour Organization International Classification of Radiographs of pneumoconiosis classifies chest radiographs according to the nature and size of opacities and extent of pulmonary involvement on a 12-point scale. Small rounded opacities are seen in silicosis and coal-worker's pneumoconiosis and linear opacities in asbestosis. Chest radiograph is insufficient to diagnose extent of the disease in a given patient and CT scan of the chest (regular and high resolution) has improved the sensitivity of identification of diffuse parenchymal abnormalities. Other procedures that may be of use are identification of heavy metals in urine; skin prick testing or specific IgE antibody titres for evidence of immediate hypersensitivity; specific IgG precipitating antibodies for agents causing hypersensitivity pneumonitis; or assays of specific cell-mediated immune responses. Sometimes, a bronchoscopy to obtain bronchoalveolar lavage fluid and transbronchial biopsy of lung tissue may be required for histological diagnosis and differentiation from specific forms of lung diseases and infections. Rarely, video-assisted thoracoscopic surgery to obtain a larger sample of lung tissue may be required for specific diagnosis.

CONCLUSION

Environmental health issues, especially lung diseases, are a major cause of disability and death in India. Despite a large number of legal provisions, the numbers are enormous and it has been estimated by the International Labour Organization that more than 400,000 people die every year due to work related problems including accidents, injuries and chronic diseases. Management of these diseases is currently limited to the prevention and treatment of symptoms and pulmonary manifestations. Increased awareness of the disease conditions, adequate preventive measures and timely interventions are critical to control these diseases.

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27.5 Drowning, Near-Drowning and Submersion Injury

Yudh Dev Singh

INTRODUCTION

Drowning is defined as a process resulting from suffocation by submersion/immersion in a liquid, usually water. Near drowning is defined as survival of the victim, at least temporarily, after suffocation by submersion in water. Drowning accounts for nearly 150,000 deaths annually worldwide, including approximately 6,000 fatalities in the United States of America. Near drowning events are estimated to occur many times more than reported drowning deaths. There are approximately 2 million survivors after a drowning event, annually, worldwide. Drowning remains one of the common causes of accidental death worldwide and continues to be associated with high morbidity and mortality.

The American Heart Association in its resuscitation guidelines suggests, that the term 'drowning' should refer to a mortal submersion event in which the victim dies within 24 hours, while the term 'submersion injury' should be used till the time of drowning-related death. In this classification scheme, the term 'near-drowning' has been abandoned.

A swimmer may fall victim to drowning because of over-exertion, exhaustion, panic, inability to cope with swift water current or effects of cold water.

DROWNING PROCESS

The process of drowning is a continuous process which starts with the victim's airway being below the surface of the liquid with breath held voluntarily. This is then usually followed by laryngospasm which is involuntary and secondary to the presence of liquid in the oropharynx. The victim is unable to breathe air during this period, leading to hypercarbia, hypoxia and acidosis due to carbon dioxide retention and oxygen depletion. During this period, the victim frequently swallows large quantities of water. Respiratory movements may become very active but no gas exchange takes place due to obstruction at the level of the larynx. As arterial oxygen tension drops further, laryngospasm abates, and the victim actively inhales varying amount of liquid. Depending on the composition and volume of the liquid aspirated and duration of submersion, changes occur in the lungs, body fluids, blood-gas tensions, acid-base balance and electrolyte concentrations. Surfactant washout, pulmonary hypertension, and shunting, all contribute to the occurrence of hypoxaemia. Water at 10°C or less has marked cardiovascular effects, including increased blood pressure and ectopic tachydysrhythmias.

A victim can be rescued at any time during this drowning process and the chain of events may be interrupted. In absence of effective resuscitative measures multiple organ dysfunction and death usually occurs, mainly due to tissue hypoxia. Post-hypoxic encephalopathy is the most common cause of death in hospitalised victims who have suffered from the drowning process.

PATHOPHYSIOLOGY

Principal physiologic consequence of immersion injury is prolonged hypoxaemia. After initial gasping, and possible aspiration, immersion stimulates hyperventilation, followed by voluntary cessation of breathing and a variable degree and duration of laryngospasm. This further leads to hypoxaemia. Depending upon the degree of hypoxaemia and resultant acidosis, the patient may develop cardiac arrest and cerebral ischaemia. Prolonged asphyxia leads to relaxation of the airway, which permits the lungs to fill with water in many victims ('wet drowning').

Most swimmers initially hyperventilate so as to prolong the duration of underwater swimming. By this procedure, they reduce the arterial partial pressure of carbon dioxide ($PaCO_2$). As the individual swims, oxygen is consumed, partial pressure of oxygen (PaO_2) falls to the levels of 30 to 40 mm Hg, but $PaCO_2$ does not rise sufficiently in time to trigger the urge to breathe. This situation may lead to cerebral hypoxia and loss of consciousness, resulting in drowning.

Lungs are the target organ of submersion injury. Other systems get affected secondary to hypoxia and ischaemic acidosis. Fluid aspirated into the lungs produces pulmonary vasoconstriction and hypertension which is mediated through the vagal stimulation. Based on available evidence from animal studies, significant pathophysiological differences between fresh-water and salt-water aspiration have been emphasised.

In fresh-water drowning hypoxaemia occurs due to inactivation of pulmonary surfactant, resulting in worsening of lung compliance and atelectasis. Perfusion of poorly ventilated areas of the lung results in intrapulmonary shunting of as much as 75% of blood flow and may lead to ventilation-perfusion mismatch. Aspirated hypotonic fluid rapidly passes from the lungs into the intravascular compartment, leading to volume overload and dilutional effects on serum electrolytes.

Hypoxaemia in hypertonic salt-water drowning is secondary to fluid movement into the alveoli caused by the establishment of an osmotic gradient between the capillary-alveolar membrane leading to massive pulmonary oedema and hypertonic serum.

The difference between salt and fresh-water drowning is more obvious among persons who are dead on arrival than among victims who are brought to the hospital alive. Both, fresh and salt-water, produce an inflammatory reaction in alveolar-capillary membrane leading to an outpouring of plasma-rich fluid into alveoli. Individuals who survive the initial course of near drowning are at risk for development of acute respiratory distress syndrome (ARDS).

Drowning Without Aspiration of Fluid (Dry Drowning)

Dry drowning is a controversial subject as few authorities do not accept this entity, but it has been reported in 10% to 20%

of drowned patients in the medical literature. It is more common in adults and is characterised by little or no fluid in lungs. Death occurs due to profound laryngospasm. Entry of water is prevented by laryngospasm. When spasm relaxes due to terminal asphyxia, outpouring of thick mucus may also prevent entry of water. Associated hypothermia may further aggravate impairment of consciousness and motor activity. Recently, the concept of dry drowning has been challenged and it is felt that presence of fluid in the lungs is must to classify victim as having died due to drowning. Victims found deceased in the water and do not demonstrate any evidence of water aspiration at autopsy should be considered as having probably died of some other cause.

MANAGEMENT

It is important to initiate aggressive basic and advanced cardiac life support measures promptly as success of initial resuscitation and duration of submersion are strong determinants of long-term prognosis.

On-Site Resuscitation

The victim should be removed from the water as soon as possible. Restoration of airway patency, breathing, and circulation must be ensured. Mouth-to-mouth breathing should be attempted at the earliest, if possible, even while the victim is in water. Time should not be wasted in attempting chest compressions while in the water since this has not been shown to be effective instead in unconscious patient the cardio-pulmonary resuscitation should be started immediately by keeping the victim's back over a dry hard surface. Heimlich manoeuvre is not recommended because attempting sub-diaphragmatic pressure may increase the risk of aspiration. Obstruction caused by foreign bodies or debris should be looked for. Victim may have other associated conditions, like seizures, head and neck injuries, and these should be kept in mind while attempting initial resuscitation on site or during transportation to a hospital.

Management in a Hospital

On arrival adequate airway must be ensured. Elective intubation may have to be considered even in the absence of respiratory depression with an intention to protect the airway. Attention should be focused to ensure adequate breathing to achieve satisfactory oxygenation and ventilation. Individuals who have hypoxaemia and unable to maintain adequate saturation with 100% oxygen may benefit from mechanical ventilator support with positive end-expiratory pressure (PEEP) while alert patient may be given a trial of non-invasive ventilation Bi-level/ continuous positive airway pressure (BIPAP/CPAP) before invasive ventilation.

Hypoxaemia and hypercarbia are detrimental to the goal of achieving successful central nervous system (CNS) resuscitation, therefore, pulse oximetry, capnography and blood gases may be monitored. Clinical evaluation of cardiac status and peripheral perfusion must be done to assess haemodynamic status. Severe metabolic acidosis may worsen myocardial function and sodium bicarbonate along with fluids may be required to reverse the abnormality of acidosis. Hypovolaemia correction with isotonic fluids may be necessary but fluids should be used judiciously as these victims have an increased risk for developing cerebral oedema.

Victims may have associated hypothermia and may need to be treated for hypothermia. As thermal conductivity of water is 20 times greater than that of air, hypothermia may occur even in tropical waters with temperature as high as 91°F, if protective clothing is not worn and victim is in water for a long time. It is advisable to remove all wet clothing, wrap the victim in a warm blanket and place in a warm area protected from wind. Re-warming with forced hot air or warm water bath may be tried. Active core re-warming by warm water, intra-gastric irrigation, peritoneal dialysis, haemodialysis and extracorporeal circulation, all utilising a system of warming by perfused fluid, have been advocated. There have been few documented survivals after prolonged cold drowning.

Patients who have nearly drowned are likely to have long intensive care unit stay, predisposing them to nosocomial infections. Despite efforts at minimising barotrauma many patients, who have nearly drowned and who required ventilatory support, may develop ARDS. The management of these victims is similar to other non-submersion injury patients who have ARDS.

Laboratory Diagnostic Studies

Diagnostic studies in an individual who had nearly drowned include serum electrolytes, serum creatinine, blood urea, arterial blood gases (ABG) to evaluate the extent of hypoxaemia, status of ventilation, and acidosis, and haemoglobin levels. Toxicology studies, including alcohol levels, may be considered based on the clinical situation. The clinician should obtain a baseline electrocardiogram to look for any cardiac arrhythmia and to evaluate the QT_c interval. Routine computed tomographic imaging of the head is not necessary at the initial stage unless an associated head injury is suspected based on the victim's neurological status.

Prevention

Epidemiologically, nearly half the number of persons who drown is in their teens and about 35% possess good swimming skills. Various factors contributing to drowning accidents include limited swimming ability, unattended children at water bodies, drugs and alcohol abuse, existing medical problems like epilepsy and risky behaviour in water, especially in rainy season in India where flash floods are not uncommon.

Mandatory lifeguards at swimming pools and beaches, improvement in recreational water bodies safety standard, relevant health education and cardiopulmonary resuscitation training of lay public has potential to reduce the death rate from accidental drowning.

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27.6 Electric Shock and Lightning Injury

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Electrical and lightening injuries are not very uncommon, nearly always accidental, and generally preventable. These environmental injuries cause aggressive pathological lesions which may result in heavy functional and aesthetic consequences. The treatment of these injuries presents many complex multi-level problems which require a proactive approach and treatment.

ELECTRIC SHOCK

Definition

The passage of electric energy through the human body triggers complex reactions which affect the anatomical, histological, biochemical and structural composition. The tissue damage caused by electric current varies from a transient increase in cell membrane permeability to immediate coagulation necrosis of large volumes of tissue.

Epidemiology

Electric shocks are more frequent in developing and under-developed countries having inefficient electric energy system. Overall electrical burns account for 4% to 6.5% of admissions to burn units. Except Turkey (16%), India is having higher incidence rate (3% to 9%) than USA (3%), China (3% to 5%) and Slovakia (2.7%). In a recent Indian study, the amputation rate due to electrical injuries was found to be 4.5% and mortality rate of 3.7%.

The electrical injuries have bimodal distribution of age with work-related injuries in adults, and accidents in children particularly below 6 years, more due to oral contact. Male to female ratio is approximately 2:1 in childhood, while in adults more than 90% of victims are men.

Pathophysiology

The type and extent of an electrical injury is determined by voltage, current strength, the resistance to flow, the duration of contact with the source, the pathway of flow, and the type of current. In the following section, each is explained briefly.

Voltage (V)

Electrical injuries are typically divided into high-voltage and low-voltage injuries, using 500 V or 1,000 V as the cut-off, but above 40 V is also dangerous .

Voltage is expressed by Ohm's law:

$$V = I \times R$$

where, I is current in amperes, R is resistance in ohms, and V is potential in volts.

Current (I)

It is the amount of energy that flows through an object. A very narrow range exists between the threshold of perception of current (0.2 to 0.4 mA) and let-go current. The level above which a person becomes unable to release the current source because of muscular tetany is a 'let-go current'. The effect of current to the body depends on the intensity and varies from tingling sensation, to let-go-current, skeletal muscle tetany, respiratory muscle paralysis, ventricular fibrillation and asystole.

Resistance (R)

It is the impedance to electrical flow across the gradient and depends on electrolyte and water content of the body tissue. Tissues with higher resistance have a tendency to heat up and coagulate which further increases the resistance. Dry skin has a resistance of approximately 100,000 ohms which further decreases with moisture. Sweating decreases the skin's resistance to 2,500 ohms to 3,000 ohms and by immersion in water to 1,200 ohms to 1,500 ohms. The level of tissue resistance varies with the tissues as shown in **Table 1**.

Table 1: Resistance of Body Tissues

Least	Intermediate	High
Nerves	Dry skin	Tendon
Blood		Fat
Mucous membranes		Bone
Muscle		

Duration of contact

In general, longer the duration of contact with high-voltage current, greater will be the heating and degree of tissue destruction caused by the current.

Type of circuit

Electrical circuits are direct current (DC) or alternating current (AC). Direct current causes single muscle contraction and throws the victim away, while by alternating current victim can grasp current source due to muscle tetany (at 40 Hz to 110 Hz).

Pathway

Amount of heat generated, type of injury and tissue/organ affected is determined by pathway of current. Greatest degree of damage occurs at the current source and contact points over the body.

Mechanisms of Injury

The primary electrical injury is burns. Secondary, blunt trauma results from falls or being thrown from the electrical source.

Types of electrical burns

Electrical burns can be classified into direct or indirect and can be classified into four subgroups. The electrothermal burns are due to direct contact while electric arc, flare and flash injury, are due to indirect injury.

1. *Electrothermal burns:* These are the result of low voltage electric burns with a limited affected area, caused by direct contact with the current source.

2. *Electrical arcs:* It is a current spark formed between two objects of differing potential that are not in contact with each other, usually a highly charged source and a ground. Because the temperature of an electrical arc is approximately 2,500°C to 5,000°C, it causes very deep thermal burns at the point where it contacts the skin.
3. *Flame:* Ignition of clothing causes direct burns from flames.
4. *Flash:* When the current does not actually enters the body, but the heat from a nearby electrical arc or current source splashes over the body causes thermal burns and is called the flash burns.

Clinical Manifestations

Clinical features are according to action of current, its pathway and organ affected in between as described in **Table 2**.

Table 2: Clinical Features according to Organ Involved

Organ/System	Clinical Features
Head/ENT	Facial burn, cataract (delayed), perforated tympanic membrane, cervical spine injuries
Cardiovascular system	Cardiac arrest and sudden death (>1000 volts), arrhythmias, ventricular fibrillation or atrial fibrillation, first or second degree heart block or bundle branch block, myocardial infarction or rupture (rarely), venous/arterial thrombosis
Skin	Variety of burns (superficial, partial or full-thickness), peculiar is 'kissing burn'
Musculoskeletal system	Muscle necrosis, mummification of tissues leading to gangrene, compartment syndrome, fracture and dislocation of long bones, spinal fractures and injuries
Nervous system	Confusion, difficulty with short-term memory and concentration, seizure, loss of consciousness, peripheral nerve damage, weakness and paresthesias of limbs, ascending paralysis, amyotrophic lateral sclerosis, or transverse myelitis (delayed)
Psychiatric	Depression, anxiety, job failure, aggressive behaviour and suicide
Respiratory	Chest wall muscle paralysis, respiratory arrest
Renal	Myoglobinuria, rhabdomyolysis, acute tubular necrosis, acute renal failure
Other systems	Rarely direct liver injury, focal pancreatic and gallbladder necrosis, intestinal perforation and fistula formation, stress ulcers, burn ileus

ENT = Ear, nose and throat.

Complications

- Cardiac arrest leading to hypoxic brain damage
- Renal failure due to myoglobinuria, acute tubular necrosis (ATN)
- Stress ulcers
- Burn infections like clostridial myositis
- Pneumonia
- Sepsis
- Multi-organ dysfunction syndrome (MODS)
- Tissue loss, fractures and amputations
- Delayed neuropsychiatric manifestations

Management

Pre-hospital care

Secure the scene, like power source should be turned off.

Spine immobilisation may be required in case of spinal injury.

Initial resuscitation

Initiate prolonged cardiopulmonary resuscitation (CPR), in case of cardiorespiratory arrest and do proper cardiac monitoring. See Chapter 11, Section 7.

Specific therapy

Rhabdomyolysis: Alkalisation of urine, intravenous fluids, mannitol and furosemide may prevent development of renal failure.

Electrolytes correction, i.e. hyperkalaemia.

Burn and wound care: Proper debridement, escharotomy, antibiotic dressing and prophylactic systemic antibiotics.

Extremity injuries: Early fasciotomy, carpal tunnel release, amputation (extensive damage).

LIGHTENING INJURY

Definition

Lightening injury is caused by a unidirectional, massive, current impulse with several return strokes back to the cloud, which is neither the direct or alternating current, lasting for a very short period, leading to mild superficial burns to various systemic injuries.

The duration of lightening bolt is 1/100 to 1/1,000 of a second, voltage of approximately 1 billion V, currents ranging from 12,000 to 200,000 A and the temperature dissipation of about 30,000 K.

Epidemiology

The incidence is likely to be more common in males of less than 35 years of age, as they indulge in more outdoor activities. Lightening is more common near the equator. Extreme temperatures are generally the most common environmental killers.

Mechanism of Injury

Lightening injury may occur by direct contact or indirect contact with the light stricken object.

Direct contact

Orifice entry: It strucks head and may enter eyes, ears and mouth to flow internally.

Indirect contact

Side flash or splash: Lightening jumps from primary striking object to a nearby person on its ground.

Ground current or step voltage: A difference in electrical potential between person's feet may occur when lightening flows through the ground, current then flows through person rather than the ground.

Blunt trauma: Injury occurs if the person is thrown away by lightening current.

Clinical Manifestations

Lightening injuries causes minor injuries, cardiac arrest and other manifestations as presented in **Table 3**.

Table 3: Features of Lightening Injury

Organ/System	Clinical Features
Head/ENT	Skull fractures and cervical spine injury (blunt trauma), tympanic membrane rupture, disruption of the ossicles and mastoid, CSF otorrhoea, haemotympanum, and permanent deafnesss
Eye	Corneal lesions, uveitis, iridocyclitis, hyphema, vitreous haemorrhage, optic atrophy, retinal detachment, and choroidoretinitis
Cardiovascular system	Cardiac arrest due to asystole, ventricular fibrillation (rare), other dysrhythmias
Skin	Mottling, burns: Linear, punctate, feathering ('Litchenberg Figures'), or thermal burns
Musculoskeletal system	Fracture and dislocation of long bones, spinal fractures and injuries
Nervous system	Keraunoparalysis (transient paralysis), permanent paresis or paraesthesias, anterograde amnesia, peripheral nerve damage, intracranial haemorrhages, seizures, loss of consciousness, delayed muscle atrophy
Psychiatric	Depression, anxiety
Respiratory	Pulmonary contusion and haemorrhages
Other systems	Blunt abdominal injuries

Complications of Lightening

- Cardiac arrest and death
- Iatrogenic complications secondary to over aggressive management
- Hearing loss from tympanic membrane rupture
- Spinal injuries
- Neurologic damage—paraplegia or haemiplegia
- Neuropsychiatric manifestations
- Chronic pain syndromes

Treatment

Pre-hospital care

- Victim and caregiver should guard themselves from another lightening injury.
- Spinal immobilisation.

Hospital care

- Observation only, if minor injuries and superficial burns.
- Immediate aggressive and persistent cardiopulmonary resuscitation in case of cardiac arrest.
- Keraunoparalysis and transient unconsciousness may require observation.
- Consultation for the injuries to ear, eyes and blunt trauma injuries from respective specialists.

Prognosis

Morbidity and mortality are largely affected by the particular type of electrical contact involved. Proper resuscitation with monitoring of limb tissue pressure and wound care can maximise tissue salvage; reduce renal failure, and increased survival of patients with lightening and high-voltage electric injuries.

CONCLUSIONS

Electrical and lightening injuries are environmental injuries causing various anatomical, structural and functional disturbances in the body. Electrical injuries may cause superficial or deep burns and various complex injuries to the organs, burn infections and renal failure. While lightening injury may not cause severe burns but can result in more cardiac and neurological damage. Electrical injuries require more intense management, like burn wound care, aggressive fluids and treatment pertaining to systemic complications than lightening injuries.

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27.7 Effects of Extremes of Temperature

Rajvir Bhalwar

INTRODUCTION

The term 'heat stress' or 'cold stress' is applied to any degree of environmental heat or cold that causes physiological thermo-regulatory mechanisms to get activated. Human beings are homoeothermic creatures whose physiology attempts to maintain a constant core body temperature of 37°C (range 36°C to 38°C). Obviously, this requires balancing of the body heat production with heat loss which is achieved by a combination of physiological mechanisms (as peripheral vasodilatation or vasoconstriction, changes in heart rate, sweating or shivering) and behavioural mechanisms (increase or decrease in voluntary physical activity, seeking appropriate shelter, etc). In addition, environmental conditions, viz. temperature, humidity and speed of air also greatly determine whether a person will be subjected to thermal stress. Therefore, prevention and management of thermal stress disorders requires an understanding of these physiological, behavioural and environmental mechanisms and manipulating them appropriately. For the purpose of thermo-regulation, the human body can be conceived of having two 'layers'—an outer periphery or 'shell' consisting of skin, subcutaneous tissue and muscles, and an inner 'core' consisting of brain, heart and viscera.

EPIDEMIOLOGY OF HEAT STROKE

Adverse effects of heat stress are an important cause of morbidity and mortality not only in the developing countries but in the developed countries as well. In India, 3,194 deaths due to heat stroke (HS) have been recorded over the 5-year period 1999 to 2003; the actual magnitude may be much more. The central and northern plains, western deserts and tropical forest areas of north-east have environmental conditions causing heat stress during the months of April to September. The risk is much higher among certain categories (**Table 1**).

Table 1: Persons at High Risk of Heat Stress

Extremes of age (<5 years or >65 years)
Pregnancy
Occupation—workers in military, agricultural, construction and industrial settings, labourers, sports-persons and miners
Low level of physical fitness
Lack of acclimatisation to environmental heat
Obesity
High ambient temperature, high atmospheric humidity, low air velocity
Alcohol use—acute and chronic
Skin diseases—extensive prickly heat, psoriasis, pyoderma
Sleep deprivation
Co-existing febrile illness, renal, thyroid, cardiovascular and metabolic diseases
Previous history of heat-illness
Use of drugs or habit forming substances—phenothiazines, anti-cholinergics, ACE-inhibitors, MAO-inhibitors, cocaine, amphetamines, anti-histamines

ACE = Angiotensin converting enzymes; MAO = Monoamineoxidase.

PATHOPHYSIOLOGY

As a part of thermo-regulatory process, even an increase of 1°C in the temperature of blood generates signals to the hypothalamic thermo-regulatory centre leading to increase in heart rate and cardiac output, which coupled with the sympathetic cutaneous vasodilatation increases the skin blood flow. Sweating is activated and its evaporation cools the body surface, unless the air surrounding the body is fully saturated with water, i.e. having relative humidity (RH) of 100%. Increasing the movement of air in contact with the body also increases cooling by promoting evaporation of sweat. Sweating, however, leads to loss of water and salt, which may be as high as 2 litres per hour under conditions of high humidity and physical exertion. If the water and salt are not replaced adequately and concurrently, the fluid reserves would be depleted, even though the body core temperature may not be very high. This condition is called *'heat exhaustion' (HE)*. However, at times, the thermo-regulatory response may be overwhelmed by the hot environment, even though the fluid and salt reserves of the body may be adequate. Such thermo-regulatory failure, coupled with exaggerated acute phase response (increased production of inflammatory cytokines and endothelium derived vasoactive factors and activation of coagulation process) and alterations in the expression of heat shock proteins (HSPs), leads to *'heat stroke'*. For these reasons, a number of cases of HE, if not properly managed, would also pass on to HS. Following HS, a multiple organ dysfunction syndrome (MODS) results from a complex interplay between the cytotoxic effects of heat and the inflammatory and coagulation responses of the host.

CLINICAL FEATURES OF HEAT STROKE

The classical clinical description of HS is the triad of hyperpyrexia (rectal temperature >40°C), central nervous system (CNS) dysfunction and anhidrosis. Anhidrosis, however, is not a diagnostic requirement since it may appear later when volume depletion is severe. Moreover, in cases which initially start as HE or cases of HS which occur among young people who have been exerting physically, the skin may be moist. Brain dysfunction is usually severe (coma, stupor or delirium), but may sometimes be subtle, manifesting as inappropriate behaviour or impaired judgement. In fact, any person who develops irrational or confused behaviour following exposure to heat stress either with or without a history of physical exertion, should be treated as a potential HS patient. Other clinical features include evidence of dehydration, shock, convulsions and, sometimes, mild icterus. Two forms of HS are recognised, viz. the classical HS (CHS) and the exertional HS (EHS) form. It is important to recognise the clinical differences between the two forms (**Table 2**).

Table 2: Differences Between Classical Heat Stroke and Exertional Heat Stroke (EHS)

Characteristic	CHS	EHS
Age group	Elderly	15 to 45 years
Previous health status	Usually compromised	Healthy
Concurrent activity	Sedentary	Strenuous activity
Habit of drug use	Often present	Usually present
Sweating	Often absent	Frequently severe
Skin	Dry	May be moist
Rhabdomyolysis	Unusual	Excessive

DIFFERENTIAL DIAGNOSIS

Heat stroke should be considered as a possibility in any patient who presents with elevated body temperature and altered mental functions. Important and common diseases which need to be excluded are tropical infectious diseases like cerebral malaria, encephalitis and meningitis. Other diseases which need to be considered are thyroid storm, phaeochromocytoma, status epilepticus, cocaine and amphetamine abuse, delirium tremens and cerebro-vascular accident especially pontine haemorrhage. The diagnosis of HS is usually one of exclusion and the typical history of exposure to hot environment during the immediate past is an indication towards heat stress hyperthermia.

LABORATORY INVESTIGATIONS

Blood should always be drawn for a peripheral blood smear for malarial parasite as well as for other infectious causes of hyperpyrexia with CNS dysfunction. Laboratory findings of HS include haemoconcentration, mild leucocytosis, elevation of blood urea, and in some patients of EHS, hypoglycaemia. Impaired blood coagulation with lowered prothrombin, low platelet counts, hypofibrinogenaemia and features of disseminated intravascular coaglation (DIC) may be seen. Serum electrolyte studies generally show normal or high chlorides, hypokalaemia, hypocalcaemia, and hypophosphataemia. Enzyme studies show increase in creatine phosphokinase (CPK), serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels. If rhabdomyolysis or acute renal failure (secondary to acute tubular necrosis) has set in, urine will show myoglobinuria, proteinuria, and hyaline and granular casts, and there will be an increase in blood uria nitrogen (BUN) levels.

Complications

The most serious complication of HS is MODS, manifesting as hepatic failure, renal failure, cerebellar damage, cerebral oedema and arrhythmias. Rhabdomyolysis and DIC are other serious complications.

PROGNOSIS

HS must be treated as an emergency. Mortality may be as high as 30% to 50% among cases where treatment is delayed. Mortality is directly proportional to the level of core temperature and its duration. Prolonged coma of more than 2 hours is a poor prognostic indicator. Among survivors, neurological recovery generally occurs but some deficit may persist in up to 20% of the cases. Survivors of HS, who have suffered for hyperpyrexia for a few hours may get permanent brain damage.

TREATMENT

HS must be treated as a serious medical emergency. Delay in institution of appropriate therapy by even few minutes may make all the difference between life and death. The treatment objectives are: firstly, rapid cooling to bring down the core temperature to below 39°C and reducing it by approximately 0.2°C per minute; secondly, rehydration and care of comatose patient; and, thirdly, to support the organ system function. Cooling measures should be stopped once core temperature falls below 39°C. The steps in the management of HS at two different levels (first aid level, primary care/solo physician level and hospital level) are shown in **Tables 3 and 4**, respectively.

Table 3: Management at First Aid Level

Record rectal temperature. If it is not possible to record rectal temperature, record oral temperature and add 0.5°C
Try and move patient to a cooler and shaded place
Remove the clothes
Spray skin with water at 25°C to 30°C or wrap the patient with a sheet soaked in water at 25°C to 30°C
Continue fanning manually or with an electrical fan
Keep vigorously massaging the skin to prevent cutaneous vasoconstriction during cooling
If available, place ice packs or towel soaked in cold water around the neck, axillae and groin
Nurse in the comatose position; clear oral secretions
Transport to the medical facility as an emergency

Table 4: Management at the Hospital (Secondary/Tertiary Care Level)

Continue cooling measures
Start monitoring core temperature with a thermometer calibrated to measure high temperature (40°C to 47°C)
In case temperature is not reducing, immerse the patient in tub containing cold or iced water, keep the head and neck outside the water surface
In case patient is shivering, give intravenous (IV) chlorpromazine 25 mg to 50 mg
Intubate the patient, establish ventilatory support, give oxygen inhalations
Continue IV fluids; maintain mean arterial pressure at 60 mm Hg; if required, consider administering a vasopressor
Frequently monitor blood electrolytes to guide the IV fluid therapy
In case there is evidence of shock, cerebral oedema or adrenal insufficiency, administer IV hydrocortisone hemisuccinate 100 mg or betamethasone 4 mg to 8 mg
If facilities exist, give a cold gastric lavage after intubating the patient
Antipyretics do not seem to have any role. There are reports about efficacy of dantrolene sodium but the same have not been proven by clinical trials
If there is evidence of rhabdomyolysis or acute renal failure, give IV normal saline, furosemide 40 mg, mannitol 0.25 g/Kg body weight and 250 ml of 4% IV sodium bicarbonate. Heparinisation may be required if there is evidence of DIC
Advice bed rest for about 7 days after recovery from heat stroke since temperature control mechanisms may remain labile after recovery

Heat Exhaustion

The features which differentiate HE from HS are that core temperature is less than 40°C and there is no evidence of CNS dysfunction, though some patients may be anxious or irritable. The salient differentiating features between HS and HE are given in **Table 5**.

PREVENTION OF ADVERSE EFFECTS OF HOT ENVIRONMENT

1. Avoid exposure to outside environment during summer, from 10 am to 5 pm, unless necessary.
2. Keep drinking water regularly, especially if exerting. Drink 250 to 300 ml water every half an hour even if not thirsty. Drink 5 to 6 litres cool water in a day. Carry a bottle of cool drinking water. Remember that thirst is not a good indicator of dehydration, and hence, one should not wait for thirst to develop before starting to drink fluids.
3. Put light coloured, loose and permeable clothes (as cotton) in 1 to 2 layers only.
4. Put on wide brimmed hat of light colour when going out.
5. Keep children <5 years or elderly >65 years away from sun as far as possible. Never leave them in closed, parked cars in hot weather.
6. Apply a sun screen ointment of sun protection factor of at least 15 when going out in sun.
7. Avoid alcohol, cocaine and other habit forming drugs.
8. Acclimatise to heat by undertaking gradually increasing intensity of physical exertion in gradually increasing hot environment, for 80 to 100 minutes daily for 10 to 14 days.
9. If feeling exhausted, too thirsty, confused or running out of memory/consciousness, move to a cool, shaded place, sit or lie down, drink cool water and seek help.

Table 5: Salient Differentiating Features Between Heat Stroke (HS) and Heat Exhaustion (HE)

Aspect	HS	HE
Cause	Inadequacy or failure of heat loss mechanisms	Excessive fluid loss leading to hypovolaemia
Warning signs	Headache, weakness, loss of consciousness	Gradual weakness, excessive sweating, anxiety, nausea, syncope
Manifestations	Hot, dry skin with little sweating; full, bounding and rapid pulse, very high temperature (usually >40°C)	Pale, greyish, clammy skin; weak, slow pulse; low blood pressure; temperature moderately raised (usually <40°C)
Management	Emergency cooling by wrapping or immersion in cool water, ice packs over head, axillae and groin; immediate evacuation to hospital	Patient placed recumbent with feet elevated; oral replacement of water and salt rarely intravenously)

OTHER ADVERSE EFFECTS OF HOT ENVIRONMENT

Heat Cramps

These manifest as spasms of muscles, especially lower extremity and shoulder, following heavy muscular exertion in hot environment, with associated intake of hypotonic oral fluids. Treatment consists of oral administration of 0.1% to 0.2% salt solution. Severe cases or those with vomiting should be given intravenous normal saline.

Heat Tetany

Symptoms include carpopedal spasms and paraesthesiae following short exposures to excessively hot environment, leading to hyperventilation and respiratory alkalosis. Treatment consists of removing the patient to a cool environment and asking him to slow down the respiration.

Heat Syncope

This manifests as syncope following exposure to heat stress as a result of peripheral vasodilatation. One should exclude other serious causes of syncope. Treatment consists of removal of patient to a cool environment and oral rehydration.

Heat Oedema

This presents with pitting oedema of hands and feet, usually in the elderly, following exposure to heat stress. Other causes of oedema should be excluded. Treatment consists of reassurance, elevation of affected limbs and, if required, compression bandage.

Prickly Heat *(Lichen Tropicus, Miliaria Rubra)*

It manifests as erythematous, pruritic, maculopapular rash. If the condition is allowed to progress, extensive prickly heat that can progress to chronic dermatitis and superinfection can occur. Prevention consists of regular baths with cool water after gently scrubbing the skin, and wearing loose, light weight clothing. Local application of calamine lotion or chlorhexidine lotion alongwith oral antihistamines is helpful. In case of severe forms, local application of 1% salicylic acid cream and antibiotics for superinfection (usually *Streptococcus aureus*) should be given.

ADVERSE EFFECTS OF COLD ENVIRONMENT

Cold stress leads to adverse effects which can be generalised (hypothermia) or local cold injuries which may be further classified as of freezing type (Frost Nip, Frost Bite) or non-freezing type (Chilblains, Trench foot, Raynaud's phenomena).

EPIDEMIOLOGY OF COLD STRESS

Extreme cold conditions occur in India in the Himalayan, Sub-Himalayan and the North Indian plains with cold waves and deaths being recorded every year. Over the 5-year period 1999 to 2003, a total of 3,524 deaths due to cold exposure have been reported; the actual magnitude may be higher. Groups at particularly high risk include military personnel, agriculturists, mountaineers and persons engaging in adventure or winter sports. From socioeconomic aspect, persons with low income, poor housing and inadequate clothing are at particularly high risk especially during the cold wave conditions. Extremes of age

(<5 years or >65 years), physical exhaustion, pre-existent malnutrition or starvation, use of alcohol, substance abuse, dehydration, and underlying diseases (hypothyroidism, hypoadrenalism, diabetes and cardiovascular disease) increase the risk of cold stress. From environmental point of view, besides low atmospheric temperature, the adverse effect is greatly accentuated if wind is blowing at a fast speed (wind chill factor) or if concomitant rain or snowing is present. Immersion/submersion in cold water bodies, as may occur when a boat overturns during winter months, also carries a risk of hypothermia, besides drowning.

PATHOPHYSIOLOGY

The physiological protective responses to generalised cold involve, first, peripheral vasoconstriction which tends to act as an "insulator" for the inner body core in an effort not to lose the core heat, and secondly, increased thermogenesis by shivering. Coupled with behavioural factors as seeking shelter, putting on clothes and increased muscular activity, the body physiology tries to normalise the core temperature. In the initial stages, there is an increase in metabolism, heart rate and cardiac output. However, as exposure to cold increases, the overall metabolism slows and there is reduction in heart rate, cardiac output and respiratory rate.

Local cold induced injuries are due to formation of 'ice-crystals' within the cells followed by rupture of cells due to endosmosis or due to tearing by ice-crystals. Distal areas of the body and areas with high surface-to-volume ratio (ears, fingers, toes, nails and cheeks) are more susceptible.

CLINICAL FEATURES OF GENERALISED HYPOTHERMIA

Early symptoms of generalised adverse effects of cold become apparent as the 'core' (rectal) temperature drops below 36°C and are clearly evident once it is below 35°C. Depending on the core temperature, hypothermia may be classified as borderline (36°C to 35°C), mild (35°C to 32°C), moderate (32°C to 28°C) and severe (<28°C). One of the earliest symptoms of hypothermia is a change in behaviour, but unfortunately, the victim is the last person to notice such changes himself. There are mild mood changes, lack of affect, apathy, uncoordinated movements, ataxia, confusion and decreased ability to sense cold. Initially, there is tachycardia, tachypnoea and shivering which can be voluntarily controlled. However, as hypothermia becomes more severe, (32°C to 35°C) there is bradycardia and decrease in respiratory rate. Higher reasoning becomes impaired (e.g. the person may not be able to count backwards from 100, subtracting 9 every time). Shivering becomes violent and cannot be stopped voluntarily. Lack of appreciation of cold may lead to 'paradoxical undressing' (the person starts removing the clothes rather than putting on more clothes). Gait becomes stuporous. As the core temperature falls below 32°C, shivering stops. Skin becomes blue and puffy. Patient becomes semiconscious and muscles start becoming rigid. Trismus is often present. There is marked bradycardia and lowering of respiratory rate. Electrocardiogram (ECG) shows the 'J' (Osborn) wave at the junction of QRS complex with ST segment in about 80% cases and this may be confused with myocardial ischaemia. Cardiac dysrythmias are very common, especially atrial/ventricular fibrillation. There is lowering of arterial partial oxygen tension, and often increases in serum aspartate aminotransferase, creatine kinase and serum amylase. If the cause of hypothermia is not immediately identifiable, then investigations directed towards thyroid and pituitary dysfunction, hypoglycaemia and drug intoxication should be undertaken. Once the core temperature drops to 28°C or less, the patient is completely unconscious with severe bradycardia. Radial pulse may not be palpable and carotid pulse may reveal as low as 2 to 3 beats per minute. Respiratory rate is also reduced to 1 to 2 per min. Muscles become rigid and pupils dilated. At this stage the patient may appear dead but may not be so. Carotid pulse must be carefully palpated in all such cases.

INVESTIGATIONS

The most important investigation in a patient of hypothermia is to accurately monitor the core temperature. If possible, a radiograph of the chest or other regions may be taken, primarily to rule out other traumatic injuries since coexisting traumas, haemorrhage and shock may worsen the manifestations of hypothermia. Blood biochemistry usually shows metabolic acidosis, azotaemia and haemoconcentration. ECG may show the 'J' wave as described above, bradycardia and dysrhythmias.

Treatment

Hypothermia should be treated as a medical emergency. Early recognition and institution of therapy may make all the difference between life and death. The basic principle of management is quick warming of the 'core' without causing simultaneous vasodilatation of the periphery, from the level of first aid till the most elaborately equipped critical care facility. The steps in management at three different levels (first aid level, primary care/solo physician level and hospital level) are shown in **Tables 6 and 7**, respectively. During the process of re-warming, one should be very careful as regards the phenomena of 'after-drop'. This happens if the extremities are also rewarmed or else the patient starts exerting again, leading to vasodilatation of peripheral vessels in arms and legs, thus releasing extremely cold blood as well as acidic metabolites (which were trapped in this part of the vasculature). Once this cold blood and metabolites are shunted back, it further cools the brain, heart and viscera as well as making the myocardium more susceptible to dysrhythmias. Hence, during re-warming, do not warm the extremities and do not let the patient exert even if consciousness has been regained.

One also needs to be careful while instituting cardiopulmonary resuscitation (CPR) in a patient of hypothermia, who may appear dead with dilated, fixed pupils and no discernible pulse or respiration. Such patient may be still alive, in a 'metabolic icebox'. Instituting CPR in such a patient may precipitate an 'after drop' and dangerous dysrhythmias. Hence, in such patients, one should carefully check the carotid pulsation and respiration to detect very low heart rate (2 to 4 per minute) and low respiratory rate (2 to 3 per minute). If there is evidence of life, one should start re-warming and not institute CPR. CPR should be started only if it is confirmed that pulse is absent. Once the pulse started, CPR should be continued as the patient is being rewarmed. There have been cases when patients with severe hypothermia

Table 6: Management at First-Aid Level

Remove wet clothing only when patient has reached a warm, dry and sheltered environment and not in the open
Immediately wrap the patient all around, including head, with warm clothes, blankets, quilts, sleeping bags whatever insulatory material is available, even newspapers or rags. Make an 'insulatory wrap' of about 4 inches thickness all around the patient. Provide a wind and waterproof outer most layer, as polythene sheets
Make hot packs with warm water bottles covered with a cloth, or warm pads, at 42°C to 45°C, and apply them to axillae, groin and neck
Do not warm the extremities at this juncture. Place arms and hands on the sides and not on the abdomen or in axillae
Do not let patient do any physical activity. Treat as a 'stretcher case'
If patient can take orally give warm, sweetend tea or milk to provide 'fuel'
Do not massage the limbs
Do not give alcohol or tobacco
Evacuate to a sheltered place preferably to a medical facility at the earliest

Table 7: Management at Hospital Level

Nurse in warm room, preferably in an ICU
Measure rectal temperature and other vital parameters
Recheck intravenous line. Draw blood for investigations
Continue 5% dextrose warmed to 37°C to 41°C. Change the fluid depending on laboratory results
Undertake endotracheal intubation (unless patient is alert and possesses intact airway reflexes). If trismus is present then blind nasotracheal tube is the only practical non-surgical option
Give warm humidified oxygen at 42°C to 45°C, 4 litres/min through endotracheal tube or facemask
Monitor cardiac rhythm and blood gases, including pH

have been given CPR for as long as 3 hours and finally revived. The patient should be declared dead only after he has been re-warmed to core temperature of 36°C and CPR fails at that temperature. The dictum is *A patient of hypothermia, in finality, is never 'cold and dead' but is 'warm and dead'*.

Accidental Hypothermia Among Elderly

Elderly persons (age >65 years) are particularly prone to develop hypothermia, especially in winter season. The age-related autonomic defects, leading to low peripheral resting-blood-flow, a non-constrictive vasomotor response to cold and easily provoked orthostatic hypotension are all aetiologic factors in this increasesd susceptibility, which may be compounded if there is concomitant phenothiazine usage, endocrine disorders, poor nutritional status and pulmonary infection. The exposure need not be to severe cold, since in elderly, hypothermia may be precipitated on exposure to even mild environment with ambient air temperatures of 15°C to 18°C. Hypothermia develops insidiously, over many hours to a few days. Therefore, health care providers should be alert for recording even lowered body temperatures among elderly, since generally in clinical practice, only higher temperatures (and not lowered temperatures) tend to be recorded. Treatment consists of *gradual* (and not rapid) re-warming by moving to a warm room and warming with blankets (**Table 7**).

LOCALISED ADVERSE EFFECTS OF COLD

Frost Nip and Frost Bite

Frost nip involves freezing of top layers of skin tissue. It is generally reversible and manifests as numbness and white, waxy or rubbery feeling of the affected skin but the deeper tissue is still soft. Frost bite is the more severe form and affects all layers of the skin and often the deeper tissues also. Frost bite is of four degrees, depending on the depth of the tissue involved. As an urgent first aid measure, remove any constrictive clothing or bands. Start local warming by placing the affected part in a warm water bath at 40°C to 42°C. If nothing is available, place the affected part in the axiliae or on the stomach of another healthy person. Analgesics and sedatives should be given for relief of pain. Initiate immunisation with tetanus toxoid and evacuate to a surgical facility at the earliest opportunity. If generalised hypothermia and local frost bite both are present, first treat the patient for generalised hypothermia. Local re-warming for frost bite should be undertaken only after core temperature has returned to normal.

Non-Freezing Cold Injuries

These include chilblains and trench (immersion) foot, occurring due to prolonged exposure to cold environment with wet conditions. Chilblains manifest with initial pallor of affected area (usually fingers, toes, cheeks or earlobes) followed by erythema, pruritus and intense pain. Prevention by way of avoidance of exposure to cold and wet conditions among susceptible persons is the most important. Otherwise, there is no specific treatment, though symptoms may be ameliorated by oral nifedipine in some cases.

Trench foot is caused by prolonged exposure of feet to cold and wet conditions. The skin is reddened with tingling pain and itching. Gradually, the skin becomes pale, mottled and finally dark purple, grey or blue. If the circulation remains impaired for more than a few hours, permanent damage to the affected part can occur. Treatment consists of gentle drying, elevation of the affected limb and keeping it at an environmental temperature of 18°C to 22°C while keeping rest of the body warm. NSAIDS may be given for relief of pain. The patient should not walk on the affected limb till fully cured. Prevention is, once again, very important and consists of keeping the feet clean and dry, dabbing the feet with aluminium hydroxide powder thrice daily, and changing into dry socks and shoes at the earliest.

PREVENTION OF ADVERSE EFFECTS OF COLD

1. Dress properly for cold weather. The basic principle for dressing for cold climate is to dress in many layers. The innermost layer should be of polypropylene with numerous air pockets, to serve as 'vapour transmission layer'. The middle layer should be 3 to 4 layers of woolen garments, which serves as the 'insulatory layer' by trapping the air. The outer most layers should be of non-permeable or semi-permeable material made of a wind and water resistant material. In addition, the clothing should be clean and dry.

2. Protect the head very well with a woolen cap, since almost 30% of the body heat is lost through the head.
3. Protection of the head, fingers and feet is extremely important, with proper woollen caps, gloves, socks and shoes.
4. As far as possible do not overheat the body by way of physical activity to the extent that it leads to excessive sweating and dampens the clothes. If clothing becomes wet, change into dry clothing at the earliest possible.
5. Insulate metallic objects which are likely to come in contact with the body and with woolen material.
6. Give special attention to children <5 years, elderly >65 years, and those with poor nutritional status or with diseases of thyroid, adrenal cortex or cardiovascular system.
7. Maintain good nutritional status and adequate hydration with frequent warm, calorie containing drinks.
8. Do not use alcohol, especially if going out in the cold. Avoid tobacco use.
9. Be on the watch-out for earliest symptoms of generalised effects (intense shivering and mental changes) or local effects (skin colour changes, blistering or loss of sensation) and institute urgent first aid.

RECOMMENDED READINGS

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27.8 High Altitude Medicine

Anuj Chawla

INTRODUCTION

An estimated 140 million people permanently live at altitudes greater than 2,500 m. In addition, thousands travel to high altitude areas each year either for work or as tourists for leisure and adventure.

Definition

High altitude (HA) has been defined as an altitude greater than 2,500 m to 2,700 m above mean sea level. An altitude of 2,700 m is a more physiological definition of HA since it results in an alveolar partial pressure of oxygen (P_AO_2) of 60 mm Hg, at which the effects of hypoxia are easily recognisable. Altitudes greater than 5,800 m are classified as extreme altitude (EA). HA poses a number of environmental challenges (**Table 1**), the most important being hypobaric hypoxia. This requires complex physiological adjustments by the body to ensure normal function. These physiological adjustments constitute 'altitude acclimatisation'.

Table 1: Major Environmental Challenges at High Altitude

Hypobaric hypoxia: Barometric pressure reduces with altitude thereby causing a reduction in the partial pressure of oxygen in ambient, inspired and alveolar air.
Low environmental temperature: The environmental temperature falls by 1°C per 150 m gain in altitude. High wind velocity at HA adds to the low temperature due to a 'wind chill factor'.
Low absolute humidity in the atmosphere: This increases the insensible water loss from the body and predisposes to dehydration.
Increased solar and ionizing radiation: Ultraviolet radiation increases by 4% with every 300 m gain in altitude and can cause harmful effects, especially in the eye and skin.

Acclimatisation to High Altitude

The earliest and most important manifestation of altitude acclimatisation is hyperventilation. This results in respiratory alkalosis, which is corrected by renal excretion of bicarbonate over 2 to 3 days. A relatively slower physiological adjustment is an increase in haematocrit, which requires weeks to develop. The hyperventilation and raised haematocrit try to correct tissue hypoxia. Other important physiological changes include raised pulmonary artery pressure (PAP) due to hypoxic pulmonary vasoconstriction, elevated sympathetic activity, increased capillary density and alteration in metabolic enzymes for optimal cellular function in a hypoxic environment. The human body is unable to acclimatise successfully at EA. A failure of or impaired acclimatisation can result in high altitude illnesses.

High Altitude Illnesses

It refers to clinical syndromes that can affect un-acclimatised individuals at HA. It commonly includes the cerebral syndromes of acute mountain sickness (AMS) and high altitude cerebral oedema (HACE) and the pulmonary syndrome of high altitude pulmonary oedema (HAPE). HA illnesses are classified based on their time of onset (**Table 2**). Acute illnesses occur within hours to days of ascent to HA, sub-acute within weeks to months and chronic, after years of stay at HA. A number of factors determine the occurrence of HA illnesses (**Table 3**).

Table 2: Classification of High Altitude Illnesses

Acute
Involving the central nervous system
Acute mountain sickness
High altitude cerebral oedema
Involving the pulmonary system
High altitude pulmonary oedema
High altitude pulmonary hypertension (HAPH)—acute onset
Sub-acute
Sub-acute infantile mountain sickness (SIMS)
Sub-acute adult mountain sickness (SAMS)
Chronic
Chronic mountain sickness (CMS) (Monge's disease)
High altitude pulmonary hypertension (HAPH)—chronic onset
Miscellaneous conditions
Retinal haemorrhage
Gastrointestinal problems
Thrombotic events
Effects of solar/ultraviolet radiation

Table 3: Determinants of High Altitude Illnesses

Rate of ascent to HA
The final altitude reached
Altitude at which the individual sleeps
Previous history of high altitude illness
Acclimatisation status of the individual
Physical activity immediately after ascent to HA
Individual susceptibility

ACUTE HIGH ALTITUDE ILLNESSES

Acute Mountain Sickness (AMS)

Definition and epidemiology

AMS is a syndrome of non-specific symptoms and is defined as the occurrence of headache along with the presence of one or more of gastrointestinal symptoms, insomnia, dizziness, lassitude or fatigue in an un-acclimatised individual who has recently arrived at HA. The incidence of AMS varies with the altitude and rapidity of ascent and ranges from 3.1% at 2,000 m to 53% at 5,000 m.

Aetiopathogenesis

The critical factor in the pathogenesis of AMS is hypoxaemia and AMS may represent the benign end of a clinical spectrum with the malignant end being HACE. However, evidence of

cerebral oedema and raised intracranial tension in AMS is inconsistent. Other pathophysiological mechanisms may include hypoxia-mediated release of vasogenic substances, activation of the trigeminovascular system, and free radical-mediated alteration of the blood-brain barrier permeability. Hypobaria may contribute to AMS by causing blunting of ventilation, impaired lymphatic drainage from the lung and changes in autonomic functions. Current evidence does not support the role of generalised fluid retention, in the pathogenesis of AMS.

Clinical features

The predominant symptom of AMS is headache, which is generally frontal, throbbing, aggravated by exertion and more severe in the mornings. It is usually accompanied by insomnia, malaise, anorexia, nausea and vomiting. Symptoms typically start 4 to 6 hours after arrival at HA and usually subside within 72 hours with rest and no further gain in altitude.

Diagnosis

The Lake Louise Scoring System (LLSS) is commonly used to diagnose AMS. This consists of a self-reported questionnaire and physical examination (**Table 4**). A self-reported score greater than 4 or a total score greater than 5 suggests AMS.

Table 4: Lake Louise Scoring System for Diagnosis of AMS

Self-reported symptoms	
Headache	
None at all	0
A mild headache	1
Moderate headache	2
Severe incapacitating headache	3
Gastrointestinal symptoms	
Good appetite	0
Poor appetite or nausea	1
Moderate nausea or vomiting	2
Severe incapacitating nausea and vomiting	3
Fatigue and/or weakness	
Not tired or weak	0
Mild fatigue/weakness	1
Moderate fatigue/weakness	2
Severe incapacitating nausea and vomiting	3
Dizziness/light headedness	
None	0
Mild	1
Moderate	2
Severe incapacitating	3
Difficulty sleeping	
Slept as well as usual	0
Did not sleep as well as usual	1
Woke many times, poor night's sleep	2
Could not sleep at all	3
Physical examination signs	
Change in mental status	
None	0
Lethargy, lassitude	1
Disoriented, confused	2
Stupor, semiconscious	3
Coma	4
Ataxia in heel to toe walking	
None	0
Balancing manoeuvers	1

Contd...

Contd...

Steps off line	2
Falls down	3
Can't stand	4
Peripheral oedema	
None	0
At 1 location	1
At 2 or more locations	2

AMS diagnosed if self-reported score >4 or total score greater than 5

Treatment

The guidelines for management of AMS are shown in **Table 5**.

Table 5: Guidelines for Management of AMS

- Do not worsen the hypoxia
  - Avoid physical exertion
  - Prevent further gain in altitude
- Correct the hypoxia
  - Inhaled oxygen @ 2 to 4 L/min
- Treat symptoms
  - NSAIDs for headache
  - Anti-emetics for nausea/vomiting
  - Tablet Acetazolamide 250 mg, 8 to 12 hourly if symptoms severe
- If symptoms persist or worsen
  - Dexamethasone 4 mg 6 hourly, orally, IM or IV
  - Descend to lower altitude
    - Actual descent where possible
    - Simulated descent using recompression chambers

Complications

AMS may progress to HACE or HAPE, if not promptly managed or if the hypoxia is worsened due to physical exertion and/or a further gain in altitude.

Prognosis and prevention

AMS is usually a benign self-limiting condition if promptly recognised and treated. It can be prevented by slowing the rate of ascent to HA (**Table 6**) and by proper acclimatisation. Tablet acetazolamide (125 to 250 mg 12 hourly) started 24 hours prior to ascent to HA and continued for three days at HA is the drug of choice for prevention of AMS. Tablet dexamathasone (4 mg 6 hourly) can be considered in case of sulphonamide sensitivity but is not routinely recommended due to the potential complications of steroid therapy and interference with the normal acclimatisation process.

Table 6: Recommended Rates of Ascent at High Altitude

- Above 2,500 m to 3,000 m altitude:
  - Gain in sleeping altitude should not exceed 300 to 600 m per day
  - Allow one rest day for every 1,000 m gain in altitude
- Delay further ascent if symptomatic, wait till symptoms subside
- Descend to lower altitude if symptoms persist or deteriorate

High Altitude Cerebral Oedema (HACE)

Definition and epidemiology

HACE is a potentially fatal condition that can develop in an individual suffering from AMS or HAPE or can occur in isolation. It is defined as the onset of ataxia, altered consciousness or both in an individual who has AMS or HAPE. The incidence varies with altitude and ranges from 0.5% to 4%.

Aetiopathogenesis

The probable pathogenesis of HACE is as shown in (**Figure 1**).

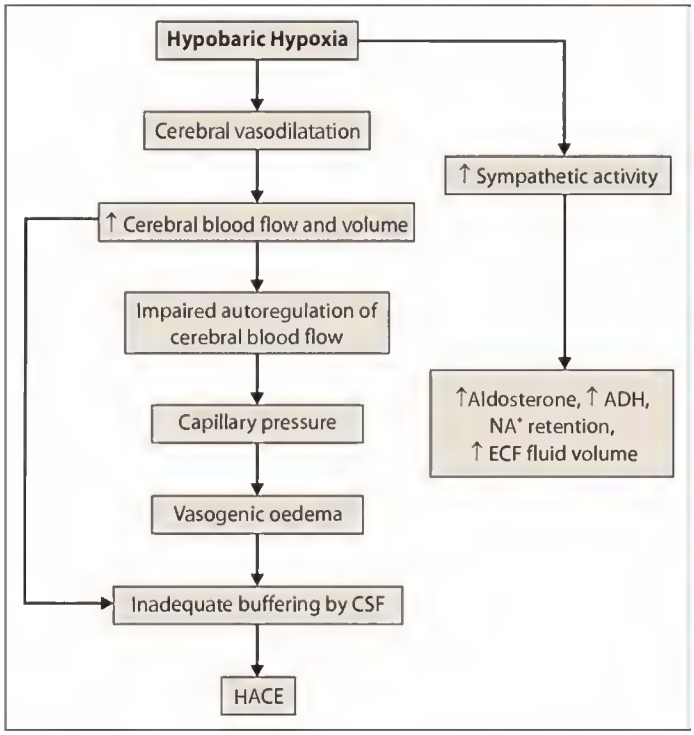


Figure 1: Aetiopathogenesis of high altitude cerebral oedema (HACE).
Source: Hackett PH, Roach RC. High altitude illness. N Engl J Med 2001; 345: 107-14.

Clinical features

A change in mental status and ataxia are the classical features of HACE. The former may range from lassitude, apathy and confusion to frank coma. Associated findings may include papilloedema, retinal haemorrhages and cranial nerve palsy.

Diagnosis

HACE is largely diagnosed clinically (**Figure 2**), since imaging facilities are rarely available at most HA locations. Where available, the magnetic resonance imaging (MRI) usually shows increased signal intensity in the region of the corpus callosum and splenium.

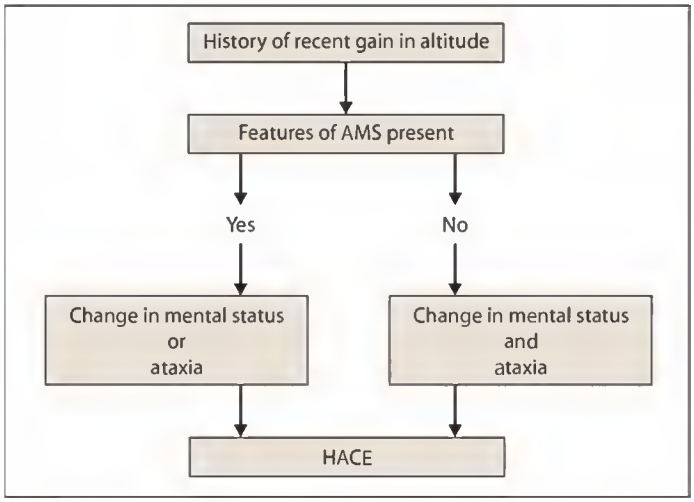


Figure 2: Algorithm for clinical diagnosis of high altitude cerebral oedema (HACE).
Source: Hackett PH, Roach RC. High altitude illness. N Engl J Med 2001; 345: 107-14.

Treatment

HACE is a medical emergency requiring immediate descent to lower altitude (**Table 7**). Simulated descent using recompression chambers can be life saving where actual descent is not possible. Portable recompression chambers, where available, can generate pressures up to 130 mm Hg and simulate a descent of about 6,000 ft (**Figure 3**).



Figure 3: An indigenously manufactured portable recompression chamber showing full pressurised state (130 mm Hg).

Table 7: Guidelines for Management of High Altitude Cerebral Oedema (HACE)

Do not worsen the hypoxia
- No physical exertion
- Prevent further gain in altitude

Correct the hypoxia
- Immediate descent to lower altitude
  - Actual descent where possible
  - Simulated descent using recompression chambers
- Supplemental oxygen via facemask at 2 to 4 L/min

Pharmacotherapy
- Dexamethasone 8 mg initially orally/IM/IV followed by 4 mg every 6 hours.
- Tablet acetazolamide 250 mg, 8 to 12 hourly if descent to lower altitude is delayed
- Injection mannitol to reduce intracranial pressure

Complications

HACE can be fatal if not managed as a medical emergency.

Prognosis and prevention

HACE is a life-threatening condition. The mortality may be as high as 25%, even with prompt institution of therapy. Prevention of HACE is by slowing the rate of ascent to HA (**Table 6**) and following a proper acclimatisation schedule.

High Altitude Pulmonary Oedema (HAPE)

Definition and epidemiology

HAPE is a non-cardiogenic pulmonary oedema characterised by pulmonary hypertension, leading to extravasation of fluid from the intravascular compartment in the lungs of healthy individuals with no underlying cardiac or pulmonary disease. HAPE usually occurs on the second or third day of arrival at HA. The reported incidence varies from 0.5% to 15%, depending on the rate of ascent and altitude reached.

Aetiopathogenesis

Elevated PAP due to hypoxic pulmonary vasoconstriction is central in the pathogenesis of HAPE (**Figure 4**). Exposure

of the basement membrane to the protein-rich oedema fluid results in secondary inflammation, activation of coagulation and generation of microthrombi in the lungs. Pre-existing inflammation may make the endothelium more prone to disruption. Vigorous physical exertion in unacclimatised individuals and exposure to low environmental temperatures may precipitate or aggravate HAPE by raising the PAP.

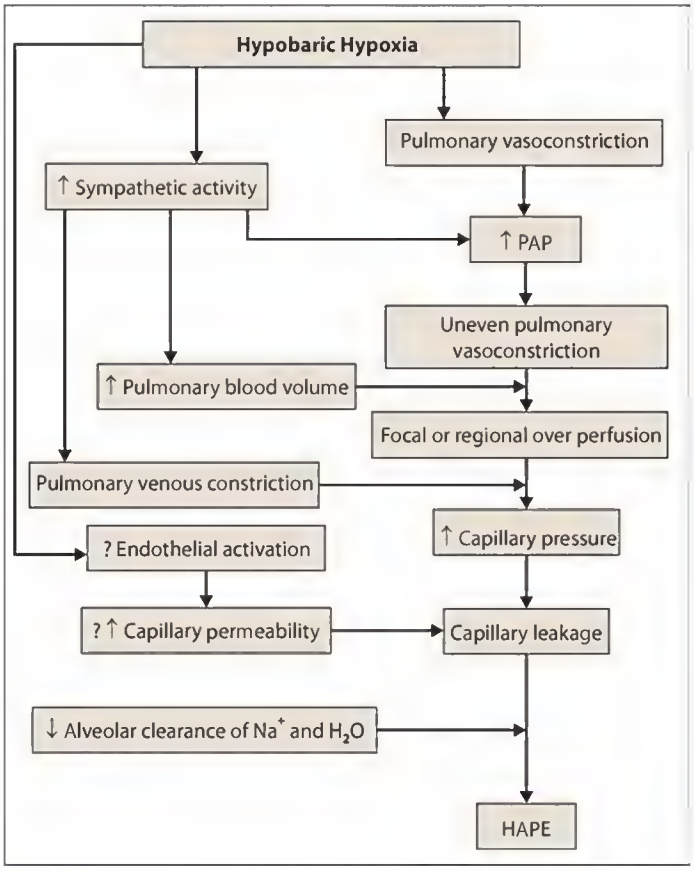


Figure 4: Aetiopathogenesis of high altitude pulmonary oedema (HAPE). *Source: Hackett PH, Roach RC. High altitude illness. N Engl J Med 2001; 345: 107-14.*

Clinical Features

Dry cough and reduced physical performance for the given altitude in an individual recently arrived at HA suggest HAPE. Dyspnoea and chest discomfort are common. Pink frothy sputum and respiratory distress occur later in the illness. Orthopnoea and haemoptysis are uncommon. Resting tachycardia and tachypnoea become pronounced as the illness progresses. Crackles and wheeze are usually present in more than one lung field.

Diagnosis

The clinical diagnostic criteria for HAPE are shown in **Table 8**. Investigations may reveal the following:

- ECG: Sinus tachycardia, right ventricular strain, right axis deviation, right bundle branch block (RBBB) and P wave abnormalities.
- Chest radiograph (**Figure 5**): Normal cardiac shadow, prominent pulmonary arteries and patchy infiltrates, generally confined to the right middle and lower lobes, may involve both lungs in severe cases.



Figure 5: Chest radiograph of a patient with high altitude pulmonary oedema showing non-homogenous opacities in the right middle and lower zones.

Table 8: Clinical Criteria for Diagnosing High Altitude Pulmonary Oedema (HAPE)

History of recent gain in altitude

WITH

Any two of the following symptoms:
- Cough
- Dyspnoea at rest
- Chest discomfort
- Weakness/fatigue

AND

Any two of the following signs:
- Crackles/wheeze in at least one lung field
- Central cyanosis
- Tachycardia
- Tachypnoea

Treatment

HAPE is managed as shown in **Table 9**. Elevated PAP usually reduces with correction of hypoxaemia. Drug therapy must be considered where administering oxygen and/or reduction of altitude is not possible. Nifedipine successfully lowers elevated PAP in most HAPE patients. Inhaled nitric oxide (NO) and phosphodiesterase inhibitors, such as sildenafil and tadalafil have shown promising results. Inhaled salmetrol has been reported useful in reducing PAP and improving oedema clearance.

Table 9: Guidelines for Management of High Altitude Pulmonary Oedema (HAPE)

Do not worsen the hypoxia
- No physical exertion
- Prevent further gain in altitude

Correct the hypoxia
- Descend to lower altitude
  - Actual descent where possible
  - Simulated descent using recompression chambers
- Supplemental oxygen via face mask @ 2 to 4 L/min

Pharmacotherapy to lower pulmonary artery pressure
- Nifedipine 10 mg orally followed by 30 mg sustained release 12 hourly

Complications

HAPE can be fatal if not recognised and treated promptly. Severe HAPE can worsen the hypoxaemia of HA and precipitate HACE.

Prognosis and prevention

HAPE can be managed with a mortality of less than 1% if recognised in time and promptly treated. Slowing the rate of ascent to HA and following a proper acclimatisation schedule can successfully prevent HAPE. Nifedipine (20 to 30 mg of extended release formulation 12 hourly) is advisable in susceptible individuals. Inhaled salmetrol has also been reported useful for prevention of HAPE.

Differential Diagnosis of Acute HA Illnesses

Many clinical conditions may mimic acute HA illnesses (**Table 10**). The diagnosis of AMS and HACE must be reconsidered if the onset of symptoms is after 3 days of arrival at HA, headache is absent, there is a rapid improvement of symptoms with fluid replacement or no improvement with oxygen therapy, acetazolamide, dexamethasone and descent to lower altitude.

Table 10: Differential Diagnosis of Acute High Altitude Illnesses

Acute mountain sickness/high altitude cerebral oedema
Dehydration
Exhaustion
Hypoglycaemia
Carbon-monoxide poisoning
Migraine
CNS infections
Acute psychosis
Stroke
Transient ischaemic attack
CNS tumour
High altitude pulmonary oedema
Bronchial asthma
Acute bronchitis
Pneumonia
Congestive cardiac failure
Pulmonary embolism
Myocardial infarction
Hyperventilation syndrome

SUBACUTE AND CHRONIC HIGH ALTITUDE ILLNESSES

Subacute Mountain Sickness (SMS)

Two distinct forms of SMS syndromes, which bear similarity with Brisket disease in cattle, have been described in humans.

Subacute Infantile Mountain Sickness (SIMS)

SIMS is reported predominantly in the Han Chinese living in Tibet. It occurs in infants born at lower altitudes and subsequently taken to HA. The prevalence increases with altitude and decreases with age. Symptoms start with poor feeding and lethargy, followed by dyspnoea, cough and signs of cardiac failure. SIMS is usually fatal. The pathophysiology involves muscularisation of pulmonary arterioles and medial hypertrophy of small pulmonary arteries, which is in contrast to concentric laminar intimal proliferation seen in primary pulmonary hypertension. The elevated PAP results in right ventricular hypertrophy and cardiac failure. Prompt reduction of altitude can lead to complete resolution of the condition.

Subacute Adult Mountain Sickness (SAMS)

SAMS was first described in 1990 in Indian soldiers stationed at extreme altitude for 3 to 6 months. Symptoms begin with shortness of breath and edema and progress to gross anasarca. Patients show features of severe congestive cardiac failure with right ventricular hypertrophy, right axis deviation and T wave inversion in leads V_1 to V_6. The pathophysiology includes severe pulmonary arterial hypertension coupled with polycythaemia, possible myocardial dysfunction and alteration in body fluid homeostasis. Abnormalities return to normal within 12 to 16 weeks of descent to lower altitude.

Chronic Mountain Sickness (CMS) or Monge's Disease

Definition and epidemiology

First described by Carlos Monge in 1925, the consensus statement of the VI World Congress on Mountain Medicine 2004 defines CMS as a clinical syndrome that occurs in HA natives or long term residents at altitudes above 2,500 m, characterised by excessive erythrocytosis, severe hypoxemia and in some cases moderate/severe pulmonary arterial hypertension, which may result in *cor pulmonale*, leading to congestive cardiac failure. The reported incidence of CMS in Tibetans is 0.91%.

Aetiopathogenesis

CMS was attributed to a loss of acclimatisation in already acclimatised individuals; however, a low hypoxic ventilatory response is no longer considered an important aetiological factor. A likely possibility is markedly raised erythropoietin (EPO) levels. The raised haematocrit due to elevated EPO raises blood viscosity, worsens tissue hypoxia, and results in further elevation of EPO levels and genesis of a vicious cycle. Patients of CMS also have increased PAP, possibly due to elevated blood viscosity.

Clinical features

The clinical features of CMS are shown in **Table 11**.

Table 11: Clinical Signs and Symptoms of Chronic Mountain Sickness (CMS)

Symptoms
Headache
Breathlessness
Dizziness
Palpitations
Sleep disturbance
Fatigue
Localised cyanosis
Burning of palms and soles of feet
Dilatation of veins
Muscle and joint pains
Anorexia
Lack of mental concentration
Alterations in memory
Clinical/Investigative findings
Excessive erythrocytosis
Haemoglobin ≥19 g/dL in females and ≥21 g/dL in males
Raised pulmonary arterial pressure (not mandatory)
Features of heart failure (not mandatory)
Chest radiograph
Prominent pulmonary arteries
ECG
Right ventricular hypertrophy
Right atrial enlargement
Proteinuria

Diagnosis

CMS is diagnosed clinically (**Table 11**) in patients living at altitudes greater than 2,500 m, with normal lung function and without chronic pulmonary or other medical conditions that worsen the hypoxaemia.

Treatment

Descent to lower altitudes is the treatment of choice. Other modalities of treatment have variable results (**Table 12**).

Table 12: Guidelines for Management of Chronic Mountain Sickness (CMS)

Migration to lower altitudes is the treatment of choice
Other modalities of treatment with variable results
Phlebotomy to reduce haematocrit
Oxygen supplementation and respiratory training
Calcium channel blockers to reduce pulmonary artery pressure
Inhaled nitric oxide 40 ppm or nitric oxide 15 ppm with 50% oxygen to lower pulmonary artery pressure
Medroxyprogesterone 20 to 60 mg/day for 10 weeks to stimulate ventilation
Tablet acetazolamide 250 mg/day for 3 weeks

Complications and prognosis

CMS may result in cor pulmonale and congestive cardiac failure. Migration to lower altitude corrects the hypoxaemia and haematocrit returns to normal in 2 to 3 weeks. Right ventricular hypertrophy and elevated PAP normalise in about two years.

High Altitude Pulmonary Hypertension (HAPH)

Definition

HAPH is a clinical syndrome characterised by raised mean or systolic PAP, right ventricular hypertrophy, cardiac failure, moderate hypoxaemia and absence of excessive erythrocytosis. It occurs in HA residents with no underlying cardio-pulmonary disease.

Aetiopathogenesis

Remodelling of the pulmonary vasculature with muscularisation of pulmonary arterioles is the likely cause of the raised PAP. The elevated blood viscosity due to erythrocytosis is probably a contributory factor.

Clinical features

HAPH presents with dyspnoea, cough, cyanosis, sleep disturbance, irritability and features of right heart failure.

Diagnosis

HAPH is diagnosed as shown in **Table 13**, after ruling out other cardio-pulmonary causes of pulmonary hypertension.

Treatment

Descent to lower altitude is desirable. The raised PAP can be reduced using calcium channel blockers (Nifedipine 20 to 30 mg 12 hourly), inhaled NO (15 ppm with 50% O_2 or 40 ppm for 15 min), phosphodiesterase inhibitors and prostaglandins.

Complications and prognosis

Prompt descent to lower altitudes improves symptoms and the PAP returns to normal in 2 to 6 months. Untreated, the condition results in right heart failure.

Table 13: Diagnostic Criteria and Investigation Findings in High Altitude Pulmonary Hypertension (HAPH)

Raised pulmonary artery pressure
Mean pulmonary artery pressure >30 mm Hg
Systolic pulmonary artery pressure >50 mm Hg
Haemoglobin
Males <21 g/dL
Females <19 g/dL
Chest radiograph
Cardiomegaly—enlargement of right atrium and right ventricle
Prominent central and peripheral pulmonary arteries
ECG
Right axis deviation
Right ventricular hypertrophy
Echocardiography
Signs of right ventricular hypertrophy/failure

MISCELLANEOUS ILLNESSES AT HIGH ALTITUDE

High Altitude Retinal Haemorrhages (HARH)/Altitude Retinopathy

Definition and epidemiology

HARH are haemorrhages of the inner and middle layer of the retina seen in lowlanders on ascent to altitudes beyond 5,000 m. HARH is rare below 3,000 m and does not occur in HA natives. When accompanied by vascular dilatation, tortuosity and optic disc hyperaemia, it is referred to as 'altitude retinopathy'. HARH may occur in association with other acute HA illness. The average incidence at altitudes beyond 5,300 m is 34%.

Aetiopathogenesis

Increased retinal blood flow and increased vascular endothelial permeability are the most likely aetiological factors. Exercise in hypoxia may aggravate the increased retinal vascular permeability.

Clinical features

Most HARH are asymptomatic. Those occurring near the fovea may produce positive scotomas.

Diagnosis

HARH usually spare the macula and occur near the superior and inferior temporal arcades. They may range from 'red flame shaped' lesions to 'dot and blot' haemorrhages. 'Cotton wool spots' have also been reported as isolated findings or associated with overlying retinal haemorrhages, especially at altitudes greater than 7,000 m. Associated findings may include dilated retinal vessels and optic disk hyperaemia.

Treatment

Spontaneous resolution within days to weeks is the rule and no active treatment is required. Descent to lower altitude is advisable if the haemorrhage appears to be enlarging on daily examination.

Thrombotic Episodes at High Altitude

Thrombotic episodes generally occur at EA and usually present as deep vein thrombosis, portal vein thrombosis, pulmonary thrombo-embolism, and stroke. Limited studies investigating haemostasis at HA have largely been inconclusive. Hypoxia *per se* does not present a special risk for thrombosis. Other factors that might possibly contribute to thrombotic episodes include

dehydration, polycythaemia, immobility due to poor weather conditions and constrictive clothing. Individuals with deficiency of coagulation inhibitors, such as protein C, may be at an increased risk. The role of elevated homocysteine levels in the pathogenesis of this condition at HA is under investigation. Thrombotic episodes are managed as per conventional guidelines and prevented by addressing the known risk factors mentioned above.

Gastrointestinal (GI) Problems at High Altitude

Apart from the nausea and vomiting of AMS and diarrhoea related to poor hygiene and sanitation, flatulence, dyspepsia and anorexia are common at HA. The aetiology is multifactorial including the role of hormones like leptin and cholecystokinin and the effect of hypoxia on GI motility. Malabsorption of fats occurs at altitudes beyond 5,000 m. Upper GI bleeds are common at HA due to increased capillary friability. The indiscriminate intake of nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of AMS may precipitate the condition. A carbohydrate rich diet is recommended at HA, being the preferred metabolic substrate. An increase in the daily caloric intake of 400 to 500 kcal is necessary to maintain sea level body weight in lowlanders at HA.

Effect of Solar/Ultraviolet (UV) Radiation

Acute exposure to increased levels of solar and UV radiations at HA primarily affects the eyes and skin, resulting in snow blindness and sun burns.

Snow blindness occurs due to exposure of the corneal epithelium to UV rays resulting in solar keratitis and blistering of the corneal epithelium in severe cases. It is characterised by photophobia, blepharospasm and intense conjunctival congestion. Anaesthetic eye drops and analgesics for reducing the pain and application of an eye ointment and patch for 24 hours are the principal modalities of treatment. Prognosis is generally very good. Snow blindness can be prevented by using UV protective eyewear with side protectors. Sunburns can be prevented by reducing the time and amount of skin exposed to direct sunlight and by using sun screen lotions.

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27.9 Aviation Medicine

JS Kulkarni

INTRODUCTION

Aerospace medicine is a multifaceted speciality, which not only deals with basic subjects like physiology and biochemistry but also deals in ophthalmology, otorhinolaryngology, aviation neuropsychiatry and pathology. Human engineering, ergonomics, biomedical, bioelectronics and aeronautics being other facets of this specialty. Unlike other streams of medicine where a doctor deals with unhealthy individuals in a healthy environment, the subject of aviation medicine deals with healthy subjects in most hostile environment, i.e. high altitude and space. Aviation stressors adversely affect the aircrew, the passengers and invalids alike. Therefore, augmenting the physiological reserves and meticulous preparation before travel are the only antidotes to the destabilising environment. The physiological consequences of rapid ascent to high altitude form the core issue in aerospace medicine.

The pressure exerted by the atmosphere (barometric pressure) falls exponentially with altitude producing a proportional decrease in the partial pressure of oxygen and other constituent gases. The pressure falls to half (387 mm Hg) of its value at an altitude of 5.48 km (18,000 ft); becomes one quarter (190 mm Hg) at 10.27 km (33,700 ft) (**Figure 1**). By about 30.48 km (100,000 ft), it becomes one-hundredth of that at sea level. The temperature in the atmosphere falls at a steady rate of about 2°C per 0.3048 km (1,000 ft); in the troposphere. This is known as the lapse rate. Thus, from an average 15°C at surface of earth it becomes –56.5°C at 12.19 km (40,000 ft); after which it becomes steady in the ozone layer.

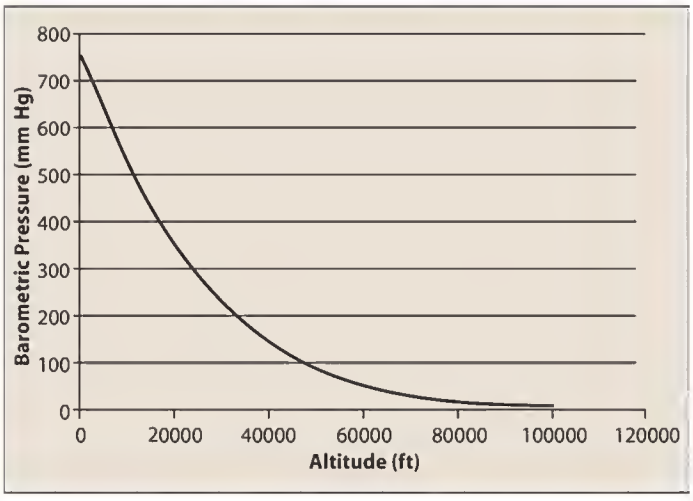


Figure 1: Barometric pressure change at rising altitude.

STRESSORS IN AVIATION ENVIRONMENT

The various stressors adversely affecting the aircrew and passengers are enumerated in **Table 1**.

Table 1: Stressors in Aviation Environment

Physical stressors	Heat, cold, humidity, noise, vibration, radiation
Physiological stressors	Hypoxia, decompression sickness, hypobaria, acceleration, motion sickness, disorientation and barotraumas
Psychological stressors	Mental workload, task saturation, poor communication and circadian disturbances
Personal stressors	Drugs, alcohol, smoking, disease, anxiety

HYPOXIA

Hypoxia is acknowledged as the single most serious physiological hazard encountered in flight at altitude. Aviation-induced hypoxia is largely hypobaric hypoxia. Hypoxia affects all systems but the main effects are on the respiratory, cardiovascular and neurological systems. These effects are much less if the human body follows the acclimatisation/adaptation process. It stimulates respiration and induces hyperventilation. Hypoxia causes an increase in heart rate with increase in cardiac output; vasodilatation in vascular beds increases the blood flow to the heart and brain while less vital parts are deprived. Cerebral circulation is sensitive to PaO_2 and $PaCO_2$. There is vasoconstriction of pulmonary vascular bed, which results in a raised pulmonary artery pressure in the presence of increased cardiac output. Gross reduction in fall of PaO_2 results in unconsciousness. Reduction of psychomotor function evidenced by diminished eye-hand coordination, reduced choice reaction time, increase in muscular in-coordination and increase in simple reaction time occurs with increasing altitudes in the said order. Cognitive function impairment seen as impairment of performance of novel tasks and memory impairment occurs between 2.44 and 3.048 km (8,000 and 10,000 ft). Visual function deterioration seen as reduction in perceived light intensity, diminished visual acuity, raised light perception threshold and tunnelling of vision starts at altitudes of 1.52 km (5,000 ft) and increases progressively. The effects of hypoxia depend primarily on the rate of ascent, duration of the stress and are also affected by physical activity (exercise exacerbates), ambient temperature (cold reduces tolerance), intercurrent illness, smoking and drugs. Hypoxia can be prevented by single or a combination of following; flying in physiological region, i.e. up to 2.44 km (8,000 ft), i.e. helicopters, gliders and microlites, pressurising the cabin to physiological levels (as seen in commercial airlines) and oxygen supplementation by way of oxygen mask, beginning at 3.048 km (10,000 ft) and given exponential increase of oxygen-enriched air till at an altitude of 10.27 km (33,700 ft) when 100% oxygen will be required. Beyond 12.19 km (40,000 ft),

oxygen is required to be administered under pressure and beyond 13.72 km (45,000 ft) aircrew need to do supportive pressure clothing as worn by astronauts.

DECOMPRESSION SICKNESS

Decompression sickness is a syndrome produced due to supersaturation of body tissues with nitrogen due to falling partial pressure of alveolar nitrogen. This leads to formation of nuclei, which expand into bubbles that give rise to the clinical picture, which may include aviators bends (joint and limb pains), chokes (respiratory disturbances), creeps (itchy, blotchy rash, formication), visual disturbances like blurring of vision, scotomas and fortification spectra, staggers (neurological disturbances). Lastly, cardiovascular or neurocirculatory collapse can occur which is an emergency condition and the recovery is accompanied with vomiting and frontal headache. The severity of symptoms depends on the altitude at which the decompression occurs, duration of exposure, the rate of ascent to altitude, hypoxia and personal variables like age, body build, obesity, physical activity and previous injury.

BAROTRAUMA

In accordance with Boyle's law, any gas in a closed/semi-closed cavity would expand when ambient pressure reduces and *vice versa*. Expanded gases in closed cavities cause severe discomfort. This pressure-induced trauma is termed as barotrauma. Generally, lungs are not affected as the expanded gases vent out through the trachea and oropharynx to the atmosphere. Expansion of gases in small intestine may cause pain and discomfort but in the large intestine they get expelled as flatus. Avoiding gas-forming foods like beans, cauliflower, carbonated beverage and alcohol help preventing this disability. Otitic barotrauma is the most common form of barotrauma. On ascent, the expanded air in the middle ear cavity escapes through the Eustachian tube into the pharynx; however, during descent it is difficult to equalise the pressure between the middle ear and the pharynx, more so in presence of upper respiratory infection. Discomfort progresses to acute severe pain and may finally end in a retracted/ruptured tympanic membrane. Eustachian tube can be forced open by simple methods like swallowing, sucking on a candy, yawning, moving the jaw from side to side or Valsalva manoeuvre (forced expiration against a closed glottis, while mouth is closed and nose pinched). Otitic barotrauma is treated with analgesics, nasal decongestants and broad-spectrum antibiotics. Similarly, sinus barotrauma is the trauma of the paranasal sinuses. During ascent, air vents easily through ostia of paranasal sinuses but during descent the ostia are readily occluded if individual is suffering from upper respiratory catarrh. The symptoms are a sudden severe pain in affected sinuses, which continues if the descent is not halted and may lead to epistaxis. The management is similar to otitic barotrauma.

ACCELERATION STRESS

Fast moving aircraft impose accelerative stress (1G = 978 cm^{-2}, i.e. acceleration due to earth) and reactive inertial stress on the body. Depending on the direction these forces act, they are classified into + G and – G in the x axis (front-back), y axis (left-right) and z axis (head-foot). Accelerative stress are within the tolerance level of the human body and do not pose a problem except to a small group of military fighter aircrew who while performing aerial manoeuvres far exceed the human tolerance to G forces like in executing sharp turns or performing loops/sharp dives. The first effect of +Gz acceleration is increase in body weight; although muscle power remains same the movements become increasingly difficult. At around +3 to +4 Gz head stoops down and upward movement of hands becomes difficult. The second effect is increase in hydrostatic pressure which forces blood into the abdomen and lower limbs and lasts as long as acceleration operates. Thus, circulating blood becomes less and there is fall of blood pressure above the level of heart. Eyes and brain suffer most. Between +3 and +4 Gz one suffers from a condition called 'gray out' if continued after 10 seconds, this causes the vision to become hazy and constricted as if looking through a foggy tunnel. The vision completely fails between +4 and +5 Gz producing 'blackout'. The blood pressure at eye level is not enough to overcome pressure inside the eyeball causing temporary blindness. Beyond +5 or +6 Gz unconsciousness occurs due to temporary stoppage of blood supply to brain. This phenomenon is also described as G induced loss of consciousness. The effects of 'blackout' disappear almost as soon as the G level is reduced, although the individual may be confused for a few seconds. Protection against this can be achieved by a combination of the following methods; a posture where the distance from the heart to the brain is reduced, viz. use of tilt back seats, voluntary manoeuvres like anti-G straining manoeuvre which raises the intra-abdominal pressure thereby maintaining the level of the diaphragm and helping in venous return to the heart and lastly the use of anti G-suits where a number of inter-connecting bladders located over the abdomen, thighs and calves expand and compress the major vascular bed below the heart-level and help maintain the level of the diaphragm and prevent extravascular loss of fluids. All these methods act synergistically and help the aircrew in overcoming the stress of accelerative forces.

NOISE AND VIBRATION

Noise and vibration are inbuilt side effects of flying. Both produce physical, physiological and psychological stress which is not of consequence individually, but may add to the overall stress of flying. Outside an aircraft the noise levels may be as high as 110 decibels. Military aircrew protect themselves from noise by helmet-headset, ground crew by ear-defenders/earmuffs and passengers by the cabin conditioning and noise abatement technologies. Vibration is more so a problem in helicopters but mild vibratory stress may however be present due to buffeting in air pockets, poor maintenance and inbuilt defects in civil airliners as well. Low backache and fatigue are the two main problems encountered due to vibration.

MOTION SICKNESS

Motion sickness occurs on exposure to real or apparent, unfamiliar motion to which the individual is not adapted. The common symptoms of air sickness are stomach awareness or discomfort in abdomen, cold sweats on forehead, neck, armpits and palms, hyperventilation, salivation, warm sensations in some parts of the body, giddiness or dizziness, apathy and lack of desire to continue activity, nausea and vomiting. In mild cases there may be only nausea and no vomiting. The eyes, vestibular and proprioceptive senses are the main inputs to the brain to assess motion and in a flying environment unresolved, strong

motion cues mediate motion sickness. Although drugs like scopolamine, promethazine, dimenhydrinate, cinnarizine have been tried with success in the prevention and management of motion sickness but may not be suitable for aircrew due to their side effects. Generally desensitisation programmes in which the individual is gradually exposed to conflicting motion inputs, which desensitise the vestibular system and adjuvant psychotherapy and relaxation techniques further help the process treat motion sickness.

SPATIAL DISORIENTATION

Spatial disorientation (SD) refers to an individual's inability to appreciate his true position in relation to the surface of the earth. Thus, a disorientated pilot is uncertain or unaware of his position or the attitude of his aircraft. The triad of orientation, i.e. eyes, vestibular system (otoliths and semi-circular canals) and proprioception are adversely affected in the flying environment and give rise to false sensations and disorientation. SD can often lead to disastrous errors and accidents. Factors like fatigue, inexperience, hypoxia, alcohol, drugs, emotional stress, lack of visual cues (cloud flying, night flying, etc.) and changeover from visual to instrumental flying and *vice versa* aggravate disorientation. Proper selection of candidates, suitable indoctrination and training and instrument flying practice help in prevention of SD. It is pertinent to remember that no one is immune to SD.

CIRCADIAN DESYNCHRONISATION

Circadian or biological rhythms have an inherent rhythmicity of 24 hours using signals of light and darkness, noise etc. Circadian desynchronisation is the failure of the human body to adjust its own routine to a clock that may bring darkness up to 10 hours earlier or later than usual. Eating, sleeping, excretion may be adversely affected and mental reactions may be slowed down considerably. These changes are more pronounced in eastbound flights. Generally a day of recovery is required for every 5-hour time change. Thus, one should attempt to sleep as close to the usual bedtime as possible. For both civil and military aircrew, the problem is more since they need to fly the aircraft as well. Preventive measures include appropriate scheduling of the work and rest periods and resynchronisation using timed exposure to artificial bright light.

ANTHROPOMETRY IN AVIATION

Anthropometry is the science of human measurements, which includes measurement of the body dimensions and other physical characteristics of the body like volumes, centre of gravity and mass of body segments. In static (anatomical) anthropometry fixed structural dimensions of the body between two specific anatomical landmarks are measured like height, arm length and contour dimension like biceps girth. In dynamic (functional) anthropometry dimensions are taken when the body is engaged in some activity, e.g. clearance, reach, range of movements of joints and strength of various actions. Anthropometry has significant application in aviation; selection of right candidate for pilot training, designing of cockpit work place, designing of ejection systems and instrument panels, improve pilot comfort and convenience and identification of bodies in aircraft accidents, fitment of flying clothing and evaluation of orthopaedic disabilities.

SPACE MEDICINE

In space, apart from hypobaria, hypoxia and acceleration the most important issue is of weightlessness. Microgravity challenges the cardiorespiratory, haematological, musculo-skeletal and immune system. Motion sickness, radiation effects, psychological and interpersonal factors (depression, anxiety and crew tensions), nutrition, personal hygiene and waste management are a multitude of other factors, which need considerable attention. 'Weightlessness' is nearly impossible to recreate on earth but certain aspects can be simulated like fluid shifts seen in space, cardiovascular changes, musculoskeletal changes, etc. The techniques employed in our country for studying few of the aspects of weightlessness are dry immersion, head-down tilt, lower body negative pressure (LBNP), head-up tilt and stabilo-platform.

CASUALTY EVACUATION

Transportation of critically ill and injured is an important health care adjunct. Foremost it is important to ascertain that air evacuation outweighs the risk of not being moved. Stabilisation of vital parameters and financial constraints are other issues that govern the decision of air evacuation. Priority one patients are those whose airlift is necessary to save life or limb, priority two are patients whose condition will be adversely affected if not evacuated or those needing specialised treatment, priority three are patients whose prognosis would benefit if transported by air and priority four are those for whom movement by air is a matter of convenience. Some medical conditions need special assessment prior to evacuation by air; acute myocardial infarction should ideally not be evacuated by air for at least 6 weeks. In a fully compensated cardiovascular condition, a cabin altitude of 3.048 km (10,000 ft) is well tolerated, but in borderline cases, supplemental oxygen will be required whenever cabin altitude rises above 1.37 km (4,500 ft). Untreated pneumo-thorax is absolute contraindication. In pneumonia, gaseous exchange in alveoli is disturbed, therefore, supplemental oxygen will be required from ground level itself. Patients with increased intracranial pressure need supplemental oxygen to eliminate the risk of minimal hypoxia. Pulmonary burns need to be excluded in all cases of burns. In-patients, who have undergone abdominal surgery recently, gases may remain trapped in the abdominal cavity and create problem. Also, trapped gas in a hernia or volvulus can expand in-flight causing pain, and in some cases compromise the circulation of the bowel. Notwithstanding all these limitations the specific advantages of air evacuation are far more significant; morale boosting, saving of time, early institution of specific and definitive treatment, reduced incidence of infection, overcoming adverse terrain and centralisation of trained medical expertise being few of them.

REGULATIONS RELATED TO AVIATION MEDICINE

The responsibility of assessing the medical fitness and laying down medical standards for the military aircrew of India rests on the Director General of Medical Services (DGMS) of the Indian Air Force. Medical fitness of all civil flight crew is not just a requirement of the International Civil Aviation Organisation (ICAO) agreement to which India is a signatory but is controlled

by the Director General Civil Aviation (DGCA), which is of considerable public interest and importance as well. In India, medical examinations for all commercial flight crew are conducted at designated Indian Air Force medical centres, whereas for private license holders medical examinations can be conducted by DGCA approved class II aviation medical examiners. All medical examinations are conducted in accordance with ICAO standards and recommended practices (Annex 1). ICAO, a specialised agency of the United Nations set up to promote safe and orderly development of civil aviation in the world, sets international standards and regulations necessary for safety, security, efficiency and regularity of air transport and serves as the medium for cooperation in all fields of civil aviation among its 185 contracting nations. India is a signatory to the ICAO convention and, hence, is committed to adopt at the minimum the ICAO standards and recommended practices.

AEROMEDICAL RESEARCH

Research in the field of aerospace medicine has been going on since last five decades or so. In the initial years, the research was oriented towards thermal stress, physiological limits of human tolerance and acceleration physiology. With advancing technology the newer problems related to human engineering, disorientation, flying clothing and psychological aspects of flying came under the ambit of research. Currently, the research is more of an applied nature, oriented towards operational efficiency and flight safety. The Armed Forces Medical Research Committee, and the Human Engineering Panel of Aeronautical Research and Development Board and Indian Council of Medical Research support research in aviation medicine. Long duration flying and disorientation desensitisation are the newer fields of research. The aviation medicine specialists also render Human Engineering Consultancy related to aircraft design and promotion of flight safety through aircraft accident investigations for military and civil aircraft.

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27.10 Radiation Hazards

AM Samuel

An understanding of the biological effects of nuclear and X-ray radiation is important for evaluating their potential uses and dangers. This is pertinent in the present scenario of technology advances wherein X-rays in the form of computed tomography (CT), positron-emission tomography (PET)-CT and radioisotopes are being used extensively in diagnosis and therapy and also due to recent incidence of Fukushima nuclear disaster in Japan.

Certain radiations are more damaging than others. Alpha radiation is the most damaging to human tissues because its particles are strongly ionising. Neutrons are also damaging to cells, because they interact very easily with body tissue which contains a lot of water. These are a highly penetrating form of radiation. Beta and gamma radiation are the least damaging forms of nuclear radiation but these are able to penetrate deeper into the body than alpha radiation. Gamma radiation and X-rays pass through the body easily.

This chapter will not cover hazards due to ultraviolet, infrared and microwave radiations but relate to ionising radiations only.

BACKGROUND RADIATION

It is important to know that one is constantly being exposed to a variety of natural and man-made background radiations. There is exposure of gamma rays from space and from the earth as cosmic radiation which is equal to 1 mSv per year on earth and 27 mSv per year in space. Cosmogenic radionucleides (C14, Be7 and He3) account for 0.28 mSv per year and natural exposures accounts for 0.1 mSv per year. Radioactive potassium 40 atoms are naturally present in the body and undergo several thousand nuclear disintegrations every second. This accounts for 0.26 mSv per year. Medical exposures account for 20%, and natural background exposures for 80% of average exposures to world populations.

IONISING RADIATION

A wide variety of ionising radiations can interact with biological systems, but there are only 5 types of radiation of importance and these are gamma, neutron, beta, alpha and X-rays.

Gamma Radiation

Gamma radiation which emanates from the nucleus of an atom is highly energetic, penetrating so that a significant part will pass through the human body without interaction. This energy deposition may occur anywhere along a given photon's path. Because of its penetrating ability, the effects of gamma irradiation can be independent of the location of the source, (i.e. internal or external to the body).

Gamma rays are commonly used for diagnostic and therapeutic purposes.

Neutron Radiation

Since neutrons are uncharged particles and can react only with the nuclei of target atoms, the probability of interaction of neutrons in the energy range is roughly comparable to that of low-energy gamma photons. The energy deposition will not be uniform.

Its present clinical application is in neutron beam therapy for the treatment of some forms of cancer.

Beta Radiation

High speed electrons in the form of beta radiation lose most of their energy after penetrating only a few millimeters of tissue. If the beta emitting material is on the surface of the skin, the resulting beta irradiation causes damage to the basal stratum of the skin. Damaged cells may be of greater significance to the total organism than killed cells, particularly if they go on to become malignant or otherwise malfunction. Killed cells are replaced quickly in most tissues with any degree of reserve capacity and do not cause significant overall clinical effects unless the cells involved are highly critical or the fraction of cells killed in a given organ is large. Beta rays are used in radioisotope therapies.

Alpha Radiation

The energy of these relatively heavy, positively charged particles is fully absorbed within the first 20 micrometers of an exposed tissue mass. Because of this, alpha radiation is not an external hazard. If alpha emitting material is internally deposited, all the radiation energy will be absorbed in a very small volume of tissue immediately surrounding each particle. These rays are highly effective in targeted radioisotope therapies.

There is now a significant progress in the development of radioisotope therapies which are internally administered and are effectively targeted to the cancerous tissues. In such situations, beta and alpha rays which can deposit their energy in a small volume of tissue will be useful and can reduce radiation exposure to the normal surrounding tissues.

X-rays

X-rays, which origin is from the electron shells of the nucleus of an atom, are a type of penetrating radiation that, depending on the dose, can reduce cell division, damage genetic material, and harm unborn children. X-rays are extensively used for diagnostic purposes.

INTERACTION OF IONISING RADIATION WITH MATTER OR TISSUES

When radiation interacts with target atoms, energy is deposited, resulting in ionisation or electron excitation. This ionisation or excitation must involve certain critical molecules or structures in a cell. It has been theorised that this localisation of absorbed energy in critical molecules could be either a direct or an indirect action.

However, the most reasonable hypothesis is that in an indirect reaction, water, both intra-cellular and extra-cellular, is the

primary site of radiation energy deposition and that the energy deposited in the water would be transferred to and affect sensitive molecules indirectly. This is done through the production of a variety of *free radicals,* such as superoxides, oxygen, hydrogen and hydrogen peroxide radicals which are highly reactive and which damage chemical bonds in molecules. Direct action is at the level of the chromosomes of the cell nucleus.

Units of Exposure and Dose

The need to quantify radiation damage became increasingly evident, despite obvious difficulties in doing so. The first two units introduced dealt with radiation in the air, and as it is absorbed in living tissue. The two corresponding quantities are called 'exposure' and 'absorbed dose'.

The unit of radiation 'exposure', adopted by the International Congress on Radiology in 1931, was the Roentgen. *A roentgen* is a quantity of X-rays or gamma-rays which will cause a precisely defined degree of ionisation in 1 kg of dry air.

The roentgen unit does not apply to any particulate radiation (such as, alpha, beta, neutron or high-speed ions), nor does it involve biological tissues. To rectify these shortcomings, the concept of *'absorbed dose'* was introduced. The unit of absorbed dose is called *a Rad* (an acronym for radiation absorbed dose).

One rad is that quantity of ionising radiation of any type that will deposit 100 ergs of energy in each gram of absorbing tissue.

The *relation between 'exposure' and 'absorbed dose'* depends on the tissue involved. The rad has now been replaced by the *Gray (Gy)* which equals to 100 rads.

Relative biological effectiveness (RBE)

Equal doses of ionising radiation are not always equally effective in causing biological damage. Such observations have led to the concept of RBE. In any given situation, when two different doses of ionising radiation produce the same measurable biological result (e.g. number of mutations, reduction in lymphocytes, incidence of cancer, degree of mental retardation, percentage of animals killed promptly) is the RBE of radiation.

Linear energy transfer (LET)

One important consideration affecting RBE is the 'quality' of the ionising radiation being used: In general, a given dose of alpha or neutron radiation is much more effective in causing biological damage than an equal dose of beta, gamma or X-ray radiation. This difference in effectiveness is related to a physical quantity called LET noted as high and low LET radiations.

Units of dose equivalence: the quality factor (Q)

In an attempt to account for such differences in biological effectiveness, a new unit of 'dose equivalence' was introduced, *called a Rem (an acronym for 'Roentgen Equivalent Man').* This unit is intended to indicate, however roughly, the relative degree of biological damage caused by a particular exposure to ionising radiation. The rem is now superceded by the *Sievert (Sv); 1 Sv = 100 rem.*

What is an effective dose of radiation?

Finally, the biological effect of radiation depends on the type of tissue being irradiated.

When radioactive materials are incorporated into the body by inhalation, ingestion, and absorption through the skin and retained, significant radiation injury can be sustained by specific tissues in which the materials are concentrated or in some instances by the whole body. The primary factors which determine the type and degree of injury are the types and amounts of the isotopes deposited and the nature and energies of the radiation emitted.

In the context of a growing use of radio-isotopes for diagnosis and therapy, one needs to understand the kinetics of the administered radio-isotope which is generally tagged to compounds for specific purposes.

A radioactive material internally administered must be eliminated from the body to remove its hazards. This can be achieved by the following procedures:

- Include renal excretion for most soluble materials;
- Elimination in the faeces for materials which are retained in the gut or which can be secreted in the bile;
- Exhalation for volatile materials and gases.

The rate at which a material is eliminated is usually expressed as *'the biological half-life'*. This is the time it takes for one-half of a given amount of material to be excreted or eliminated. The biological half-life may be variable. *'Effective half-life will be a function of their physical and biological half-lives considered together'.*

In the event of excess radio-isotopes either due to mis-administration or accidents, methods for detoxification are needed.

Chelating agents, e.g. calcium or zinc diethylenetriamine pentaacetic acid (DTPA), if administered soon after the exposure, are effective in enhancing the elimination of certain radio-isotopes not fixed in tissues. Potassium iodide or iodate if given prior to or soon after an intake of radio-iodine, will reduce the uptake of radio-iodine by the thyroid gland. Similarly, orally administered Prussian Blue will reduce the absorption of cesium from the gut and alginate will reduce strontium absorption.

CELLULAR EFFECTS OF RADIATION

Mechanisms of Damage

Injury to living tissue results from the transfer of energy to atoms and molecules in the cellular structure. Ionising radiation causes atoms and molecules to become ionised or excited. These excitations and ionisations can:

- Produce free radicals.
- Break chemical bonds.
- Produce new chemical bonds and cross-linkage between macromolecules.
- Damage molecules that regulate vital cell processes (e.g. deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins).
- The cell can repair certain levels of cell damage. At low doses, such as that received everyday from background radiation, cellular damage is repaired rapidly.
- At higher levels, cell death results. At extremely high doses, cells cannot be replaced quickly enough and tissues fail to function.

Tissue Sensitivity

An important factor which is an individual response of a cell to radiation induced changes at the cell level is the parameter called tissue sensitivity. Hence, all individuals will not react identically to the same dose of radiation. Some individuals will be more sensitive to radiation than others. Hence, this aspect needs to be understood especially when therapy with radiation is considered.

The probable reason is a balance between damage to tissue and the capability for tissue repair. Some individuals will have a better ability for repair than others and the final outcome would be reflection of this balance in an individual.

Radiation sensitivity of a tissue is: proportional to the rate of proliferation of its cells, and/or inversely proportional to the degree of cell differentiation.

In general, actively proliferating cells are most sensitive to radiation. Thus, cellular radio-sensitivity tends to vary inversely with the degree of differentiation. Vegetative cells comprising of differentiated functional cells of a large variety of tissues are generally the most radio-sensitive. Examples include: free stem cells of haematopoietic tissue, cells deep in the intestinal crypts, primitive spermatogonia, granulosa cells of developing and mature ovarian follicles, basal germinal cells of the epidermis, germinal cells of the gastric glands, large and medium sized lymphocytes and mesenchymal cells.

Therefore, the most sensitive are blood forming cells, followed by skin, bone, teeth, muscle and nervous system. This also means that a developing embryo is most sensitive to radiation during the early stages of differentiation and an embryo/foetus is more sensitive to radiation exposure in the first trimester than in later trimesters of pregnancy.

Differentiating cells are somewhat less sensitive to radiation. The best examples of this type of cell are the dividing and differentiating cells of the granulocytic and erythrocytic series in the bone marrow, differentiated spermatogonia and spermatocytes in the seminiferous tubules and the ovocytes.

Totally differentiated cells are relatively radio-resistant. This class includes hepatocytes, cells of interstitial gland tissue of the gonads, smooth muscle cells, and vascular endothelial cells.

Fixed non-replicating cells are most radio-resistant. This group includes the long-lived neurons, striated muscle cells, short-lived polymorphonuclear granulocytes and erythrocytes, spermatids and spermatozoa, and the superficial epithelial cells of the alimentary tract.

Observed cellular effects of radiation, whether due to direct or indirect damage, are basically similar for different kinds and doses of ionising radiation.

Manifestations of Radiation Damage

This is dose dependant and the absorbed energy deposited. It is important to understand these concepts in diagnostic applications as one need to minimise cell damage as much as possible. For therapeutic applications, one needs to ensure cell death that is the predominant effect to be obtained.

One of the simplest effects to observe is *cell death,* the course of which can be described by various terms as described below:

Pyknosis: The nucleus becomes contracted, spheroidal, and filled with condensed chromatin.

Karyolysis: The nucleus swells and loses its chromatin.

Protoplasmic coagulation: Irreversible gelatin formation occurs in both the cytoplasm and nucleus.

Karyorrhexis: The nucleus becomes fragmented and scattered throughout the cell.

Cytolysis: Cells swell until they burst and then slowly disappear.

Non-lethal changes in *cellular function* can occur as a result of lower radiation doses. These include:

1. Delay in certain phases of the mitotic cycle. This inhibition occurs before prophase in the mitotic cycle, at a time disrupting cell growth, resulting in depletions of all populations.
2. Irradiated cells may show both increased and decreased permeability.
3. Changes in motility.

At a *molecular level* there is damage to enzymes, DNA and biological pathways. Damage to cell membranes, nucleus and chromosomes occur at a sub-cellular level. Cellular effects are observed as cell death, inhibition of cell division, and carcinogenesis.

Systemic disruption occurs at the tissue level and death with shortening of life is a manifestation of whole body radiation. If a population is involved there are genetic changes in individuals.

Radiation-Induced Chromosome Damage

Cell nuclei contain chromosomes which in turn contain the genes controlling cellular somatic and reproductive activity. These chromosomes are composed of DNA, the macromolecule containing the genetic information. This is a large, tightly coiled, double-stranded molecule, and is sensitive to radiation damage. Radiation effects range from:

- Complete breaks of the nucleotide chains of DNA;
- Point mutations which are essentially radiation induced chemical changes in the nucleotides which may not affect the integrity of the basic structure;
- Intermediate effects, such as abnormal bonding between adjacent molecules and alterations in viscosity resulting in translocations, trisomies, truncation and other abnormalities.

Genetic Effects

Laboratory studies in animals indicate increased mutation rates with small doses of radiation. As radiation dose increases, mutation induction also increases. *Mutations per unit dose decrease at low dose rates.* However, viable mutations are still extremely rare. Most of the mutations are lethal, and thus, self-limiting. It must be kept in mind that radiation doses increase natural mutation rates and that the mutations produced, and not visibly detected, are permanent in regard to future generations.

Bystander effects due to untargeted cells not hit by direct radiation, results from exposures to cells in the vicinity. The effects can lead to genomic instability, cell death, apoptosis, mutations, chromosomal aberrations and other cellular changes. At low doses bystander effects may be more important than targeted effects. Targeted effects are predominant in high dose exposures. This means that the effects are more

widespread in the surrounding tissues as well as in the tissues directly exposed to the ionising radiation due to the bystander phenomenon.

The transmission of damaging effects to the non-targeted tissues are by signals mediated via plasma and factors. The exact mechanism is yet to be proved.

CLINICAL MANIFESTATION OF RADIATION EFFECTS

Each of the numerous cell renewal systems making up an animal's total cellular mass is normally in an equilibrium state between cell formation, proliferation, maturation, and death. Some systems, such as the adult central nervous system in higher animals, are stabilised at the end-point of maturation, and the functional cells of such a system are not replaced if lost or destroyed. Other organ systems, such as the liver, which do not normally replace cells at a rapid rate, have the potential to regenerate large numbers of cells if needed. Other organ systems, such as the skin, the reproductive system, the gastrointestinal tract, and the haematopoietic system in the bone marrow, maintain a continuous high cell turnover rate. Bone marrow also has a large reserve capacity in the adult. A large fraction of it is normally non-functioning but has the potential to be functional if required. Failure of a particular organ system may or may not lead to death of the animal, depending on the importance of that system's functions, i.e. failure of gonadal function would not be lethal, whereas failure of bone-marrow function would be.

Acute Radiation Syndrome (ARS)

Acute exposure of a person to moderate to high dose of radiation can lead to mild symptoms of nausea, vomiting to severe symptoms leading to immediate death (**Table 1**).

Table 1: Dose and Effects of Radiation Syndrome

Dose	Effect
<50 rads (0.5 Gys)	Generally no clinical effect; subject asymptomatic
50 to 100 rads (0.5 to 1 Gys)	Mild nausea; WBCs increased and then decreased
100 to 200 rads (1 to 2 Gys)	Nausea, vomiting, fatigue; WBCs increased and then decreased; recovery in 2 to 4 days
200 to 400 rads (2 to 4 Gys)	2 to 3 days of nausea, vomiting, fatigue; WBCs markedly decrease, platelets decrease; epilation, diarrhoea, bleeding; recovery in 1 to 3 weeks; death occurs in 4 to 6 weeks
300 to 500 rads (3 to 5 Gys)	LD 50; dose lethal to 50% of persons exposed
400 to 600 rads (Gys)	Severe nausea, vomiting, diarrhoea and sore throat; WBCs very low, platelets very low; recovery period brief or absent; symptoms recur with bleeding and diarrhoea; death occurs in less than 30 days
600 to 1,000 rads (6 to 10 Gys)	Severe and continuous nausea, diarrhoea, and vomiting; death occurs in 1 to 10 days
>1,000 rads (>10 Gys)	Severe illness, disorientation, ataxia, burning sensation and shock; death occurs in 10 to 36 hours

Lethality (LD_{50})

When comparing the effects of various types or circumstances, that dose which is lethal to 50% of a given population is a very useful parameter. The term is usually defined for a specific time, being limited, generally, to studies of acute lethality. The common time periods used are 60 days for large animals and humans. Medically, other figures of interest are the dose that will kill virtually noone, (LD5), and the dose that will kill virtually everyone (LD95). Approximations of those doses are within the ranges 200 to 300 cGy (free in air) and 600 to 700 cGy (free in air), respectively.

Recovery Processes

Understanding the process of recovery from radiation damage is necessary in determining the protocols for radiation therapy. If there is time between therapy fractions and repair takes place, effective results will not be seen.

A variety of recovery processes may reduce radiation damage to a varying extent. For example, when a chromosome is broken, the broken ends tend to rejoin, thus reconstituting the chromosome, but occasionally the broken ends seal over before rejoining, thus leaving permanent chromosome damage. If two (or more) chromosomes are broken within the same cell, rejoining of inappropriate broken ends can occur and it may lead to permanent chromosomal change of a different kind. Repair of the broken ends of chromosomes, like all other repair processes following radiation damage, is not specific in respect of radiation damage.

Intra-cellular repair occurs when individual irradiated cells have the ability to repair themselves as long as the amount of intra-cellular damage does not exceed a threshold value.

Repopulation brought about by stem cell proliferation is a particularly important recovery mechanism in both the bone marrow and the gastrointestinal tract whenever the radiation exposure has been large enough.

Repair is a biological process specific to a particular kind of damage which comes into play whatever the agent which causes that damage. The third, a combination of the first two types of recovery, can be very approximately quantified for lethality in humans by the use of the operational equivalent dose formula in cases where the irradiation period is protracted over several hours or longer.

Delayed Effects

The above description is often the early effects of radiation. However, radiation effects can manifest several years later. Hence, it is important to ensure, when radiation of any form is used in the diagnostic and therapeutic management, the awareness of patients about the consequences which might occur many years later. The risk factors for a particular type of manifestation of delayed effects of radiation should be kept in mind when exposing a patient to radiation.

The present increase in the life span of persons all over the world can be a hazard for the development of higher incidences of delayed radiation effects.

General

Late or delayed effects of radiation occur following a wide range of doses and dose rates. Delayed effects may appear months to years after irradiation and include a wide variety of effects involving almost all tissues or organs. Some of the possible delayed consequences of radiation injury are: life shortening, carcinogenesis, cataract formation, chronic radiodermatitis, decreased fertility, and genetic mutations.

Carcinogenesis

Irradiation of almost any part of the body increases the probability of cancer. The type formed depends on such factors as area irradiated, radiation dose, age, and species. Irradiation may either increase the absolute incidence of cancer or accelerate the time or onset of cancer appearance, or both. There is a latent period between the exposure and the clinical appearance of the cancer. In the case of the various radiation-induced cancers seen in mankind, the latency period may be several years. Latent periods for induction of skin cancers in people have ranged from 12 to 56 years after X-ray irradiation. Fifteen years is reported as a latent period for bone tumours from radium.

A leukeamogenic effect was expected and found among Hiroshima and Nagasaki survivors. Peak incidence occurred 6 years after exposure and was less marked for chronic granulocytic leukaemia than acute leukaemia. The incidence was inversely related to distance from the hypocentre.

British persons receiving radiotherapy for spondylitis showed a dose response relationship for leukaemia, with peak incidence occurring 5 years after the first exposure. Studies have demonstrated that ionising radiation can induce more than one kind of leukaemia in people, but not chronic lymphocytic leukaemia.

Predisposing factors for tumour development include heredity, age, hormones, and prior exposure to physical trauma, chemical agents and ionising radiation. The actual processes by which cancer is induced are not known. Somatic mutations, virus infections, and precancerous abnormalities in tissue organisation and vascular supply have all been postulated.

Cataract formation

A late effect of eye irradiation is cataract formation. It may begin anywhere from 6 months to several years after exposure. While all types of ionising radiation may induce cataract formation, neutron irradiation is especially effective in its formation, even at relatively low doses. Cataract formation begins at the posterior pole of the lens and continues until the entire lens has been affected. The threshold for detectable cataract formation in 2 Sv (sievert) [200 rem (Roentgen equivalent, man)] for acute radiation doses and 15 Sv (1500 rem) for protracted doses.

Chronic radiodermatitis

Delayed, irreversible changes of the skin usually do not develop as a result of sub-lethal whole-body irradiation, but instead follow higher doses limited to the skin. These changes are common complications in radiation therapy. Erythema occurs at low doses ranging from 60 to 80 Sv followed by skin necrosis and ulceration at higher doses. Chronic exposure over 20 Sv can lead to dermatitis with skin cancers.

Genetic or heritable effects

Genetic or heritable effects appear in the future generations of the exposed person as a result of radiation damage to the reproductive cells. They have been extensively studied in plants and animals, but risks for genetic effects in humans are seen to be considerably smaller than the risks for somatic effects. Therefore, the measures used to protect the exposed person from harm are equally effective to protect future generations from harm.

Genetically significant dose (GSD) is that dose if received by any member of the population which would be expected to produce the same number of genetic abnormalities as are produced by the actual doses received in various individuals. GSD for natural background is 3.6 mSv per year, medical exposures is 0.4 mSv and nuclear medicine procedures is 0.14 mSv.

Dose and Effect

Stochastic effects: These effects have no threshold and the severity of the effect does not vary with the dose. The probability of occurrence, however, increases as the dose increases. Cancer is a stochastic effect, particularly leukaemia which has a latent period of 2 to 10 years post exposure. The risk for leukaemia is significantly increased above acute doses of 40 rads (0.4 Gy). There is a longer latent period for solid tumours (10 to 40 years), such as squamous cell carcinoma of the skin and adenocarcinoma of the breast or lung. There may be some associated increased risk for childhood cancer following exposure in utero. Genetic effects are also considered under this category.

Non-stochastic effects or deterministic effects: The severity of the effect varies with the dose and the effects are not seen below a certain threshold level of radiation. A minimum dose of 200 rem (2 Sv) is required for the development of cataracts. The threshold for developing a vision impairing cataract under conditions of prolonged, fractionated exposure is felt to be 800 rem. Temporary sterility in males can be seen following acute doses of 15 rem (0.15 Sv), while permanent sterility can be seen after doses of 350 rem (3.5 Sv). In females, permanent sterility can be seen following doses of 250 to 600 rem (2.5 to 6.0 Sv).

Dose response curve

It is believed that at low dose rates, defence mechanisms in the cells can operate to repair some of the damage caused by radiation. In this region of low dose, the effect (i.e. the probability of producing cancerous cells) is thought to be proportional to the dose. At higher dose rates, greater than 100 mGy per hour, two or more ionising events might occur in the critical parts of cells before the repair mechanism would have a chance to operate. At this point, the slope of the dose-effect curve increases and the effect will depend on the square of the dose, D2, rather than just on D (**Figure 1**).

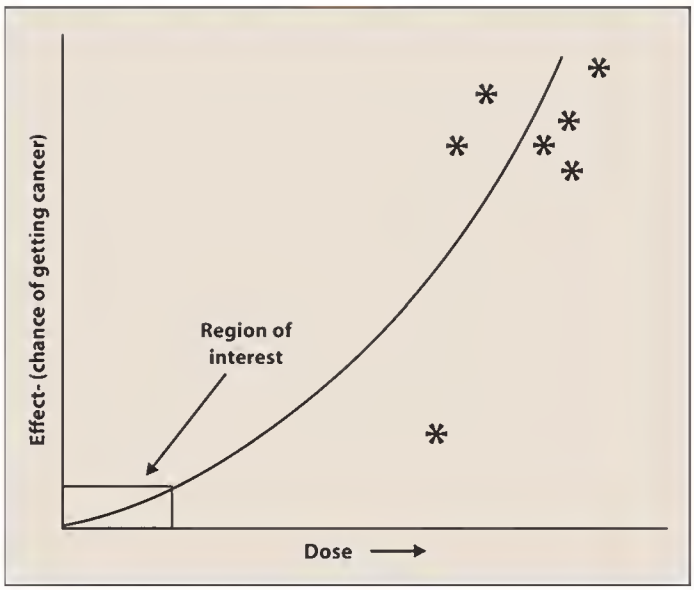


Figure 1: The dose effect curve showing exponential increase in cancer risk with high dose radiation.

This means that if the whole body is exposed to 1 Sv of ionising radiation, an extra 4% chance of contracting a cancer that will be fatal many years after the exposure. The word 'extra' is used because one normally has a 20% to 25% chance of dying from cancer.

Other stochastic effects also occur. Radiation can cause changes in DNA, the 'blueprints' that ensure cell repair and replacement produces a perfect copy of the original cell. Changes in DNA are called mutations.

Sometimes the body fails to repair these mutations or even creates mutations during repair. The mutations can be teratogenic or genetic. Teratogenic mutations are caused by exposure of the foetus in the uterus and affect only the individual who was exposed. Genetic mutations are passed on to offsprings.

Potential Effects of In Utero Exposure

Prenatal death occurs if the radiation is received during perimplantation. The most sensitive period for neonatal death to occur following radiation exposure is between 3 to 5 weeks of gestation. The most sensitive period for congenital abnormalities is during the period of organogenesis. Growth retardation can also be seen in irradiated foetuses. Long-term effects of the radiation include sterility, genetic effects, induction of malignancies, and neurologic impairment.

Mental retardation: Mental retardation can be seen following in-utero radiation exposure and is the most commonly documented abnormality in humans who are prenatally exposed. The foetus is most susceptible to radiation delivered during the 8 to 15 week period, and somewhat less susceptible between 16 and 25 weeks. The risk of mental retardation is dose related and is only about 4% for a 10 rem (0.1 Sv) dose, while it may be as high as 43% for a 100 rem (1 Sv) dose. There may be a threshold for retardation between 20 and 40 rem (0.2 to 0.4 Sv), but this has not yet been proven.

Malignancy: The increased risk of cancer in the foetus is estimated to be approximately 500 deaths before the age of 10 years among 1 million children exposed shortly before birth to 1 rad [2 x 10 (to the –4) per rad]. The leukaemia risk for the child is greatest if radiation was received during the first trimester.

Considerations for Pregnancy Termination

1. Threshold dose for developmental effects approximately 0.1 Gy.
2. Normal rate of preclinical loss >30%. At 0.1 Gy, increase of 0.1% to 1%.
3. The foetal absorbed dose >0.5 Gy at 7 to 13 weeks: substantial risk of IUGR and central nervous system damage.
4. 0.25 to 0.5 Gy at 7 to 13 weeks: parental decision with physician's guidance.

MINIMISING HEALTH EFFECTS OF IONISING RADIATION

Life style abnormalities, natural disasters and accidents are greater risk factors than exposure to small amounts of radiation as encountered in medical exposures and in radiation workers.

Some scientists assert that low levels of radiation are beneficial to health (this idea is known as hormesis).

Although exposure to ionising radiation carries a risk, it is impossible to completely avoid exposure. Radiation has always been present in the environment and in our bodies. However, we can avoid exposure. Although one cannot sense ionising radiation, there is a range of simple, sensitive instruments capable of detecting small amounts of radiation from natural and man-made sources.

1. *Dosimeters:* These can measure an absolute dose received over a period of time. The TLDs are normally used to obtain your official dose of record. TLDs are processed routinely at the end of each calendar quarter. TLDs are sensitive to beta, gamma, and neutron radiation.
2. *Self reading pocket dosimeters (SRPDs):* The term SRPDs applies to a variety of devices which can be read by the wearer to determine the dose received. SRPDs are used as supplemental devices to aid in dose tracking during activities where elevated doses are possible.
3. *Pocket ion chambers (PIC):* These are small instruments which operate on the principle electroscope. Typically, the range of the PIC is 0 to 200 mR. This is one of the most common supplemental dosimeters used in radiation areas.
4. *Electronic dosimeters (ED):* These are sometimes used instead of and in addition to PICs when it is helpful to have additional capability of dose or dose rate alarm functions.
5. *Geiger counters and scintillometers:* These measure the dose rate of ionising radiation directly.
6. *Film badge dosimeters:* These enclose a photographic film which will get exposed to radiation.

In addition, there are 3 ways for personal protection:

1. *Time:* Limiting or minimising the exposure time to reduce the dose.
2. *Distance:* The intensity of exposure reduces as a square of the distance from the source.
3. *Shielding:* Barriers of lead, concrete or water are protective against radiation, such as gamma and neutrons. That is why certain radioactive materials are stored or handled under water or by remote control in rooms constructed of thick concrete or lined with lead. There are special plastic sheets for stopping beta rays and air will stop alpha particles.

It should be noted that the setting of a dose limit is equivalent to specifying a maximum acceptable level of risk. It is not acceptable to be exposed to the full extent of the limit if a lower dose can be reasonably achieved. The average dose received by an occupationally exposed worker is less than 0.2 mSv per year.

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27.11 Environmental Disasters

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Emergency management is the discipline that involves preparing for disaster before it occurs, disaster response (e.g. emergency evacuation, quarantine, mass decontamination, etc.), and rebuilding society after natural or human-made disasters have occurred. In general, any emergency management is the continuous process to manage hazards in an effort to avoid or ameliorate the impact of disasters. Effective emergency management relies on integration of emergency plans at all levels of government and non-government involvement.

PHASES IN EMERGENCY MANAGEMENT

Mitigation

Mitigation efforts attempt to prevent hazards from developing into disasters altogether, or to reduce the effects of disasters when they occur. The mitigation phase differs from the other phases because it focuses on long-term measures for reducing or eliminating risk. Mitigation is the most cost-efficient method for reducing the impact of hazards; however it is not always feasible.

Preparedness

Preparedness is a continuous cycle of planning, organising, training, equipping, exercising, evaluation and improvement activities. It ensures effective coordination and the enhancement of capabilities to deal with natural disasters, acts of terrorism, and other man-made disasters.

Response

This phase includes the mobilisation of the necessary emergency services and first responders in the disaster area.

Recovery

The recovery phase aims at restoring the affected area to its normal state. The focus of this phase is different from response phase; recovery efforts are started after immediate needs are addressed.

EMERGENCY MANAGEMENT IN INDIA

National Disaster Management Authority of India, a government agency under the Ministry of Home Affairs is India's Institutional Mechanism for effective disaster management. In recent years, there has been a shift in emphasis from response and recovery to strategic risk management and reduction. There is more emphasis on community participation rather than a government-centred approach with network of Emergency Response Centres and Crisis Management Group and strengthening the Institutional Frameworks for regulatory.

Efforts involve the provision of emergency management training for first responders, the creation of a single emergency telephone number, and the establishment of standards for EMS staff, equipment and training.

TRIAGE

Triage means to sort. When there is sudden flux of patients in emergency room or at the site of disaster one needs to prioritise which patients need treatment earlier than others. Triage is essential in medical emergencies, including the pre-hospital setting, disasters, and during emergency room treatment.

Types of Triage

Simple triage

Simple triage is usually used in a scene of a mass-casualty incident. It helps to sort patients into those who need critical attention and immediate transport to the hospital and those with less serious injuries. This triage can be started before transportation becomes available.

Simple triage and rapid treatment (START)

START is a simple triage system that can be performed by lightly-trained lay and emergency personnel in emergencies. It does not intend to supersede or instruct medical personnel or techniques. Colour codes (flags) are attached to patients for identification and management. Triage separates the injured into four groups:

- The deceased who are beyond help (Black).
- The injured who can be helped by immediate transportation (Red).
- The injured whose transport can be delayed (Yellow).
- Those with minor injuries, who need helpless urgently (Green).

Advanced triage

In advanced triage, doctors decide that some serious patients should not receive advanced care because they are unlikely to survive. Advanced care will be used on patients with less severe injuries. However, advanced triage has ethical implications. It is used to divert scarce resources away from patients with little chance of survival in order to increase the chances of survival of others who are more likely to survive.

ENVIRONMENTAL DISASTER

An environmental disaster is a disaster that is due to human activity and should not be confused with natural disasters; but forced human movement, as in Haiti, can cause cholera, after flooding from hurricane. Industrialisation all over the world has introduced several chemicals in the environment causing exposure to wide variety of toxic agents for the people living in such environment. The respiratory tract tends to bear the maximum brunt of such exposure leading to upper and lower respiratory tract inflammation. The upper respiratory tract through the anatomical structures like nasal turbinates and the cough reflex usually removes maximum amount of toxic gases inhaled. The dose reaching into the lower respiratory tract however is cumulative and produces long-term inflammation due to impairment of mucociliary clearance and alveolar macrophage defence.

General Mechanism of Injury Due to Toxic Chemicals

Massive acute exposure leads to inhalation of irritant gases resulting in acute inflammatory reaction in the respiratory mucosa mainly in the form of capillary damage and oedema, and severity of damage essentially depends on concentration of gas in the environment, solubility in water and duration of the exposure.The inflammatory reaction produced by noxious gases is similar for almost all agents but the severity differs depending on the above mentioned factors.It can range from mild respiratory inflammation to alveolar oedema, shock and disseminated intravascular coagulation (DIC) syndrome—the last one accounting for most of the fatalities in inhalational disasters.

Following are two examples of large scale disasters due to environmental accidents.

The gas leak in Bhopal (MP), 1984, the union carbide gas leak

December 3, 1984 has become a memorable day for the city of Bhopal in Madhya Pradesh, India. Shortly after midnight, a poisonous gas cloud escaped from the Union Carbide India Limited (UCIL) pesticide factory. The cloud of poisonous gas containing 15 metric tons of methyl isocyanate (MIC) escaped from the factory covering an area of more than 30 square miles. The casualty was four thousand and many more suffer from chronic disease consequential to gas exposure, today. This incident happens to be one of the worst known industrial environmental disasters.

Chernobyl: Russian nuclear power plant explosion (1986)

Reactor stress at nuclear power plant in Ukraine resulted in ten times increase in energy production than the normal level and finally culminated into explosion by the escaped steam and formation of an atmospheric cloud containing approximately 185 to 250 million curies of radioactive material caused fire instantly killing 31 people. Immediate aftermath of the earthquake and Tsunami in Japan, March 2011 was the melting of fuel rods in the nuclear reactors causing nuclear blast radiation disaster. Graded response to nuclear/radiologic emergencies has become necessary. Growing concern over ocean contamination.

Radiation

It is naturally present in our environment and has been since the birth of this planet. Life has evolved in an environment, which has significant levels of ionising radiation. It comes from outer space (cosmic) and the ground (terrestrial). The average annual radiation exposure from natural sources is about 300 millirem (3 millisieverts). In addition, man-made sources of radiation from medical, commercial and industrial activities contribute another 60 mrem (0.6 mSv) to our annual radiation exposure. One of the largest of these sources of exposure is medical X-rays. Diagnostic medical procedures account for about 40 mrem (0.4 mSv) each year.

Biological effects of radiation

Biological effects of radiation on living cells may result in three outcomes; firstly, injured or damaged cells repair themselves, resulting in no residual damage; secondly, cells die, much like millions of body cells do everyday, being replaced through normal biological processes; and thirdly, cells incorrectly repair themselves resulting in a biophysical change.

Ammonia

It is mostly used in fertilisers, as a solvent in textile, leather, paper, and pulp industries and also in petroleum refining processes and cold storage. Exposure occurs mostly in the setting of an industrial accident. Toxicity depends on duration of exposure. It usually gets dissolved in moisture present in eyes, oral cavities, pharynx, and lungs and gets converted into ammonium hydroxide which is responsible for its corrosive action. Patients usually present with headache, salivation, swelling around eyes and lips, lacrimation, blurred vision, corneal opacification with scarring if head and face are involved. Cough, dyspnoea, bronchospasm, and consolidation occur when lungs are involved. Abdominal pain and severe vomiting leads to shock in patients with gastrointestinal tract involvement. Skin manifestations include erythema, oedema, blisters and vesicle formation. Treatment is to remove the patient from environment, if skin exposure occurs wash the whole body thoroughly with water. Administration of intravenous fluid becomes necessary in those with severe vomiting and hypovolaemia. Corticosteroids can be used during acute exposure along with antibiotics. Ventilatory support may be required in some cases.

Sulphur Dioxide

See Chapter 3 on Section 27 Environmental Medicine.

Carbon Monoxide

Carbon monoxide is a colourless, odourless gas formed when substances containing carbon are burnt with an insufficient supply of air. The combustion of fuels such as petrol, gas, coal and wood generate emissions of carbon monoxide. Motor vehicles are the main source of in urban areas. Exhaust emissions contain carbon monoxide from incomplete burning of fuel in the engine. Carbon monoxide can have serious health impact on humans. When inhaled, the carbon monoxide binds to the haemoglobin in the blood (and becomes carboxyhaemoglobin) in place of oxygen and is carried through the blood stream. This reduces the oxygen-carrying capacity of the red blood cells and decreases the supply of oxygen to tissues and organs, especially the heart and brain. This can be a serious problem for people with cardiovascular disease. Most people in the community need to be exposed to a level of 200 ppm for several hours before they start to feel effects. Carboxyhaemoglobin formation is reversible when the person is no longer exposed to carbon monoxide.

Treatment

The treatment for carbon monoxide poisoning is to immediately remove the victim from the exposure without endangering oneself. The main medical treatment for carbon monoxide poisoning is 100% oxygen by a tight-fitting oxygen mask. Oxygen hastens the dissociation of carbon monoxide from haemoglobin, improving tissue oxygenation by reducing its biological half-life. Hyperbaric oxygen is also used in the treatment of CO poisoning; hyperbaric oxygen also increases carboxyhaemoglobin dissociation and does so to a greater extent than normal oxygen. Hyperbaric oxygen may also facilitate the dissociation of CO from cytochrome oxidase. Further specific treatment for other complications such as seizure, cardiac abnormalities, pulmonary oedema, and acidosis may be required. Late development of neuropsychiatric impairment is one of the most serious complications of

poisoning. Prevention remains a vital public health issue, requiring public education on the safe operation of appliances, heaters, fireplaces, and internal-combustion engines, as well as increased emphasis on the installation of carbon monoxide detectors.

Chlorine

Chlorine is a halogen element used as a reagent in plastic manufacturing and paper industries and also used in drinking water and swimming pool water to kill harmful bacteria. It is also used as part of the sanitation process for industrial waste and sewage. Chlorine gas can be pressurised and cooled to change it into a liquid so that it can be shipped and stored. When liquid chlorine is released, it quickly turns into a gas that stays close to the ground and spreads rapidly. Chlorine gas can be recognised by its pungent, irritating odour, which is like the odour of bleach. The strong smell may provide an adequate warning to people that they have been exposed. The gas appears to be yellow-green in colour. Chlorine itself is not flammable, but it can react explosively or form explosive compounds with other chemicals such as turpentine and ammonia. Mechanism of toxicity is the generation of hypochlorous acid, hydrochloric acid and chloramine gas which is formed when ammonia and bleach are mixed. These by-products cause coagulative necrosis and oxidative damage. Symptoms of respiratory tract usually predominate after chlorine exposure. During or immediately after exposure to dangerous concentrations of chlorine, the following signs and symptoms may develop like cough, chest tightness, burning sensation in the nose, throat, and eyes, watery eyes, blurred vision, nausea and vomiting. Burning pain, redness, and blisters appear on the skin if exposed to chlorine gas. Difficulty in breathing may appear immediately if high concentrations of chlorine gas are inhaled, or may be delayed if low concentrations of chlorine gas are inhaled. Pulmonary oedema occurs on severe exposure. Management usually involves leaving the area where the chlorine was released and getting to fresh air. Remove clothing and rapidly wash entire body with soap and water, and get medical care as quickly as possible. Treatment is largely supportive as no antidote for chlorine is available.

Nitrogen Dioxide

Exposure to oxides of nitrogen occurs in welders using acetylene torches, coal miners, chemical industries manufacturing dyes, farmers who work with silage when it is called as silo fillers disease, smoke from cigarettes, cigar pipes and diesel fumes. Nitrate concentration is increased in grain plants by the use of fertilisers. Nitrates combine with organic acid to form nitrous acid which in turn decomposes to nitrous oxide (N_2O), nitrogen tetraoxide (N_2O_4) and nitrogen penta oxide (N_2O_5). N_2O and N_2O_4 are responsible for injury to lungs. The threshold limit of nitrous oxide is 5 ppm, and humans exposed to even to 50 ppm for short duration are also at risk of developing acute lung injury. Nitrogen dioxide is a powerful oxidant and is capable of causing extensive damage to respiratory epithelial cells. Clinical course can be divided into following stages:

Super acute stage: This phase follows immediately after exposure. Patients suffer severe hypoxia and formation of methaemoglobin. Most are critically ill and may succumb before medical aid can be made available.

Acute phase: Exposed person exhibits dyspnoea, nausea, headache, tachycardia, and weakness, and may complain of pleuritic chest pain. These symptoms develop after a lag-period of few hours. Bronchospasm appears in most cases and pulmonary oedema in few.

Subacute and chronic phase: Pulmonary oedema clears in few days and patient passes into an asymptomatic phase lasting for 2 to 5 weeks. The X-ray of chest appears normal and the patient may have mild dyspnoea. After 3 to 6 weeks there is a relapse of symptoms and the patient develops progressive dyspnoea, cough, and cyanosis. Chest X-ray shows multiple, discrete, nodular opacities. In severe cases, hypoxia and CO_2 retention may be fatal.

The treatment is mainly supportive. Methaemoglobinaemia, if present, should be treated with IV methylene blue. Corticosteroids may be helpful in some cases.

Ozone

See Chapter 3 of Section 27 Environmental Medicine.

Isocyanates

These compounds are used in paint, furniture, rubber and pesticide industry. Commonly used isocyanates are toluene diisocyanate (TDI), methylene diphenyl diisocyanate (MDI), naphthalene diisocyanate (NDI), hexamethylene diisocyanate (HDI). These compounds cause pulmonary and skin manifestations. Pulmonary manifestations are mainly due to bronchoconstriction and may lead to toxic bronchitis and asthma, accelerated decline in FEV1 and extrinsic alveolitis. Skin manifestations range from localised itching to widespread eczema. Treatment is symptomatic.

Phosgene

It is a colourless gas heavier than air with a musty odour resembling mown hay, commonly used in pesticide industry. On exposure it produces irritation with coughing and sense of suffocation. Large exposure can cause increased capillary permeability resulting in large shifts in body fluids and shock with pulmonary oedema. Marked bronchiolar and bronchial congestion occurs early and emphysematous lesions may occur as delayed sequelae.

General Treatment

Treatment of all noxious gas exposure is similar as basic mechanism is identical for many of them. Prime importance should be given to maintenance of airway and circulation. As per requirement continuous positive airway pressure (CPAP) and intermittent positive airway pressure (IPPV) should be provided. Antibiotics should be used only if infection is suspected, otherwise prophylactic antibiotics have no role. Corticosteroids are recommended in acute phase to prevent bronchiolitis. Methylprednisolone 1 gm every 12 hourly can be used for three days.

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Section 28

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28.1 Geriatric Medicine

Vinod Kumar

DEFINITION AND EPIDEMIOLOGY

Geriatric medicine is the specialised branch of medicine that deals with medical problems of older persons. United Nations term older persons as those aged 60 years or above and in India also, cut off point is 60 years. This cut off point is purely arbitrary and does not necessarily indicate the onset of ageing process or age-related disorders in an individual. In fact, older persons are highly heterogenous, lot showing great variations in age-related physiological decline and age-related disorders. Generally, age-related decline in strength, vision, memory, locomotion, nutrition, immunity and homeostasis develop slowly while onset of disease may be abrupt.

There is a steady increase in the ageing of our population and therefore geriatric medicine has to be established in our country while it is well-established in other countries. Demographic trends reveal that population of older persons is growing faster than that of general population. Since 1950, life expectancy in India at birth has almost doubled from 32 years to 65 years. Total Indian population was 350 million in 1950, 1112 million in 2006 and this is projected to be 1572 million in 2050, i.e. a percentage increase of 40% in a matter of 44 years. In contrast, population of older persons (60+) which was 19 million in 1950 and 90 million in 2006 will be 330 million in 2050, thus showing a much greater increase (270%). Moreover, amongst them, the older ones (above 80 years) are growing at a fast pace. Their population which is 0.8 million in 1950, 9 million in 2006 which is projected to be 53 million in 2050, i.e. a rise of almost 500%. These very elderly people are usually weaker, more frail, insecure and dependent, and suffer more often from age-related diseases, neglect and abuse as compared to young olds (60 to 79).

GERIATRIC MEDICINE VERSUS GENERAL MEDICINE

Older persons frequently suffer from multiple disorders, require long-term treatment with multiple drugs and may often need physical and rehabilitative therapy for various residual disabilities. Some diseases occur more often and some occur almost exclusively in older persons. Degenerative disorders like cardiovascular disease, chronic obstructive pulmonary disease, diabetes, osteoarthritis and infection-related disorders like pneumonias, urinary tract and other infections occur more frequently in older persons while diseases such as Alzheimer's disease, prostatic hypertrophy, postmenopausal osteoporosis, and macular degeneration occur almost exclusively in old age. Clinical presentation of many disorders in old age may be atypical and different. In old age, myocardial infarction may occur without chest pain, infection may be without fever and hypertension may be without a rise in diastolic pressure. Obstructive jaundice in older person is more likely to be of malignant origin. Bacteriuria, impaired glucose tolerance and premature ventricular contractions do not have the same degree of prognostic gravity as in younger subjects. An older person is more vulnerable to confusion or drowsiness in response to an acute event compared to young person. Thus, approach to a geriatric patient should be different. Developing a rapport with an older patient, art of history taking and of being a patient listener, assessing him comprehensively and ordering only limited but necessary investigations, are some of the requisites of a geriatric physician.

CLINICAL ISSUES IN GERIATRIC PRACTICE

Older persons seek medical advice more than any other segment of adult population. In a developing country like India, where demographic transition has occurred faster, but public hygiene has remained inadequate, older persons often suffer from double burden of diseases, i.e. both degenerative and infection-related diseases. Consequently, increasing number of people surviving longer into old age suffer from type 2 diabetes, coronary heart disease, hypertension, stroke, chronic obstructive pulmonary disease, Alzheimer's disease, osteoarthritis, osteoporosis, prostatic hypertrophy, cataracts, macular degeneration, and cancer, etc. and at the same time they are vulnerable to infections involving respiratory (including TB), urinary and digestive tract. Acute infections may present atypically with absence of fever and leucocytosis; instead, they may present with impaired intellect/memory, incontinence, instability or immobility—the so called 'geriatric giants'. Malnutrition, occult hypothyroidism, renal injury, depression, urinary incontinence and sexual problems are also common in old age. For a detailed description of geriatric disorders, reader is referred to consult a 'Textbook of Geriatrics'. Following description highlights some of the important diseases in old age.

The Frail Older Person and the Frailty Syndrome

Older persons who become physically weak, tired, underweight, and unable to easily walk are termed as frail. They have reduced physiological reserve and are unable to carry out activities of daily living in stressful situations. They are often 80+ and may get disabled by falls, infections, drug reactions or bereavements. When frail individuals have several impairments like undernutrition, osteoporosis, muscle loss, neuronal loss, it is then termed as frailty syndrome. Frail subjects are prone to falls and fractures. Undernutrition is brought about by reduced appetite and taste, bowel dysfunction, and physical inactivity in old age while hormonal factors and calcium/vitamin D deficiency additionally contribute to osteoporosis. Muscle loss or sarcopaenia in old age is due to reduced protein intake, sedentarism, diabetes, and atherosclerosis. Hormonal deficiency also leads to frailty. Gradual neuronal loss and cognitive impairment occurs in many frail older persons. Prevention and treatment of frailty syndrome includes physical activity, adequate protein, calcium and vitamin intake, use of ACE inhibitors and hormone replacement therapy together with control of underlying disorders.

Osteoporosis

Ageing is associated with progressive bone loss and osteoporosis with increased risk of hip and other fractures. It is more prominent

in menopausal women due to cessation of oestrogen secretion. Risk factors for osteoporosis fractures include female sex, advancing age, small built, calcium and vitamin deficiency, sedentarism, smoking, alcoholism and caffeine excess. Diagnosis is made by measuring bone mineral density (BMD) by dual energy X-ray absorptiometry (DEXA) which is also useful in predicting fractures and monitoring of therapy. Detection in asymptomatic stage and prevention of fractures is important. Preventive methods include adequate intake of calcium (1,200 mg/dL) and vitamin D (400 to 800 IU/dL), walking and antigravity weight bearing/muscle strengthening exercises, fall prevention, smoking cessation and avoidance of alcohol intake. Sunlight exposure for at least 15 minutes a day for 3 times a week is good source of vitamin D. Hormone therapy for osteoporosis has now been largely replaced by use of safer drugs like bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, zandronate), selective oestrogen receptor modulators, the SERMs (raloxifen, tamoxifen), calcitonin and teriparatide.

Falls in Older Persons

Falls are common in old age due to various diseases and are contributed by changes that occur with ageing. Balanced and upright posture in humans is maintained by central structures of cortex, sub-cortex and cerebellum which co-ordinate the sensory inputs from visual, vestibular and proprioceptive organs and by muscular activity, especially of the lower limbs. With ageing, physiological changes occur in the nervous system like impairment of vision and hearing, reduction of proprioceptive and vibratory sensations, increased sway, altered gait and poor positional control predispose to falls.

Falls best defined as sudden unintentional change in position causing a subject to land on ground or on lower level constitute a common problem in older persons. Recurrent falls mean two or more falls in six months. Risk factors are advancing age, female sex, cognitive and sensory impairment, polypharmacy and poor psychosocial and environmental factors. Falls may cause mild, moderate or severe bodily injury and even fractures and subdural haematoma. More than 80% of hip fractures in older persons are due to falls. Causes of falls are multiple. Drugs and even an unrelated acute event like pneumonia or dyselectrolytaemia can manifest as fall. An easy way for students to remember common causes of falls is to recall the words FALL SINDROME in which I replaces Y in the word syndrome (**Table 1**).

Table 1: Causes of Falls

F	Falls from extrinsic causes – uneven floors, defective staircases, footwear and poor lighting
A	Arrhythmias
L	Lower limb Neuropathy
L	Lower limb diseases like Osteoarthritis, Foot calluses, Bunions, and Hammer toes
S	Syncope – Aortic stenosis, Heart block, Mitral prolapse, Obstructive Cardiomyopathy
I	Instability
N	Neurological diseases – Vertebro-Basilar Insufficiency, Hemiplegia, Pakinsonism
D	Defects of Cognition, Vision and Hearing
R	Recurrent falls
O	Orthostatic hypotension and Orthopaedic problems of old age
M	Muscle weakness, especially of the lower limbs
E	Epilepsy and Seizures

A thorough history of the patient and family members, systemic clinical examination to identify various diseases and their relationship to falls and relevant investigations are essential. Assessment of cognition, muscle strength, postural stability, proprioceptive sensation and balance should be carefully carried out. Treatment of older persons presenting with falls include management of injury and associated illnesses, if any. Specific treatment depends on the underlying condition. Regular exercise and use of limbs are imperative. Interventions to improve strength, balance and endurance are also important.

Dementia

This is a clinical syndrome characterised by a decline in cognitive, intellectual and memory function due to disease process affecting the central nervous system. There is difficulty in many functions like problem solving, judgement, abstract thinking, geographic orientation, etc. There is no loss of consciousness and hence it is different from delirium. Minor memory lapses, such as forgetting one's keys or forgetting names do not ordinarily mean dementia. However, if one gets lost in familiar surroundings or fails to recognise spouse, diagnosis of dementia can be considered. Dementia is detected by the use of criteria of the diagnostic and statistical manual of mental disorders (DSM IV). Many diseases can result in dementia. Commonest are Alzheimer's disease (AD), a progressive and irreversible cause of dementia and the multi-infarct dementia (MID) also known as vascular dementia. Other causes of dementia are subdural haematoma, normal pressure hydrocephalus, hypothyroidism, head trauma, alcoholism, brain tumour and vitamin B12 deficiency, many of which are reversible with treatment.

Generalised neuronal loss in the cortex is the main histological change seen in cases of dementia. There is diffuse cerebral atrophy accompanied by enlargement of third and lateral ventricles. Atrophy of hippocampus is prominent. Senile plaques and neurofibrillary tangles (NFT) characterise AD. Plaques are extracellular lesions and are scattered throughout the cerebral cortex and hippocampus. They consist of beta amyloid. NFTs are in the nerve cell cytoplasm and contain tau proteins.

Clinical features include slow onset of forgetfulness, loss of interest in surroundings, impairment in social skills and personality. Depression may occur in early stages. Disorientation in time and space later followed by language impairment, aphasia, apraxia fits and paralysis are common. Finally, patient may start vegetating and death may ensue by intercurrent infection. Diagnosis of AD is supported by any of the neuro-imaging modalities like CT scan, magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT) and by ruling out other causes of dementia. Unless a dementia is due to treatable cause, management depends more on care of the patient rather than by curative methods. This is most applicable to AD. Advice to family and social support are key actions of treatment, drugs are practically of no value. Neuroprotectives, N-methyl-D-aspartic acid (NMDA) antagonists, anti-inflammatory agents and cholinesterase inhibitors like tacrine, donepzil, rivastigmine and galantamine are claimed to have beneficial effects on cognitive functions. Ancillary treatment includes alprazolam for disturbed sleep, anti-psychotics for restlessness and haloperidol for emotional stability.

Urinary Incontinence

It is involuntary passage of urine through urethral orifice, a common problem in older persons and a common cause of hospitalisation. It is commoner in females. It contributes to pressure sore, urinary tract infection and depression. Risk factors include smoking, chronic cough, depression, obesity, multiparity, oestrogen depletion and constipation. Apart from sanitation problems and interference in daily life, severe cases of urinary incontinence can have important social repercussions.

Causes of urinary incontinence are either established or transient (**Table 2**). Causes of established urinary incontinence include cerebral or spinal cord lesion, stroke, dementia, bladder disease, Parkinsonism and myelopathy. Latter are best recalled by student by using the mnemonic DIAPERS.

Table 2: Transient Causes of Urinary Incontinence

D	Delirium
I	Infection of urinary tract
A	Atrophic senile vaginitis
P	Pharmaceuticals or drug induced
P	Psychological causes like depression
E	Excessive urine output
R	Restricted mobility
S	Stool impaction

Evaluation of urinary incontinence is done by history and physical examination including neurological, rectal and gynaecological examination. Specific tests include cystoscopy, urodynamic studies, cystometry and sphincter electro-myography. Treatment depends on the cause. Many cases are relieved spontaneously. General measures include psychological support, behaviour modification, frequent toileting schedule, provision of bedpans and urinals, urethral sphincter and pelvic floor exercises, bladder training, treating of infections and in extreme cases supra-absorbable pads, pessaries and indwelling catheters. Biofeed training is sometimes resorted too. Pharmacological treatment includes anti-cholinergics and spasmolytics for hyper-reflexive or unstable bladders. Examples are oral imipramine 25 mg twice a day or oxybutyrin 2.5 to 5 mg three times a day or propanthaline. Oestrogens can be useful for atrophic vaginitis.

Menopause, Andropause and Hormone Replacement Therapy

As a short-term consequence of oestrogen deficiency, menopause is accompanied by vasomotor symptoms (hot flushes, sweating), urogenital atrophy (dryness of vagina, dyspareunia, urinary incontinence) and depressive moods while postmenopausal morbidity of coronary heart disease, osteoporosis, dementia and cancers is believed to be due to chronic oestrogen deficiency. Oestrogen or hormone replacement therapy (HRT) should therefore have some benefits. For premenopausal women, 20 µg of ethinyl estradiol plus 1 mg of norethindrone (progestin) daily for 21 days can eliminate vasomotor symptoms and restore regular cyclicity. They also protect against ovarian and endometrial carcinomas and increase the bone density. But, a history of thromboembolism, breast cancer, unexplained vaginal bleeding, smoking and liver disease is contradiction to the use of HRT. In that case, progestin only drugs, e.g. 0.35 mg of norethindrone daily or medroxyprogestrone (Depo-provera injection 150 mg IM every 3 months) can be given even though it does not regularise the cycles.

Although postmenopausal hormone therapy (PHT) is also known to provide benefits for vasomotor, urogenital and psychological symptoms, its long-term use in osteoporosis is no longer preferred due to serious side effects. With regard to colorectal cancer, some risk reduction has been reported with HRT, but its role is doubtful in cognitive decline and dementia. With regard to cardiovascular disease prevention also, role of HRT is of questionable value. In the heart and oestrogen/progesterone replacement study (HERS), not only the fact that 4 years of HRT resulted in no difference in coronary heart disease compared to placebo, but there was, in fact, a 50% increase in the risk of coronary events. Removing or adding of progestin made no difference to the results. Furthermore, results of Women's Health Initiative (WHI) study suggested an early increase in cardiovascular risk on HRT use both in terms of coronary heart disease and stroke.

Definite risks of HRT include endometrial cancer, venous thromboembolism, breast cancer and gall bladder disease. Risk of endometrial cancer goes up with the duration of therapy with unopposed oestrogen treatment. Use of progestogen eliminates this risk of endometrial cancer. Risk of breast cancer also increases with duration of oestrogen treatment and addition of progestin further raises this risk. Risk of thromboembolism is increased both by oestrogen alone and by oestrogen/progestin combination.

Like menopause in females, andropause occurs in males due to decline of androgenic hormone with ageing. Andropause, however, not universal to all men, is a gradual process and is not associated with any sudden event like menopause in females. There is a decrease in testosterone and serum inhibin with an increase in sex hormone binding globulin (SHBG). Apart from fatigue, depression, loss of energy and sex drive, andropausal males have increased risk of cardiovascular problems and osteoporosis. Treatment of andropause is testosterone replacement therapy. Testosterone enanthate can be given intramuscularly every two weeks. Testosterone should not be used for preventive purposes. Prostate and breast cancers, enlarged prostate, liver, kidney and heart disease and diabetes are contraindications for testosterone treatment.

Age-Related Macular Degeneration (AMD)

AMD is the leading cause of painless, slowly progressive visual loss in older persons. The term AMD is used to describe a variety of pigmentary and atrophic changes in the macula associated with the best corrected vision of 6/9 or worse. AMD is bilateral and progressive but its early recognition by routine eye checkups and photocoagulation form the most important strategy. Precise prevalence rates of AMD in our country are not available. In USA, AMD affects 11% of population of 65 to 74 years old and 28% of population over 74 years old. Because the ageing population is rapidly increasing, burden of AMD will increase in India also.

AMD is divided into two types: the dry or non-exudative form and the wet or exudative form, latter being less common, but encountered more frequently and is more responsible for

severe visual loss. Fluorescein angiography, amsler grid and contrast sensitivity are useful investigative methods to evaluate AMD. Treatment for dry AMD is non specific. Antioxidants and sunglasses have been used. Many patients benefit by organ LASER photocoagulation. Recurrences are, however, high after photocoagulation. Recently introduced non-LASERS as the form of photodynamic therapy (PDT) or transpapillary thermo therapy (TTT) are other therapeutic options. Monthly intravitreal injection of leucentis (ranibizumab) or avartin (bevacizumab) significantly retards visual deterioration and improves the vision in AMD cases.

Pressure Sores

These are also known as bed sores or decubitus ulcers. These lesions of skin breakdown occur with significant frequency in those older persons whose body parts are subject to pressure, friction, shearing (two layers of skin slide on each other) and maceration (softening of skin by moisture). Skin, subcutaneous tissue, muscle and even bone and joints can be involved. Risk factors include immobility, inactivity, faecal and urinary incontinence, malnutrition and decreased consciousness. Anaemia, infection, peripheral vascular disease, oedema, diabetes mellitus, stroke, dementia, alcoholism, fractures and malignancies compound the problem. In advanced cases, osteomyelitis may be present. Strategies to prevent bed sores include frequent changing in the patient's position, avoiding head end elevation beyond 30°, using special beds, surfaces like convoluted foam bed, alternating pressure mattresses, water mattresses, air fluidised beds and keeping the skin clean and dry. Treatment of pressure sores involves intensive nursing care. In the later stages, treatment of wound infection and mechanical, surgical or chemical debridement may be done. Irrigating solutions other than normal saline should be avoided. A wet-to-dry dressing is gently packed according to wound size and shape.

HEALTHY AGEING

Curative or tertiary care for numerous acute and chronic geriatric diseases is quite expensive and does not address the issue of maintaining long-term good health related quality of life by cost-effective strategies for disease prevention. Positive health practices of regular physical exercise, healthy diet, no-smoking, vaccinations, periodic checkups and stress management practised over the life course form the basis of healthy ageing and are capable of compressing the duration of period of morbidity in old age. Joint family system, informal support network, social and spiritual enrichment also contribute to healthy happy old age. Timely detection and correction of clinical and socioeconomic impairments and taking corrective measures compliments healthy ageing. Based on standard techniques, a comprehensive geriatric assessment of vision, hearing, locomotion, cognition, nutrition, depression, activities of daily living (ADL), instrumental activities of daily living (IADL), home environment, living arrangements, social and family support, financial dependence, smoking and alcoholism can be carried out by health provider in about 45 minutes.

REHABILITATION AND PHYSICAL THERAPY

Rehabilitation refers to a combination of physiatrist, i.e. physical, occupational and speech therapy, psychiatric counselling; social, and economic rehabilitation. Obviously, a number of experts are needed. In India, vital role of cost-effective community based rehabilitation (CBR) by trained community health worker and cost-effective indigenous assistive devices will be more relevant. Rehabilitation is often needed after prolonged bed rest, e.g. stroke, hip fracture, myocardial infarction, etc. to help regain functional independence and carry out ADL as a useful member of the society once again. Rehabilitation includes various exercises, training in ADLs (bathing, feeding, toileting and transferring) and IADLs (cooking, cleaning, shopping, etc.), treatment of pain and inflammation, etc.

TERMINAL AND RESPITE CARE

More than others, older persons need palliative or terminal care which is a total care of terminally ill patients with untreatable diseases like cancer and Alzheimer's and covers physical aspects like pain and distress as well as psychological, social and spiritual aspects. Terminal care can be offered at home, the hospice and at a general hospital. A hospice is neither a hospital, nor a home but in fact a combination of both where a dedicated team of physician, nurse, social worker and a counsellor provide effective relief through nursing, medical and social care, including bereavement counselling. General hospital settings are largely unsuitable for terminal care as the system is geared towards cure based on short-term stay while the home may be ideal. An important component of terminal care is care of the dying patient. Patient's preferences should dictate the type of care to be provided in bringing about a satisfying end from patient's point of view. A knowledge of law, will, power of attorney, and resuscitation is also important for patient's wishes.

Respite care is temporary supportive care of an older person by a substitute care giver. Respite care is often sought by the original care giver to, relieve the strain of care giving which may prove to be physically, emotionally and financially draining on him and other family members.

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28.2 Sexual Medicine

Prakash Kothari

Sexual disorders are one of the most common disorders of human functioning and deserve attention of almost all physicians regardless of their particular speciality. An overview of sexual disorders is given in this chapter.

DIAGNOSIS OF A SEXUAL DISORDER

For a precise diagnosis of male and female sexual dysfunctions, four cardinal parameters need to be probed in particular along with the routine history of the patient.

Male	***Female***
Desire	Desire
Erection	Lubrication
Penetration	Penetration
Orgasm	Orgasm

These four parameters cover every possible facet of the reported sexual dysfunction and helps quickly in pinpointing the diagnosis. The evaluating method of history taking is precise and effective in a clinical/office set-up. This procedure has already been successfully tried in more than 50,000 patients.

Desire

Sexual desire is an instinctual inclination towards sensual gratification. In other words, it is the readiness to feel erotic. Increase or decrease in sexual desire can be evaluated by considering the information about frequency of sexual thoughts and masturbation or frequency of sexual intercourse. Increase or decrease in desire could be because of psychogenic or organic causes. The common psychological causes leading to decline in sexual desire could be because of depression, schizophrenia, following intake of certain drugs like anti-hypertensives, psychotropics, anti-androgens, cimetidine and certain ayurvedic preparations which contain rauwolfia alkaloids and addictive agents like *ganja*. Sometimes, dislike of partner or partner's behaviour, disturbed interpersonal relationship and fatigue may interfere with an individual's sexual desire. Testes manufacture testosterone and gets metabolised in the liver. Any testicular or hepatic pathology can lead to reduction in desire. Often chronic debilitating illnesses and androgen insensitivity syndrome could contribute to decline in desire.

Desire could increase in mania and in schizophrenia (because of loosening of inhibitions). Often sudden increase in desire could be following frontal lobe brain tumours, head injuries and temporal lobe epilepsy. It may also suddenly increase following intake of alcohol or marijuana.

Erection

It is essential to differentiate psychological erectile dysfunctions from organic erectile dysfunctions. If a man is able to achieve and/or sustain an erection of adequate quality in one situation (i.e. sleep, early morning on full bladder, during masturbation), but unable to achieve the same at the time of coitus; then the problem is situational (psychogenic) and not constitutional (organic). This is the hallmark to differentiate the two varieties of erectile dysfunctions. Psychological erectile dysfunction is characterised by sudden onset and selective nature while in organic erectile dysfunction, the onset is usually gradual and it is non-selective in nature. That means an individual will have erectile dysfunction in all situations and with all partners.

Erectile dysfunction could be primary or secondary. If an individual experiences the erectile dysfunction from the very beginning, it is known as primary and if it is developed later (after normal functioning for a specific period), it is called secondary.

Lubrication

Lubrication is the barometer for female sexual arousal. It is akin to erection in males. Decrease or increase in lubrication may lead to coital discomfort and/or pain. The common causes of inadequate lubrication are lack of adequate foreplay or arousal, local vaginal infections and endocrine imbalance. There could be increase in lubrication because of allergy or increased sexual arousal, often because of unknown aetiology.

Penetration

A man may have adequate sexual desire, stiff erection but would lose his stiffness prior to penetration. This is largely because of anxiety over sexual situation coupled with fear of failure. Sometimes despite the adequate erection and continued sustenance, penetration may not be possible because of inadequate knowledge of female sexual anatomy and sexual positions. Any evidence of pain in the penis at the time of penetration could lead to decline in erection. Often phimosis (pain and/or difficulty in retracting the foreskin over the glans penis) could be the cause. Vaginismus and rarely obstructive vaginal pathology in females could be responsible for a man's inability for successful penetration. Vaginismus is a condition where there is an involuntary spasm (severe contractions) of the outer one-third of the vagina during an attempt, or in anticipation of an attempt of vaginal penetration, thereby making penile penetration impossible. Hence, examination of the female partner is necessary prior to implementing the therapy even in a case of male sexual dysfunction. There are occasions where an individual may lose an erection immediately after penetration. This could be because of anxiety, distraction or a lax vagina leading to inadequate peno-vaginal contact.

Orgasm

Orgasmic disorders have so far been described as ejaculatory disorders in male despite the fact that there is a clear-cut neurophysiological distinction between the two. Orgasm occurs between the two ears whereas ejaculation in men and vaginal contractions in women occur between the two legs. Orgasm in

males is usually followed by ejaculation. However, orgasm can occur without ejaculation and vice-versa. In females, the peak of sexual pleasure, i.e. orgasm is usually accompanied by rhythmatic contractions in the vagina. The feeling of 'enough and nothing more!' is the litmus test to gauge whether a woman has experienced orgasm or not. Orgasm in a male and a female can be best defined as 'an explosive, cerebrally encoded, neuromuscular response, at the peak of sexual arousal by psychobiological stimuli, the pleasurable sensations of which are experienced in association with *dispensable* pelvic physiological concomitants'. Ejaculation in men and vaginal contractions in women is not a must for orgasm.

CLASSIFICATION OF ORGASMIC DISORDERS

Orgasmic disorders can be best classified as early, delayed, impaired (reduced) and absent (inability to experience) orgasmic responses.

Early Orgasmic Response (EOR)

If an individual experiences orgasm earlier than his expectation, which is within the rational limits, is termed as early orgasmic response. EOR is a better terminology than premature ejaculation in males as it does not propagate the myth that ejaculation and orgasm are synonymous and the diagnostic label focuses on exact pathology *per se (Though EOR in women is not described hitherto in the literature, it does exist in the females).*

Delayed Orgasmic Response (DOR)

Here, an individual does experience orgasm, but with a delay. The common causes include reduced arousal, fear, fatigue, anaemia, diabetes and reduced testosterone levels. Sometimes, inadequate penovaginal contact, e.g. lax vagina leading to not so firm grip on penis could be a contributing factor.

Impaired Orgasmic Response (IOR)

This categorises a condition in which there is reduction in the intensity of orgasmic pleasure. This could be psychogenic, due to low testosterone levels and sometimes following drugs like brown sugar and cocaine. Myopathies and neuropathies are known to cause this particular disorder.

Absent Orgasmic Response (AOR)

In this condition, an individual fails to experience orgasmic pleasure in the conscious stage. If there is no evidence of ejaculation including absence of sleep emissions, then this condition may be described as a 'total' AOR. Myopathies and neuropathies are the frequent causes of this particular disorder.

This classification is precise, focuses exactly on the pathology and does not propagate any myths. In addition, the classification has a distinct advantage of male and female parallelism. The classification EOR, DOR, IOR and AOR encompasses all the male and female orgasmic disorders.

Following the orgasm, the ejaculate usually comes out through the urethral meatus in spurts, i.e. antegrade ejaculation. But at times following orgasm, the ejaculate does not come out in antegrade fashion and instead goes backward into the bladder due to bladder neck disturbances, e.g. surgery involving bladder neck, etc. This is known as retrograde ejaculation. Sometimes, there may not be any formation of semen (absent ejaculate) for example in prepubertal boys, elderly individuals with very low serum testosterone and sometimes following long-term use of drugs like carbamazepine. In this situation, the orgasmic ability of an individual remains intact but there is no antegrade or retrograde ejaculation whatsoever. Sometimes, vaginal contractions in females are akin to ejaculatory contractions in males. Majority (but not all) of women may experience vaginal contractions at the time of orgasm.

EXAMINATION AND INVESTIGATIONS

Along with routine physical examination, one needs to check perianal sensations, anal sphincter tone and autonomic nervous system imbalance as and when required. Screening tests like routine blood (to rule out any anaemia), blood sugar fasting and 2 hours after lunch, lipid profile need to be carried out as a routine. Serum testosterone and sex hormone binding globuline (SHBG) may be advised if there is clinical suspicion of testosterone deficiency. Other hormone investigations like prolactin, thyroid may be advised to rule out any underlying pathology.

Other Investigations

Nocturnal penile tumescence rigidity (NPTR) monitoring

NPTR monitoring by Rigiscan can help in determining the rigidity and sustenance of erection. This is a precise and non-invasive test to rule out psychogenic erectile dysfunction or confirm organic erectile dysfunction.

Intrapenile injection

This procedure involves an injection of vasoactive drugs (papaverine combined with chlorpromazine or phentolamine and/or prostaglandin E1) directly into the corpora cavernosa of the penis. The erectile response and the amount of drug that is required to produce erection, gives a clue to the clinician whether the erectile dysfunction is psychogenic or organic.

Doppler examination

This is a non-invasive technique which helps in determining the patency of the superficial and deep blood vessels of the penis and their ability to dilate after an injection of vasoactive drugs.

Penile blood pressure

This is a screening test used for erectile dysfunctions. Penile systolic blood pressure (obtained by using a Doppler probe and tying a special cuff around the penis) divided by the systolic blood pressure of the arm, gives the peno-brachial index (PBI). Abnormal reading may give indication of vascular insufficiency leading to erectile dysfunction.

Infusion cavernosometry and cavernosography

Cavernosometry involves infusion studies with normal saline, helpful in diagnosing venous leaks responsible for inadequate erection. Cavernosography is a graphic study by X-rays of the penis (by injecting contrast medium), which determines the abnormal draining channels responsible for erectile dysfunctions.

Electromyography (EMG)

EMG studies could help to diagnose neurological lesions causing erectile dysfunction, impaired or absent orgasmic response and in conditions like squirtless seminal dribble (emission).

Note: EMG, infusion studies and PBI are not much utilised now.

TREATMENT

In psychosexual dysfunctions, the physician must emphasise the fact that he is treating a relationship and not the individual. The treatment aims at symptom removal which may require adequate blending of supportive psychotherapy coupled with behaviour modification and use of medication, etc. as and when necessary. Clearing of the myths and misconceptions and imparting adequate knowledge of sex and sexuality usually helps undo ignorance and reduce anxiety. However, if there is any evidence of major depression, schizophrenia, disturbed marital relationship and those with rigid defenses need to get their problem sorted out prior to implementing sex therapy.

The starting point for the most sexual dysfunctions would be sensate focus exercises. This includes sensuous interplay by avoiding sexual interaction. Intercourse is forbidden in initial stages, hence the performance anxiety is allayed completely. The couple is immersed in situation of physical intimacy short of intercourse. The initial sessions consist of tactile stimulation without any genital touch. Here, one partner tries to explore the areas with maximum arousal and verbalises his/her feelings, likes and dislikes. Partners are requested to touch each other in a way that helps trigger relaxation and not anxiety. If one is passive during an exercise, and the partner's touch is triggering the anxiety, then one needs to convey the same to the partner. The main thought patterns which contribute to anxiety are spectatoring, racing thoughts and performance thoughts. These exercises help to relieve sexual boredom and gradually increase sexual arousal. Although sexual desire and arousal are not the same, often they do reinforce each other. Enhanced arousal leads to increased sexual desire which in turn leads to more arousal. The main focus is on non-demand interactions. When you are the active partner, caress for your own pleasure. When you are passive, allow yourself to follow the sensations and enjoy them without any anxiety to respond. Initially, the genital touch is prohibited but later genital touching is permitted without demand to produce erection.

Treatment of Male Sexual Disorders

Strategy for psychological erection disorders

- Pleasure without erection
- Pleasure with erection
- Extra vaginal orgasm
- Penetration without orgasm
- Coitus

Some cases of psychological and organic erectile dysfunctions can be helped effectively by medicines like sildenafil citrate (50 to 100 mg). The medicines need to be taken an hour before the anticipated sex act, preferred on empty stomach and one can take maximum of one tablet in 24 hours. The effect usually lasts for 6 to 8 hours. This particular tablet has no role on desire or orgasm, but it helps to enhance the rigidity and sustenance of already achieved partial (semi stiff) erection. This medication is contraindicated in those who are taking nitrates (for heart conditions or hypertension), alpha blocker for prostate problems and those who have retinopathy. The other drug is tadalafil (10 to 20 mg) that has a more lasting effect up to 24 to 36 hours. However, patients reported a shade better quality of erection with sildenafil as compared to tadalafil (**Table 1**).

Table 1: Medicines and Its Side Effects

Generic Name	Sildenafil	Tadalafil*
Availability in milligrams	25/50/100	10/20
Onset of action (minutes)	30 to 45	30 to 45
Duration of action in hours	6 to 8	24 to 36
Interference in absorption with food	Yes	No
Side Effects**		
Headache	+++	++
Visual disturbances	++	
Flushing	++	++
Back pain and myalgia	+	++
Dyspepsia	+++	++
Rhinitis	++	++
Flu-like syndrome	+	++

** May cause dizziness; ** As encountered by the author in his clinical practice*

In those patients, where there is evidence of testosterone deficiency (revealed by clinical and metabolic evaluation), testosterone may be implemented orally or by injection. Intramuscular depot injections of testosterone undecanoate need to be taken once in 3 months. Often these medicines are more effective, once the testosterone deficiency is overcome. In elderly individuals, however, care needs to be taken to do prostate specific antigen investigation and transrectal ultrasonography of prostate prior to implementing testosterone therapy.

The second option could be intra-penile self injection with vasoactive drugs, such as papaverine in combination with chlorpromazine, phentolamine and prostaglandin E1. Prostaglandin E1 can be used alone also. However, 1 out of 3 patients report of pain in the penis following injection of prostaglandin E1. Sometimes the erection achieved by the papaverine injection fails to subside leading to priapism. In such situations, physicians should be aware of the method to relieve the same, failing which a surgeon can help drain the blood from the penis resulting in detumescence of the penis. However, prostaglandin E1 is relatively free from the side effect of priapism, though more expensive and has difficult availability.

If the above procedure fails, one may consider penile implant prosthesis surgery for the erectile dysfunction. Following this surgery, the pleasure at the time of orgasm and the ability to father a child remains unchanged. The types of penile implant surgeries available are listed in the **Table 2**.

Table 2: Types of Penile Implant Surgeries

	Non-Inflatable	Inflatable
Cost	Less	More
Appearance	Always erect	Under your control
Comfort	Less	More
Hardness	Fixed	Adjustable
Device failure	Less	More
Surgery	Less time	More time and skill
Failure rate	Less	More
Types	Flexible	Three-piece
	Malleable	Two-piece
		One-piece

Treatment of Orgasmic Disorders (Male)

Early orgasm (Premature ejaculation)

Many techniques have been used to delay orgasm. The methods commonly used may include doing mental arithmetic during the sex act, applying a local anaesthetic ointment to the glans penis prior to penetration and wearing a condom to decrease sensitivity. Other methods include the following:

- Pelvic muscles exercises
- Interrupting and restarting the flow of urine repeatedly
- Practising *Vajroli mudra* and *Ashwini mudra*
- The 'squeeze or stop-start' technique

The author in his clinical practice found these methods good as adjuncts, but not as a mainstream treatment regime.

Paroxetine (20 mg), or clomipramine (25 mg), to be taken 4 hours and 6 hours, respectively prior to the anticipated sex act help delay climax in most individuals. Sometimes, a combination of paroxetine (10 mg) and clomipramine (10 mg), 6 hours prior to the anticipated sex act has also proved beneficial. Depoxetine (30 to 60 mg), 2 hours prior to coitus can help delay in climaxing in most individuals. This medicine has relatively fewer side effects and found to be more effective.

Delayed orgasm (Retarded ejaculation)

Along with supportive psychotherapy and behaviour modification, enhancing sexual arousal is the main key of the treatment programme. Researchers have observed that diabetes may be the cause of orgasmic/ejaculatory disturbance. However, it seems to impair erectile mechanism much more frequently as compared to orgasmic mechanism. Testosterone deficiency, if present, needs to be treated and may help increase sexual arousal in cases of delayed orgasmic responses. Pubo-coccygeal (PC) muscle exercises may prove to be beneficial. Positions like woman's legs crossed and doggie usually prove beneficial in providing better grip and friction, leading to enhanced sexual arousal culminating in early climax.

Impaired and absent orgasm

Addictive drugs like brown sugar and cocaine are known to cause these dysfunctions. Hence, it is best to remain away from them. PC muscle exercises may prove to be beneficial. Enhanced sexual arousal by any means may prove useful. Vibrating the undersurface of the glans penis by a simple body vibrator can help achieve orgasm/ejaculation.

Treatment of Female Sexual Disorders

Vaginismus

Treatment essentially comprises of supportive psychotherapy, behavioural desensitisation, relaxation exercises and gradual insertion of user friendly vaginal dilators/trainers. Anxiety born out of any myths and misconceptions needs to be cleared. It needs to be emphasised that vagina is highly elastic and is capable of accommodating any size of object, be it a finger for genital examination or head of a baby during delivery. Prognosis in the treatment of vaginismus is excellent. No psychotropic drugs or surgery is required in the course of treatment.

Painful sexual intercourse (Dyspareunia)

Most often, when the woman is not adequately aroused and the man makes an attempt to enter, because of lack of lubrication, it leads to painful penetration at the time of intercourse. Hence, devoting more time to foreplay helps resolve the majority of problems. Local vaginal infection and hormone imbalance could also hamper lubrication. Other less common reasons for persistent pain at the time of intercourse could be because of hymenal and other obstructive vaginal pathology, urethral disorders or congenital malformations of the vulva or vagina. It could also occur following post-operative scars and atrophic vulvo-vaginitis, common in menopausal years.

Orgasmic disorders

Early orgasm in females has not been described hitherto. But this particular disorder needs to be treated in the same manner as one is treating the early orgasmic disorder (premature ejaculation) in males. Delayed/impaired/absent orgasm in females can be best helped by increasing sexual arousal, pelvic floor muscle exercises, modifying the coital position, using a lubricant or substituting necessary diet and/or hormones (if there is a clinical and metabolic evidence of deficiency). Supportive psychotherapy and behaviour modification are of crucial importance.

Lax vagina

This may occur following childbirth. It can be best prevented by proper management of labour with perineal support, an adequate and timely episiotomy and perinatal exercises. A lax vagina can be benefitted by Kegel's exercises. It involves contraction of the perineal muscles—a phenomenon akin to holding the urine and releasing it. Twenty such contractions and relaxations, three times a day, may help increase the muscle tone. If this does not work, one may consider vaginal reconstructive surgery for severe cases.

While treating the sexual disorders, the physician needs to be comfortable with his own sexuality as well as the subject of sexuality. Human understanding, empathy and offering of the adequate sex knowledge are the most powerful remedies, the value of which tends to be neglected in this modern age. Their increased application can obviate the majority of the use of tranquilisers and the so called sex tonics.

RECOMMENDED READINGS

1. Masters & Johnson. *Human Sexual Inadequacy*, USA: Little Brown & Co.
2. Kothari P. *Sex & You*. India, Mumbai: VRP Publishers.

28.3 Sports Medicine

Anant Joshi

Since the beginning of the modern Olympic age, the world of sports and athletic performance has undergone several important transformations. Sports have become professional; it pays to play which makes it mandatory to give your best and for that, fitness is the key.

An offshoot of the corporate culture, recreational athletics (weekend warriors) are on the increase. The overburdened executive, who exercises over weekends to get rid of stress, is often more concerned about his weight, aerobic capacity, strength and this is injury prone than the professional athlete.

Exercise science or the science of exercise is the application of medical sciences to sports to better human performance and the application of sports or exercise as a therapy in the management of disease.

Sports medicine, in the present day sense, has a relatively short history. In 1912, the first official Congress for Sports Medicine was held in Germany. The modern definition of sports medicine was coined in 1958 in Cologne-'Sports Medicine includes those theoretical and practical branches of medicine which investigate the influence of exercise, training and sport on health and disease and study the bad effects of lack of exercise to produce useful results for prevention, therapy, and rehabilitation of the athletes.

SPORTS MEDICINE AS A SPECIALITY

With sports becoming increasingly professional, the athlete needs all possible inputs to improve performance. A top tennis star today moves with his contingent of a personal trainer, a coach, a psychologist and a nutritionist.

Till recently, sports medicine was a hobby of doctors who participated in sports. Today it is a profession and sub-speciality in itself. Departments of exercise science exist in universities offering degree and diploma courses. Olympic federations and national sports team have their own sports testing facilities. Exercise physiologists, physicians, surgeons, psycho- and physio-therapists, trainers are all part of an ever expanding team of sports medical specialists.

ATTRIBUTES (COMPONENTS) OF FITNESS

For the athlete, 'your weight is right for your height' is just not enough.

Sports activities can be divided according to their energy requirements, motor skills requirement and power requirements. Some activities are predominantly aerobic, e.g. long distance running; others are anaerobic, e.g. sprint events; and still others require a combination of both, e.g. middle distance running. Football, rugby, badminton are examples of activities that require alternate aerobic and anaerobic commitment. Power events often demand great acceleration like linear as in shotput and javelin throw, and circular or centrifugal as in discus and hammer throw. Gymnastics and diving are events that require extreme skill, although not by the exclusion of strength or power.

Every sport requires a blend of different fitness attributes. These include aerobic, anaerobic capacities, muscular strength, local muscular aerobic and anaerobic endurance, muscular power, flexibility, speed of reaction and motor correctness.

FUNCTIONAL EVALUATION OF AN ATHLETE

Unlike the usual medical consultation, an athlete needs an evaluation of his strength, flexibility, endurance, power and reaction time. These are parameters that are paramount for better performance rather than staying alive.

The functional evaluation of an athlete is a complex task. It is not just sufficient to know about the functioning of the heart, lungs, nervous system and the peripheral circulatory system, but the functioning of the organism during muscular work of high intensity is also necessary. In addition, the movement and mechanical aspects required of the human machine during specific sports should also be studied. This calls for close co-operation between a physiologist and a biomechanics expert. Some of the parameters investigated during fitness testing of an athlete include cardiac frequency (at rest, during work and during recovery), oxygen consumption in relation to weight, oxygen pulse (VO_2/cardiac frequency), pulmonary ventilation, respiratory quotient and lactic acid estimation. Muscular strength, flexibility, power, endurance, reaction time give an estimate of musculoskeletal and neuromuscular conditioning.

Athletes are tested in a lab setting or 'on the field' environment. Testing a swimmer on a treadmill makes little sense and hence a variety of ergometers have been designed to simulate sports specific actions, the swimming fluke being an example.

'THE ATHLETE'S HEART'

Chronic physiological overload causes an increase in the heart size, as well as increase in the heart's range to perform and is as a result of physiological hypertrophy of the muscle mass (Linzbach) and of regulatory dilatation of both ventricles. This is in opposition to an increased heart size due to disease (myogenic dilatation) resulting from overload (pressure or volume) or primary myocardial damage. During the years of growth, between 14 and 18 years, endurance training results in a particularly rapid increase in heart size. Physicians unaware of the athlete's heart are often responsible for declaring an athlete with a large heart as 'unfit'.

SPORTS THERAPY

Remedial exercises have been used in treating ailments as diverse as osteoarthritis and osteoporosis, to hypertension and coronary artery disease, and to counteract the effects of ageing. Osteoarthritis needs non-load bearing exercises and

osteoporosis just the reverse. Aerobic exercise is used as a 'fat burner' in the management of obesity. 'Endorphins' liberated during exercises act as 'stress busters'.

Obesity not caused by dysfunction of the endocrine system, the main cause seems to be decreased energy output together with excessive energy input. Even with a well-controlled diet it is difficult to lose weight. In order to come up with an exercise programme for an obese individual, it is important to evaluate how healthy the subject is and his or her residual physical capacity. This clinical and instrumental check-up should help the physician assess the cardiovascular, respiratory and musculoskeletal systems and gauge the percentage of body fat that needs to be reduced. It is also important at this stage to know the factors that would limit or hinder the training programme, e.g. presence of arthritis or asthma. A specific and personalised training routine can then be planned. The motivation and general psychological state of the obese patient must be considered to reduce the frequent phenomenon of 'quitting', which is often the basis of failures. Physical reconditioning of the obese must be programmed to improve body fat mass to lean tissue mass, reactivate muscles that have become hypotonic and hypotrophic due to disuse, restore physiological mobility of major joints and recondition cardiovascular and respiratory systems.

The training programme can be divided into three major parts:

First, rhythmic, low frequency and intensity callisthenic type exercises that will improve mobility. Once mobility is achieved, muscular conditioning through anti-gravitational stimulus like lifting light dumbbells or medicine balls.

The second part is aimed at improving the efficiency of the cardiovascular, respiratory and musculoskeletal systems. Exercises are now based on 'movement' and have to be of 'sub-maximal' intensity where heart rate rises to 60% of theoretical maximum heart rate. Workloads should be progressively increased. For the obese, initially, instead of running or walking, cycling or swimming is recommended for weight loss.

'Endurance' sports activities can now be introduced for a sustained weight loss or maintenance programme.

Thirdly, 'balanced training' or 'controlled' exercise is fundamental to fitness and should be designed on a scientific basis. The importance of 'rest' cannot be over emphasised.

Prescribing exercise is an art by itself. The type, intensity, duration and frequency of exercise are quantified. Periodic checks help in monitoring the progress or usefulness of exercise and help in subsequent modifications. Sports therapy is not used in isolation. It supplements other methods of treatment. Exercise can reduce drug dependence and dosage in the management of ailments like diabetes and hypertension.

THE SCIENCE OF TRAINING

Training, a systematic repetition of exercises, aims at achieving a better performance. Science has become increasingly important in the process of training and enables training to be more focused.

General and specific elements of training have to be analysed separately. As an example, let us consider strength as one of the motor characteristics that needs to be developed. Various methods of training contribute to different kinds of muscle strength. Isotonic or dynamic exercise result in lesser increase of strength but its effect lasts longer than the isometric type and it causes less co-ordination disturbances.

Principles of Exercise

Specificity

'You get what you train for', adaptation is specific to a stressor and the affect of a stressor is specific to an individual. The specific adaptation to imposed demand (SAID) principle is the cornerstone of athletic training. Thus, strength training will bring about greater changes in muscular strength than in cardio-respiratory fitness.

Overload

Christensen in 1931 showed that training with a standard workload substantially lowered the heart rate; say 180 to 160 beats per minute. Further training of the same intensity did not modify this heart rate response, but if training was increased in severity, the original work could be completed with a slower heart rate, perhaps down to 140 beats per minute. Progressive increase could be in terms of extent (more km, repetitions) or intensity (more kg, faster runs) or in terms of density (shorter intervals of rest between exercises, repetitions, sets, units 2 to 3 per day) and so on.

Reversibility

'Effects of exercise are not permanent'. Just as regular exercise produces training, subsequent lack of exercise produces 'de-training'. When either intensity, duration, frequency of exercise is reduced, the degree of adaptation brought about by the training load will gradually weaken. Strength losses are faster than mobility losses. Status improvements brought about by 'special' methods over a short term are lost quicker than those brought about by 'slower' methods over a longer term. If a limb is totally immobilised, the losses may be up to 5% per day.

Cross transfer

Some cross transfer effects of exercise do occur. Overloading one area will also put some extra stress on others as well. Although endurance running is not the ideal method for developing leg strength, a runner will have greater leg strength than someone who does not exercise at all.

Repeated overstressing causes progressive fatigue

Physical training is only one of the stressors that bombard the body everyday. Domestic and social life, career studies, institutional demands are all stressors and eventually add up to contributing to a fatigue state.

Science has lent objectivity to training. Recent studies have made it possible to measure the limits of physical adaptability to sports training – maximum muscle power can be increased by 50%; aerobic power by 35% and anaerobic power by 60%.

NUTRITIONAL ASPECTS: FOOD AND FLUID

Dietary manipulations to increase carbohydrate loading are carried out by endurance athletes for increasing muscle glycogen stores two- or three-fold.

While lack of certain foodstuffs may bring about a decrease in functional capacity, or even illness, it has yet to be proved that excessive consumption of foodstuffs will increase functional

capacity. Most people over-estimate their dietary requirements. Overeating causes decreased performance and faster ageing than a well balanced diet.

Seventy per cent of the human body is composed of water, most of which is contained inside cells. Heat and stress cause sweating. When sweating, fluid is drawn from this intracellular supply with resulting adverse effects on cell metabolism. Fluid loss becomes apparent when 1% to 2% of the body weight has been lost as sweat. When fluid loss amounts to 4% to 5% of the body weight the capacity for physical hard work is reduced by nearly 50%. During exercise in a hot environment, water loss can be considerable and can amount to 5 litre or more per hour.

To maintain physical efficiency, fluid replenishment is necessary. Cooler fluids (25 to 30°C) are absorbed better than hot ones. Presence of glucose and other sugars retards this absorption. Up to 60% to 70% of a 400 mL draft of water leaves the stomach in 15 minutes while only 5% of a drink containing 10% sucrose leaves in the same time. For rapid absorptions, drinks should not contain more than 2.5% of carbohydrates.

It is well known that sweat contains electrolytes in addition to water. However, the concentration of sodium and chloride in sweat is only about one-third that of plasma, so that relatively more water is lost than salt and sweating leaves body fluids more concentrated. Costill has suggested that electrolytes be replaced after exercise by drinking a glass of orange or tomato juice and by adding a little more salt to diet.

Taking into account fluid absorption and stomach emptying times, it has been recommended that fluid replacement should be done by the athlete during less intense periods of exercise and less concentrated solutions should be drunk at more frequent intervals. The sensation of thirst is not an accurate guide when it comes to replacing fluid loss by sweat. Slaking one's thirst generally provides only half the amount of fluid required. Anyone who indulges in strenuous physical activity is advised to drink considerably more than he thinks he needs.

SPORTS INJURIES

The only time the human body is called upon to surpass itself deliberately is during sports. An athlete gives 'his heart out', exercisers 'go all out', and in trying to overcome the physical, physiological and psychological limits, injuries do occur.

A wide spectrum of sports injuries are seen from niggling sprains and career-threatening ligamentous tears to life-threatening dislocations.

Injury frequency has increased drastically with the development of professional and recreational sports activities. Speculations have been made about possible factors that may influence the occurrence of such injuries. Today's athletes have increased the intensity and duration of training and that too in unfavourable environmental conditions. Exercising in groups where the fit and the unfit are clubbed together, like in an aerobics class, results in the uninitiated individual doing more than what the body can take.

Sports injuries may be acute or chronic, 'extrinsic' or 'intrinsic'. Extrinsic injuries are those caused by faulty surfaces, shoes, protective gear, sports apparatus or apparel and environmental factors. Intrinsic injuries which account for a majority of sports injuries are a result of faults in body conditioning (through training) or technical errors (poor sports technique).

Orthopaedic surgeons who are trained to tackle bones and joints are often inadequately exposed to soft tissue musculoskeletal injuries. Muscle injuries which by far account for most sports injuries are thus often underdiagnosed, missed and mistreated. Shin splints and tennis elbows are poorly understood and treated. A tennis elbow may be caused by faulty technique—using the wrist, elbow in front of the body or wrong grip size or just heavy balls. Treating all tennis elbows by pain relieving medication or a steroid injection without analysing the cause would be foolhardy.

OVERUSE INJURIES

A category of injury peculiar to the athlete is an overuse injury. Athletes often overuse and abuse their bodies due to the misconception amongst athletes and coaches that more is better.

Overuse injuries do not immediately cripple the athlete. Repetitive exposure of tissue to low magnitude forces results in injury at the microscopic level. Repeated overload as in running or jumping are often associated with overload injuries to the lower extremity. In the running gait, a force in the range of 3 to 5 times the body weight ascends up the lower extremity at heel strike. This force behaves like a sound wave with a short duration (20 to 40 ms) with rapid dissipation. Considering an impact of 250% of the body-weight, a runner absorbs at ground contact 110 tons on each foot per mile. The forces for longer distances can be imagined, considering that a long distance runner who runs 100 miles per week plants each foot about 3 million times a year. Factors predisposing to overuse injuries can be intrinsic or extrinsic. Intrinsic causes would include malalignment (pronated feet, femoral anteversion), leg length discrepancy, muscular imbalances. Poor training methods (exercising to the point of pain), hill work, sloping or hard surfaces are extrinsic factors that can predispose to injury. Although the muscle tendon unit is the most commonly affected structure, even bone is not immune to overuse injury.

Treatment

Overuse injuries are treated by rest, relief of local inflammation, and the gradual reintroduction of controlled and protected activity. If the recurrence is to be prevented, it is also important to ensure that the future training load is controlled more carefully and adjusted more gradually. For example, changes from endurance running to sprinting, or from road to track, must be gradual. Shoes should be examined for the adequacy or arch support and heel-cushioning. The squash racket's handle should be thickened to prevent further strains of the common extensor origin. The swimmer's arm action should be analysed to reduce impingement of rotator cuff tendons on the coracoacromial arch. The road runner should be advised to interpose the occasional run on grass.

DIRECT SOFT TISSUE TRAUMA

Many sports put the participants at risk of direct trauma to muscle, tendon, ligament, and subcutaneous tissues by contact with the ground, the opponent, a ball or an opponent's bat. Strict enforcement of the rules, a properly prepared playing surface, and tuition in the skills of the sport will prevent some of these injuries but they can never be avoided completely.

Acute Treatment

Much of the pain and disability resulting from soft-tissue trauma is not due to the injury itself but to bleeding in and around the damaged tissues. Extravasated blood causes pain and limitation of movement at first by a space-occupying effect, then by causing local inflammation. Later, rehabilitation is hindered by fibrotic adhesions. Acute management concentrates on preventing this sequence of events.

The prevention of bleeding depends on ice compression, and elevation (mnemonic 'ICE'). The local application of cold for 10 to 20 minutes will induce vasoconstriction and has the added benefit of relieving pain. Venous hydrostatic pressure at the site of injury is reduced by elevation of the injured limb for 2 to 24 hours. Extravasation of blood is limited by a compression bandage applied immediately after the ice is removed, and maintained for 2 to 24 hours. Elevation is not only the simplest of the three measures to implement, it is probably also the most important and the most neglected.

Recovery is faster if a nonsteroidal anti-inflammatory agent is administered, in full dosage, for 3 to 5 days after soft-tissue injury. Prompt orthopaedic advice should be obtained.

Rehabilitation

Absolute rest is usually inappropriate after the first 24 hours. Selective, graded and protected activity is preferred to immobilisation. Before return to competition can be permitted, balance and co-ordination skills must be relearned.

STRESS FRACTURES

The repeated application of stress to a bone may result in a 'fatigue' or 'stress', fracture. The most common sites are the tibia, the distal fibula, and second and third metatarsals. Femoral stress fractures are also seen. There is no history of acute trauma; there need not be any pain at rest. Initial radiographs may appear normal, and later may show callus formation. Radioisotope bone scan may be necessary to confirm the diagnosis. A simple bedside test is the sharp pain produced by insinuation of the suspect of the area of bone with a physiotherapist's ultrasound applicator.

Treatment

Aims of treatment are to avoid complete fracture and allow the bone to heal. This requires temporary abstinence from the sport. Weight bearing should be avoided if it is painful. Strength and endurance should be maintained by isometric exercises and by a change of activity like cycling or swimming (for metatarsal or fibular fracture).

FRICTION SYNDROME

Local inflammatory response to overuse may be evident with pain, swelling, discolouration, warmth, and palpable crepitations. Examination may reveal nothing. Re-examination immediately after a provocation test may be helpful.

Treatment

Nonsteroidal anti-inflammatory drugs, 1 to 2 weeks of relative rest, stretching, isometric exercises and gradual resumption of activity, are advocated. Local injection of steroids may be helpful, if the above measures fail. Surgical decompression is occasionally required.

SUDDEN CARDIAC DEATH

Sudden cardiac death during sports tends to attract the attention of the press but is in fact very rare. Although vigorous physical activity carries a transiently increased risk of sudden cardiac death, this is greatest in those who are habitually least active and are overweight than in those who are most active.

Prevention

Exercise electrocardiography has been advocated as a screening procedure for all middle age sportsmen. However, it is not a prerequisite for exercise training unless there are symptoms suggestive of myocardial ischaemia, strongly positive risk factors for coronary disease, a family history of premature sudden death or dysrhythmias, or a personal history of exercised-induced syncope. Instead, anyone unaccustomed to vigorous exercise should be taught that its intensity should be at first modest and should increase gradually. The exercising person should also be taught to recognise symptoms of underlying cardiac disease and seek medical advice.

TRAUMA AND VIRAL INFECTIONS

Herpes simplex virus infection may occur due to abrasive contact during sport, especially between wrestlers or between rugby front-row forwards. Hepatitis B and HIV infection may occur as a result of contact of one player's blood with another player's broken skin. This may be seen in wrestling, rugby, judo and boxing.

OTHER EXERCISE-INDUCED ABNORMALITIES

These are amenorrhoea, iron deficiency anaemia and rhabdomyolysis.

28.4 Diet in Medical Diseases

Siddharth N Shah

Significant advances in the area of clinical nutrition have occurred in the last decade. Healthcare professionals and the patients have appreciated the role of nutrition in promoting optimal health. This nutrition awareness has created the need for more and precise information on all aspects of nutrition and clinical dietetics related to patient care. This chapter primarily conveys information concerning the role of diet in few diseases and also gives diet plans for the same. The general principles of diet therapy are listed in **Table 1**. However, it is recommended that each patient must be assessed individually and a diet plan formulated considering his/her nutritional status, associated illnesses and various deficiencies that need to be corrected.

Table 1: Guidelines to Good Dietetic Therapy

Reach and maintain ideal body weight
Be careful of serving sizes
Avoid skipping meals
Increase your daily activity
Preserve lean body mass

DEVELOPING A NUTRITION PLAN

Diet is the cornerstone in management of various diseases. To lose weight, for heart diseases or for diabetes, a few small changes in eating habits can make a big difference. Healthy eating does not have to be monotonous. The easiest approach to improve eating habits is to use the food pyramid as a guide (**Figure 1**).

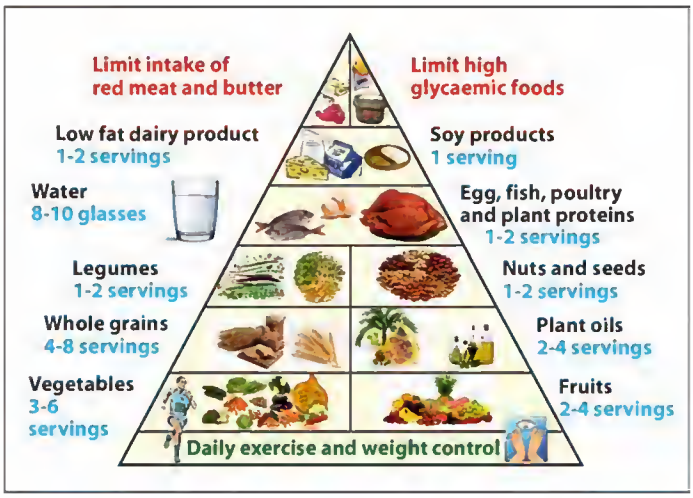


Figure 1: The food pyramid. Each section of the pyramid is a food group. The smaller the section, the less of that type of food one should eat.

OBESITY

Obesity is a predisposing factor for various complications like atherosclerosis, diabetes mellitus, arthritis and high blood pressure. A diet low in calories and fat, and high in fibre is recommended. It is designed to provide less than the required energy by the body and use up the fat stores of the body, especially with a structured exercise programme, which is a balance of energy intake versus energy expenditure.

Dietary Guidelines for Obese Patients

- Set realistic short-term and long-term goals.
- Avoid fasting or feasting/skipping any meals.
- Always eat breakfast with good choice of cereals.
- Do not eat in between the meals. Have low calorie/high volume food items.
- Avoid ready to eat food items, concentrated food items like sweets, fried items, etc.
- Do not sleep immediately after eating.
- Do not eat while watching television, opening refrigerator, cooking, serving or reading.
- Thoroughly chew each and every morsel of food, remembering that it takes around 20 mins to realise satiety.
- Avoid alcohol and follow dietary recommendations.
- Physical exercise is a must to burn away, excessive fat.

Principles of Diet

Energy

A low calorie balanced diet providing atleast 1,200 Kcal/day is considered safest and most effective for weight loss in majority of obese patients. Energy restriction below 800 to 1,000 Kcal/day is not recommended as it may lead to deficiencies of other nutrients and also the body goes in a negative feedback of conserving energy (reducing BMR). A triad of a calorie restricted balanced diet, increased physical activity and control of associated illness and various deficiencies goes a long way to achieve and maintain weight loss. Unrealistic/very low calorie/starvation diets may lead to yo-yo syndromes, gallstones, etc.

Protein

A normal intake of 1 g/kg ideal body weight (IBW) is recommended for tissue repair.

Fats

Fats in the diet should be restricted as they are concentrated sources of energy. Both visible and invisible fats should be restricted in the diet. A minimum level of 15 to 20 g visible fat should be maintained in the diet, to provide palatability and essential fatty acid requirement.

Carbohydrates

Simple carbohydrates should be avoided. Potatoes, sweet potatoes, yam, banana, rice should be used prudently. A diet high in fibre provides satiety and long-term compliance.

Vitamins and minerals

Multivitamin and mineral supplements may be advised because calorie-restricted diets may be inadequate in some nutrients. Extra salt in the diet causes retention of water in the body. Thus moderate salt restriction is helpful.

Water

Water is allowed in liberal quantity. Fluids like thin buttermilk, dal water, unstrained soups, sugar free lime-water provide variety in the fluid and also fill-up the stomach; thereby reducing subsequent meal intake.

Fibre

High fibre foods like green leafy vegetables and fruits can be included in the diet freely in the form of thoroughly washed vegetable salads (raw or boiled), unstrained-unseasoned soups. These foods give a sense of satiety and regulate bowel movements too.

Food exchanges

A food exchange is a grouping of food items which are of approximately similar nutritive value; so as to enable one to plan and select meals with ease and convenience and also provide variety.

Cereals

Each of these provides 100 Kcal.

Two medium size dry chapatti = 1 cup roasted/plain rice flakes = 1 cup cooked rice = 1 cup rawa upma = 1 bread slice (large).

One can have around 7 to 10 exchanges or servings daily, depending upon the requirement.

Pulses and legumes

Each of these provides 100 Kcal.

Two cups thin dal = 1 cup thick dal = ¾ cup cooked pulses = 1 big cup sambhar.

One can have 2 to 3 exchanges each day.

Nuts and oilseeds

Each of these provides 100 Kcal. Three-fourth cup grated fresh coconut = 1 handful of groundnuts/cashew nuts/sesame seeds/almonds.

Vegetables

Each of these provides 25 to 30 Kcal

Veg. A: 1 big cup of dark green leafy vegetables.

Veg. B: three-fourth cup of any other vegetables like brinjal, beans, ladies finger.

Veg. C: half cup root vegetables like potato, beet root, yam, sweet potato, etc.

One can have 2 to 3 servings each day, depending on whether one is on a calorie diet and/or carbohydrate enriched/restricted diet plan.

Fruits

One fresh medium sized citrus fruit/half pulpy fruit supplies roughly 50 Kcals.

One can have 2 to 3 exchanges each day. Fruits are best eaten as a mid-morning or a mid-evening snack rather than along with the meals.

Milk and milk products

Each of these gives 100 Kcal.

One-cup cow's milk/3/4th cup buffalos milk/1-cup curds/8 medium sized pieces of paneer, made from cow's milk.

One can have 2 or more exchanges each day.

Fat

Each of these gives 90 Kcal.

Two tsp of oil/ghee/vanaspati/3 tsp of butter.

One can have 2 to 3 exchanges each day.

Sugar

Each of these gives 100 Kcal.

Five tsp of sugar/jaggery/2 tsp of honey.

One can have 1 to 2 exchanges each day.

Meat

Each of these provides 85 Kcal.

One serving of meat/fish/poultry = ½ cup cooked curry/1 egg (boiled).

Vegetarians may substitute meat exchange with an extra exchange of pulse or milk.

One can have 1 exchange each day.

Free foods

Black-coffee/tea, plain sodas, unsweetened lime juice, clear soups, thin buttermilk made from double skimmed milk curds, masala (without coconut or oil base), ginger, vinegar, gelatine (unsweetened), coriander, mint, garlic, mustard, bay leaf, cinnamon, nutmeg, pepper.

A prudent diet, structured exercise programme (to preserve the lean body mass), a positive attitude, a determination to improve quality of life (QOL) remains the cornerstone of any diet programme. Weight loss programme can majorly (with the exception of genetic/physiologic causes) be termed as 'lifestyle modification programme'.

DIABETES MELLITUS

Diabetic diets need not a complete deviation from the normal diet. A traditional Indian diet can be made suitable for diabetics with few modifications in the nutrient intake based on age, sex, weight and physical activity. The diet is designed to improve blood glucose and lipid levels, encourage healthy eating patterns, promote consistent food intake and avoid undue starvation or overeating, thereby improving quality of life. In many ways, it is similar to a weight loss diet.

Principles of Diet

Energy

The calculated calorie requirement should allow the patient to achieve and maintain ideal body weight (IBW) and the desired waist-hip ratio (WHR). The total calorie requirement is calculated based on the level of physical activity and an individual's actual weight. Based on body weight, the following guidelines can be used for calculating the energy requirement of diabetic patients.

For overweight person – 20 Kcal/kg/day IBW

For ideal weight person – 25 to 30 Kcal/kg IBW

For underweight person – 40 Kcal/kg/day IBW

For pregnant diabetic woman – 30 to 35 Kcal/kg/day IBW

The total daily intake of calories from the various macronutrients can be distributed as shown.

Distribution of calories

Carbohydrates should constitute 60% to 65% of total calories, proteins and fats 15% to 20% each.

These can further be divided into meals, which can be small frequent meals, avoiding the load on pancreas and stimulating it to produce insulin in regular doses and intervals, or it can be modified to the lifestyle of the patient.

Carbohydrates

An Indian diet predominates in this nutrient. Diabetics need not restrict carbohydrates. Simply modifying the type of carbohydrates in the diet will help achieve euglycaemia. Simple carbohydrates obtained from honey, sugar, jaggery, sugarcane, jam, glucose, etc. are readily absorbed and are to be avoided completely. Complex carbohydrates, such as cereals, whole grains, dals, pulses, sprouts, fruits and vegetables do not raise blood sugar quickly. Glycaemic index (GI) and glycaemic load (GL) both should be taken into consideration.

Proteins

The recommended dietary allowance (RDA) for protein is 1 gm/kg IBW. Pregnant women, lactating women and children require more protein compared to an adult in order to meet their physiological needs. Skimmed milk and milk products (except cream, butter), dals and pulses, nuts, oilseeds, fish, egg, poultry and meat are rich sources of protein. Cereals are fair sources of protein. For Type 1 diabetic children 1 to 1.5 gm protein/kg IBW is recommended. 'Lente' carbohydrate provides a good quality protein in addition to complex carbohydrate.

Fats

Fats are concentrated source of energy. Excess of fat in the diet increases the risk of obesity, and the process of atherosclerosis. Visible fats like ghee, butter, vanaspati contain a high proportion of saturated fats, which tend to increase serum cholesterol levels. Vegetable fats, such as sunflower oil, safflower oil, and corn oil contain a high proportion of polyunsaturated fatty acids (PUFA), which are helpful for controlling cholesterol levels. Some amount of n_3 to n_6 ratio of fat that is derived from milk and milk products, egg, flesh foods, nuts and oilseeds are known as invisible fats. A diabetic diet should provide both visible and invisible fat in limited quantities. A diabetic patient can take 15 to 20 gm visible fat per day to meet EFA requirement and maintain palatability of the diet.

Vitamins and minerals

They both are essential for the body. Cereals, pulses, dals, milk, dark green leafy vegetables, fresh fruits, egg and fish are common sources of these nutrients.

Fibre

Dietary fibre is beneficial in Type 2 DM as well as Type 1 DM. Fibre present in vegetables, certain fruits, legumes and fenugreek seeds (methi seeds) are soluble in nature and is effective in controlling blood sugar and serum lipid levels. Insoluble fibre present in cereals and millets like ragi, jowar and bajra provides bulk and roughage inducing satiety and improves long-term blood glucose tolerance.

Diet Plans

The diet plan is given in the **Table 2**.

The Glycaemic Index and Glycaemic Load

The glycaemic index (GI) is a numerical system of measuring how fast a carbohydrate triggers a rise in circulating blood sugar. Foods are tested and compared to the standard food glucose. The GI of glucose and white bread is set at 100.

$$GI = \frac{\text{Blood glucose area of test food}}{\text{Blood glucose area of reference food}} \times 100$$

A list of carbohydrates with their glycaemic values is shown below. A GI of 70 or more is high, a GI of 56 to 69 inclusive is medium, and a GI of 55 or less is low.

Food	Glycaemic index (GI)
Simple sugars	
Glucose	85 to 111
Honey	32 to 87
Sucrose	55 to 68
Fructose	12 to 25
Cereal products	
Whole wheat	67
Oat bran	42 to 75
White bread	67 to 87
Whole wheat bread	52 to 87
Corn flakes	80
Macaroni	64
Rolled oats	66
Puffed rice	132
Puffed wheat	110
White rice	50 to 64
Brown rice	66 to 87
Pulses	
Soya bean	15 to 20
Green peas, dried	39 to 54
Vegetables	
Sweet potato	44 to 78
Yam	74
Potato	74 to 97
Corn	37 to 62
Fruits	
Apple	39
Orange	35 to 51
Banana	46 to 70
Grapes	25
Raisins	56 to 60
Milk and milk products	
Ice cream	52
Yoghurt	14 to 23
Whole milk	11 to 40
Skim milk	32

The glycaemic load (GL), is a relatively new way to assess the impact of carbohydrate consumption. A GI value tells you only how rapidly a particular carbohydrate turns into sugar. It does not tell you how much of that carbohydrate is in

Table 2: Diet Plan in Diabetes Mellitus

Meals	1,400 Kcal	1,600 Kcal	1,800 Kcal	2,000 Kcal
Breakfast	1-cup tea with ½ cup skimmed milk (no sugar). 1 slice of whole wheat bread (without butter or cheese) (preferably in the form of a sandwich) *or* 2 dry phulkas *or* 2 dry khakhras *or* 2 idlis (without coconut chutney) *or* 1 cup cooked vegetable upma/ roasted rice flake chiwda/sundal.	1-cup tea with ½ cup skimmed milk (no sugar). 2 slices of whole wheat bread (without butter or cheese) (preferably in the form of a sandwich) *or* 2 dry phulkas *or* 2 dry khakhras *or* 2 idlis (without coconut chutney) *or* 1 cup cooked vegetable upma/ roasted rice flake chiwda/sundal.	1-cup tea with ½ cup skimmed milk (no sugar). 3 slices of whole wheat bread (without butter or cheese) (preferably in the form of a sandwich) *or* 3 dry phulkas *or* 3 dry khakhras *or* 3 idlis with ½ cup sambhar (without coconut chutney) *or* 1 cup unsweetened corn flakes *or* 2 dosas (made on a non-stick pan) with rasam *or* 1 cup cooked vegetable upma/sundal.	1-cup tea with ½ cup milk (no sugar). 3 slices of whole wheat bread (without butter or cheese) (preferably in the form of a sandwich) *or* 3 dry phulkas *or* 3 dry khakhras *or* 3 idlis with ½ cup sambhar (without coconut chutney) *or* 1½ cup unsweetened corn flakes *or* 2 dosas (made on a non-stick pan) with rasam *or* 1½ cup cooked vegetable upma/sundal.
Mid-morning	—	1-cup plain skimmed milk.	1-cup plain skimmed milk.	1-cup plain skimmed milk.
Lunch	1 bowl thoroughly washed raw vegetable salad/unseasoned vegetable soup 2 phulkas (without ghee).	1 bowl thoroughly washed raw vegetable salad/unseasoned vegetable soup 2 phulkas (without ghee). ½ cup cooked rice.	1 bowl thoroughly washed raw vegetable salad/unseasoned vegetable soup 3 phulkas (without ghee) ½ cup cooked rice.	1 bowl thoroughly washed raw vegetable salad/unseasoned vegetable soup 3 phulkas (without ghee) ½ cup cooked rice.
	¾ cup dal or 1 cup sambhar or ½ cup lean non-veg (non-fried, without skin) curry or ½ cup sundal. ½ cup cooked vegetables. ½ cup skimmed milk curds. Restrict use of coconut/peanuts, sugar, jaggery, and fried non-veg.	¾ cup dal or 1 cup sambhar or ½ cup lean non-veg (non-fried, without skin) curry or ½ cup sundal. ½ cup cooked vegetables. ½ cup skimmed milk curds. Restrict use of coconut/peanuts, sugar, jaggery, and fried non-veg.	¾ cup dal or 1 cup sambhar or ½ cup lean non-veg (non-fried, without skin) curry or ½ cup sundal. ½ cup cooked vegetables. ½ cup skimmed milk curds. Restrict use of coconut/peanuts, sugar, jaggery, and fried non-veg.	¾ cup dal or 1 cup sambhar or ½ cup lean non-veg (non-fried, without skin) curry or ½ cup sundal. ½ cup cooked vegetables. ½ cup skimmed milk curds. Restrict use of coconut/peanuts, sugar, jaggery, and fried non-veg.
Evening	1-cup tea with ½ cup skimmed milk (no sugar). 1 cup roasted rice puffs (no sev or puri) or 2 Marie biscuits.	1-cup tea with ½ cup skimmed milk (no sugar). 1 plain whole wheat bread (no butter or cheese) or ¾ cup roasted rice flakes (no nuts) or 1 cup roasted rice puffs or 4 Marie biscuits.	Same as breakfast (type and quantity)	Same as breakfast (type and quantity)
Dinner	Same quantity as lunch.	Same quantity as lunch.	Same quantity as lunch.	Same quantity as lunch.
Bed-time	1 medium fruit (except banana, chickoo, mango, custard apple).	1 medium fruit. (except banana, chickoo, mango, custard apple).	1-cup plain skimmed milk or 1 medium fruit (except banana, chickoo, mango, custard apple).	1-cup plain skimmed milk and 1 medium fruit (except banana, chickoo, mango, custard apple).
	Total oil for the days cooking 2 to 3 tsp.	Total oil for the days cooking 2 to 3 tsp.	Total oil for the days cooking 4 tsp.	Total oil allowance for the days cooking 4 tsp.

a serving of a particular food. The amount of available carbohydrate in a specific food serving multiplied by the GI value is called the glycaemic load (GL) value of the food. You need to know both things to understand a food's effect on blood sugar.

The carbohydrate in watermelon, for example, has a high GI. But there is not a lot of it, so watermelon's glycaemic load is relatively low.

A GL of 20 or more is high, a GL of 11 to 19 inclusive is medium, and a GL of 10 or less is low.

GOUT

A diet low in fat and purine is advised to decrease elevated blood uric acid levels. Before imposing dietary restriction, factors inhibiting the excretion of the accumulated uric acid should be excluded, e.g. presence of alcohol, excess tannins, fat. A thorough assessment of the diet by a registered dietician/ medical nutrition therapist will help in estimating the sources of purine in patient. Increased amounts of fluid will help excrete the accumulated uric acids.

Energy

It should be adjusted to 500 Kcal below the normal requirement for overweight/obese patients. Care should however be taken to avoid very low calorie diets (VLCD). Exercise helps weight reduction. However, strenuous exercise (weight bearing) should be avoided. Similarly, fasting/low carbohydrates should be avoided as it precipitates a gouty attack due to ketosis.

Carbohydrates

Liberal use of fruits and vegetables is recommended. Use of soluble fibre is particularly helpful.

Protein

Organ meats and legumes are best avoided due to their high purine content. Skimmed milk and its products should be used liberally to meet the protein requirements.

Fats

A low fat diet will promote weight reduction and relieve symptoms of gout by facilitating urinary excretion of accumulated uric acid.

Alcohol

Alcohol consumption should be completely avoided as it may inhibit urinary excretion of urates.

Fluid

Liberal fluid intake in the form of thin buttermilk, vegetable soups, etc. will facilitate urinary excretion of accumulated uric acid and also prevent formation of calculi. However, avoid cold drinks, carbonated beverages, large amounts/strong decoctions of tea and coffee.

Table 3 shows list of foods moderate to high in purine.

Table 3: List of Foods Moderate to High in Purine

Liver, kidney, shell fish, meat extracts – meat gravies, shrimp, sardine, soups with meat stock, chicken, ham, tuna fish, mushroom, mutton, crab, oyster, lobster
Whole milk, cream, ice cream, cheese
Sweetbread, bakers and brewer's yeast
Lentil, pulses
Cauliflower, peas, spinach, mushrooms, brinjal and sometimes cabbage
Chickoo and custard apple

PEPTIC ULCER

The diet for chronic peptic ulcer disease is designed to restrict foods or beverages that may cause gastric irritation and/or stimulate excessive gastric acid secretion. General recommendations for the diet are given in Table 4.

Table 4: General Recommendations for the Diet in Peptic Ulcer

Eat balanced meals in a day in a relaxed mood
Avoid too hot or too cold foods
Avoid spicy and strongly flavoured foods
Avoid alcohol, caffeine containing beverages, cigarette smoking and tobacco chewing, spearmints and peppermints
Good physical and emotional rest is essential
Avoid fried foods

Principles of Diet

Energy

Energy of 35 to 40 Kcals/kg is recommended, as these patients are generally malnourished due to the 'so called' dietary restriction. Malnutrition affects the rapidly dividing cells of the GIT and could affect healing.

Proteins

Proteins have a buffering effect. Milk proteins are considered better compared to non-vegetarian foods as they do not irritate gastric mucosa or stimulate acid secretion. A good amount of protein in the range of 1.2 gm/kg IBW should be provided.

Carbohydrates

Adequate amounts of simple carbohydrates should be given. Avoid food items with fibres. Soluble fibres should be encouraged to meet the daily fibre requirements.

Fats

Fats delay gastric emptying and also help in meeting the caloric requirement. Fats from fried snacks and sweets may be avoided, as they are difficult to digest, may cause nausea and aggravate the symptoms.

Vitamins and minerals

Deficiency may occur with self-imposed limitation of green leafy vegetables and other foods. Adequate vitamin C and iron is necessary for proper healing of ulcer.

Fibre

Fibrous foods, such as raw vegetables, leafy vegetables, fruits (with peel), irritate mucosal lining. Thus only soft cooked vegetables and fruits are allowed during flare-ups.

pH of food

Most foods are considerably less acidic than the inherent gastric pH. Therefore pH of a food prior to ingestion has little therapeutic implication except for patients with lesions of mouth/oesophagus.

Alcohol

Alcohol consumption causes mucosal lining damage and may worsen existing disease/interfere with the treatment of peptic ulcer.

Miscellaneous

Stimulants, e.g. coffee, caffeine, spices, stimulate acid secretion and may also reduce lower oesophageal sphincter pressure. Some bland diet may do well in acute flare-up.

Aroma of cooked foods also stimulates acid secretion. Thus cooked food should be bland in taste and flavour. Spices, condiments, pickles, vinegar, chillies, garlic and onions are not permitted in the diet.

LIVER DISEASES

The diet advised must provide adequate calories and essential nutrients, including essential amino acids to prevent malnutrition and extensive liver damage.

Diet in Infective Hepatitis

A high protein, high carbohydrate, moderate fat diet is recommended.

Carbohydrates

Simple carbohydrates given in large quantities improve liver function by building adequate hepatic glycogen stores and prevent endogenous protein breakdown by their protein-sparing effect.

Protein

High protein diet helps to regenerate liver cells. 1.0 to 1.2 gms/day is allowed in mild jaundice. Proteins may be restricted in decompensated liver disease and in case of increased conjugated bilirubin.

Fats

Fats make food palatable and also help to meet the essential fatty acid requirements. Fried foods may cause nausea.

Vitamins and minerals

Supplementation may be necessary to prevent imbalances.

Miscellaneous

Alcohol should be avoided, as it is directly hepatotoxic.

Utmost hygienic condition should be observed in preparing and handling food.

Cirrhosis of Liver

It is important to consider the dry body weight of patient while calculating nutrient requirements.

A high carbohydrate diet, moderate to high proteins (1.0 to 1.2 gm/kg dry body weight) carefully watching for signs of hepatic encephalopathy, moderate fats with supplementation of vitamins and minerals is recommended.

HYPERTENSION

Principles of diet are same as in healthy adult except for sodium restriction. An average Indian diet contains 10 to 15 gm of salt. Salt should be restricted to 4 to 5 gm/day as per follows:

Guidelines for a Low Salt Diet

Avoid using salt at the table. Do not add salt in chapatti, rice, curd, and salads. The diet can be made palatable by judicious use of garlic, ginger, mint, lemon, vinegar, jeera powder, mustard and black pepper. Low sodium salts are high in potassium and may be beneficial but should be used carefully in patients with an underlying renal problem.

List of Foods High in Sodium

Dairy products: butter, cheese, ice creams, etc.

Ready to eat food items: canned foods, sauces, chutneys, ketchup, papad, pickles, salad dressings, mayonnaise, etc.

Fried foods: chips, wafers, sev, chiwda and other fried snacks.

Bakery products: salted biscuits, cakes, pastries, bread rolls, and khari biscuits

Non-veg items: shellfish, dry fish, fried non-veg, non-veg gravies and organ meats.

Baking powder, Ajinomoto.

Salt restriction may not be compulsory for the patients receiving diuretic therapy.

DASH diets (Dietary Approaches to Stop Hypertension) recommend the use of 5 to 7 servings of fruits and vegetables and helps by providing roughage, vitamins, minerals, and anti-oxidants.

ISCHAEMIC HEART DISEASE

Principles of Diet

Carbohydrates

Simple carbohydrates should be avoided as they contribute towards endogenous production of cholesterol and triglycerides.

Energy

Weight reduction/achieving IBW with a low calorie diet helps to relieve the extra burden on heart.

Proteins

A normal intake of 1 to 1.2 gm/kg IBW is suggested. Animal proteins should be best avoided/used judiciously with restrictions due to their high cholesterol content.

Fats

Fat content should be restricted to lower the serum cholesterol levels. A vegetarian diet is helpful as it is low in fat, cholesterol and high in fibre.

Rich sources of cholesterol

Butter, cheese, cream, ghee, egg yolk, liver, red meats.

Poor sources of cholesterol

Egg white, fish, lean cuts of chicken, skimmed milk, cottage cheese (prepared from skimmed milk), vegetable oils, fruits, vegetables, whole grains.

Role of PUFA have been identified in prevention of heart disease. It is important to obtain right amount of different fatty acids in the diet and avoid excessive intake of any one kind. The desirable polyunsaturated fatty acids/saturated fatty acids (PUFA/SFA) ratio is about 0.8 to 1.0. **Table 5** gives PUFA/SFA ratio of common fats.

Although the ratio of PUFA:MUFA:SFA is controversial, the latest recommendation is 1:1.5:1.

Table 5: Ratio of Polyunsaturated Fatty Acids to Saturated Fatty Acids of Common Fats

Oil	PUFA/SFA ratio
Safflower oil	8.2
Sunflower oil	6.4
Corn oil	4.46
Soybean oil	4.07
Cotton-seed oil	1.96
Sesame oil	2.66
Peanut oil	1.82
Coconut oil	0.04
Butter	0.06

RENAL DISEASES

Diet plays a central role in the management of kidney diseases.

Principles of Diet in Glomerulonephritis

In acute stages, an effort should be made to maintain fluid and electrolyte balance and provide sufficient non-protein calories.

Energy

Poor appetite may interfere with energy intake. The calorie intake can be increased up to RDA by use of jellies, sugar, butter, oil, desserts, etc. using the allotted amount of protein sources.

Carbohydrates

Simple carbohydrate diet like fruit juices with glucose, sweetened tea, etc. should constitute the main bulk of calories. Excessive sweets may however cause nausea.

Protein

Unless oliguria or renal failure develops, proteins are not restricted. Proteins are to counteract the loss of albumin in case albuminuria exists. The emphasis is upon proteins of high biological value especially egg and milk. The limitation placed on second-class protein needs restriction of dals, pulses, nuts, beans which are otherwise good sources of calories also.

Fats

Normal quantities are allowed as excretion of their end products do not depend on kidney function.

Sodium

Sodium restriction to 1,000 mg is necessary with existing oedema, hypertension or oliguria.

Fluid

In oliguria, fluids are restricted to prevent further oedema. Allowance depends on the hydration levels, previous day's urine output, fever, vomiting, diarrhoea and high environmental temperature.

Diet in Chronic Renal Failure (Conservative Management)

Efforts should be made to reduce the nitrogenous waste load on the kidneys. Knowledge of the usual dry body weight and proper assessment of the actual food quantity consumed by an experienced medical nutrition therapist is of utmost importance. Additionally, a good psychological and emotional support goes a long way in improving QOL. A summary of diet in various diseases is given in **Table 6**.

Goals of Nutrition Care in the Management of ESRD

- To prevent deficiency and maintain good nutrition status and growth, in cases of children through adequate protein, energy, vitamin and mineral intake.
- To control oedema and electrolyte imbalances by controlling sodium, potassium and fluid intake.
- To prevent/retard the development of renal osteodystrophy by controlling calcium, phosphorus and vitamin D intake.
- To enable the patient to eat a palatable, attractive diet that fits his/her lifestyle as much as possible; thereby improving QOL.

Energy

35 to 40 Kcals/kg dry present body weight; wherein carbohydrates and fats form the bulk. Non-protein cereals like arrowroot, sago, root-vegetables like potato, sweet potato, help to meet the requirement of non-protein, high-energy food items.

Proteins

Protein intake of 0.7 to 0.8 g/kg present dry body weight ensures meeting the patient's requirement of daily basis. Reducing the protein further than this actually raises the serum creatinine levels due to tissue catabolism. Major amounts/portions of protein allowances should come from first class proteins (FCP), sources of which include milk and milk products, egg and non-vegetarian food items.

Fats

Moderate amounts of fat will give palatability and also add calories, in addition to meeting the EFA requirements.

Sodium

Salt restriction of 2 to 3 gm is usually recommended to maintain the electrolyte balance. Higher amounts may further aggravate hypertensive nephropathy changes.

Potassium

Moderate potassium in the diet, in the range of 1,500 to 2,000 mg, is allowed. High potassium obtained through fruit juices, coconut water, etc. may cause cardiac arrhythmias. Salts that are otherwise high in potassium should be avoided.

Fluid

Allowance depends on the hydration levels, previous day's urine output, fever, vomiting, diarrhoea and high environmental temperature.

Enteral nutrition

Enteral nutrition consists of provision of nutrients through a tube when oral intake is inadequate, for the purpose of maintaining or restoring nutrients status. It is given to all patients with 'functioning GI tract' who are unable to consume adequate amount of nutrients orally to meet their nutritional requirements.

PRINCIPAL GOALS OF NUTRITION SUPPORT

- This is to support protein synthesis rather than suppress proteolysis. This will help to initiate the anabolic phase leading to patient's convalescence.
- Understand the body's metabolic response to injury and illness.
- Assess the nutritional status of the patient in order to decide whether nutritional intervention is indicated.
- Determine the optimal route of nutrient intake.
- Provide substrate (carbohydrates, proteins, fats, vitamins and minerals) for the ongoing metabolic functions.
- Limit catabolism and maximise protein synthesis.
- Bolster immune function and improve wound healing.
- Improve cardiac and respiratory function by restoring glycogen stores in the cardiac and diaphragmatic muscles.
- Correct acid-base and electrolyte disturbances.
- Potentially modify the systemic inflammatory response.
- Be aware of, anticipate and minimise feeding (technique of delivery and metabolic) related complications.
- Understand the ability of total parenteral nutrition to serve as a drug vehicle and to help in the correction of metabolic derangements.
- Confirm adequacy of nutrition support and response to support.

Although it is not known how long a hyper-metabolic patient can tolerate starvation, the loss of lean tissue that occurs in catabolic patients (20 to 40 gm N_2) suggests that depletion to a critical level may occur in 7 days.

The need for nutrition support is based on current status of the patient's nutritional reserves and an estimate of the associated stress/severity of the underlying disease, with a heightened systemic response. Anticipated time delay before which the patient can resume feeds/normal diet.

Nutritional Supplements

It may not be always possible to meet the nutritional requirements of a patient, especially if the nutritional intake is poor or the catabolism is high. Artificial nutritional supplements

available in the market are of great help during these times. There are a wide variety of disease specific nutritional supplements available. Carbohydrates may be provided as simple sugars or complex carbohydrates such as fibre. Most proprietary formulae are lactose and gluten free. Nutrition support in critically ill patients is aimed at preventing the negative effects of starvation during the course of disease and at minimising the negative effects of protein catabolism. Healthy, malnourished non-septic patients utilise mainly carbohydrates for energy production and convert excess glucose into fat. In contrast, patients with sepsis show an increase in oxygen consumption and utilise mainly stored fat to meet their energy requirements. The same effects are seen in a non-septic critically ill patient. Consequently, it is recommended that the portion of fats in artificial nutrition be increased for patients with either sepsis or non-septic critical illness. Care is taken to avoid essential fatty acid deficiency. Studies show that the peptide system is less affected than the free amino acid pathway in malnourished patients. Administration of peptides can thus prevent protein deficiency. Furthermore, due to the lower osmolality, peptide based formulas are better tolerated than amino acids. Trace elements, vitamins and minerals are also added in doses equivalent to RDA. Many supplements are available with immune boosters like glutamine and arginine.

In stress or catabolic states, a high protein, moderate carbohydrate, moderate fat with immuno-modulators is required.

Table 6: Diet in Various Diseases

Disease condition	Energy (Kcals)	Carbohydrate (gm)	Proteins (gm)	Fats (gm)	Fibre (gm)	Salt (mg)	Exercise
Obesity	20 Kcals/kg IBW, not <1,000 Kcals/day	60 to 65% more of complex carbohydrates Avoid simple sugars	15 to 20%	15 to 20% Maintain EFA	15 to 20 gms/ 1,000 Kcals	Preferably restricted	Must
Diabetes mellitus	25 to 30 Kcals/kg IBW	55 to 60% more of complex carbohydrates Avoid simple sugars	15 to 20%	15 to 20% Maintain EFA PUFA:MUFA: SFA = 1:1.5:1	15 to 20 gms/ 1,000 Kcals	—	Must
Peptic ulcer	35 to 40 Kcals/kg IBW	65 to 70% more of simple carbohydrates Avoid complex sugars	1.2 to 1.5 gm/kg IBW	Moderate	Avoid roughage Softly cooked vegetables and peeled fruits (non citrus)	Avoid salty, spicy, processed, canned foods	—
Gout	weight reduction to IBW desired, 25 Kcals/kg IBW	60 to 65% more of complex carbohydrates Avoid simple sugars Very low CHO = ketosis = worsening of gout	1.2 to 1.5 gm/kg IBW Avoid Non-vegetarian food sources	Low fat facilitates urinary excretion of urates	High	—	Helps achieve IBW. Excess aggravates attack
Hypertension	25 Kcals/kg IBW	60 to 65% more of complex carbohydrates Avoid simple sugars	1 to 1.2 gm/kg IBW Choose lean meat	15 to 20% Maintain EFA PUFA: MUFA: SFA = 1:1.5:1	15 to 20 gm/ 1,000 Kcals 'DASH' diets are beneficial	4 to 5 gm/day	Helpful
IHD	25 Kcals/kg IBW	60 to 65% more of complex carbohydrates Avoid simple sugars	1 to 1.2 gm/kg IBW Choose lean meat	15 to 20% Maintain EFA PUFA: MUFA: SFA = 1:1.5:1 n3:n6 = 5 to 7:1 Cholesterol <300 mg/dL	15 to 20 gm/ 1,000 Kcals 'DASH' diets are beneficial	4 to 5 gm/dL More severe in CCF	Helpful
Jaundice	35 to 40 Kcals/kg IBW	65 to 70% more of simple carbohydrates Avoid complex sugars	1.2 to 1.5 gm/kg IBW	Moderate	Avoid roughage Softly cooked vegetables and peeled fruits (non citrus)	No restriction required	Adequate rest required
Cirrhosis of liver	35 to 40 Kcals/kg Dry body weight	65 to 70% more of simple carbohydrates Avoid complex sugars	1.2 to 1.5 gm/kg dry body weight Watch for impeding signs of cirrhosis	Moderate	Avoid roughage Softly cooked vegetables and peeled fruits (non citrus)	2 to 3 gm/day	—
ESRD	35 to 40 Kcals/ Dry body weight	65 to 70% more of simple carbohydrates Avoid complex sugars	0.8 gm/kg dry body weight	Moderate to high for palatabilty and EFA requirements	Moderate	2 to 3 gm, depending on the oedema and control of HTN	—

28.5 Care of Terminally Ill

Anil Chaturvedi

"Getting well is not the only goal.
Even more important is learning to live without fear,
To be at peace with life, and ultimately death".

– Bernie Siegel, MD

INTRODUCTION

Care of terminally-ill is care beyond cure. When a patient will no longer respond to curative treatment and is considered to have a terminal illness, it becomes the responsibility of those who care for him/her to ensure that the patient is helped to live the remaining life as fully as possible. This means that we should use all our available resources to relieve the patient's suffering and promote his/her well-being. The patient's time is limited and we must deliver effective, high quality care first time around; we cannot get it right the next time.

To ensure death with dignity, patients need holistic care. Physical, social, emotional, practical, and spiritual needs must be met. Holistic care demands time, attention and skills from nursing staff, who in turn must be supported to give this care. Terminal illness is not only a medical problem, but it has moral, ethical, legal, social, cultural and spiritual dimensions.

Terminal illness is defined as:

- Such illness, injury or degeneration of physical or mental condition, which is causing extreme pain and suffering to the patient and which, according to reasonable medical opinion, will inevitably cause the untimely death of the patient concerned, or
- Which has caused a persistent and irreversible vegetative condition, under which no meaningful existence of life is possible for the patient.

Patients and their families are clear about what they want and need from the health care system at the end of life: freedom from distressing symptoms, such as pain and dyspnoea; the opportunity to communicate with physicians and others about death and dying; and the knowledge that they will be attended to and comforted by their physicians as they approach death. These goals are focussed on improving the quality of life of people living with a serious, chronic and life-threatening illness, irrespective of prognosis. Palliative care can be provided at any stage of illness and should be provided, in particular, simultaneously with all other appropriate medical treatments. Patients approaching the end of life certainly need palliative care but so do other patients who have acute exacerbations of chronic illness, such as heart failure, chronic obstructive pulmonary disease (COPD), cirrhosis, dementia, and cancer.

Palliative care is defined as 'the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms and of psychological, social and spiritual problems is paramount. Common physical and psychological symptoms are outlined in **Table 1**. The goal of palliative care is achievement of the best possible quality of life for patients and their families'. Although palliative care has emerged as a recognised subspeciality, primary care physicians and their patients are eager to maintain strong relationships at the end of life which emphasise more than just the patient's disease. Therefore, it is imperative for physicians to equip themselves 'with the necessary information' and training in order to ensure their patients a 'good' death to the best of their ability. Palliative care is both an art and a science. The clinical course in the last days of terminally-ill patients is shown in **Figure 1**.

BASIC PRINCIPLES OF PALLIATIVE CARE

- Affirms life.
- Regards dying as a normal process.
- Neither hastens nor postpones death.
- Relieves pain and other symptoms.
- Integrates medical, psychological, and spiritual aspects of care.
- Offers a support system to patients and families.

All people have goals and hopes, and enjoy having control over their lives. Over time, each person develops a very personal sense of what brings greatest meaning and value and adds most to his or her quality of life. People in the hospital often feel that they are losing control. As their illness progresses, their goals and hopes may change. It is the physician's role to communicate with the patient and family, clarify their goals and priorities, and develop a plan of care based on this information. Regular reassessment of goals and priorities ensures that the patient, family, physician, and health care team are working together to maximise the patient's quality of life.

Table 1: Common Physical and Psychological Symptoms of Terminally-Ill Patients

Physical Symptoms	Psychological Symptoms
Pain	Anxiety
Fatigue and weakness	Depression
Dyspnoea	Hopelessness
Insomnia	Meaninglessness
Dry mouth	Irritability
Anorexia	Impaired concentration
Nausea and vomiting	Confusion
Constipation	Delirium
Cough	
Swelling of arms or legs	
Itching	
Diarrhoea	
Dysphagia	
Dizziness	
Loss of libido	
Faecal and urinary incontinence	
Numbness/tingling in hands/feet	

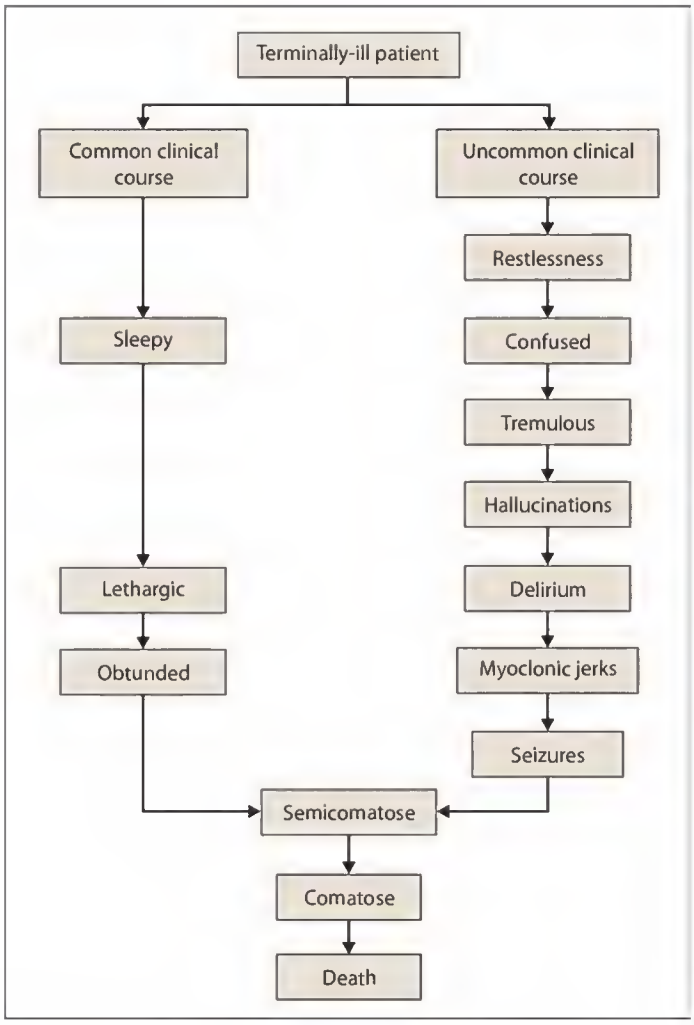


Figure 1: Clinical courses in the last days of terminally-ill patients.

Some potential goals of care are listed in **Table 2** and negotiating these goals are mentioned in **Table 3**. Historically, there has been a dichotomous division of goals of care, with a primary focus on curing illness rather than on relieving suffering in the dying patient.

Table 2: Potential Goals of Care

Cure of disease
Avoidance of premature death
Maintenance or improvement of function
Prolongation of life
Relief of suffering
Optimised quality of life
Maintenance of control
A peaceful death
Support for family and loved ones

Table 3: Seven Steps in Negotiating Goals of Care

Create the right setting
Determine what the patient and family know
Explore what they are expecting or hoping for
Suggest realistic goals
Respond empathetically
Make a plan and follow it through
Review and revise periodically, as appropriate

Medical Management at the End of Life

'Medical treatment' means treatment intended to sustain, restore or replace vital functions which, when applied to a patient suffering from terminal illness, would serve only to prolong the process of dying and includes:

- Life-sustaining treatment by way of surgery or administration of medicine or any other medical procedure; and
- Use of mechanical or artificial means, such as ventilation, artificial nutrition and hydration, and cardiopulmonary resuscitation.

ARTIFICIAL NUTRITION AND HYDRATION

Ceasing to eat and drink is a normal part of dying, not its cause. Understandably, families often become distressed when their loved one refuses food, at least in part because feeding has great cultural significance. Families often request artificial nutrition and hydration in the mistaken hope that it will prolong life, promote comfort, or improve functional status and quality of life. Unlike in the setting of acute illness, where these interventions may play an important role in recovery, in end-stage dementia, stroke, and cancer, artificial nutrition and hydration typically do not confer clinical benefit and may pose risks. For patients who are dying imminently, minimising fluids may increase comfort by preventing and reducing pulmonary and peripheral oedema, pleural effusions, ascites, and death rattle. Physicians play an important role in helping families understand the appropriate role of artificial nutrition and hydration. They may also direct families away from feeding and toward more productive actions that promote patient comfort, such as moistening the mouth with a swab or putting petroleum jelly on dry lips.

IMMINENT DEATH

As patients approach the final 24 to 48 hours of life, families may notice changes that, although normal, can be distressing if left unexplained. In addition to developing death rattle or dry mouth, patients may have Cheyne-Stokes breathing pattern, irregular breathing or slow and gasping respirations. Breathing may pause for as long as 20 to 30 seconds. Urine output may fall, especially if patients are not drinking and not receiving artificial hydration, and patients may become incontinent of urine and stool. The extremities typically become cold, mottled, blue, and swollen. In all cases, gentle reassurance that the changes family is witnessing are a normal part of dying, can ameliorate anxiety and fear. It can be comforting for families to know that physicians are aware of and anticipating these changes, and watching for specific signs and symptoms can assist clinicians with prognosis.

PSYCHOLOGICAL SUPPORT AND SPIRITUAL ISSUES

The experience of the end of life encompasses the psychologic, social, spiritual, and physiologic state of a patient. Providing comprehensive care to dying patients demands that physicians attend to these issues, in addition to relieving distressing physical symptoms.

COMMUNICATION

Being available to take calls and to answer questions from the patient and family provides a comfort and a confidence all its own. Be open. Be honest. Be available. Have a well thought-out, agreed-on, and

documented plan of care so that the patient, family, other health care providers, and covering physicians know what to expect and how to manage any changes in the patient's symptoms or status.

COMMUNICATING WITH RELATIVES

When a patient is terminally-ill, his or her relatives will need support, information and counselling. Meeting the needs of relatives can help to promote good communication between the patient and their family, thus improving the patient's psychological well-being.

Relatives express the need to:

- Be with the dying patient.
- Help to care for the dying patient.
- Be reassured that the dying patient is receiving good professional care.
- Be informed of diagnosis, treatment and prognosis. Information should be regularly updated.
- Discuss and plan care of the patient if the patient is to be discharged.
- Be informed of the patient's impending death if this is thought to be imminent.
- Have comfort and support from other relatives and friends.
- Have opportunities for rest, sleep and facilities for washing and changing, meals.
- Have adequate privacy.
- Receive spiritual support from appropriate sources, if required.
- Receive support and acceptance from ward staff.

CONCLUSIONS

Physicians do care for dying patients. There is much that physicians can do to provide high-quality care to patients approaching the end of life. By providing expert symptom management; discussing issues, such as prognosis and death, sensitively, compassionately, and providing emotional, spiritual, psychological, and social support, physicians can provide dignity and comfort to the dying.

"This little life is all we must endure,
The grave's most holy peace is ever sure,
We fall asleep and never wake again;
Nothing is of us but the mouldering flesh
Whose elements dissolve and merge afresh
In earth, air, water, plants, and other men".

– James Thomson

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28.6 Exercise and Yoga in Health and Disease

S Dwivedi, Shiva Narang

Exercise and yoga both are essentially lifestyle related activities which enhance the physical, mental and spiritual development of an individual in a complimentary way. Exercise is a physical activity that is planned, structured, repetitive, and is meant for conditioning of any part of the body, while yoga is conceptualised as a way of life consisting of certain regulatory principles, breathing exercises, physical postures, and meditation. Exercise is dominantly utilised to improve health and maintain fitness while yoga is considered to enhance mental ability and additionally has some therapeutic potential in certain psychosomatic disorders.

HISTORY

The benefits of exercise have been known since antiquity. However, it was Morris (1953) who first conclusively proved the link between heart disease, physical health and exercise (or lack of it). He noted that men of similar social class and occupation (bus conductors versus bus drivers) had markedly different rates of heart attacks, depending on the level of activity. Bus drivers, by and large, having sedentary occupation had a higher incidence of heart disease, while bus conductors always on the move had a lower incidence. This was a landmark in study proving the link between physical activity and coronary heart disease and was later confirmed by many studies.

FORMS OF EXERCISE

Exercise can be categorised as follows: short-term maximal exercise, such as sprinting or climbing stairs; endurance exercise, such as running or walking for long distances and progressive increases in exercise until maximal capacity is reached. Types of exercise include isometric and isotonic (aerobic) exercise. In isometric exercises, the exercise is done against resistance, for example weight lifting, pushing or pulling. In isotonic exercise, there is increased oxygen consumption by exercising muscle. These are good for cardiovascular fitness and examples are walking, running, cycling and swimming.

ADVANTAGES OF EXERCISE IN HEALTH AND DISEASE

- Strengthening muscles
- Ensuring cardiovascular fitness
- Honing athletic skills
- Achieving/maintaining weight loss
- Boosting immune system
- Prevention of coronary artery disease (CAD), hypertension, Type 2 diabetes (T2DM) and obesity
- Management of CAD, hypertension, T2DM, obesity, musculoskeletal disease, anxiety, depression, etc.

BENEFITS OF EXERCISE IN HEALTH AND DISEASE

There are large numbers of physiological benefits of exercise, such as improvement in muscular function, strength and improvement in the body's ability to take and use oxygen. As one's ability to transport and use oxygen improves, regular daily activities can be performed with less fatigue. This is particularly important for patients with cardiovascular disease, whose exercise capacity is typically lower than that of healthy individuals. There is also evidence that exercise training improves the capacity of the blood vessels to dilate in response to exercise or hormones, consistent with better vascular wall function and an improved ability to provide oxygen to the muscles during exercise. Studies measuring muscular strength and flexibility before and after exercise programmes suggest that there are improvements in bone health and ability to perform daily activities, as well as less likelihood of developing back pain and disability, particularly in older age groups.

Benefits of regular exercise on cardiovascular health include increase in exercise tolerance; reduction in body weight, blood pressure, LDL and total cholesterol and concurrent increase in HDL-cholesterol and insulin sensitivity. Recent observational data from the Nurses' Health Study and the Women's Health Study have demonstrated similar relationships among physical activity, exercise, fitness, and outcome for women. It is said that even a small amount of exercise is cardio-protective.

Manson *et al* suggest that an hour per day of moderately intense exercise is closer to optimal, and most evidence suggests that progressive amounts of exercise lead to a progressive reduction in cardiac risk. A meta-analysis of 30 cohort studies involving more than 2 million person-years of observation demonstrates a nearly linear decline in the risk of CAD with increasing levels of physical activity.

There is also evidence that moderate weight loss normalises fasting hyperglycaemia in patients with poorly controlled T2DM. The Finnish Diabetes Prevention Group and Diabetes Prevention Program (DPP) have revealed that a low fat, low calorie diet and moderate exercise reduces the risk of developing T2DM by almost 58%.

Exercise also plays an important role in the management of certain musculoskeletal diseases, such as ankylosing spondylitis, fibromyalgia and osteoarthritis by maintaining mobility and avoiding deformity.

Recent reports also suggest that regular physical activity relieves symptoms of depression, anxiety and improves mood. Regular physical activity may reduce the risk of developing depression.

As effects of exercise on blood pressure, glucose levels, and lipids are, in part, acute effects of recent exercise, it is advised that people should try to exercise daily to minimise the number of days missed. The Center for Disease Control and Prevention and the American College of Sports Medicine recommend at least 30 minutes of moderately intense physical activity on most, and preferably all days of the week.

LIMITATIONS OF EXERCISE

Fatiguability, repetitive nature, and loss of motivation are the main drawbacks. There is a transient increase in the risk of developing cardiac-related complications (for example, a heart attack or serious heart rhythm disorder) during exercise. However, this risk is extremely small. For adults without existing heart disease, the risk of a cardiac event or complication is estimated to be one in 4,00,000 to 8,00,000 hours of exercise. The scope of exercise is also limited in disease states.

We shall now move on to yoga, which is an ancient practice having wide utility both in health and disease.

YOGA

Yoga is a healing system practised for more than 5,000 years. The first Hindu teacher to actively advocate and disseminate various aspects of Yoga to a Western audience was Swami Vivekananda, who toured Europe and the United States in the 1890s. The word 'yoga' comes from the Sanskrit word *yuj*, which means 'yoke or union' implying a union between the mind and the body. Patanjali, the exponent of yoga defined it as hindering of wavering mind. It is essentially based on mind and body relationship aiming complete 'homeostasis' between the two through eight steps; namely *yama* (moral behaviour), *niyama* (healthy habits), *asana* (physical postures), *pranayama* (breathing exercises), *pratyahara* (sense withdrawal), *dharana* (concentration), *dhyana* (contemplation) and *samadhi* (higher consciousness) (**Figure 1**). Yoga in its pragmatic form combines healthy habits with physical postures, breathing exercises and meditation.

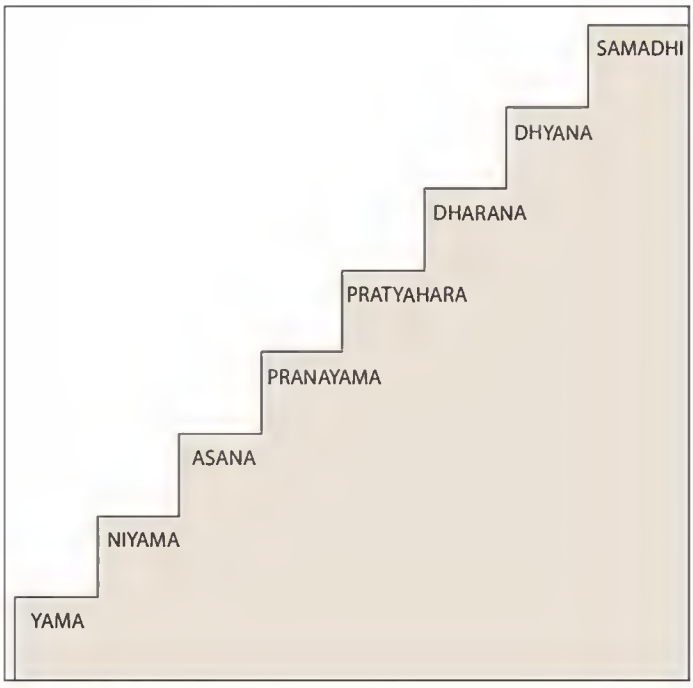


Figure 1: Stages of yoga.

The benefits of healthy habits, various physical postures, breathing exercises and meditation are now being intensively investigated and rationalised. Yogic exercises create awareness regarding body postures, alignment and patterns of movement. These asanas (physical postures) make body more flexible and help individuals to relax, even in a stressful environment.

Yoga has been basically used as part of general health regimen to achieve physical fitness, spiritual development, and relaxation. It has also been recommended for a variety of disease conditions including anxiety disorders or stress, depression, asthma, hypertension, diabetes and CAD.

Advantages of Yoga in Health and Disease

- Reduction in heart rate and blood pressure
- Increase in lung capacity
- Improved muscle relaxation
- Improvement in overall physical fitness, strength, and flexibility
- Positive change in levels of certain brain or blood chemicals
- Useful in treatment of CAD, hypertension, T2DM, thyrotoxicosis, anxiety neurosis, acid peptic disease, irritable bowel syndrome, and ulcerative colitis.

Yoga—role in various disease

Yoga has a definite complementary role in treatment of various disorders like CAD, hypertension, thyrotoxicosis, T2DM, anxiety neurosis, acid peptic disease, irritable bowel syndrome and ulcerative colitis. It has been demonstrated to help control hypertension and diabetes mellitus. Beneficial effects of yoga, particularly *shavashana* (corpse posture) and *pranayam* (regulated breathing exercises) on mild hypertension have been well documented. Similarly, regular yogic exercises (asanas) like *suryanamskar* (sun salutation postures), *tadasan* (mountain posture), *trikonasan*, (triangle posture), *padmasan* (lotus posture), *pranayam* (regulated breathing exercises), *paschimottanasan* (seated forward bend posture), *ardhmatsyendrasan* (half spinal twist posture), *pavanmukthasan* (wind removing postures), *sarpasan* (cobra posture) and *shavasan* (corpse posture) alongwith modern drugs have been found to lower fasting and postprandial blood glucose levels with lower dosage requirement of oral hypoglycaemic drugs. Yogic exercises have also been found to be useful for maintaining good glycaemic status for long periods of time. It has been suggested that yogic practices have a positive role in the prevention of diabetes. Besides hypertension and diabetes, life style modifications and stress management based on yogic principles mainly meditation, *shavashana* (corpse posture) *and pranayam* (regulated breathing exercises) have been advocated to reverse the process of CAD.

Limitations of Yoga

Yogic exercises are generally considered to be safe in healthy people when practiced appropriately. Studies have found it to be well tolerated, with few side effects. However, people with certain medical conditions should not use some yoga practises. For example, people with disc disease of the spine, extremely high or low blood pressure, glaucoma, retinal detachment, risk of blood clots, ear problems, severe osteoporosis, or cervical spondylitis should avoid some inverted poses. Although yoga during pregnancy is safe, it should be practiced under expert guidance.

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28.7 Adult Immunisation

RK Singal, AK Agarwal

Immunisation is a well-established practise in the paediatric age group. However, it has not received the same attention in adults. The dynamic nature of adult immunisation is evident from the continuous development of new vaccines, new indications and new dosing schedules. The emergence of H1N1 influenza, and of a vaccine for its prevention, underlines the need to remain constantly updated in this field.

TETANUS

In the absence of effective treatment, immunisation is the preferred method for tetanus prevention. All adults who have previously not been immunised against tetanus should be given a full course of immunisation. All pregnant women must be immunised.

Two new tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines (Tdap) are available for adults. These include [i] Adacel® that contains tetanus toxoid, diphtheria toxoid, and five pertussis antigens and [ii] Boostrix® that contains tetanus toxoid, diphtheria toxoid, and three pertussis antigens. The vaccine is administered as a 0.5 ml intramuscular injection in the deltoid.

Tetanus immunoglobulin (Tetglob™, Bharat Serums, Mumbai, India) provides passive protection. It is administered as a deep intramuscular injection in a dose of 250 IU. The recommended schedule for immunisation is shown in **Table 1** and the schedule for a person who has sustained a wound is shown in **Table 2**.

Table 1: Tetanus Immunisation Schedule

Group	Schedule
18 to 64 years, Childhood immunisation complete	Booster dose of Td or Tdap vaccine once in 10 years till the age of 65
>18 years, not immunised	Three doses of Td or Tdap. First two doses four weeks apart, third dose 6 to 12 months after second dose
Health care workers in contact with the patient	Single dose of Tdap vaccine, if >2 years since last dose
Women planning pregnancy	One dose of Tdap, if not received previously
Pregnant women who received Td >10 years ago	One dose of Td vaccine in the second or third trimester
Pregnant women who received Td 2 to 10 years ago	One dose of Tdap in the immediate postpartum period
Pregnant women never immunised	Three doses of Td in the second or third trimester; first two doses at least 4 weeks apart, third dose 6 to 12 months after second dose

Td = Tetanus toxoid, diptheria; Tdap = Tetanus toxoide, diphtheria, acellular pertussis.

Local reactions (generally erythema and induration with or without tenderness) are common after immunisation. Rare cases of Guillain-Barre syndrome have been reported after immunisation. A previous history of neurological illness, especially Guillain-Barre syndrome following administration of another vaccine, is a contraindication for immunisation.

Table 2: Tetanus Immunisation Schedule for Adults Sustaining a Wound

History of Tetanus Toxoid Doses	Clean Minor Wound	All Other Wounds
Unknown or less than three doses	Tdap/Td	Tdap/Td, TIG
Three or more doses	Tdap/Td if more than 10 years elapsed since last tetanus toxoid dose	Tdap/Td if more than 5 years have elapsed since the last tetanus toxoid dose

TIG = Tetanus immunoglobulin; Tdap = Tetanus toxoid, diphtheria, acellular pertussis; Td = Tetanus toxoid, diphtheria.

RABIES

With a large population of unvaccinated stray dogs, rabies continues to be prevalent in India. The fact that no treatment is available for established disease and a fatal outcome is universal, highlights the importance of immunisation, the only effective preventive measure. The spread of rabies can best be prevented at a population level by vaccinating all stray and pet dogs.

Pre-Exposure Prophylaxis

It is recommended for high risk groups like veterinarians, laboratory personnel working with rabies virus, medical and paramedical personnel treating rabies patients, dog catchers, forest staff and zoo keepers.

Post-Exposure Prophylaxis

Depending on the severity of the exposure and categories of exposure, the recommended treatment for each is shown in **Table 3**. All exposures in the wild are category III exposures. Rodents are not reservoirs of rabies virus. Small rodents (e.g. squirrels, chipmunks, rats, mice, hamsters, guinea pigs, and gerbils) and lagomorphs (including rabbits and hares) are rarely infected with rabies and have not been known to transmit rabies to humans.

Following exposure, wound care consists of washing the wound with soap and water while avoiding touching the wound with bare hands. Post-exposure immunisation can be discontinued if the animal is healthy after 10 days.

Vaccines available in India include purified duck embryo, purified chick embryo, Vero cell (cell line from kidney epithelial cells of African Green monkey) derived and human diploid cell vaccine.

Rabies immunoglobulin, used to provide passive protection, is available as a human and an equine preparation. Anaphylactic shock may occur following the administration of equine preparations. Skin testing should be performed before giving

the injection by injecting 0.1 mL of equine rabies immunoglobulin, diluted 1:10 in saline, intradermally into the flexor surface of the forearm to raise a bleb of 3 mm diameter. An equal amount of saline is injected as control in the other forearm. After 15 minutes, an increase in diameter to >6 mm of wheal surrounded by flare is taken as a positive skin test.

Table 3: Categories of Exposure and Recommended Treatment for Rabies

Category I

Touching, feeding of animals or licks on intact skin

Recommendation: If history is reliable, no prophylaxis is indicated

Category II

Minor scratches or abrasions without bleeding or licks on broken skin and nibbling of uncovered skin

Recommendation: Wound management and use of vaccine

Category III

Single or multiple transdermal bites, scratches or contamination of mucous membrane with saliva (i.e. licks), exposure to bats

Recommendation: Wound management plus rabies immunoglobulin plus immunisation

Passive immunisation: It provides immediate protection to previously unvaccinated individuals. Human rabies immunoglobulin (HRIG) is used in a dose of 20 IU/kg (maximum 1,500 IU). If HRIG is not available, equine rabies immunoglobulin should be used in a dose of 40 IU/kg (maximum 3,000 IU). Rabies immunoglobulin should be infiltrated into and around the wounds; leftover immunoglobulin, if any, should be given intramuscularly at a site away from the site of vaccine administration. Passive immunisation is not indicated in individuals who have previously received the vaccine.

Table 4: Recommended Dosage Schedule for Rabies Vaccine

Situation	Dosing schedule
Pre-exposure prophylaxis	Days 0, 7, 28
Post-exposure prophylaxis (no prior immunisation) (Category II or III exposure)	Days 0, 3, 7, 14, 28 + RIG on day 0
*Post-exposure prophylaxis – New CDC guidelines**	*Days 0, 3, 7, 14 + RIG on day 0*
Re-exposure after a full course of immunisation	Days 0, 3
Re-exposure after incomplete course of immunisation	Treat as if previously not vaccinated

RIG = Rabies immunaglabulin; Dase = 10 IU/kg af human RIG ar 20 IU/kg af equine RIG infiltrated araund the waund. Leftaver RIG shauld be injected intramuscularly at a site away fram that af vaccine administratian.

**CDC. Use of a reduced (4-Dose) vaccine schedule for past-expasure praphylaxis ta prevent human rabies.*

Recammendatians af the Advisary Cammittee an Immunisatian Practices. MMWR Morb Mortal Wkly Rep 2010; 59(RR-2):1-9.

The vaccine is administered intramuscularly in the deltoid or in the anterolateral thigh. It should not be given in the gluteal region since the high fat content of this site retards vaccine uptake. Recommended dosage schedules are shown in **Table 4**. Bites sustained during sleep or those due to unidentified animals should presumptively be treated in India as if due to a possibly rabid animal. No consensus is available regarding the management of bites due to wild rodents and treatment needs to be individualised. Rabies vaccines and rabies immunoglobulin are safe during pregnancy, lactation and in immunocompromised states including human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). Minor reactions at the local site of injection and rare cases of anaphylaxis have been reported. Immunospuppresive drugs should be avoided during the course of immunisation.

HEPATITIS B

Hepatitis B and its complications like hepatic failure, cirrhosis and hepatocellular carcinoma account for significant morbidity and mortality. Hepatitis B immunisation remains the most effective measure to prevent hepatitis B virus (HBV) infection.

Percutaneous or mucosal exposure can occur in injection-drug users; household contacts of persons with chronic HBV infection; health care workers; patients with chronic kidney or liver disease; HIV-positive patients; diseases where blood products or multiple blood transfusions are required, and patients undergoing major surgeries. Sexual exposure (homosexuals, promiscuous heterosexuals, commercial sex workers and sex partners of HBsAg-positive persons) may also be associated with transmission of the virus.

Immunisation is indicated for all unvaccinated adults at risk for HBV infection and all adults seeking protection from HBV infection, including post-exposure prophylaxis.

Hepatitis B vaccine, a recombinant DNA vaccine, is available as a single-antigen formulation and also in fixed combination with other vaccines. For immunocompetent adults, 20 µg of recombinant vaccine is administered at 0, 1, and 6 months as an intramuscular injection in the deltoid muscle using a 24 to 38 mm needle. Protective antibody levels, defined as anti-HBs antibody titers of 10 mIU/mL or higher, are seen in approximately 30% to 55% of healthy adults aged <40 years after the first dose, 75% after the second dose, and >90% after the third dose.

Prevaccination Screening

It is not cost-effective in India. It may be cost-effective in adult populations with a prevalence of HBV infection of >20%, such as household, sexual, and needle-sharing contacts of HBsAg-positive persons; HIV infected persons; injection drug users; men who have sex with men; patients with chronic liver disease (CLD) and end-stage renal disease (ESRD). Prescreening requires testing for HBsAg, anti-HBs and anti-HBc. If HBsAg is positive or Anti-HBs titres are more than 10 mIU/mL, immunisation is not required. In those in whom both anti-HBc and anti-HBs are negative, immunisation should be administered. If Anti-HBc alone is positive, a test dose of the vaccine should be given and anti-HBs titers repeated after a month. Immunisation is required only in those who have titers of less than 10 mIU/mL at one month.

If the *vaccine schedule is interrupted* after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least eight weeks. If only the third dose has been delayed, it should be administered as soon as possible.

Post-Exposure Screening

It is indicated in patients with ESRD, CLD, HIV infection, sex partners of HBsAg-positive persons, infants born to HBsAg-

positive women and certain health care workers at high risk exposure of to blood or body fluids.

Non-responders who are HBsAg and anti-HBc negative should receive a further full course of immunisation as fourth, fifth and sixth doses. Retesting should be done 1 to 2 months after the last dose. If there is no response, 40 µg of recombinant vaccine is administered at 0,1, and 6 months. For patients with chronic kidney disease (CKD) and other immunosuppressed patients, 40 µg of recombinant vaccine is administered at 0, 1, 2, and 6 months.

A *booster dose* should be administered when anti-HBs levels decline to less than 10 mIU/mL (<100 mIU/mL in patients on dialysis). For CKD patients, the need for booster doses should be assessed by annual anti-HBs antibody titre testing. Testing for antibody titers and administration of booster doses of HBV vaccine are generally not indicated in persons with a normal immune status. Other than local injection site reactions and rare cases of anaphylaxis, no serious adverse events have been reported. The vaccine is safe during pregnancy.

PNEUMOCOCCAL DISEASE

Pneumococcal polysaccharide vaccine (PPV) substantially reduces the risk of development of invasive pneumococcal disease but not all-cause mortality. Routine administration of the vaccine to all adults is not a cost-effective strategy. Immunisation is recommended in patients undergoing splenectomy (preferably at least two weeks prior to surgery) and one-time reimmunisation is indicated after five years in these patients. Many indications for which immunisation is recommended in developed countries, such as the healthy elderly and high-risk patients, are not considered indications for immunisation in India.

The PPV contains 25 µg each of purified capsular polysaccharide from 23 serotypes of *Streptococcus pneumoniae*. A single dose of 0.5 mL is administered by the intramuscular or subcutaneous route. This vaccine can be co-administered with live vaccines, such as the influenza vaccine. It is safe and adverse events, except local reactions are few. With the exception of the first trimester of pregnancy, there are no contraindications to vaccine use.

INFLUENZA

Seasonal influenza, an infection transmitted by respiratory droplets, causes significant illness especially in the elderly and the immunocompromised. Since treatment options are limited, immunisation is an attractive option. In 2009, the emergence of a new recombinant strain of the virus H1N1, lead to a pandemic affecting individuals on all continents. The response to this pandemic has been rapid and a vaccine is already in use.

An Indian Expert Group on Adult Immunisation found no evidence to recommend the use of seasonal influenza vaccine in adults. In Western countries, this vaccine is routinely recommended for the elderly, those with COPD and patients with chronic pulmonary, renal or cardiac disease.

Data are not available to guide the use of H1N1 influenza vaccine in India. This vaccine has routinely been administered in Western countries during the winter of 2009. Priority groups to whom vaccine should be given first are shown in **Table 5**.

Seasonal Influenza

Two types of vaccine are available: trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV). The TIV is administered by an annual, single intramuscular dose of 0.5 ml. The LAIV is administered by the intranasal route and is approved for use in adults aged up to 50 years.

H1N1 Influenza 2009

Immunisation against seasonal influenza does not provide cross-protection against H1N1 influenza. Specific vaccines have been developed against the H1N1 strain. A single dose of the vaccine provides protection starting as early as three weeks. Vaccine efficacy ranges from 70% to 90%. Available vaccines include a killed inactivated vaccine and a live-attenuated intranasal vaccine (LAIV). The former is given as a single dose of 0.5 ml [15 µg hemagglutinin of A/California/7/2009 (H1N1) pdm] intramuscularly in the deltoid. The live attenuated vaccine is given in a single dose of 0.2 mL divided equally between each nostril.

Inactivated vaccine against the 2009 H1N1 flu virus can be given at the same visit as any other vaccine, including PPV. The LAIV (nasal spray vaccine) against the 2009 H1N1 virus can be administered at the same visit as any other live or inactivated vaccine except seasonal live-attenuated influenza vaccine because of concerns about competition between the two vaccine viruses.

Adverse effects are similar for immunisation against seasonal influenza and H1N1 influenza. Inactivated vaccines, administered by injection, commonly cause local reactions, such as soreness, swelling and redness at the injection site. Inactivated vaccines should not be given to individuals with egg protein allergy. Live vaccines are given via a nasal spray, and can commonly cause runny nose, nasal congestion, cough, and sore throat, low grade fever, irritability and headache. H1N1 influenza vaccine can be safely given during pregnancy. LAIV should not be administered to persons with asthma because of the potential for increased risk of wheezing post-vaccination, unless the potential benefits outweigh the potential risks.

TYPHOID

Immunisation may help reduce disease burden in areas with a high incidence of this disease. The vaccine should be given to all adolescents. Administration to all adults is not recommended. However, during an outbreak, the entire community may be vaccinated.

Two vaccines, injectable Vi polysaccharide vaccine and live oral Ty21a vaccine, are recommended for use. Live oral Ty21a vaccine is an orally administered, live-attenuated Ty2 strain of *Salmonella typhi* in which multiple genes have been mutated chemically. The lyophillised vaccine is available in two formulations: a liquid suspension (in sachets) or as enteric coated capsules. Four doses are given on alternate days. This series has to be repeated once in three years as a booster dose. The capsule formulation should be taken orally with plain, cold or lukewarm water. The sachet should be given with 100 mL of safe water with buffer to protect the B-subunit against gastric acidity. Following the administration of the vaccine, food should be taken only after one hour. Proguanil and anti-bacterial drugs should not to be given for 3 to 7 days before and after the course of vaccine.

Table 5: Summary of Immunisation Schedule for Adults

Vaccine	Target Population	Dose	Dosage Schedule	Protection Rate	Remarks
Hepatitis B (Recombinant DNA vaccine)	All adults	20 µg IM in deltoid muscle *(do not inject into buttocks)* 40 µg IM in haemodialysis and other immuno-compromised patients	0, 1, 6 months	>90% after the third dose	Testing for protective concentration of anti-HBs antibody (>10 mIU/mL) should be performed 1 to 2 months after the last dose of the vaccine series. Persons with >10 mIU/mL are considered to be immune. Immunocompetent persons have long-term protection and do not require further testing, however, immunocompromised persons might need annual testing to assess anti-HBs antibody levels. The level should be >100 mIU/mL in CKD patients
Pneumococcal Polysaccharide vaccine (23 valent polysaccharide vaccine)	Two weeks prior to elective splenectomy. One time revaccination with PPV after 5 years is recommended in patients with functional or anatomic asplenia	0.5 mL IM or s.c.	Single dose	0% to 66%	The scientific evidence for the efficacy of PPV has been a very controversial issue. Evidence for the efficacy of PPV in high-risk groups is lacking. In resource-limited settings, routine PPV vaccination is not recommended for healthy elderly (>65 years) and high-risk patients, such as those suffering from chronic organ failure, diabetes, nephritic syndrome, or HIV infection
Seasonal influenza [Trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV)]	Elderly, COPD, chronic pulmonary, renal or cardiac disease	TIV: 0.5 mL IM LAIV: 0.2 mL Intranasal	Annual, single dose	70%	Evidence insufficient for use in India
H1N1 Influenza [killed inactivated vaccine; live attenuated intranasal vaccine (LAIV)]	Pregnant women Health care workers Age 6 months to 24 years Age 25 to 64 years with high-risk medical conditions	Killed inactivated vaccine: 0.5 mL IM Live vaccine: 0.2 mL (half in each nostril)	Single dose	Above 90%	Do not give killed vaccine to those with egg allergy. Avoid LAIV in asthma
Typhoid (Injectable Vi polysaccharide vaccine; Live oral Ty21a vaccine)	All adolescents	Vi polysaccharide: 0.5 mL IM or s.c. Live Ty21a: 1 capsule, orally four doses on alternate days	Vi polysaccharide: Booster every 3 years. Ty21a: Repeat series once in 3 years	51% to 55%	Entire community during an outbreak
Cholera [Oral: Shanchol Lipopoly-saccharide of formalin killed *V. cholera* (5 strains)]	Adults in endemic areas and during potential/actual outbreaks	300 to 600 IU of different strains	Two doses 1 to 6 weeks apart. Booster every second year	67%	Protective efficacy of 67% over two years in all age groups
Meningococcal (Polysaccharide – Bi- and Quadri-valent Conjugate)	Travellers, pilgrims and people attending fairs and festivals. Health care personnel. Haj pilgrims administered a single dose of quadrivalent vaccine	Polysaccharide: 0.5 mL s.c.	Single dose	85% to 95%	Does not induce herd immunity; no effect on nasopharyngeal carriage. Safe in pregnancy and in HIV + patients

Contd...

Contd...

Vaccine	Target Population	Dose	Dosage Schedule	Protection Rate	Remarks
Japanese encephalitis (live-attenuated SA 14-14-2 vaccine)	1 to 15 years	0.5 mL s.c.	Single dose	90% to 100%	Recommended in adolescents
Yellow fever (live, attenuated virus preparation made from the 17D yellow fever virus strain)	Travellers visiting Africa and South America	0.5 mL s.c.	Single dose	95%	Protective antibodies develop 10 days following immunisation
Human papilloma virus (Bivalent HPV 16/18 vaccine; Quadrivalent HPV 6/11/16/18 vaccine)	Girls 10 to 12 years Men 9 to 26 years to prevent genital warts	0.5 mL IM	Bivalent: 0, 1, 6 months Quadrivalent: 0, 2, 6 months	97% to 100%	Immunise before sexual activity commences
Herpes zoster (lyophilised preparation of the Oka strain of live-attenuated varicella zoster virus (VZV))	Adults >60 years Chronic medical conditions with an increased risk of herpes zoster	0.65 mL s.c.	Single dose	51%	Protect from light before reconstitution Use immediately to minimise loss of potency

Nate: Details af immunisatian against tetanus and rabies are pravided in Tables 1 ta 4.

s.c. = Subcutaneous; IM = Intramuscular.

Live attenuated influenza vaccine, human papilloma virus vaccine and oral Ty21a typhoid vaccines varicella and herpes zoster vaccines are contraindicated during pregnancy. The safety of Japanese encephalitis vaccine and of yellow fever vaccine has not been established in pregnancy and their use should be avoided. All other vaccines may be safely administered to pregnant women.

Booster doses are required only for hepatitis B (those with low anti-HBs titres), cholera (every 2nd year) and typhoid (every 3 years) immunisation.

The Vi polysaccharide vaccine is a subunit vaccine composed of purified Vi capsular polysaccharide from the Ty2 *S. typhi* strain and elicits a T-cell independent IgG response that is not boosted by additional doses. The target value for each single dose is about 25 µg of the antigen.The Vi vaccine is given as a single subcutaneous or intramuscular dose of 0.5 mL. A booster is recommended every three years.

Both live oral Ty21a and Vi polysaccharide vaccines have an efficacy of 51% to 55% at three years and may be co-administered with other killed/live vaccines. Abdominal discomfort, nausea, vomiting, fever, headache and rash or urticaria have been reported in some patients after oral Ty21a vaccine administration. Vi polysaccharide immunisation can result in fever, headache and erythema or induration. The Ty21A vaccine should not be used during pregnancy. In HIV seropositive individuals with a CD4+ T-lymphocyte count >200/mm^3, both Ty21a and Vi vaccines can be administered. However, in HIV-seropositive individuals with a CD4+ T-lymphocyte count <200/mm^3, Vi vaccine should be used.

CHOLERA

Immunisation, a part of the strategy for reducing cholera related morbidity, is primarily targeted at children. However, in endemic areas and during potential/actual outbreaks, adults may also be given the vaccine.

Two types of vaccines are used: (1) injectable killed whole cell vaccine; and (2) oral cholera vaccine. The injectable killed whole cell vaccine provides protection for a duration of only 3 months. Two doses of the vaccine are administered one week to one month apart. The use of this vaccine is no longer recommended.

Among the oral cholera vaccines, Dukoral (WC/rBS) consists of 1 mg of recombinant cholera toxin B subunit plus 2.5 x 10^{10} of four *V. cholerae* O1 strains. In adults, Dukoral (WC/rBS) is administered as two separate doses, 1 to 6 weeks apart. It confers 85% to 90% protection for six months. The protection remains at about 60% after two years.

A variant of the WC/rBS oral cholera vaccine that does not contain the cholera toxin recombinant B-subunit was available as Vabiotech vaccine (made in Vietnam). It was administered in two separate doses given one week apart.

The manufacture of this vaccine has been taken over by Shantha Biotechnics, with the trade name Shanchol. This preparation was evaluated in Kolkata in a randomised controlled trial including over one lakh participants. It was found to have a protective efficacy of 67% over two years in all age groups with few adverse effects. Based on these results, the WHO, in a position statement published in March 2010 recommends the use of the oral vaccine with initial immunisation (two doses) followed by a booster dose every second year. With the oral vaccine, diarrhoea, fever, vomiting and abdominal pain have been reported to occur in some patients.

MENINGOCOCCAL DISEASE

The case fatality rate for meningococcal infections is 10% to 15%. Immunisation plays an important role in preventing these infections. Outbreaks of meningococcal disease occur in crowded living conditions, such as in dormitories; in military recruits and in jail inmates. Immunisation should be restricted to high risk populations or for travellers, pilgrims and people attending fairs and festivals. Health care personnel handling outbreaks and laboratory workers need to be immunised.

Two types of vaccines are available: (i) polysaccharide vaccines; and (ii) conjugate vaccines. Polysaccharide vaccines are available as bivalent (A+C) or quadrivalent (A, C, Y, W135) preparations. The vaccine is available as a lyophilized vaccine containing 50 µg of polysaccharide per dose. After reconstitution with sterile saline solution, the vaccine has to be used on the same day, preferably within 8 to 12 hours. A single dose of 0.5 mL of the reconstituted vaccine is administered subcutaneously in the deltoid region. The vaccine does not induce herd immunity and has no effect on nasopharyngeal carriage.

For Haj pilgrims, a single dose of quadrivalent vaccine is given in accordance with the requirements of the Government of Saudi Arabia. Other than minor injection site reactions, adverse effects are rare. The vaccine can be safely given to pregnant women and HIV positive persons.

JAPANESE ENCEPHALITIS

Japanese encephalitis (JE), caused by a mosquito-borne flavivirus, is the most common vaccine-preventable cause of encephalitis in India. In endemic countries, JE is primarily a disease of children. No effective treatment is available for JE. The JE vaccine is primarily useful in the age group of 1 to 15 years. The vaccine is not recommended for routine use in adults. Vaccines used for immunisation are (i) mouse brain-derived inactivated vaccine that uses the Nakayama strain (e.g. BIKEN/ JE-VAX®) and (ii) PHK cell-cultured, live-attenuated vaccine (e.g. SA 14-14-2 vaccine). The SA 14-14-2 vaccine is administered subcutaneously as a single 0.5 mL dose in India. The vaccine is safe and few adverse effects have been noted.

YELLOW FEVER

This is a mosquito-borne viral disease that occurs only in some parts of Africa and South America. Travellers planning to visit such areas should be vaccinated. Yellow fever vaccine is a live-attenuated virus preparation made from the 17D yellow fever virus strain. A single subcutaneous injection of 0.5 mL of reconstituted vaccine is used. Mild headache, myalgia, low-grade fever, and other minor symptoms may occur after immunisation. Rare cases of post-vaccinal encephalitis have also been reported. Protective antibodies develop 10 days following immunisation.

HUMAN PAPILLOMA VIRUS

Carcinoma of the cervix is the commonest malignancy in Indian women. Infection with high risk strains of the human papilloma virus, such as HPV-16 and HPV-18 has been implicated in the pathogenesis of cervical cancer. Immunisation against these viral strains has been shown to reduce the incidence of carcinoma cervix. Immunisations should ideally be done before sexual activity commences. The Indian Academy of Pediatrics has included the HPV vaccine as a Category 2 vaccine and recommended its use in girls aged 10 to 12 years.

Two vaccines are currently licensed: A bivalent HPV 16/18 vaccine containing 20 µg each of L1 HPV16 and L1 HPV18 (GlaxoSmithKline - Cervarix™) and a quadrivalent HPV 6/11/16/ 18 vaccine containing L1 HPV6 and L1 HPV 18 (20 µg each) and L1 HPV 11 and L1 HPV16 (40 µg each) (Merck Sharp and Dohme – Gardasil™). Cervarix is given 0.5 mL intramuscular in the deltoid at 0, 1, and 6 months. Gardasil is given 0.5 mL intramuscular in the deltoid at 0, 2, and 6 months.

Vaccine efficacy is approximately 97% to 100% and protection lasts for at least five years. Booster doses are not recommended. Interruptions in the vaccine schedule, longer than one year, necessitate re-starting the schedule. The quadrivalent vaccine may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. It would be most effective when administered before exposure to HPV through sexual contact.

Local injection site reactions and headache are common. The vaccine is contraindicated during pregnancy and in patients with a history of hypersensitivity to any of the vaccine components. It can safely be given during lactation and to immunodeficient individuals.

HERPES ZOSTER

The vaccine is recommended for immunocompetent individuals aged 60 years or older. Herpes zoster vaccine has been found to decrease the incidence of herpes zoster by 51% and of post-herpetic neuralgia by 67%. The vaccine was licenced by the US FDA in May 2006. Unlike other adult vaccines, this vaccine requires freezer storage and is the most expensive vaccine routinely recommended for older adults.

CHICKEN POX

Vaccination against varicella is not recommended in developing countries.

The recommended immunisation schedule for adults (except for tetanus and rabies) is summarised in **Table 5**.

RECOMMENDED READINGS

1. CDC. Recommended Adult Immunisation Schedule – United States, 2010. *MMWR Morb Mortal Wkly Rep* 2010; 59:1-4.
2. CDC. Use of a Reduced (4-Dose) Vaccine schedule for postexposure prophylaxis to prevent human rabies. Recommendations of the Advisory Committee on Immunisation Practices. *MMWR Morb Mortal Wkly Rep* 2010; 59(RR-2):1-9.
3. CDC. Update on Influenza A (H1N1) 2009 Monovalent Vaccines. *MMWR Morb Mortal Wkly Rep* 2009; 58:1100-1.
4. Donahue JG, Belongia EA. The looming rash of herpes zoster and the challenge of adult immunisation. *Ann Intern Med* 2010;152:609-11.
5. Expert Group of the Association of Physicians of India on Adult Immunisation in India. Executive Summary. The Association of Physicians of India Evidence-Based Clinical Practice Guidelines on Adult Immunisation. *J Assoc Physicians India* 2009; 57:345-56.
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28.8 Perioperative Management

Prabha Adhikari

'*Primum non nocere*' (first do no harm) is the motto of medicine and the same holds good for perioperative medicine which is an art, based on weighing risks against benefits. There are certain questions faced by the surgeon and the patient who has to undergo surgery. Preoperative evaluation should try to answer the following questions:

1. What are the risks of surgery and general anaesthesia?
2. What are the predictors of those risks?
3. Can they be reduced by pre-operative measures?
4. What are the anticipated intraoperative and post-operative complications?
5. What are the measures in the event of these complications?

Perioperative management encompasses pre-operative evaluation, recommendations for prevention of intraoperative and post-operative complications, and management of post-operative complications.

PRE-OPERATIVE EVALUATION

First, classify your patient under ASA Scale, which will give a general idea to the surgeon and anaesthetist regarding risk of mortality and then classify the patient as high risk cardiac case, high risk pulmonary case, other high risk case or healthy individual (**Table 1**).

Table 1: American Society of Anaesthesiologist Physical Scale and Mortality Prediction in the Perioperative Period (For Emergency Surgery Mortality Doubles)

Class	Description	Mortality Rate
I	Healthy individual	0.1%
II	Mild systemic disease	0.2%
III	Severe systemic disease	1.8%
IV	Incapacitating systemic disease, which is a constant threat to life	7.8%
V	Moribund patient, who is likely to die with or without surgery	9.4%

ASSESSMENT OF CARDIAC RISK

Modified Goldman's Risk Index for non-cardiac surgery (**Table 2**) assesses the risk involved in cardiac patients for non-cardiac surgery. Recent myocardial infarction (MI), grade III or IV angina and active congestive heart failure, are the most important risk factors for cardiovascular mortality and morbidity.

Complications that occur in these high risk patients are acute myocardial infarction, cardiogenic pulmonary oedema, ventricular arrhythmia or cardiac death. Based on the scores, risk class is derived as shown in **Table 3**.

Other risk factors for cardiac disease which are not included in the Goldman's risk index include diabetes mellitus, poorly controlled hypertension, and poor exercise tolerance. Inability to exercise for at least two minutes on a bicycle at a rate of 50 revolutions per minute to a heart rate >99/min is a strong predictor of perioperative complications. Hence, all these points need to be considered, in addition to Goldman's risk index, in predicting cardiovascular morbidity/mortality.

Table 2: Modified Goldman's Risk Index for Non-cardiac Surgery (Detsky's modification) (Score >20 High Risk)

Risk Factors	Risk Score
Coronary artery disease	
MI within 6 months	10
MI more than 6 months old	5
Angina class III	10
Angina class IV	20
Unstable angina within 3 months	10
Alveolar pulmonary oedema or signs of CCF	
Within 1 week	10
Ever	5
Critical aortic stenosis	20
Arrhythmias	
Rhythm other than sinus or sinus plus Atrial premature beats >5	5
Greater than 5 ventricular premature beats	5
Poor general medical status	5
PO_2 <60 mm Hg, PCO_2 >50 mm Hg or Potassium <3 mEq/l, Bicarbonate <20 mEq/l or BUN >50 mg/dl, creatinine >3 mg/dl or Abnormal SGOT or signs of chronic liver diseases or Bedridden state due to non-cardiac causes	
Age >70 years	5
Emergency surgery	10

Table 3: Risk Class from the Goldman's Risk Index

Class	Scores	Mortality Rate
Class I	0 to 5	6%
Class II	6 to 12	7%
Class III	13 to 25	20%
Class IV	>26	100%

In 1999, Lee *et al.* revised Goldman's criteria for cardiac risk index and developed six independent predictors/variables which correlated with post-operative cardiac complications. Patients with more than 2 variables have a postoperative cardiac complication rate of ~10% and are considered to be high risk (**Table 4**).

Table 4: Revised Goldman's Criteria for Cardiac Risk Index

LEE Variables

1. High risk type of surgery
2. Ischaemic heart disease (includes any of the following: history of myocardial infarction, history of a positive exercise test, current complaint of chest pain that is considered to be secondary to myocardial ischaemia, use of nitrate therapy, or electrocardiography with pathologic Q waves)
3. Congestive heart failure
4. History of cerebrovascular disease
5. Pre-operative treatment with insulin
6. Pre-operative serum creatinine >2 mg/dL

LEE Criteria – Revised Cardiac Risk Index

Number of variables	Risk of major post-operative cardiac complication
0	0.4%
1	0.9%
2	7%
3	11%

Major risk factors: control and stabilise before surgery

- Unstable or severe angina
- Recent MI
- Decompensated HF
- Significant arrhythmias
- Severe valvular disease

Intermediate risk factors

- History of ischaemic heart disease
- History of compensated or previous HF
- History of cerebrovascular disease
- Diabetes mellitus
- Renal insufficiency

Minor risk factors

- Advanced age (greater than 70 years)
- Abnormal ECG (LV hypertrophy, left bundle branch block, ST-T abnormalities)
- Rhythm other than sinus
- Uncontrolled systemic hypertension

Elective Non-Cardiac Surgery and Anti-Platelet Therapy in Patients with Previous PCI

Anticoagulants like subcutaneous fractionated or unfractionated heparin do not substitute the antiplatelet protection of thienopyridine and/or aspirin therapy in patients with bare-metal or drug-eluting stents undergoing non-cardiac surgery.

Delay elective surgery until more than 1 year post drug-eluting stent placement (DES). In case it needs to be done, risk assessment with cardiologist for discontinuation of clopidogrel or ticlopidine for 5 days, or prasugrel for 7 days perioperatively is necessary. Proceed to surgery with aspirin or, if indicated, with dual antiplatelet therapy. If dual therapy or aspirin was discontinued give a single aspirin 325 mg dose immediately preoperative period and post-operatively continue aspirin and resume dual therapy as soon as feasible, preferably by 2nd/3rd day.

In patients who underwent balloon angioplasty only, delay surgery until more than 14 days post-balloon angioplasty. At more than 14 days proceed to surgery with aspirin. If aspirin therapy was discontinued, give a single aspirin 325 mg dose immediately pre-operatively and continue aspirin, postoperatively.

In patients with Bare metal stents, delay surgery until more than 45 days (preferred; minimum 30 days) post bare-metal stent placement. However, if surgery needs to be done whether before or after 45 days risk assessment should be done with cardiologist for discontinuation of clopidogrel or ticlopidine for 5 days, or prasugrel for 7 days pre-operatively. Proceed to surgery with aspirin or, if indicated, with dual antiplatelet therapy. If dual therapy was discontinued give a single aspirin 325 mg dose immediately pre-operatively. Post-operatively continue aspirin and resume dual therapy as soon as feasible, preferably by 2nd/3rd day.

Investigations in High Risk Cardiac Cases

In high risk cases, ECG, Echocardiography for detection of LV dysfunction, stress testing, intraoperative cardiac monitoring for arrhythmias, ST-T changes and invasive haemodynamic monitoring, such as arterial pressure, central venous pressure, pulmonary wedge pressure for high risk cases scheduled for high risk surgeries.

RISK OF PULMONARY COMPLICATIONS (PULMONARY RISK CASE)

There is no risk score in pulmonology to predict complications. However, there are general risk factors which predict post-operative pulmonary complications (**Table 5**).

Table 5: Pulmonary Risk Factors

Age >70 years
Obesity
Smoking history
Poor nutrition
Antecedent respiratory infection
Intrathoracic or upper abdominal surgery
Prolonged anaesthesia time
Poor general medical status
Pre-existing pulmonary disease: Obstructive lung disease is a greater risk than restrictive lung disease

Anticipated Complications

Minor complications

These include bronchitis, tracheobronchitis, and exacerbation of COPD.

Major complications

These include atelectasis, pneumonia, respiratory failure, need for prolonged ventilatory therapy, and pulmonary embolism.

Pre-operative Evaluation

It includes detailed history, respiratory rate, presence of cyanosis, clubbing, oedema, presence of emphysema, rhonchi, increased forced expiratory time, absent or decreased tidal percussion (indicative of COPD), Scadding sign (in-drawing of suprasternal notch with each inspiration) and fine crepitations indicative of

restrictive lung disease. Obstructive lung disease has more deleterious effects on a surgical patient.

Investigations for High Risk Care

Chest radiograph, spirometry, FEV1/FVC and FEV1 reliably predict risk of complications. Peak expiratory flow rate (PEFR) measurements done serially may predict post-operative complications. Persistent hypercapnia on arterial blood gas analysis in a patient with COPD is associated with pulmonary morbidity. Sputum microbiological studies and ECG are needed in some patients.

Measures to Reduce Complications

Several measures help in reducing complication rates (**Table 6**). In our own experience, daily postoperative PEFR measurements is highly recommended for prediction of complications. Artificial ventilatory facilities, throat suction, measures for adequate oxygen delivery, facilities for pulse oximetry, and arterial blood gases should be available.

Table 6: Measures to Reduce Pulmonary Complications Post-Operatively

Pre-operative measures
Smoking cessation (minimum of 8 weeks prior to surgery)
Optimise airway function – bronchodilators, corticosteroids, control of infection by antibiotics, chest physiotherapy
Weight reduction, if obese
Education on post-operative deep breathing exercise, importance of coughing, or use of incentive spirometry, wherever available
Post-operative measures
Early mobilisation and ambulation
Prophylactic lung expansion manoeuvres: deep breathe hourly or incentive spirometry
Adequate analgesia
Prophylaxis for deep vein thrombosis

Surgery in a Patient with Diabetes Mellitus

Half of all diabetics undergo surgery at sometime in their lives. Diabetic surgical patients have special problems due to metabolic, vascular and neurological impairments. They are also prone for infection and delayed wound healing.

Metabolic problem

Both ketosis, the effect of under treatment and hypoglycaemia, the effect of over treatment can adversely affect patients during surgery.

Vascular disease

CAD may induce acute myocardial infarction, cerebrovascular disease may induce stroke due to haemodynamic instability or hypoxia during surgery. Nephropathy may lead to acute kidney injury and other metabolic complications.

Autonomic neuropathy

It may induce haemodynamic instability and cardiac arrhythmias. Anxiety, anaesthesia and surgery may create stress and release anti-insulin hormones and consequently hyperglycaemia leading to infections and delayed wound healing. Insulin dependent diabetics have a higher risk of deep vein thrombosis.

Pre-Operative Evaluation

Assess glycaemic status: Fasting and post-prandial blood sugar and HbA1c. If the HbA1c is >9%, insulin should be started. If above 12%, consideration should be given to improving control before elective surgery is undertaken.

Assess cardiac risk by detailed history and cardiac risk score.

Evidence of peripheral vascular disease may indirectly suggest co-existing coronary artery disease.

Look for carotid bruits.

Assess for cardiac autonomic neuropathy by electro-cardiogram for CAD and heart rate variability (HRV) after deep breathing. HRV of <5 beats/min signifies serious cardiac autonomic neuropathy and prone for arrhythmias.

Assess renal risk by blood urea, creatinine, electrolytes, urinary proteinuria, and microalbuminuria.

Detect hypertension or orthostatic hypotension.

Pre-Operative Measures

Optimise treatment of diabetes and control of hypertension.

Aims of the treatment

- Avoid ketosis or hypoglycaemia. Hypoglycaemia may go unrecognised in a patient under anaesthesia and may lead to permanent damage. The ideal blood glucose level is 150 to 200 mg/dl. Tight control of 80 to 150 mg/dl is recommended for those with shorter duration of diabetes.
- Adequate insulin administration.
- Anticipate cardiac or renal problems.

Control of blood glucose during surgery

All patients must have their fasting capillary blood glucose checked on the day of surgery.

Diet controlled diabetics and well controlled diabetics on metformin or short acting sulfonylureas—no food, no glucose, and no insulin.

Those on long-acting sulphonylureas—these drugs are stopped one day prior to surgery

They need intravenous glucose on the day of surgery. All major surgeries and insulin treated patients are managed with GIK infusion as follows:

Glucose-insulin-potassium regimen: Skip morning dose of insulin. 5 to 10 units of insulin + 10% dextrose + 10 MEq potassium – at the rate of 100 ml/hr starting half an hour before surgery (if diabetes poorly controlled, 10 to 20 IU of insulin and 5% dextrose can be used). Use of 5% dextrose with 10 IU of insulin and 10 MEq of potassium has been used with excellent results.

Post-Operative Management

Patient needs continued glucose infusions with insulin till oral feeds are started. Once oral feeds are started, either rapid acting insulins may be used or alternatively only basal insulin may be given if patients are tube fed or on liquids only. Once they are taking regular meals, pre-operative insulin regimen may be administered.

Other post-operative measures

Frequent capillary blood glucose monitoring, repeat ECG, early ambulation and prophylaxis for deep vein thrombosis for high risk cases and incentive spirometry.

SURGERY IN A HYPERTENSIVE PATIENT

Hypertension, per se, is not a risk factor for surgery. However, a poorly controlled hypertensive with or without CAD can develop haemodynamic instability during surgery, which can be deleterious to the heart. Hypertension should be well controlled prior to surgery. A blood pressure of >180/110 mm Hg warrants to postpone the surgery. However, Stage I and Stage II hypertension with no additional cardiovascular disease risk, can proceed for surgery. Patients on ACE inhibitors or ARB may develop post-operative hypotension if volume depleted.

Recommendations

The patient should continue his antihypertensive drug even on the day of surgery with a sip of water and continue the same post-operatively after resumption of oral feeds. Only diuretics need to be stopped 24 to 48 hours prior to surgery. Patients on diuretics need a serum potassium check before surgery. Acute uncontrolled perioperative hypertension can be controlled with sodium nitroprusside, nitroglycerine, hydralazine, diazoxide or labetalol injection. Beta blockers appear to be particularly attractive agents for the treatment of pre-operative high blood pressure. Beta-blockers effectively modulate blood pressure fluctuations; reduce perioperative coronary ischaemic episodes, post-operative atrial fibrillation, and other cardiovascular complications. Drugs like sublingual nifedipine and enalapril cause unpredictable responses and may cause significant hypotension, which can be deleterious in patients with coronary artery disease and cerebrovascular disease.

HOW MUCH SHOULD YOU INVESTIGATE A HEALTHY INDIVIDUAL?

Who is a healthy individual? One who has no disease, does not smoke or consume alcohol, exercises regularly and has normal weight and nutrition is considered normal. If age is less than 40 years the investigations needed are haemoglobin and blood glucose. Haemoglobin, blood glucose, blood urea, and ECG are needed if age is between 40 and 50 years. The serum creatinine and chest radiograph are additional investigations to the previously mentioned tests in patients more than 60 years of age.

However, the situation in India may be totally different. Routine chest radiograph may uncover common diseases like tuberculosis. Eosinophil count is also important as tropical pulmonary eosinophilia, which is common in India, may predispose to bronchospasm during intubation. Elective surgery needs postponement in the event of a recent respiratory infection.

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28.9 Law and Medicine

NK Grover

INTRODUCTION

The practice of Medicine involves not only scientific and technical knowledge, but also social, ethical and moral issues. The chosen person for delivery of health care—'the doctor' is perceived by society that he should be able to deliver a comprehensive range of healthcare activities, social work responsibilities and they would seek a 'Friend, Philosopher and Guide' in the doctor. The concept of health care has evolved to mean a comprehensive scheme, which promotes good health, prevents ill health, cures the sick and rehabilitates the disadvantages. This is a scheme which involves interaction amongst economic upliftment, public health, health education, targeted prevention and cure. Attempts to match the range and extent of health care to available resources constitute a yet unresolved ethical dilemma. The phenomenal advances in medical practice in recent times have elevated medical practise from its empirical avenues to a precision technology which has increased the cost very significantly. Failure to appreciate this qualitative change has led to the ethical dilemmas in doctors and the society in modern times.

There has been a significant change in the relationship between the patients and the physicians, from that of the 'Prime Healer Equivalent to God' to a mere 'Service Provider' in the present era. But the practice of medicine is guided by the principle '*Primun non nocere*' at least do no harm to the patient.

DOCTOR-PATIENT RELATIONSHIP

Doctors have always enjoyed respect much more than any other professional—a friend, philosopher, guide and even revered as 'Next only to God' because they have served to mitigate illness and promote health. The cornerstone of the doctor-patient relationship has been confidence, faith and trust which have gradually been eroded. The social position of doctor has changed to that of a service provider with obligation to inform and perform 'consented treatment'. This has happened due to many reasons like high tech, high cost medicine, rise in consumerism, increasing expectation of society and western influence where 'liability litigation' is order of the day.

The doctor-patient relationship has many moral, ethical and legal aspects while the relation has conventionally been fiduciary or trustee in nature. In today's era it has taken the shape of legal contract with many obligations. British Medical Association recommends healthy relationship between the two based on the concept of 'partnership and collaborative efforts' arrived by frank conversation, communication, consideration and consent. Such process allows patient to choose his preference and line of treatment with the guidance of physician leading to informed consent and shift of responsibility of outcome of disease and treatment of patient to some extent onto the patient in addition to treating doctor.

CONSENT

This is the crux and pivot which allows a doctor to manage illness in an appropriate manner. The consent is implied in outdoor consultation, for indoor treatment for any intervention or operation, it has to be taken in writing. It is an ethical and legal requirement and an essential obligation on the part of treating doctors, not obtaining a valid consent amounts to breach of duty. It should be as informed as possible, in the language patient understands and always properly documented. To give valid consent, a patient should be in sound state of mind, above the age of 18 years and put his signatures/thumb impression duly witnessed. Further consent today is the key to 'defence of doctor'. Special situations like serious patients require high risk or special or explicit consent. However, in emergency and life-threatening situations, the treatment cannot be withheld for want of consent. Special situations like unknown, unconscious patient or patient with insane mind require special avenues to tide over the issue of informed consent. In cases of infants and children consent may be given by the parent or guardian.

PATIENT'S CHARTER

Since enactment of Consumer Protection Act (1986) and its Amendment in 1993, the Central Consumer Protection Council (CCPC) in 1994, developed a 'Health and Patients Charter' which was notified by Government of India in February 1996. Some of its important features are:

1. Right to Healthcare and Humane Treatment
2. Right to Choice of Care
3. Right to Acceptable Safety
4. Right to Adequate Information
5. Right to Consent and Refusal
6. Right to Confidentiality
7. Right to Redressal of Grievances
8. Right to Health Education
9. Right to Participation and Representation
10. Right to Healthy Environment

The practitioners of medicine and institutions providing health care are obliged to respect patient's rights and privileges. Hospitals have similarly been made responsible with extra obligations like 'Right of Access' to all health facilities without any discrimination of sex, religion, caste or economic status. Emergency care, proper record keeping, patient safety protocol, standard of care, proper disposal of medical waste, etc. have specific guidelines and laws. Their preservation/destruction/certification and the medico-legal aspects require full understanding of responsibility by medical professionals. Hence doctors should carefully follow the stipulated rules to avoid any litigation in future.

MEDICAL ETHICS

Medical Council of India (MCI), a statutory body, was established in 1934 and re-enacted as MCI Act (1956) by the Parliament, Government of India. It is vested with powers to regulate and maintain standard of medical education, permissible standard of medical ethics and provision of penalties in the event of any violation of Code. Code of Medical Ethics was revised in 1970 and amended in December 2009 where it has enunciated doctor-pharmaceutical industry relationship in addition to existing ethical norms. Each doctor has to abide by this. MCI was superseded by the Board of Governors vide Indian Medical Council Amendment Ordinance 2010 vide Government of India Gazette Notification No. 2 of 2010 dated 15th May, 2010 to improve its functioning and tide over some of the alleged irregularities like nepotism, favouritism and financial irregularities.

MEDICAL NEGLIGENCE

'Negligence has been defined as omission to do something which a reasonable man guided by ordinary considerations would do or doing something which a reasonable and prudent man would not do' (Black's Law Dictionary). The word 'Negligence' under Legal Glossary (Govt. of India) means want of attention to what ought to be done or looked after, lack of proper care in doing something which a reasonable professional guided by considerations which ordinarily regulate the conduct of human affairs would do or not doing something which a prudent and reasonable man would not do. The British and Indian courts have repeatedly upheld this principle that conditions must be fulfilled to prove and have been enunciated by established latest judgments of Supreme Court of India.

The medical negligence arises only when you owe a duty. There is dereliction (breach) of that duty and damage (harm, complication or death) occurs which is 'directly attributable' to treatment given to the patient and not a mischance or complication which is well documented.

Types of Medical Negligence

Negligence has many manifestations, e.g. it may be active, passive, comparative, collateral, concurrent, continued, contributory, hazardous, gross, wilful, reckless and even criminal depending on the circumstances. Ordinarily, medical negligence is tried under Civil Laws, Laws of Contract, Tort or Consumer Protection Act, but in India it has criminal liability also.

Civil Laws Governing Medical Negligence and Laws of Contracts

When a doctor accepts or undertakes to treat a patient, in legal sense he is entering into a contract with the patient to render services adequately but not entering into any contract for curing the patient. He undertakes to use best of his skills and knowledge at all steps in diagnosis, treatment, administration of medicines, surgery and postoperative care, etc. This obligation is further augmented by law, commonly known as 'Law of Torts'. In Law of Torts, 'Tort' can be defined as 'Breach of Legal Duty' which is independent of contract and this breach entails damages. For medical professionals domain of 'Specific Tort' covers professional negligence. The patient can file a suit for damages/compensation by taking recourse to law of contract as well as Torts in Civil Courts.

Consumer Protection Act

To overcome the issue of cost and time taken by Civil Courts to settle the medical liability cases, Government of India promulgated a simple legal remedy 'Consumer Protection Act (1986)'. This Act provides for settlements of medical negligence suits and award compensation by Three Tier Redressal Mechanism, i.e. Forum at District level, State level, National Consumer Redressal Commission. Finally, Appellate Tribunal can also entertain cases directly where the financial stakes are high. After the National Commission one can only appeal to the Supreme Court.

Criminal Medical Negligence

There is very thin line of margin which can bring medical negligence within the ambit of criminality and attach liability under penal laws. To be so, negligence must be grave, gross, intended or wilful and with total disregard to the life of patient and doctor should have acted in haste without due care or without a valid consent. Supreme Court has clarified that medical negligence will ordinarily be charged under Section 304A of IPC. This is a bailable offence and if proved draws up to 2 years of rigorous imprisonment and fine or both.

OTHER ACTS OF MEDICAL NEGLIGENCE

Besides the Indian Penal Code (1860), there are certain specific Acts which deal with the medical negligence in so far as the criminal liability is concerned and these are briefly discussed hereinafter.

Medical Termination of Pregnancy Act, 1971

It provides that pregnancy can be terminated by a registered medical practitioner, on fulfilment of certain conditions. Under the provisions of this Act, a pregnant woman who has attained the age of 18 years pregnancy can be terminated with her due consent. In case of a woman who has not attained the age of 18 years or who has attained the age of 18 years and is a lunatic, pregnancy cannot be terminated except with written consent of her guardian. Under Section 4, MTP has to be done by a registered medical professional who is qualified to carry out this procedure and also at a place which is recognised and duly registered for medical termination of pregnancy.

The Pre-Natal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994

The Act provides for the regulations of prenatal diagnostic test or techniques for the purpose of detecting the sex of unborn child and its misuse which may lead to female foeticide. Any medical geneticist, gynaecologist, registered medical practitioner or any person who owns a genetic counselling centre or genetic laboratory or a genetic clinic or is employed therein, renders his professional and technical services and who contravenes any of the provision of the Act or Rules shall be punishable with imprisonment for a term up to 3 years which may extend to five years and with fine of 50,000/-. The offence, under this Act, is cognizable, non-bailable and non-compoundable.

Registration of Births and Deaths Act, 1969

The Act provides that every birth has to be registered with the Government and similarly every death has also to be

registered. If not implemented then any professional or organisation who does not comply or who refuses to issue a certificate with effect to the same can be punished as per law.

The Transplantation of Human Organs Act, 1994

The Act provides for the regulation of removal, storage and transplantation of human organs for therapeutic purposes and for prevention of commercial dealing in human organs and matters concerned with or incidental thereto. The Act provides punishment for removal of human organ without authority (Section 18). Section 19 deals with punishment for commercial dealings in human organs. Section 20 deals with residuary offences which have not been provided in other sections of the Act.

Article 21 of the Constitution of India, provides as under:

No person shall be deprived of his life or personal liberty except according to procedure established by Law. The Courts while interpreting Article 21, have held that Article 21 (One of the Fundamental Rights guaranteed by the Constitution), cannot be given a meaningful interpretation unless the Right to Life covers the real meaning of the word 'life', which includes right to proper health, which includes treatment as well. The courts have severely punished the doctors who have failed to provide First Aid or proper treatment for various reasons including want of money, etc. The courts have given a very broad perspective to Article 21 of the Constitution vis-à-vis the medical profession and have applied the dictum of Fundamental Right. Reference here is made of guidelines laid in RN Katara Public interest litigation wherein Supreme Court has laid that every doctor is obliged to provide treatment in emergency.

General Principles of Handling Case of Medical Negligence

These have been lucidly and elaborately explained in the decision of Three Judge Bench of Supreme Court in Jacob Mathew versus State of Punjab and other (2005). Further Justice Markandey Katju in his famous judgment in Supreme Court (Sep 2009), has analysed and described various aspects of medical negligence and cautioned that merely because a complaint has been made that a treatment has been unsuccessful or caused mishap, doctors should not be harassed. Medical professionals operate in a sphere where success cannot be achieved in every case. Very often success and failure depend upon factors beyond the professional's control. The judgment has clearly laid down the procedure in the event of complaint of medical negligence against doctor/hospital whether in District/State/National Consumer Forum or Civil or Criminal Court. The complaint has to be referred to competent doctor/committee of doctors specialised in the field. Only when found by experts that there is a *prima facie* case of medical negligence, should notice be issued to doctor/hospital. He further warned the police officials not to arrest or harass doctor. He emphasised the courts and consumers to base their opinion on the reports, findings of experts in medical science and must not substitute their own views over those of specialist.

INDIAN PENAL CODE 1960

Some clauses relevant to the medical profession are:

Section 304A IPC—Causing Death by Negligence

Whoever causes the death of any person by doing any rash or negligent act not amounting to culpable homicide shall be punished with imprisonment of either description for a term which may extend to 2 years or with fine or with both.

Section 304 IPC—Punishment for Culpable Homicide not Amounting to Murder

Whoever commits culpable homicide not amounting to murder shall be punished with imprisonment for life or imprisonment of either description for a term which may extend to 10 years and shall also be liable to fine if the act by which the death is caused is done with the intention of causing death or of causing such bodily injury as is likely to cause death, or with imprisonment of either description for a term which may extend to 10 years or with fine or with both, if the act is done with the knowledge that it is likely to cause death but without any intention to cause death or to cause such bodily injury as is likely to cause death.

Sections 312-316 of IPC

Sections 312-316 of the Indian Penal Code (IPC) deal with miscarriage and death of an unborn child and depending on the severity and intention with which the crime is committed, the penalties range from 7 years to life imprisonment for 14 years and fine.

Section 312—Causing Miscarriage

Whoever voluntarily causes a woman with child to miscarry shall, if such miscarriage is not caused in good faith for the purpose of saving the life of the woman, be punished with imprisonment of either description for a term which may extend to 3 years or with fine or with both and if the woman be quick with child, shall be punished with imprisonment of either description for a term which may extend to 7 years and shall also be liable to fine.

Section 313 of IPC—Causing Miscarriage without Woman's Consent

Whoever commits the offence defined in the preceding section without the consent of the woman, whether the woman is quick with child or not, shall be punished with imprisonment for life or with imprisonment of either description for a term which may extend to 10 years and shall also be liable to fine.

Section 314 of IPC—Death caused by Act done with Intent to Cause Miscarriage

Whoever, with intent to cause miscarriage of woman with child, does any act which causes the death of such woman, shall be punished with imprisonment of either description for a term which may extend to 10 years and shall also be liable to fine.

But if act is done without the consent of woman, shall be punished either with imprisonment for life or with the punishment above mentioned.

Section 315 of IPC—Act done with Intent to Prevent Child being Born Alive or to Cause it to Die after Birth

Whoever, before the birth of any child, does any act with the intention of thereby preventing that child from being born alive or causing it to die after its birth and does by such prevent that child from being born alive, or causes it to die after its birth, shall, if such act be not caused in good faith for the purpose of saving the life of the mother, be punished with imprisonment of either description for a term which may extend to 10 years or with fine or with both.

Section 316 of IPC—Causing Death of Quick Unborn Child by Act Amounting to Culpable Homicide

Whoever does any act under such circumstances, that if he thereby caused death he would be guilty of culpable homicide, and does by such act cause the death of a quick unborn child, shall be punished with imprisonment of either description for a term which may extend to 10 years and shall also be liable to fine.

THE DRUGS AND COSMETICS ACT

The laws relating to drugs are called the Drugs and Cosmetics Act. They deal with various aspects of manufacture, sale, supply and distribution of drugs including fixation of prices.

The Drugs and Cosmetics Act 1950 (26 of 1950)

The first Act was promulgated in the year 1940. It was amended in the year 1950 and is now known as the Drugs and Cosmetics Act 1950 (26 of 1950). It provides for the control of the sale, supply and distribution of drugs. Drug Controller of India (Ministry of Health), Government of India is responsible for regulation, import and introduction of new drugs as well as permission for drug trials in India. There is a provision for fixing of prices and maximum quantities which can be held or sold.

The Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954

This Act briefly deals with the control of advertisement and in certain cases deals with prohibiting advertisement of certain drugs for magic treatment of certain diseases and disorders. This also lays down the prohibition of misleading advertisement relating to drugs.

CONCLUSION

The subject of ethics, civil, criminal laws governing medical negligence and practice of medicine is vast. Some areas like Medicolegal Cases, Autopsy/Postmortem, Research and Drug Trials, Quality Assurance, Nursing Home Act, Shop and Establishments Act, Patient Safety Concerns, Disposal of Medical Waste are important areas which need detailed discussion but are not covered in this chapter. But it is the responsibility of doctor to know about these rules and regulations so that he can always be on right side of law. We now know that there are a plethora of rules, laws, regulating medical practise and medical negligence the profession need not fear in their practice. The law has always been considerate to the medical profession while dealing with medical negligence and takes due consideration of the circumstances, facility and infrastructure available to the doctor.

The courts have always maintained that doctors have to provide due care with diligence and it is not expected of him to provide the very best which a brilliant doctor may offer but the basic which a ordinary doctor ought to know. The Supreme Court has opined that doctor can only be prosecuted if there is 'gross medical negligence'.

Similarly, the courts have observed an increase in frivolous and vexatious litigations. To avoid these, reverse fines have also been imposed on litigants. Definite guidelines are enunciated to protect the dignity and physical safety of doctors and the para-medical staff working with them.

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28.10 Travel Medicine

Yash Pal Munjal

INTRODUCTION AND DEFINITION

'Travel medicine' has gained considerable importance and understanding because of the phenomenal increase in the people travelling across the globe. According to estimates by World Tourism Organisation, international tourist arrivals worldwide during 2010 were approximately one billion and it will escalate to 1.6 billion by the year 2020. Travel is associated with health hazards. It is estimated that 20% to 70% of the travelling population reports a health problem, 1% to 5% seek medical attention and 0.1% to 1% need acute emergency medical care and evacuation. It is estimated that one person in every 100,000 dies due to one reason or the other. Accidents contribute significantly to morbidity and mortality. This has led to the development and progress in 'Travel medicine'.

Travel medicine is an inter-disciplinary speciality concerned not only with the prevention of infectious diseases during travel but also the personal safety of the travellers and avoidance of risks. It also provides information about avoiding health risk to the places and the people where the sick individual is visiting. The Travel Medicine may be considered in the following broad heads:

PRE TRAVEL—GENERAL ADVICE

Any person travelling outside the frontiers of his/her country should seek advice from doctors trained in this speciality or the speciality clinics dealing with travel medicine. This advice ideally should be sought about 8 to 12 weeks before the date of travel and in cases where the travel is planned at the last moment even just before the visit is undertaken. The doctor must understand the following factors if he has to give useful and coherent advice to the travellers:

- Mode of transport
- Destination(s) – demography, disease profile of the country and places to be visited
- Duration and season of travel
- Purpose of travel
- Standards of accommodation and food hygiene
- Behaviour of the traveller
- Underlying health of the traveller

Traveller should be prepared for any eventuality—changes in the travel plans, loss of money, baggage and documents. Therefore, it is suggested that the individual should take an extra supply of medication for about two weeks. A duplicate copy of all the documents should be in the baggage including passport and related documents, detailed history of vaccination and prescription from the doctor, eye glasses and a small telephone directory of numbers for insurance and credit card replacements. A copy of such documents may also be kept at home which can be accessed easily by a relative or friend.

Every traveller should preferably have a health travel insurance, and must understand clearly the extent to which travel related reimbursement is permissible and expenditure can be incurred. They should carry with them a 'first aid kit' so that they can attend to themselves in an emergency. The contents of the basic medical kit (first aid items) are adhesive tape, antiseptic wound cleanser or soap, bandages, scissors, safety pins, emollient (lubricant) eye drops, insect repellent, insect bite treatment, antihistamine tablets, oral rehydration salts, antidiarrhoeal medication and common antibiotics which the traveller can use himself in case of diarrhoea, infections of the skin and soft tissue, respiratory and urinary tract along with antimalarial medication, antibacterial ointment, antifungal powder and insecticide besides adequate supplies of condoms and oral contraceptives. Special precaution has to be taken for travellers at the extreme of ages, pregnancy and associated disability. Some of the specific issues are discussed in the following paragraphs.

SPECIFIC ADVICE

Accidents

Accidents are one of the major causes of disability and mortality. This gets compounded with the varying 'On Road Travelling Norms' followed in other countries. Drinking and driving should not be mixed. The traveller should not drive a particular type of vehicle which he is not conversant with. It is also advisable to have protective gear especially while riding two-wheeler transport.

Animal Exposure

Exposure to animals at places of travel can increase the risk of zoonotic diseases as well as rabies. Rabies is endemic in some under-developed countries and the traveller is advised not to engage contact with unfamiliar animals. Rabies exposure prophylaxis may be useful for travellers who are on long visits to some of the endemic areas.

Medicinal Interactions

The traveller should be conversant with all the drugs which he is carrying and any drug—drug interaction thereof. It is useful to remember that antacids and antidiarrhoeal drugs frequently interfere with the absorption of other medications. While purchasing extra supplies in other countries, be careful with regard to quality of drugs. Therefore, always purchase medicines from a good quality store and get a receipt.

Sexually Transmitted Diseases

Travellers become uninhibited during vacations abroad when they may engage themselves in unprotected sexual activity. Therefore, it is important that they carry with them good quality and adequate supplies of condoms while travelling. Women should carry oral contraceptive pills. STD organisms are antibiotic resistant in some of the countries, therefore absolute care and protection is a must.

Exposure to Ultraviolet Radiation

In tropical countries, or at high altitude, the sun exposure can be more intense than expected. Travellers should use broad

spectrum sun screen creams with UVA and UVB protection. Tetracycline and ciprofloxacin which are often recommended for travellers' diarrhoea or malaria prophylaxis can cause sun-induced rashes. In addition, sun glasses may be useful.

Swimming

Travellers are advised to undertake swimming only in hygienic and chlorinated pools because the other waters may be contaminated with bacteria from sewer or industrial waste, etc. Travellers must note about the risk of schistosomiasis in the area. If the traveller is bathing in questionable sources of water he should dry up vigorously and as rapidly as possible. Protection of feet must be ensured.

High Altitude

Travelling to places where the altitude is above 10,000 feet may cause acute mountain sickness. This usually presents with dizziness, headache, fever, chills or vomiting. Severe illness includes high altitude pulmonary oedema, confusion and extreme lethargy (high altitude cerebral oedema). The travellers are advised to travel at high levels slowly, acclimatise themselves to high altitudes and should not undertake strenuous activity.

Use of alcohol and tobacco should be significantly reduced. For minor sickness acetazolamide can be used. Rest and acclimatisation may relieve discomfort. If extreme symptoms appear, traveller must be evacuated to lower levels as quickly as possible.

Arthropod-Borne Diseases

This can be a reason for morbidity and prolonged sickness. A bite by an insect or reptile may cause pain or inflammation at the site of the bite or sting. Certain generalised reactions are known due to the venom injected or allergic reaction. Moreover arthropods can transmit serious potentially life-threatening diseases including malaria, yellow fever, dengue haemorrhagic fever, filariasis (mosquitoes), viral encephalitides (mosquitoes, ticks), onchocerciasis (black flies), leishmaniasis (sand flies), African trypanosomiasis (tsetse flies), American trypanosomiasis or Chagas diseases (reduvid or kissing bug), plague and tungiasis (fleas), typhus (fleas, lice, ticks) and relapsing fever (lice and ticks).

Arthropods vary according to different geographical conditions. Vaccines are available to protect individuals against some of these illnesses. Therefore, it is preferable to use them but the advice must be tailored to the geographical area to be visited.

Following precautions and preventive steps can be helpful:

- Avoid walking in the countryside especially in the evening. Always wear light coloured long sleeved shirts and long pants with preferably gum boots. Wear footwear at all times and always shake footwear before wearing.
- Use insect repellents, bed nets and good camps.
- Sleep in air-conditioned or well-screened rooms or under bed nets in areas where arthropod borne diseases are present.
- Prior to sleeping, spray the room/net with anti-insecticide spray. The net should be of good quality and should cover the bed on all sides.
- Avoid perfumes, scented creams, lotion, etc.

Malaria

Travellers visiting countries which are considered malarial zones are advised to take prophylactic treatment. This treatment has to be based on the type of Plasmodia and their resistance patterns in the area of travel. The broad outline for prophylaxis is given in the **Table 1**.

Table 1: Medications and Regimes for Malaria (Prevention)

Name of Drug	Dose	Side-effects
Chloroquine Phosphate (Chloroquine sensitive areas)	Paediatric dose: 5 mg per kg per week Adult: 500 mg once a week Start 1 week before travel and continue 4 weeks after travel every week on same day of the week	Side effects are uncommon and could be dizziness, headache, nausea and vomiting Can exacerbate psoriasis Discontinue medicine if visual changes occur
*Mefloquine (Areas with Chloroquine resistance)	Paediatric dose: 5 mg per kg if weight is less than15 kg Adult: 250 mg once a week Start 1 to 2 weeks before travel and continue 4 weeks after the travel. Take it after the travel. Take it after food and with plenty of water.	Dizziness, vomiting, anxiety, restlessness, ectopics. May exacerbate already existing psychiatric disturbances or depression. Can trigger and interact with anti-epileptic and cardiac drugs. Do not use in major psychiatric disorders, seizure disorders and cardiac conduction defects.
*Doxycycline Hyclate	100 mg/dL Start 1 to 2 days before travel and continue 4 after the travel	It can cause skin rashes and an intense burn with exposure to sun weeks (use extra sun screen) and vaginitis in women. Do not take with milk products or antacids. Do not use in children below 8 years, pregnant women and nursing mothers.
*Atovaquone/ Proguanil	Weight based for children 250 mg/100 mg/dL beginning 1 to 2 days before and discontinue 7 days after. Take with food or milk	Side effects are uncommon Can cause severe or uncontrolled vomiting, diarrhoea, fever, nausea, stomach pain, loss of appetite, dark urine, clay coloured stools, jaundice or mouth sores. Do not use in renal failure, pregnancy or nursing mothers. Use with caution in patients with liver disease
*Chloroquine Phosphate + Proguanil	Same as above This combination may be started 1 to 2 days before entering and continued for 4 weeks after arrival	Same as above

** Useful in resistant P. falciparum.*

Traveller's Diarrhoea

Traveller's diarrhoea has been defined as the occurrence of three or more loose stools each day or any number of loose stools accompanied by abdominal cramps, fever, vomiting occurring among travellers usually from developed to developing countries. It affects 20% to 70% of travellers when travel is confined to 2 weeks or less. Developing countries of Asia, Africa and Latin America are high risk areas. Intermediate risk areas are Caribbean Islands, Israel, Southern Europe, South Africa and China while North America, Europe, Japan and Australia are low risk areas.

Incidence is highest among very young (40%) presumably owing to increased contamination and decreased immunity. Incidence is high in the 15 to 29 years age group (29%), perhaps owing to adventurous style travel and the ingestion of higher volume of potentially contaminated food. Unpeeled fruits, uncooked vegetables (salads) and cooked meals that have been stored at inadequate temperatures or cooked at insufficient temperatures are believed to be main source of enteric pathogens for travellers. Onset of diarrhoea is usually within the first week of travel. Duration of illness usually is short and self limiting to 24 hours in 20%, 2 to 7 days in 14% to 16% and 1 week or longer in 20% of cases. The average individual will experience four loose stools associated with abdominal cramps in 20% to 60% of cases, bloody stools (15%), fever (10%) and vomiting (10%). Clinical characteristics of illness are related to organisms responsible.

Prevention

- Drink safe water.
- Avoid uncooked cold food which is not boiled or steaming hot.
- Avoid food from street vendors
- The safe beverages include:
  1. Boiled water beverages—tea or coffee.
  2. Carbonated bottled drinks (keep in mind that large intake of mineral water can cause mild diarrhoea from the cathartic effect of the minerals).
  3. Canned/boxed fruit juices.
  4. Bottled/canned alcohol containing beverages—beer or wine in moderation.

Recommendations for water treatment include the following:

- Boil and cool water before drinking.
- Use iodine tablets as directed. Be careful if using for pregnant women as it may interfere with foetal development.
- Use chlorine dioxide tablets as directed.
- Use a portable water filter available at Sports Goods Stores or General Stores. Several versions of portable UV light sources are available including litre water bottles with UV light or filters built in.

Treatment

Initial treatment should consist of using binders like bismuth and/or loperamide. In case it is severe and associated with fever, antibiotics may be used. If not controlled and/or associated with fever treat like any other acute infective diarrhoea.

Vaccinations for Travellers

Vaccinations for people travelling abroad are generally safe. The advice regarding vaccination varies according to the geographical area to be visited. All vaccinations for travellers are listed in **Table 2**.

The details about the dosage and frequency of immunisation are given in the Chapter on 'Adult Immunisation' (Chapter 7, Section 28).

Pregnant Traveller

Pregnant women have a less effective immune response which makes them more vulnerable to have severe or potentially fatal complications from infections, such as malaria, typhoid fever and amoebiasis. The pregnant traveller should get current and specific advice from experts who can contribute significantly to her safety, health and her future new born. Civil aircrafts do not allow travel beyond 36 weeks of pregnancy.

Table 2: Vaccinations for Travellers

Category	Vaccine	
Routine Vaccination	Diphtheria, Tetanus and Pertussis	Pneumococcal Disease
	Hepatitis B	Poliomyelitis
	Haemophilus influenzae Type B	Rotavirus[a]
	Human Papillomavirus[a]	Tuberculosis[c]
	Influenza[b]	Varicella
	Measles, Mumps and Rubella	
Selective use for travellers	Cholera	Rabies
	Hepatitis A[d]	Tick-Borne encephalitis
	Japanese Encephalitis[d]	Typhoid Fever
	Meningococcal Disease[d]	Yellow Fever[d]
Required Vaccination	**Yellow Fever (See Country List)	Meningococcal Disease and Polio (required for Saudi Arabia specially for Haj pilgrims)

*** It is applicable in certain countries to consult.*

a. These vaccines are currently being introduced in some countries.

b. Routine for certain groups and risk factors, selective for general travellers.

c. No longer routine in most industrialised countries.

d. These vaccines are also included in the routine immunisation programme in several countries.

Avian Flu

The travellers going to areas affected by H5N1 virus must have received seasonal influenza vaccine. They should avoid all direct contact with birds including domestic poultry or touching surfaces contaminated with poultry secretions. All food from poultry including eggs should be cooked thoroughly. Egg yolk should not be liquid or runny. Seek immediate medical help if affected with fever, cough, rhinorrhoea, difficulty in breathing, etc.

SOME OTHER TRAVEL RELATED COMMON AILMENTS

Jet Lag

'Jet lag' is a syndrome consisting of symptoms, such as fatigue, weakness, drowsiness and irritability. It is caused by disruption of circadian cycle. Various unproven but widely recommended measures include increased hydration, exercising (i.e. walking in the plane), administration of melatonin and administration of short acting hypnotics.

Diet and nutrition play an important role in the management of jet lag. High carbohydrates and protein diet is advocated. Alcohol and caffeine should be used in moderation.

Motion Sickness

It is caused by travelling and consists of pallour, cold sweating, nausea and vomiting. The drugs with a proven record of safety and efficacy are scopolamine, antihistamines (dimenhydrinate, meclizine) and dextroamphetamine. Of these drugs, the transdermal scopolamine patch is the most effective with less side effects.

Table 3A: Insulin Adjustment Schedule – Eastbound Travel Across Six or More Time Zones

Dose Schedule	Day of Departure	First Morning at Destination	10 hr after Morning Dose	Second Day
Single dose schedule	Usual dose of Insulin	Two-thirds of usual insulin dose	Test blood glucose. Give remaining one-third a.m. dose if glucose is >240 mg/dL	Usual dose
Double dose schedule	Usual a.m. and p.m. doses of insulin	Two-thirds of a.m. dose	Test blood glucose. Give usual evening dose and remaining one-third morning dose if glucose >240 mg/dL	Usual two doses

Table 3B: Insulin Adjustment Schedule – Westbound Travel Across Six or More Time Zones

Dose Schedule	Day of Departure	Test Blood Glucose 18 hr after a.m. Dose	First Morning Destination
Single dose schedule	Usual Insulin dose	One-third of usual morning insulin dose followed by snack or meal if blood glucose is >240 mg/dl	Usual dose of insulin
Double dose schedule	Usual a.m. and p.m. dose (10 to 12 hours after the morning dose)	As above	Usual two doses of insulin

Travel for Operated Patients

During ascent in air travel there is expansion of gases in body cavities to the tune of about 25%. It is important that at least 10 days should have elapsed between any intrathoracic or intra-abdominal surgery before flying. Similarly, minor dental procedures like root canal therapy or fillings are advised to wait for approximately 24 hours before flying.

Pulmonary Disease

The presence of chronic pulmonary disease, such as bronchitis, emphysema and asthma may limit their pulmonary gas exchange. Such conditions could become exacerbated even within the pressurised cabin of an airline. The cabin pressures maintained within commercial airline do not necessarily conform to those occurring at sea level.

In these patients, pulmonary function should be maximised to maintain the best FEV1 possible by continuing bronchodilators and corticosteroid therapy before and during flights. If the traveller is unable to tolerate the lowered cabin pressure, request for supplemental oxygen should be made.

Cardiac Disease

Most of the in-flight deaths are caused by cardiac problems, such as myocardial infarction or cardiac arrest. The emergency medical kit of airlines is generally inadequate. The availability of external defibrillator on the airlines and resuscitation skills among flight attendants may avert approximately 50% of these deaths, which occur due to ventricular fibrillation. Further cardiac patients should carry all medications, a copy of the recent ECG and those with pacemakers should carry ECG performed with and without pacemaker activation.

Diabetes Mellitus

All diabetics should carry medications, syringes, needles and snacks with them. They must carry a card mentioning their physician's name, telephone number, type and dose of insulin/other medication used. **Tables 3A and B** show the changes in dose schedule during east or west bound travel.

SPECIAL HEALTH CONSIDERATIONS FOR TRAVELLERS WITH CHRONIC DISEASES

The following broad principles must be kept in mind for advising travellers with chronic diseases. Asses status of disease and management to be followed during travel.

Medical Examination after Travel

It is advisable for all the travellers to have a medical examination on their return, if especially they have an existing chronic disease, such as COPD, diabetes mellitus, chronic respiratory disease or on anticoagulants. If they develop any sickness following their return home or they had been treated for any illness during travel especially malaria or any serious infectious disease or patients who have travelled for more than 3 months in a developing country should have medical examination. Again, it is pertinent to note that the traveller should provide adequate information about the place, duration of visit, pre-travel infection and malaria prophylaxis. Malaria may be considered an emergency especially if a person develops fever on his return and must be reported as well as proper consultation taken from the doctor.

CONCLUSION

Travel is undertaken for leisure, business, visiting family and relatives. Therefore, it is imperative that one must stay healthy and the traveller should get vaccinated, examined, and get medical insurance done before travelling to a particular country. He must see the Official Site for any ongoing raging or infective epidemic and demographic disease profile. Post travel medical examination is equally important as pre-travel medical advice.

RECOMMENDED READINGS

1. Health Information for International Travel (CDC: edition 2010, http://wwwn.cdc.gov/travel/contentYellowBook.aspx).
2. International Travel and Health (WHO: edition 2011, www.who.int/ith).

28.11 Nanotechnology and Nanomedicine

Ramchandra D Lele

INTRODUCTION

The word 'nano' is derived from the Latin word which means 'dwarf'.

The prefix 'nano' refers to one-billionth. When applied to linear measurement, a nanometer is one-billionth of a meter. The term nanotechnology is now used to refer to the creation of new objects with nano-scale dimensions between 1 and 100 nanometers. The width of a DNA molecule is approximately 2.5 nm. Most proteins are in the range of 1 to 15 or 20 nm. The width of cell membranes is in the range of 6 to 10 nm.

Nanotechnology was first predicted by Nobel Laureate Richard Feynman in 1959. The 10^{12} cells in the human body themselves are very complex and efficient nano-machines and chemists and biochemists have been working at the nanoscale for some time without using the 'nano' lable. Most research in molecular biology already takes place on a nanoscale. Most areas of nanoscience aim to learn from biological nanosystems.

The invention of light microscope (1632) allowing magnification × 400 diameters, apart from revealing micro-organisms, opened the vista of study of living matter at micrometer size establishing the cell as a unit of life, and specific cell types for specific functions and the concept of cellular pathology. The invention of electron microscope by Ernest Ruska in 1931 (Nobel Prize 1986) allowing magnification X 12,000 diameters, and freeztech EM (X 95,000 diameter) led to the identification of subcellular organelles—lysosomes, peroxisomes, Golgi apparatus, endoplasmic reticulum, mitochondria and nuclear components chromosomes, and the concept of lysosomal, mitochondrial and chromosomal disorders. In the brain, EM revealed the synaptic vesicles (300 to 600 Å) which store neurotransmitters and microtubules as conveyors of a two way traffic between a nerve cell body and its dendrons and axons (one Angstrom is 10 nm).

The invention of the scanning tunneling microscope in 1981 by Binig and Rohrer (Nobel Prize 1986) allowed the measurement of and manipulation of individual atoms on a surface. Scanning probe microscopes now extensively used in bio-scientific research are so sensitive that they can detect differences in one base pair in DNA hybridisation. Nanoscale oligonucleotide arrays for gene expression research encompassing the entire human genome on a single chip eliminates the need for labeling DNA strands which simplifies the process of diagnosis. Another Nobel Prize winning breakthrough in nanoscience was the discovery of spherical buckminister fullerenes by Kroto *et al.* in 1985—compounds containing 60 atoms of carbon arranged in a lattice of hexagonal and pentagonal specific connections sometimes likened to the surface of a soccer ball. The C60 fullerenes are 1 nanometer in diameter. Fullerenes have captured the imagination of pharmaceutical research for a number of their unique properties as drugs or components of targeted drug delivery (**Table 1**).

Some years after the discovery of fullerenes, carbon nanotubes or basically open-ended buckyballs were invented, which led to numerous potential scientific and commercial applications including novel display units for computers. Some nanotubes have superconducting properties which are utilised in the new generations of computer systems and electric transmission systems.

Beyond biology, there is enormous interest in nanotechnology. The properties of nanoscale objects and material are quite different from the properties of the same chemical materials created with larger dimensions, as a result of the fundamental principles of quantum physics. Strength, electrical conductivity melting point, colour, and optical and magnetic properties are all potentially affected (Thrall 2004).

There is growing interest in the use of biomolecules as components in electrical circuits and computing systems to permit further miniaturisations with increased computational capacity. The feasibility of using DNA hybridisation to solve complex mathematical problems has been demonstrated at a proof-concept level.

DNA is more than just the secret of life. DNA is now a versatile component of nanoscopic structures and devices. DNA molecules of long length can be made with a sequence of building blocks chosen at will, enabling us to take new paths not yet taken by Nature.

Researchers at Mc Gill University Chemistry Department Montreal have created the first examples of DNA nanotubes that encapsulate and load cargo and then release it rapidly and completely when a specific external DNA strand is added.

DNA machines with moving parts are employed as nano-mechanical sensors, switches and tweezers as well as more elaborate robotic functions. Nanorobots could actually be programmed to repair specific diseased chromosomes in cells or for delivery of Si RNA. Scientists have developed methods for detecting micro RNA from living cells as potential therapeutics for silencing cancer and disease-related genes.

Nanotechnology is the art and science of manipulating individual atoms to create useful materials and devices on a scale of 1 to 100 nanometers (10^{-9}) and to create miniature systems with novel functionality, such as nanorobots.

Nanomaterials are biomaterials used, for example, in orthopaedic or dental implants or as scaffolds for tissue engineered products. Their surface modifications or coding greatly enhance the biocompatibility. These materials can be subclassified into nanocrystalline and nanostructured materials.

Nanocrystalline materials are used in drug encapsulation, bone replacement, prostheses, e.g. artificial limbs, facial prosthetics, neuroprosthetics and implants.

Super paramagnetic iron oxides (SPIOs) also known as monocrystalline iron oxide nano particles (MIONs) have shown

Table 1: Nanotechnology Relevant to Medicine

Nanotechnology	
Nanomaterials	**Nano-devices**
Nanocrystalline	NEMS/MEMS
Nanostructured	Respirocytes
Polymer	Microarrays
Nanoparticles 10 mm	
Dendrimers 1.5 nm	
Micelles 10 to 100	
Drug-Conjugates	
Non-polymer	
Carbon nanotubules 1 to 100 nm	
Metallic nanoparticles <100 m	
Quantum dots 1 to 9.5 m	
Silica nanoparticles	

promise for a number of magnetic resonance imaging applications both as naked particles and as magnetic lables. SPIO particles remain in circulation for long time permitting MRI imaging of arteries and veins. In prostate cancer using lymphotropic superparamagnetic nanoparticles of 2 to 3 nm size, micrometastases of 2 nm size in retroperitoneal lymph-nodes of normal size can be detected by MRI.

Nanostructred materials provide special shapes or functionality, e.g. Quantum dots, dendrimers, fullerenes and carbon nanotubes, metallic and ceramic nanoparticles (silica, alumina, silica-coated lipid miscalls).

Nanodevices are miniature devices in the nanoscale some of which include nano and micro electro-mechanical systems (NEMS & MEMS), microfluidics (control and manipulation of micro or nanolitres of fluids) and micro-arrays (different kinds of biological assays, e.g. DNA, protein, cell and antibody). Examples include biosensors and detectors to detect trace quantities of bacteria, airborne pathogens and some intelligent machines like respirocytes, biovores and vasculoid. Medical nanodevices can be implanted or injected into the blood stream to monitor wellness and to automatically repair systems that deviate from normal.

C60 fullerenes (**Figure 1**) have 60 potential carbon binding sites compared to only six on a benzene ring. This offers opportunities to use fullerenes as scaffolds for complex nanoassemblies, e.g. attachment of targeting antibodies along with chemo-therapeutic agents or radioactive materials for the treatment of cancer. Because of their rigidity, fullerenes can be complexed with other molecules by using precise measurements and configurations based on the properties of the target, to achieve targeted therapy.

Carbon nanotubes (**Figure 2**) are hexagonal networks of carbon atoms 1 nm in diameter and 1 to 100 nm in length, as a layer of graphite rolled up into a cylinder. Nanotubes can be single walled (SWNT) or multiwalled (MWNTs), have ordered structure with high aspect ratio, ultra light weight, high mechanical strength, high electrical and thermal conductivity and high surface area, which makes them useful for diagnostic as well as drug delivery systems. Nanotubes are used to construct nanotweezars proteins, antibodies or DNA can be conjugated to biotinylated SWNTs for biomedical applications.

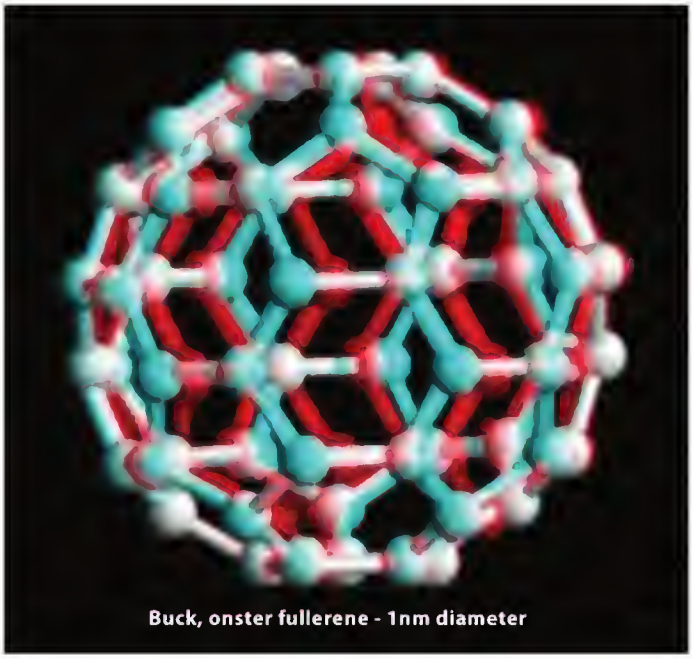


Figure 1: C60 fullerenes.

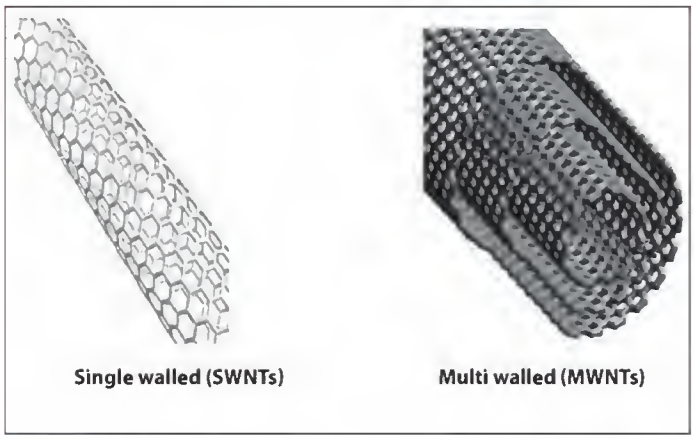


Figure 2: Carbon nanotubes.

Metallic nanoparticles <100 nm because of their easy surface functionalisation are useful as biosensors (gold or silver nanoparticles linked to DNA, proteins, peptides and sugars). They have been used for drug delivery, bioassays, detection and imaging, as an alternative to quantum dots.

Gold nanoparticles (**Figure 3**) are very good at absorbing and scattering light. 35 nm size gold particles tagged to EGFR-Ab can be sprayed on a tissue biopsy specimen. They adhere to cancer cells with 600% greater affinity than normal cells. With a simple microscope and white light cancer cells will show up as shining particles.

Silver nanoparticles (7 to 20 nm) kill Gram-negative bacteria effectively than Gram positive bacteria and also have good antifungal activity when introduced into dressings for wound healing. They also show good anti-inflammatory activity, suppress MMP and TGFβ1 which accelerate wound healing without leaving a scar.

Nanoparticles of iron are non-irritant to the GI tract hence ideal treatment for iron deficiency anaemia.

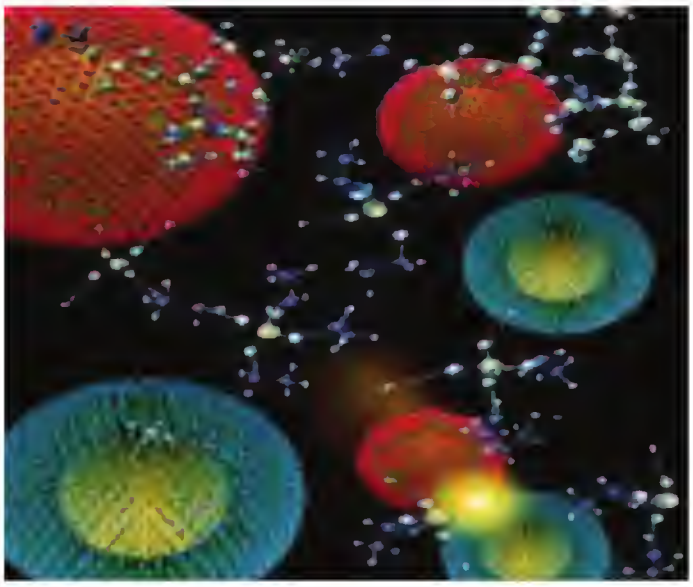


Figure 3: Surface functionalised gold nanoparticles.

Quantum dots (QD) (Figure 4) (2 to 9.5 nm) are semiconducting materials with a semiconductor core (CdSe) coated by a shell (e.g. ZnS) to improve optical properties and a cap enabling improved solubility in aqueous buffers. They glow when stimulated by ultra light. They can be linked to DNA molecules or proteins to form long-lived probes. They can track biological events through biological pathways thus providing diagnosis at the molecular level, such as early detection of mutagenic DNA changes—bioimaging or real time monitoring or tracking of intracellular processes by optical imaging and MRI, detection and analysis of bio-molecules, immunoassays, DNA hybridisation and non-viral vectors for gene therapy, transport vehicles for DNA, proteins, drugs or cells and therapeutic tools for cancer treatment.

Silica-coated nanoparticles (Lipid micelles) can be used for directed cancer therapy. Lipid micelles containing LHRH as a targeting agent can deliver iron oxide particles to LHRH-positive cancer cells.

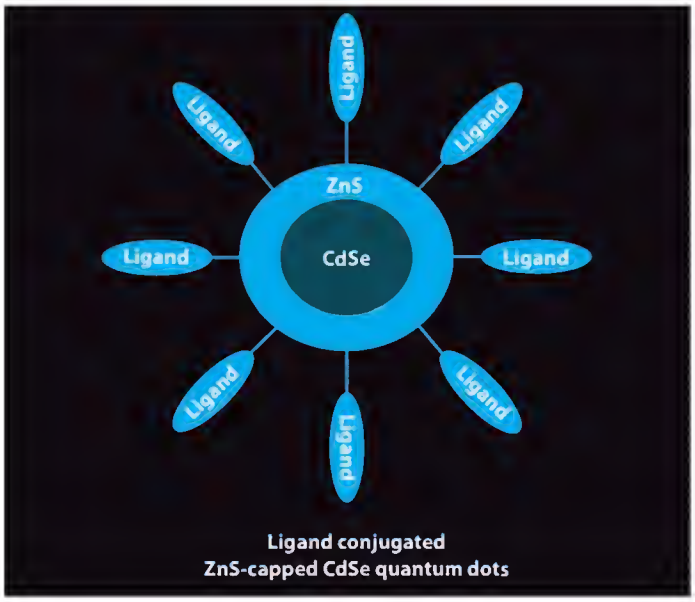


Figure 4: Quantum dots.

Polymeric nanoparticles are colloidal carriers 10 nm to 1 μm size are ideal for controlled and targeted drug delivery due to some inherent properties like biocompatibility, non-immunogenicity, non-toxicity and biodegradability.

Dendrimers (Figure 5) are hyperbranched 1 to 5 nm tree-like structures providing vast surface area and have compartmentalised chemical polymer. They serve as versatile nanoscale platforms for creating multi-functional devices capable of detecting and treating cancer through targeted drug delivery. A single dendrimer can carry a molecule that recognises cancer cells, another molecule, a therapeutic agent that can kill these cells and a third molecule recognising the signals of cell death. They can be tailored or modified into bio-compatible compounds with high biopermeability and low cytotoxicity. Their hollow interior permits delivery of drugs, vaccines, MRI contrast agents, metals and genes to targeted sites.

Polymeric micelles (Figure 6) (10 to 100 nm) ampiphilic block copolymers have hydrophilic surface preventing non-specific uptake by reticuloendothelial system. These dynamic systems are used for systemic and controlled delivery of water-insoluble drugs at target sites.

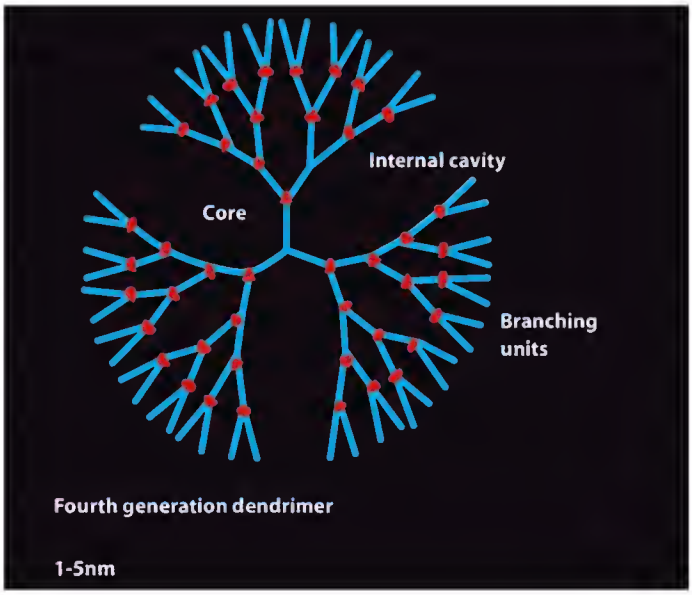


Figure 5: Fourth generation dendrimers.

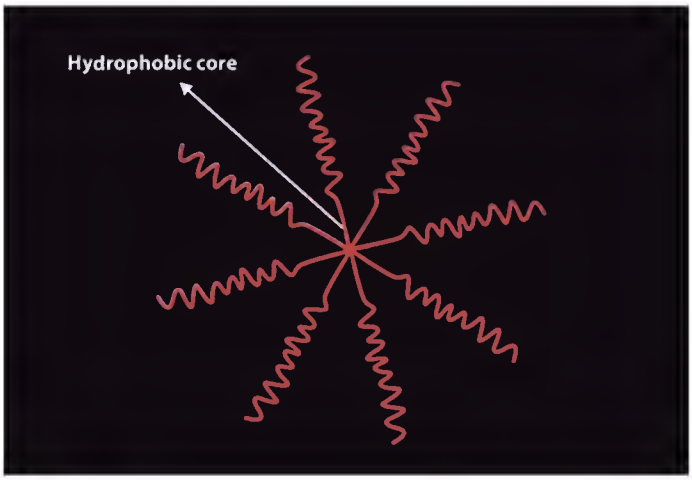


Figure 6: Polymeric micelles.

Polymer drug conjugates (**Figure 7**) are designed to increase the overall molecular weight by conjugation with low molecular weight drugs which facilitates their enhanced permeation and retention (EPR) in tumours taking advantage of leaky vasculature. Nanocarriers can alter the biodistribution and pharmacokinetic parameters of drugs.

Folate nanoparticles have high specific affinity for human cancer cells hence they improve uptake of encapsulated drugs.

Nanocarriers overcome the problem of poor bioavailability, short half-life, insolubility, instability and undesirable side effects and toxic effects of anti-cancer cells.

Liposomes (**Figure 8**) (50 to 100 nm) are extensively used for novel and targeted drug delivery. Small unilmellar vesicles (SUV) are less than 100 nm in size while large unilamellar vesicles (LUVs) are larger than 100 nm. Multilamellar vesicles (MLVs) consist of several lipid bilayers separated from one another by aqueous spaces after ranging from a few hundred to thousands of nm in diameter variety of surface modification approaches permit controlled and targeted drug delivery in cancer, leishmaniasis, ophthalmic condition, etc.

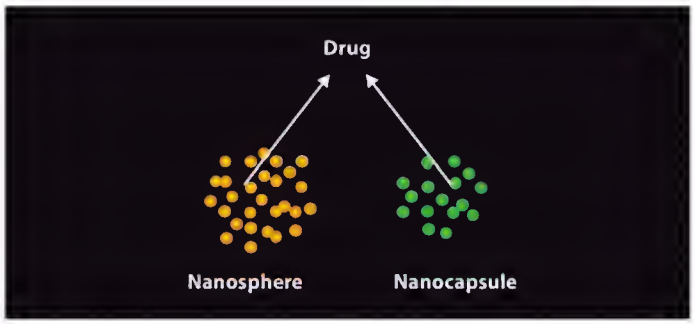


Figure 7: Polymer drug conjugates.

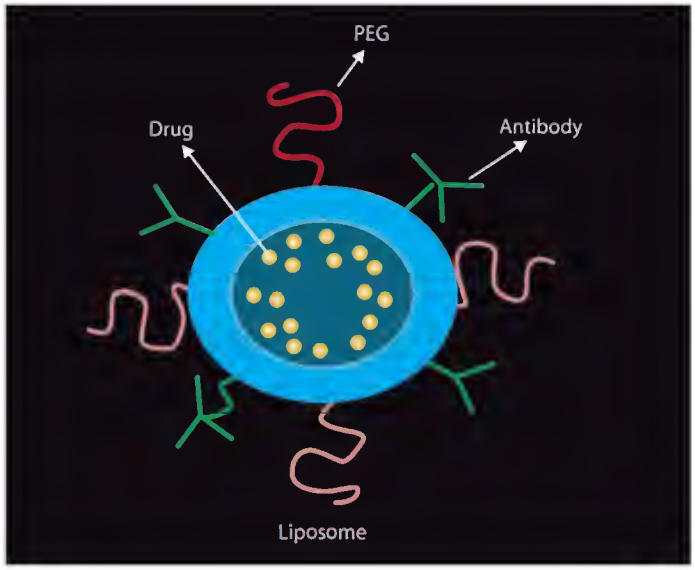


Figure 8: Liposomes.

MEDICAL APPLICATIONS OF NANOTECHNOLOGY

Nanomedicine is the medical application of nanobiotechnology which opens up new ways to diagnose and treat disease and repair damaged cells and tissues. There is an increasing ability to manipulate individual molecules and to combine biomolecules with other nanoscale structures. This ability offers the opportunity for unlimited new diagnostic and therapeutic applications.

Medical nanodevices can be implanted or injected into the blood stream to monitor wellness and to automatically participate in the repair of systems that deviate from normal.

Nanopore fillers show superior performance compared to micropore filters. Improved filtration in drug production is designed for better purity, sterility and apyrogenicity.

Nanotechnology is putting the goal of building a 'lab-on-a-chip' within reach. By using very small channels, only nanogram quantities of analytes and reagents are required. Such device will make sophisticated tests widely and immediately available at lower costs in the clinic, at home, or at patient's bed side.

Nanotechnology has the power to radically change the way cancer is diagnosed, imaged, and treated. There are ongoing efforts to design novel nanodevices capable of detecting cancer at its earliest stage, pinpointing its location within the body and delivering anticancer drugs specifically to malignant cells, totally avoiding normal cells, and to monitor the effectiveness of therapy.

Nanoscale devices smaller than 50 nanometres can easily enter most cells, while those smaller than 200 nanometres can transit out of blood vessels. Hence, they can interact with biomolecules on both the cell surface and within the cytoplasm delivering therapeutic agents within the target cell or even within specific organelles, such as mitochondria, Golgi apparatus. Dendramers are nanoscale delivery devices which can deliver DNA into cells for gene therapy. Unlike viral vectors they do not evoke an immune response. Despite its small size a nanoscale device is capable of holding tens of thousands of small molecules, such as drugs or contrast imaging agents. Even toxic drugs can be delivered at much smaller doses in a controlled and time release manner.

In humans there is only one mechanism to repair UV induced DNA damage while simpler organisms have two or sometimes three repair systems. Using nanoparticle biosensor technology we can supply the missing first step (glycosylase) to enhance DNA repair in human cells.

Nanocarriers penetrate better the leaky tumour cell membrane with 100 to 1,000 nanometre sized pores.

Molecular Biosensors for Nanodelivery

Moleular biosensors are designed to sense their environment within a cell and minimally perturb that cell's basic function, hence they are frequently used inside living cells to monitor basic cell biochemistry in response to drugs, environmental factors, etc.

Molecular biosensors provide sensing extracellular and intracellular environments and to provide feedback for action, such as drug or gene delivery.

Conventional drug delivery systems have no feedback control. Molecular biosensors provide feedback control for stable expression of a therapeutic gene such as DNA repair enzyme. For example, a biosensor sensing radiation-induced oxidative stress and DNA damage can initiate through a synthetic ARE transcription of DNA repair enzyme in the damaged cell only (and not in normal cells).

Similarly, for the treatment of Hepatitis C virus, targeted tetracycline transactivator protein based biosensor seek out infected liver cells, with HCV viral E protein on its surface and deliver ribozymes (molecular scissors) to the IRES region of the virus inside the living cell so that it cannot make new virus. This approach has much fewer side-effects than the current interferon-ribavirin therapy which at best succeeds in only 30% of cases.

Nanoshell Associated Photothermal Therapy (NAPT)

Nanoshells have a core of silica coated with an ultra thin metallic layer, usually gold. By adjusting the core and shell thickness, nanoshells can be designed to absorb and scatter light at a desired wave length. Using nanoshells that absorb light in the near infrared (NIR) region and then convert it into heat (40°C), and delivering them specifically to cancer cells via enhanced permeability and retention (EPR) effect, selective photothermal ablation can be achieved in a non-invasive way using a laser in the NIR region.

Nanoshells also have an interesting application in the treatment of insulin-dependent diabetes mellitus. Instead of several daily injections of insulin, the patient will use a ball point pen size infrared laser to heat the skin wherein a nanoshell polymer containing insulin has been injected. The heat from the nanoshell will cause the polymer to release a pulse of insulin. The nanoshell polymer system could remain in the body for months. (Nanospectra Bioscience www.nanospectra.com).

Molecular Nanotechnology (MNT)

DNA-based nanomachines are computer-controlled molecular tools, such as nanomoters, and molecular tweezers, much smaller than a human cell. Nanorobots will function as artificial red cells (respirocytes), artificial macrophages (microbiovore), artificial platelets, mitochondria etc.

Molecular nanotechnology (MNT) or nanorobotics will allow performance of direct invivo molecular surgery on individual human cells. The ability to design, construct and deploy large numbers of microscopic medical nanorobots will make this possible. A nanorobot can sense hypoxia and deliver VEGF at site for neoangiogenesis (**Figure 9**).

It is an interesting thought that the human body is full of micro-robots in the form of endothelial progenitor cells (EPCs), red blood cells, leucocytes (neutrophils, monocytes/macrophages, lymphocytes) and fibroblasts, that are constantly moving inside our bodies, repairing damaged tissue, attacking invading microbes, gathering foreign particles and transporting them to various organs for disposal from the body. Hence, it is possible to develop prototype microscale assemblers using micro-electromechanical systems (MEMS) and nano-electro-mechanical systems (NEMS). Interesting examples are: 'Microbiovore' an artificial white blood cell, 'respirocyte' an artificial red blood cell, vasculoids and artificial platelets.

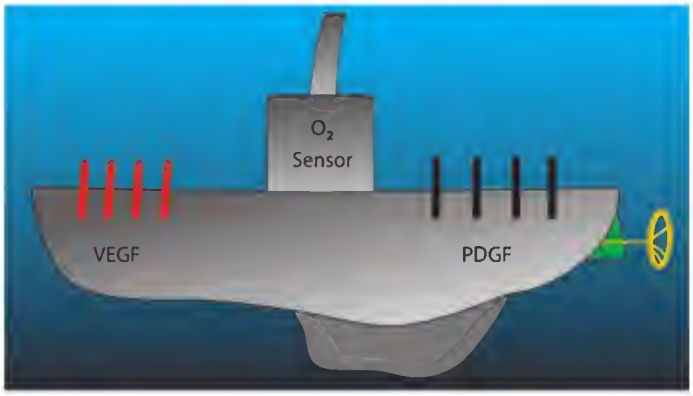


Figure 9: Nanorobot.

VEGF = Vascular endothelial growth factor; PDGF = Platelet-derived growth factor.

Microbiovore (**Figure 10**), an artificial white blood cell, is an oblate spheroidal nanomedical device measuring 3.4 μ diameter along its long axis and 2 μ diameter along its short axis, consisting of 610 billion precisely arranged structural atoms in a gross geometric volume of 12 μ^3, and a dry mass of 12.2 picograms. It is 80 times more efficient in phagocytosis than macrophages, in terms of volume/second digested per unit volume of phagocytic agent. During each cycle of operation the target bacterium is bound to the surface of the microbiovore in the blood stream like a fly on fly paper via species—specific binding sites, and transported to the ingestion port. After sufficient mechanical mincing it goes to a digestion chamber wherein a pre-programmed sequence of 40 engineered enzymes are successively injected and extracted six times progressively reducing the morcellate ultimately to monoresidue aminoacids, mononucleotides, glycerol, free fatty acids and simple sugars. These simple molecules are then harmlessly discharged back into the blood stream through an exhaust port, completing the 30-second cycle. Microbiovores can clear the most severe septicaemia within a few hours or less time compared to weeks by the natural mechanism.

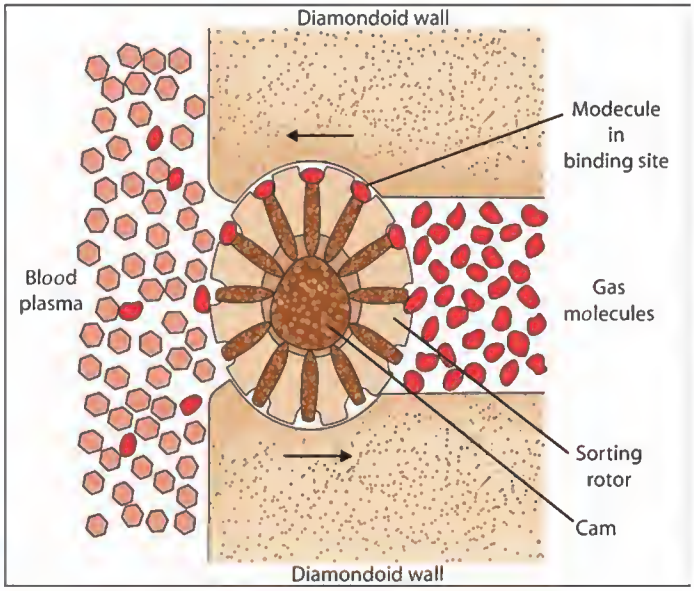


Figure 10: Microbiovore.

Respirocytes

Robert Freitas has designed an artificial mechanical 'respirocyte' (**Figure 11**), which is a one micron size diamondoid 1,000 atmospheric pressure vessel with active pumping powered by endogenous serum glucose. It is able to deliver 236 times more oxygen to the tissue per unit volume than natural RBC and to manage carbonic acidity. Gas concentration sensors on the outside of each device let the nanorobot know when it is time to load O_2 and unload CO_2 (at the lung) or vice versa (at the tissues). Injection of a 5 mL therapeutic dose of 50% respirocyte-saline suspension

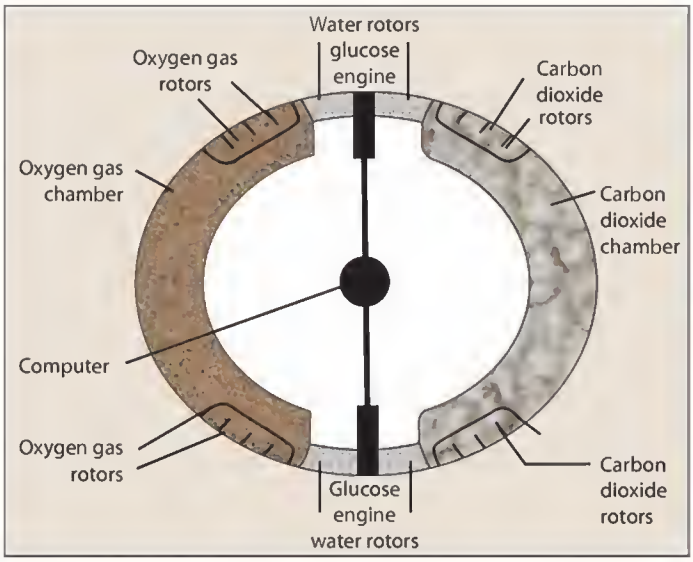


Figure 11: Respirocytes.

delivers 5 trillion respirocytes that can replace the gas carrying capacity of the patient's entire 5 litres of blood.

Vasculoid

The vasculoid (**Figure 12**) is a single complex, multisegmental nanotechnological robotic system capable of duplicating all essential thermal and biochemical transport functions of the blood, including circulation of respiratory gases, glucose, hormones, cytokines, waste products and cellular components. The vasculoid system conforms to the shape of existing blood vessels and serves as a complete replacement for natural blood.

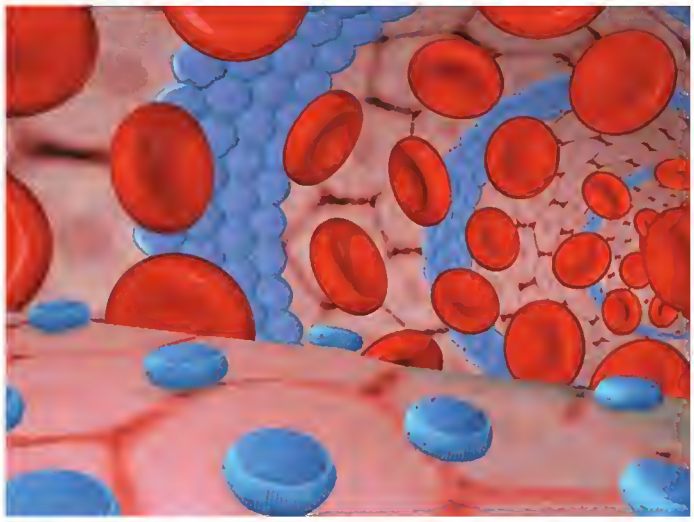


Figure 12: Vasculoid.

Artificial Platelet (Clottocyte)

An artificial mechanical platelet appears to halt bleeding 100 to1,000 times faster than natural haemostasis (**Figure 13**). A single clottocyte reliably detects a blood vessel break and rapidly communicates this fact to its neighbours,

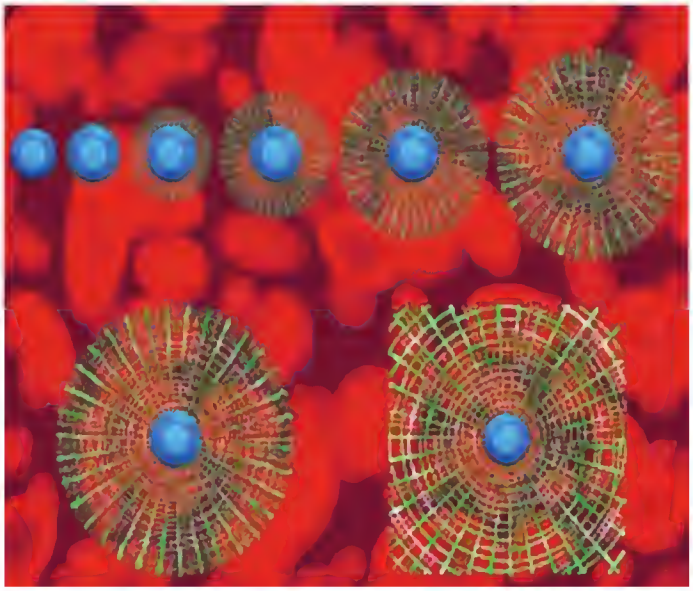


Figure 13: Artificial platelets (Clottocyte).

immediately triggering a progressive controlled mesh-release cascade.

THE FUTURE

Nanotechnology is considered to be a next big wave after information technology and biotechnology according to National Science Foundation (NSF). Revenues from nanotechnology can touch $ one trillion by 2015.

Specialised nanoemulsions, made up of tiny soyabean oil droplets 200 nm in diameter, suspended in water, studded with bits of pathogenic organisms and swabbed into the nose, may be the influenza vaccines of the future. They are taken up by dendritic cells and produce immunity in mucosal tissues of the nose, mouth, lungs.

Animal models of HIV have shown the feasibility of vaginal mucosal immunity by local application of HIV vaccine in mice.

Living systems are governed by molecular behaviour at nanometer scales where the disciplines of physics, chemistry and biology and computer simulation all converge. Detecting gene expression can be made dramatically more efficient through utilisation of nanofabricated surfaces and devices. Expanding our ability to characterise an individual's genetic make up will revolutionise diagnosis and therapy of the individual patient.

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